Clinical Equine Oncology

Clinical Equine Oncology

Derek C. Knottenbelt OBE BVM&S DVM&S Dip ECEIM MRCVS

Consultant Professor in Equine Medicine
University of Glasgow, UK
Emeritus Professor in Equine Internal Medicine
University of Liverpool, UK

Janet C. Patterson-Kane BVSc PhD Dip ACVP MRCVS

Veterinary Pathologist
IDEXX Laboratories, Inc.
West Sacramento, CA, USA

Katie L. Snalune BSc MA VetMB Cert EM (Int.Med.) Cert ES (Soft Tissue) MRCVS

Clinical Head of Hospital
Newnham Court Equine Clinic
Kent, UK



ELSEVIER Edinburgh London New York Oxford Philadelphia St Louis Sydney Toronto 2015

ELSEVIER

© 2015 Elsevier Ltd. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

ISBN 978-0-7020-4266-9

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
A catalog record for this book is available from the Library of Congress

Notices
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ELSEVIER your source for books, journals and multimedia in the health sciences
www.elsevierhealth.com

ELSEVIER Book Aid International Working together to grow libraries in developing countries
www.elsevier.com • www.bookaid.org

The publisher's policy is to use paper manufactured from sustainable forests

Printed in China

For Elsevier
Content Strategist: Robert Edwards
Content Development Specialists: Wendy Lee/Carole McMurray/Veronika Watkins
Project Manager: Andrew Riley
Designer/Design Direction: Miles Hitchen
Illustration Manager: Jennifer Rose, Karen Giacomucci
Illustrator: Antbits

Preface

Writing and constructing a major textbook is not to be undertaken lightly! Before a project such as this can even be proposed, there has to be a reason for it. 'Why do we need a book on equine cancer medicine?' 'Will it help practitioners in particular to improve the quality of their practice and will it be of benefit to the horse itself as a species?' Those were just a couple of the questions we asked before we set out on the project. It did not take long to realize that there is no other similar textbook on the subject. There are, of course, many excellent textbooks on general medicine and surgery relating to the horse and many of these have significant oncology content. There are those books that are focussed on one particular anatomical system or syndrome. Lameness, skin diseases and dentistry are just three of them. There are dedicated textbooks dealing with infectious disease, reproductive medicine and surgery, and surgical and medical tomes that are comprehensive sources of information. The increasing specialization of equine practice is a worldwide phenomenon that has resulted in the development of dedicated training requirements in defined aspects of practice and this is both a laudable and a positive contribution to the improving standard of medical and surgical care that we provide to our patients and their owners. However, in spite of cancer medicine being a major human and small animal specialism, cancer medicine in the horse clearly lags a long way behind. A quick search on cancer on any literature database will confirm the exponential rise in publications at all levels that deal with cancer in humans, small animals and experimental conditions. Furthermore, single-case reports on equine oncological topics abound in the modern scientific literature. There is, however, no dedicated equine oncology textbook and indeed, whilst the literature is littered with 'case reports' and small case series, there has been no concerted or constructive effort to expand this important area of medicine.

The demographics of the equine population are changing dramatically. In the developed world, horses are increasingly being kept into old age and so with greater numbers of older horses, we have to expect greater numbers of cases of cancer in the population. Even in the developing world, significant improvements in management and care mean that horses, mules and donkeys are living for longer, and again this will inevitably mean increasing numbers of cancer cases. There is a clear need for a focussed comprehensive text on equine cancer medicine and surgery. That is our main reason for setting out to produce this book on equine oncology.

The horse remains an important aspect of human life. In places where horses are 'pleasure and leisure' animals, they provide enormous enjoyment and also bring financial returns to nations and to individuals. The equine industry employs vast numbers of people and equine 'sport' provides physical exercise for people between 2 and 90 years of age. No other sport does that!

In the developing world, the Equidae are genuinely life-saving or, at the least, life-changing. The family donkey or pony empowers women in particular and relieves human burden. The loss of a donkey or pony, for a simple rural farmer, for example, can be catastrophic, and has implications for livelihood, lifestyle and even for life itself. We have a duty to support the concept that 'horses' are here to stay and that, realistically, there are no viable alternatives to the equine beast of burden in vast areas of the world. Of course, the concept of 'carbon'-guzzling machines as an alternative may be seen as a way of reducing the welfare compromises that are commonly publicized but simply fail to answer the real-life situation. It is only through improved animal welfare that we can enhance the lives of countless millions of people worldwide.

Whilst many advances have been made in almost every area of equine veterinary practice, cancer medicine has never attracted much in the way of research interest or even clinical specialization. It is a matter of considerable regret and not a little disgrace that the veterinary profession has failed to grasp this particular nettle and that equine cancer medicine attracts so little attention.

Over the last 100 years or so, there have been some significant surveys on equine tumour prevalence, which confirm that the horse suffers a wide range of neoplastic disorders but that the numerical majority of the tumours affect the skin. These tumour types are well recognized and some sort of consensus has evolved on the best treatments and management. Less has been done to try to understand the diseases themselves, even though the opportunities to do so are clearly enormous! The tumours can usually be seen, easily examined in detail and easily biopsied, and usually can be diagnosed definitively.

Modern information systems allow owners and veterinarians alike to access vast amounts of material, though much of the internet-delivered information is of little overall value. A lot of it is blatantly misleading and often positively harmful. As owners become more aware of the availability of treatments and as their access to comments and facts improves, they become more demanding. That is no bad thing – an enquiring and challenging client serves to ensure that the best possible approach is taken and means that the veterinarian must keep up to date and be aware of the latest developments in diagnostic approaches, particularly in treatment. It drives evidence acquisition, and that in turn, drives progress.

This book is arranged in three sections. *Section I* sets out to provide a platform for understanding the cellular basis of cancer and its aetiopathogenesis, along with the broad principles of diagnosis, treatment and management of cancer cases.

Section II sets out the finer details of the main groups of cancer in horses and provides an in-depth description of the literature and what is generally known about the various conditions. It is an attempt to bring a degree of evidence-based information into the various tumour conditions. In-depth understanding of a particular tumour type from a pathological perspective provides interest and hopefully stimulates research and the acquisition of clinical evidence. There are, of course, varying amounts of information available relating to the various tumour types; the 'big five'

in equine cancer are: sarcoid, melanoma, (squamous cell) carcinoma, lymphoma and mastocytoma, and inevitably they are emphasized. However, here we have tried to consider even the rarest of reported tumours on the basis that something is rare simply because it is seldom encountered; and when it is encountered, we need some information about it that might help! Rare tumours offer very different challenges to the clinician, since the evidence may be sparse, to say the least. And yet evidence is only gained through critical scientific and clinical investigations. Gradually, the bricks will be laid on the walls and evidence will build up, to the benefit of the patients themselves.

We hope the *Section III* will provide busy practitioners with a ready reckoner in respect of the tumours that occur in each of the 10 body systems. We have tried to make this reasonably comprehensive and we hope that it will enable a clinician to diagnose at least the majority of tumours and to have rapid access to clinically useful information when a diagnosis is provided clinically or by the pathologist.

To aid this process, disease summary boxes have been included for each of the major tumour types in this final section, condensing the main points under 'Notes', 'Clinical features', 'Diagnostic confirmation', 'Management' and 'Prognosis' headings. Incidence is graded by colour:



common rare very rare

Colour-coding is also used to indicate prognosis:



hopeless poor guarded good

Clinicians might benefit a great deal from the pathological input, while pathologists might similarly gain from seeing the cases that they are consulted upon. The relationship between pathologists and clinicians is a vital part of the developing sphere of equine oncological medicine. We hope this will be an expanding resource to readers over the years as more cases are added to it.

Inevitably, with a broad project such as this, there is a degree of overlap and repetition between the sections but we make no apology for this, simply because the three main sections will, we believe, be read and consulted at different times under different conditions. We have set out to make it as comprehensive as we can but we have, of course, been constrained in the amount of text and the number of images we could include. We hope that the book will provide a basis for the recognition of equine oncology as a specialism and as an important and challenging clinical topic.

Cancer medicine is a serious challenge to us all and we hope this book will help to widen clinical and research interest in aspects of cancer medicine in horses for the future good of the horse. We have set out to redress the imbalance as best we can, recognizing that there is more unknown than known in equine oncology. We extrapolate at our peril, of course, but that is an inevitable result of 'being behind', so we call for more effort both in the clinical circumstances and in research.

We commend this book to you – there are inevitably some aspects that we have had to reduce and even exclude but we feel sure this is a constructive contribution to equine medicine that will bring clinical and welfare benefits to the horse and donkey.

Even a cursory glance at the index pages of most equine journals will attest to the importance of cancer medicine; more and more publications on isolated cases and small case series are being published. We welcome this and we are excited by the prospect of increasing interest and increasing awareness of equine oncological disease amongst owners and veterinarians alike!

Derek C. Knottenbelt

Acknowledgements

A project of this size necessarily involves moral and physical/professional support from a lot of people!

We are grateful to the founders of modern clinical oncology and in particular to Professor Alain Theon, who has almost single-handedly driven the development of radiation therapy and chemotherapy in horses. He has been an inspiration to many people (including ourselves) for many years. In addition to his immense achievements in the science and practice of equine oncology, he has made considerable contributions to this book through his pictures, advice and support.

We would very much like to thank all those who have so willingly contributed pictures and information to the book. They are far too numerous to list here. The reality is that countless owners and veterinarians have helped us – be assured we are deeply indebted to you all. We would particularly like to thank the following for their help: Tim Mair, Garance Christen, Ophelie Clottu, Victoria Coppas, Olly King, Alexandra Imhasly, Fred Pauwels, Susan Jones, Maarten Oosterlinck, Dylan Gorvy, Eugenio Gillan-Garcia, Luiz Mendes, Katherina Pieber, David Donaldson, Jennifer Stuart, Veronica Roberts, Marisa Rodrigues, Santiago Gutierrez-Nibeyro, Richard Blundell, Susanna Monteiro, Sidney Rickets, Alistair Foote, Andy Durham, Gail Leeming, Cynric Temple Camp, Christoph Koch, Gabor Bodo, Fernando Malalana, Neil Townsend, Barbora Bezděková, Petr Jahn, Carney Jackson, Dennis Brooks, David Wilkie, Paddy Dixon and Guy Grinwis. Marianne Sloet has remained an amazing supporter of this project, offering her help at every opportunity, and we thank her also for being such a great friend.

We are also especially grateful to Jeremy Kemp-Symonds for his help with the Laser surgery and Photodynamic therapy sections (Ch. 9). He has extensive experience of both, and his contribution is therefore invaluable. Professor Youssef Tamzali has contributed to the section on Electrochemotherapy (also in Ch. 9) and, again, his experience of its use in a wide range of skin tumours in horses provides useful evidence for efficacy. Youssef has remained enthusiastic about the success of this project and his support is greatly appreciated.

Ceri Adams-Stevens has been a Trojan during the preparation of this project. She has contributed a great deal in the engine room of text production, and to the management of the references for each section in particular. She has been a true stalwart. We are deeply grateful to her.

Robert Edwards, Veronika Watkins, Andrew Riley and Clive Hewat of Elsevier have been stalwart supporters who have tolerated our literary and time-keeping inadequacies with good humour. Thank you also to the back-room art team – great work! The picture quality is terrific and a credit to you all, just as it is to us. Without the enthusiasm, support and help of Wendy Lee, we would surely have never completed this project – thank you, Wendy, you are amazing! The innovative nature of this book and its unusual presentation is a real credit to the enthusiasm and drive of the whole publishing team!

Dedication

This book is dedicated to the HORSE, the DONKEY and the MULE. Without the permissive and submissive domestication of the horse as a species, mankind would probably still be breaking stones and rubbing sticks to make fire. We are where we are in evolution because of the horse. It's payback time now – the horse needs us and we still need the horse.

Don't walk in front of me,
I may not follow.
Don't walk behind me,
I may not lead.
Just walk beside me and be my friend.
(Albert Camus, 1913–1960)



1 Introduction

A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimulus which evoked the change.[1]

The term 'cancer' is derived from the Greek word *karkinos*, or crab, which is thought to relate to the 'crab-like' appearance of blood vessels on tumours, the vessels resembling a crab's claws reaching out (Fig. 1.1). Cancer is the general name for a large and complex group of diseases in which cells in a part of the body begin to grow out of control. Although there are many kinds of cancer, they all start because abnormal cells acquire an abnormal and potentially harmful growth pattern. Untreated cancers can cause serious illness and even death; the term 'cancer' is widely feared, since the perception is widely held that it is almost synonymous with death. This has imparted a rather negative attitude to the broad range of cancers that affect animals but it has also provided impetus for research. The understanding of the origins of cancer has advanced dramatically over the last 3–4 decades as a result of the revolution in molecular biology and the dramatic advances in molecular technology. Powerful experimental tools have been placed in the hands of cancer scientists and physicians and these have made it possible to explore the most minute aspects of the complex molecular machinery that govern the replicative and functional processes of a cell. Comparative examination of normal and tumour cells has been possible to establish the specific defects that cause cancer cells to replicate and behave abnormally.

One of the first written descriptions of cancer and its treatment is in an Egyptian papyrus dating from around 3000 BC, the Edwin Smith Papyrus.[2] This recorded eight cases of human breast cancer, but commented then that there was 'no treatment for the condition'. In 400 BC, as part of his *Humoral Theory of Disease*, Hippocrates, the accepted father of modern medicine, attributed cancer to an excess of 'black bile'. He used the words 'carcinos' and 'carcinoma' to describe tumours and hence the term 'cancer' was coined. Hippocrates is credited with being the first to recognize the difference between benign and malignant tumours. He believed that it was best to leave cancer alone because those who received 'treatment' had a poorer survival outcome than those who did not; he already recognized the benefit of not interfering if no positive outcome could be guaranteed or at least expected.

Galen (AD 130–200), a Greek physician believed cancer was curable in its early stages and proposed that advanced tumours should be operated upon either by 'cutting around the affected area' or by cauterization. He already had an awareness of the basic requirements of cancer therapy – to treat the condition early when the tumour was small and to ensure that the whole tumour was removed. He also made the first suggestions on the aetiology – proposing that it was the result of unhealthy diets and bad climates!

Moses ben Maimon, known in English as Maimonides and in Hebrew as Rambam (1138–1204), is widely regarded as the greatest Jewish philosopher of the medieval period. He also achieved fame as a physician.[3] In his fifth medical treatise he recognized that large tumours required wide surgical excision, 'such that the roots of the tumour and its surroundings up to the point of healthy tissue [should be] removed'. He also recognized the limits of surgery when the tumours involved were close to major organs. He was aware that when they could either not be totally removed or affected adjacent organs and tissues that were intolerant of removal, the outlook was much worse and the 'removal' process was more complicated. The same challenges face the oncologist today in spite of the sophistication of modern medicine.

It was only in the early eighteenth century that interest in the problems and challenges of cancer were revisited. In 1713, an Italian physician Bernardino Ramazzini, the acknowledged father of occupational medicine, noticed the high incidence of breast cancer and the virtual absence of cervical cancer among nuns.[4] This observation identified the basis of the importance of hormonal factors in cancer and environmental exposure/challenge. His work is a very early example of an elegant and meticulous epidemiological study that led to a new approach to cancer medicine.

In 1775, the London physician Dr Percival Pott identified that chimney sweeps had an occupation-related cancer risk. Soot that collected under their scrotum was associated with scrotal cancer. These discoveries led to additional studies, which identified other occupational cancer risks. The identification of these risks forced health and safety measures to be taken, including the need to 'wash thoroughly'. As

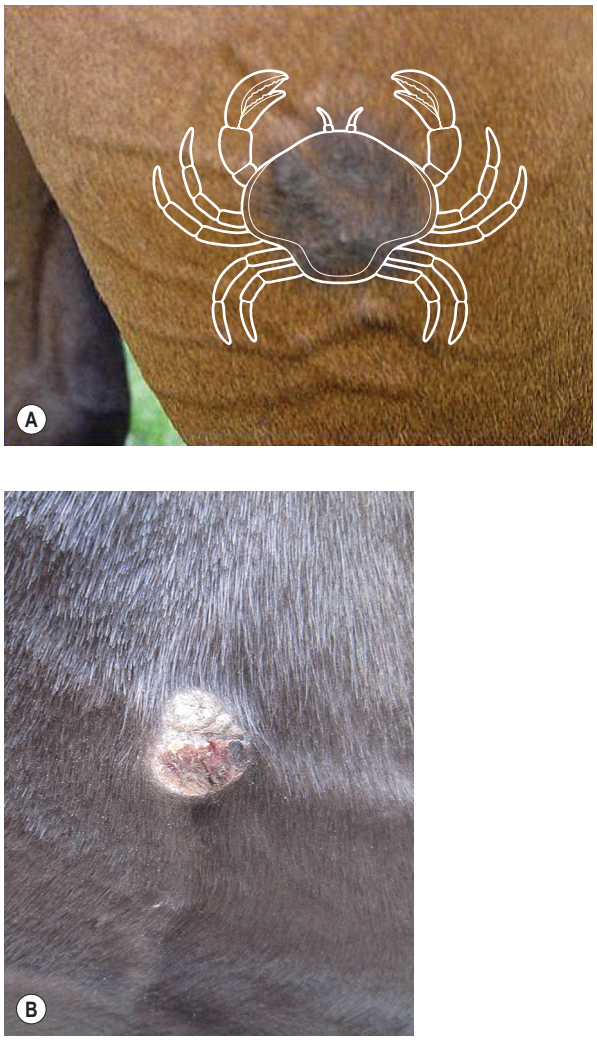


Figure 1.1 The crab-like appearance of tumours. The term 'cancer' was used to account for the crab-like appearance of a visible tumour with its radiating blood vessels and tumour extensions into adjacent tissues. **(A)** A verrucose haemangioma. **(B)** An equine sarcoid. Both have radiating blood vessels that give the tumours a 'crab-like' appearance. The similar 'crab-like' gross appearance of the dissected tumours is also thought to have been an origin of the term 'cancer' but of course the histological invasion of tissues was not recognized until the modern medical era.

soon as suitable measures were taken, the incidence of that particular cancer fell dramatically. It was the first genuine record of a preventive measure that eliminated a particular and highly dangerous cancerous disease.

The causes of cancer remained uncertain until 1910, when Francis Rous provided scientific backing to the 'viral theory of cancer' by inducing tumours through injecting cell fluid extracts obtained from the 'Rous sarcoma' in chickens. Possibly the greatest advance into the role of 'chromosomal abnormalities' in cancer was, however, made by Theodor Boveri, in 1914. Boveri proposed the 'somatic mutation theory of cancer'; this theory suggested that cancer was caused by abnormal chromosomes.

In 1939, Charles Huggins and his group, started studying androgen levels and the appearance of prostate cancer in dogs. Huggins was later awarded the 1966 Nobel Prize for Medicine in recognition of this work. The research succeeded in showing the relationship between hormones and certain cancers. This laid the groundwork for hormone therapy for certain cancers. This important research proved that administration of the female hormone oestrogen slowed the growth of prostate cancer in males. Hormone therapy, also called 'androgen ablation', is now a common treatment for prostate cancer and he also recommended 'the Huggins operation' – castration – for particularly advanced cases. In separate research, he showed that some breast cancers can be slowed by removing the sources of endogenous oestrogen – the ovaries and adrenal glands. Medications that block the natural production of oestrogen are now part of the standard treatment of breast cancer. Prior to Huggins' research, cancer had generally only been treated with surgery and painkilling drugs.

While investigating chemical warfare agents during the Second World War, in 1942, Louis Goodman noted that the blood of soldiers exposed to nitrogen mustard had abnormally low levels of white cells. He reasoned that nitrogen mustard might open new approaches other than surgery and radiation in the management of some forms of lymphoma, then the only effective anti-cancer therapies available. Goodman found that the substance significantly retarded the progression of lymphoma by causing serious tumour cell damage. His rather paradoxical conclusion, that this biologically 'harmful' effect might be harnessed in the treatment of cancer, led to the first paper reporting the use of nitrogen mustards as chemotherapeutic agents against various human lymphoid tumours.[5]

The 'DNA provirus' hypothesis of cancer was proposed in 1960 by Howard Temin. In this, he proposed that certain RNA viruses were capable of inserting their genetic material into the DNA of host cells and that at least some of the genetic components of these inactive 'proviruses' could eventually be expressed and thereby could contribute to the formation of cancer. In 1976, Varmus discovered the first cellular oncogene[6] and this research was rewarded with a Nobel Prize in recognition of its fundamental importance to cancer medicine.[6,7] The role of papilloma viruses in equine cancers (and in particular sarcoid) was identified in the latter half of the twentieth century.

The first recognition of cancer metastasis was made by Joseph Recamier. In his 1829 treatise *Recherches sur le traitement du cancer*, he used the term 'metastasis' as a definition for the spread of cancer to remote sites in the body. A major development followed in 1838, when Johannes Muller, a German pathologist, began to establish cancer histopathology as an independent branch of medical science. Over the remainder of the eighteenth century, individual pathologists and surgeons developed the science of 'oncological medicine' and this led to the publication of Steven Paget's 'seed and soil' theory of cancer, in 1889. This landmark study involved the careful analysis of over 1000 autopsy records of women who had breast cancer and he reported that the patterns of metastasis were not random. He proposed that tumour cells (the seeds) have a specific affinity for specific organs (the soil) and metastasis would only result if the seed and soil 'were compatible' (p. 53). Although there are some well-recognized difficulties with this hypothesis, it still stands the test of time in modern cancer medicine pathophysiology.

Following the discovery of X-rays by Wilhelm Conrad Röntgen in 1895, and the pioneering work of Marie and Pierre Curie, the diagnosis of cancer was significantly

improved – radiography proved to be a non-invasive and, in some cases, accurate method of establishing the presence of serious cancer conditions. However, during all the enthusiasm for the diagnostic capabilities of ionizing radiation (and X-rays in particular), their harmful and cancer-inducing properties were not appreciated during the early development of radiology. Marie Curie died in 1934 of aplastic anaemia, probably brought about by her years of exposure to radiation.

The beneficial (therapeutic) effects of radiation on cancer were probably discovered serendipitously; scientists and physicians were unable to explain why radiation regressed or slowed the progression of some tumours. The question as to who discovered the curative or anti-cancer effects of radiation should go to two general practitioners in Stockholm, Tor Stenbeck and Tage Sjögren, who in 1899, identified the benefit of radiotherapy. They cured a patient with malignant basal cell carcinoma using 99 radiation treatments over a 3-month period.[8] As with the Swedish case, in the early days, cures or treatments were largely restricted to superficial cancers and there was a high rate of recurrence of tumours in treated patients; this was probably simply due to the crude nature of the treatment and the massive and rather empirical doses of radiation that were used. Through the late 1930s, linear accelerators were developed to provide a more rational, controlled and successful treatment regimen and since then, radiation has become the 'gold standard' treatment for many cancers in humans and animals (admittedly to a lesser extent in the veterinary species).

The question, 'Why does cancer not occur more frequently?' became the focus of the role of genetics in the natural suppression of cancer cells within the body. The importance of genetics in cancer was first identified in 1986 by Friend and colleagues, in their studies with the retinoblastoma gene (Rb), which was also one of the first genes identified as being associated with an inherited (familial) form of cancer.[9] The importance and awareness of mutations in the aetiology and progression of cancer have increased dramatically with the development of new rapid genomic technology.

Since the mid-1990s, the knowledge base for cancer pathogenesis and treatment has developed exponentially. This simply reflects the perceived importance of cancer as a whole and it has also been magnified by the plethora of tumour types that have been identified even within a single broad classical disease entity. It is almost impossible to keep up with the published science in oncology! In 1995, the first DNA microarray chip was constructed and used to measure gene expression levels in plants.[10] This technology has been advanced dramatically and is now used to study many human and veterinary cancers. Currently, 'gene chips' are being investigated as tools in the development of individualized treatment plans.[11] The first successful creation of tumour cells was reported in 1999; human epithelial and fibroblast cells were transformed into tumour cells in a laboratory by the co-expression of telomerase (hTERT), the simian virus 40 large-T oncoprotein and an oncogenic allele of HRAS.[12] Our ability to 'make' an experimental cancer cell in the laboratory is clearly reflective of the detailed understanding of oncogenesis and provides an ideal basis for the development of focussed therapeutic approaches with a greater specificity for tumour-transformed cells.

The emphasis on early detection of tumours and the development of more and more sophisticated therapy has led to an 'expectation of success' in patients and owners that is not always realistic. However, enormous progress has been made in our understanding of the disease processes involved in the transition from normal cells to those that have a life-threatening behaviour. The causes of cancer have challenged research scientists and medical and veterinary practitioners since cancer was first identified. Cancer has been recognized in even the earliest writings of man and its complexity means that it is no surprise that it still challenges both the veterinary and medical professions.

Historically, three main hypotheses have been proposed for the origins of cancer, with each having a strong following as well as strong antagonists. One of these models proposed the concept that cancer was a disease of abnormal cell differentiation in which abnormal or errant cells behaviour resulted in progressive and repeated abnormal 'choices' of pathways in cell differentiation. Considering that the process of differentiation of the phenotype of the cells occurs without genetic changes, this model suggested that the development of cancer was an epigenetic process: the alteration of cell behaviour/phenotype in the absence of a genetic alteration. This theory had, therefore, important implications in recognizing that there were genetic origins in cancer.

An alternative hypothesis involved the effects of viruses, since a number of tumours were known to be associated with virus infections in both human and animal species. Examples that supported the theory included the Rous sarcoma virus of chickens, which was shown in 1911 to be involved in tumour development; this retrovirus was the first oncovirus to be described. The concept of the viral aetiology of cancer suggested that the virus, or more commonly a part of the virus, was able to insinuate itself into the genetic structure of the host cells, thus making it able to transform the cells from a normal behaviour into a malignant state.

It is now accepted that cancer probably results from mutations that promote autonomy rather than dependency. In cancer, there is disturbance of the delicate balance between the cell replication cycle and the controlling influences from within the cell and from outside it. These changes can result in the cell continuing to replicate, even in the presence of strong cellular signals that would normally inhibit or destroy the cell. Many of these controlling signals are cell and tissue-type specific, so that the genetic alterations that provide for a growth advantage may be different in different tissues. To complicate matters still further, the inherent genetic instability of cells with a liability to cancerous transformation also results in changes that have redundancy and so that, even in the same tissue, a tumour can develop from different genetic changes; this makes the use of genetic mechanisms in diagnosis more complicated and encourages the holistic approach when all aspects are combined together to reach a positive conclusion on the true nature of the tumour.

Cancer can, with a high degree of confidence, be viewed as a genetic disease that results in the abnormal proliferation of a single lineage of cells derived originally from a single cell that has undergone some form of genetic mutation. The resulting clonal expansion and increasing genetic instability result in the variations in the clinical behaviour of the cells. The completion of the sequencing of the equine genome gives us a much better opportunity to define the various

forms of cancer in horses. The completed map should permit the abnormal genes to be identified and so, while this may not yet provide any significant improvement of our management of the tumours, it will at least categorically define the type of tumour and the definitive mutations that occur and hopefully that will lead to an increased awareness of the prognosis for many cases. The concept that cancer growth and progression is the result of a single clonal expansion of a small proportion of the tumour cells arises from the observation that in many malignancies, no matter what method was used to assay the proliferative potential, only a small proportion of cancer cells are in fact able to proliferate extensively and continuously. This is indeed a fortunate aspect of cancer pathology.

The challenge of cancer to the medical and veterinary professions is increasing significantly. It is certainly true that the prevalence of tumours in horses is increasing. This is largely due to changes in demographics, with increasing numbers of horses being kept into older age and to the improving recognition of tumours by both owners and veterinarians. Over 80% of reported equine tumours involve the skin or the subcutaneous tissues; this may be somewhat misleading, since these tumours are the obvious ones to an observer and they are also those that have had most research and therapeutic developments. Given the superficial and obvious nature of most tumours in horses, it is easy to conclude therefore that the majority of tumours should be curable, provided that suitable early access to the case can be obtained. However, there are major problems that arise as a result of mismanagement and/or irresponsible neglect of the tumours and so the overall prognosis is significantly worse than perhaps it should be.

From a veterinary perspective, it is important to realize that much of the experimental work that is carried out on the causes and treatments of cancer are developed and 'tested' in laboratory animals and the reality is that the 'return' to the animal kingdom for this sacrifice has been paltry to say the least. Cancer is no less important in veterinary species than in mankind and many of the lessons that have been learned have involved animal sciences. As the demographics of the equine population changes with the increasing number of older animals in the population and as animal welfare has become increasingly more important to owners and veterinarians alike, more cases are being presented and so veterinary (equine) cancer medicine has at last started to be viewed as a specialist subject worthy of specialist research input. Cases are being detected earlier and given their true clinical importance. Diagnostic and therapeutic advances are slower in equine practice than other arms of medical and veterinary medicine. Although this is probably understandable, given the size of the patient and therefore the logistics, and the cost of any diagnostic processes or therapeutic interventions, it does mean that much of the clinical advancement is driven by extrapolation or by university teaching hospital case materials.

It is often stated that cancer is many different diseases but probably this is simply because cancer in different organs and tissues has different implications and manifestations. The common overall feature to all cancers is that it is a direct result of the failure of cell regulation with inappropriate and ultimately uncontrolled cell proliferation. There are clearly significant clinical and pathological differences between a skin carcinoma and an adenocarcinoma of the large colon, but it is also important to recognize that there are also major differences in the way in which cancer manifests within one organ in different patients. This latter fact is possibly related to differences in phenotypic heterogeneity among the cells of a particular cancer type. It is this heterogeneity that contributes so much to the difficulty of diagnosis of the various cancers – it has been said that, 'cancer has as many manifestations as there are cases of cancer', thus implying that no two cases will be the same. Not only does this concept add to the difficulty of diagnosis but possibly, even more importantly, it might explain the singular differences that are encountered in the treatment responses. A particular treatment might be very effective in one case and have far less effect in an ostensibly identical tumour in another patient. In the horse, this applies as much as in any other species, and this in turn leads to the 'unexplained failures' and amazing successes that individual clinicians might achieve. Cancer medicine tends then to be a rollercoaster of elation and depression. Fortunately, in the equine species, there are a few well-recognized common tumour states and most of these have visible differences and so treatment choices remain fairly narrow. A good example is the equine sarcoid (pp. 203 and 545), which although it is primary neoplasm of fibroblasts, has at least six morphological forms that can be recognized – each of these has some form of therapeutic limitations.[13]

References

1. Willis R. The spread of tumours in the human body. London: Butterworth; 1952: 46–55.
2. Morton TT, Moore RJ. A chronology of medicine and related sciences. Aldershot: Scholar Press; 1997.
3. Frank JB. Moses Maimonides: Rabbi of medicine. Yale J Biol Med 1981; 54:79–88.
4. The American Cancer Society Inc. The history of cancer. Atlanta: The American Cancer Society Inc.; 2002: 13–17.
5. Goodman LS, Wintrobe MM, Dameshek W, et al. Nitrogen mustard therapy; use of methyl-bis(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. J Am Med Assoc 1946; 132:126–132.
6. Varmus HE, Shank PR. Unintegrated viral DNA is synthesized in the cytoplasm of avian sarcoma virus-transformed duck cells by viral DNA polymerase. J Virol 1976; 18:567–573.
7. Marx JL. Cancer gene research wins medicine Nobel. Science 1989; 246: 326–327.
8. Berven E. The development and organization of therapeutic radiology in Sweden. Proceedings of the 47th Annual Meeting of the Radiological Society of North America, 1961: 19–23.
9. Friend SH, Bernards R, Rogelj S, et al. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. Nature 1986; 323:643–646.
10. Schena M, Shalon, D, Davis RW, et al. Quantitative monitoring of gene expression patterns with a complementary DNA microarray. Science 1995; 270:467–470.
11. Wulfkuhle J, Espina V, Liotta L, et al. Genomic and proteomic technologies for individualization and improvement of cancer treatment. Eur J Cancer 2004; 40:2623–2632.
12. Hahn WC, Counter CM, Lundberg AS, et al. Creation of tumour cells with defined genetic elements. Nature 1999; 400:464–468.
13. Knottenbelt DC. A clinical classification of the equine sarcoid. Clin Tech Equine Pract 2005; 4:278–295.

2

The challenges and problems of equine oncological practice

While cancer is probably not regarded as the most important overall clinical condition of the horse, it is a significant cause of morbidity and mortality. It is unfortunate that in the absence of proper central recording systems, the true incidence rate (often erroneously referred to as the 'incidence') for cancer is not established to any significant degree of certainty either internationally or by country or region. (The annual incidence rate is defined as the number of new cases of cancer developing in the population in a defined time period – usually 1 year.) As most surveys published involve hospital submissions, often to referral/second-opinion centres (many of which are based in universities), there are inherent problems in using these figures to estimate prevalence or incidence in the equine populations as a whole. Animals referred to specialists are usually of a higher monetary or emotional value to the owner. These horses are also more likely to be presented with conditions that are more complex or more difficult to diagnose and treat; this is in contrast to conditions easily treated in the field by the practitioner or not referred for whatever reason, that will be excluded from such analyses. Additionally, it is often impossible to know what the total size of the equine population is.[1] Trends in incidence rates often provide very significant information that can help establish possible aetiologies or factors that predispose to cancer development. The temporal incidence rate measures the rate of new case development in a defined period of time (e.g. week, month, year, decade, etc.). The sex and breed incidence rate defines the rate at which new cancers develop in defined sexes or breeds.

Neoplastic disease has nevertheless been reported in every body system of the horse, although the general consensus, based on university teaching hospital caseloads and a few slaughter house and necropsy studies, is that the commonest overall system involved in tumour development is the integument.[1] This predominance of skin tumours may bias any general conclusions about neoplastic disease in the horse.

Cancer in its various forms in the horse has particular difficulties and challenges. Recognition of the significance is often much less than an equivalent domestic pet or of course a human patient. This has meant that over many years, in spite of the horse having significant morbidity, there has been little effort to establish an evidence-based approach to many of the cancer problems that challenge the practicing veterinarian and the specialist alike. It is probably fortunate for the horse that the majority of tumours that are reported in the species are cutaneous or at least superficial and this makes their clinical recognition much easier. Skin tumours are more likely to be noticed, sampled or excised and submitted to diagnostic laboratories, and therefore noted in surveys. Many cancers that are not directly visible are commonly overlooked and, therefore, many cases do not get diagnosed. This does indicate, however, that even when only considering skin cancer, for a veterinary pathologist dealing with a significant equine caseload, it is an important consideration that requires knowledge and expertise.

It is also unfortunate that the mysteries of cancer are often used to 'smooth' out a diagnosis in a difficult case, whether it has the condition or not. This is clearly counterproductive in terms of equine welfare and is also a major block to advances in our understanding of tumours and their effects in horses. Many specialist centres will recognize that cases are referred for investigation of clinically significant symptoms without thought of the possibility of neoplastic disease or are diagnosed with 'cancer' when the symptoms of non-cancerous disease cannot be explained by simple and recognized diseases.

The early diagnosis of cancer is seen in most species as a primary clinical aim and, notwithstanding the problems associated with the diagnosis and management in horses, this should surely be the objective also of the equine clinician. The main priority for a clinician dealing with horses (regardless of whether the case is one of neoplastic disease or not) is the quality of life for the animal. This takes absolute precedence over any other consideration, but of course the quality of life of a patient may be compromised during treatment in the expectation of a complete cure or at least a palliation of the signs so that there is an overall improvement in quality of life. The most fundamental problem with assessing quality of life for a horse is the difficulty in assessing how much pain and/or discomfort a horse suffers, either through the disease itself or through the treatment of the disease or both. There is a reasonable tendency to anthropomorphize the situation that the animal faces and whilst this is an acceptable way to assess it, it is probably far more complex than this. One horse can be highly sensitive to pain but another may be far more stoical and donkeys are probably one of the most stoical creatures known – in spite of obvious and severe disease they usually maintain a stoic and implacable outward appearance. The donkey is therefore often treated as a 'stupid, non-feeling' creature but this is very far from the case; they suffer as do all creatures – they just do not like showing it. We are left with our own

individual professional ideas of where the acceptable boundaries lie and what we are individually prepared to allow a horse to suffer by way of pain and discomfort. Cancer medicine will inevitably involve profoundly difficult decisions that may conflict with the opinions of others, both professional and lay.

The main aims of any clinical oncology facility dealing with equine cancer cases can be summarized in four points:

1. To save lives
2. To relieve suffering and improve the welfare of equine patients
3. To recognize when the case is beyond medical or surgical help and welfare issues dictate that euthanasia is required in a timely fashion; this does not always mean immediate euthanasia is required
4. To improve the knowledge base in cancer medicine with robust evidence-based studies to establish better diagnostic facilities, best practice in therapy and to provide a better indication of the prognosis.

The objectives in the longer term must surely be:

- To prevent cases as far as possible by giving sensible advice and instituting management processes, based on a sound understanding of the aetiopathogenesis of the various conditions
- To detect tumours earlier and to institute appropriate therapy to minimize the clinical effects and maximize the prognosis
- To improve awareness in owners regarding the detection and treatment of tumours in horses
- To provide faster and better-quality treatment that is within the inevitable financial constraints of horse ownership
- To develop centres of excellence in equine oncology, so that equipment can be used sensibly and so that evidence can be gained on best practice
- To encourage research efforts in the general area of equine oncology.

All these objectives are laudable of course, but each one brings significant problems that are more challenging in the horse than in any other domestic species. There are difficulties with almost every aspect of cancer medicine in horses. The horse is a large animal with an inherent behaviour pattern that is not usually tolerant of pain. Horses usually have a finite value and owners may be unwilling or unable to undertake the best treatments because of financial constraints. On the other hand, the horse is not usually treated as a 'commodity' like a farm animal and in contrast to domestic pets, they usually also have major commercial value – they cost a lot to buy. Increasingly, emotional value is also involved; many owners have a deep affection for their horses and this means that both financial and emotional value are involved in any decisions that have to be taken in regard to treatment or other diagnostic procedures. Fortunately, there is still a sympathetic sentiment, which means that owners do appreciate that a horse that is in unremitting suffering to no end requires euthanasia. The human is the only 'animal' civilized society that will watch and accept incurable suffering. The horse deserves to be given the best possible support, but equine cancer medicine unfortunately lags far behind that in most other species.

The analysis of many successes and failures in the management of cancer reveals the important role of the clinician who deals with the case.[2] The speed of diagnosis relative to the onset of the tumour and the timely intervention at a stage when the chances of success are greatest are key factors in the process of successful outcomes.

> *Where guesswork, an amateurish approach and defeatist attitude may fail, an intelligent and compassionate understanding and prompt skilful treatment may succeed.*

There has been very little attempt to investigate equine cancer diseases – most of the literature reports involving large numbers are surveys of tumour incidence in university teaching hospitals,[3–7] abattoir studies or are case descriptions of a single or few cases.[3–6,8] This is entirely understandable, since the diagnosis of cancer in horses is largely restricted to those tumours that affect the skin and are therefore belittled and regarded as an incidental nuisance or those that are life-threatening internal tumours, for which there is a perception that 'nothing can be done anyway'. The latter horses have most often been simply destroyed upon diagnosis, whether the animal really needs to be destroyed or not.

In the USA in 1940, it was estimated that the cancerous (malignant) and benign tumour rate in the normal working horse population was 40 and 389, respectively, per 100 000 horses and that of those, 11 and 6 per 100 000 horses, respectively, died or were destroyed as result of the tumour state.[9] Thus, at that time, it was concluded that there is a marked predominance of non-life-threatening benign neoplasms in the horse.[1] Published figures from veterinary schools indicate that tumours account for about 1–3% of surgical cases.[4] The most prominent are invariably the equine sarcoid, squamous cell carcinoma (of the eye region and of the penis in particular), granulosa cell tumour and melanoma. In a retrospective study of equine neoplastic disease presented to a US university pathology department over a 4-year period, only 21 neoplasms were diagnosed from 687 equine necropsies (3.1%) and 215 from 635 submitted biopsy specimens (33.9%); a total of 236 neoplasms were therefore identified in 1322 cases (17.9%).[5] Again, the most common neoplasms were sarcoid (43.6%) and squamous cell carcinoma (24.6%). Papilloma (5.5%), nerve sheath tumour (4.2%), melanoma (3.8%), lipoma (3.0%), granulosa cell tumour (2.5%), fibroma (2.1%), cholesteatoma (1.3%) and lymphosarcoma (1.3%), were less commonly identified (Table 2.1). In an abattoir survey of 1308 presumably healthy horses destined for the food chain in the UK, 139 horses (11%) had a total of 151 neoplasms; 71 horses (5.4%) had thyroid gland neoplasia (adenoma), 24 (1.8%) had adrenal gland masses (phaeochromocytoma), 20 (1.5%) had mesenteric lipomas. Melanoma (14 cases; 1.1%), myoma (four cases; 0.3%), disseminated sarcoma (four cases; 0.3%), granulosa cell tumour of the ovary (three cases; 0.2%) and two cases (0.15%) had sarcoid (see Table 2.1). This study was remarkably different from the previous university and other studies, in that skin tumours were by no means the most prevalent tumour type. The major difference between this latter study and others is that the population of horses was clearly different, being destined for meat use as opposed to being subjected to necropsy in a post-mortem facility, i.e. these were an ostensibly healthy population as opposed to being an inherently unhealthy population.

Table 2.1 The overall prevalence of tumours encountered in a histological/necropsy survey of cases submitted specifically for diagnosis and a study in ostensibly normal horses presented for slaughter

Tumour type	Percentage of neoplastic cases submitted for histology/necropsy (n = 1322)[9]	Percentage of healthy horses presented for slaughter found to have tumours (n = 1308)[8]
Skin tumours		
Sarcoid	43.6	0.15
Melanoma	3.8	1.1
Papilloma	5.5	
Nerve sheath tumour (neurofibroma)	4.2	
Organ tumours		
Granulosa cell tumour	2.5	
Lymphoma (~sarcoma)	1.3	
Lipoma	3.0	1.5
Fibroma	2.1	
Cholesteatoma	1.3	
Thyroid neoplasia		5.4
Adrenal gland tumour		1.8

It is hard to compare the two studies but they do have some interesting differences possibly associated with the different class of animal involved.

In terms of the various organs involved, there have been several studies of the prevalence and incidence of cutaneous and mucocutaneous tumours in horses.[10] Most identify that the commonest tumours of the horse affect the skin; around 30–50% of pathology submissions (necropsy and biopsy) involve skin tumours. Among the skin tumours reported in this survey, sarcoid, squamous cell carcinoma, dermal melanocytic tumours of various types, papilloma and mast cell tumour were the most prevalent, accounting in total for around 88% of the skin tumour group. The majority of the skin tumours were, as in most surveys, sarcoid and these were identified in Paint, Quarter Horse and Arabian horses, and was the only common tumour in donkeys and mules. Squamous cell carcinoma constituted 18.3% of all neoplasms, with ocular (periorbital, palpebral and conjunctival forms) being the most common. Penile carcinomas also occurred with some frequency. The results of this study would probably be no surprise to experienced clinicians in primary practice or referral clinics because the same broad results have been identified in several other significant studies of tumour prevalence. The variations in breed numbers in different geographical areas and population demographics may have some influence on the incidence of particular tumour types but, for the most part, the findings would probably be more or less consistent in all horse, donkey and mule populations. Apart from the sarcoid, little has been published about the prevalence of tumours in wild Equidae.

Apart from skin tumours, the breed prevalence of various tumour types has not been explored fully in horses but, anecdotally at least, there are some breeds that seem more liable to certain types of tumour. For example, it is widely accepted that the Appaloosa, Shire and Clydesdale appear to be more liable to ocular and periocular carcinomas. In one study, Appaloosa, Arabian and Quarter Horses were over-represented in the sarcoid affected population when compared with Thoroughbred horses.[11,12] A familial relationship to the development of a recognized tumour type is also a strong indicator of genetic susceptibility, although of course there may be common management and exposure factors when families of horses are kept under the same conditions. A familial tendency to sarcoid has been identified and similar tendencies have also been identified in other conditions and are well recognized by horse owners and equine veterinarians.[13,14] Again, there may be confounding factors that might predispose to cancer development, such as a pale, non-pigmented skin colour – in itself that may have no extra liability to cancer from a genetic perspective – but the colour is still a genetically controlled factor.

It is generally accepted that equine melanomas occur most commonly in grey horses over the age of 5 years and that, at least in the early stages, the tumours are benign. Since grey is a dominant colour in horses and since a very high proportion of grey horses will be affected to some degree, at least some aspects of susceptibility to neoplastic disease must be genetically based. Within breeds, familial lines of horses are known to have a predisposition to certain tumours. This has been most obvious in sarcoid tumours, where sequential generations of horses in a family have been severely affected.[15] There are plentiful non-equine examples of genetic predispositions to cancer development and the fact that some breeds and some families of horse are more liable to one form of tumour or another should probably not be surprising.

It is clear that specific tumour types have a tendency to occur in defined sites; this applies in particular to sarcoid (p. 545), melanoma (p. 239) and squamous cell carcinoma (p. 220). A clinical study of 296 Lipizzaner horses, found that dermal melanomas were present in 50% of them, with most being found in older horses.[16] In 75.6% of cases, melanotic tumours were detected on the ventral skin surface of the tail or in the perianal skin. A significant proportion of them ultimately become malignant, so this is probably an indicator that age is related, at least on balance, to developing malignancy. However, there are reports of isolated cases of aggressive tumour development in both melanoma, sarcoid and internal tumours, such as lymphoma, in very young horses (even neonates). In contrast to melanomas in solid-coloured horses, which are characterized by early metastasis, this study found that melanomas in grey horses showed less malignancy but a relatively high heritability. The heritability estimate of 0.36 with a standard error of 0.11 indicates a strong genetic impact on the development of melanoma in ageing grey horses, but other aspects and epigenetic factors may also be involved.

In most species, there is a general acceptance that neoplastic disease increases in prevalence with age. Historically, horses seldom survived into their old age and there was a widely held perception that cancer was commoner in middle-aged/young adult horses. For example, lymphosarcoma is said to affect horses between 5

and 10 years of age. The demographics of the equine population are changing, as more and more horses live to old age. Age-related incidence of tumours can be expected in any population of animals simply through time-related cell mutations and exposure to carcinogens. Clinically, it may be of more value to consider the population most prone to neoplasia, i.e. geriatric horses. In one necropsy survey conducted at the University of Kentucky Livestock Disease Diagnostic Center (n = 817 horses ≥15 years), there was an incidence of neoplasia of 8% in 15–19-year-old animals, rising to 17% in horses >30 years.[17] However, although the results of North American surveys have indicated a clear age-dependence for malignant tumours, that is not the case for benign lesions; in fact one such study showed an age-related decrease in benign neoplasia involving the skin in contrast with other veterinary species.[9] The reason for this bias is probably that many younger horses are affected by benign cutaneous papilloma and sarcoid. Notwithstanding the controversy regarding the true nature of pituitary enlargement in older horses (equine Cushing's disease/pituitary adenoma), there is clearly an age-related increase in the incidence of pituitary 'adenoma'. The same can surely be said of the melanoma – older grey horses are invariably affected to some extent and it could possibly be said that 'every grey horse will develop a melanoma if it lives long enough!' Age also has an implication in respect of the malignancy of some of the neoplastic diseases. This applies perhaps more definitely to penile squamous cell carcinoma, where the condition appears to have a more aggressive course when it occurs in geldings under 8 years of age and a more benign behaviour when it occurs in horses over the age of 15 years (p. 630).

The sex of the animal will have obvious implications for cancer development. Mares may have ovarian tumours, such as granulosa (thecal) cell tumour, while stallions may have testicular tumours (such as seminoma or interstitial carcinoma). Mares are the only sex that is likely to get primary mammary tumours, although their very low incidence makes it almost impossible to identify potential trigger factors – 'does pregnancy and lactation increase or decrease the likelihood of their development?' Geldings are more liable to penile carcinoma but 'does early castration increase or decrease the liability to carcinoma?' In Equidae the neoplasm with the strongest sex association is squamous cell carcinoma; genital forms of carcinoma are one of the commonest tumours encountered in horses. Interestingly, gastric carcinoma consistently occurs more frequently in male horses than in female horses.[18]

Management and geographical location may also influence the development of tumours, particularly of the skin. Eyelid, conjunctival and facial carcinomas are far more common in hot, sunny, tropical regions, even to the extent that they are almost expected in suitably coloured animals. The connection between two or more predisposing factors is important. Clearly the more 'force' that is applied to the process of carcinogenesis, the more likely a horse is to have a tumour. For example, an Appaloosa horse probably has a genetic predisposition to carcinoma of the third eyelid (membrana nictitans) but when the conjunctiva is non-pigmented that tendency might be greater and when the horse is then subjected to an environment where it would be exposed to high levels of ultraviolet radiation (such as in tropical climates), the tendency is even greater. Similarly, carcinoma of the penis is far commoner in geldings than stallions, so management measures, such as castration, may influence the tendency for the development of the tumour and when that is coupled with non-pigmented penile skin and failure to carry out routine hygiene checks in geldings, the likelihood of carcinoma probably increases significantly. Castration of many male horses at an early age may at least partially explain why testicular tumours are considered to be rare in equines in comparison with other domestic/companion animal species, including dogs.[19] Again, disappointingly, there is little evidence-based information on the role of environment, feeding and other management, such as the use of chemical anthelmintics, rugs and UV protectors, in carcinogenesis. This means it is very hard to provide good guidance to owners of horses that may or may not be predisposed to cancer development.

References

1. Reid SW, Howie F. Factors associated with neoplastic disease in the horse. Equine Vet Educ 1992; 4:66–68.
2. Ackerman HJ, del Regato JA. Cancer diagnosis, treatment, and prognosis. In: del Regato JA, Spjut HJ, eds. Ackerman and del Regato's Cancer: diagnosis, treatment, and prognosis, 5th edn. St Louis, MO: CV Mosby; 1977.
3. Baker JR, Leyland A. Histological survey of tumours of the horse, with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
4. Cotchin E. A general survey of tumours in the horse. Equine Vet J 1977; 9:16–21.
5. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
6. Pascoe RR, Summers PM. Clinical survey of tumours and tumour-like lesions in horses in south east Queensland. Equine Vet J 1981; 13:235–239.
7. Johnson PJ. Dermatologic tumours (excluding sarcoids). Vet Clin N Am Equine Pract 1998; 14:625–658.
8. Cotchin E, Baker-Smith J. Tumours in horses encountered in an abattoir study. Vet Rec 1975; 96:339.
9. Priester WA. Skin tumours in domestic animals. Data from 12 United States and Canadian Colleges of Veterinary Medicine. J Natl Cancer Inst 1973; 47:1333–1344.
10. Valentine BA. Survey of equine cutaneous neoplasia in the Pacific Northwest. J Vet Diagn Investig 2006; 18:123–126.
11. Angelos J, Oppenheim Y, Rebhun W, et al. Evaluation of breed as a risk factor for sarcoid and uveitis in horses. Anim Genet 1988; 19:417–425.
12. Mohammed H, Rebhun W, Antczak DF. Factors associated with the risk of developing sarcoid tumours in horses. Equine Vet J 1992; 24:165–168.
13. James VS. A family tendency to equine sarcoids. S.W. Veterinarian 1968; 21:235–236.
14. Gerber H. Sir Frederick Hobday Memorial Lecture. The genetic basis of some equine diseases. Equine Vet J 1989; 21:244–248.
15. Martens A, de Moor A, Ducatelle R. PCR detection of bovine papilloma virus DNA in superficial swabs and scrapings from equine sarcoids. Vet J 2001; 161:280–286.
16. Seltenhammer MH, Simhofer H, Scherzer S, et al. Equine melanoma in a population of 296 grey Lipizzaner horses. Equine Vet J 2003; 35:153–157.
17. Williams N. Disease conditions in geriatric horses. Equine Disease Quarterly 2000; 8(2). http://www.ca.uky.edu/Gluck/q/2000/jan00/Q_jan00.htm#geriatric.
18. Moore JN, Kinter LD. Recurrent oesophageal obstruction due to squamous cell carcinoma in a horse. Cornell Vet 1976; 66:590–597.
19. Brinsko SP. Neoplasia of the male reproductive tract. Vet Clin North Am: Equine Pract 1998; 14:517–533.

3 Tumour nomenclature

Introduction 11
Benign and malignant tumours 13
Assessing tumour activity and behaviour in vitro and in vivo 18

Introduction

The science of oncology has its own vocabulary and, while this may seem to be an unnecessary complication, its development has provided clinicians with very useful terms that have simplified the understanding of oncology and facilitated communication between medical colleagues and scientists. Tumour nomenclature also provides a uniform and universal means of identifying tumours and contributes meaningfully to the management and prognosis.

A neoplasm is termed 'benign' if the mutations that have taken place allow the tumour an advantage over local tissues only – the tumour remains confined at its original site, but this does not mean that its effects will not be clinically serious, factors such as size, location, susceptibility to trauma and/or functionality of the tumour cells (e.g. endocrine activity) have a strong bearing on the tumour's significance.

A tumour is termed 'malignant' if a series of mutations occurs that enables the tumour cells to destructively invade local and surrounding tissues and then to metastasize to remote sites; not all do so successfully. The term 'cancer' is usually applied to malignant neoplasms.

The genetic/clonal origin of tumours means, of course, that it is reasonable to assume that tumours comprise one single cell type; of course this does not mean that a tumour mass comprises only cells of that type since the bulk of the tumour is made up of abnormal (cancer) cells, stroma, supporting and inflammatory cells, blood vessels and endothelial cells, as well as other tissue types that might become 'innocently' incorporated into the expanding tumour mass. Additionally, as part of the process of increasing malignancy, there is a generation of multiple genotypic variants (subclones) of these genetically unstable cells, such that by the time the neoplasm is clinically recognized, the cells are heterogeneous and subject to selection pressures (e.g. immune cell attack) that favour cellular subclones more able to survive, invade and/or metastasize. Some tumours are composed of more than one cell type, arising from germ cells/stem cells/progenitor cells (see p. 399) or potentially (and rarely) from two cell types (e.g. carcinosarcoma).

For the most part, tumours are classified according to their cellular origin (p. 201) as:

- Epithelial (endodermal, mesodermal [e.g. renal tubule epithelium] and ectodermal)
- Mesenchymal (mesodermal)
- Neurogenic, neuroectodermal or germ cell (or stem cell) tumours
- Haematopoietic (mesodermal).

The terms 'malignant' and 'benign' form the basis of the nomenclature of tumours in all species (Table 3.1). They, however, represent just the broadest of categorization. As will be seen later, this simple classification is not always clear and as such, it may have less clinical value than the further sub-classifications. Therefore, a more detailed and useful classification has evolved, which uses the site of origin of the tumour (i.e. the cell or tissue from which a tumour arises) and the particular (and often unique) microscopic appearance and characteristics. Although even this classification has some difficulties, it is logical and provides a degree of consistency that allows tumours to be categorized and so define at least some aspects of prognosis and therapy. In some instances in human oncology, neoplasms are named after the physician who first described them. For example, the malignant lymphoma called Hodgkin's disease was described in 1832 by the English physician Thomas Hodgkin. In a few circumstances, such as for example Paget's disease, the name could be grossly misleading, since there are several diseases that have the same name, only one of which is a cancer. Furthermore, whilst the name conjures up an immediate 'mental picture' of the disease and a certain element of 'romance' in people who know about its origin, it is meaningless to those who do not. The name of the discoverer actually adds nothing extra to the understanding of the condition but it does retain some recognition of the 'discoverer'. Fortunately, this system has not been applied to any equine tumours, although that may reflect the fact that no-one has been interested enough in the horse to discover new tumours!

A complication arises when tumour-like masses are identified and their differentiation is a basic first principle of tumour classification. Fundamental issues that will need to be addressed are shown in Figure 3.1 and include:

1. *Is this a tumour or not?* There are many circumstances when tumour-like states are encountered as a result of inflammatory or developmental disorders. A tumour, by definition, is a tissue swelling, although the term tumour has, become synonymous with 'cancer'. It is important to differentiate inflammatory swellings from cancerous or neoplastic swellings and conditions. Potential tumour-like conditions that will necessarily fall into the differential diagnosis of tumours in the

Table 3.1 The basic differentiating features of benign and malignant tumours

	Benign	Malignant
Extent of cell differentiation/anaplasia	Limited/absent Well-differentiated cells (recognizably similar to normal tissue type)	Marked Lack of differentiation that is variable in extent, with the most undifferentiated cells being referred to as anaplastic; atypical cell structure/form. Well-differentiated malignant tumours may be difficult to distinguish histologically from benign tumours
Local invasion	Limited Usually cohesive with well-demarcated margins that do not invade local normal tissues. This does not necessarily equate with encapsulation, but such lesions are frequently encapsulated	Extensive Locally invasive with ill-defined margins. Some are more structured and expand locally, requiring close histological examination for detection. The presence of a capsule does not rule out malignancy
Rate of growth/ expansion	Slow progression Periods of rapid/slow expansion or static and may have some periods of apparent regression/remission	Rapid (or variable/slow) Erratic growth patterns
Mitotic index	Low Few mitotic figures and these are normal in appearance	High Usually cohesive with well-demarcated margins that do not invade local normal tissues. This does not necessarily equate with encapsulation, but such lesions are frequently encapsulated
Blood supply	Variable	Variable (usually high)
Metastasis	No	Yes (frequently present) The more undifferentiated the tumour, the more likely are metastases

It is important to realize that not every case will fit precisely into categories and the transition to malignancy is probably best regarded as a continuum. Also, different tumour types have different rates of progression and clinical threat; even within the same tumour type, there is enormous variation. It is probably true to say that the only predictable thing about cancer is that it is unpredictable.

practical situation include inflammatory nodules, which may resemble proliferative tumours, and destructive disorders, which may resemble invasive destructive tumours, as well as non-inflammatory, non-neoplastic conditions. Differentiation of the true neoplastic states is a basic clinical objective requiring skill and patience. An error of diagnosis made as result of a casual or inadequate clinical assessment may have serious consequences.

2. *Is this mass a neoplasm/cancer?* The differentiation between non-neoplastic conditions is a fundamental responsibility of the clinician and pathologist and often samples are required to differentiate them (Fig. 3.2). Not all cancerous conditions consistently/persistently produce a swelling – in some cases, there is a destructive component to the condition and then there may be a separate set of differential diagnoses that need to be considered.
3. *Is this neoplasm benign or malignant?* Differentiation between benign and malignant tumours is possibly the single most important aspect of the investigation after the basic tumour type has been established. By definition, benign tumours will usually have less prognostic severity than malignant ones, but it is important to realize also that benign tumours can be very serious in other ways, such as space-occupying effects or may cause functional limitations.
4. *Is this tumour treatable?* The client and clinician will wish to establish an answer to this quickly and if possible, with certainty. This is the point at which evidence-based medicine (see p. 416) becomes important. The owner needs to understand what is known about the condition, in terms of its clinical behaviour and its responses to the various treatment options that are available and practicable. Only when all aspects are considered together can an informed decision be made.
5. *What is the prognosis (with or without treatment)?* The long-term outlook is possibly the biggest factor for horse owners and veterinarians. Simply knowing what the cancer might do and how it might affect both the horses' state of health and its usefulness makes decisions on the management easier and more rational. Of course some cancers will have no or limited treatment options and others may have well established treatments that will define the prognosis to a lesser or greater extent. The development of new treatments means that assessment of prognosis changes and so the clinician needs to keep up to date with published reports and scientific papers. There is little worse than a clinician basing life and death decisions on old, outdated information. Tumour size and location are significant factors in determining the prognosis for a cancerous mass (Fig. 3.3). For the most part, tumours are progressive in their expansion and growth so as might be expected the prognosis will inevitably be influenced by the duration of the tumour.

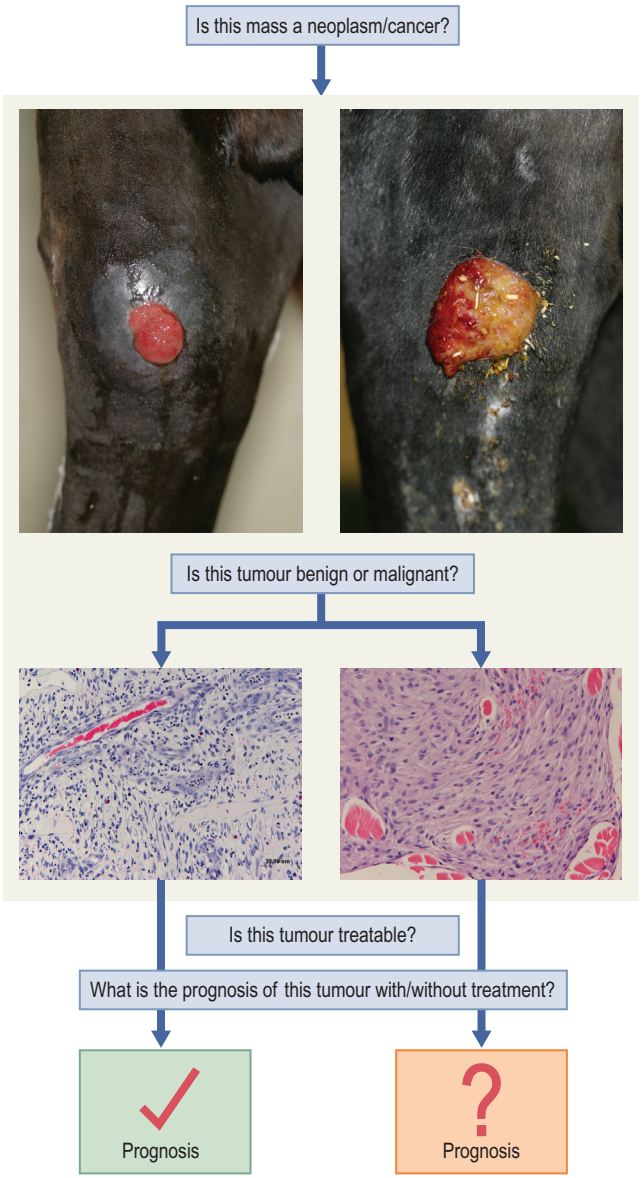


Figure 3.1 The similarity in appearance of a non-cancerous mass and a cancerous growth. These two masses on the lateral tarsus of two horses illustrate the similarity of appearance between a non-cancerous mass (granulation tissue, left) and a cancerous growth (sarcoid, right). The diagnosis is clearly vital, since the prognosis and treatment for the two conditions are very different.

Benign and malignant tumours

Cancerous tumours are classically defined as benign or malignant, based upon a set of clinical and pathological criteria (Fig. 3.4; see also p. 17). Those that are benign do not spread or cause cancer, while malignant tumours are cancerous and may invade other parts of the body. The division between the two categories of neoplastic tumours is not always clear and in many tumour states (but not invariably), there is natural progression through stages of cancer development from a benign mass to a highly dangerous malignant state. That progression varies temporally in individual tumours and in individual animals with that tumour type. The reasons for these variations are

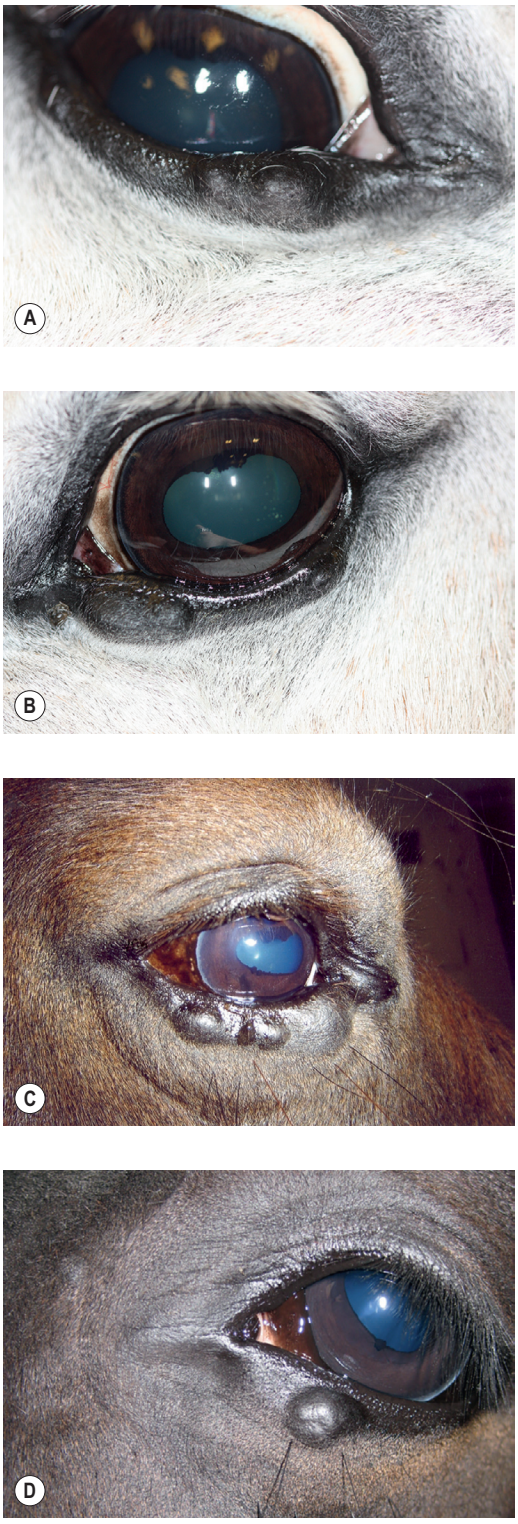


Figure 3.2 Palpebral nodules. These palpebral nodules look very much the same and it would clearly be easy to mistake them for each other on clinical examination alone. **(A,B)** Two images from the same horse. While the lesion in the right eyelid **(A)** proved to be an eosinophilic nodule (collagenolytic granuloma), that in the lower left eyelid **(B)** was a focal melanocytoma. **(C)** The nodules in the lower and upper eyelids of the bay 12-year-old pony were focal lymphomas and were part of a wider, more generalized neoplastic problem. **(D)** A focal sarcoid in the eyelid margin with significantly different implications from all the other similar looking nodules shown in this panel. No assumptions should be made about any condition without a full investigation, which might include biopsy, ultrasound, radiography or other diagnostic procedures.



Figure 3.3 Three different tumour types illustrating the variability in prognosis. From a prognostic perspective, the first question that is asked is, 'Is this tumour treatable?' – if not, then, 'Can it be managed and will it/does it have an adverse effect on the patient?' Tumour **(A)** is a haemangiosarcoma with a high (malignancy) grade – removal of the tumour might be 'in time' to preclude metastatic spread but this clearly has a very different outlook to the sebaceous adenocarcinoma shown in **(B)**. Although there is little evidence base for them, surgical resection is likely to be curative. The sarcoid tumour **(C)** has no metastatic capacity but is clearly limiting on function and untreatable and so has a very poor prognosis.

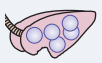
						
	Normal	Transformed	Benign	Malignant	Micro-metastatic	Metastatic
Differentiation	+	–	–	–	–	–
Contact inhibition	+	–	–	–	–	–
Anchorage dependence	+	–	–	–	–	–
Genetically stable	+	–	–	–	–	–
Proper host response	+	+/–	–	–	–	–
Tumorigenic	–	+/–	+	+	+	+
Invasive	–	–	–	+	+	+
Able to disseminate	–	–	–	–	+	+
'Normal' morphology	+	–	+/–	–	–	–
'Normal' histology	+	n/a	+/–	–	–	–
Growth at ectopic site(s)	–	–	–	–	–	+

Figure 3.4 Main features that can be used to differentiate between benign and malignant tumours. Some of the main features that can be used clinically and physiologically/pathologically to differentiate between benign and malignant tumours are shown here. It is easy to view each of these features as black or white features but tumours are best viewed as entirely unpredictable. Therefore, careful examination of all the features of a tumour will help to build up a 'consensus' opinion as to whether a particular lesion is best fitted to one or other category. In addition, malignancy itself carries a graded scale ranging from mild to extreme. *(Figure reprinted from Matrisian LM, Welch DR. Invasion and metastasis: In: Mendelsohn J, Howley PM, Israel MA, et al. (eds) The molecular basis of cancer, 3rd edn. Philadelphia: WB Saunders; 2008: 254. (Fig. 19.3); copyright 2008, with permission from Elsevier.)*

not always clear but the clinical interpretation of the pathological diagnosis of the particular tumour must take account of the known or suggested variability. In fact, benign tumours can still be very dangerous if they occupy vital space or alter local function sufficiently to compromise the animal (Fig. 3.5). For example, a very benign tumour within an eye or in the brain would inevitably have consequences. A benign functional endocrine tumour, e.g. a pituitary adenoma, may be a genuine threat to the animal and cause significant morbidity (see p. 376); in contrast a benign thyroid adenoma can be quite alarming but usually has no clinical implication, even when relatively large (Fig. 3.6).

The owner of a horse whose tumour has been confirmed as 'benign' may be very relieved by that knowledge and may not fully understand that it might still result in considerable threat to the horse's life. Nevertheless, a diagnosis of 'malignancy' will invariably and quite justifiably cause greater concern. However, not all malignant tumours are immediately life-threatening and the patient may well have some useful life ahead. A good example is the equine melanoma, where many tumours start out as pathologically benign and end-up malignant – that transformation in any particular tumour may be very slow and in any case, there may be no material disadvantage to the horse, provided that the dissemination of the tumour is limited and the rate of growth of the metastatic tumours is low. Additionally, 'benign' is not always synonymous with 'treatable' and 'malignant' does not always mean 'untreatable'. For example, a benign melanoma in the ciliary body is probably untreatable, but a malignant tumour of a similar type on the perianal skin may be easily removed (with the caveat that micro-metastasis may have already taken place).

Benign tumours

A benign tumour is a tumour that lacks the ability to metastasize or spread. The term 'benign' implies a mild and

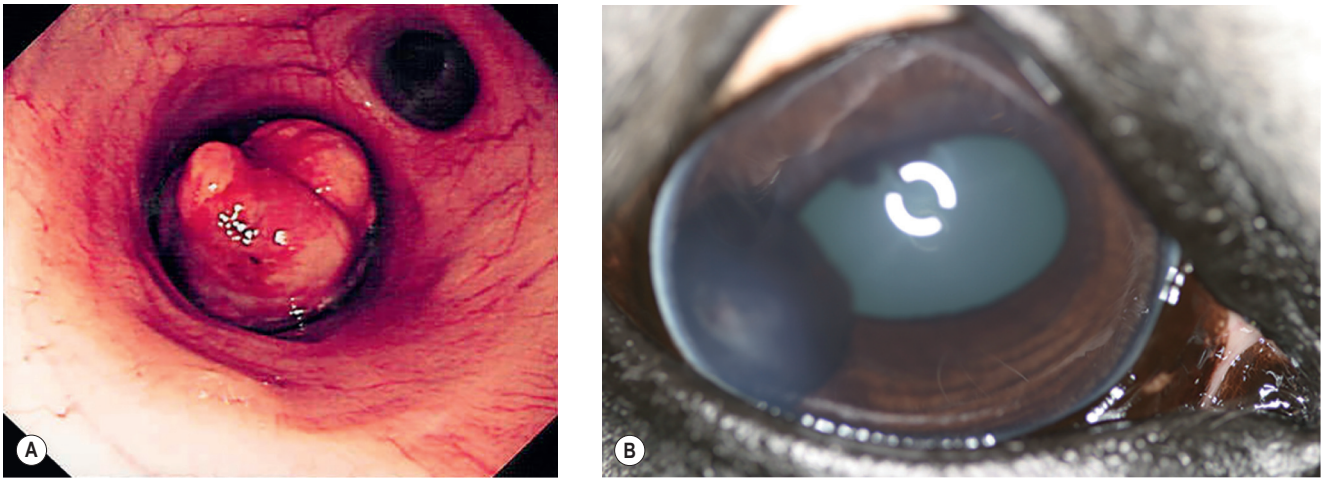


Figure 3.5 Pathological behaviour is not always the most important parameter of a tumour. Small tumours in vital places may have severe, even life-threatening effects, whilst large tumours may be clinically irrelevant. Nevertheless, confirmation of malignancy will usually have profound implications over an indeterminate period. Some benign and malignant tumours progress slowly, whilst others are much more rapid and their clinical and pathological effects will be correspondingly faster or slower. **(A)** Bronchial granular cell tumour is the commonest primary lung tumour of horses. These tumours are usually benign and localized but they may have a profound clinical consequence. **(B)** This iridal melanoma was confirmed as malignant histologically but remained slow growing and localized for 8 years before becoming a significant problem.



Figure 3.6 A unilateral enlargement of the thyroid gland in a 14-year-old mare. Endocrinological tests revealed no abnormality and the tumour continued to expand slowly without causing any space-occupying effects. It was removed on the basis of potential transformation to malignancy and on cosmetic grounds. The tumour was soft and of a more or less uniform consistency that bulged when sectioned. There were no deleterious effects following the surgery.

non-progressive disease. Benign tumours are considered to be 'non-cancerous' and by definition, are not locally invasive or malignant. Benign tumours are typically (but not always) surrounded by an outer surface (fibrous sheath or capsule) that probably inhibits their ability to behave in a malignant manner (see Fig. 3.6); this aspect probably hinges on the lack of the tumour cells to 'break out' of the confining/restricting basement membranes. There are conflicting opinions regarding capsule formation; first that it is a passive phenomenon caused by pressure exerted by the expanding mass on surrounding, pre-existing collagenous tissue. The second opinion is that it is essentially a foreign-body response instigated to try to 'wall off' the neoplasm.

Both the appearance of the individual cells and the histological architecture in benign tumours are similar to the normal tissue. Many benign tumours are harmless but by virtue of their size and location, they can have significant clinical effects and definable morbidity. Examples of this include tumours which produce a 'mass effect' (compression of vital organs, e.g. blood vessels), such as the benign mesenteric lipoma (Fig. 3.7), or productive tumours of endocrine organs (which may overproduce certain hormones). Examples include granulosa/thecal cell tumour of the ovary and the common pituitary enlargement in older horses that was historically regarded as an adenoma (p. 641).

Many types of benign tumours have at least the potential to develop into malignant cancers; this state probably arises from additional genetic changes in a subpopulation of the tumour's neoplastic cells (p. 47). The cells in the lesions, as in most tumours which frequently progress to cancer, show defined abnormalities of cell maturation and appearance, collectively known as 'dysplasia'. These cellular abnormalities are not seen in benign tumours that rarely or never turn cancerous, but are seen in other pre-cancerous tissue abnormalities, which do not form discrete masses. A prominent example of this phenomenon is the squamous papilloma or squamous dysplasia that occurs on the penile skin of geldings in particular (p. 630). In some circumstances, these may become transformed to (aggressive) malignant carcinoma, but in most, they remain very benign. Some authorities prefer to refer to dysplastic tumours as 'pre-malignant' and reserve the term 'benign' for tumours which rarely or never give rise to cancer (Fig. 3.8).

Most benign tumours are named by attaching the suffix *-oma* to the name of the tissue or cell from which the cancer arose. For example, a tumour that is composed of cells related to bone cells is called an 'osteoma', a benign tumour that derives from dental cementum is termed a 'cementoma', and when the cell type is fat it is termed 'lipoma'. This rule is followed, with a few exceptions, for tumours that arise from mesenchymal cells (the precursors of bone and muscle).

The term *adenoma*, for instance, designates a benign epithelial tumour that either arises in endocrine or other glands (e.g. sebaceous or mammary glands) or forms a

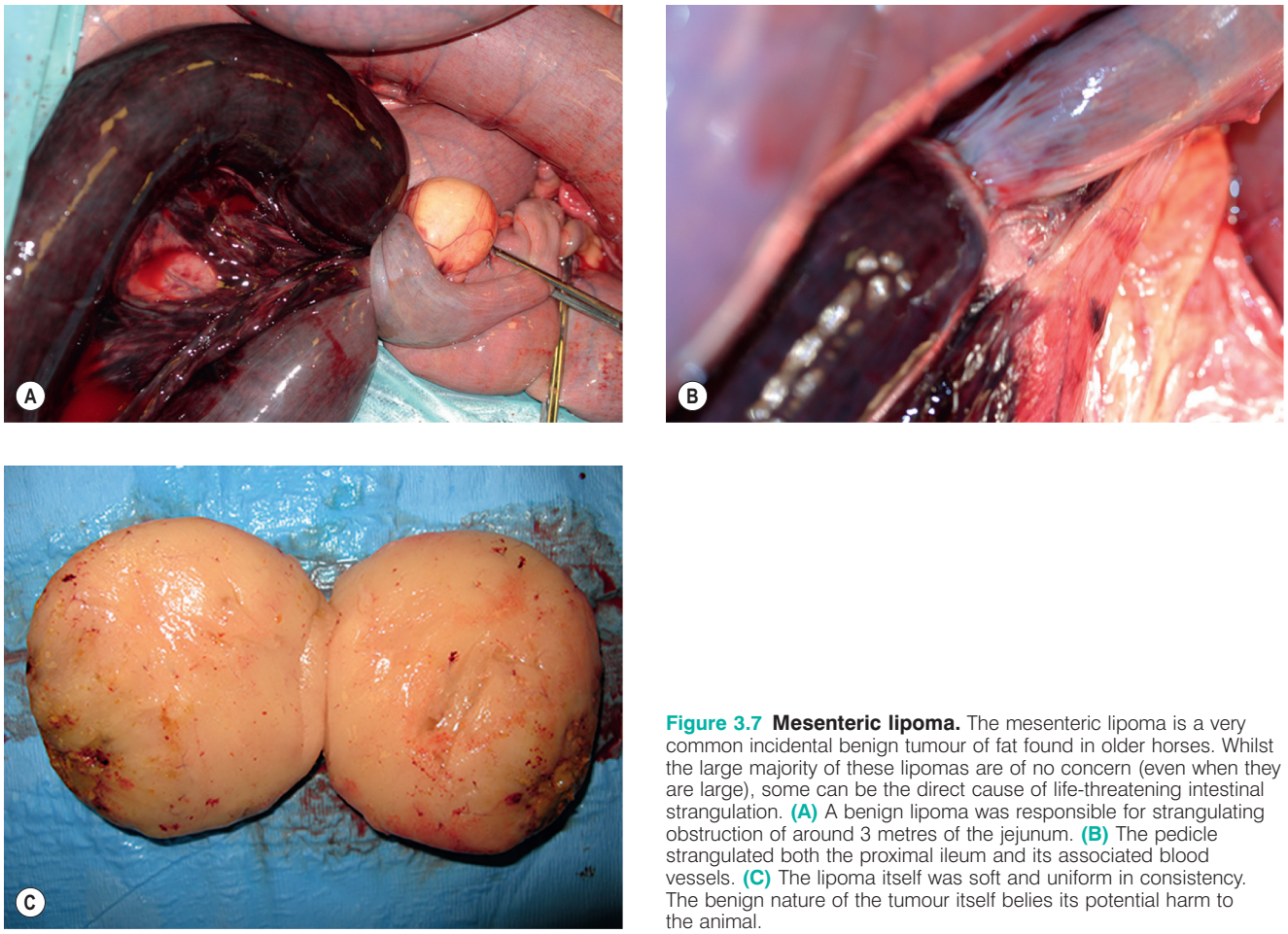


Figure 3.7 Mesenteric lipoma. The mesenteric lipoma is a very common incidental benign tumour of fat found in older horses. Whilst the large majority of these lipomas are of no concern (even when they are large), some can be the direct cause of life-threatening intestinal strangulation. **(A)** A benign lipoma was responsible for strangulating obstruction of around 3 metres of the jejunum. **(B)** The pedicle strangulated both the proximal ileum and its associated blood vessels. **(C)** The lipoma itself was soft and uniform in consistency. The benign nature of the tumour itself belies its potential harm to the animal.



Figure 3.8 A pre-carcinomatous/dysplastic tumour state. (A) This rather mild surface pre-carcinomatous/dysplastic tumour state was encountered in a 15-year-old gelding. The yellow adherent material over the sites (revealed by washing and removal of the material) was largely inflammatory and fibrinous material admixed with keratin **(B)**. The keratin production is consistent with well-differentiated cells. Treatment of the sites resulted in a complete resolution apart from in one lesion, where a more aggressive transformation has taken place. **(B,C)** The small pallid circular areas of leukoplakia are consistent with early dysplastic changes in the keratinocytes. They are characteristically well-differentiated but are pre-carcinomatous changes. At this stage, they are usually treatable and even curable.

glandular structure. A tumour of that contains large cysts is called a 'cystadenoma', e.g. ovarian cystadenoma.

Benign tumours arising from epithelial cells (those cells that form sheets that line the skin and internal organs) are classified in several ways and therefore have a variety of names. Sometimes, classification is based on the cell of origin, whereas in other cases it is based on the tumour's microscopic or gross appearance. The mesenteric lipoma is a very common incidental benign tumour of fat found in older horses (see Fig. 3.7). Whilst the large majority of them are of no concern (even when they are large), some can be the direct cause of life-threatening intestinal strangulation. In this case (Fig. 3.7), a benign lipoma was responsible for strangulating obstruction of around 3 metres of jejunum. The benign nature of the tumour itself belies its potential harm to the animal.

When a tumour gives rise to a mass that projects into a lumen, it is called a *polyp* (Fig. 3.9). Most polyps are epithelial in origin. Strictly speaking, the term 'polyp' should be restricted to benign growths; a malignant polyp should be referred to as a 'polypoid cancer' in order to avoid confusion.

A *papilloma* is a benign, exophytic epithelial tumour, built up of finger-like projections from the skin or mucous membranes. When used without context, it is usually used to describe 'warts', which are reactive 'responses', usually to a papilloma virus infection (Fig. 3.10). There are, however, a number of other conditions characterized by papillomatous changes, including the sarcoid (p. 203) and the squamous papilloma precursor of carcinoma (see Fig. 3.10C).

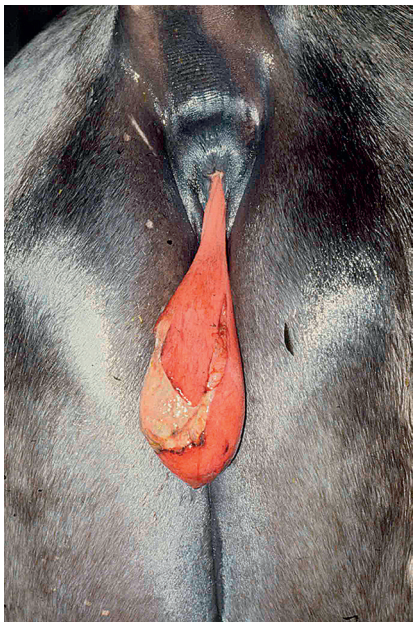


Figure 3.9 A rectal polyp with its classical polypoid appearance. This tumour is benign and was attached to the dorsal rectal wall some 20 cm from the anus. It was very easily treated and did not recur. A 'polyp' is the general descriptive term used to describe any mass of tissue that projects outward from the normal surface level of a mucous membrane or the skin, being a structure growing from a relatively narrow base or a slender stalk. In horses, polyps occur mostly in the gut and nasal cavities.

Malignant tumours

'Malignant' is the term applied to tumours that behave in an aggressive and invasive manner.

The method for classification and description of malignant tumours follows similar rules in using prefixes and suffixes. The tissue of origin again provides the basis of the name. The suffix *-sarcoma* indicates neoplasms that arise in mesenchymal tissues and the name of the cell of origin is added; for example, a malignant tumour derived from fibroblasts would be termed a 'fibrosarcoma' and a tumour of blood vessels would be called a 'haemangiosarcoma'. Tumours deriving from epithelial tissues use the suffix *-carcinoma*. Most cancers arising from the ectoderm and endoderm are carcinomas, since these cells primarily become surface epithelium and gland parenchyma. Thus, a tumour of squamous epithelium is termed a 'squamous cell carcinoma' and one that affected the basal cells of the skin would be called a 'basal cell carcinoma'.

Just as *-adenoma* designates a benign tumour of epithelial origin that takes on a gland-like structure, so *-adenocarcinoma* designates a malignant epithelial tumour with a similar growth pattern. Usually the term is followed or preceded by the organ of origin, e.g. sebaceous adenocarcinoma of the skin and adenocarcinoma of the colon.

Malignant tumours of the blood-forming tissue are designated by the suffix *-emia* (Greek: 'blood'). Thus, *leukaemia* refers to a cancerous proliferation of white blood cells (leucocytes). Cancerous tumours that arise in lymphoid organs (such as the spleen, thymus or lymph glands) are termed 'malignant lymphomas'. The term *lymphoma* is often used without the qualifier *malignant* to denote cancerous lymphoid tumours; however, this usage is



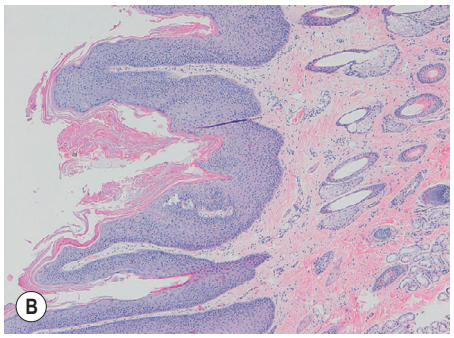




Figure 3.10 Papillomatous lesions. **(A)** A typical viral papilloma on the muzzle of a young gelding. **(B)** This is a benign virally induced tumour which is very recognizable histologically when the characteristic frond-like epidermis with a fibrovascular 'core' is present with marked epidermal hyperplasia. **(C)** Not all papillomatous lesions are insignificant. This squamous papilloma on the penile skin is a pre-carcinomatous state and that again can be easily recognizable histologically.

confusing, since the suffix *-oma*, as mentioned above, more properly designates a benign neoplasm.

The suffix *-oma* is also used to designate other malignancies, such as 'seminoma', which is a malignant tumour that arises from the germ cells of the testis. In a similar manner, malignant tumours of melanocytes (the skin cells that produce the pigment melanin) should be called 'melanosarcoma', but for historical reasons the term *melanoma* persists.

Most cancers arising from the ectoderm and endoderm are *carcinomas*, since these cells primarily become surface epithelium and gland parenchyma. Of course, the ectoderm is also the source of nervous tissue, but tumours arising here are less common than carcinomas.

Cancers arising from the mesoderm can be carcinomas (e.g. adrenal, genitourinary), sarcomas (solid connective tissue and all muscle types) or cells of haematopoietic origin (leukaemias, lymphomas).

The cells and the histological architecture in malignant cancers are bizarre. The grade of a cancer, depending on the tumour type and system used, may be a function of one or more factors, including how bizarre the cells look (see Figure 3.14) the mitotic rate; their architectural arrangement or density of packing; how deeply or extensively the tumour cells invade underlying or surrounding tissues; or the presence or extent of tumour cell necrosis. The higher the grade, the more likely the cancer is to behave aggressively. It should be noted that grading is not appropriate for all types of cancer; some endocrine neoplasms, for example, can have a 'benign' appearance and yet have metastasized throughout the body. The stage of a cancer is how far the clinician knows it has spread (p. 19).

Staging and grading of tumours are concepts that are widely used in human, and to a lesser extent, in small animal veterinary practice. They are not usually applied to equine cancers for a multitude of rather weak reasons! The lack of a significant bank of cases makes it difficult to predict what is going to happen and the absence of effective diagnostic methods adds to the complications. Some form of clinically useable staging that predicts, with some degree of accuracy, what the tumour will most likely result in, would be a really helpful development for horses.

All tumours, whether benign or malignant have two basic components:

1. The proliferating abnormal, tumour cells that constitute the *parenchyma*; they determine the overall behaviour and the pathological consequences of the tumour.
2. A supportive *stroma* comprising variable connective tissue components, extracellular matrix and blood vessels. The growth and evolution of the tumour is strongly dependent on the nature of the stroma, and this is clinically recognizable and pathologically useful.

An adequate stromal blood supply is a critical factor in the natural history of a tumour (p. 48).

Assessing tumour activity and behaviour in vitro and in vivo

The classification of the severity and clinical nature of a neoplasm can be made through the process of grading/staging. This expresses the level of differentiation (*grade*) and the extent of spread of the tumour (*stage*). However, attempts to establish this system in horses has commonly been frustrated by the lack of correlation between the clinical and histological features. Grading is therefore not yet widely employed and, instead, a morphological description is more commonly used.

Grading



Knowing what the tumour is, is a fraction of what needs to be known about its pathological behaviour.

The American Joint Commission on Cancer provides guidelines for grading tumours using a simple system that classifies cancer cells in terms of how abnormal they appear compared with normal tissue cells, when examined under a microscope.[1]

The objective of a grading system is to provide useful guidance about the probable growth rate of the tumour and its tendency to spread. This is achieved through attempting to quantify the degree of cell differentiation and the number of mitoses within the tumour; this is expressed as a proportion of the cells present and so correlates quite well with the extent of tumour aggression.

Based on the microscopic appearance of cancer cells, pathologists may describe tumour grade in 4 degrees of severity (G1–G4) (Fig. 3.11). The term *GX* is used when the grade cannot be assessed ('undetermined grade'):

- The cells of *Grade 1* tumours resemble normal cells and may have a relatively normal function. Thus, a Grade 1 carcinoma (Fig. 3.11) might produce keratin and may be histologically very similar to normal cells. It would tend to grow and multiply slowly. Grade 1 tumours are generally considered the least aggressive in behaviour. There is recognizable differentiation of the cell type involved and low numbers of mitotic cells.
- Cells of *Grade 2* tumours have noticeable abnormalities, but are still recognizable as the parent tissue. They may have less proliferative ability and are much less physiologically normal (see Fig. 3.11).
- The cells of *Grade 3* (*or Grade 4*) tumours are more difficult to relate to normal cells of the same type. Grade 3 tumours tend to grow more rapidly and spread faster than tumours with a lower grade (see Fig. 3.11).
- *Grade 4* is the most undifferentiated and rapidly dividing tumour behaviour and these tumours are more usually termed 'anaplastic', on the basis that totally undifferentiated cells are seldom encountered (see Fig. 3.11). Given that they have an almost infinite variety of functional and behavioural changes it is usually very hard to differentiate and identify these tumours without specific immunohistochemical and specialized procedures which being invariably required to pathologically identify the tumour type. Often, the tumour type itself can be deduced clinically from intuitive supposition but this is a minor part of the process of tumour investigation and management.

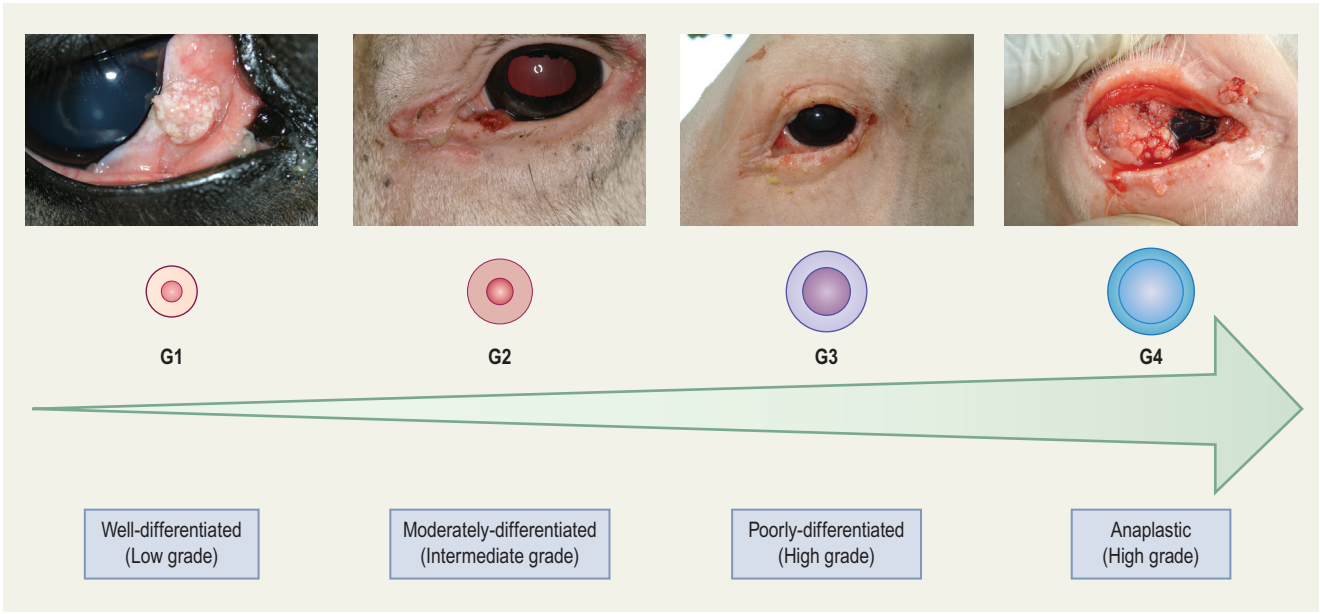


Figure 3.11 Tumour grading. The grade of a tumour gives a strong guide to the likely clinical and pathological behaviour of the tumour. The range is from well-differentiated cells that closely resemble the parent cells (G1) to the most undifferentiated cells that often bear little morphological similarity to the parent cells (G4). In the latter case, specific stains are often required to identify the parent cell type. A series of palpebral/conjunctival carcinomas ranging from the benign well-differentiated squamous papilloma/squamous dysplasia through to the most severe, poorly-differentiated and infiltrated carcinoma is illustrated. The G4 case had metastatic local lymph node involvement. Tumour grading is a system that is widely adopted in equine oncology because of its simplicity and its applicability to the common tumours of the horse. There are constraints on the other systems of classifying the clinical behaviour of tumours in horses.

Since the grading system is not a strict division, subtle variations in the grading system that take account of more sophisticated tissue staining methods are used to grade each tumour type, but the general principle is to attempt to quantify the extent to which the tumour cells differ from cells of the appropriate normal/parent tissue. Whilst histological grade, also called 'differentiation', refers to how much the tumour cells resemble normal cells of the same tissue type, nuclear grade refers to the size and shape of the nucleus in tumour cells and the percentage of tumour cells that are dividing (mitotic rate). The latter is usually expressed as a number of mitotic figures per high power (×400) microscopic field or per 10 high power fields. Grading may play a role in treatment decisions where appropriate information is available. Cells of Grade 3 or Grade 4 tumours are more difficult to quantify.

Although the grade is a useful pathological parameter, it is not necessarily an accurate index of the pathological behaviour because the histological appearance and clinical behaviour may not be closely correlated. In an attempt to avoid spurious 'opinion', tumours are also graded histologically, according to the degree of differentiation from normal, using terms such as well-differentiated/moderately-differentiated/highly-undifferentiated, etc. (Fig. 3.12).

To some extent, the classification of a certain tumour may vary between different pathologists, as this is, in reality, a spectrum of change.

Note

Grading is probably less useful than staging in most circumstances, but since staging is seldom used in horses, the grade is a more commonly employed description and is probably better understood.

Staging

Applying a stage to the spread of the tumour relies on performing examinations and tests to establish the extent of the cancer within the body and it particularly refers to whether the disease has spread from the original site to other parts of the body (i.e. whether it has metastasized); it is therefore an index of the degree of cancer progression. It is, potentially at least, a more useful measure of the tumour's nature than the grading system. The size of the primary lesion, the extent of spread into the adjacent tissues and local lymph node(s), and the presence of remote metastatic dissemination are incorporated into the system. It is important to know the stage of the tumour in order to provide a likely prognosis, to plan the best treatment and to monitor the effects of treatment procedures.

Although there are two recognized systems in human medicine (the 'TNM' system and the 'Ann Arbor' system), neither one is ideal for the equine species, and somewhat regrettably, neither is widely employed in equine practice. This is probably understandable, since two of the major assessed parameters are not easily incorporated into equine oncology, but there has been no real effort to develop systems of tumour classification that apply to the particular difficulties of equine oncology.

TNM tumour staging

The preferred UICC (Union for International Control Cancer) staging system is the TNM system. It uses the tumour size (T), the involvement of regional lymph nodes

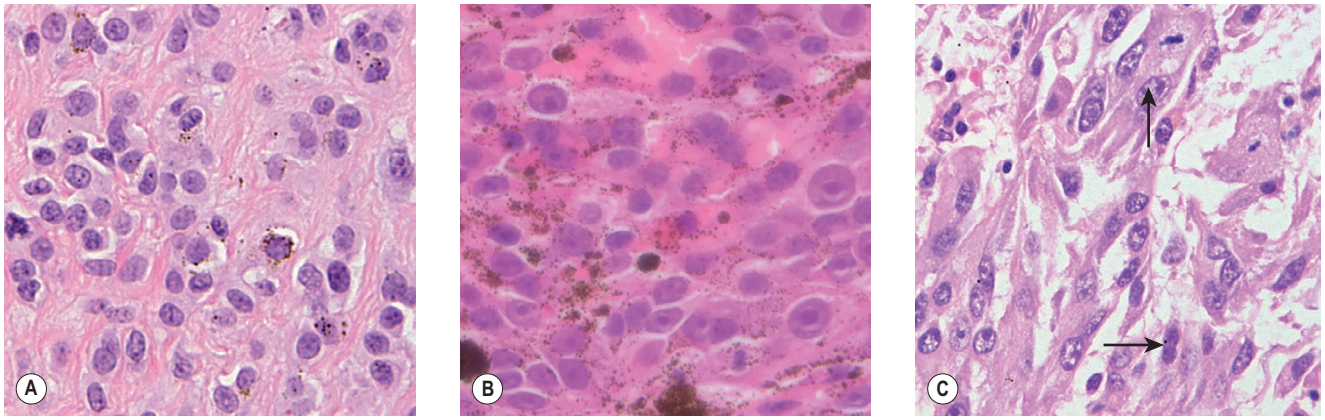


Figure 3.12 The equine melanoma. **(A)** Well-differentiated tumour cells in a melanocytic naevus that are polygonal or round with small amounts of melanin pigment and minimal nuclear or cytoplasmic size variation. The cells are subtly different in morphology and cell function. Well-differentiated melanoma cells are the earliest changes that will be seen and, often, special stains have to be used to identify them. **(B)** A moderately-differentiated melanoma, in which the polygonal tumour cells show significant variation in nuclear size and the nuclei contain prominent, central nucleoli (some melanin pigment is still observed). The loss of cellular differentiation occurs in stages and cells that are moderately-differentiated will retain some of the normal function (i.e. accumulation of melanin) but will have more obvious cellular changes with a higher replication (mitotic) rate. **(C)** A poorly-differentiated melanoma, in which the tumour cells are spindle-shaped, contain minimal pigment and significant numbers of mitotic figures, and are difficult to recognize as being of melanocytic origin. The undifferentiated tumour shows little resemblance to the parent cell type in both morphology and function. The equine melanoma affords an excellent example of the stages of cellular differentiation. From a histological perspective, it can be hard to separate early well-differentiated melanoma from normal melanocytes. The further down the path of loss of differentiation, the more difficult it becomes to identify the parent cell type. Mitotic figures (arrows) and abnormal cell structures are commonly found in advanced poorly-differentiated tumours.

(N) and the extent of metastases (M) to numerically express some concept of the severity of the tumour.

Measured/assessed parameters

T: This describes the size or the direct extent of the primary tumour. The size is dictated by the numerals 1–4; small tumours are termed '1' and very large ones '4'. Where the tumour is restricted to the epithelium, it is termed in situ (or intraepithelial) and the suffix *-is* is added to the T as in T-*is* signifying that the tumour is still restricted by the basement membrane. A good example of such a tumour is afforded by the in situ squamous cell carcinoma of the cornea or lateral limbal conjunctiva in horses (Fig. 3.13).

N: The degree of spread to regional lymph nodes is classified as 1–3; '1' being that the first local drainage node is involved and '3' means that the most distant available node in the precise pathway of the lymphatic drainage is involved:

- N0: Tumour cells absent from regional lymph nodes
- N1: Regional lymph node metastasis present (at some sites, tumour spread to the closest or a small number of regional lymph nodes)
- N2: Tumour spread to an extent between N1 and N3 (N2 is not applied at all sites)
- N3: Tumour spread to more distant or numerous regional lymph nodes (N3 is not used at all sites).



It is standard procedure in human medicine to biopsy or even remove lymph nodes when a primary mass is excised but most veterinarians do not do this! When they do, it is usually by accident, but it is obviously very useful in terms of staging and the initial diagnosis. Biopsies must be wedge biopsies at least, rather than punch or needle biopsies (see p. 108).

M: The letter M is simply whether distant metastasis is absent (M0) or present (M1).

In order to ensure consistency of expression, the letter X is used where the parameter was not assessed or investigated.

Further letters are commonly appended to the TNM system to try to provide more useful information, particularly about the pathological/histological investigations. These include:

G (1–4): This describes the pathological *grade* or extent of differentiation of the cancer cells. 'Low-grade' tumours are those that are well-differentiated and the cells therefore appear similar to normal cells, whereas 'high-grade' tumours appear poorly-differentiated, often to the extent that the parent cell type cannot immediately be recognized (Fig. 3.14).

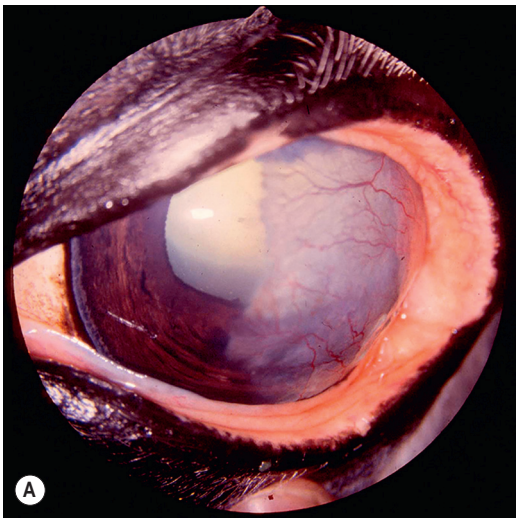
R (0/1/2): Where tumours are removed surgically, the completeness of the *tumour excision* is described; whether the boundaries are free of cancer cells (R0) or not (R1 – marginal boundaries or R2 – no boundaries and the tumour extends beyond the boundary). In the latter case, recurrence can be expected and further excision may be indicated if feasible.

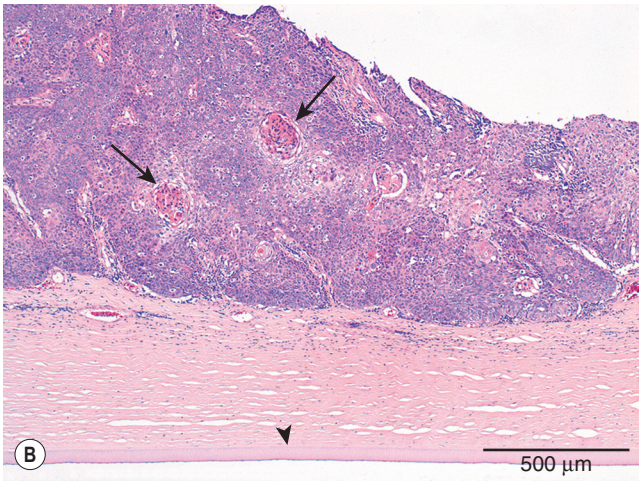
L (0/1): *Invasion into lymphatic vessels* is classified as absent (L0) or present (L1).

V (0/1/2): *Invasion into veins* is described as absent (V0), present microscopically (V1) or macroscopically (V2).

C (1–5): This is a modifier of the *certainty* (quality) of the last-mentioned parameter and can be used to assist a third party in making decisions as to whether a classification is reliable or less certain.

Thus, a large aggressive tumour might be described as T4/L3/M2, while a benign local tumour might be shown as T1/N0/M0. The system is more flexible than the other classifications and allows a clearer description to be made.





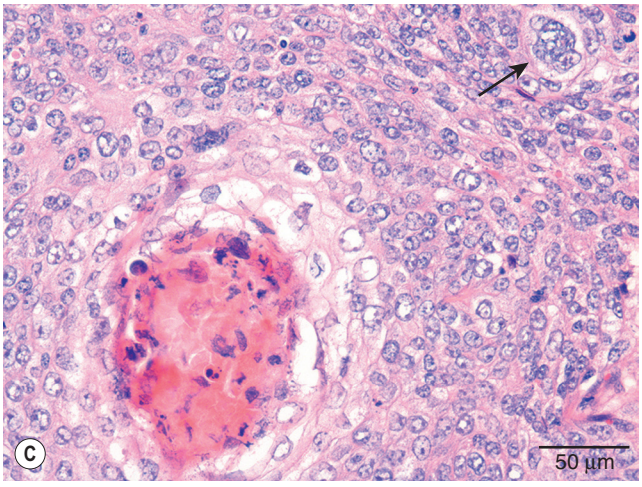


Figure 3.13 An in situ intraepithelial carcinoma. (A) A good example of an in situ (intraepithelial) carcinoma of the cornea of a Dutch Warmblood carriage horse gelding, aged 16 years. Grossly, it is possible to examine this with a slit lamp and get some idea of the depth of the tumour. It is well vascularized and highly active. **(B)** Histologically, there is marked irregular proliferation of the surface epithelium with multifocal areas of apoptosis and dyskeratotic cells (arrows). Note the intact Descemet's membrane (arrowhead) (H&E). **(C)** Magnified image of the cancer showing accumulation of necrotic and partly keratinized cells surrounded by a layer of pale, swollen keratinocytes. Occasional cells with marked nuclear atypia can be seen (arrow) (H&E). *(Figures B and C courtesy of Dr Guy Grinwis, Veterinary Pathology, Utrecht.)*

The additional letters are used to provide significant extra information and the G classification is a critical addition, since it attempts to establish the severity of the pathological behaviour of the cells involved and, in that way, it retains elements of the grading system as well.

Ann Arbor tumour staging

The Ann Arbor staging system is used primarily for human lymphoma. In this system, the principal stage is determined by location of the tumour:

Stage I indicates that the cancer is located in a single region, usually one lymph node and the surrounding area. Stage I often will not have outward symptoms. This might usefully apply, for example, to the isolated lymphoma that occurs in the conjunctiva in horses (p. 620).

Stage II indicates that the cancer is located in two separate regions, an affected lymph node or organ and a second affected area, and that both affected areas are confined to one side of the diaphragm – that is, both are above the diaphragm, or both are below the diaphragm. This is seldom applicable in horses, in any case, but there are some lymphosarcoma cases that have restricted distributions within the thorax or the abdominal cavity (e.g. hepatosplenic lymphosarcoma, p. 535).

Stage III indicates that the cancer has spread to both sides of the diaphragm, including one organ or area near the lymph nodes or the spleen. This stage usually merges with stage IV in horses, since most lymphosarcoma cases that have multiple foci are classified as diffuse or generalized.

Stage IV indicates diffuse or disseminated involvement of one or more extralymphatic organs, including any involvement of the liver, bone marrow or nodular involvement of the lungs. Most equine lymphosarcomas ultimately fall into this category.

Modifiers are used to add to the stage in some particular circumstances and these are expressed as letters:

A: Signifies the *absence* of systemic implications.

B: The *presence* of systemic signs. This is used if the disease is '*extranodal*' (i.e. not in the lymph nodes) or has spread from lymph nodes to adjacent tissue.

S: Applied to show that the tumour has *spread* to, or involves, the spleen.

X: If the largest detectable tumour is over 10 cm in size.

Additionally, there are other aspects that are used in human medicine; the relative width of the mediastinum and the findings at laparotomy are used, but these aspects are much less applicable to the horse, since imaging the required detail is, at present at least, impossible and the logistics of laparotomy is a significant barrier.

The Ann Arbor staging system takes no account of the pathological behaviour of the tumour and so is probably less useful as a prognostic indicator without the subtle modifications that have been applied to the system (the 'Cotswold modifications'). Nevertheless, this system might easily be applied to the lymphoma group of diseases in the horse.

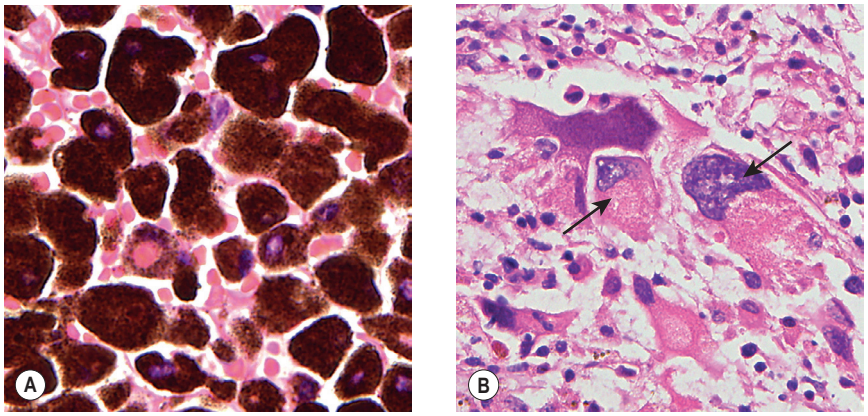


Figure 3.14 Low-grade and high-grade melanoma. **(A)** A low-grade melanoma. There is plentiful accumulation of melanin and the cells (after bleaching) will be more or less polygonal and uniform, with few mitotic figures. **(B)** A high-grade melanoma. An anaplastic melanoma shows large, irregularly-shaped giant tumour cells, some with giant nuclei (arrows). These are difficult to relate to either the normal cell type or better-differentiated forms of melanocytic neoplasia. The transition between the two grades from a diagnostic perspective is gradual, but the changes within a tumour itself can be (and usually are) abrupt and correspond to clonal expansion of abnormal cells following mutations.

These staging systems are not used widely at present in horses, possibly because the overall prevalence of tumours is low (or at least because they are poorly described in the literature) and because few are fully understood and completely characterized. The system does, however, enable better comparisons between treatments and prognosis and so there is merit in the development of a suitable dedicated system in equine oncology.

Reference

1. American Joint Committee on Cancer. AJCC cancer staging manual, 6th edn. New York: Springer; 2002.

4

Biology of tumour growth

The molecular and genetic (cellular) basis of cancer	23	Tumour progression and proliferation	47
Carcinogenesis	39	Metastasis	53
		The growth of tumours	60

The molecular and genetic (cellular) basis of cancer

For tissues to function normally, the cells must replicate, repair and renew; this process is naturally a carefully controlled balance between the proliferation and differentiation of cells and their death. Therefore, tissues and organs need a predictable cell structure and physiology to function normally; the life-cycle of cells is controlled to ensure that their specific genetic blueprint is accurately expressed, so that each copy of the cell is a perfect replica and is able to function identically. Control of the cell-cycle is pivotal to achieving the required balance between formation and natural cell destruction; a fundamental feature of cancer is the dysregulation of the cell replication cycle.

The mechanisms and pathways that influence and regulate the cell-cycle are very complex but can be simplified. Within every living cell there is a cell-cycle 'clock' that determines whether or not a cell should divide. This 'clock' effectively controls, and regulates intracellular processes and integrates the regulatory signals received by the cell with the current health status of the individual cell. This dictates the progression through natural replication to ensure that there is an effective and useful generation of new identical and healthy daughter cells.

The cell-cycle can be conveniently, if simplistically, divided into four individual phases (Fig. 4.1): these are simply convenient divisions for understanding the way a cell replicates, but it is wrong to view this as a production line that has distinct halts or pauses. It is, however, regulated by distinct physiological events within the cell. The process is smooth and continuous and there are significant differences between organs that are undergoing growth (i.e. increasing the absolute numbers of cells) and those which have reached maximal size and which are then limited to maintenance of function. The ordered progression through the cell-cycle is an intricate process that is governed by positive and negative signalling molecules both externally and internally.

Broadly, the cycle can be divided into the 'business' phases, which include the S-phase (synthesis), during which DNA is replicated, and the divisional phase, the

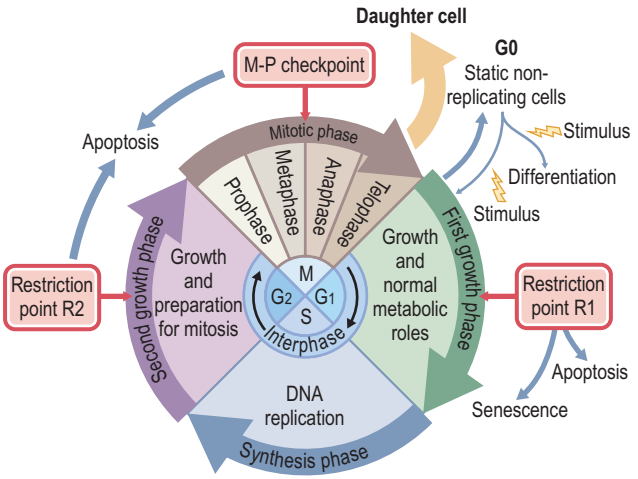


Figure 4.1 The cell-cycle. The cell-cycle is the fundamental method of cell replication. The completed cycle, which comprises four recognized stages, results in the production of a daughter cell identical in every way to the 'parent cell'. The first growth phase (G1) is the stage where intracellular metabolism and growth prepares the cell DNA for replication – the manufacture of the building materials required. This is followed by DNA synthesis stage (S) – DNA is prepared. The second growth phase (G2) is the stage that prepares the cell for mitosis. The mitotic phase (M) is the stage of replication during which the cell undergoes cellular division in the classical manner to produce two identical cells. At the end of cell division, the cell may be diverted back into the cell-cycle for further replication but the large majority of cells are 'shunted' into the G0 stage, in which most cells spend their functional lives. Some cells differentiate into specialized cells and may then remain static for life without any further replication. Nerve cells are good examples of this process. Other cells perform their functions in organs and structures but with suitable stimulus they can be redirected back into the cell-cycle to restore organ integrity of functionality. At various points in the cell-cycle, 'decisions' have to made on the stability and purpose of the process. There are three restriction points at which fundamental checks are made to ensure the integrity of the cycle. The R1 restriction point is governed by genes of the p53 family and this point checks that the genetic codes are correct. If not, the cell is either blocked for further replication and is 'passed' into a state of static non-functionality (senescence), or the pathways for apoptosis are triggered and the cell is dismantled in an orderly fashion. The R2 and the M-P restriction points serve similar purposes and can divert cells with 'irreparable' problems to an apoptotic pathway. In this way, the construction of the new cell is strictly monitored and controlled to ensure perfection. Any cellular alteration that either evades the restriction points or damages the restriction point function will be potentially dangerous in producing an abnormal cell clone.

M-phase, in which mitosis, cell (division), takes place. DNA is packaged, the cells divide and DNA is distributed appropriately to the daughter cells (see Fig. 4.1). The S- and M-phases are separated by G-phases (GAP), during which the genetic structure is 'proofread' and checked for perfection to ensure that the DNA replication is completed and parcelled correctly prior to the division of the cell in the M-phase. The first GAP-phase (G1) separates the M-phase from the S-phase, whilst the second gap phase (G2) separates the S-phase from the M-phase.

Additionally a G0-phase can exist when the cells are held in a static state or quiescent; in this circumstance the cells leave the cell-cycle by the absence of external signals that drive replication. When there are no external signals the cells are usually in the quiescent (G0) phase but when external, pro-differentiation, signals arrive either as result of the death of an adjacent cell, or through external endocrine and cytokine mediators, the cell then re-enters the cell-cycle. Organs naturally have to grow in addition to replicate and so this also explains how organs can expand in response to defined stimuli from other endocrinological or cytokine signals.

Progression through the four phases of the cell-cycle is exquisitely controlled by multiple components, which control transition between the stages at checkpoints; these are stages at which 'decisions' are made about whether the cell can progress or whether reparative processes need to be instigated or diversion of the cell towards a static non-dividing state or destruction are taken. This regulation allows DNA replication and cell division to be coordinated and also protects against DNA damage. The presence of any damage or error in the DNA results in prevention of progression through the main checkpoints of the cell-cycle and leads to cell-cycle arrest. Arrest of the cell-cycle does not mean that the cell is necessarily destroyed, since at these stages decisions are taken concerning whether the damage is repairable or, if the damage is severe, whether the cell needs to be diverted towards a planned and processed dismantling of the cell – apoptosis. It is this control of the cell-cycle progression and apoptosis that ensures cell integrity and identicalness and this is the fundamental basis also of cancer cell formation.

The cyclins are one important recognized group of proteins involved in the pathways of the cell-cycle; they regulate the transition from one stage to the next at the checkpoints through regulating cyclin-dependent kinases (CDKs), which regulate the process in the G1- and S-phases (Fig. 4.2). One of the most important checkpoint controls is the transition between the G1- and S-phases, which commits the cell to subsequent division. The process of control at this checkpoint can be inhibited by proteins, such as p53 and CDK inhibitors or can be enhanced by external mitogenic growth factors. The other transition is between the G2- and M-phases (see Fig. 4.1). Failure to control transition through the checkpoints of the cell-cycle leads to uncontrolled or excessive cell proliferation. This genomic instability also increases as damaged DNA is replicated through sequential generations of daughter cells.

The control of the cell-cycle and apoptosis (naturally planned or controlled cell death without local or remote harm) are central to the development of cancer. The process is complex and is being continually explored by researchers. The progression of a cell through the cell-cycle is positively

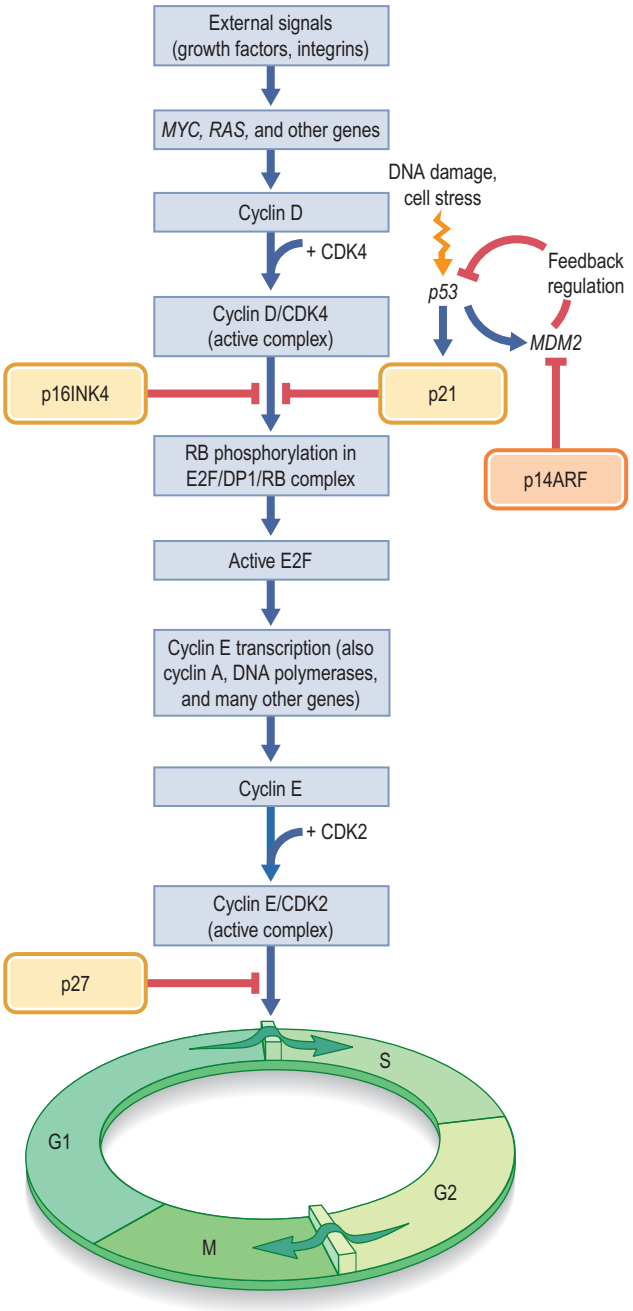


Figure 4.2 The role of cyclins, CDKs and cyclin-dependent kinase inhibitors in regulating the G1/S cell-cycle transition. Schematic illustration of the role of cyclins, CDKs and cyclin-dependent kinase inhibitors in regulating the G1/S cell-cycle transition. External signals activate multiple signal transduction pathways, including those involving the *MYC* and *RAS* genes, which lead to synthesis and stabilization of cyclin D (there are several D cyclins, but, for simplification, we refer to them as 'cyclin D'). Cyclin D binds to CDK4, forming a complex with enzymatic activity (cyclin D can also bind to CDK6, which appears to have a similar role as CDK4). The cyclin D–CDK4 complex phosphorylates RB, located in the E2F/DP1/RB complex in the nucleus, activating the transcriptional activity of E2F (E2F is a family of transcription factors, which we refer to as 'E2F'), which leads to transcription of cyclin E, cyclin A and other proteins needed for the cell to go through the late G1 restriction point. The cell-cycle can be blocked by the Cip/Kip inhibitors p21 and p27 and the INK4A/ARF inhibitors p16INK4A and p14ARF. Cell-cycle arrest in response to DNA damage and other cellular stresses is mediated through *p53*. The levels of *p53* are under negative regulation by *MDM2*, through a feedback loop that is inhibited by p14ARF. *(Figure reprinted from Kumar V, Abbas A, Fausto N. Robbins and Cotran pathologic basis of disease, 7th edn. Philadelphia: WB Saunders; 2004: 291 (Fig. 7.29); copyright 2004, with permission from Elsevier.)*

regulated by a family of cytokines (enzymes) known as 'cycline-dependent kinases' (CDKs).

A tumour is formed by the clonal expansion of a single cell that has incurred some genetic damage that imparts recognizably abnormal characteristics to it. The loss of cellular growth control is the result of a single, or more usually a series, of genetic changes in the affected cells and arises basically from an evolutionary selection of the cells that survive best – it is in fact a process that mimics evolution itself! Oncogenes, tumour suppressor genes and DNA repair genes are the most significant genetic influences in cancer pathogenesis; they are those genes that directly or indirectly affect the regulation of the basic cell processes (see later).

Non-lethal genetic damage is the most fundamental 'bottom line' of cancer biology. This genetic damage can be acquired through exposure to environmental challenges that can be exogenous (genuinely environmental) or from the endogenous products of cell metabolism. Examples of the former include chemicals, radiation or viruses. The damage may also be inherited, i.e. derived directly from one or other parent line. In addition, there are some spontaneous mutations that occur randomly without apparent cause. Additionally and importantly, cancer cells have an inherent genetic instability that increases the likelihood of genetic mutations or epigenetic changes in response to micro-environmental conditions surrounding the cell itself.

Single and/or sequential mutation of the relatively few important genes involved in cancer development lead to uncontrolled cell replication and proliferation with additional mutations that arise as a result of additional mutagenic occurrences acting on inherently unstable genetic components of the mutated cells, leading first to an ability to invade basement membranes and then to an ability to spread/metastasize. Although in many species the genes involved in major cancer processes have been identified, there is little specific information on the horse. However, the mutations can result in cancer through excessive function, malfunction or non-function and each of these properties will clearly influence the nature of the tumour itself.

There are four principal recognized genes that are the targets for the genetic damage that leads to the development of cancer. These are:

1. Growth promoting proto-oncogenes
2. Growth inhibiting tumour suppressor genes
3. Genes that regulate natural/organized cell death (apoptosis)
4. DNA repair genes.

Classically, the first two of these are discussed together.

Oncogenes: Oncogenes are hyperfunctional forms of normal genes that promote autonomous cell growth and replication. They have been identified as integral to the development of cancer and exert their influences on crucial stages of the cell-cycle involved in regulating the crucial stages of the cell-cycle and may involve growth factors, growth factor receptors, intracellular cell signalling proteins and nuclear transcription proteins. Their normal counterparts are called 'proto-oncogenes'; these are the physiological regulators for cell proliferation and differentiation and are effectively the drivers of normal cell replication and their expression is under the influence of normal mitogenic signals. In contrast, oncogenes are capable of promoting cell replication and growth independent of the normal mitogenic signals. Effectively, they 'don't listen' to the commands for their behaviour and produce oncoproteins, which resemble the normal products, but they are devoid of regulatory elements. Once this is triggered, the process becomes autonomous and remains independent of regulatory signals. Cancer cells have strategies to acquire self-sufficiency.

The mechanism for conversion from proto-oncogene to oncogene can arise from:

- Point mutations in which a single DNA base pair mutation may result in the production of a hyperfunctioning protein
- Chromosomal rearrangement in which a chromosomal translocation result in a proto-oncogene being relocated at another site where it may be able to overexpress itself. The translocated gene/genes may also fuse genes together and so express hyperfunctional proteins
- Gene amplifications may occur: multiple copies of a proto-oncogene may lead to excessive production of proteins and, although the protein may be normal, it is in excess and so will have profound effects on cell functionality
- Viral insertion mutagenesis occurs when a viral gene causes activation of proto-oncogenes.

The significant effects of the gene transformation from proto-oncogene to oncogene include overproduction, which in turn leads to dysregulation of normal cell growth, increased proliferation, loss of apoptosis and potential transformation to malignancy. Since the 1970s, dozens of oncogenes have been identified in human cancer but relatively few have been identified categorically in the horse. Many cancer drugs target these DNA sequences and their products.[1]

Tumour suppressor genes: These are genes that naturally prevent abnormal cellular proliferation and genetic instability: they can be viewed as the cellular policemen/repairmen! The protein products of these genes are intimately involved in a variety of cell functions including the cell-cycle control/checkpoints, cell signalling, triggering of apoptosis and repair of faulty DNA. Inactivation or loss of tumour suppressor genes by mutation or deletion will necessarily lead to loss of function, reducing the effectiveness of restriction at cell control points, thereby promoting growth and replication. Simplistically, these genes serve to recognize the potential of mutations and act to protect the cell or the body by repairing damage, triggering cell death to ensure that the changes are not taken a step further, and stabilizing the genetic structure so that cells are 'shunted into a siding' where they remain harmless.

Tumour suppressor genes can be inactivated by:

- Point mutations or small deletions/insertions of genetic material
- Chromosomal abnormalities, such as translocations and insertions
- Epigenetic changes, such as DNA methylation.

Inactivation or loss of these genes by mutation or deletion leads to loss of function and a reduction in the restrictions of cell division or growth. This results in an inherent and inevitable genetic instability and loss of apoptosis, which shifts the balance of the cells towards malignant behaviour (Table 4.1).

Table 4.1 The role of tumour-suppressor genes and their protein products in human examples

Tumour suppressor gene	Function of TSG expressed proteins	Clinical examples (in human medicine)
p53	Arrest of cell-cycle Triggering of apoptosis Repair of damaged DNA	The most commonly mutated gene in most cancers
Retinoblastoma	Cell-cycle regulator at restriction checkpoints	Retinoblastoma Lung cancer
BRCA1 & 2	Transcription factors DNA repair	Familial breast and ovarian cancers
APC	Inhibitors of cell signal transduction	Colon, stomach and pancreatic cancer
WT-1	Nuclear transcription	
P161NK 4	Inhibitors of cyclin-dependent kinase (CDK)	Pancreatic/ oesophageal carcinoma and melanoma

After Peedell C, Stark DPH, eds. Basic cancer biology. In: Concise clinical oncology. Oxford: Butterworth–Heinemann; 2005: 13; copyright 2005, with permission from Elsevier. A similar table for equine neoplastic disease would be very difficult to prepare, since so little is known about equine neoplastic disease.

Under normal circumstances, these genes act recessively; both copies of the gene (alleles) must be mutated to produce the loss of function – mutation of a single gene acquired from parent is not enough in itself to cause a problem, but where there is a single mutated gene the patient may have a predisposition to cancer development. A good example of such a state occurs when there is an inherited single mutation in the *p53* gene (p. 40), which greatly enhances the lifetime risks of cancer. Such a patient might easily develop multiple cancers rather than just a single type.

The guardian of the genome: (T)*p53* gene

The *p53* gene is the single most common gene to be mutated in human cancers and there is no reason to doubt that it is also an important aspect of equine/veterinary tumours. The *p53* gene is a transcription factor that can be activated by checkpoint kinases to cause cell-cycle arrest.[2] The major functional activities of the p53 protein are cell-cycle arrest and the initiation of apoptosis in response to DNA damage. The *p53* gene is actually a member of a multigene family with similar functions. *p73* is usually regarded as the 'big brother' of *p53* and is located on another locus; it encodes similar proteins that can also cause cell-cycle arrest, as well as apoptosis in appropriate conditions. *p63* is the newest member of the family of protective genes to be identified.

p53 is regarded as the 'molecular policeman' or the 'guardian of the genome'; it plays a major role in cell-cycle arrest and control of some DNA repair genes and is also intimately involved in apoptosis that follows the detection of significant DNA damage (Fig. 4.3); it is called in to apply the emergency brakes when DNA is damaged in particular

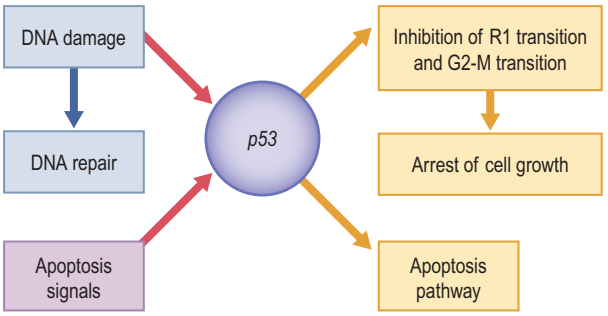


Figure 4.3 ***p53* and DNA repair genes.** The role of *p53* and DNA repair genes in cell-cycle arrest and apoptosis.

by gamma, X-ray and ultraviolet irradiation or mutagenic chemicals. It is also called in, in the absence of DNA damage, when oxidative injury, senescence and other cell stressors are present.[3] Cells may undergo *p53*-mediated apoptosis following chemotherapy or radiotherapy but loss of the *p53* gene function (loss of the gene or its critical damage) alone results in survival of cells that have been damaged by the treatment or by any other insult. The *p53*-deficient cells are therefore more resistant to chemotherapy and to radiotherapy as well as being much more sensitive to the adverse effects of other genetic mutations, however those are induced. In fact, *p53* is a pivotal player in the prevention of cancer development and its progression through the early stages of cancer transition to the most severe forms of tumour development! In normal circumstances, some cells have no ability to repair or replicate, e.g. nerve cells, and these cells usually lack the mechanisms that trigger cell-cycle progression.

The natural checkpoints in the cell-cycle function to limit inappropriate cell proliferation and cell survival and collectively block cell transformation. The *p53* tumour suppressor pathway that induces cell-cycle arrest or apoptosis has an important effect on the fate of a cell. This gene, which in the horse is located on the short arm of chromosome 17, is therefore a fundamental and vital one for the normal cell function and protection. (More exactly the *TP53* gene is located from base pair 7 571 719 to base pair 7 590 867 on chromosome 17 at position 13.1.) Remarkably, it is by far the most common single gene that is mutated in human cancer conditions and we have no reason to doubt that a similar situation occurs in veterinary species including the horse.[3]

The multiple families of protective genes (*p53*, *p63* and *p73*) can probably compensate for each other to some extent and that may explain why even when one of the genes is damaged, loss of cell-cycle control is not as severe as it otherwise might be.[4]

When normal cells are subjected to molecular stress (such as might occur with exposure to radiation), DNA damage or oxygen depletion, they are usually either efficiently arrested at one or more of the cell-cycle barriers or are directed towards apoptosis, or both. Checkpoint reparative mechanisms may be triggered to allow a cell to re-enter the cell-cycle and these processes are largely under the control of the *p53* gene family (*p53*, *p63* and *p73*). The gene plays a pivotal role in maintaining genomic stability and undertakes the genetic surveillance following exposure to damaging

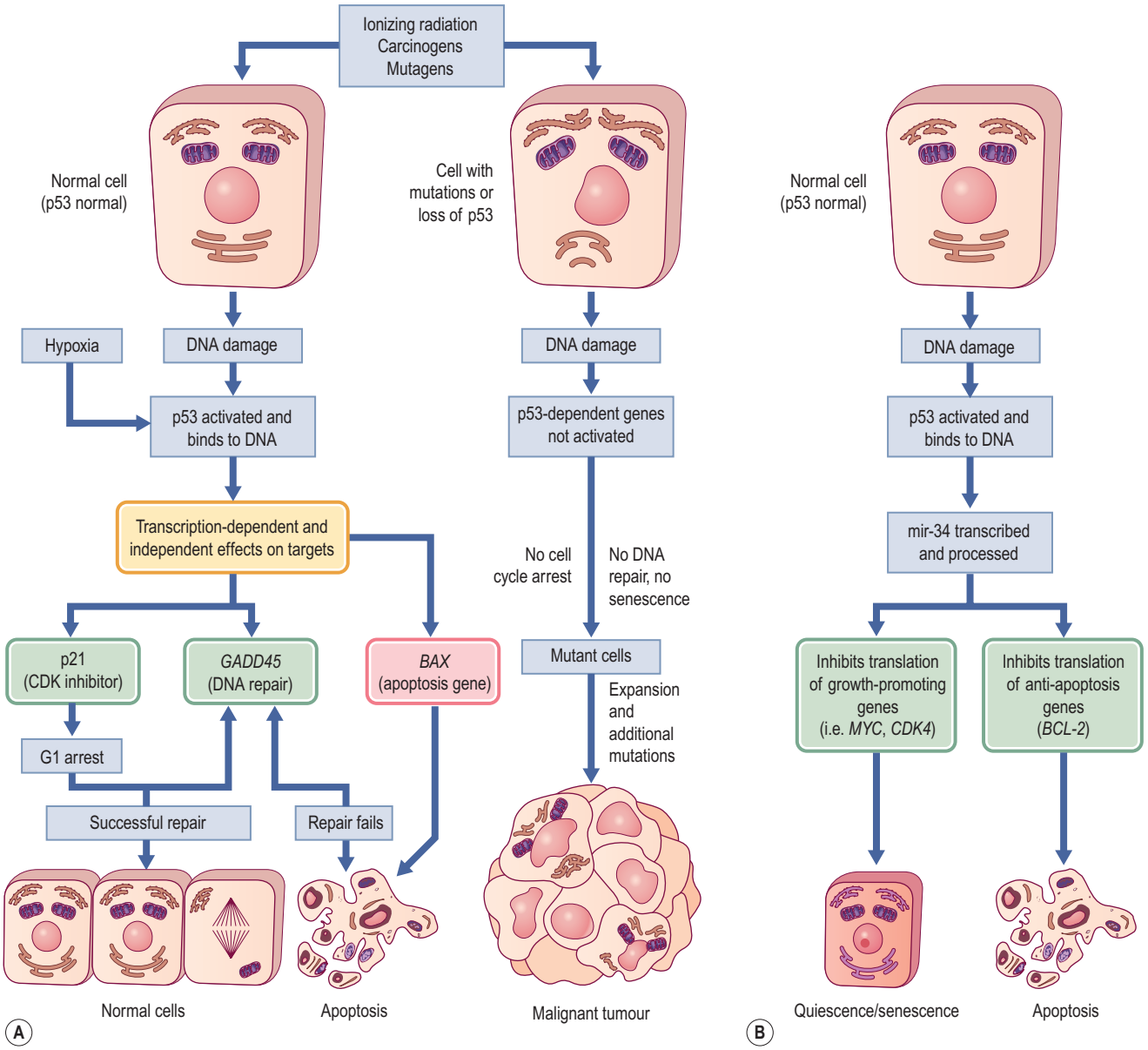


Figure 4.4 Repair of DNA. (A) The role of p53 in maintaining the integrity of the genome. Activation of normal p53 by DNA-damaging agents or by hypoxia leads to cell-cycle arrest in G1 and induction of DNA repair, by transcriptional upregulation of the cyclin-dependent kinase inhibitor *CDKN1A* (p21) and the *GADD45* genes. Successful repair of DNA allows cells to proceed with the cell-cycle; if DNA repair fails, p53 triggers either apoptosis or senescence. In cells with loss or mutations of p53, DNA damage does not induce cell-cycle arrest or DNA repair, and genetically damaged cells proliferate, giving rise eventually to malignant neoplasms. **(B)** p53 mediates gene repression by activating transcription of miRNAs. p53 activates transcription of the mir-34 family of miRNAs. Mir-34s repress translation of both proliferative genes, such as cyclins, and anti-apoptotic genes, such as *BCL-2*. Repression of these genes can promote either quiescence or senescence as well as apoptosis. *(Figure reprinted from Kumar V, Abbas A, Aster J. Robbins and Cotran pathologic basis of disease, 8th edn. Philadelphia: WB Saunders; 2010: 291 (Fig. 7.32); copyright 2010, with permission from Elsevier.)*

insults, such as gamma and UV radiation, chemicals and oxidative stress (Fig. 4.4).

Homozygous loss of the *p53* gene probably occurs in the large majority of cancers, in all species.[5] In most cases, both alleles are affected equally and there are (in contrast to the *Rb* gene) few occasions when there is a heterozygous inherited state. These changes are therefore most often acquired rather than inherited in the germ line of the cells. Only rarely will an individual inherit a single mutant *p53*, and in this case (as is the case with the *Rb* gene), this will result in an increased tendency to further mutation and so to cancer development.

The role of the *p53* gene is in fact more complex in that it has related genes that also have an influence. The *p63* and *p73* genes are members of the multi-gene family that controls many of the genetic functions that protect against mutation. *p53* deficits can most likely be compensated to some extent in some circumstances by the normal function of the other genes in the group. These genes link cell damage with DNA repair, cell-cycle arrest and apoptosis. *p53* plays a fundamental role in the process of DNA repair by arresting the cell-cycle at the G1-phase and triggering activity of DNA repair genes. The *p53* gene family directs a cell with irreparably damaged DNA to undergo apoptosis, thus

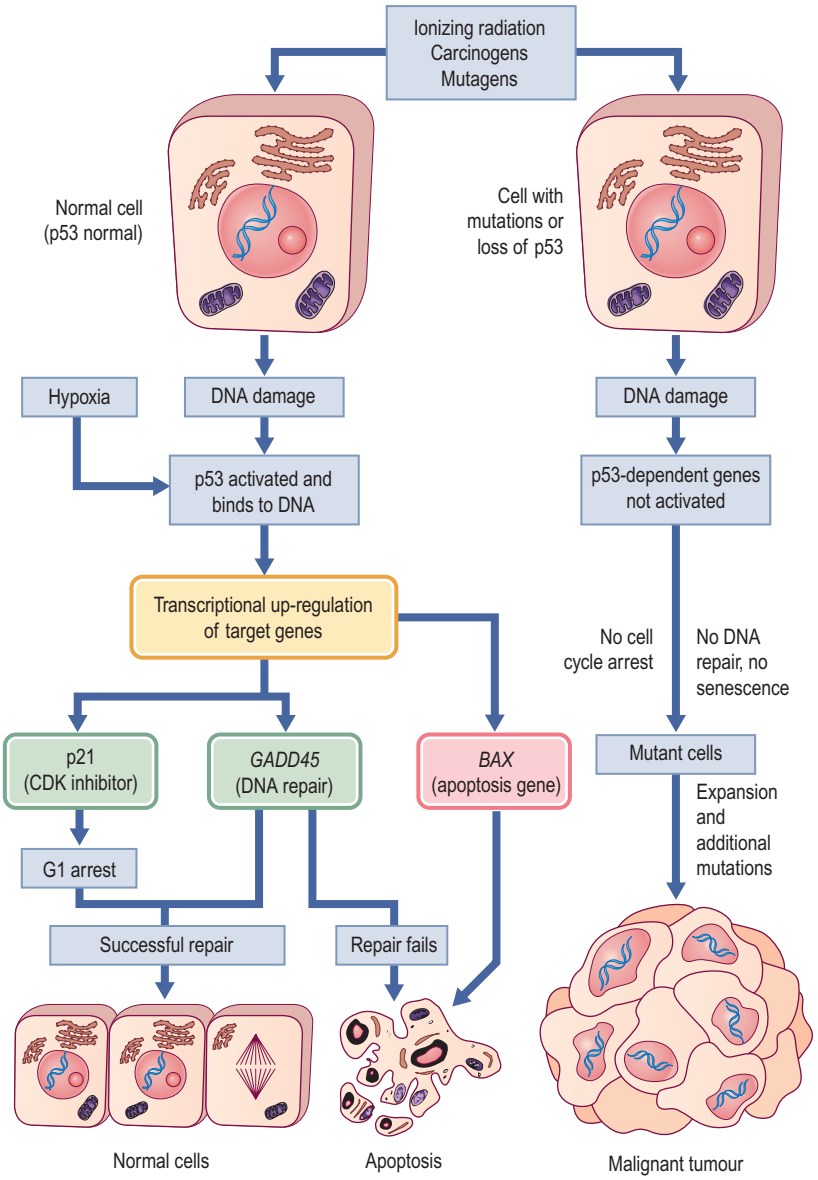


Figure 4.5 The *p53* gene. *p53* plays a pivotal role in maintaining the integrity of the genome in any cell. When the *p53* gene is activated by a cell insult, such as radiation, chemical toxins or hypoxic insult, the cell is arrested in G1-phase. DNA repair is triggered by transcriptional upregulation of the cyclin-dependent kinase inhibitor p21 and the *GADD45* gene complex. If the DNA is successfully repaired, the cell is 'allowed' to proceed through the cell-cycle. If however, DNA repair fails or the damage is too severe to 'contemplate' repair, p53-induced apoptosis occurs – the cell is shunted into the recycling depot. If *p53* itself is damaged or mutated, DNA damage does not induce arrest or repair and then genetically damaged and genomically unstable cells are left to proliferate uncontrollably. Every daughter cell will carry the same basic 'fault' and the lack of repair also means that mutational changes are more likely to occur and pass unrecognized – the cell becomes genomically unstable and can move progressively towards more abnormal cell behaviour, leading eventually to malignancy (see p. 39). *(Figure reprinted from Kumar V, Abbas A, Fausto N. Robbins and Cotran pathologic basis of disease, 7th edn. Philadelphia: WB Saunders; 2004: 303 (Fig. 7.37); copyright 2004, with permission from Elsevier.)*

removing the threat of an uncontrollable cell replication or indeed uncontrollable necrosis of the cell resulting in inflammatory mediator release.

Without the controlling function of the *p53* family of genes, DNA is not repaired and the mutations are fixed within the dividing cell in such a way that the cell develops a single and almost inevitable pathway to malignant transformation (Fig. 4.5).

The role of the *p53* in controlling apoptosis following DNA damage is also involved in some forms of chemotherapy and radiation therapy. Both of these common therapeutic approaches are effective because they induce DNA damage and subsequent apoptosis. Tumours that retain their p53 function are more likely to respond to such treatments than tumours that carry mutant alleles of the *p53* family of genes. In the human field, this is an important aspect of determining the likely effects of both chemotherapy and radiation therapy; some tumours have a fully functional *p53* and respond well, while others, which carry a *p53* mutation, are relatively resistant to chemotherapy or radiation or both. Cancer therapy with the ability to increase normal p53 activity in tumour cells that have retained the p53 activity is one approach that is being explored. A second potential option is to establish ways of killing cells that have a defective p53 function, since then the cell becomes irrelevant. The latter includes strategies that use modified viruses (usually adenovirus) that lyse cells that lack the p53 function.

It is important to realize that there are other genes that function as tumour suppressors but they are largely identified through detection of specific deletions in cancer cases, it is hard to extrapolate in these circumstances to the horse from the human situation. Significantly, the *p53* gene does not appear to be adversely affected in equine sarcoid tumours.

DNA repair genes

DNA repair genes are the intracellular 'repair workers'. They support and maintain genetic stability and are specifically involved in the repair of damaged DNA.

Additionally, they exert an indirect effect on cell proliferation or survival by influencing the ability of the organism to repair any non-lethal damage in other genes, including proto-oncogenes, oncogenes, genes that regulate and control apoptosis and tumour suppressor genes. Additionally and importantly, compromise in the function of the DNA repair genes can predispose to mutations and so predispose the development of multi-mutational damage and the neoplastic transformations that are recognized as cancer.

DNA repair refers to a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome. In a normal mammalian body, normal metabolic activities and environmental factors, such as UV light and radiation, can cause structural damage to DNA molecules and can therefore adversely affect or even eliminate the cell's ability to transcribe the gene that the affected DNA encodes. Other noxious stimuli induce potentially harmful mutations in the cell's genome, which affect the survival of its daughter cells after it undergoes mitosis. DNA repair processes are therefore critical to cell and organ survival and maintenance. The process of DNA repair has to be extremely sensitive and very accurate in its response to subtle, often minute, changes in the DNA. When cellular apoptosis does not occur, the loss of DNA repair functions causes permanent DNA damage. This leads to irreparable DNA damage, including double-strand breaks and DNA cross-linkages and further genomic instability and mutation. In many circumstances, this also leads to loss of tumour suppressor gene function and conversion of proto-oncogenes to oncogenes, which in turn leads to increased cancer susceptibility.

The rate of DNA repair is dependent on many factors, including the cell type, the age of the cell and the extracellular environment. A cell that has accumulated a large amount of DNA damage, or one that no longer effectively repairs damage incurred to its DNA, can enter one of three possible states within the cell-cycle:

1. *An irreversible state of dormancy* 'senescence' (see also p. 36): When a cell enters this state, the cell simply grows old gracefully without any harmful consequences and waits for eventual death – similar to a state of 'retirement'!
2. *Cell suicide* 'apoptosis' or 'programmed cell death' (see p. 29): Here the cell is actively and carefully 'decommissioned' or dismantled in such a way as to prevent any concurrent damage arising as a result of cell death and destruction. This is in contrast to necrosis in which harmful cell enzymes and products are released and which is inevitably associated with inflammation (p. 32).
3. *Unregulated cell division*: This can lead to the formation of a tumour that may become cancerous.

The DNA repair ability of a cell is therefore essential to the integrity of its genome and thus to its normal functioning and that of the organ. Many genes that were initially shown to influence lifespan have been found to play a role in DNA damage repair and protection.[6] Failure to correct molecular lesions in cells that form gametes can introduce mutations into the genomes of the offspring and thus can even influence the rate and process of evolution; not all mutations are harmful – some can imbue 'advantage' without significant harm.

Cell destruction

The other side of the life-cycle of a normal cell is cell death. In the same way that cell growth is regulated by growth-promoting and growth-inhibiting genes, cell survival is dependent on genes that control the life-cycle, lifespan and prevent uncontrolled or unnecessary death of the cell.

Cell death occurs by two main mechanisms and one lesser mechanism: the former are necrosis and apoptosis (p. 29) (Figs 4.6, 4.7). The process of autophagy is the third less-understood mechanism for cell destruction (p. 32). Necrosis is a 'passive' response to cellular injury in which the cells swell and lyse. This releases their contents into the interstitial space. This triggers local inflammatory pathways resulting in detectable cellular and often systemic effects, inflammatory responses and, potentially, to serious health problems. In contrast, apoptosis is an 'active' process of planned, coordinated and regulated 'decommissioning' of the various cell components in such a way that there is no local or systemic consequence. This is clearly an advantage to the organism, given the number of cells that are being destroyed in any body system every day. The three mechanisms can be recognized within tumours by their distinctive changes through standard histology (Fig. 4.8) and by ultramicroscopy (see Fig. 4.7).

Apoptosis

Cells undergo apoptosis (natural planned cell death) in response to a variety of cellular 'insults', such as UV light, chemical or physical damage, viral infection and as a result of ageing. Apoptosis is a cellular response process in which cells play an active role in their own death (which is why apoptosis is often referred to as 'cell suicide' or 'programmed cell death'). In this process, the cells are 'dismantled' in a controlled, regulated fashion without release of any significant mediators that might induce an inflammatory response or cause local or remote cell or organ injury. Apoptosis is therefore physiologically and pathologically distinct from necrosis, in which uncontrolled cell death leads to lysis of cells; this 'chaotic' destruction releases chemicals and mediators that induce inflammatory responses, which in turn invariably has remote effects on other organs and tissues. Apoptosis, or programmed cell death, is a normal component of the development and health of multicellular organisms. There is clear advantage in activation of the apoptotic pathway in cells that have sustained significant, irreparable DNA damage in both preventing and minimizing the risks of uncontrolled expansion of mutated/transformed cells and in preventing necrosis.

The triggering of apoptosis in a cell is a complex process that can involve different stimuli; unbalanced growth signals and damage to the cell membrane or the DNA are just some of the possibilities. Although the exact pathways are yet to be determined fully, almost inevitably, the *p53* gene family is fundamentally involved in the process. *p53* is an in important pro-apoptotic gene that induces apoptosis in cells that are unable to repair their genetic damage. When a cell is damaged as a result of oxidative stress or treatment with certain drugs or by exposure to radiation, apoptosis is triggered through expression of the p53 protein. Cells that have a *p53* mutation may not be triggered to undergo apoptosis by such damage. Many cancer cells have a

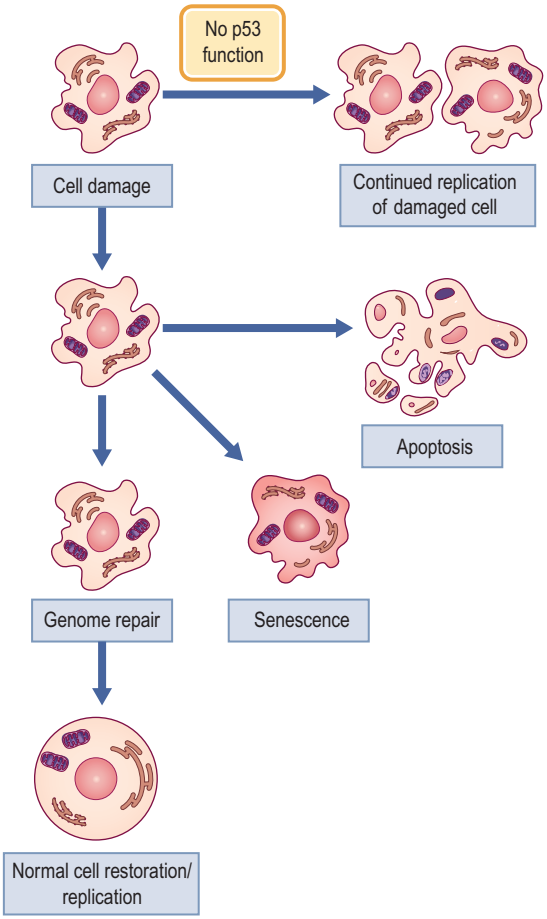


Figure 4.6 Mutation of the p53 gene complex. The *p53* family of genes are recognized as the 'molecular policeman or the guardian of the genome' because of the fundamental role they play in the prevention of progression of abnormal cells through the cell-cycle. Mutation of the *p53* gene complex and other chromosomal losses/ alterations are involved in the progression to malignancy and metastasis. Since the genomic surveillance of cells as they proceed through the cell-cycle is governed by *p53* and other like genes, damage to these will inevitably lead to sustained and replicated abnormality. The genomic instability that follows damage to the controlling genes makes subsequent mutation more likely and more able to bypass the surveillance systems. Simplistically, the role of the surveillance genes can be likened to a motor repair technician who 'triages' the cars to detect faults and passes them to the right kind of repair technicians. The options available to the master technician are: (a) The repair can be completed and the car can be rendered safe and reliable – the cell is 'fixed' and returns to the cell-cycle with no adverse consequence. (b) The technician can recognize that the car is beyond repair and divert the process to the breakers who can dismantle the car with no deleterious effects – the cell is subjected to apoptosis. (c) The damage to the car might be sufficient to warrant simply storage of the car in a state that neither allows use or destruction – the cell is held in a static state without the ability to replicate but is not subject to apoptosis. (d) The car may have 'undetectable damage' that the technician cannot identify and so the cell passes into the cell-cycle to replicate identically damaged cells but future mutations may be more evident. The car can be re-checked at a future date and the damage can be dealt with. (e) Where the technician is damaged, sleeping, drunk or dead – the triage is not carried out and the repair technicians are not called into action and so the cell can pass naturally and persistently through the cell-cycle in a progressively unstable state! Damage to *p53* genes and its 'peers' is an extremely dangerous state.

significantly decreased ability to undergo apoptosis in response to various stimuli including DNA damage because these cells are able to tolerate increased levels of genetic instability. Since some chemotherapeutic agents used in cancer medicine act by inducing apoptosis, the loss of

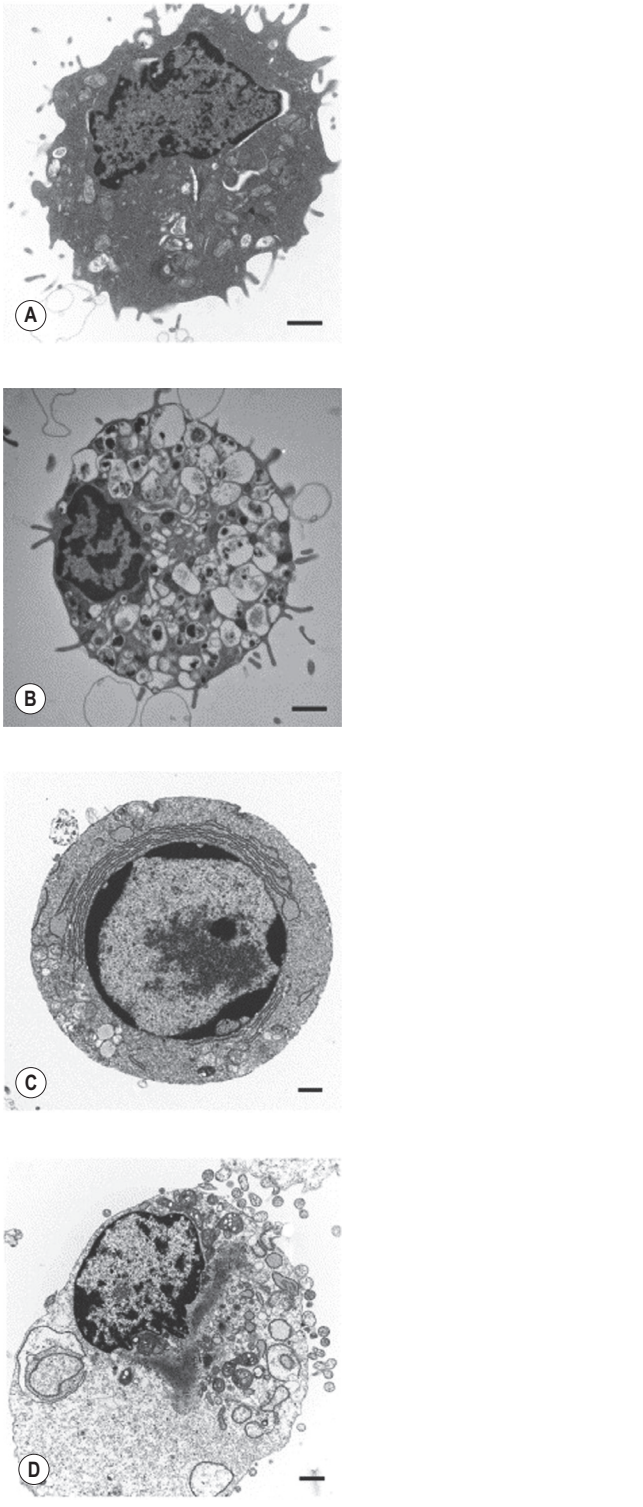


Figure 4.7 Morphological characteristics of cells. Morphological characteristics of a normal cell **(A)**, compared with cells undergoing **(B)** autophagic; **(C)** apoptotic; and **(D)** necrotic cell death. Although the morphological characteristics of an apoptotic cell are well-defined, autophagic vesiculation can be seen in all three forms of cell death. In the context of apoptosis or necrosis, autophagy could be additive or may serve to protect cells from death. Indeed, bioenergetic failure, which will lead to necrosis, can be thwarted by the upregulation of autophagic degradation to maintain proper adenosine triphosphate levels. *(Figure reprinted from Dorsey FC, Steeves MA, Cleveland JL. Apoptosis, autophagy, and necrosis. In: Mendelsohn J, Howley PM, Israel MA, et al., eds. The molecular basis of cancer, 3rd edn. Philadelphia: WB Saunders; 2008 (Fig. 15.1); copyright 2008, with permission from Elsevier.)*

apoptotic genes can have a profound detrimental effect on drug efficacy – some tumours therefore simply do not respond to drugs that act in this way.

Upon receiving specific signals instructing the cells to undergo apoptosis, a number of characteristic changes occur in the cell. A family of proteins known as 'caspases' are typically activated in the early stages of apoptosis. These proteins break down or cleave key cellular components that are required for normal cellular function, including structural proteins in the cytoskeleton and nuclear proteins, such as DNA repair enzymes. The caspases can also activate other degradative enzymes, such as DNAses, which begin to cleave the DNA in the nucleus.

Apoptotic cells have a characteristic histological appearance – in contrast to necrosis, the apoptotic cell has chromosomal condensation and nuclear fragmentation with shrinkage of the cell size and loss of cell contact with its neighbours (see Fig. 4.8). The next stage of the process involves 'blebbing' of the cell membrane and formation of apoptotic bodies that contain small, isolated bits of the cell content (chromatin) surrounded by cellular membranes (Fig. 4.9). These bodies are attractive to local phagocytic cells and are digested without any significant secondary consequence or inflammation. The processes that take place inside the cell to render the blocks of nuclear and other proteins harmless are complex. The process is careful, regulated and self-protective.

Cellular evasion of apoptosis

Normal cell growth is regulated by the opposing growth-supporting and growth-inhibiting genes. Cell survival is also controlled by natural genes that support and inhibit apoptosis. One of the most striking features of cancer cells is their ability to evade the process of apoptosis – this leads to the concept of 'immortality' of cancer cells. The accumulation of cancer cells may arise either as a result of activation of oncogenes or inactivation of tumour suppressor genes. Additionally the cells can accumulate because of the detrimental mutation of genes that control and trigger apoptosis. An extensive list of related genes that regulate apoptosis has been identified in both normal and cancer cells; the first and possibly most significant is the *BCL-2* gene.[7]

The natural lifespan of a cell, organ or body is controlled by the finite number of divisions that cells can undergo (Fig. 4.10). Normal cells eventually become arrested in a

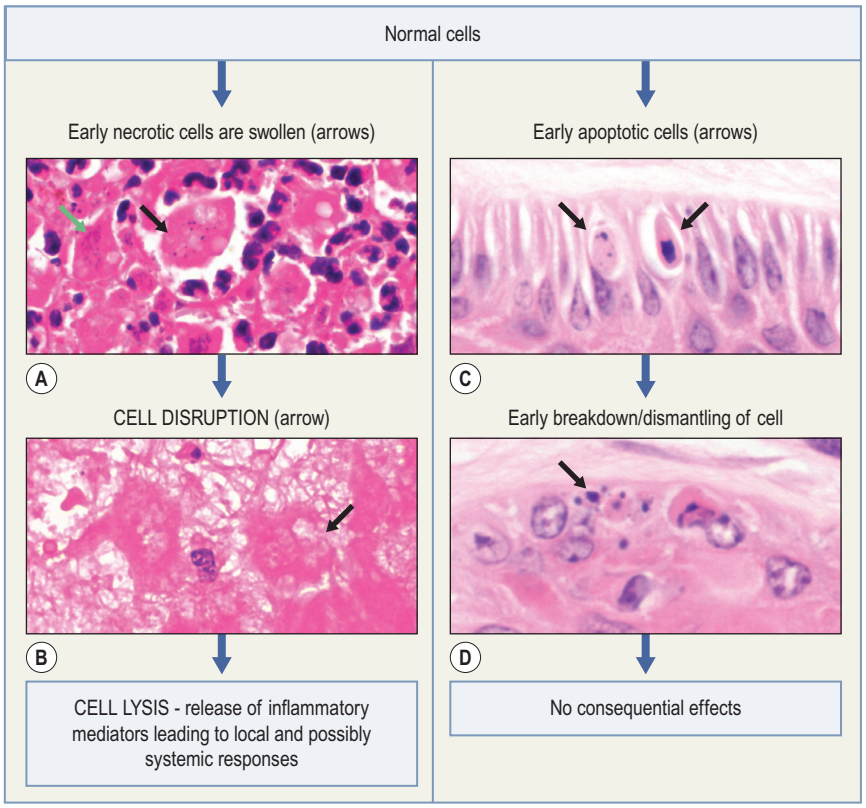


Figure 4.8 Cell death. The manner of a cell's death is a critical feature in respect of the extent of local and possibly remote damage that is caused by the process. Where a cell dies through the process of cell swelling **(A)**, and subsequent disruption (necrosis) **(B)**, there are local consequences that arise as a result of the release of a wide range of intracellular cytokines and mediators. This results in a local inflammatory response and possibly even remote physiological effects. In contrast, apoptosis is a more orderly dismantling of the cell, so that through a process of planned destruction **(C)**, the release of intracellular components **(D)**, is without either local or remote destructive effects and no inflammation follows. **(A)** The necrotic cells are swollen and their hypereosinophilic cytoplasm contains vacuoles, and they are surrounded by neutrophils (with dark-staining, segmented nuclei). The cell indicated by the green arrow shows fading of the nuclear chromatin, defined as karyolysis. The cell indicated by the black arrow shows nuclear karyorrhexis, i.e. a pyknotic nucleus that has undergone fragmentation. **(B)** More advanced necrosis with complete loss of cellular detail and evidence of lysis (arrows). **(C)** Apoptotic epithelial cells (arrowed) with shrunken, hypereosinophilic, rounded cytoplasm. The nucleus of the cell on the left is fragmented, and that of the cell on the right is pyknotic (shrunken and dark-staining). **(D)** These apoptotic cells are fragmenting into small 'apoptotic bodies' that contain dark-staining nuclear fragments (arrow). There are no inflammatory cells.

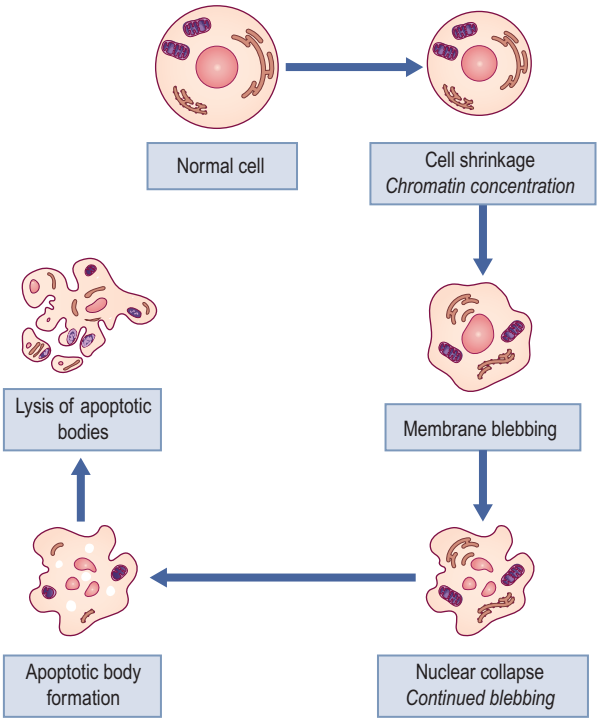


Figure 4.9 Apoptosis. The progress of a cell through apoptosis (K22).

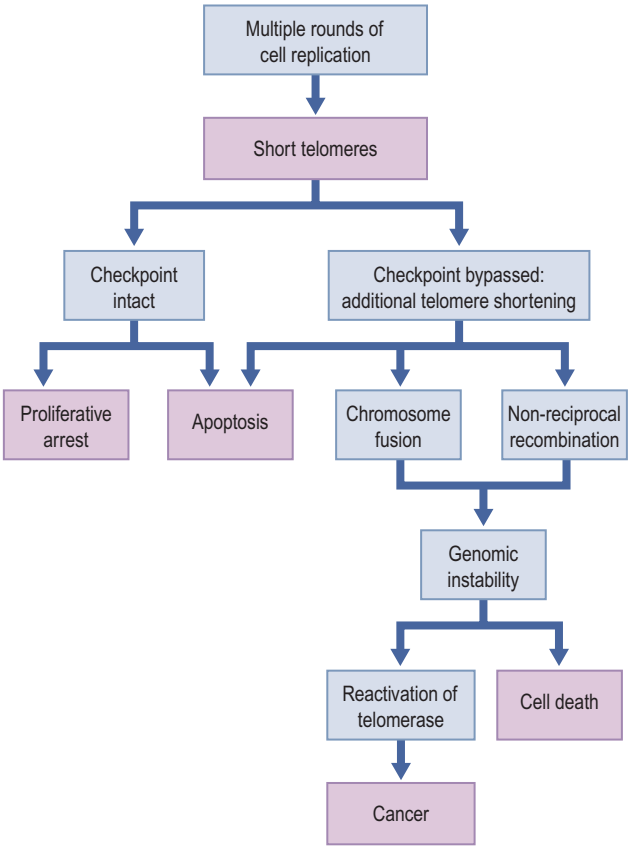


Figure 4.10 Cellular responses to telomere shortening. The responses of normal cells, which have intact cell-cycle checkpoints, and of cells with checkpoint defects. *(Figure adapted from Wong JMY, Collins K. Telomere maintenance and disease. Lancet 362:983; copyright 2003, with permission from Elsevier.)*

terminally, non-dividing state – 'replicative senescence'. It is likely that the finite number of potential divisions for any cell is governed by the shortening of the specialized structures at the end of chromosomes, known as telomeres. When these are shortened to a defined extent, the loss of telomere function triggers activation of p53-dependent cell-cycle arrest.

Telomeres are an essential and universal cellular substructure that is essential for chromosomal stability. They prevent chromosomes from fusing with each other and are involved intimately in nuclear architecture, in chromosomal localization and in the repression of expression of adjacent genes.

The telomere length, in effect, becomes a clock that counts down the available number of cell divisions that the cell type can undergo (Fig. 4.11). The pathways the cell can take from that point include a static 'senescent' state with no further replicative activity (with origin hypoplasia as cells shrink) or entry into an apoptotic state resulting in the reduction in the number of cells present and organ atrophy. Telomerase is the cell enzyme that prevents shortening of the telomeres in germ cells; normal somatic cells do not possess this. If loss of the telomerase is the reason why cells finally die, cancer cells clearly have developed a strategy to overcome this natural process; telomere maintenance is a feature of almost all cancers and, in over 90% of cancers, this is due to the upregulation of telomerase. Cancer cells have therefore found a means whereby the shortening of the telomeres does not occur and this is because telomerase is present in many cancer cell types.[8] This may account for the limitless replicative potential (immortality) of cancer cells.

Autophagy

The term 'autophagy' literally means 'self-eating' and is used to describe the degradation of cellular components by the lysozyme, a cell membrane-bound compartment containing degradative enzymes capable of dismantling macromolecules within the cell. It is a tightly regulated collection of processes that plays a normal part in cell growth, development and homeostasis, helping to maintain a balance between the synthesis, degradation and subsequent recycling of cellular products (Fig. 4.12). Autophagy is a major natural protective mechanism by which a 'starving' cell diverts nutrient resources from unnecessary processes to the more essential, life-preserving processes and this is assumed to be a significant supportive process for rapidly dividing cancer cells that become hypoxic or deprived of the nutritional requirements for rapid growth/replication.

There are inevitable intimate links between autophagy, which is a preservative approach, and apoptosis. It is likely that many of the synthetic processes involved in apoptosis involve the recycling of proteins derived from autophagy. Autophagy is a required pathway for tumour development and/or maintenance. It is a mechanism that can be triggered rapidly and might provide essential nutrients during periods of hypoxia and starvation. Autophagy will of course not always be supportive of tumour survival but rather when the capacity for autophagy is exceeded normal cells will undergo apoptosis whilst cancer cells will undergo necrosis; the latter is clearly a destructive and dangerous state compared to the former.

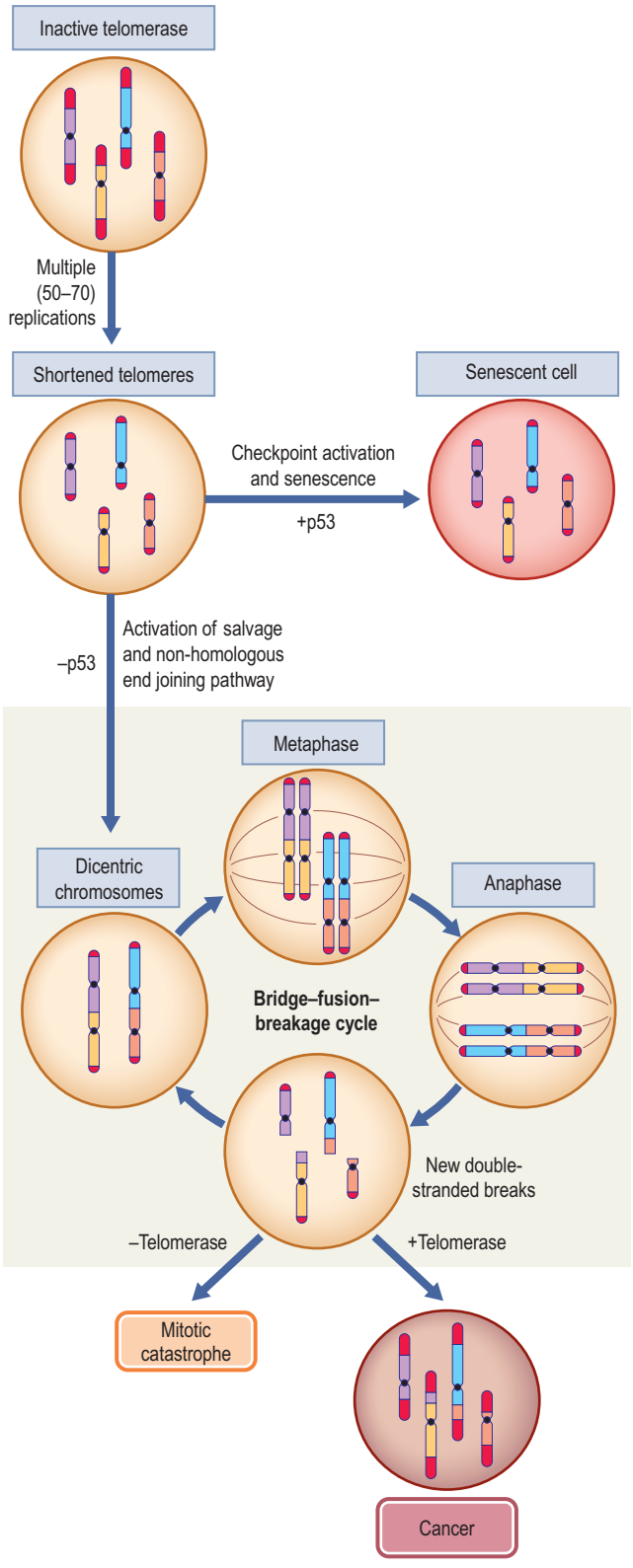


Figure 4.11 Sequence of events in the development of limitless replicative potential. Replication of somatic cells, which do not express telomerase, leads to shortened telomeres. In the presence of competent checkpoints, cells undergo arrest and enter non-replicative senescence. In the absence of checkpoints, DNA-repair pathways are inappropriately activated, leading to the formation of dicentric chromosomes. At mitosis, the dicentric chromosomes are pulled apart, generating random double-stranded breaks, which then activate DNA-repair pathways, leading to the random association of double-stranded ends and the formation, again, of dicentric chromosomes. Cells undergo numerous rounds of this bridge–fusion–breakage cycle, which generates massive chromosomal instability and numerous mutations. If cells fail to re-express telomerase, they eventually undergo mitotic catastrophe and death. Re-expression of telomerase allows the cells to escape the bridge–fusion–breakage cycle, thus promoting their survival and tumorigenesis. *(Figure reprinted from Kumar V, Abbas A, Aster J. Robbins and Cotran pathologic basis of disease, 8th edn. Philadelphia: WB Saunders; 2010: 297 (Fig. 7.35); copyright 2010, with permission from Elsevier.)*

In cancer cell biology, autophagy does appear to be inhibited or altered through genetic mutation, so that cells that would normally be broken down remain, and in that way it has common features with apoptosis. It is important however to recognize that the two processes are not one and the same.

Necrosis

Necrosis can be defined as an uncontrolled, chaotic and disordered process of cell destruction. It is a passive response that carries with it significant local and possibly systemic effects that are recognized as inflammatory responses. There are of course many circumstances when cells might become necrotic: toxins, bacterial and viral damage, hyper- and hypothermia, mechanical damage and, importantly, ischaemia and hypoxia are some of the possibilities. Necrosis ensues when there is overwhelming failure at the cell level. Morphologically, necrosis involves plasma membrane disruption with marked swelling of the cellular organelles and, in particular, the mitochondria. Leakage of intracellular contents into the interstitial space occurs and they induce an inflammatory response. Immediately prior to the complete disruption of the cell there may be extensive leakage of cellular degradation products but ultimately the cell is simply destroyed and all the contents are released into the surrounding sites – some may appear in the bloodstream and cause remote effects on other organs and tissues (Fig. 4.13).

Pathways leading to necrosis involve complex cellular and enzymatic processes that in fact may have an ordered series of events that are preceded by disruption of the plasma membranes, mitochondrial dysregulation of calcium concentrations, excessive accumulation of reactive oxygen species (ROS) and disruption of intracellular proteases. The whole process of cell necrosis can be influenced by genetic factors and can also be influenced epigenetically.

Where apoptosis and autophagy are inhibited, necrosis can 'take over' the process of cell destruction and therefore it can be viewed as the last resort for an organism to protect itself from serious cellular damage. This does not always have to be the obvious physical or chemical damage that necrosis is usually attributed to. Rather, it can be the result of any serious cell disruption that cannot be dealt with by one or other (or both) of the other two major mechanisms.

Necrosis is an important part of tumour biology, since many cells will undergo necrosis even when they have begun the process of the more controlled apoptosis or autophagy. If apoptotic cells are not cleared in a timely

fashion or if the cell is sufficiently disrupted to cause more rapid and profound intracellular damage than can be handled by the proper orderly processes, necrosis will ensue – this is commonly termed 'secondary necrosis', but it is important to recognize that it might simply be a fail-safe mechanism for the removal of potentially harmful cells. Tumour necrosis is a common feature of rapidly expanding cancers that can arise through bio-energetic failure or hypoxia (possibly through avascular necrosis); put simplistically, the tumour outgrows its own blood supply and its energy demands exceed supply.

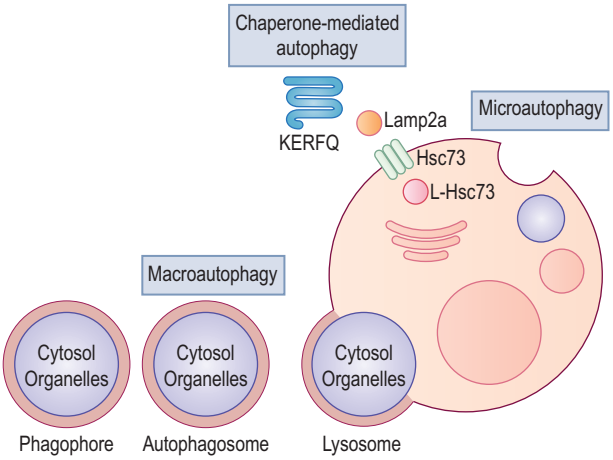


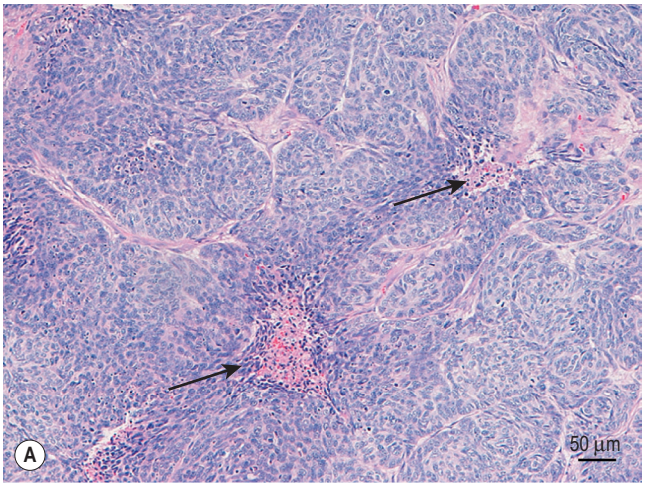
Figure 4.12 Autophagy is lysosome-mediated destruction. Autophagy is the delivery of cytosolic material to the lysosome for degradation/recycling. Three major pathways for lysosomal delivery are known and, as a result, are separated into three classes of autophagy. Microautophagy is the direct invagination of the lysosomal membrane, which engulfs cytosolic material resulting in a vesicle that pinches into the lumen of the lysosome and is subsequently degraded. Chaperone-mediated autophagy is the direct targeting of proteins via a *cis*-peptide sequence (KERFQ) by the chaperone Hsc73, which then unfolds and translocates the protein into the lumen of the lysosome for degradation by Lamp2a and Hsc73. Macroautophagy results from the formation of a double-membrane vesicle (autophagosome) that can engulf both bulk cytoplasm and organelles, such as mitochondria. Once formed, the outer membrane of the autophagosome then fuses with the lysosome delivering the inner vesicle and its contents for degradation. *(Figure reprinted from Dorsey FC, Steeves MA, Cleveland JL. Apoptosis, autophagy, and necrosis. In: Mendelsohn J, Howley PM, Israel MA, et al., eds. The molecular basis of cancer, 3rd edn. Philadelphia: WB Saunders; 2008: 213 (Fig. 15.6); copyright 2008, with permission from Elsevier.)*

Immune evasion

In normal circumstances, immune surveillance is responsible for surveying the body for malignant cells and then, having identified them, destroying them. The evidence that immune surveillance is an important aspect of the defence against tumours is supported by the fact that tumours, in humans at least, are far more common in individuals that have degrees of immunocompromise. However, in spite of this, tumours are still a frequent occurrence in individuals with a normal immune status; this confirms that there must be ways in which the tumour evades the immune system. The reality is that there are no shortages of the mechanisms that tumour cells use to outwit the defences of the host and can find ways of surviving even when there is a fully intact host immune system.

In order to survive either within the tissues or in the lymphovascular channels during metastatic dissemination, tumour cells have to evade the hosts' immune processes. Escape from immune surveillance or immune evasion can be achieved in a number of ways (Fig. 4.14). It is likely that several mechanisms co-exist in any particular tumour type and circumstance and so these defined processes may be up- or downregulated in any particular case:

- *Selective 'evolution' of cloned cells*: Clones that have a strong immunogenicity will naturally be eliminated, whilst those that have a strategy to avoid the immune system will survive. This may simply reflect an evolutionary selection of the cell that has the best survival strategy. Once that clone has been selected, it will continue to develop along the same Darwinistic lines through sequential mutations and generations. Once a tumour starts growing, it seldom stops and the first series of mutations are therefore widely viewed as the critical ones.



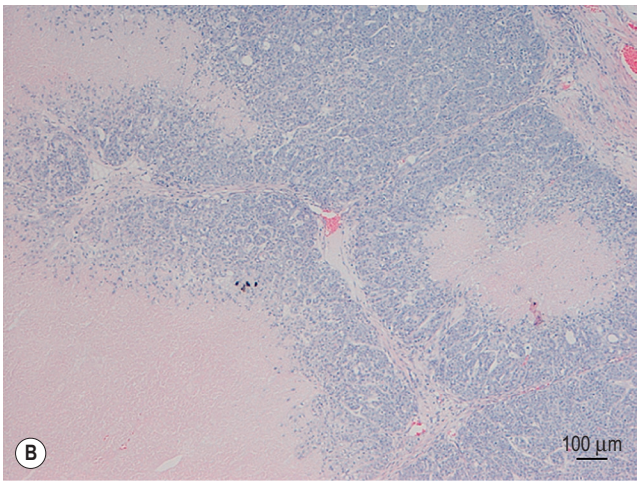


Figure 4.13 Basal cell and mammary carcinoma. (A) Basal cell carcinoma with multifocal small areas of necrosis (arrows) characterized by hyper-eosinophilia and loss of cellular detail, and fragmentation of nuclei (karyorrhexis, karyolysis) (×20). **(B)** Mammary carcinoma with multifocal extensive necrosis, characterized by complete loss of cellular detail and increased eosinophilia (×4).

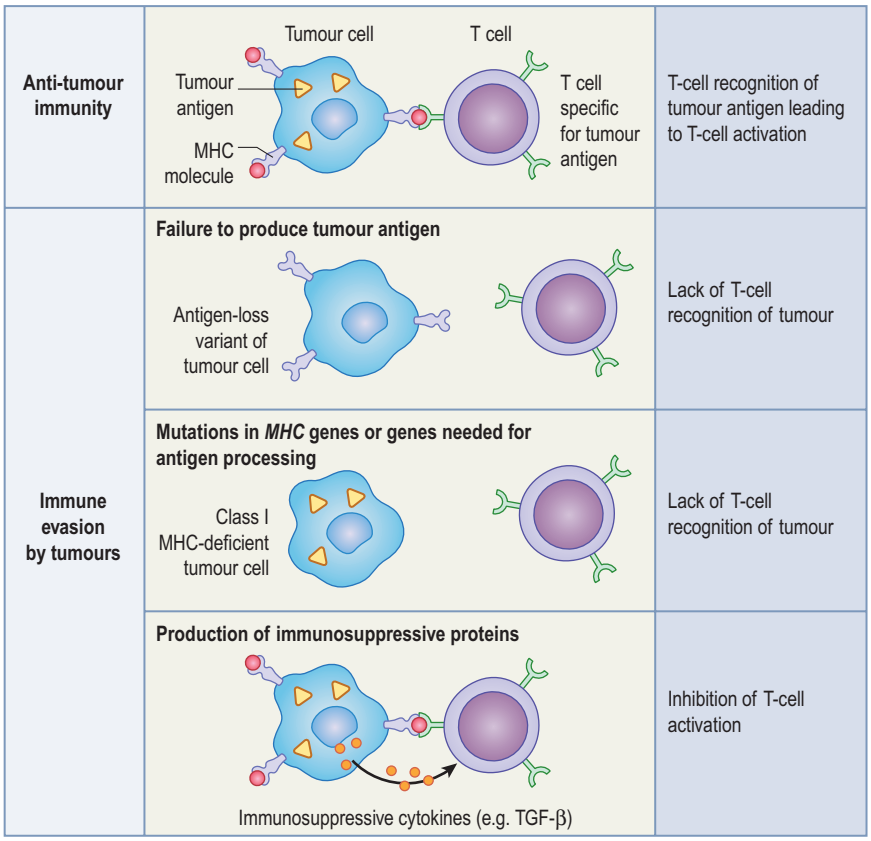


Figure 4.14 Mechanisms by which tumours evade the immune system. Immune evasion is a cornerstone of the pathogenesis of cancer. Loss of recognition of the cancer cells is largely but not exclusively an immunological phenomenon. Normally, tumour cells would be recognizable by T cells and the cell would be destroyed by one means or another. However, where the T cells fail to recognize the antigenic variant of the tumour cell, or where mutations in *MHC* result in an MHC class I deficient tumour cell or where tumours produce immunosuppressive proteins (so-called shield proteins), the immune system will not recognize the cells and so they will be left to replicate unmolested. *(Figure reprinted from Abbas AK, Lichtman AH. Cellular and molecular immunology, 5th edn. Philadelphia: WB Saunders; 2003: 319; copyright 2003, with permission from Elsevier.)*

- *Reduced expression of tumour antigens*: The tumour cells may have masked or suppressed cell surface antigens and this may be a result of excessive production of (normal) autogenous glycocalyx molecules that naturally 'sheath' the tumour cells; they produce a self-masking complex of chemicals that militate against immune recognition and, effectively, this camouflages the cell. Where significant changes occur in the glycocalyx of cancerous cells, the immune system may become capable of recognizing and destroying them, but if the glycocalyx is 'normal', the cells could evade the immune system effectively.
- *Reduction in major histocompatibility complex (MHC) expression*: Tumour cells may fail to express normal levels of MHC class I molecules and so would be capable of evading attack by cytotoxic T cells. Cytotoxic T cells simply overlook the tumour cells because there is no signal to recognize them.
- *Production/overexpression of anti-T-cell factors such as transforming growth factor-beta (TGF-β)*: Some of the natural growth factors produced by the immune system may have a paradoxical effect in supporting tumour growth. Activated lymphocytes and macrophages in particular can produce factors that support tumour cell replication whilst suppressing the immune responses.
- *Direct immunosuppressive effects*: It is accepted that many of the potential oncogenic agents, such as radiation, viruses and chemicals, induce concurrent immunosuppression. Tumours can, however, be directly immunosuppressive themselves. For example, TGF-β is a recognized potent immunosuppressant and so the abnormally high expression of this will inhibit tumour immunity. In effect the tumour is self-preserving.
- *'Hiding' from the immune system in 'safe' sites such as the central nervous system in such a way that the host's immune system has no material access*: This is a mechanism that is dependent on intact 'barriers' such as the blood–brain barrier.

Immune evasion is clearly a target for therapeutic measures. Immunotherapy such as interferon or interleukin-2 may exert their positive effects by modifying tumour antigenicity. Monoclonal antibody systems are similarly used to target specific cancer cells and thereby render them immunologically 'visible'. Harnessing and preferably enhancing the natural protective abilities of the immune system and suppressing the tumour's ability to encourage and support tumour growth are significant targets for the management of some of the most problematic tumours, such as the equine sarcoid and the equine melanoma.

An interesting alternative hypothesis for immune evasion has been proposed by Matzinger.[9] This hypothesis recognizes that even though a newly formed tumour cell produces antigens that are not expressed by its normal tissue fellows, there may still be no immune recognition of the potential harm of that cell. There may in fact be no significant intrinsic differences between the dangerous cell and the normal ones. The cells do not trigger the so-called danger signals in the dendritic cells. Matzinger went further by proposing the concept that antigen-presenting cells respond to 'danger signals' – most notably from cells undergoing injury, or stress or 'bad cell death' (as opposed to apoptosis or

controlled cell death). The alarm signals released by these cells let the immune system know that there is a problem requiring an immune response. The so-called 'Danger Model' covers a broad range of cell interactions including normal physiologic events such as maternal/fetal immunity but also many pathological ones, including autoimmunity, cancer treatments and vaccines and transplantation. Matzinger points out that although it offers an explanation of how an immune response is triggered and how it ends, it does not (yet) offer an explanation of why the immune system responds in different ways to different situations. She hypothesized that tissues send signals to the immune system that determine the immune response appropriate for that tissue. This model has not won universal acceptance. Some immunologists believe that the immune response is mainly fuelled by innate evolutionarily-conserved 'pattern recognition receptors', which recognize patterns expressed by microbes such as bacteria and do not see cell death in the absence of pathogens as a primary driver of immune response. These ideas, however, do not explain how the immune system rejects tumours.

The role of calreticulin in tumour development

Under normal physiological conditions, cellular homeostasis is partly regulated by a balance of pro- and anti-phagocytic signals. Recent research has identified that, subsequent to tumour-transforming mutations, a cell may in some circumstances carry the 'seeds of its own destruction', in that it expresses a surface protein (calreticulin) that signals macrophages around it to engulf and destroy it – a sort of 'EAT ME' signal.[10] Calreticulin is a calcium-binding chaperone that has several functions in the immune response. In the endoplasmic reticulum (ER), calreticulin facilitates the folding of major histocompatibility complex (MHC) class I molecules and their assembly factor tapasin, thereby influencing antigen presentation to cytotoxic T cells.[10]

Although calreticulin is normally ER-resident, it is found at the cell surface of living cancer cells and dying cancer and non-cancer cells; calreticulin promotes phagocytic uptake of the cell expressing the protein on its surface. Calreticulin may also be expressed in normal cells that are damaged in any other non-cancerous manner – a mechanism that would encourage cell destruction and self-preservation. Furthermore, increased calreticulin expression was an adverse prognostic factor in diverse tumours, including neuroblastoma, bladder cancer and non-Hodgkin's lymphoma. These findings identify calreticulin as the dominant pro-phagocytic signal on several human cancers, provide an explanation for the selective targeting of tumour cells by anti-CD47 antibody, and highlight the balance between pro- and anti-phagocytic signals in the immune evasion of cancer. Cancer cells expressing calreticulin may therefore simply be 'behaving' in a normal self-protective manner. In this event one might expect the tumour cells to be engulfed and destroyed as part of the overall natural anticancer/anti-damage strategy. In tumour vaccine models, drugs that induce cell surface calreticulin confer enhanced tumour protection in an extracellular calreticulin-dependent manner.[11] However, it does appear that some of the worst types of cancer are the ones that produce the most calreticulin.

Why then are cancer cells allowed to go beyond this stage and further evade the host's immune system? Most cancer cells are in fact destroyed and this may be one of the significant mechanisms for this self-protective process. If this was a totally efficient system, we would have no cancer! However, it appears that a significant proportion of the cancer cells (but by no means all) also display a 'DON'T EAT ME' signal, called 'CD47'. Where this signal is present it appears to prevent macrophage-mediated cell destruction. CD47, which prevents cancer cell phagocytosis by the innate immune system, is highly expressed on several human cancers including acute myeloid leukaemia, non-Hodgkin's lymphoma and bladder cancer. The cells are now able to efficiently evade the host's immune system and, as further mutations occur, to develop into a more dangerous tumour with the same 'DON'T EAT ME' signal (Fig. 4.15).

The significance of this aspect of tumour cell behaviour lies in the possibility of targeting the 'DON'T EAT ME' signals with directed therapeutic measures, such as an

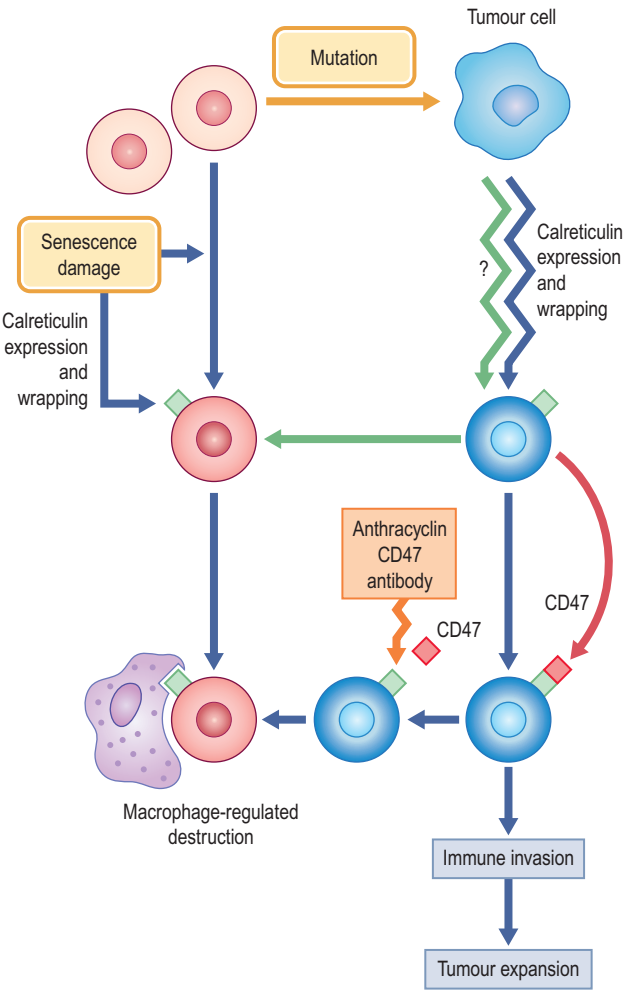


Figure 4.15 Calreticulin. Calreticulin plays an important role in encouraging the macrophage-mediated destruction of senescent and mutated cells. In effect, it imparts an 'EAT ME' signal to the cells destined for destruction. This important protective mechanism is modified by tumour cell expression of CD47. This in effect covers the 'EAT ME' signal with a 'DON'T EAT ME' signal and this, in turn, then prevents macrophage recognition of the mutated cells. The 'DON'T EAT ME' signal can be negated by the use of a specific anti-CD47 antibody or the use of chemicals such as anthracycline. There is little information on this in any equine cancers but it seems plausible that some at least will have this immune-evasion capability, even in the absence of *p53* damage.

anti-CD47 antibody or drugs such as anthracycline; blocking CD47 with a monoclonal antibody results in phagocytosis of cancer cells and leads to in vivo tumour elimination, yet normal cells remain mostly unaffected.[12] This would be a simple way of restoring the immune 'visibility' of the 'EAT ME' signal, so that the tumour cells would be destroyed by macrophages.

Cellular senescence

Cellular senescence stops the growth or replication of cells. Cell senescence is broadly defined as the physiological programme of natural terminal growth arrest, which can be triggered by alterations of telomeres or by different forms of stress. After a fixed number of divisions dictated largely by telomere shortening (p. 30 and Figure 4.11), normal tissue cells become arrested in a terminally non-dividing state called 'replicative senescence'. This process was first recognized in cell culture where cells simply stopped replicating after a defined number of generational divisions (often between 20 and 40 but with a wide variation in the number for different cell types). This phenomenon is also known as 'replicative senescence', the 'Hayflick phenomenon' or the 'Hayflick limit'. The process of natural senescence is largely controlled by the two most potent tumour suppressor genes, *p53* and *pRb*. Mutations in these two genes are by far the commonest changes found, at least in human tumour physiology. It is now confirmed by in vivo evidence that abnormal cell senescence is a pivotal mechanism that constrains the malignant progression of many tumours.

This natural process is assumed to be related to the progressive shortening of the telomeres of the chromosomes (p. 30); this enables the cell to 'count-down' to its state of retirement/senescence. Once the telomeres are shortened to a predefined point, the cell triggers its *p53* gene-related cell-cycle checkpoints. The cell cannot pass into the normal replicative cell-cycle and moves instead to a state of senescence or apoptosis (p. 29). Of course such a defined terminal stage would be counterproductive in germ cell/stem cell lines and so these cells have a sustaining telomerase enzyme. This enzyme is not present in normal somatic cell lines, where replication and repair are not present, e.g. nerve cells.

In most species, cancer incidence increases with age and this is suggested to be fuelled by mutational accumulation and by the age-related changes in tissue integrity that result from the direct functionality of the accumulated senescent cells (Fig. 4.16). This model is well supported in most species, but in the horse it is somewhat less convincing, since the incidence of most of the serious cancer states occur in the middle years of a horse's life. Nevertheless, the contributions that older cells have towards cancer have to be recognized.

Neoplastic transformation involves events that inhibit the programme of senescence and tumour cells were believed, until recently, to have lost the ability to progress though natural senescence – i.e. they were thought to be immortal. However, cancer cells acquire the behaviour of germ cell lines and therefore have limitless replicative potential. It was assumed that cancer cells had to devise a way of preventing telomere shortening and it appears that telomerase enzymes are a critical aspect of cancer cell survival (p. 30). In about 85% of tumours, this evasion of cellular senescence is the result of up-activation of their

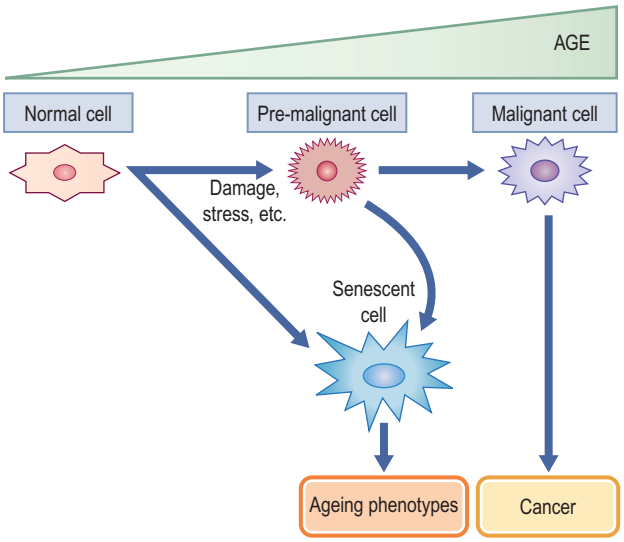


Figure 4.16 Senescence. Both normal ageing cells and tumour cells are influenced by the process of senescence. The natural ageing process induces the process but it can also precipitate mutation into a precancerous state. This possibility is enhanced by the changes within the ageing cell itself and, thus, an ageing phenotypic population of cells develops. Most will be diverted towards apoptosis or autophagy, but a few will mutate and take a path towards cancer development. *(Figure reprinted from Campisi J. Cellular senescence. In: Mendelsohn J, Howley PM, Israel MA, et al., eds. The molecular basis of cancer, 3rd edn. Philadelphia: WB Saunders; 2008: 224 (Fig. 16.3); copyright 2008, with permission from Elsevier.)*

telomerase genes.[8] This simple observation suggests that reactivation of telomerase in healthy individuals could greatly increase their cancer risk.[13]

It has now become apparent that tumour cells can be readily induced to undergo senescence by genetic manipulation or by treatment with chemotherapeutic drugs, radiation or differentiating agents. Treatment-induced senescence, which has both similarities with and differences from, replicative senescence of normal cells, was shown to be one of the key determinants of tumour response to therapy in vitro and in vivo. Although senescent cells do not proliferate, they remain metabolically active and produce secreted proteins with both tumour-suppressing and tumour-promoting activities. Expression of tumour-promoting factors by senescent cells is mediated, at least in part, by a panel of senescence-associated cyclin-dependent kinase inhibitors. Clinical and preclinical studies indicate that expression of different biological classes of senescence-associated growth-regulatory genes in tumour cells has significant prognostic implications. Elucidation of the genes and regulatory mechanisms that determine different aspects of tumour senescence holds out hope for new therapeutic approaches to improving the efficacy and to decreasing the side-effects of cancer therapy.

Cell interactions

Histological examination of tumours will invariably reveal that most masses comprise many different cells – not just the tumour cells and their associated blood vessels. The tumour stromal micro-environment comprises fibroblasts, adipocytes, macrophages, mast cells, vascular elements and a variable mix of inflammatory cells of the innate and

acquired immune system, all embedded and interrelating within the extracellular matrix. It is therefore impossible to ignore the contributions that other cell types and other mediators and bioactive chemicals have on the tumour cells: 'no cancer cell is an island unto itself'. The interaction between the various stromal inhabitants is highly complex and poorly understood at present. Fibroblasts, type-1 collagen, stromal derived growth factor-α, transforming growth factor-β are just some of the possible players in the process. Some will have an enhancing effect on cancer progression in some circumstances but it is also possible that some will have inhibiting or limiting effects also in other circumstances. It is well recognized, for example, that mast cell tumours 'attract eosinophils' into the site and so they may in fact be a predominate cell type; tumour recognition will often require a skilled histopathologist who can recognize the congregations of mast cells with an abnormal morphology and a higher than normal mitotic rate (Fig. 4.17). It is probably safe to say, however, that overall cancer progression is significantly affected by the cells that surround the tumour itself.

Additionally, the altered gene expression of the tumour cells will inevitably influence the behaviour of the surrounding cells. There are the obvious inter-relationships, such as those that control vascularization (p. 48), but all the components in the region will communicate with each other and with the neoplastic cells to contribute to the overall uniquely variable aberrant tumour organ. In many cases, the trigger for neoplastic progression (the critical shifts that move the tumour from a benign to malignant state) may even derive from signals within the stromal micro-environment. Fibroblasts are now recognized as an influence on cancer progression and it has been said that the tumour micro-environment is 'wound healing gone awry'.[14,15] The fibroblasts within the tumour micro-environment are now termed 'carcinoma-associated fibroblasts' and their role in cancer progression may relate to increased expression of proteolytic enzymes and other proteins including S100. This aspect can be used during histological examination to confirm the presence of a cancer state. There are alternative hypotheses for the role of the fibroblast in particular (Fig. 4.18).

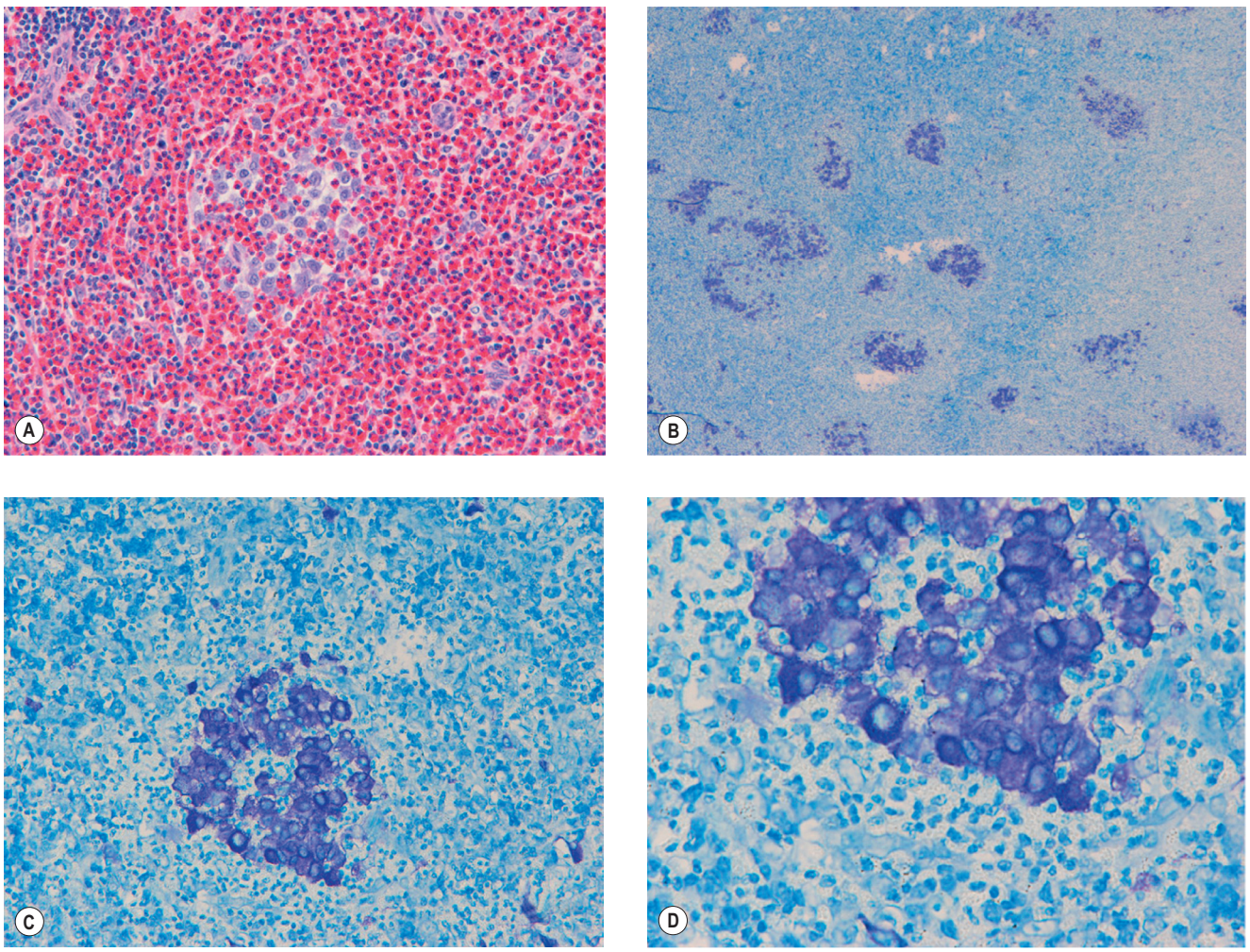


Figure 4.17 The complexity of the relationship between neoplastic cells and normal cells. **(A)** A mast cell tumour of the eyelid showing a large accumulation of eosinophilic polymorphonuclear cells (×100). It is easy to misinterpret this unless a special stain (in this case toluidine blue) is used to identify congregations of mast cells **(B)** (×100) and then to examine those specifically for evidence of neoplastic change (**C,D** ×200 and ×400, respectively). This illustrates the complexity of the relationship between neoplastic cells and normal cells; in this case, the mast cells result in an abnormal accumulation of eosinophils.

It is also clear that matrix metalloproteinase enzymes (MMPs) play an important role in the remodelling of the extracellular matrix (ECM) of the tumour micro-environment. Epithelial to mesenchymal transition occurs when there is break down of cell–cell adhesion and decreased expression of epithelial markers and increased expression of mesenchymal markers, such as vimentin. These changes are associated with increased motility of the abnormal cells and this is another histologically useful characteristic. MMPs support cancer progression by direct stimulation of tumour replication and also by regulating apoptosis, inflammation, angiogenesis, invasion and metastasis. Mainly, the issue is that they are overexpressed and the MMP profile in the environment of a tumour can be abnormal in many ways; what is certain, however, is that where MMPs are over-expressed there is a significantly higher tendency towards angiogenesis, tumour progression and metastasis.

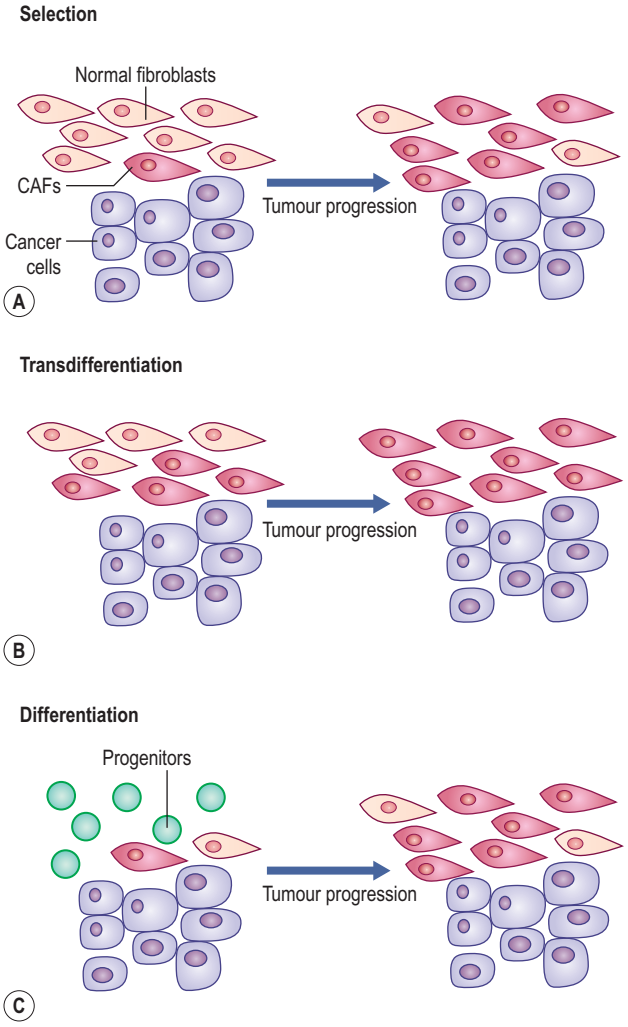


Figure 4.18 Possible models for generation of carcinoma-associated fibroblasts within carcinomas. (A) Clonal selection from a small population of fibroblasts or progenitors that have undergone genetic alterations. **(B)** Transdifferentiation from normal cells, such as normal fibroblasts. **(C)** Differentiation from progenitor cells. *(Figure reprinted from Orimo A, Weinberg RA. Stromal fibroblasts in cancer: a novel tumor-promoting cell type. Cell-cycle 2006; 5:1597–1601, with permission.)*

Carcinogenesis

Ever since the medical and veterinary professions have recognized cancer, there has been a determined search for its causes – '*What causes cancer*?' – in the expectation that if a 'cause' could be identified, it could be prevented, avoided or at least treated specifically.

Carcinogenesis or oncogenesis (literally 'the creation of cancer') is a process by which normal cells are transformed into cancer cells. It is generally true that genetic mutations form the basis of cancer (see above) but whilst it is accepted that spontaneous mutations do occur in all living creatures, the vast majority of these do not have any harmful effects. Spontaneous mutation and inherited mutations do certainly contribute to the overall pathology, but the large majority of significant mutations are acquired, probably in response to environmental mutagen challenge. Carcinogenesis is characterized by a progression of changes that occur at cellular and genetic levels that ultimately re-programme a cell to undergo uncontrolled cell division and therefore produces a malignant mass. The concept of multistep carcinogenesis and the two-hit hypothesis are the basis of modern cancer understanding.

The Knudson hypothesis

Also known as the 'two-hit hypothesis', the Knudson hypothesis suggests that cancer is the result of accumulated mutations to a cell's DNA and is possibly the most basic approach to the significance of mutations (Fig. 4.19).[16] In

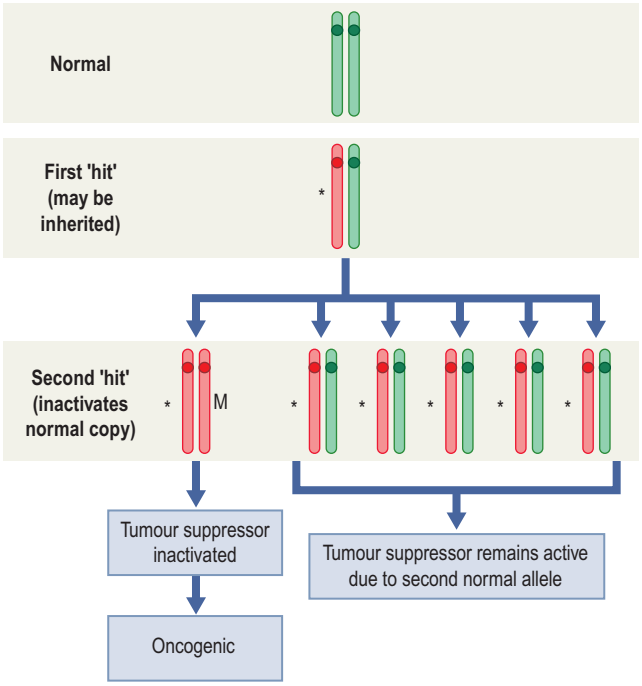


Figure 4.19 The so-called 'two-hit hypothesis' of cancer pathogenesis. This probably applies to most cancers in the early stages, but genomic instability predisposes further mutation and progression. It is most unlikely that a single mutational change will result in a dramatic and serious tumour, although that has been described in some rare tumour types. *(Figure reprinted from Haslett C, Chilvers ER, Hunter JAA, Boon NA, eds. Davidson's principles and practice of medicine, 18th edn. Edinburgh: Churchill Livingstone; 1999: 21 (Fig. 1.17); copyright 1999, with permission from Elsevier.)*

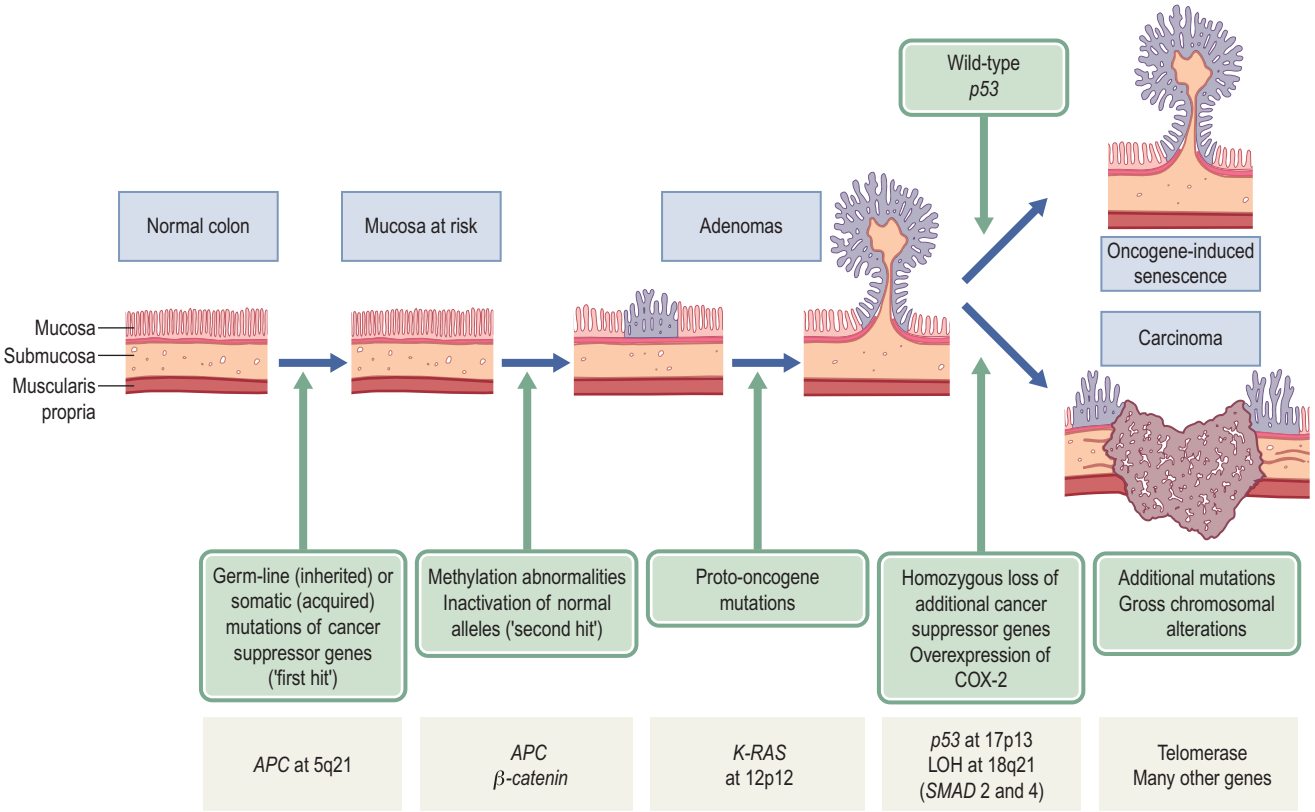


Figure 4.20 Molecular model for the evolution of human colorectal cancers through the adenoma–carcinoma sequence. Although *APC* mutation is an early event and loss of *p53* occurs late in the process of tumorigenesis, the timing for the other changes may be variable. Note also that individual tumours may not have all of the changes listed. Top right, cells that gain oncogene signalling without loss of *p53* eventually enter oncogene-induced senescence. *(Figure reprinted from Kumar V, Abbas A, Aster J. Robbins and Cotran pathologic basis of disease, 8th edn. Philadelphia: WB Saunders; 2010: 308 (Fig. 7.40); copyright 2010, with permission from Elsevier.)*

order that a mutation is expressed, it probably has to be reflected in both alleles of the gene. A single gene mutation, which might be inherited or acquired, is not enough to trigger the progressive development of a tumour. Where a single gene is inherited, the patient can be assumed to be 'more liable' to cancer development, since the next stage will require that only one mutation occurs. There are difficulties with this approach, since the triggering mutation would have to affect the same gene on the other chromosome – random mutations would possibly make that less likely. This may, however, explain why the development of tumours in 'susceptible' families may take many years to develop. DNA repair genes are clearly a significant target for carcinogenic agents.

It is now thought likely that whilst the two-hit theory applies for the basic conversion of a cell to a neoplastic genotype, further mutations are almost inevitable, since the most prominent genes that are mutated are the 'housekeeper genes' – *p53* and its family (p. 26). There are likely to be epigenetic factors involved as well, which alter the expression of genetic changes.

The multistep carcinogenesis proposal

The multistep carcinogenesis proposal involves alterations in sequential steps involving mutational changes that overcome the cell-cycle's self-regulatory mechanism. This then leads from early mild changes that may or may not be clinically detectable to the development of metastatic tumours (p. 52) (Figs 4.20, 4.21).

Recent advances in molecular biology have increased our understanding of cancer and the malignant process. It is now widely recognized that cancer results from mutations of genes that regulate cell division and cell growth. The scope for genetic mutation is very high given the number of cells that are undergoing cell-cycle processes at any time and, in addition, some of the genetic abnormalities can be inherited. Fortunately, only a few genes are integrally involved in the development of cancer.

A large number of agents cause genetic damage and this can be of a type and severity that can result in neoplastic transformation of individual cell types; usually the faster dividing cells are thought to have an increased susceptibility to mutation (p. 47). It is generally accepted that some cells are more liable to induced mutations than others.

Mutations are taking place in all cell types all the time – but few have any harmful consequences. Mutations impart the genetic instability that in turn makes the cell more sensitive to further insults, and mutations become increasingly likely as cells undergo multiple genetic alterations.

Tumour growth and progression is a tissue and cellular phenomenon. The individual cells that make up a multicellular organism are governed by endocrine and paracrine signals and messages deriving from local and remote sites, and affect cell surface receptors. These receptors

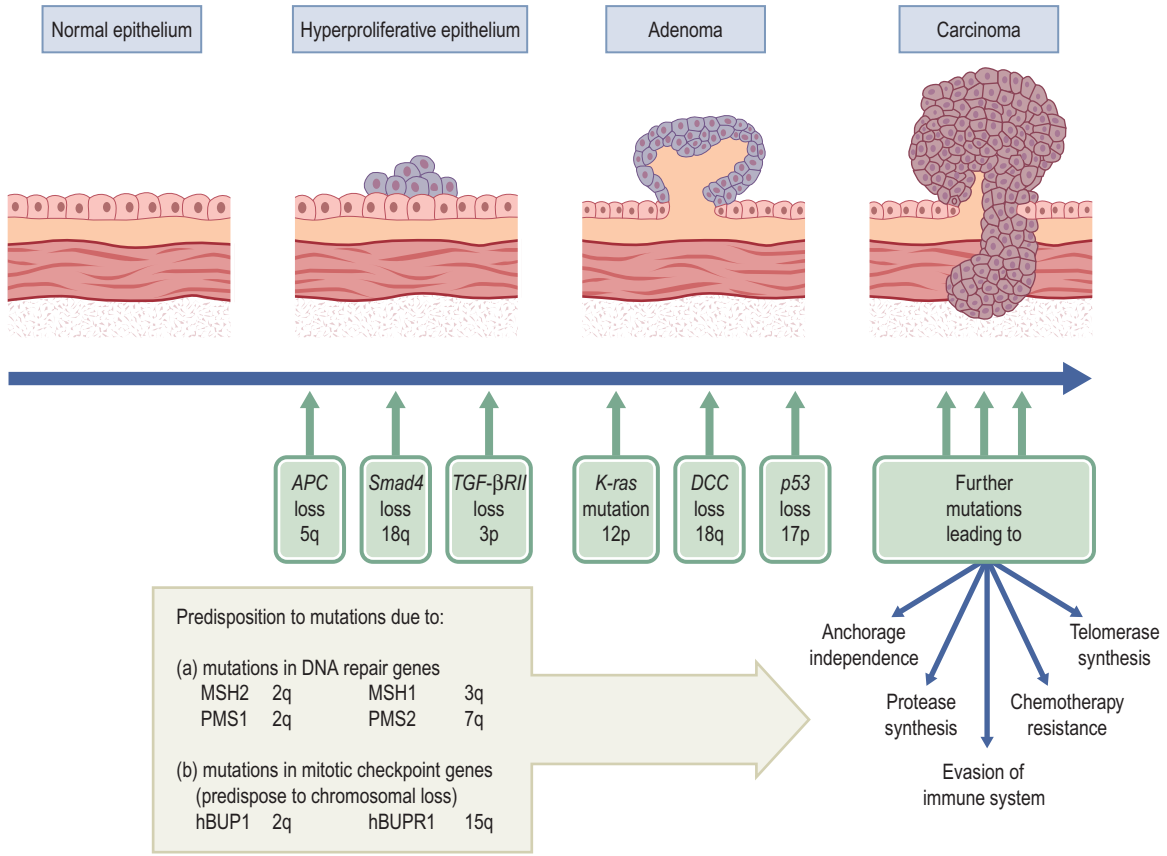


Figure 4.21 The multistep origin of cancer. Molecular events implicated in colorectal carcinogenesis. *(Figure reprinted from Haslett C, Chilvers ER, Hunter JAA, Boon NA, eds. Davidson's principles and practice of medicine, 18th edn. Edinburgh: Churchill Livingstone; 1999 (Fig. 1.18); copyright 1999, with permission from Elsevier.)*

ensure the survival and replicative properties of the cell. Carcinogenesis is a multistep process at both the cell and genomic levels. A malignant cancer significantly alters function and characteristics, including excessive growth and cell numbers, local invasiveness and the ability to metastasize to remote body sites. The fundamental point about these characteristics is that they develop sequentially and this process is termed 'tumour progression'. A tumour therefore may progress from a mild benign change with low implications to a faster-growing, larger mass and then to an invasion of the local region; finally, tumours develop the ability to metastasize to remote sites – it is the two latter stages that are ultimately the most dangerous. It is also important to realize, however, that even in the early stages, there may be functional issues that could have profound effects on remote organs and body functions. Functionality of a cell is dependent on the degree to which it is differentiated, i.e. the degree of normality of its function. Endocrine tumours can be benign but highly functional. This is usually associated with an early progression stage in the development of a tumour condition (p. 66). Some carcinogens also interfere with cell division, by changing the structure or number of chromosomes in new cells after cell division.

Carcinogens can be classified as genotoxic or non-genotoxic:

- *Genotoxic carcinogens*: In this case, the carcinogens interact physically with the DNA to damage or change its structure. Genotoxins cause irreversible genetic damage or mutations by binding to the DNA. Genotoxins include chemical agents, such as *N*-nitroso-*N*-methylurea (NMU), and significantly also many of the drugs used in cancer therapy as well as ultraviolet light and ionizing radiation. Certain viruses can also act as carcinogens by interacting with DNA, and this induction is a recognized primary origin of neoplastic transformation.
- *Non-genotoxic carcinogens*: These alter the way in which DNA expresses its information without direct changes in the DNA structure; they act in other ways to promote abnormal cell growth and replication. These carcinogens may also cause cell-cycle disruption when the cell or tissue is more susceptible to DNA damage from another source, such as hormones and some organic compounds. Examples of non-genotoxic carcinogens or promoters of tumour transformation include heavy metals, such as arsenic, and hormones, such as oestrogen.

Carcinogens are conventionally categorized in different levels, based on their potential to cause cancer in humans. Whether the same criteria can be applied to horses is unknown, but it is surely true that cancer is generally less prevalent in horses than humans and this may reflect the more natural lifestyle of horses. Exposure to chemicals, radiation and viruses that promote progression of a cancer is far more likely in a human population with tobacco smoking, alcohol and other insults adding to the risk.

The chain of events involved in carcinogenesis can be triggered by one or more of the three classes of carcinogens. These are responsible for the mutational changes and include chemical carcinogens. However, straightforward exposure to a carcinogen does not necessarily mean that cancer will occur – other significant factors, such as the type of carcinogen, the duration of the exposure and the frequency of exposure are additional factors that have an effect on the likelihood of cancer development. Carcinogen exposure is not always 'obvious' and exposure to environmental conditions, chemicals and viruses can be covert. Once a tumour develops, there is an inevitable 'search' for the possible causes and almost anything can potentially be blamed. For example, there are anecdotal reports of clusters of lymphoma cases that have occurred in horses grazed in close proximity to industrial factories, nuclear installations, high-voltage electrical power lines or polluted water courses. It is impossible to either confirm or to deny the role of any of these circumstances as a cause or to predict that cancer will occur under any defined conditions.

The mechanisms for the development and progression of cancer are the important factors for clinicians, since by the time the patient is presented with a cancerous condition, the specific cause of the process may not be detectable. Exposure to radiation many years previously may ultimately lead to tumour transformation and it is one of the enigmas of cancer medicine that there is no predictability in terms of the time or type of mutation and the tumour extent. If a tumour is caused by radiation exposure, it may well have taken place many years before the tumour became obvious.

The majority of the carcinogens identified in human medicine would not normally be a threat to horses, e.g. smoking and alcohol consumption, but it is likely that others might well act in a similar fashion. It is not recorded, for example, whether pit ponies working in mines had a higher incidence of cancers than the normal population. Exposure of horses to high environmental radiation appears to have less effect than the same exposure applied to humans; sentinel horses within the maximal danger zone of nuclear accidents seem to have remained ostensibly healthy with a breeding population that appears, at least from outside, to be unaffected. The wild horses (and other animals and birds) in the region continue to breed without obvious problems, in spite of being patently radioactive themselves. Humans exposed to a fraction of the radiation that the horses receive are reported to have had a high incidence of cancers. It is clear that the dose of radiation and its intensity are important factors, since immediately following the disasters, both the animals and humans suffered badly.

Chemical carcinogenesis

In 1775, Sir Percivall Pott reported a strong association between exposure to soot and the development of scrotal cancer (later found to be squamous cell carcinoma) in chimney sweeps.[17] This was the first occupational link to cancer and the first demonstration that a malignancy could be caused by an environmental chemical carcinogen. Since then, a wide variety of carcinogenic chemicals have been identified, some having more or less convincing evidence of carcinogenetic properties. Interestingly, some of these are also the chemicals that are used to treat some forms of cancer! As more and more chemical carcinogens are identified, the paranoia of avoidance increases; fortunately, for all the induced changes that chemicals cause, the proportion of cells that become cancerous is minute. However, there are undoubtedly some very dangerous materials that have much more potent cancer initializing and promoting effects on living cells.

Over the years since the relationship between human scrotal cancer and chimney sweeps was established in the eighteenth century, many chemicals have been identified as 'putative' or 'certain' carcinogens either by in vitro 'proof' of cause and effect or in vivo by circumstantial supposition. Whilst some aromatic hydrocarbons and other chemicals are recognized carcinogens, naturally occurring plant alkaloids are also implicated. The role of tobacco in human cancer is an established incontrovertible fact. Ironically, many of the chemicals that are used to treat cancer and other conditions also have carcinogenic properties – it is their ability to alter DNA or the metabolism of cells that provides their therapeutic effects, but few have specific effects only on the cancer cells.

Carcinogenesis, however instigated, is a multistep process and chemical carcinogenesis is no different (Fig. 4.22). A series of changes have to occur before a cell will become truly malignant.[18] However, most chemical carcinogens have a 'hit and run' effect – the chemical does not need to persist and, in addition, it can cause changes in several genes at the same time. This process is probably best regarded as infinitely variable.

Chemicals exert their carcinogenic effects either by direct action on the DNA of cells or by indirect action through metabolic or enzymatic conversion to a chemical that will have a carcinogenic effect. The recognized stages of chemical carcinogenesis are:

1. Initiation
2. Promotion
3. Progression.

Each of these stages is characterized by morphological and biochemical modifications and result from genetic mutation and/or epigenetic influences. The genetic modifications include the natural or induced mutations in genes controlling cell proliferation, cell death and DNA repair, i.e. mutations in proto-oncogenes and tumour suppressing genes (p. 23). The epigenetic factors, also considered as being non-genetic in character, can also contribute to carcinogenesis via epigenetic mechanisms, which silence gene expression. The control of responses to carcinogenesis through the application of several chemical, biochemical and biological techniques facilitates the identification of those basic mechanisms involved in neoplastic development. There are likely to be far more carcinogenic changes than are recognized – the vast majority result in non-viable or repairable changes in DNA. Fortunately, carcinogenesis is probably very inefficient but it might also be that natural immune and genetic cell-cycle controls could be said to be very efficient. The outcome of this is that cancer is still a rare event, even though many chemicals have the potential to cause cancer changes. So long as the repair and proapoptotic mechanisms are not affected, the chances of progression to a malignancy are very low.

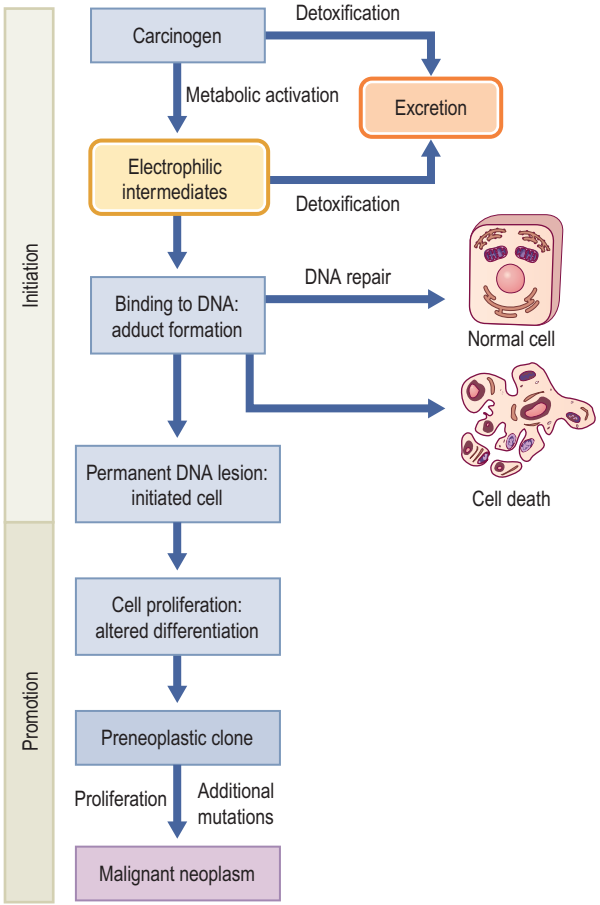


Figure 4.22 The multistep nature of chemical carcinogenesis. The multistep nature of chemical carcinogenesis can be usefully divided into initializing changes and changes that promote and progress the changes to become true tumours. There are repeated control points at which the process can be halted, provided that the mechanisms to do this are not themselves impaired. *(Figure reprinted from Kumar V, Abbas A, Fausto N. Robbins and Cotran pathologic basis of disease, 7th edn. Philadelphia: WB Saunders; 2004: 321 (Fig. 7.49); copyright 2004, with permission from Elsevier.)*

- *Initiation*: This arises from cell exposure to a sufficient concentration of carcinogen for a sufficient time. The initiation process is not enough on its own to cause transformation – the cell is rapidly rendered liable to change. The extent of alteration can be very minor and there may be no material alteration in cell behaviour, but the DNA change is permanent and has memory – it is sustained through successive cell-cycles. Chemicals that initiate carcinogenesis are very diverse in structure and effect. These chemicals fall into two significant categories:
  - Those with strong direct effects primarily on DNA, but also possibly on RNA or other intracellular proteins. Often the damage is so severe that the cell will die but the dangerous circumstances are clearly when the damage is sub-lethal.
  - Indirect pro-carcinogens, which require metabolic conversion to ultimate carcinogens capable of transforming cells to a cancer state. This may take several metabolic steps and so is highly dependent on the individual responses and metabolic state of the host. Many of the chemicals are fortunately detoxified and then excreted before they can actually cause any serious damage. The healthy function of the liver is pivotal in this respect and particularly for chemicals that are ingested. Contacted chemicals and inhaled chemicals may be distributed widely before the liver has any chance of detoxifying them. Most of the known carcinogens are metabolized by cytochrome P450-dependent mono-oxygenases; the genes that encode for these are polymorphic and so individuals may have lesser or greater capacity to metabolize potential carcinogens and therefore greater or lesser liability to carcinogenic changes.
- *Promotion and progression*: Initiation by itself is not sufficient for tumour formation. Promoters are chemicals or bioactive products that support the continued survival and proliferation of the initiated/mutated cell. The promoters 'raise the bar' by inducing tumorigenic changes in previously initiated cells. The promoters themselves cannot harm cells that have not had an initiating stage. Usually their effects are reversible. The promoters also support and sustain progression of the tumour – the more stimuli there are and the longer they apply, the greater the progression will be. Initiated and normal cells respond differently to the activity of the promoters – usually the mutated cells are more responsive to the promotional effects and so they expand and replicate faster than normal cells, an effect that is probably a result of the loss of controlling/braking effects on cell-cycle progression.

Table 4.2 Some of the known or suggested chemical carcinogens that might possibly be responsible for tumour transformational mutations in horses

Agents	Natural/chemical	Therapeutic agents
Alkylating/acylating	Dimethyl sulphate	Cisplatin/carboplatin Cyclophosphamide Chlorambucil Melphalan Lomustine Mitomycin C (secondary)
Aromatic amines/dyes	Naphthalene	Indicator dyes
Plants/minerals	Pyrrolizidine alkaloids Asbestos	
Microbial products	Aflatoxin B Griseofulvin	
Drugs	Insecticides/fungicides	

This list is largely extrapolated from other species but includes chemicals that horses might contact.

Whilst the majority of direct-acting chemical carcinogens are inorganic or organic chemicals that have alkylating and acylation properties, there are some that are plant alkaloids or microbially derived organic compounds such as aflatoxins (Table 4.2). Some of the latter are used as drugs and include griseofulvin; many of the alkylating chemotherapeutic agents are by definition mutagenic and so potentially carcinogenic in turn (see p. 129). Examples of

these 'carcinogenic' therapeutic drugs that are used in equine practice include: cisplatin, 5-fluorouracil and mitomycin C.

Radiation carcinogenesis

All high-energy radiations, including ultraviolet radiation (present in sunlight), X-rays and gamma radiation, are potentially carcinogenic. Electromagnetic ionizing radiations (X-rays and gamma rays in particular) and particle radiations (alpha and beta rays) are capable of causing significant mutations in cells. The nature of the emitted radiation (alpha, beta, gamma or neutron and the radioactive strength), its consequent capacity to cause ionization in tissues and the magnitude of radiation exposure, are the main determinants of the potential hazard. Low-energy waves, including radio waves, microwave radiation, infrared radiation and visible light, are generally not thought to be capable of inducing any tumours in their own right.

Ionizing radiation causes DNA damage and is therefore positively mutagenic; this in turn necessarily makes it also, potentially at least, carcinogenic to any tissue in the body. It is suggested that radiation damage is more likely to cause loss of DNA repair and tumour-suppressor genes and, clearly, this will create a circumstance that will tend to produce genomic instability and consequent malignancy. However, in common with other carcinogens, interactions and additional carcinogens may be required in many circumstances. Low-level ionizing radiation may induce irreparable DNA damage (leading to replicational and transcriptional errors needed for neoplasia or may trigger viral interactions), leading to premature ageing and cancer. The inherent instability of the DNA within radiated cells means that other carcinogens may well have a greater likelihood of inducing tumour transformation and ultimately malignancy. The latency period between the exposure and tumour development varies widely. In fact, tumour development may occur many years after the exposure, since its development may rely on secondary events (even including epigenetic factors) that may or may not occur within set time scales. This might in fact be a reason why horses do not seem to be as sensitive to radiation as other species: the reduced overall exposure, the horse's lifespan and its environment may conspire to protect it from radiation-induced malignancy.

However, a single exposure to radiation may in fact be enough to cause tumour transformation or at least sufficient DNA instability to induce cancer. The carcinogenicity of radiation depends of the type of radiation, duration of exposure and the specific penetration of the radiation. For example, alpha radiation has low penetration and is not a hazard outside the body, but alpha emitters are carcinogenic if inhaled or ingested. Marie Curie, one of the pioneers of radioactivity, died of cancer probably caused by repeated high-dose radiation exposure during her experiments.

Rapidly dividing cells in the bone marrow, the intestinal epithelium, thyroid testes, ovary and skin cells are, at least theoretically, particularly sensitive to ionizing radiation. In the horse, intestinal cancer is extremely rare and myeloid tumours are sporadic events that affect horses of all ages, types, breeds and in all geographical locations. Horses exposed to significant long-term ionizing radiation appear to be very resistant to pathologically significant radiation-induced mutations. In the horse, the opportunities for significant radiation exposure is very limited and the experiences of the nuclear accidents suggests that horses may be more 'resistant' to the effects of radiation than some other species. There are no reports of horses having developed cancer after exposure to X-rays or the limited exposures of gamma radiation that may be used therapeutically in radiation therapy. Nevertheless, the risk has to be recognized.

Ultraviolet radiation exposure and particularly prolonged exposure to UV-B light (280–320 nm) is a significant carcinogen in horses and in other species. The general (but not invariable) restriction of the development of carcinoma to non-pigmented skin of horses (especially where the skin is not protected by thick hair) is well recognized by equine clinicians (Fig. 4.23). The mechanism involves significant damage to the *p53* gene family and the DNA repair processes. UV-B light induces malignant transformation through the formation of pyrimidine dimers in the DNA of keratinocytes in particular.[19] If the cell is to be restored to normal, it must be repaired by pathways that are controlled by the p53 and other DNA repair mechanisms. Thus, since the *p53* gene is

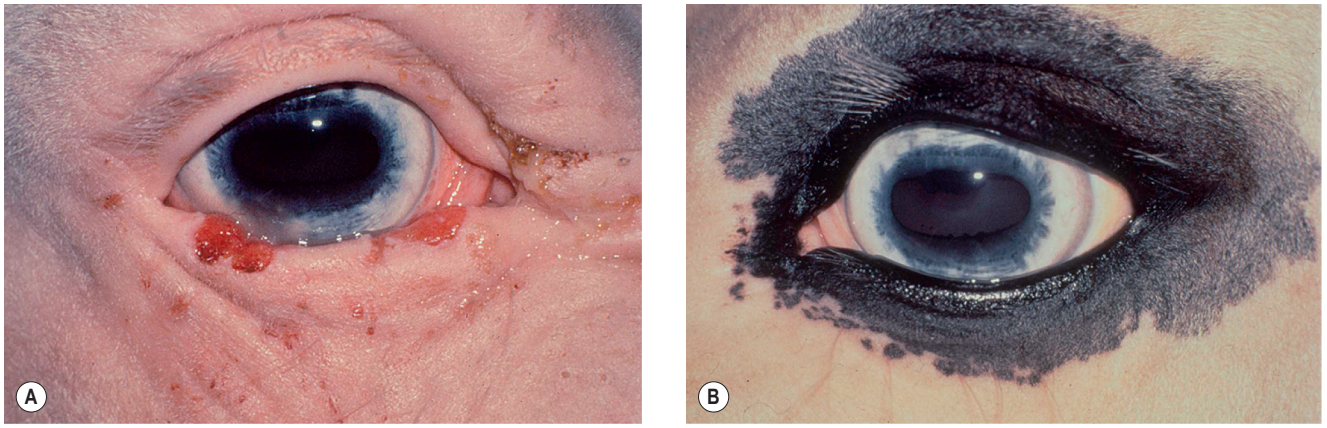


Figure 4.23 Palpebral Carcinoma. Two eyes of the same horse taken at the same time. The albino, non-pigmented right eye **(A)** has developed aggressive destructive carcinoma. The left eye **(B)** is protected from carcinoma by the pigmented skin. Note that the upper lid is spared. It is suggested with some confidence that the carcinogen in this case was sunlight. *(Figures courtesy of Sheila Crispin.)*

itself damaged, exposure to high levels of UV-B light has a high risk of inducing cancer. It appears that black or brown pigmented skin is much less likely to develop carcinoma and so this can be viewed as protective. There are genetic and epigenetic factors that also influence the tendency for tumour transformation from exposure to UV-B light. There do also appear to be breed predispositions apart from the simple relationship to non-pigmented skin or mucous membrane (in the case of the muzzle, the conjunctiva or the cornea). The Clydesdale and Shire breeds of horse appear to be predisposed to light exposure-related carcinoma development.

Melanomas have been strongly associated with the exposure to high UV light concentrations in other species and the suggestion has been made that this is also a significant factor in horses. Given that melanomas are very common in sites where the sun surely does not shine (inside the guttural pouch, under the tail and in the penile and preputial skin), exposure to UV radiation or other wavelengths of light, it seems unlikely in any case to be a significant factor in the pathogenesis of melanoma in horses.

There are plentiful descriptions of malignancy in humans following burn injuries with reports of squamous cell carcinoma, basal cell carcinoma, melanoma and sarcoma being amongst the diagnoses. Burn-induced neoplasia was reported in two cases (carcinoma and fibrosarcoma) and the author has also encountered a squamous cell carcinoma at the site of a severe burn on the back of a horse.[20] All cases reported in horses appear to be delayed by some years (latent burn-induced neoplasm) and so it is probable that the effect from the burn is to increase the likelihood of carcinoma through exposure to other carcinogens. It is unlikely that by itself the burn would be a carcinogen, in horses at least (the concept of a burn-induced co-carcinogen in humans has been suggested).[21] It seems unlikely that the affected tissue would be pre-malignant before the burn, since similar tumours in the affected regions are not reported in normal horses. There is a clinical implication in this, since burn injuries should probably be monitored more closely over the long term and any sites that fail to heal adequately should be biopsied carefully and repeatedly. Early recognition of tumour transformation at the site of burn appears to have a high rate of malignancy, so treatment needs to be instituted promptly.[20]

Microbiological/infectious agents of carcinogenesis

Infectious agents are recognized as a significant aspect of carcinogenesis in many species and there are some important equine cancer conditions that have at least a putative relationship with infectious agents; these include sarcoid and some carcinoma tumours. The recognition of a causative relationship between a tumour and an infectious agent introduces the prospect of prevention by controlling or preventing the infection. Before concluding that an infectious agent is indeed acting as a carcinogen (either directly or indirectly), detailed epidemiology and molecular biology must be applied. Just because an infectious agent is present in a tumour (whether grossly or in a molecular state) does not necessarily mean that it is the driving force behind the tumour progression. Some more ubiquities infectious agents could in fact be 'hit and run' instigators of cancer – they may initiate a change and then disappear without even leaving a molecular fingerprint! There may be many as-yet undetermined agents involved but, by the same token, it is easy to make an infectious agent a scapegoat for the aetiology of a tumour.

There are three major mechanisms by which infectious agents cause cancer. Singularly, little is known about the relevance of these in horses, but it is hard to imagine that the horse might be significantly unique for these not to be potentially involved at least.

1. *Persistent infection/persistence of the infectious agent*: This is a common cause of significant cancer development in other species, including cattle, cats and humans, but may not be common in horses. Where an infectious agent persists, it may cause the slow transformation of DNA through production of reactive oxygen species as a result of sustained macrophage activity. Chronic inflammation may provide opportunities for repeated cycles of cell damage and the combined effects of this challenge to the integrity of DNA coupled with oxidative insults may trigger tumour initiation, promotion and progression. This mechanism may be involved in gastric carcinoma in horses that appears to have a relationship to gastric *Draschia* spp. and *Habronema* infestations. It is not established whether *Helicobacter pylori*, which has been associated with human gastric ulcers and carcinoma, is a significant infection in horses; in any case, gastric carcinoma is an extremely rare disorder in horses (pp. 230 and 459) for which no defined aetiological agent has yet been suggested.
2. *Direct transformation induced by an infectious agent*: This is usually a virus which acts by activation of a cellular oncogene pathway or via the direct suppression of a tumour suppressor gene. In the horse, this is probably one of the mechanisms for the pathogenesis of the equine sarcoid, which is putatively related to the presence of an oncogene derived from the bovine papilloma virus (BPV) (p. 203).
3. *Secondary effects of an infectious agent*: Secondary/systemic or disseminated effects of viral infections can result in direct immunosuppression and consequent failure of the host's immune process to recognize the infected or transformed cell by the immune system. This aspect is the major factor in the significant increase in cancer incidence amongst human HIV patients. It is not reported to be an issue in the horse.

Several DNA and RNA viruses have been shown to be carcinogenic in animal species.[22] The effects are exerted by their mutagenic/insertional genetic changes; to induce a tumour transformation, foreign DNA must be inserted into the genome and that must persist in DNA form down generations of the host cell. Since a single (or less commonly a few) gene(s) is seldom enough to produce neoplastic transformation, further steps are invariably required to create a tumour and these may be epigenetic, endocrine, paracrine, autocrine or chemical in nature. In contrast to the 'hit and run' carcinogenesis of many of the chemicals and radiation carcinogens, viral agents are relatively slow and rather unpredictable. An additional factor is the specific site into which the viral oncogene must be inserted before it will

induce the same response. The mode of virally-induced tumours can be divided into:

- *Acutely-transforming viruses*: In this group the viral particles carry a gene that encodes for an overactive oncogene called 'viral-oncogene (v-onc)' and the infected cell is transformed as soon as v-onc is expressed.
- *Slowly-transforming viruses*: In this case, the virus genome is inserted near a proto-oncogene in the host genome. The viral 'promoter' or other transcription regulation elements, in turn, cause overexpression of that proto-oncogene, which, in turn, induces uncontrolled cellular proliferation. Since viral genome insertion is not specific to proto-oncogenes and because there is a low chance of the insertion being at a specific locus near that proto-oncogene, slowly-transforming viruses have very long tumour latency compared with acutely-transforming viruses, which already carry the viral-oncogene.

Transforming retroviruses carry oncogenes derived from cellular genes that are involved in mitogenic signalling and growth control. DNA tumour viruses encode oncogenes of viral origin that are essential for viral replication and cell transformation; viral oncoproteins complex with cellular proteins to stimulate cell-cycle progression and this led to the discovery of tumour suppressors. Viruses are now accepted aetiological factors of several important human cancers. The infectious nature of viruses distinguishes them from all other cancer-causing factors; tumour viruses establish long-term persistent infections in humans; cancer development is best regarded, as an accidental side-effect of viral replication strategies.[23] Amongst an increasing number of candidate viruses, hepatitis B virus and hepatitis C virus, Epstein–Barr virus, human papilloma viruses, human T-cell leukaemia virus type I are now known to be related to defined cancers. In the horse, this is far less well-defined and, thus far, only one cancer has been identified as categorically associated with a known virus – the equine sarcoid. Recent studies have however identified bovine papilloma virus (BPV) in squamous cell carcinoma sites and even in some non-neoplastic pathological conditions. The role of the virus is not certain, but if it is found to be a significant aetiological factor, there will be considerable implications, since BPV is the only known virus to cross the species barrier and cause disease.

Viral systems support the concept that cancer development occurs by the accumulation of multiple cooperating intracellular events. Perhaps the best recognized of these, in horses, is the equine sarcoid, which has been consistently shown to be linked with various variants of the BPV.[24] The sarcoid is a benign locally invasive dermal fibroblastic tumorous condition, with a wide variety of morphological types (pp. 203 and 545), that occurs commonly in horses, donkeys, mules and zebra. Whilst the true aetiology of the disease remains enigmatic, BPV DNA (type 1 & 2) is frequently demonstrable in equine sarcoid tumour tissues; up to 90% or more of samples show some BPV viral DNA. However, the exact role of the virus in the disease process and its contribution to the phenotypic differences in sarcoids is not known. Viral oncogenes *E5*, *E6* and *E7* transcripts were detected in a high proportion of sarcoid tumours and this study provided the first evidence for a direct involvement of the virus in the pathogenesis of a significant equine tumour.

There are controversial aspects of the relationship, however, with some opinions being more biased towards direct oncogenicity and others towards a reactive (infectious) state rather than a genuine cancer transformation. The relationship between human cervical cancer and the human papilloma virus (HPV) is well established; HPV appears to cause tumours through integration of viral DNA (*E6* and *E7* genes) into the genome of infected cells, making it a true oncogene.[25] This transformation is only step 1 in the process and subsequent steps in the progression of carcinogenesis are required to culminate in the development of a significant neoplasm.

However, there are significant differences in this outcome from the position in horses in respect of BPV. First, the human virus affects humans, while BPV's effects on equidae represent the only known papilloma virus to cross the species barrier. Second, the human circumstance arises from continued presence of the virus itself over a prolonged period of time; again, this is a circumstance that is not reported in sarcoid, since the vegetative virus has not yet been identified. Third, HPV causes carcinogenic alteration in an epithelial cell rather than in a fibroblast. Fourth, and perhaps most notable, prophylactic vaccination for HPV in humans prevents the development of cervical cancer, whilst vaccination of horses with BPV has no detectable protective effect against the subsequent development of sarcoid. It is important to point out that there is also no seroconversion to BPV in horses with sarcoid, so the relationship between the virus and the tumour is probably best regarded as a true oncogene.

Viruses are usually not complete carcinogens and the known human cancer viruses display different roles in transformation.[23] Many years may pass between initial infection and tumour appearance and most infected individuals do not develop cancer, although immunocompromised individuals are at increased risk of viral-associated cancers. A number of significant pro-carcinogenetic interactions have been identified involving chemicals and viruses.[26]

Certain parasitic worms are known to be carcinogenic in humans, including *Clonorchis sinensis*, and *Schistosoma* spp. There have been anecdotal suggestions that gastric parasites, including *Habronema* and *Draschia* spp., may be associated with gastric carcinoma. Given the frequency of these infestations and rarity of gastric carcinoma, this has to be a tenuous relationship.

Other factors that promote tumour development

- *Age*: cancer is widely regarded as a disease of old age in many species, but in the horse this does not seem to be as important. Many of the major tumour types, including lymphoma and carcinoma, are more prevalent in the middle-aged horse. The reasons for this are far from clear.
- *Diet*: Dietary factors that promote cancer development are not common in horses but gastric carcinoma and intestinal adenocarcinoma may be associated with some dietary components, but are not reported in horses.

- *Stress (mental/physical)*: Anecdotal reports of tumour exacerbation following actual or perceived stress in horses have been made. Often these are focussed on the equine sarcoid, but whilst the concept of stress exacerbation is found in other species, it is very difficult to confirm whether the changes are genuinely related to any or all of the physiological changes associated with the stress response. Concurrent medication with immunosuppressive doses of glucocorticoids is not reported to result in obvious tumour advancement.
- *Concurrent disease*: The role of concurrent disease in oncogenesis in horses is uncertain. Immunocompromise will inevitably have an influence that may support cancer progression but is unlikely itself to be responsible for tumour transformation. Probably, the most well-recognized immunocompromise in horses arises from the pituitary pars intermedia dysfunction (PPID/equine Cushing's disease); in this state a sustained abnormally high concentration of endogenous glucocorticosteroids is present. Whilst affected horses are probably much more liable to viral and bacterial infection, there is no published evidence that they have a higher incidence of cancer transformations than in younger or unaffected horses of the same age.

Medical treatment for concurrent disease may involve the administration of drugs: however, that may very well have a pro-mutational effect. An example of this is the antibiotic mitomycin C, which is known also to be a DNA alkylating drug causing cross-linking and intra-strand abnormalities that could result in cancerous mutations. Cisplatin is another potentially hazardous carcinogen that is used with some frequency in horses (pp. 129 and 146).

Tumour progression and proliferation

It is well established that almost all tumours become more aggressive and acquire greater malignancy potential over time. This phenomenon is called 'tumour progression'. The philosophy that tumours 'get bigger, more difficult and more dangerous if left' has become a dogma of cancer medicine. Whilst it is easy to accept that progression is a common event, it involves a complex of cellular and stromal inter-reactions in which there is an inevitable variability. No two cancers can be expected to behave in an identical fashion, as they progress temporally and spatially. It is accepted that this natural progression (no matter how variable in nature) is the result of sequential changes that result in an overall predictability about the eventual outcome – the common endpoint can be reached via many different pathways. The mechanism for this progression is now known to be a result of the development of subpopulations of cells that differ in their ability to replicate, invade and metastasize. They will inevitably also differ in the degree of differentiation, their response to autocrine, paracrine and endocrine stimuli and, importantly, they may also vary in their susceptibility to anti-neoplastic drugs and radiation. It is easy to view a tumour as being a homogeneous collection of clonal cells but this is far from the case – by the time a tumour is visible (p. 60) it is invariably extremely heterogeneous.

The manner of a tumour's progression through its early stages to its most devastating final outcome is a matter that demands considerable respect! The fear of cancer is completely justified – reference to the term during discussions with an owner will usually trigger a significant response. From a purely lay perspective, cancers are feared because they get 'bigger, more difficult and more dangerous' with time. This is a sentiment that is widely understood by humans in respect of their own health but it is a matter of regret that the same sentiment is not applied to their horses by many owners, – even when they have themselves had first-hand experience of cancer and have had to live under its threat. Understanding how cancer starts and how it progresses are fundamental aspects of clinical medicine.

Tumour progression was first described in 1975 as 'the acquisition of permanent, irreversible, qualitative change in one or more characteristics of a neoplasm'.[27] Basically, changes are now recognized as being alterations in the cell-cycle that have a genetic basis and this has fitted squarely into the understanding of the cell-cycle. The basis for the 'multi-gene' theory of cancer, the 'Nowell Hypothesis', has developed from the pool of cellular research findings in cancer conditions (see p. 24).

Cancer includes a wide number of related diseases characterized by the uncontrolled expansion of abnormal cells. Much of the basis of clinical oncology is founded on the assumption that most cancer cells are immortal, or at least are capable of proliferating indefinitely, and have a tendency to dissemination which culminates in patient morbidity or even mortality.

It is easy to think that the cancer cells are an independent population that behaves in a particularly 'selfish' way in becoming 'parasitic' on the host. However, it is now clear that the micro-environment of the tumour cells acts as a co-conspirator during carcinogenesis and progression. The extracellular matrix is also a significant player in the development of the tumour. Although angiogenesis has been the focus of most attention in this area, the peri-tumoral and even the intra-tumoral stromal micro-environment are recruited to the benefit of the tumour; these could include fibroblasts, adipocytes, macrophages, mast cells, vascular components and, in many cases, inflammatory cells of the innate and acquired immune systems. All these structures have intercellular communication links and they can also link with the neoplastic cells themselves. The stromal micro-environment contributes significantly to the development and indeed the clinical and pathological appearance and behaviour of the tumour.

The progression of a tumour from one of benign and confined growth, to one that is invasive and metastatic, is probably the single most important clinical effect of cancer progression. It remains the major cause of poor clinical outcomes in cancer patients. Invasion and metastasis of tumours is a complex, multistep process that requires tumour cells to progressively alter their ability to adhere, degrade the surrounding extracellular matrix, migrate, proliferate at a secondary site and stimulate angiogenesis. Knowledge of the process has greatly increased and this has resulted in the identification of a number of bioactive molecules that are fundamental to the process. The involvement of these molecules has been shown to relate also to the survival, proliferation and dissemination of

tumour cells. Processes such as tumour cell adhesion, migration and the tumour cell's ability to degrade and escape the primary site are significant. Additionally there is the concurrent requirement for the tumour to develop and sustain its vascular supply through a complex process of angiogenesis. These bioactive molecules may provide important therapeutic targets for additional therapies in controlling the process of invasion and metastasis.

The mutation selection hypothesis of tumour progression is one that is usually viewed as a genuine possibility to explain the progression of a tumour from a single cell to an overwhelming neoplastic disease. It hinges on the concept of genetic instability within cancer transformed cells.[28] The progressive genetic fragility and instability of the transformed (mutated) cells in turn provide a further susceptibility to additional mutational changes with relatively less aggressive oncogenic stimuli. It is fortunately likely that this process of progression is not very efficient. Probably the majority of the cells undergoing mutational progression would be unable to survive against the gradient of the immune system and the direct effects of the mutation on the cell itself but those that could survive would be 'fitter' and therefore more likely to develop into phenotypically recognizable clones with a consequent cell behaviour pattern that might be more dangerous to the host animal. This encourages a random generation of variants within the population of tumour cells (Fig. 4.24).

Genetic heterogeneity requires divergence of single transformed cells into wider phenotypes with distinct clones of progeny. Under this theory of 'random genetic fragility', it is perhaps hard to understand why tumours of the same basic type do not have much more variation through progression. It could in contrast at least go some way to explain why there are often very subtle differences in tumour physiology and therapeutic response. The staged progression from a locally benign tumour to a locally invasive form and on to a cell with metastatic capability seems almost too prescriptive for a random series of events, but the genetic changes are such that each stage may become more 'likely' as the genetic instability advances. In effect, this widening specialization of clones of cells with different phenotypes mimics the natural development of organ cells from pluripotent stem cells and it may therefore be a predictable series of events that follows some basic instigating factor. At a cellular level, progression appears to follow a sequence.

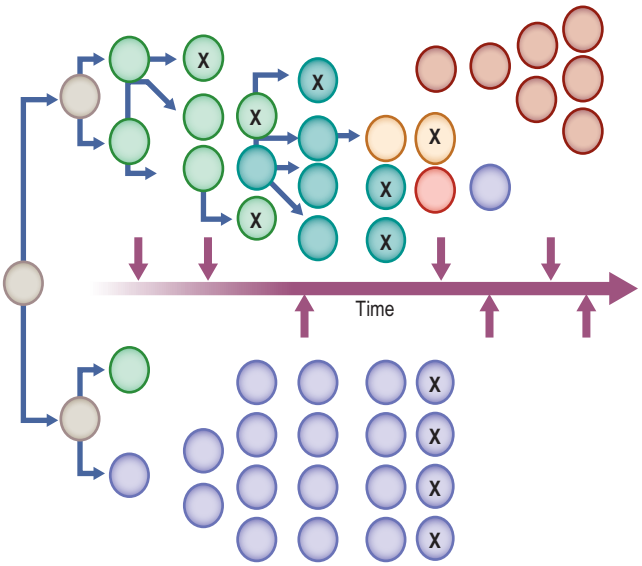


Figure 4.24 Mutation-selection theory of tumour progression. In general, tumour cells have higher rates of mutation than normal cells; however, the mutation rates vary by cell. With low mutation rates, the population is more susceptible to a lethal selective pressure (blue cells). The upper series of cells are generating variants continually, some of which are eliminated by selective pressures (arrows) or some of which are overwhelmed by other cells with more robust growth characteristics (green, X). Note that the cells comprising the population are different over time. The change in population composition is the basis of tumour progression. *(Figure reprinted from Matrisian LM, Welch DR. Invasion and metastasis. In: Mendelsohn J, Howley PM, Israel MA, et al., eds. The molecular basis of cancer, 3rd edn. Philadelphia: WB Saunders; 2008 (Fig. 19.2); copyright 2008, with permission from Elsevier.)*

Angiogenesis

Angiogenesis is a normal process in growth and development, as well as in wound healing and in granulation tissue formation. Indeed, it has been suggested that a wound is a tumour that heals and a tumour is a wound that does not heal. However, although there are inherent similarities in some aspects of the healing process, progression of tumour development is the basis of cancer formation. Angiogenesis is also a fundamental step in the transition of tumours from a dormant state to a malignant one; however, malignancy is not strictly dependent upon it.

Tumours have a singular ability and propensity to support the development and growth of new blood vessels (angiogenesis); this is clearly an essential part of the tumour survival strategy. Once a tumour reaches 1–2 mm in size (1×10^6 cells), it must develop its own blood supply if it is to continue to develop; this is assumed to be the maximum distance that nutrients and oxygen diffusion can 'spread' from blood vessels.[29] Beyond this size, the tumour cannot expand further without its own dedicated blood supply because the cells would die as a result of hypoxia and starvation.

There appears to be a 'switch' or 'trigger' that encourages and supports the growth of new blood vessels at some rather arbitrary stage in the development of many tumours. It is suggested that this is at least partially triggered by a relative hypoxia that supports, and angiogenic gradient that in turn guides, the developing blood vessels towards the tumour. Up to that point, which could be weeks or even years after the cells develop neoplastic properties, the tumour may remain small and then, suddenly, the tumour appears to trigger an angiogenic capability. From this point on, the size and aggression of the tumour usually changes dramatically; as neovascularization occurs, the tumour is supplied with oxygen and nutrients in abundance and the newly formed vascular endothelial cells secrete growth factors, including insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). In so doing, they stimulate still further the activity and replication of adjacent tumour cells. The effects become self-supporting and result in an accelerating tumour development. It is now clear that tumours can secrete the entire group of cytokines and bioactive proteins that are required for the formation of new capillaries (Fig. 4.25).

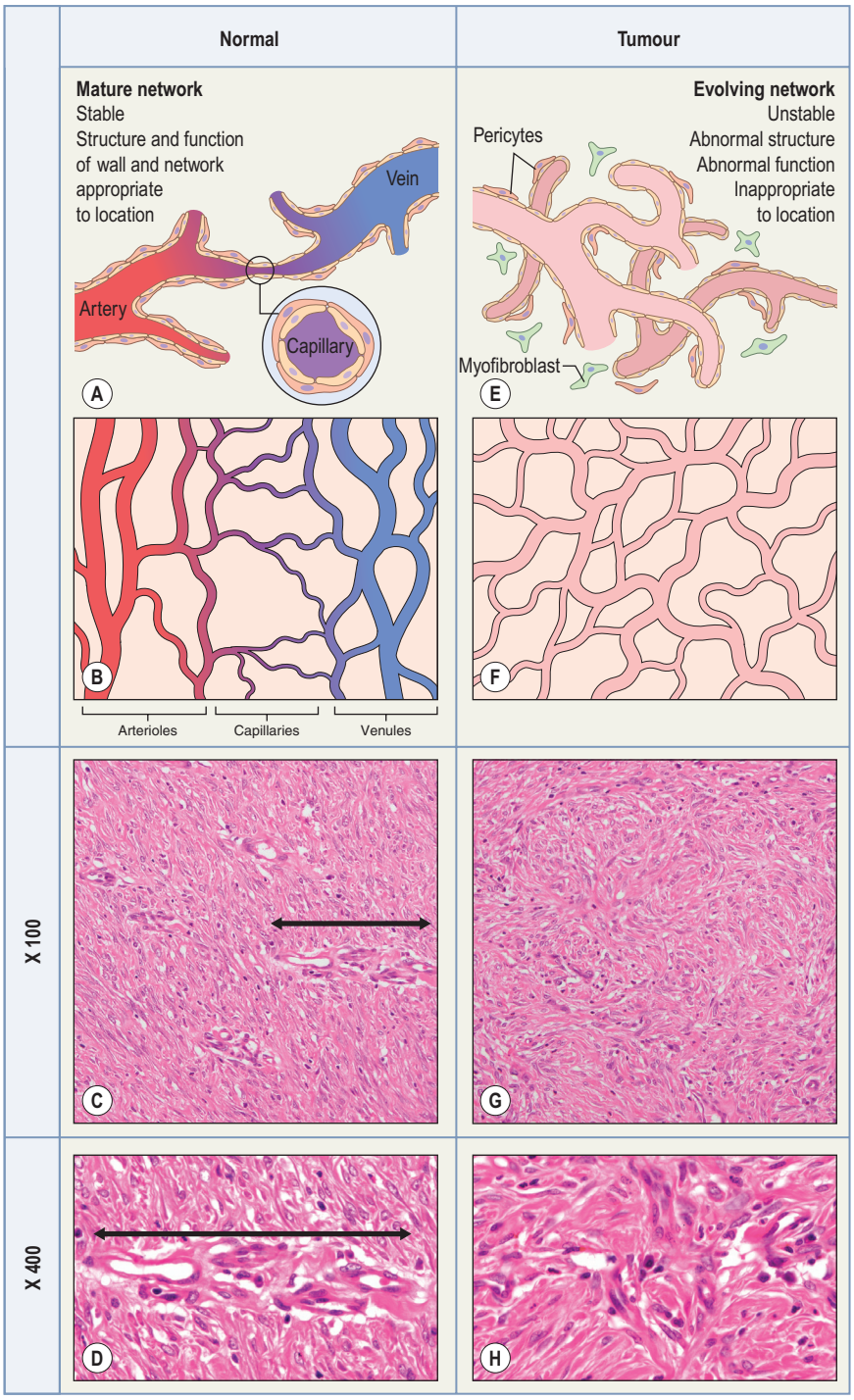


Figure 4.25 Angiogenesis. The process of angiogenesis is a fundamental part of natural tissue formation, tissue repair and of tumour formation. However, there are profound and histologically detectable differences between the various processes and morphology of the blood vessels in these three circumstances. **(A–D)** In natural or normal tissue reparative (non-cancer) circumstances, the formation of new blood vessels is an orderly and coordinated process that effectively links the arterioles and venules with a meshwork of capillaries that ensure even distribution of nutrient and oxygen supply to the tissue involved **(A,B)**. Histologically, the vessels are uniform and arranged in a recognizable manner – usually in parallel lines at right angles to the tissue structures (arrows, **C,D**). This same 'natural' reparative angiogenesis is well demonstrated in granulation tissue, as shown here. This angiogenesis is capable of being 'shut down' when the stimulus for its existence ceases. In order to develop beyond 1–2 mm, a tumour has to have a blood supply; a dedicated blood supply is required to provide for an abnormal tumour nourishment demand and for the invasion and metastatic spread of tumour cells. Angiogenesis is, thus, a necessary biological correlate of malignancy. The process of tumour angiogenesis is governed by an unpredictable and varied complex of normal and abnormal vascular generating growth factors and by hypoxia, which in turn may be induced by rapid tumour cell replication and proliferation. This undefinable and varied 'soup' of cytokines and varying physiological stimuli results in a chaotic formation of abnormal blood vessels **(E,F)**. This chaotic arrangement of poorly structured, thin and often fragile vessels has no meaningful organization **(G,H)** – it seems to occur at random and therefore results in bleeding, tissue hypoxia and even necrosis. These events can usually be detected histologically, with relative ease and the panel of abnormality can be used to deduce some of the clinically important tumour properties. Tumour angiogenesis is perpetuated by continued production of the angiogenic 'cytokine soup' and, as result, does not shut down at all unless the tumour cells are destroyed. *(Figure reprinted from Kumar V, Abbas A, Fausto N. Robbins and Cotran pathologic basis of disease, 7th edn. Philadelphia: WB Saunders; 2004: 310 (Fig. 7.41); copyright 2004, with permission from Elsevier.)*

Here again, the 'loss' of *p53* family of genes plays a pivotal role in cancer progression. Under normal physiological conditions, normally the *p53* gene family plays an important role in the 'rational' development of new blood vessels in normal tissue circumstances with expression of inhibitors of vascular development, as well as repressing the production of pro-angiogenic genes. Loss of the *p53* gene function (p. 26) results in a more permissive environment for the development of new vascular elements. In angiogenesis, *p53* can be viewed as a 'planning officer' who controls the development of a road network and ensures that the building work follows defined quality and planning systems.

Additionally, tumour angiogenesis can occur by recruitment of endothelial precursor cells or by causing budding of existing capillaries (or both). It is easy to assume that because the system is so supportive of neovascularization/angiogenesis that the blood vessels would be 'normal'. The fact is however that they are almost invariably abnormally tortuous and irregularly-shaped. Tumour blood vessels have perivascular detachment, vessel dilation and irregular shape. Thrombosis and necrosis can also be present. These features are always recognized histologically by pathologists examining tumour tissues.

Tumour vessels also grow continuously in contrast to the normal rather static/quiescent nature of natural blood

vessels; it assumed that the angiogenesis is self-fuelling and is, in any case, not completely coordinated and, furthermore, probably lacks the natural inhibitive processes that would provide normal regulation of vessel growth – there is no 'switch-off' mechanism that would limit the growth and extension of blood vessels.

Angiogenesis also plays a vital role in the development of metastases. Without the vascular component, tumour cells cannot readily spread to distant sites (apart of course from lymphatic and direct/contiguous spread (p. 56). Once the tumour has a blood supply, it will usually become much more invasive and will be more inclined to develop the potential for metastasis (the formation of secondary tumours).

The singular importance of neovascularization to the tumour development and progression has been identified as a potential target for therapy. Recent evidence also suggests that treatment modalities such as radiation therapy may actually work in part by targeting the genomically stable endothelial cell type, rather than the genomically unstable tumour cells. New blood vessel formation is a relatively fragile process, subject to disruptive interference at several levels. In short, the therapy is the selection agent, which is being used to kill a cell component. Tumour cells evolve resistance rapidly due to rapid generation time (days) and genomic instability (variation), whereas endothelial cells are a good target because of a long generation time (months) and genomic stability (low variation supporting a degree of predictability of therapeutic intervention). Immunological mechanisms, such as monoclonal antibodies targeting the 'trigger' or 'notch' mechanisms, are being explored widely – there are clear advantages to the reduction in blood supply to a tumour.

Tumour invasion

Tumour invasion is one of the fundamental distinguishing features of malignancy. 'Invasion' is the term given to the ability of the tumour to invade the basement membrane and penetrate the underlying stroma. Typically, the process requires major alterations in cell morphology and phenotype. These changes are invariably mutational and reflect the advancing genetic instability of the tumour cells. Genetic changes through this mechanism result in disruption of cell–cell adhesion.

Both invasion and metastasis are pathological and clinical hallmarks of the natural history of malignant tumours. It is widely recognized that both of these properties represent advanced stages in the progression of a tumour (advanced in this sense may not mean long-standing) and it is accepted that, at least from a clinical perspective, as a rule they have a significantly negative influence on prognosis.

It is convenient to divide the metastatic cascade into three components but this is inevitably oversimplistic. These three main aspects of the process are:

1. Local invasion of the extracellular matrix
2. Vascular dissemination
3. 'Seeding' of tumour cells into remote sites with local clonal expansion (and usually invasion).

Local invasion is an active and dynamic process and it has a major role to play in the clinical and pathological behaviour of a tumour.[30] The process of invasion involves a complex relationship between the tumour cells and the extracellular matrix, as well as the surrounding normal tissue cells. Tumour cells must interact with these components if they are to enter the metastatic/invasion cascade. The first aspect of the invasive process is the breaching of the basement membrane, and then the tumour, having gained access to the extracellular matrix, can start to break down intercellular barriers and extend its growth.

The two components of the ECM (the basement membrane and the interstitial stroma) provide a critical barrier to tumour cell dissemination and invasion. There are both autocrine and paracrine stimuli for the process to be triggered; the cell leaves the primary environment and migrates either locally (invasion) or remotely (metastasis).

Invasion. Invasion is an active process that can be usefully divided up into five main sections – each of which is spatially and temporally related to the others (Fig. 4.26):

1. *Modulation of tumour cell adhesion through active processes to loosen intercellular junctions*: The dissociation of cells from each other arises from alteration of intercellular adhesion molecules (Fig. 4.26). One of the possible consequences of tumour cell transformation is the downregulation of the cadherin family of glycoproteins that are responsible for cell–cell adhesion. Loss of adhesion between cells is a natural 'trigger' for apoptosis and so, as the normal cells are separated, they die and leave spaces into which the tumour cells can expand. Tumour cells have an ability to attach to glycoproteins in the ECM and do not undergo apoptosis when their intercellular adhesion is disrupted. Tumour cells also have an ability to alter the ECM to their own advantage, in ways that promote invasion and metastasis. Tumours that remain in the epithelium/endothelium, and do not invade the basement membrane, are recognized as intraepithelial or in situ tumours in tumour staging (p. 19) and this is a really important stage in the determination of prognostic pathology of a tumour. 'If it stays where it is, the outlook is better'.
2. *Degradation of the basement membrane and enhanced extracellular matrix (ECM) degradation*: The basement membrane is an avascular, acellular complex of glycoproteins, which together form a supportive matrix that is itself supported by collagen. It specifically separates the epithelium/endothelium from the mesenchymal tissues. In cancer progression terms, degradation is most likely to be due to abnormal primary tumour cell production or secondary induced production of matrix metalloproteinase enzymes (MMPs) from fibroblasts and inflammatory cells. It is possible also that the tumour cells themselves have a primary role in their production. 'Once the basement membrane is breached or damaged, the pathway to migration is established'.
3. *Active tumour cell migration (locomotion) through the basement membrane and zones of ECM proteolysis*: Tumour cell migration (see Fig. 4.26) through the basement membrane is an active process, instigated and potentiated by tumour-derived (autocrine) mediators and cytokines. The process is further 'encouraged' by cleavage products of the ECM (e.g. collagen and laminin) and the local secretion of natural mediators

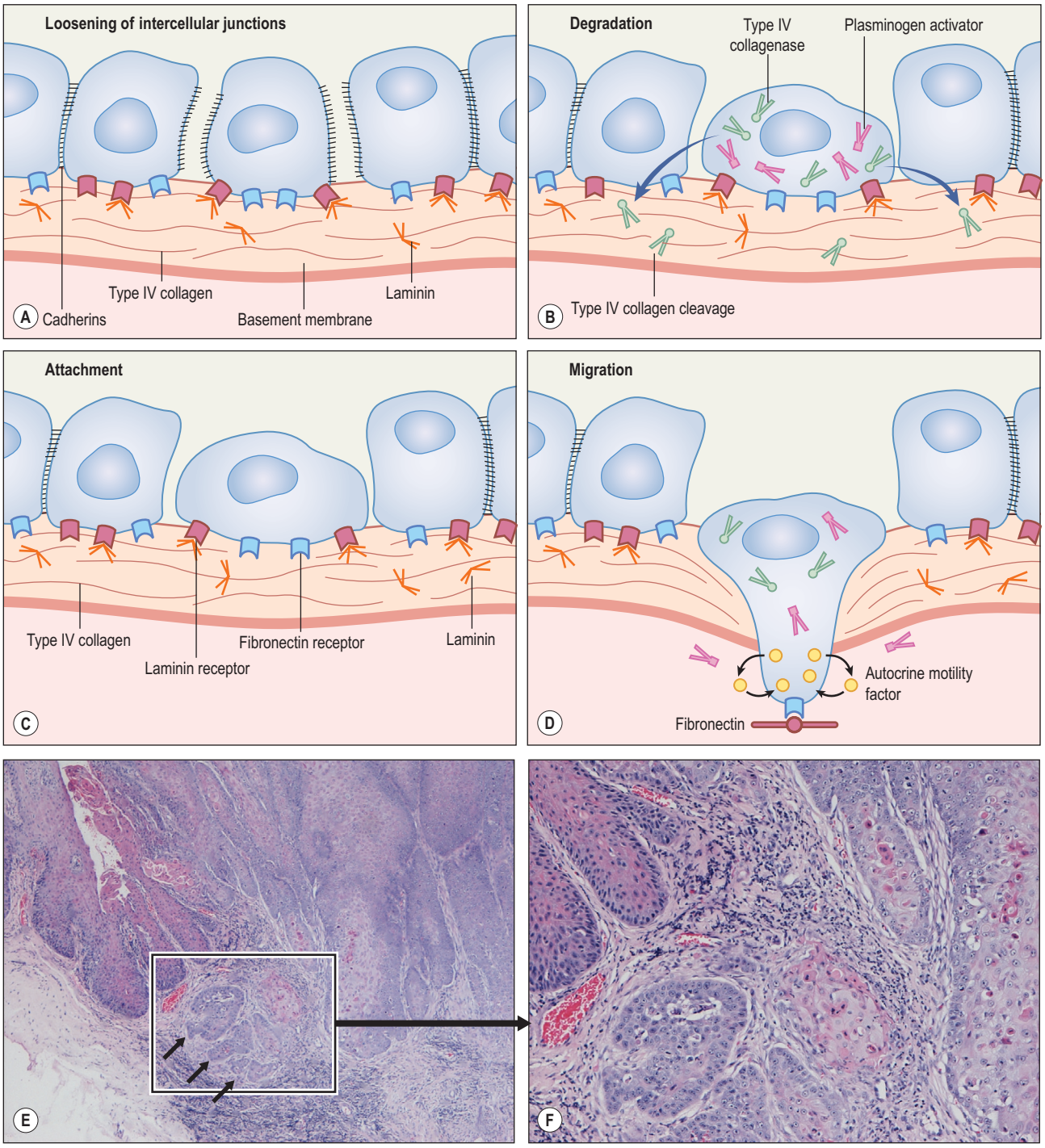


Figure 4.26 Invasion of epithelial basement membrane. **(A–D)** Sequence of events in the invasion of epithelial basement membrane – the first stage of the transition between in situ cancer and invasive cancer. Tumour cells detach from each other because of reduced adhesiveness – loosening of the intercellular junctions. The cells secrete proteolytic enzymes that degrade the basement membrane. Following that, the cells bind to proteolytically generated binding sites (attachment stage) and, once this has occurred, tumour cell migration is triggered (migration stage). **(E,F)** Squamous cell carcinoma of the third eyelid; nest of neoplastic cells invading the tissue deep to the basement membrane (arrows). (E: ×4; F ×40). *(Figure reprinted from Kumar V, Abbas A, Aster J. Robbins and Cotran pathologic basis of disease, 8th edn. Philadelphia: WB Saunders; 2010 (Fig. 7.37); copyright 2010, with permission from Elsevier.)*

that appear to have a particularly 'helpful' effect on tumour cells. 'Migration of tumour cells into the adjacent tissues means the tumour has broken out of its confined location'.

4. *Altered tumour cell proliferation rate*: As the cells encounter other tissue cells and structures, the rate of tumour cell proliferation can be upregulated or downregulated. It is important to realize that within the ECM, there are inhibiting components as well as those that encourage invasion, and so the precise behaviour of a particular cell may vary in different locations and under different circumstances. The most 'successful' tumours are probably those that co-opt the local cells and ECM to their advantage and to the detriment of the

host. 'A tumour cell that recruits the local tissues to its own advantage is a tumour cell that will survive and divide'.

5. *Continued angiogenesis*: As the tumour advances through the ECM, angiogenesis has to 'move with it'. This is easily supported since the tumour cells themselves and the local environmental effects create a mild hypoxia which in turn triggers the development and expansion of new blood vessels with further active secretion of vascular endothelial growth factor (VEGF). Apart from the most aggressive tumours and those in which the blood vessel formation is chaotic to the extent of being incapable of carrying blood, this is seldom a constraint upon tumour development and invasion. An additional issue of course is the intimacy of the relationship between blood vessels and the cancer cells, which allows intravascular spread (and therefore metastasis) to develop. 'A tumour that can encourage its own source of nutrition is necessarily dangerous'.

The stromal micro-environment of a tumour

Although there is inevitable and understandable focus on the neoplastic cell in a tumour, it is important to realize that tumours are NOT composed solely of the abnormal cell clone. Tumours are far more commonly composed of a highly complex mixture of tumour cells (derived from the parent cell but usually comprising several post-mutational cell lines with different properties), innate and adaptive immune cells, fibroblasts, vascular endothelial cells and usually other cells as well. Each cell type has its own behaviour pattern within the 'soup' of endocrine, paracrine and autocrine stimuli that surround it. In addition, there is an intercellular matrix that binds the cell complex into a defined and recognizable clinical feature. A large number of cell-derived mediators are involved in an almost infinite combination of concentration and type, and successful tumour cells must be able to co-opt these cells and mediators to their own advantage and promote their own development and progression into invasive and ultimately even metastatic forms. The complex of cells and their mutual interrelations dictates the clinical morphology of the tumour. Where there are fewer matrixes, the tumour might be found to be denser and harder and where there is more matrix, it might be softer and less defined. This clinical feature of 'softness or hardness' of the mass is, as might reasonably be expected, reflected in the histological features of the tumour. Whilst many tumours have a more or less characteristic textural nature, there are significant differences within the same histological tumour type. For example, many sarcoid tumours are very firm, with very little extracellular matrix and a lower blood supply, but others are softer and this corresponds with a significantly higher amount of extracellular matrix (Fig. 4.27).

The precise construct of the tumour overall is a unique product of all the cells that are inter-reacting within the tumour confines and the amount and density of the extracellular matrix. The tumour cells interact with each other in a complex way and some of the changes support cancer cell motility – it is not always the cancer cell itself that

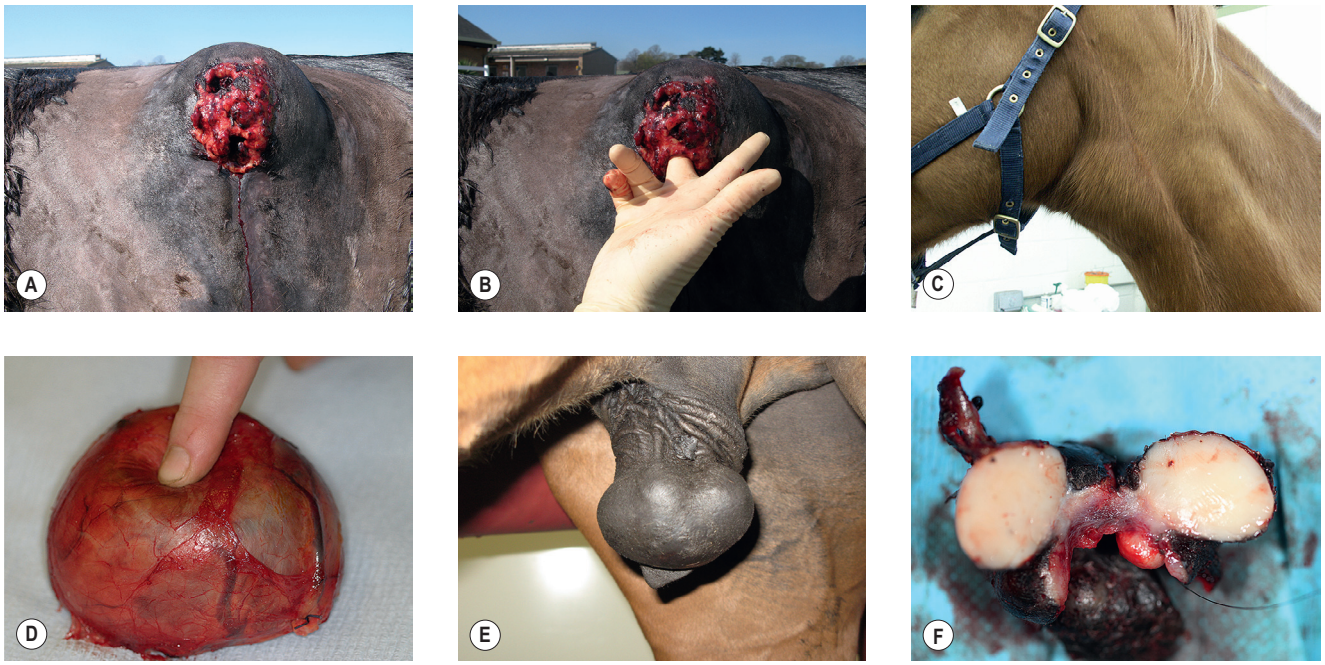


Figure 4.27 Morphological diagnosis. The consistency of a tumour is often related to the amount and nature of the extracellular matrix and the density and type of the cells within it. This is a feature that is used histologically to support a morphological diagnosis in many cases and to provide prognostic information on a tumour. **(A,B)** A malignant histiocytoma (giant cell tumour) on the back of a 12-year-old Welsh cross gelding. The tumour was soft and 'mushy' in consistency and bled readily. The ECM was plentiful with disorganized fragile blood vessels within it alongside areas of necrosis. **(C,D)** A thyroid carcinoma that had a rubbery soft consistency, but which was composed of uniformly spongy but solid tissue. The matrix here was less dense and there were more cells within the tumour without areas of necrosis and disorganization. **(E,F)** The nodular sarcoid is characteristically very firm/solid with sparse extracellular matrix and densely packed fibroblasts. There is usually limited vascular component in the nodular forms of the disease. This feature can sometimes be used to differentiate sarcoid from fibrosarcoma, although the boundary between the two is blurred and subject to individual interpretation. Many sarcoids have a more or less firm consistency that simply reflects the extent of the extracellular matrix.

creates the suitable migratory conditions for the 'spread' of a tumour into local adjacent tissues. Indeed, there is little understanding of why some tumours invade more than others. This is well illustrated in the equine sarcoid – the cell type is more or less constant in this tumour type and yet, some lesions on the horse remain confined in well-defined, firm nodular forms, whilst others are highly invasive and softer in nature. Both inflammatory and normal connective tissue cells have a complex relationship with the tumour cells and the normal interrelationship between these two cell types is in turn altered by the cancer cells themselves. There are pro-survival mediators and cytokines that promote progression of the tumour and macrophages are thought to have pro-metastatic influences.[31]

Additional changes in tumour consistency, and therefore the ease with which cells can migrate, involve intra-tumoral necrosis and inflammation. Tumours that have a high replication/doubling rate may outgrow their own blood supply and become necrotic. Since tumours require a blood supply and a matrix to move through, localized tissue necrosis can be seen as both an advantage and a disadvantage to the tumour.

Where the tumour cells are reliant upon a certain complex of cell and mediator contacts for survival, proliferation and metastasis, there is scope for therapeutic interference through targeting normal cells and mediators, as opposed to the cancer cells themselves. Using the 'soil and seed' analogy, this might in effect alter the soil sufficiently for the seed to 'settle and germinate' at the site or to fail to thrive or, preferably, fail to survive at all.

Metastasis

The genetic theory of metastasis

Invasion and metastasis are the hallmarks of malignant tumours and these two features are the primary reasons for cancer-related morbidity and mortality in most species. It is a remarkable fact that some tumours never metastasize, e.g. the equine sarcoid, and others do so with relative ease. Many theories have been proposed regarding the mechanisms and reasons for the variations, but it is now widely accepted that it is almost certainly a genetically-based phenomenon but that there are external/epigenetic factors that mitigate for or against the development of metastatic tumours. The equine sarcoid (p. 203, p. 545) is an excellent example of a tumour that can become highly aggressive, and it can be highly invasive locally, but it has no ability at all to metastasize and no recorded case so far has shown any of the features of metastatic dissemination. On the other hand, haemangiosarcoma and undifferentiated sarcoma, which are both extremely rare in any case, have a much high propensity for metastasis. Furthermore, in spite of many millions of cells that invade the bloodstream and lymphatic vessels, the process of metastasis is highly inefficient and in horses, in particular, metastatic tumour development is extremely rare.

There is clear evidence that the development of malignancy and metastatic conversion has a fundamental genetic basis. The most plausible explanation for the phenomenon of invasion and metastatic spread of tumours is the clonal evolution model. This model suggests that as mutations occur, the inherent instability of the genome of the cell results in cellular heterogeneity as clones of cell lines develop, each of which may have particular less desirable features. The accumulation of mutations over time within the cancer cell clone leads the tumour transformed cell into a progressively more dangerous pathological behaviour pattern, as clones of more 'aggressive' tumour cells develop within the primary mass. It appears that sequential mutations are required before a cell will develop the ability to invade locally (p. 48) or metastasize to remote sites; it is not always a predictable two- or three-step process – in fact it might be an almost random series of events. Some cancers may require many mutations before the invasive and metastatic properties develop. While there are obvious difficulties with the hypothesis, the clonal evolution model is generally the accepted process that is used to explain the progression (Fig. 4.28). The main difficulty with the hypothesis is the

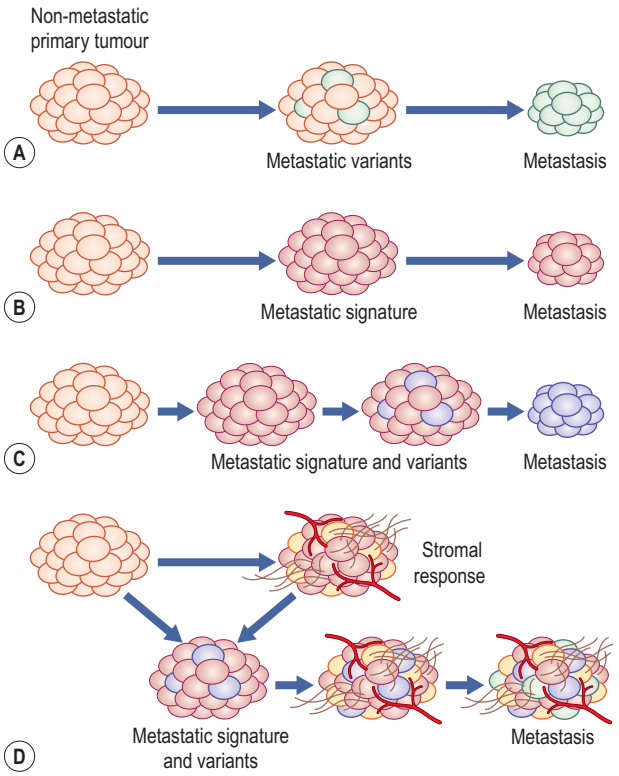


Figure 4.28 Development of metastasis from a primary tumour. There are four recognized mechanisms whereby metastasis can develop from a primary tumour. **(A)** The inherent genomic instability of a tumour clone supports the development of further mutational clones, some of which may have metastatic capability – the so-called 'metastatic variant'. **(B)** The tumour cells have a gene expression for metastatic potential in most/all of the cells of the tumour – the so-called 'metastatic signature'. **(C)** A combination of A and B, in which some cells will mutate and induce a metastatic phonotype, while others will develop from the inherent metastatic signature. **(D)** The ability to metastasize is influenced significantly by the consistency and composition of the tumour stroma (see also Fig. 4.27). Local paracrine/autocrine and tumour environment factors (including angiogenesis) drive metastatic variants into a replicative state with clonal expansion of potentially metastatic cells, no matter how the primary change was instigated. The stroma may regulate angiogenesis, local invasiveness and resistance to/evasion of immunological tumour elimination, along cells within the primary tumour to become metastatic. *(Figure reprinted from Kumar V, Abbas A, Aster J. Robbins and Cotran pathologic basis of disease, 8th edn. Philadelphia: WB Saunders; 2010 (Fig. 7.38); copyright 2010, with permission from Elsevier.)*

predictability that occurs – certain tumour types lead to predictable metastatic development and, therefore, the random mutation option seems less likely than a more defined series of changes leading to a particular genetic capability. Is it possible that a random collection of genetic mutations would culminate in a predictable endpoint?

The 'metastasis signature' theory suggests that sequential mutations 'support' or 'lead' to other mutational changes: i.e. from the start, there is a certain predictability about the mutations that can occur (Fig. 4.28). Therefore, according to this hypothesis, the process is not random once it is triggered. Expression of the 'metastatic signature' has been correlated with a poor prognosis and has been shown to be consistent in several types of cancer.[32] Unsurprisingly perhaps, the prognosis is worse for individuals whose primary tumours express the metastatic signature, i.e. the tumour progression does not depend on 'bad luck', as in the clonal evolution model but instead is an inevitability.

Whatever triggers the process of progression, in the first instance, the tumour moves towards an invasive behaviour that breaks through the constraints of the basement membrane (p. 51). Thereafter, further changes occur that shift the paradigm towards more universal cell growth and/or an ability to survive in a variety of other tissue sites without apparent constraint. Some cancer cells acquire the ability to penetrate the walls of lymphatic and/or blood vessels, after which they are able to circulate through the bloodstream (circulating tumour cells) to other sites and tissues in the body; this process is known as 'lymphatic' or 'haematogenous' spread, respectively (Fig. 4.29). Invasion of

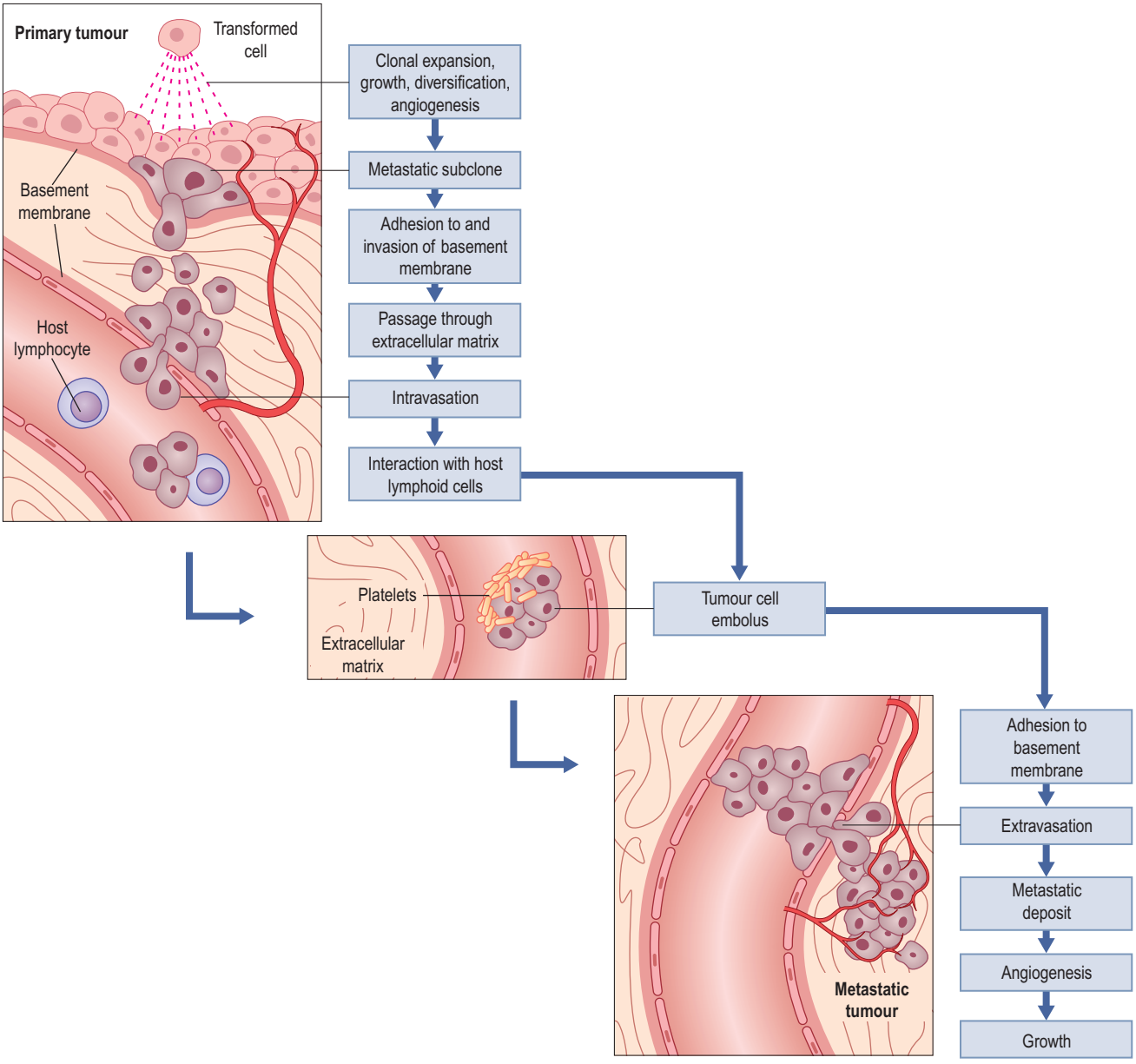


Figure 4.29 Development of malignancy. At a cellular level, the ability of the tumour cells to break through the basement membrane is the first major step in the development of malignancy (see Fig. 4.26). The additional ability to break through the outer basement membrane of blood and lymphatic vessels allows the tumour cells to invade into the lumen of vessels and so permitting dissemination. Transcoelemic dissemination occurs in the same way but the cells 'break out' of the tissue into body spaces, such as the pleural and peritoneal cavities, or the pericardium or even into the cerebrospinal fluid. *(Figure reprinted from Kumar V, Abbas A, Aster J. Robbins and Cotran pathologic basis of disease, 8th edn. Philadelphia: WB Saunders; 2010 (Fig. 7.36); copyright 2010, with permission from Elsevier.)*

blood vessels follows the same pathway as invasion of other structures (p. 48).

However, although the clinical effects of metastatic tumour development are profound and often disproportionate to the original tumour, only relatively small subsets of tumour cells develop the ability to invade and possibly even fewer acquire the ability to metastasize effectively; fortunately, it seems the process is extremely inefficient. It may therefore be the exception rather than the rule that cancer cells develop the ability to invade and metastasize. Of course the number of tumour cell clones that undergo the 'correct' mutations can be very low but their ability to survive in a variety of different circumstances means that their absolute numbers can become enormous – away from their 'home' in their new 'environments' they are often far less subject to local inhibitory and physical constraints.

Additionally, when tumour cells have the capacity and possibility to spread and 'settle' in remote tissues, their clinical influence becomes correspondingly greater. A small malignant melanoma in the perineum of a grey horse may look singularly innocuous but its early micro-metastasis could lead to tumour development in the brain, heart valves and even the spinal cord. In any of these locations, even small tumours can have a profound effect on the patient, resulting in significant morbidity and even mortality.

The sequential processes leading to metastatic development within a tumour can be defined in genetic steps, but this is an unpredictable and ill-defined process that up to now has not really been fully clarified. As a counter to the theory, it is clear that some tumour types develop the genetic propensity for metastatic and invasive behaviour at a very early stage – long before any such change is apparent. This suggests that perhaps the basic changes are present very early – 'the metastatic signature' is present from the outset and this will dictate the long-term outcome of the tumour – possibly even from the outset. Epigenetic and local cellular micro-environmental influences may be a crucial factor in determining whether a tumour will invade or metastasize or both. It is possible that the two 'systems' could be co-existent in fact and that this might explain why metastatic tumours are usually rare but usually very aggressive.[32]

The main question that is being asked is, '*Is there a specific genetic change that results directly in metastatic potential?*' In considering the genetic basis of tumorigenesis, there may be oncogenes that promote metastasis and natural genes that might suppress that change. The balance between the two might be tilted through either abnormal development of a promotional (metastatic) oncogene or the loss of the metastasis suppressor genes. A metastatic suppressor gene is a gene whose loss promotes the development of metastasis without any effect on the primary tumour. Whether these genes occur naturally or are the result of mutation is uncertain. In contrast, metastasis oncogenes promote or favour the development of a pro-migratory cell line.

Metastatic tumours are relatively common in the late stages of the progression of many cancer conditions in all species and their development is one of three hallmarks of malignancy (in contrast to benign tumours). Metastasis can be viewed as one of the last phases of the maturation of a cancer. To some extent perhaps, the horse appears to have fewer tendencies to these changes than most other species, but this may simply reflect the fact that the cases are seldom followed through to their natural conclusion. The horse probably also suffers from fewer tumour types than many other species and the more aggressive tumours tend to be extremely rare types or very rare variations of more benign tumours. This may be seen as an evolutionary protective ability but it would seem unlikely that the horse with its slower generational interval would be less likely to develop an evolutionary advantage than another faster replicating species – may be they just lead better lifestyles with less mutational opportunity.

Given the necessarily profound genetic instability and mutation that result in metastatic tumour development, it is very likely that the neoplastic cells will continue to undergo further genetic and epigenetic changes in both the parent tumour and the metastatic tumours. The primary routes of metastatic spread are via the bloodstream to distant sites (haematogenous metastasis), via lymphatic vessels to local lymph nodes (lymphatic metastasis), by direct invasion of adjacent organs and structures and by seeding across body cavities (p. 59). Different types of tumour appear to have different preferred metastatic pathways and even the sites of primary tumour development may influence the method of spread. In 1889, Paget, one of the forefathers of cancer medicine, suggested that the target organ for a metastatic tumour was related to its ability to survive in that location – the so-called 'soil and seed' hypothesis.[33] This suggested that there were certain survival requirements for the development of particular types of secondary/metastatic tumours. The concept is still attractive, since it is easy to visualize that tumour cells would require suitable survival conditions in which the correct balance between positive and negative growth signals would exist. After metastatically-capable tumour cells come to rest at another site, they may re-penetrate through the vessel or walls into tissue sites (usually the next capillary to be in line) where they may (or may not) continue to multiply and eventually another clinically detectable tumour is formed (Fig. 4.30). The new tumour is known as a metastatic or 'secondary' tumour.

Most tumours can, at least in theory, metastasize, although this is inevitably to very variable degrees (e.g. basal cell carcinoma rarely metastasize and sarcoid probably never does); their ability to complete the process requires multiple sequential changes and 'cooperative' changes in the local tumour milieu. There is a certain degree of organ selectivity in the development of metastatic tumours that involves obvious physical and mechanical factors so that there is a tendency for the tumours to develop at the first capillary bed or lymph node following the primary tumour. However, this is not an invariable outcome, so the 'soil and seed' hypothesis may involve the requirement for suitable 'soil' for particular 'seeds'. Some tumours have a particular tendency to spread to bone, for example, and may bypass the next capillary bed in line; in this case the best soil is beyond the first filter.

When tumour cells metastasize, the cells are identical to those in the original tumour – at least at first. This means, for example, that, if gastric carcinoma metastasizes to the lungs, the secondary tumour is made up of abnormal gastric epithelial cells, not abnormal lung cells. The tumour in the lung is then called *metastatic gastric carcinoma*, not *lung cancer*. Thereafter, since they already possess the invasive, metastatic and immune evasion characteristics, the tumour

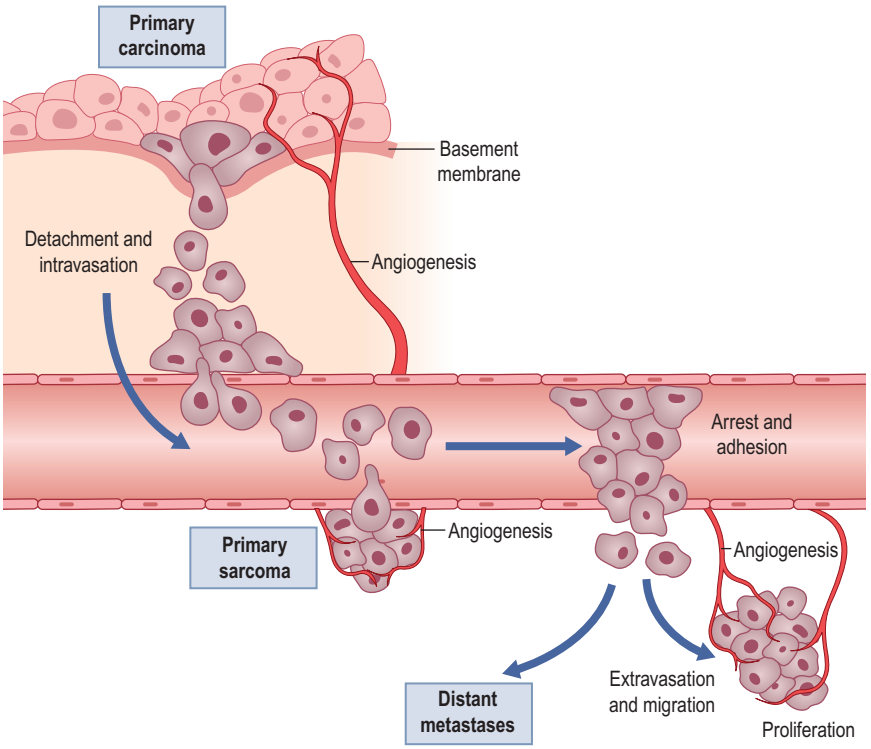


Figure 4.30 Major steps in metastatic spread of tumours. The major steps in metastatic spread of tumours involve the progressive development of mutationally-induced alteration of cell behaviour. In the first instance, the tumour develops its own blood supply by inducing angiogenesis (see Fig. 4.25). The next stage involves the penetration of the basement membrane and the invasion of the deeper tissues (see Fig. 4.26). Progressive mutations result in the ability of the cells then to penetrate lymphatic or blood vessels. Some tumour cells then detach and can be transported to remote sites where they may arrest and adhere to the vascular endothelium. Here the cells must be able to invade the capillary walls and survive in the target tissue. If suitable conditions exist at the remote site, they may grow into a secondary/metastatic tumour that sooner or later needs to develop its own blood supply to supply nutrients for further growth; the so-called 'soil and seed' requirement has to be fulfilled, i.e. the cell must be able to survive in the target tissues. This process is fortunately notoriously inefficient. *(Figure after Tannock IF, Hill RP, eds. The basic science of oncology, 3rd edn. New York: McGraw–Hill; 1998, reprinted with permission.)*

cells could (re)gain access to the blood or lymphatic circulation or may break out across coelomic cavities and seed into adjacent tissues and so develop tertiary tumours.

The process of metastasis can be divided into distinct steps, including:

- *Escape of tumour cells into the circulation from the primary tumour (intravasation)*: This process is poorly understood and there may be physical pressure effects as well as aspects of angiogenesis and matrix-driven paracrine and autocrine supportive stimuli. The actual entry of a tumour cell into the bloodstream is clearly a complex process that must involve proteolytic enzymes, but whether the intravasation takes place into normal blood vessels or into tumour-derived (abnormal) vessels is not clear. Intravasation into lymphatic vessels is also part of the process – but again the mechanism for that process is not yet established. Invasion of the tumour-derived blood and lymphatic vessels would seem to be the most logical and physically easiest route, since they are known to have an increased permeability. Regardless of the route, cells can enter the circulation in enormous numbers – up to 4×10^6/g of tumour/day has been suggested in some tumour types. This does not, however, correlate well with the number of metastatic tumours that will develop. It is probably therefore very fortunate that metastasis is a very inefficient process.
- *Survival in the circulation*: There is strong evidence that a much higher number of cells escape into the circulation than ever develop into distant tumours.[34] This suggests that metastatic spread is a very inefficient process with a high rate of attrition in the seeding population of cells. Many tumour cells are probably destroyed by natural killer (NK) cells or monocytes within the circulating milieu. Tumour cells are more fragile than normal cells and, in any case, would probably not be able to survive the physical pressures within the bloodstream. It is assumed that many are killed by shear forces alone.

  It may also be that a relatively low number of seeding cells that escape into the circulation have the extra genetic/mutational capacity to develop in remote sites. It is not certain whether the population of cells that do develop is genetically different from the point of formation or whether they acquire further mutations during their intravascular migration.

  Within the circulation, tumour cells tend to aggregate into larger clumps of cells, a process that is enhanced by the homotopic nature of the tumour cells and by the heterotopic adhesion between the tumour cells, platelets and leukocytes. This may serve one of three purposes:

  1. The larger clump of cells may be more inclined to 'stop' in a smaller capillary bed and the surrounding cells may then give the tumours cells an advantage in terms of attachment and extravasation.
  2. Heterotopic clumping may also protect the pressure-vulnerable tumour cells from shear force destruction.
  3. Clumping may be a way of exposing the tumour cells to the natural cellular defence mechanisms and so they may conversely be more inclined to be destroyed.

  Several other possibilities also exist, including the fact that certain circumstantial factors have to be present before the cells can seed effectively. This adds a possible epigenetic dimension to the metastatic process.
- *Arrest in a new capillary bed site in a remote organ/tissue*: There is a difference between arrest and 'entrapping'. Both processes are encountered in the process of

metastatic development, but it is likely that the most important is true arrest, which occurs when there is a selective adhesion of the tumour cells to the vessel walls. Tumour cells with a high capacity for endothelial adhesion (as opposed to simply being physically trapped) are significantly correlated with metastatic potential. As soon as tumour cells bind to the endothelium, the endothelial cells retract and come to overlap the tumour cell. Tumour cells appear at first to adhere to the sub-endothelial basement membrane. Thereafter, they trigger the process of intravasation.

Since the lung and the liver probably represent the most common sites for secondary tumour development in the horse, as well as other species, it seems likely that the pulmonary and hepatic vascular endothelium are a particular target for tumour cells. Classically, this is taken to mean that tumour aggregates will sequester into the next available capillary bed. Although this would be the most frequent occurrence, it is not always the case. However, it is entirely possible that the tumour cells will neither lodge nor adhere at this level and may then pass to another vascular bed, where the conditions are more suitable; seemingly there is no 'rule' that dictates that the metastases have to develop within the 'next' capillary bed. Subject to the local restrictions and tropisms the cell may pass the next capillary bed – finding no suitable site to adhere – and then might find a suitable capillary bed in another organ altogether. Thus, secondary tumours do not always have to be restricted to the next capillary bed encountered.

As a component of metastatic inefficiency the vast majority of arrested tumour cells (and possibly an even higher proportion of entrapped tumour cells) will undergo rapid apoptosis and will then of course have no pathological implication. This adds a degree of inefficiency to the process of metastatic tumour pathogenesis.

- *Escape from within the vessel into the tissue site (extravasation)*: In order to survive, the cancer cells must of course evade the immune system both locally at source and in the circulation, as well as ultimately in the new site. The tumour cells must find a suitable environment in which to thrive; this is generally considered to be a significant limiting step for cancer progression and further inefficiency. Although the arrest and adhesion appears to be an inefficient step, the intravasation has a higher efficiency – a much higher proportion of cells that adhere actually migrate into target organs.[35] Although this may be over-simplistic, the mechanisms for intravasation are assumed (possibly justifiably) to be those that are also associated with invasion (p. 51).
- *Migration into the interstitial space at the new site and establishment of the cell with initiation of tumour growth in the new site*: This process requires that the tumour cells evade the host's defences and then proliferate with vascular and local tissue contributions.[36] Here again there are opportunities for arrested growth, restricted expansion/growth or, in some cases, even enhanced progression. In the latter circumstances, the tumours may find the local 'soil' even more suitable for growth than the original site and this is a major limiting stage in tumour progression.

  The tumour cells can be eliminated by local inflammatory and immune cells and this is yet another significant contribution to the overall metastatic inefficiency with host immune processes often seemingly able to overcome a high proportion of the abnormal cells – even when the cells had evaded the immune system at the tissue of origin. Tumour cells may, however, also subvert immune and inflammatory cells to their own advantage; the cells themselves and their products can be strongly supportive of cancer cell proliferation in some circumstances.[37] Secondary tumours can be larger and faster than the primary mass as a direct result of this enhanced development; the 'soil' at the new site may be more supportive of the 'seed' than that of the original site.
- *Initiation of angiogenesis to provide nutrients and oxygen to the growing tumour mass*: The process of angiogenesis may be similar to that of the parent tumour. However, there may be significant differences that may alter the local behaviour of the new (metastatic) tumour. It is thought that tumour cells can 'co-opt' local endothelial cells to ensure continuity of blood supply at the new site. In some circumstances, the rate of growth can be higher or lower than that of the parent tumour, depending on the local supportive and inhibitive growth signals derived from the metastatic micro-environment.
- *Metastatic spread from secondary tumours via any of the recognized pathways to other remote capillary beds resulting in tertiary tumours*: This is a very rare occurrence and in horses at least it is probably best viewed as a theoretical consideration.

However, even though the effects of metastases are inevitably profound both clinically and biologically, it is a remarkably inefficient process. Research has shown conclusively that whilst many millions of cells are released into the circulation from a malignant tumour, only a tiny minority of these will actually become active secondary tumours. The reason for this inefficiency may be a key to establishing strategies that prevent dissemination. In addition, the body resists metastasis by a variety of mechanisms through the actions of a class of proteins known as metastasis suppressors, of which about a dozen are known in the human; none are recognized clearly yet in horses.[38]

Whilst the recognition of the presence of local metastasis is relatively easy in most species, it is more difficult in the horse, since there are significant and often insurmountable imaging and anatomic issues that may mask early metastatic tumour development. Where it is present, it does however represent the end stage of a tumour's development in horses, just as it does in other species. There is little more harm that the tumour can do from that stage onwards (Fig. 4.31).

In the large majority of metastatic tumours, the primary tumour can be identified; once the tissue type has been established, a logical suggestion can be made as to the likelihood of a primary tumour being within a certain organ or region. However, in a significant proportion of cancer patients, a primary tumour may not be identified; an 'occult'

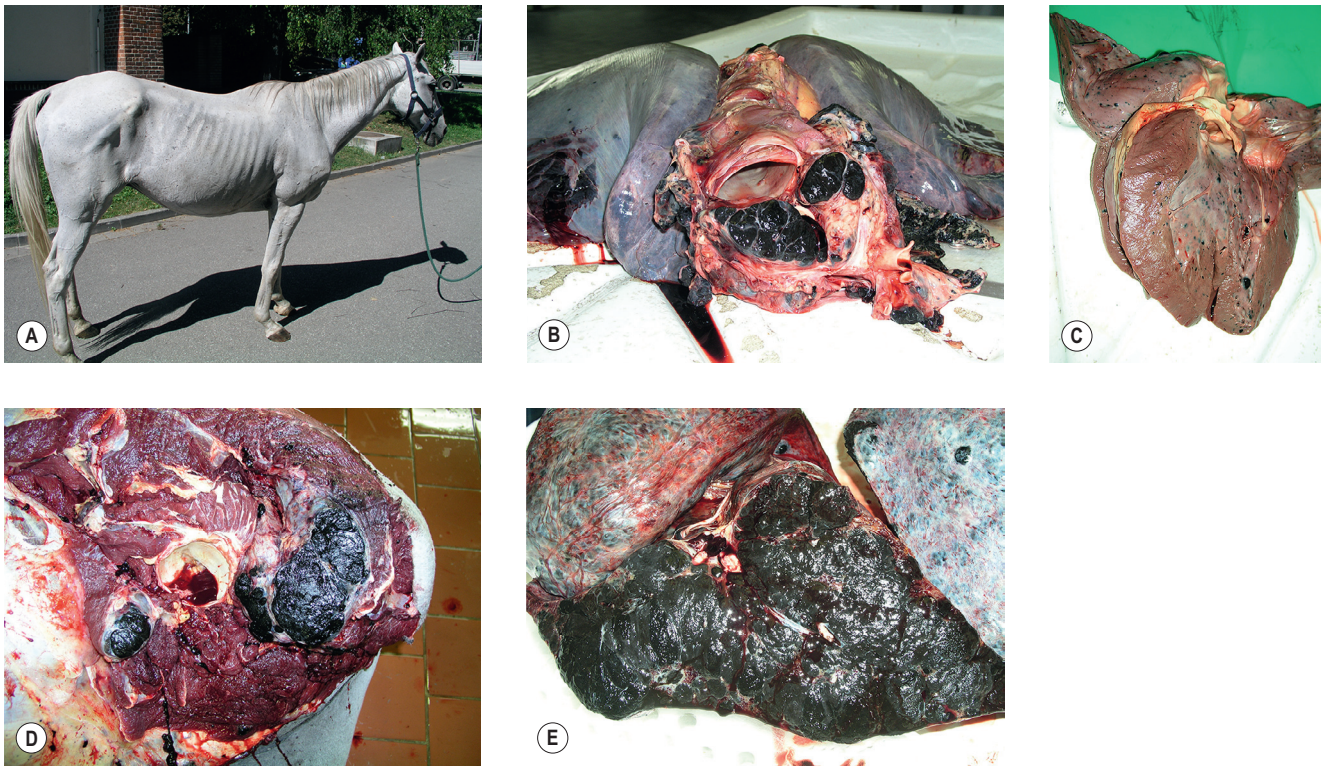


Figure 4.31 The 'soil' and the 'seed'. **(A)** This 14-year-old grey mare had a recent history of rapid weight loss, anaemia and exercise intolerance, nonspecific signs that can be associated with cancer. She had several small perineal melanomas but, using ultrasonography, it was clear that she also has disseminated tumours throughout her body with multiple organ compromise. The basic assumption was that most of these were metastatic from some primary tumour but it was not possible to provide convincing evidence of a primary lesion. The 'soil and seed' theory is possibly well-illustrated here with large tumours on the mediastinal lymph node **(B)**, myocardium **(C)**, skeletal (gluteus) muscles **(D)**, spleen **(E)** and other organs. No significant tumours were found in the lung parenchyma and the kidneys and gut were spared completely – presumably the 'soil' was not suitable for the 'seed'. *(Figures courtesy of Petr Jahn.)*

or 'unknown primary tumour' is then blamed. There are several possible explanations for this state:

- First, the primary tumour may be of an insignificant (non-detectable) size, which does not necessarily equate with malignancy: some very small tumours have a very aggressive nature, whilst some large tumours have little implication in terms of metastatic behaviour. It is the tumour type that dictates the propensity for spread, not its size. In some cases, the primary tumour can become 'obvious' later on, though whether that is a significant event is another matter!
- A second explanation for the lack of detectable primary tumour (sometimes even at autopsy) is that the primary tumour may have regressed – leaving behind only its disseminated 'offspring'. It is not known how often this might happen in any species and even less is known about equine tumours. Imaging of the indicated suggested primary organ of origin only occasionally reveals a distinctive primary tumour. In melanomas in grey horses (pp. 237 and 572), it is probably impossible to identify a potential primary metastasizing tumour when there are many other tumours present (see Fig. 4.31). The question arises as to whether it matters what the primary tumour is or whether it can be treated in some way, since by the time disseminated tumours are present the prognosis is generally bleak at best.
- The third possible explanation is that the tumour is not easy to define or detect by existing diagnostic methods. In the horse, in particular, imaging of internal tumours is severely constrained. Additionally, little is understood about the particular cancers of horses and their pathological behaviour. However, even when the gross or histological features of a particular tumour are difficult to define, the use of sophisticated immunohistochemical methods allows pathologists to give an identity to many of these metastases, even when they are very poorly-differentiated (pp. 20 and 115). In the event that specific staining of biopsy samples reveals the true character of a tumour, its origin can probably be surmised and diagnostic effort used to identify the primary mass (immunostaining/immunohistochemistry).

Even a cursory histological examination of the smallest tumours will usually reveal that the cells making up the tumour are pleomorphic, even if they originate from a single cell. It is also true that the individual cells may behave in different ways. Tumour heterogeneity is remarkably evident in virtually every phenotype examined – it may be that there are in fact few truly identical cells, even within the clone of a tumour type. The major heterogeneity factors include positional, temporal and genetic heterogeneity.

Routes of metastasis

Metastasis can occur by one or more of four recognized mechanisms (Fig. 4.32):

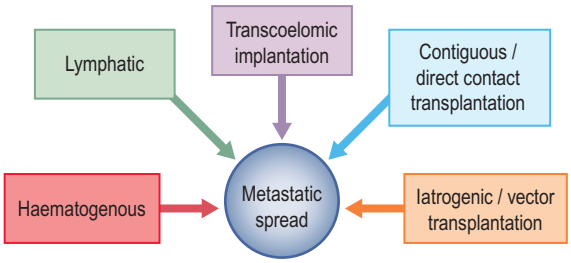


Figure 4.32 The five routes of metastasis. Metastatic spread can occur by one or more of the five routes shown here.

1. *Haematogenous spread*: This is a typical outcome of sarcomas but it is also the favoured route in certain carcinomas (e.g. those originating in kidneys); the thinner venous blood vessel walls could be more liable to penetration than arteries, so metastatic tumours more commonly follow venous flow pathways. For example, intestinal carcinoma and adenocarcinoma usually extend first to the liver via the portal vein and only in a second step would they extend to the lungs. Given that the tumour cells have to 'lodge' and then extravasate into the new site without the supportive contribution of a primary tumour state and local epigenetic and paracrine processes, this might explain to some extent at least why so few cells actually develop into metastasis tumours; getting out of the 'prison' of a primary tumour with damaged walls and supporting systems that allow escape more readily is likely to be far easier than breaking into an intact castle with strong defensive walls and active surveillance systems. It is also not clear how long an individual tumour cell can survive within the circulation before it is detected immunologically or becomes effete for lack of surrounding support. Recruitment of platelets and macrophages as a protective barrier may help to preserve the tumour cell (the 'seed'), as well as make it physically larger and more liable to arrest or sequester in small vessels. However, this process may also give the immune processes a chance to both detect and destroy the cancer cell.
2. *Invasion of lymphatic vessels*: A tumour cell that invades lymphatic vessels is carried to regional nodes and ultimately to other parts of the body; transport via the lymphatics is the most common pathway for the initial dissemination of carcinoma tumours.

   Cancer cells may extend or involve the local lymph nodes (regional lymph nodes) near the primary tumour – this is a component and feature of the lymphatic spread of tumours. This is usually termed 'nodal involvement', 'positive nodes' or 'regional disease'. 'Positive nodes' is a term that would be used by human medical specialists when the patient's lymph nodes near the primary tumour test positive for malignancy, either histologically or palpably. In the case of the horse, this is an unusual reference – not because the tumours do not extend to local lymph nodes but rather because there are very few easily palpable lymph nodes in horses. This means that alternative methods, such as ultrasonography (p. 93) or endoscopy (p. 103), may have be used to examine local lymph node involvement. This is also one of the reasons staging (p. 19) is seldom applied to equine cancers.

   Localized spread to regional lymph nodes near the primary tumour is not normally strictly counted as metastasis, although this is a convincing sign of a worse prognosis.
3. *Spread and seeding across body cavities (transcoelomic spread)*: Metastasis may occur by direct seeding, which is called 'transcoelomic spread'. This affects the peritoneal, pleural, pericardial or sub-arachnoid spaces. For example, carcinoma of the equine stomach and carcinoma of the bladder frequently spread transperitoneally to the visceral surface of the liver and gut and to the parietal peritoneum. Transcoelomic dissemination is also a feature of the very rare mesothelioma in the horse (p. 474). The shedding of tumour cells into a body cavity can be diagnostically useful. For example, in the case of gastric carcinoma and mesothelioma, the neoplastic cells can be detected by the simple expedient of a paracentesis cytology (p. 97). In this respect, there are significant differences in the various tumour types. Lymphoma within the peritoneal cavity is seldom exfoliative and so abnormal cells may not be found. In contrast, thoracic lymphoma has a greater tendency to exfoliation and so abnormal cells may be found relatively consistently (p. 503).
4. *Transplantation*: Transplantation is defined as 'the mechanical carriage of fragments of tumour cells by surgical instruments during operation or the use of needles during diagnostic procedures'. This is widely feared since dissemination could then be 'blamed' on the surgeon. In particular, it is one of the reasons that biopsy of equine melanoma is feared by many clinicians. However, in the event that the tumour is found to have an aggressive pathological nature, it would seem likely that micro-metastasis has already taken place and then the added contribution of a carefully performed biopsy is probably not significant in terms of the outcome. However, there is no evidence either way in the horse.

Transplantation by vector or direct contact between individual sites may also occur. The former may be a method whereby sarcoid is spread from site to site across the patient and the latter may occur when tumour cells are exfoliated from the surface of an ulcerated tumour into a 'receptive' site. Using the soil and seed analogy, the 'seed' is scattered onto the 'soil' where it may germinate. This method of tumour spread is an occasional feature of carcinoma (Fig. 4.33) and sarcoid. The possibility of spread from one animal to another is also a matter of considerable interest. The precedent for this in veterinary medicine is in the canine transmissible venereal granuloma and the Tasmanian devil (*Sarcophilus harrisii*) 'devil facial tumour disease' (sarcoma). In both these circumstances, tumour cells are transferred physically (venereally during coitus or during fights, respectively) against the resistant gradient of the MHC protection. The cells appear to express modified MHC molecules and so they are more 'transmissible' than normal cells. Whether this occurs in any equine tumours, such as the equine sarcoid, is debatable and unknown.

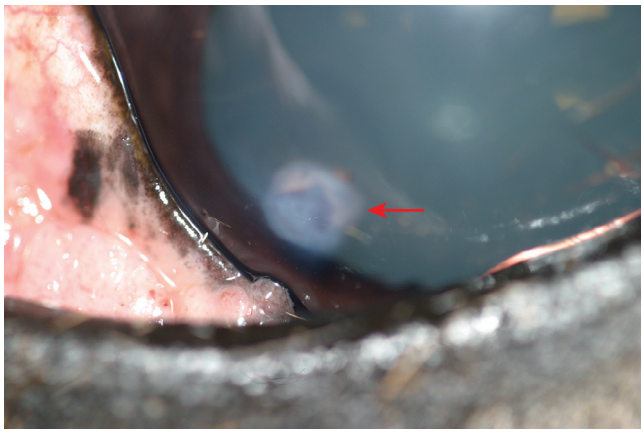


Figure 4.33 Carcinoma of the nictitans. This 7-year-old Clydesdale gelding developed a rapidly growing malignant carcinoma on the nictitans and close examination revealed an area of corneal opacity (arrow) at the site where the margin of the nictitans lay at rest. A scraping from the site revealed cancerous keratinocytes and this was confirmed following surgical removal at the time of the nictitans ablation surgery.

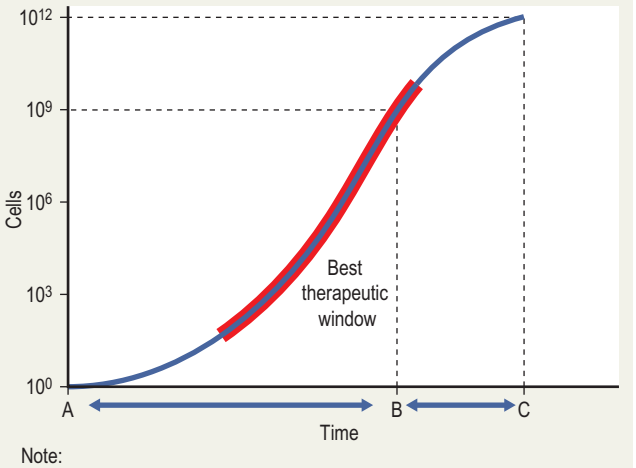
The growth of tumours

All tumours start out as a single cell and with sequential divisions of clones of neoplastic cells until a true and visible/detectable tumour develops. Many of the characteristics of the basic pathological nature of the tumour are present immediately; in most cases, that tumour adopts the features of the predominate cell. However, within the expanding mass of cells, the inherent genetic instability results in different clones of related cells and these may have a profound influence on the nature of the clinical behaviour. The size of the tumour itself, however, is largely dictated by the rate of cell division and the presence or absence of limiting factors to its growth.

The Gompertzian model

One of the biggest challenges that faces oncologists in their quest for solutions to tumour cases is the fact that tumours are not physically visible or detectable until they have a finite size. 'The Gompertzian mathematical model' (Fig. 4.34) is the classic method used to describe both the changes and the challenges of human tumours; it is likely that a similar circumstance can be applied to horses. It is generally accepted that a tumour becomes clinically detectable, either physically or biologically, when it reaches 1×10^9 cells. This involves around 30 doublings of the parent cell. This means that by the time the tumour has become evident, 30 generations have passed.

This model clearly shows the rate of tumour growth slowing as it matures and becomes larger. Chemotherapy and radiation treatment methods are most potent when used against rapidly dividing cells (p. 129); thus, therapy is most effective when tumours have a higher fraction of dividing and proliferating cells with shorter doubling times; this is the steepest part of the Gompertzian curve. It can be seen that this feature corresponds well with stages of the tumour that are below clinical detection. Treatment is likely to be significantly less effective in larger (easily detected) mature tumours, which have fewer proliferating cells (i.e. the upper flatter part of the curve). It is easy to understand why cancer therapy is so frustrating and why methods for early diagnosis are so important.



Note:

B is the point in time that the tumour becomes clinically apparent.

C is the point in time that the tumour causes death.

A–B is the time interval between the development of the first cancerous cell and clinically apparent disease (pre-clinical disease).

B–C is the time interval between clinical detection of tumour and death (clinical disease).

As is clear from the curve, the time interval A–B is much greater than B–C. This helps to explain why tumours have often spread prior to the development of clinical symptoms.

Chemotherapy is most likely to be effective during the steepest part of the curve, i.e. before the tumour is clinically detectable.

Chemotherapy is less effective when the curve flattens out and this partially explains why response rates are lower with very large tumour burdens.

Figure 4.34 The Gompertzian curve. The classical growth curve of a tumour is described in the Gompertzian curve. *(Figure redrawn from Peedell C. Concise clinical oncology. Oxford: Butterworth–Heinemann; 2005: 64 (Fig. 6.1); copyright 2005, with permission from Elsevier.)*

By the time the tumour reaches 1×10^{12} cells, it is usually capable of killing the host animal. This curve clearly illustrates the fact that by the time a tumour is 'detectable', it has already passed through most of its life-cycle. The tumour might already be capable of true independent survival and unlimited replicative potential. Micro-metastases might already have occurred; by the time a tumour is seen, it could easily therefore be 'too late' to control it at all.

Furthermore, the proliferation rate is not constant throughout the lifetime of the tumour – there are periods when the tumour grows faster and others when it grows slower. However, within this short-term variability, as a general principle, the rate of growth slows down as tumours enlarge and there is a reduction in the overall number of proliferating cells. Additionally, there is an increased rate of cell loss, probably as result of reduced blood supply, decreased cellular nutrients and increased autocrine-related random cell death. This all combines to result in an overall reduction in 'doubling time': the doubling time is the interval over which the cell numbers will double.

References

1. Croce CM. Oncogenes and cancer. N Engl J Med 2008; 358:502–511.
2. Benard J, Douc-Rasy S, Ahomadegbe JC. TP53 family members and human cancers. Hum Mutat 2003; 21:182–185.
3. Liu MC, Gelmann EP. P53 gene mutations: case study of a clinical marker for solid tumours. Semin Oncol 2002; 29:246–250.
4. Soussi T. p53 mutations and resistance to chemotherapy: a stab in the back for p73. Bull Cancer 2003; 90:383–385.
5. Bogaert L, Van Poucke M, De Baere C, et al. Bovine papillomavirus load and mRNA expression, cell proliferation and p53 expression in four clinical types of equine sarcoid. Gen Virol 2007; 88:2155–2161.
6. Browner WS, Kahn AJ, Ziv E, et al. The genetics of human longevity. Am J Med 2004; 117:851–860.
7. Evans GI, Vousden KH. Proliferation, cell-cycle and apoptosis in cancer. Nature 2001; 411:342–343.
8. Hiyama E, Hiyama K. Telomerase as tumour marker. Cancer Lett 2003; 194:221–222.
9. Matzinger P. Tolerance, danger and the extended family. Ann Rev Immunol 1994; 12:991–1045.
10. Chao MP, Jaiswal S, Weissman-Tsukamoto R, et al. Calreticulin is the dominant pro-phagocytic signal on multiple human cancers and is counterbalanced by CD47. Sci Transl Med 2010; 2:63–94.
11. Raghavan M, Wijeyesakere SJ, Peters LR, et al. Calreticulin in the immune system: ins and outs. Trends Immunol 2013; 34:13–21.
12. Obeid M, Tesniere A, Ghiringhelli F, et al. Calreticulin exposure dictates the immunogenicity of cancer cell death. Nat Med 2007; 13:54–61.
13. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000; 100:57–70.
14. Radisky D, Hagios C, Bissell MJ. Tumours are unique organs defined by abnormal signalling and context. Semin Cancer Biol 2001; 11:87–95.
15. Bhowmick NA, Nielson EG, Moses HL. Stromal fibroblasts in cancer initiation and progression. Nature 2004; 432:332–337.
16. Knudson AG. Two genetic hits (more or less) to cancer. Nat Rev Cancer 2001; 1:157–162.
17. Dobson J. Percivall Pott. Ann R Coll Surg Engl 1972; 50:54–65.
18. Tennant R. Chemical carcinogenesis. In: Franks LM, Teich NM, eds. An introduction to the cellular and molecular biology of cancer, 3rd edn. Oxford: Oxford University Press; 1997: 106–125.
19. Dumaz N, van Kranen HJ, de Vries A, et al. The role of UVB light in skin carcinogenesis through the analysis of p53 mutations in squamous cell carcinomas of hairless mice. Carcinogenesis 1997; 18:897–904.
20. Schumacher J, Watkins JP, Wilson SR, et al. Burn-induced neoplasia in two horses. Equine Vet J 1986; 18:410–412.
21. Giblin T, Pickrell K, Poii W, et al. Malignant degeneration in burn scars; Marjolin's ulcer. Ann Surg 1965; 162:291–297.
22. Carrillo-Infante C, Abbadessa G, Bagella L, et al. Viral infections as a cause of cancer (review). Int J Oncol 2007; 30:1521–1528.
23. Butel JS. Viral carcinogenesis: revelation of molecular mechanisms and etiology of human disease. Carcinogenesis 2000; 21:405–426.
24. Nasir L, Reid SWJ. Bovine papillomaviral gene expression in equine sarcoid tumours Virus Res 1999; 61:171–175.
25. Stoler M. The biology of human papilloma viruses. Pathology Case Reviews 1997; 2:8–20.
26. Martin CM. Virus-carcinogen interactions. Bacteriol Rev 1964; 28:480–489.
27. Foulds L. Neoplastic development. London: Academic Press; 1975.
28. Nowell PC. The clonal evolution of tumour cell populations. Science 1976; 194:23–28.
29. McDougall SR, Anderson ARA, Chaplain MAJ. Mathematical modelling of dynamic adaptive tumour-induced angiogenesis: Clinical implications and therapeutic targeting strategies. J Theor Biol 2006; 241:564–589.
30. Bissel MJ, Radisky D. Putting tumours in context. Nat Rev Cancer 2001; 1:46–48.
31. Condelis J, Pollard JW. Macrophages: obligate partners for tumour cell migration, invasion, metastasis. Cell 2006; 124:263–265.
32. Ramaswamy S, Ross KN, Lander ES, et al. A molecular signature of metastasis in primary solid tumours. Nat Genet 2003; 33:49–54.
33. Paget S. The distribution of secondary growths in cancer of the breast. Lancet 1889; 1:371–373.
34. Weiss L. Metastatic inefficiency. Adv Cancer Res 1990; 54:159–211.
35. Chambers AF, Groom AC, MacDonald IC. Dissemination and growth of cancer cells in metastatic sites. Nat Rev Cancer 2002; 2:563–572.
36. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer 2003; 3:453–458.
37. Overwijk WW. Breaking tolerance in cancer immunotherapy: time to act. Curr Opin Immunol 2005; 17:187–194.
38. Yoshida BA, Sokoloff MM, Welch DR, et al. Metastasis-suppressor genes: a review and perspective on an emerging field. J Natl Cancer Inst 2000; 92:1717–1730.

5

Clinical effects of cancer in horses

Introduction 62
Clinical signs and consequences 62
Specific nature and pathological behaviour 65
Differential diagnoses 66
Physical appearance 68

Introduction

Cancerous conditions are fortunately rare in horses; apart from the few very common conditions, such as cutaneous sarcoid, melanoma and squamous cell carcinoma, however, this may relate to skin tumours being more easily noticed and/or of clinical relevance. In some post-mortem studies, thyroid neoplasms have actually been the most common but these are usually non-functional and often small in size.[1,2] In addition, the majority of the skin tumours are sarcoids (the commonest overall neoplasm of the horse), melanomas (largely, but not exclusively restricted to grey horses) and squamous cell carcinomas. This means that in simple numerical terms, the skin is usually the target organ for the clinically important signs of cancer in horses.

Cancers are obviously far more threatening to the host than benign tumours but it would be wrong to assume therefore that benign tumours cannot cause significant (even life-threatening) problems. Tumours of all types can have profound effects and many can (and do) kill the host – the 'bottom line', however, is that cancer is important because of its clinical effects on the patient; a cancer is a 'parasite', since it derives its total nutrition from, and at the same time harms, the 'host'. Some cancers only cause trivial effects but others are catastrophic and between those two extremes lie an almost infinite variety of clinically detectable effects.

Although malignant tumours will inevitably be more dangerous and life-threatening, it is important to realize that any tumour can cause morbidity and even mortality; even the most benign tumours may in fact be life-threatening. Thus, whilst the maximum survival of a serious disseminated lymphosarcoma case is usually around 6 months, cutaneous lymphoma cases can have a much longer survival time – often up to 4–5 years, or more (Fig. 5.1).

In some circumstances, the tumour can cause significant morbidity or even mortality, whilst still having a very benign pathological nature. A local sarcoid or melanoma may have no detectable systemic signs but both can deteriorate significantly. In the case of the melanoma, there may be a dramatic dissemination of truly malignant melanosarcoma with severe systemic signs or it may simply enlarge enough to cause a major functional problem (Fig. 5.2). Where the tumour involves or engulfs nerve tissue, the effects are reflected in a neurological symptom relating to the location of the damage (Fig. 5.3).

Cancers can progress significantly from benign to malignant and this may be a spontaneous series of events or it may be triggered by some other insult. It is well established that inadequate surgical excision of a tumour can result in significant exacerbation but the reasons for this are not always clear. It is possible that localized alterations in cell interactions (which might have been suppressing tumour progression and development) may be removed or that inflammatory changes that follow interference can cause altered cellular and cytokine profiles. The equine sarcoid is widely recognized as a tumour of skin only. It has several defined forms (p. 545); and it is recognized that each of the less aggressive forms can deteriorate in certain circumstances into a very dangerous locally invasive and destructive tumour, known as the 'malignant sarcoid' – even though the tumour is not capable of distant metastasis.[3] This may explain why many clinicians are reluctant to interfere with some tumour types.

The physical releasing of a tumour from the confines of a naturally occurring capsule can also remove constraints on the growth of the tumour; this can occur for example when a nodular sarcoid ulcerates and the relatively confining fibrocellular capsule is breached. There may also be circumstances when the partial removal or even the simple interference may release cytokines that may alter the behaviour of remote tumours of a similar type or release cells that could disseminate.

Clinical signs and consequences

Broadly speaking, tumours can have primary or secondary clinical consequences, as result of the following.

Tissue type

The type of tissue involved in a tumour will of course be related to the anatomical location and to its potential to cause secondary effects. The type of tissue also may have some bearing on the likelihood of malignancy. This is possibly the most fundamental aspect of the clinical effects of a cancer.

Size/extent

Tumours that expand significantly may have a direct space-occupying effect either by compression or distortion of other



Figure 5.1 An aggressive melanosarcoma. **(A)** This 14-year-old grey gelding had a small cluster of melanomas above his anus for some years without apparent change. Within a few months and without obvious cause **(B)**, they dramatically increased in size and the large lesion was excised **(C)**. At this stage, areas of beige and pink tissue were visible around the margins of the mass. There were large numbers of melanomas in other organs, including the guttural pouches. Histology revealed an aggressive melanosarcoma and within a matter of months, the horse was destroyed on humane grounds. As a general rule, this cancer is progressive and often results in death.

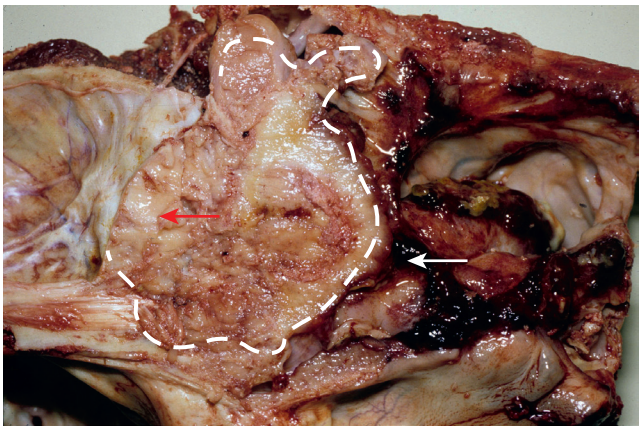


Figure 5.2 Nasal adenocarcinoma. An extensive nasal adenocarcinoma developed within the ethmoidal region in this 9-year-old cross-bred gelding. The gelding had shown persistent mild serosanguinous epistaxis with episodes of more significant bleeding. The gelding was dull and showed prominent forebrain signs. A fetid breath was noticed and endoscopy revealed the extent of the problem. The diagnosis was made from a biopsy taken using a uterine biopsy instrument (see p. 89). At necropsy, the extent of the tumour invasion was remarkable and the tumour had invaded through the cribriform plate (red arrow). The haemorrhage derived from an ulcerated/necrotic area of tumour and extensive destruction of nasal architecture is obvious (white arrow).



Figure 5.3 Melanoma within the spinal canal. This 12-year-old grey gelding developed a progressive severe bilateral hindlimb weakness and profound right-side gluteal muscle atrophy. A large, invasive and poorly-defined melanoma was identified associated with the right sacral plexus and ataxia was attributed to melanoma within the spinal canal in the lumbosacral region. *(Figure courtesy of Wendy Talbot.)*

local tissues or through obstruction of another organ's function. A good example of this is a benign nasal polyp (pp. 64 and 488). A small polyp in the nasal cavity would have no material implication and indeed would probably only be identified incidentally. However, the whole nasal cavity can be obstructed by the expanding mass which, by virtue of its specific nature, simply expands along the lines of least resistance towards the nares and the pharynx. The tumour expansion produces precise conformity to the space available. The clinical effect is nasal airflow obstruction and, in some cases, the more subtle (and less easily identified) obstruction of paranasal sinus drainage. In spite of the clinical implications, this particular tumour is extremely benign. Simple removal results in an immediate restoration of function and, in this case, there is usually no local distortion or long-term implication. The condition is cured easily and completely (Fig. 5.4).

Minor expansion of tumours that are confined within anatomically limiting regions/organs will inevitably have more serious implications. It is usually accepted that direct pressure on the hypothalamic region of the brainstem of the expanding pituitary gland in cases of pituitary adenoma (hyperplasia) in pituitary pars intermedia dysfunction (equine Cushing's disease) is responsible for at least some of the symptoms of the condition (e.g. blindness, hyperhidrosis, hyperthermia) and failure of coat shedding (hypertrichosis) (wrongly referred to as hirsutism). A small granulosa cell tumour (p. 641) may have no physical implications but, if the tumour were to become larger, its physical weight could cause some tension on the ovarian ligament and that might cause significant abdominal pain (colic). In the event that such a tumour becomes even larger, it may result in fatal haemorrhage from rupture of the ovarian artery.

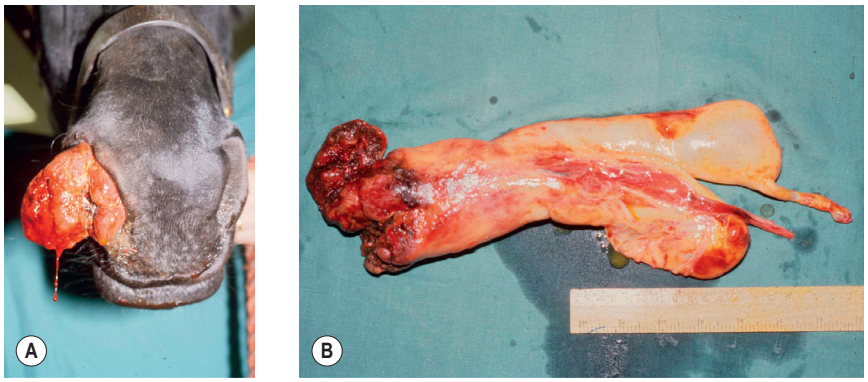


Figure 5.4 Nasal polyp. (A) An alarming, fast growing mass that occluded the right nasal cavity of a 9-year-old horse was thought to be a highly malignant tumour. In fact, it was only attached by two small pedicles **(B)** and was easily removed by gentle traction. This is a good example of a polyp.

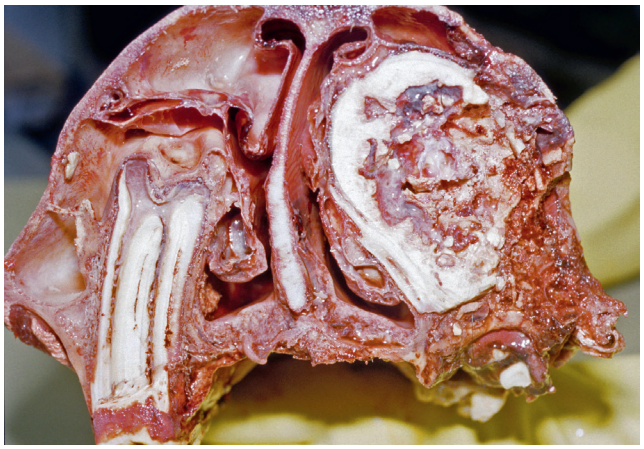


Figure 5.5 An odontoma. A 14-year-old Welsh pony gelding developed a large facial swelling and severe stertor. No air flow could be detected in the right nostril and endoscopy on the right side was impossible. At necropsy, a large tumour of dental origin (odontoma) was found and this occupied the entire maxillary sinus and caused space-occupying occlusion of the right nostril and deviation of the nasal septum to the left also with partial nasal occlusion.

Location

It is impossible to separate the size of a tumour from the location – clearly, smaller tumours in a more confined location would have greater secondary space-occupying or functional effects than larger ones in an area where there are no significant confines. These considerations will necessarily influence the prognosis and the treatment options. A small localized sarcoid in an accessible site will be a far lesser therapeutic challenge than a very extensive large one in a difficult or inaccessible site.

The precise anatomical location of a tumour is clearly important. Where a tumour occupies a confined space, even small expansions might have significant effects on the surrounding, more important, structures. Although the tumour itself may be insignificant, its effects become related to dysfunction of the adjacent organ(s) or space-occupying effects. Thus, for example, an expanding tumour within the brain causes very serious secondary effects. Expanding space-occupying tumours that distort the local anatomical structures will affect function. For example, an expanding paranasal sinus carcinoma can obliterate the ipsilateral nostril and may even expand enough to limit breathing in the contralateral nostril (Fig. 5.5).

Probably the commonest example of location having an impact is the occurrence of spinal melanomas. Although no primary tumour of the vertebral column has been recorded in horses, metastases of malignant melanoma into the dorsal spine or vertebral body or into the spinal cord itself occur with some frequency.[4,5] The clinical signs may be caused by bulging of the tumour into the spinal canal and/or as a result of a pathological fracture. Melanoma can also affect the cerebrum, where the effects may be very hard to attribute clinically to melanoma expansion or local neurological deficits.[6] Mentation and voluntary movement may be seriously affected but the diagnosis may only be found at post-mortem examination. Typically, the clinical signs are related to the function or dysfunction of the compressed structure, so that spinal melanoma cases are presented as ataxic.

Common changes associated with pituitary pars intermedia dysfunction have been termed 'pituitary adenoma'. Although it is certainly true that some affected glands are hyperplastic rather than a tumour, a few are genuinely neoplastic. In either event, there may be compression of the brainstem with associated signs of hyperthermia or even blindness. Compression of the brain from an expanding nasal carcinoma occurs late in the progression of the tumour, since the brain is protected by the calvarium.

In horses, adenoma in the pituitary gland induces a symmetrical increase in volume (p. 585) and, due to its extension, the tumour can significantly compress the hypothalamus and optic nerves. In addition, this tumour has profound functional effects derived from hyperplasia and hyperfunction of the pars intermedia. Secondary effects on other parts of the pituitary gland can be a result of compression. In contrast, an expanding lacrimal gland carcinoma or an extra-adrenal paraganglioma or an orbital melanoma within the orbit is confined and so will cause secondary exophthalmos, possibly with secondary neurological effects in the eye. The eye will usually remain sighted, but if the eyelids cannot blink effectively there will be secondary effects on the cornea. Ultimately, there may also be secondary effects through distraction/tension on the optic nerve and so blindness may follow.

Tumours that occur in locations where expansion has no material implication (e.g. a pedunculated lipoma on the mesentery or a thyroid adenoma) will expand outward with no direct material significance.

Location also matters in respect of diagnosis and treatment. External tumours are usually directly visible, whilst internal ones usually require other diagnostic methods, such as rectal palpation, endoscopy, radiography

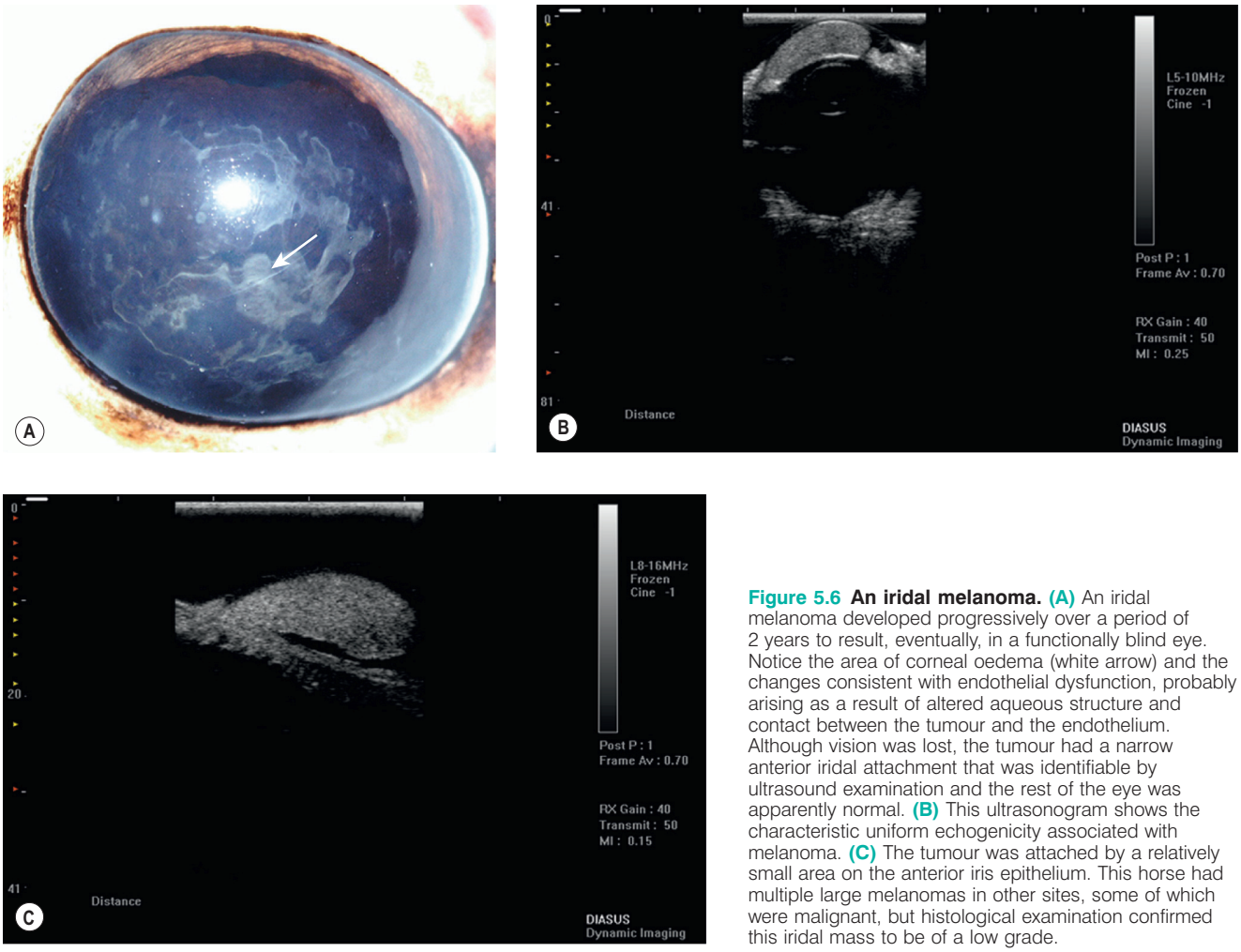


Figure 5.6 An iridal melanoma. (A) An iridal melanoma developed progressively over a period of 2 years to result, eventually, in a functionally blind eye. Notice the area of corneal oedema (white arrow) and the changes consistent with endothelial dysfunction, probably arising as a result of altered aqueous structure and contact between the tumour and the endothelium. Although vision was lost, the tumour had a narrow anterior iridal attachment that was identifiable by ultrasound examination and the rest of the eye was apparently normal. **(B)** This ultrasonogram shows the characteristic uniform echogenicity associated with melanoma. **(C)** The tumour was attached by a relatively small area on the anterior iris epithelium. This horse had multiple large melanomas in other sites, some of which were malignant, but histological examination confirmed this iridal mass to be of a low grade.

or ultrasonography for diagnosis. An external or easily accessible tumour can usually be investigated and sampled relatively easily. Accessibility is a fundamental aspect of the treatment options that a clinician might consider. Using the example of the pedunculated lipoma in an old horse, accessibility to it would require entry into the abdomen whilst the thyroid adenoma is directly accessible from outside.

The space-occupying effects are usually the most important major consequence of benign tumours. Functionality can be significantly altered. For example, an iridal melanoma can develop in a pain-free non-damaging form until it completely fills the anterior chamber of the eye – the eye is then functionally blind (Fig. 5.6).

Similarly, an equine sarcoid that invades the upper eyelid can result in difficulty with blinking and consequent secondary eye damage.

Number

Whilst a single tumour in a suitable location can cause a significant problem (see Fig. 5.6), multiple tumours would be expected to have greater direct effects; additionally, if the tumour is associated with paraneoplastic or functional effects, then those effects might expect to be more severe.

A single bronchogenic granular cell tumour (p. 500) in a main stem bronchus can cause significant clinical effects, including chronic coughing, haemoptysis, epistaxis and reduced performance. Secondary effects might be associated with loss of pulmonary function and infection of the compromised lung region. Where a large number of tumours occur, such as the very common mesenteric lipoma, there may be increased opportunities for other related pathologies. There would clearly be a higher overall chance of a strangulating intestinal obstruction if there were many tumours present (of course, size and exact location, as well as the precise anatomical features of the individual lesions, might also have an influence).

Specific nature and pathological behaviour

One of the most important aspects of a tumour's existence is its pathological behaviour. The difference between benign tumour behaviour and malignant tumour behaviour is singularly important, since tumours that remain localized and have little functionality will have a far lesser clinical significance. That does not mean, however, that a benign tumour necessarily has no significance. Tumours that have a locally invasive nature may have a more destructive local

effect, whilst those that metastasize will necessarily have remote effects that are often life-threatening. Tumours that have an inherent malignancy often have remote paraneoplastic effects (p. 70). Tumours that have an ulcerated surface or a necrotic centre will have secondary systemic implications. Even some benign tumours such as sarcoids, melanomas or ethmoid haematoma can ulcerate and cause clinically significant blood or plasma loss and may also become secondarily infected or infested to the clear detriment of the patient (p. 489).

Functionality

The extent to which a tumour resembles its parent cell type largely dictates its functionality. That means that where a tumour occurs in an organ that has some defined endocrine, paracrine or autocrine function, it will necessarily have remote or local effects on target cells. Mares with granulosa-theca cell tumours, which are by far the most common type of equine ovarian cancer, tend to have reproductive dysfunction because the tumour causes an increase in various hormone levels (testosterone and inhibin in particular). Excesses and imbalances of the hormones can profoundly affect a mare's reproductive behaviour and her personality – they tend to be aggressive and stallion-like in their attitude to other horses. Some cases have much less hormonal imbalance and so these may simply be acyclic and infertile. Not all tumours of endocrine glands are functional – thyroid adenomas are notoriously bland in terms of their function and most appear to have no physiological effects.

Functional loss can present in a misleading way. For example, the main (most obvious) external sign in a horse with multicentric lymphosarcoma may be diarrhoea. A careful clinical examination might identify significant cutaneous nodules; in the same way a single cutaneous haemangioma/haemangiosarcoma lesion may be missed in a horse with unilateral hindlimb lameness, which could be due to disseminated tumours. It is always worth establishing the whole range of presenting signs before making a tentative diagnosis.

Probably the most recognized 'functional tumour' of the horse is the pituitary adenoma. Although there remains much speculation and controversy over the enlarged pars intermedia that are found (often incidentally) in a high proportion of older horses, some are certainly classified as adenomas.

Other functional tumours include:

- C-cell tumours of the thyroid (p. 591)
- Sertoli cell tumour (p. 638)
- Pituitary adenoma (p. 585)
- Thyroid adenoma/carcinoma (p. 587)
- Phaeochromocytoma (functional tumour of the adrenal medulla, see p. 593).

One of the important issues about the functionality of tumours revolves around their production of abnormal bioactive substances that influence the behaviour of other body systems and other local tissues. Some tumours are inclined to induce a wide variety of physiological and clinical effects. These form a recognized but unpredictable series of clinical signs that are grouped together as the 'paraneoplastic syndromes'. These paraneoplastic effects are reviewed in Paraneoplastic Syndromes (Ch. 6).

There may be additional elements of bone marrow suppression, secondary effects from immune-mediated thrombocytopaenia and anaemia and a wide range of organ malfunctions that arise from a single tumour. Metabolic disturbances are common in cancer patients, including the horse. They may be the result of underlying malignancy and its manifestations, the result of the systemic responses to the tumour itself or indeed to the treatment. Since it is well recognized that malignancy has a profound depressing effect on the immune system, comorbid medical conditions are commonly encountered. Since early recognition of internal tumours, which are by their nature those that would be expected to have the most metabolic effects, are not usually recognized by either owners or clinicians, these may be the main presenting signs in a significant number of cases. This also means that 'unexplained' medical conditions might require a much closer clinical investigation than normal; this might apply particularly to recurrent opportunistic infections, skin disease and anaemia.

The functionality of the tumour cells is usually taken as an index of the extent of differentiation or genetic transformation. Functionality suggests well-differentiated cellular changes. Catecholamine secretions from the adrenal medulla in phaeochromocytoma (p. 593) are probably near normal in structure. It is the volume of them that is abnormal.

Tumour cells that behave like the parent cells are usually associated with benign tumours, whilst those with marked aberrations of function are viewed as undifferentiated. In some circumstances, the extent of differentiation can be recognized histologically by the extent of abnormal function of the cell. A squamous cell carcinoma with prominent keratin production would normally be classified as well-differentiated, whilst one that has no recognizable keratin production is classified as undifferentiated and therefore more likely to be malignant (Fig. 5.7).

Functional tumours of endocrine glands are by definition well-differentiated. The observable clinical effects relate to normal hormone production, but usually are secreted in a less physiologically controlled manner. A good example of this is the abnormal hormone concentrations secreted from granulosa (thecal) cell tumours of the ovary (p. 641).

Duration

The duration of a tumour will also reflect the clinical signs. Usually duration is associated with size but that is not always the case. The duration might also have a profound influence on the extent of malignancy, since the longer duration of a tumour the more liable it might be to have second or third mutations. This clearly is not an invariable rule, since some very benign tumours simply remain so for many years and even possibly the whole life of the horse.

Differential diagnoses

It is probably impossible to consider the various factors outlined above in isolation. They will have close inter-relationships and several of these factors can be encountered at the same time. It is wise to keep the possibility of neoplastic disease on the list of differential diagnoses for any set of clinical signs (no matter how unlikely that might seem at first) – at least until an alternative diagnosis can be

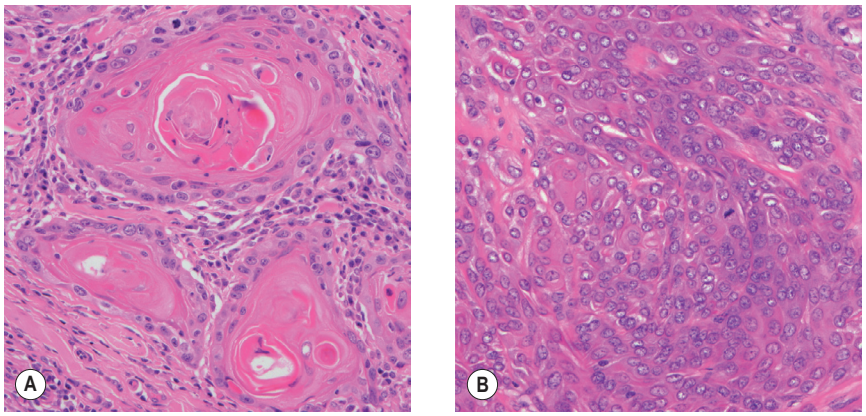


Figure 5.7 Squamous cell carcinoma. The functionality of cells can be an indicator of the extent of their cancer progression. **(A)** A squamous cell carcinoma with functionality in producing keratin (so-called keratin pearls) indicates functional and therefore early or mild mutation. **(B)** An undifferentiated squamous cell carcinoma that produces almost no keratin is consistent with an advanced mutational stage. (H&E; ×200)

established. However, there is also a significant danger in ascribing any sign to a 'cancerous condition' – cancers in horses are rare for the most part.

The signs may be primary when the cancer actively involves a major organ and causes pathology directly. For example, pharyngeal carcinoma causes difficulty with swallowing and the signs presented may be related to that difficulty – nasal return of food and saliva can be encountered (and incidentally can be rightly or wrongly ascribed to other conditions as well). A space-occupying melanoma occurring on the iris affects the function of the iris and may result in physical visual compromise as well as glaucoma as a result of impairment of aqueous drainage.

Even when the condition is in an advanced stage, diagnosis may rely on a combination of clinical investigations. Often each of these tests and investigations will add some weight to a presumptive diagnosis but often a single test is required to confirm the diagnosis. For example, a single primary bronchial granular cell tumour could present simply as a harsh deep persistent and non-responsive cough (p. 500); in the absence of any other detectable basic clinical evidence this might lead to an error of diagnosis. When treatment for a respiratory tract infection or an allergic airway disease syndrome fails, further diagnostic measures such as endoscopy may be performed. There may be no haematological or biochemical changes and there may be no auscultative abnormalities. Ultrasound and even radiography can be unrewarding.

For example, a renal adenocarcinoma (see p. 652) may obliterate a large proportion of one kidney, but overall renal function may not appear to be compromised at all because of the large functional reserve of the kidney.[7] However, it may result in colic and haematuria. Renal carcinoma can have a wide variety of clinical effects, ranging from colic, ascites and weight loss to haematuria, and in addition can have quite severe paraneoplastic syndromes, including anaemia and paraneoplastic pruritus.[8]

While the existence of significant clinical consequences will help a clinician to make a diagnosis of cancer, all neoplastic masses must be taken seriously until their true nature is established. The significance of this cannot be overstated, since early recognition and early treatment are fundamental to a satisfactory outcome. In many cases, the decision to delay clinical investigation is taken by the owner and then the case may only be presented once there are primary signs at the site or advanced secondary signs. Most internal cancers are only detected when there are external and readily visible signs and, by that time, most are in an advanced state (Figs 5.8, 5.9).

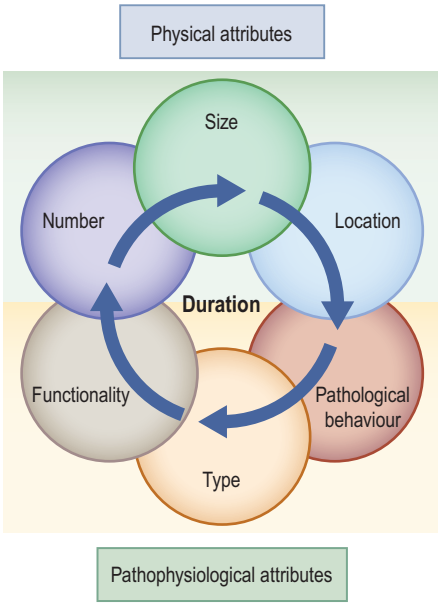


Figure 5.8 The clinical effects of a tumour. The clinical effects of a tumour depend on several inter-related factors. It is easy to imagine that a single tumour has an inevitable clinical consequence but there is nothing predictable about cancer. It is probably fairer to say that no two tumours have the same clinical implications, no matter how similar they look in a different horse. The main factors involved in establishing the clinical signs of cancer are shown above and can be divided effectively into physical and pathophysiological effects.

Ulceration and infection

Bleeding and infection at the sites of ulcerated exposed tumours can be a major issue with the owner–horse relationship and this will inevitably have an effect on the systemic wellbeing of the horse. There are several possible issues, including chronic blood loss, which could occur internally and result in blood loss anaemia and icterus. External blood loss, whether chronic or acute, will result in blood loss anaemia, but probably no icterus.

The most serious internal tumours of horses (and a few of the superficial ones too) affect immunity. This means that ulceration or other trauma applied to the tumour is often

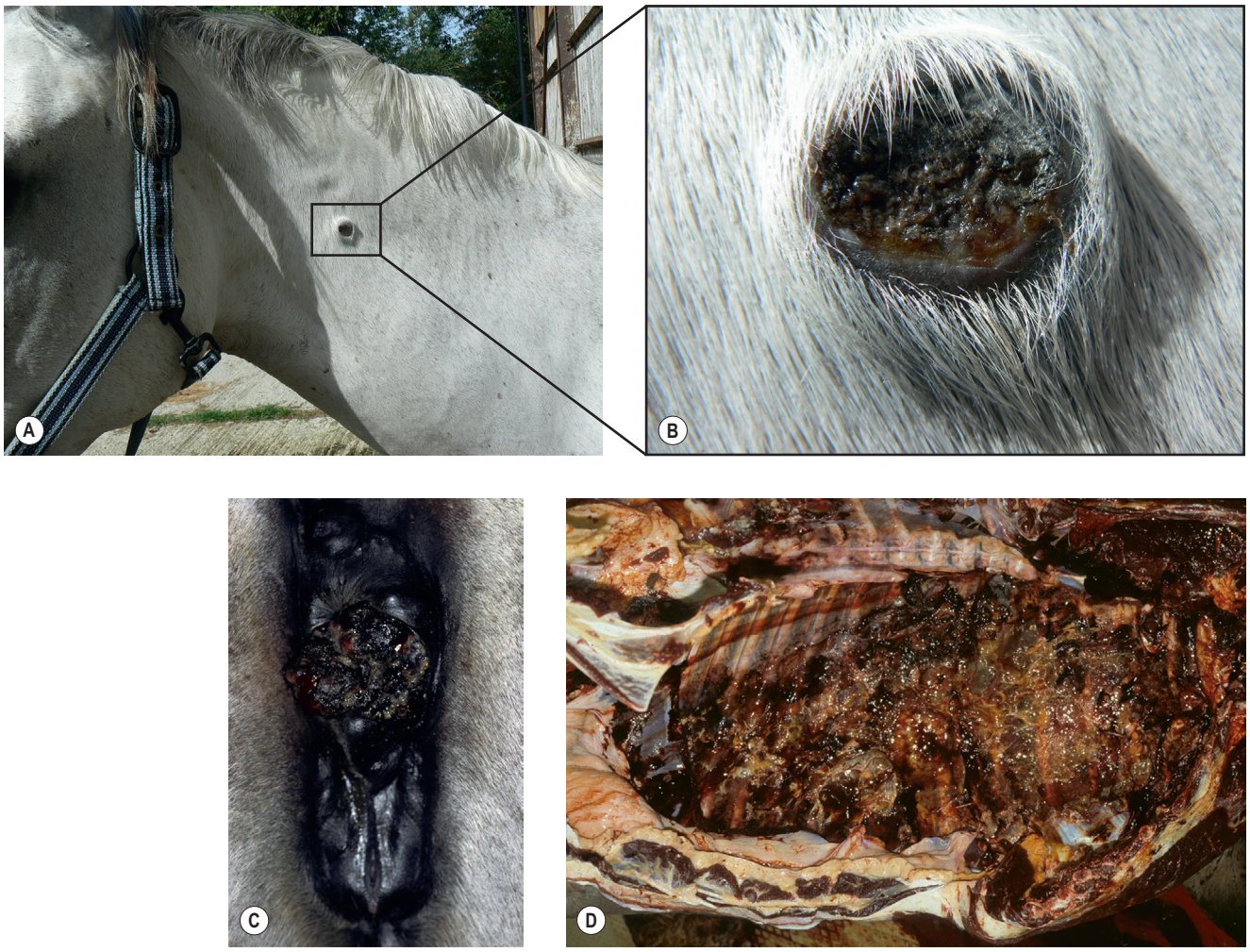


Figure 5.9 The significance of the major clinical features of a tumour using a melanoma as an example. (A,B) An isolated ulcerated melanoma. Treatment of this lesion would be expected to be successful through simple surgical excision. Its localized, defined and single features support a good prognosis. The tumour probably has no clinical implication at this time. However, histological examination is essential to establish the nature of the tumour as benign rather than malignant and that the whole tumour was in fact excised. **(C,D)** There is a danger of assuming that an isolated tumour is necessarily always benign. This ulcerated melanoma was one of a few nodular lesions in the peri-anal skin of this 7-year-old pony mare. Close examination of the tumour revealed pink and grey areas that were shown to be highly malignant and some weeks later the horse was presented with severe colic and respiratory signs. Disseminated melanoma was identified and the animal was euthanized. Widespread melanomas – some without pigment – were found in several major organs, including the thoracic cavity, as shown here, but excluding the lungs themselves. *(Figures A and B courtesy of Chris Riggs.)*

complicated by infection and then ongoing necrosis adds to the difficulty.

Symptoms that arise as a result of thrombosis (with consequent necrosis and rupture of tumours, including localized tissue necrosis with vascular necrosis) may result in catastrophic acute or chronic internal bleeding.

Physical appearance

An added difficulty that faces the equine clinician is the fact that many tumours are of more concern to the owner than to the horse (either physically or physiologically). Often the clinician will have to make a common sense (humane) guess as to whether the tumour is likely to be distressing for the horse in any way. Even large ulcerated tumours that from a human perspective would be considered to be causing unacceptable suffering may elicit no detectable adverse response in the horse. There are no inter-horse social implications of a tumour, no matter how bad and how unpleasant that tumour might appear to owners or veterinarians. Whether a clinician has to consider the psychological effects of a disease on the horse is a matter of considerable debate and philosophical controversy. The reason this is important is often illustrated in cruelty litigation cases where a horse has what we would consider to be an 'unacceptable' disease state: for example a very large ulcerated and infected sarcoid mass in the inguinal region. In this case, the human perspective is clear – we believe that the horse is in fact suffering as result, or at least we consider that it is *likely* that the horse is suffering. However, such a horse may behave completely normally, his appetite might be normal and there might well be no other significant metabolic or physical indicators of suffering. The patient is not ostracized or punished or otherwise harmed by his companions, who show no sign of abhorrence or disgust. It is probably impossible to define what constitutes clinical suffering, but we inevitably extrapolate

from the human circumstance; if it upsets us or if it would be expected to cause pain in a human, then that is what is usually used. For these reasons, this book does not consider the social and other implications of tumour states on the horse itself. That is a matter for the individual veterinarian and owner.

References

1. Cotchin E, Baker-Smith J. Tumours in horses encountered in an abattoir survey. Vet Rec 1975; 97:339–341.
2. Damodaran S, Ramachandran PV. A survey of neoplasms of Equidae. Indian Vet J 1975; 52:531–534.
3. Knottenbelt DC. A suggested clinical classification for the equine sarcoid. Clin Tech Eq Prac 2005; 4(4):277–295.
4. Schott HC, Major MD, Grant BD, et al. Melanoma as a cause of spinal cord compression in two horses. J Am Vet Med Assoc 1990; 196:1820–1822.
5. Rodriguez F, Forga J, Herráez P, et al. Metastatic melanoma causing spinal cord compression in a horse. Vet Rec 1998; 142:248–249.
6. Patterson-Kane JC, Sanchez LC, Uhl EW, et al. Disseminated metastatic intramedullary melanoma in an aged grey horse. J Comp Path 2001; 125:204–207.
7. Haschek WM, King JM, Tennant BC. Primary renal cell carcinoma in two horses. J Am Vet Med Assoc 1981; 179:992–994.
8. Wise LN, Bryan JN, Sellon DC, et al. A retrospective analysis of renal carcinoma in the horse. J Vet Intern Med 2009; 23:913–918.

6

Paraneoplastic syndromes

Anorexia-cachexia and wasting syndromes 73
Tumour lysis syndrome 74
Hypercalcaemia/hypocalcaemia 75
Pyrexia 75
Anaemia 75
Erythrocytosis (polycythaemia) 76
Thrombocytosis/thrombocytopaenia 77
Hypoglycaemia 77
Hypercupraemia 77
Hyperfibrinogenaemia, hyperglobulinaemia and monoclonal gammopathy 77
Paraneoplastic pruritus 78
Paraneoplastic pemphigus and other dermatological paraneoplastic signs 79
Ulcerative coronitis 80
Paraneoplastic bullous stomatitis 80
Protein-losing enteropathy 80
Renal failure 81
Amyloidosis 81
Hypertrophic (pulmonary) osteopathy (Marie's disease) 81

Paraneoplastic syndromes are defined as diseases or combinations of clinical signs that arise as a direct consequence of a cancer in the body but not deriving from the simply physical presence of the tumour; they are therefore pathophysiological processes rather than physical processes. They are a broad group of clinically and biochemically recognizable disturbances caused by non-metastatic systemic effects that accompany malignant disease; they are the indirect effects of cancers.[1] Thus, coughing as result of a bronchial tumour or colic arising because of a pedunculated lipoma are not paraneoplastic signs but anaemia resulting from a malignant tumour of the sinuses is a paraneoplastic effect. A paraneoplastic syndrome is not produced by the primary tumour itself or by its metastases, nor is it caused by compression, infection, nutritional deficiency or treatment of the tumour. Clinical signs deriving from paraneoplastic physiological changes are invariably distinct from those associated with the primary organs from which they derive. In spite of their 'delicacy', paraneoplastic signs may be far more detrimental to the patient than the primary tumour (at least in the short term) and, indeed, in many circumstances, the paraneoplastic effects are the ones that result in catastrophic outcomes. Additionally, the signs may be severe enough to limit or even prevent effective treatment of the underlying tumour condition. In contrast, if the tumour source of the bioactive causes of the paraneoplastic signs can be removed or treated, the paraneoplastic signs will resolve. Recurrence of the signs then can be used to indicate recurrence or recrudescence of the tumour (either at the same site or remotely).

Although the pathogenesis remains unclear, the symptoms are usually attributable to substances that are secreted by the tumour cells themselves or may be the result of antibodies directed against the tumour cells that cross-react with other tissues. The signs are mediated by tumour-derived factors that circulate in the blood, such as cytokines and hormones – some are very similar to the naturally occurring ones and others are less conserved. The former will usually have predictable effects, whilst the latter will usually induce bizarre effects that may be less recognizable. In the former cases, fever, cachexia and hypoglycaemia are the main symptoms. In the latter cases, there may be evidence of autoimmune disease and this is often directed against the skin or blood cells in particular, resulting, respectively, in paraneoplastic pemphigus or pruritus and anaemia and haemorrhagic diatheses. Immune-suppression is a common paraneoplastic effect that has profound effects on the host's ability to resist infection and, indeed, further progression of the cancer. Although particular tumours may have a particular propensity for paraneoplastic signs, specific tumour types do not necessarily induce any particular type or group of paraneoplastic signs. Similarly, no particular paraneoplastic syndrome is a characteristic of a particular type of tumour. The range of options is almost infinite and will depend on tumour, host and other concurrent factors in the individual horse.

The importance of paraneoplastic syndromes is often underestimated in the horse and the signs are often under-recognized or misinterpreted before the underlying pathology is either recognizable or identifiable. Paraneoplastic syndromes may be the first or most prominent manifestation of morbidity and very often the paraneoplastic nature of the sign is overlooked. This results in clinical investigations and treatments that are often inappropriate and almost inevitably delay the proper methodical clinical investigation. Delays in the investigation of a cancer case may not alter the prognosis but certainly once a tumour has advanced significantly the prospects of any treatment success fall away rapidly. By the same token, inclusion of the paraneoplastic diagnostic possibilities in the differential diagnosis or diagnostic refinement process of both common

and challenging clinical situations will surely lead to an earlier and more accurate diagnosis. This in turn will significantly improve the therapeutic opportunities and hopefully the prognosis. Additionally, alterations in the paraneoplastic symptoms can be used to monitor progression or the effects of treatments.

Clinically, paraneoplastic syndromes can cause greater morbidity than the actual physical presence of the malignant tumour. When a patient without a known cancer presents with one of the 'typical' paraneoplastic syndromes, a diagnosis of cancer should be considered and investigated. The appearance may be the first sign of a malignancy and may be so severe that appropriate therapy for the underlying cancer is not initiated.

Paraneoplastic syndromes can affect most organs and tissues. Their significance lies in both their direct metabolic effects and as specific causes of morbidity and even mortality. They are clinically important for a number of reasons. The paraneoplastic effects may be the first (and often the only) sign of serious internal malignant disease. Early recognition of the signs and their significance may allow the clinician to suspect internal neoplasia. That in turn might make treatment easier and more effective. The changes that occur may be a cause of significant patient morbidity and even mortality.

Whilst there are singular advantages in their detection as an early warning mechanism, the presence of significant metabolic derangements may adversely affect the treatment of the underlying malignancy.

Many are either treatable or at least palliatively manageable and others may respond positively to the successful treatment of the underlying neoplasm.

The aetiopathogenesis of the various syndromes (and combinations of syndromes that can occur in any particular individual) is highly complex and very variable. There have been a number of suggestions as to the mechanisms behind the paraneoplastic syndromes, including:

- Endocrinological events that lead to abnormal production of physiologically active mediators and hormones
- Haematological effects
- Neurological effects primarily on the autonomic nervous system
- Secondary systemic responses to tumour presence.

There are four broad targets for the paraneoplastic effects:

1. *Mucocutaneous and skin syndromes*: syndromes that particularly affect the skin where the mucosa and cutaneous skin meet (e.g. dermatomyositis, paraneoplastic pemphigus, paraneoplastic pruritus)
2. *Neurological syndromes*: syndromes that affect the brain and spinal cord (e.g. encephalomyelitis) and sometimes peripheral nerve function
3. *Haematological syndromes*: syndromes that affect the blood (e.g. granulocytosis and anaemia)
4. *Endocrine and metabolic syndromes*: syndromes that affect the endocrine system (e.g. hypercalcaemia).

Additionally, there are some syndromes that do not fit in these four categories (e.g. membranous glomerulonephritis) and psychosomatic effects that are not easily understood in any case and are very rarely encountered in horses.[2]

Recognition of paraneoplastic syndromes (Table 6.1) is important for several reasons:

- Paraneoplastic signs can (and often do) appear early in the development of a cancer and may in fact occur long before the main tumour is detected. This applies particularly in horses. The recognition may therefore be a significant early indicator of a tumour state. This also means that the existence of a cancer state can be easily overlooked; indeed, the signs may be related to other disease and this can lead the clinician into an error of diagnosis that may have profound implications both for the horse and owner, who has to bear the costs involved in the investigations.
- Treatment of the metabolic abnormalities will probably be a significant part of the management of the case. Many paraneoplastic states can be managed but some are much more difficult, e.g. membranous glomerulonephritis or neurological effects. Removal of the tumour (if feasible) may resolve the paraneoplastic state but it may not, and then the signs have to be managed – they can cause significant morbidity and mortality. Paraneoplastic syndromes can lead to severe clinical signs and may lead to emergency cases being presented. For example, a horse may be presented with haemoglobinuria and profound anaemia that could be a result of paraneoplastic changes.
- The severity of the paraneoplastic signs may, in some cases, reflect the severity/or extent of the neoplastic disease but this is not usually the case – paraneoplastic signs may be severe in cases of a small highly active tumour or may be mild in cases of advanced tumour states. The paraneoplastic outcomes are probably best regarded as unpredictable. However, clinical monitoring and quantitative measuring of these signs may give an indication of the rate of progression of a tumour state or improvement in the case of treatment being offered.

The range of reported symptoms, such as hormonal imbalances or immune responses, can be attributed either to substances emanating from a tumour or from a systemic reaction to a tumour. The cardinal feature is that the signs are remote from the site of a malignant neoplasm or its metastases. The first reports of a paraneoplastic syndrome were made by a nineteenth-century French physician M. Auchè, who described the relationship between neurological disorders and systemic tumours in cancer patients in 1890.[3]

Paraneoplastic syndromes are fortunately rare disorders that are probably triggered by alterations of the immune system that occur as a result of the neoplasm. Broadly, these syndromes result from substances produced by the tumour and they occur remotely from the tumour itself. The symptoms may be endocrine, neuromuscular or musculoskeletal, cardiovascular, cutaneous, haematological/biochemical, gastrointestinal, renal or miscellaneous in nature.[4]

The clinical features of the syndromes can easily be mistaken for other naturally occurring disorders, but since they are a secondary consequence of the tumour's presence, treatment of the syndromes themselves (however easy or difficult that may be) will not necessarily result in a permanent cure unless the primary (tumour) condition is treated as well. They can be due to a number of causes, including:

- *Metabolic derangements*: they are derived from altered physiological processes directly or secondarily.

Table 6.1 Reported paraneoplastic syndromes encountered in horses

System	Syndrome	Equine cases reported	Comments for equine species
Endocrinological	Hypercalcaemia	****	Lymphoma and some carcinoma cases; common but not invariable
	Hypoglycaemia	****	Metabolically active tumours producing insulin-like growth factor; common
	Cachexia/anorexia	****	Variable; common
Neurological Neuromuscular	Seizure	*	Central nervous system tumours/pituitary adenoma
	Blindness	**	Liver tumours
Renal	Polycythaemia	*	Rare
	Membranous glomerulonephritis	*	Very rare. Possibly commoner than is reported
Dermatological	Pruritus	***	Renal carcinoma/disseminated carcinoma/sarcomas
	Pemphigus	**	Renal carcinoma/lymphoma
	Ulcerative coronitis	**	Alimentary lymphosarcoma
	Bullous stomatitis	*	
	Ichthyosis	?	Anecdotal
Haematological Biochemical	Anaemia	****	All serious tumours (variable)
	Thrombocytosis	*	Rare
	Thrombocytopaenia	****	Lymphoma (immune mediated)
	Erythrocytosis	*	Renal tumours/metastatic carcinoma
	Neutrophilia	****	All tumours (variable)
	Neutropenia	*	All tumours (unusual)
	Thrombosis	*	Significance/relationship uncertain
	DIC	**	
Alimentary	PLE	****	Lymphoma/adenocarcinoma
Musculoskeletal	Myasthenia	?	Rare/uncertain if present in horses
	HyPO	**	Rare; significant indicator of thoracic/abdominal masses
	Arthritis/arthrosis	*	Uncertain
Circulatory	Vasculitis	***	Common/ill-defined; nonspecific
	Dysrhythmia	*	Phaeochromocytoma

The evidence for the existence of some of these is tenuous, since there are few proper scientific studies on cancer of any type in Equidae. DIC, disseminated intravascular coagulopathy; PLE, protein-losing enteropathy; HyPO, hypertrophic pulmonary osteopathy. ***Note:*** *The more starts there are the commoner the paraneoplastic sign is associated with that tumour type. Where no information is available we have placed a ?.*

- *Hormones or other biologically active products*: these are expressed by the tumour cells and are common outcomes of cancer. Hypercortisolaemia with consequent hyperglycaemia can occur in some circumstances. However, hypogylcaemia is usually more common and arises from direct secretion of insulin-like growth factor, which is a relatively common metabolic product of cancer cells. Hypocalcaemia occurs from the secretion of an abnormal protein called 'parathyroid hormone related peptide', which mimics the effects of natural parathormone. A functional tumour of the chromaffin cells of the adrenal medulla can create sustained or paroxysmal abnormally high blood pressure accompanied by sweating and a high heart rate.
- *Blockade of the effect of a hormone through the action of abnormal mediators*: this is typified by the secretion of antidiuretic hormone-like peptides that preclude the production of dilute urine. Fluid retention and electrolyte imbalances then arise.
- *Autoimmunity*: this arises from the induced failure of the immune system to recognize its own constituent parts as *self*, which allows an immune response against its own cells and tissues.
- *Immune-complex production*: this arises as result of abnormal proteins that are recognized as such by the immune system. The immune complexes can be deposited on vascular endothelium, causing vasculitis or vascular occlusion and ischaemia or organ failure. The latter is exemplified by immune complex deposition in the renal glomerular vessels, with consequent loss of glomerular function and so renal failure can develop.
- *Immune suppression*: whilst most of the immunosuppressive effects of tumours occur locally in and around the tumour itself and may be the primary mechanism for tumour evasion of the host's immune system, other immunosuppressive effects also occur. It is accepted that alterations in systemic TAA-specific T-cell immunity also occurs in patients with malignant

disease.[5] A marked decrease in the expression of CD3 chain expression as well as tyrosine kinases occur, all of which play a critical role in the signal transduction events that lead to T-cell activation. These changes are accompanied by a decreased tyrosine kinase phosphorylation and diminished calcium influx. These findings provide a molecular basis for T-cell dysfunction in cancer patients. In human cancers, T cells and NK cells form a high proportion of carcinoma, melanoma, and lymphoma patients have decreased CD3 chain expression and decreased in vitro response to antigens or mitogens. Circulating T cells are biased in their cytokine profile or otherwise functionally compromised in patients with malignant disease. Since alterations in circulating T-cell function, as determined by CD3 chain expression, proliferative index or NFB activity, are associated with the extent of alterations in TIL function and tumour stage, CD3 chain expression may be a marker of immune competence in patients with malignant disease; individuals who have normal CD3 chain expression are most likely to respond more favourably to biotherapy. Taken together, these findings suggest that a loss of effector T-cell function through targeted apoptosis might severely compromise anti-tumour functions of the host immune system and contribute to tumour progression. It also results in the aberrant lymphocyte homeostasis characterized by a rapid turnover of T cells, especially CD4+ T cells.

Additionally, the tumour may not induce generalized lymphocyte dysfunction, including the reduced ability to produce IL-2 and IFN-γ. Among lesser known, but clearly important immunosuppressive effects that tumours mediate, is the ability to induce T-cell apoptosis.

One or more of these effects can be identified in a proportion of equine cancer patients, although fever is the most common presentation, in horses at least. Several clinical pictures may be detected, many of which simulate more common (usually) benign conditions. A good example is the paraneoplastic pemphigus syndrome, which is histologically and clinically identical to the spontaneously occurring autoimmune disease. This is not surprising, since the remote effects are defined by the pathological induced process rather than the tumour type involved.

The clinical spectrum associated with the various paraneoplastic syndromes is very wide and a significant range of signs can be encountered; multiple body systems can be involved, although quite commonly a single sign, for example fever or hypercalcaemia, is prominent. In other species, a large number of cancer patients show CNS involvement, but this is not a regular reported event in horses; possibly this is due to the slow progression of symptoms seen in most equine malignancies or to failure of recognition of subtle changes in behaviour and central and peripheral nerve functions.

As an example, a well-recognized paraneoplastic syndrome in many species involves inappropriate secondary secretion of anti-diuretic hormone (ADH). The effects of this include disturbances of fluid and electrolyte balance and inability to pass diluted urine; there may be wider secondary effects including inappetence, lethargy and even muscle cramping. Whether these occur in horses is not certain but it is possibly more likely to be due to the fact that they are not attributed to a paraneoplastic state or that they are simply overlooked during inadequate clinical investigation.

Anorexia-cachexia and wasting syndromes

The formal definition of cachexia is 'the loss of body mass that cannot be reversed nutritionally'.

Cachexia is probably the most debilitating and life-threatening effect of cancer.[6] It is associated with combined weight loss, anorexia and pica and is certainly one of the cardinal features of cancer in horses. Where this is present, it is strongly correlated with a very poor prognosis. The condition remains one of the most profound metabolic alterations in cancer cases.

Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia. The combined effects of cachexia and anorexia could, in some circumstances, be attributable to paraneoplastic effects but they are a recognized entity in their own right. The progressive loss of body mass (fat as well as lean mass) is a feature of many internal cancer conditions in the horse. Commonly, this is accompanied by other (paraneoplastic) signs, including anaemia, anorexia (which exacerbates the weight loss) and weakness, which is usually profound. Oedema (subcutaneous, ascites and distal limb filling) may be a prominent feature also. Resting energy expenditure is significantly increased and energy and protein intake is reduced as result of anorexia and inappetence – this combination accelerates the loss of body mass. The rate of weight loss is variable, but in common with the similar state in other animals and man, the rate is relatively slow at first but accelerates, and careful questioning of the owner will usually identify this progression.

The origins of cancer cachexia might easily be 'blamed' simply on the 'parasitic' nature of the tumour, but this is not the main driving force behind the condition. Similarly, whilst it is logical that anorexia would result in weight loss, usually the progression is not commensurate with that aspect of the tumour. In cancer cachexia-anorexia states, the overall picture of wasting is disproportionately severe when compared with the degree of anorexia (Fig. 6.1).



Figure 6.1 Cancer cachexia. This 6-year-old Anglo-Arab gelding was diagnosed with multicentric lymphoma and had lost an estimated 30% of his body weight over a 6-week period. His appetite was moderate and intermittent. He shows the characteristic features of cancer cachexia, i.e. profound progressive weight loss involving loss of muscle mass and fat.

In contrast to the physiological lowering of basal metabolic rate in primary starvation, the basal metabolic rate of cancer patients is usually significantly elevated and so calorific requirements are high. Additionally, in cancer cachexia there is a continuous and roughly equal loss of fat and lean mass through the period of weight loss and this contrasts with the straightforward loss of fat in the early stages of starvation[7]; in starvation, lean mass is conserved as long as possible at the expense of fat stores. Increasing oral or parenteral calorific and protein intake does not prevent the continuing weight loss.

The reasons behind the anorexia are unclear in the human and even more so in the horse. Nevertheless, horses with serious internal cancers, such as gastric carcinoma, lymphoma or disseminated secondary carcinomas, will have a variable appetite. Whether this is a result of discomfort, loss of taste or smell senses or from an early onset of a sense of satiety, is matter of conjecture and extrapolation from other species that may not be truly justifiable. Affected horses frequently exhibit bruxism, salivation, eructation and slow eating of any or all the offered food materials. There may be significant changes from day-to-day, with some days being better than others. Affected horses often have complicating gastric ulceration, which could be misinterpreted as the primary problem. In the authors' experience, controlling the ulceration with proton pump blocking drugs (such as omeprazole or with sucralfate) has little benefit on the progression of the condition – even when the ulcers are controlled or cured. It is also often accompanied by anaemia and immunosuppression – effects that are harder to explain but which are probably also paraneoplastic events. When several signs associated with paraneoplastic syndromes are present, the diagnosis of cancer is usually justified, although of course that is simply the first step along the diagnostic process.

In spite of the frequency with which this occurs in cancer cases, its origins are not clear. It is likely that it involves catabolic substances generated by the tumour or by the body's reaction to it. These include cytokines specifically secreted by the tumour and other bioactive molecules secreted by the host in response to the cancer state.[8] Indeed, most of the changes associated with cancer cachexia, including the loss of appetite and the alterations in fat metabolism, can be induced experimentally by the exogenous administration of tumour necrosis factor (TNF), which is also nicknamed 'cachexin' (also 'cachectin') for this reason. It is assumed that TNF is secreted by the tumour cells and by macrophages in and around the tumours. Whilst this alone may be a major player in the syndrome, it is very likely that other mediators, such as interleukin-6 (IL-6) and interferon-gamma (IFN-γ) as well as the tumour-secreted proteolysis inducing factor (PIF), act synergistically with the TNF. The complex, multifactorial origin of cachexia precludes a uniform pathophysiological profile and it is probably true to assume that no two cases will present identically.

It is certain that cancer cachexia is under-recognized and is frequently misdiagnosed, being blamed on parasitic infestations, dental defects, starvation or gastric ulceration syndromes, some or all of which may well be present anyway. Cancer cachexia carries an inevitable increase in morbidity and mortality. The survival time of horses with cancer cachexia is significantly less than those without.[9] They may also tolerate treatment less well and it is probably fortunate that most cases with the cachexia-anorexia syndrome are recognized easily and are destroyed humanely. As soon as the syndrome is obvious, owners will often take strenuous measures to improve calorific and protein intake – often using ingenious measures, but it is invariably in vain; clear evidence of anorexia-cachexia syndromes indicates a very poor prognosis.

Tumour lysis syndrome

In human medical oncology and haematology, the tumour lysis syndrome (TLS) is a well-recognized oncological emergency, characterized by severe metabolic derangements including acute renal failure.[10] The syndrome is encountered most often in in patients undergoing treatment for lymphoproliferative malignancies (leukaemia and lymphoma), by radiation, chemotherapy or corticosteroids; it is sometimes encountered in untreated patients. The major risk factors are usually a large tumour burden, high growth fraction (and therefore a high sensitivity to therapy), increased circulating lactate dehydrogenase (LDH) and pre-existing renal disease.

The tumour lysis syndrome probably arises from rapid tumour cell turnover, with concurrent necrosis/lysis, and that probably explains the proportionality of the sign to the size and replication rates of the tumour. Extensive tumour cell destruction will necessarily release ions, mediators and metabolic by-products (both normal and abnormal) in abnormal amounts into the circulation. The hyperphosphataemia can be attributable at least in part to the fact that malignant cells often contain up to four times as much phosphate as normal cells.[11]

The main diagnostic clinical features are usually cardiac arrhythmia and seizure identified haematologically as hyperkalaemia, hyperphosphataemia, elevated serum creatinine concentration and possibly hypocalcaemia and elevated lactate dehydrogenase.

It is not yet established whether this syndrome occurs in horses with any regularity, but a significant number of untreated cases that have been reported in the literature do have evidence of renal disease, as well as significant electrolytic changes along the same lines.[10,12] An equine case of mesothelioma with convincing signs of TLS has been reported.[13] This animal showed hyperkalaemia, hyperphosphataemia, hypocalcaemia, elevated lactate dehydrogenase and acute renal failure; the tumour was extensive and had a very large growth fraction.

This syndrome should be suspected if a horse is presented with acute renal failure and suspected or proven cancer. High uric acid and oxalate concentrations will also have significant effects on the renal tubular cells and so concurrent elevations in urinary gamma-glutamyl transferase might assist in the diagnosis.

Since the metabolic changes are profound, affected animals may have clinically significant cardiac dysrhythmia and may even suffer sudden death. Most current textbooks on equine medicine fail to recognize sudden death as a possibility in advanced cancer cases but it seems likely that this syndrome does exist in horses. Since most serious equine tumour cases present without any pathognomonic

signs and diagnosis is reliant upon a combination of more or less subtle changes, any alterations that would fit with the TLS should be taken seriously.

A proportion of the cases presented to the authors with 'idiopathic' synchronous diaphragmatic flutter (usually ascribed to hypocalcaemia and usually transiently responsive to suitable calcium therapy) are found to have internal neoplasia but this is not often reported. This is possibly complicated by the induced hypocalcaemia that is recorded from a pseudohyperparathyroidism that is more often found in horses. The normal equine calcium homeostasis is different from other species and this may confuse the issue significantly if blood calcium is the only measured parameter. The condition may also be encountered in the absence of treatment and is attributed to metabolic complications arising from lysis of tumour cells.

A possible reason why the syndrome is not better recognized in horses is the obvious fact that few seriously ill cancer cases are subjected to treatment that is likely to lyse large numbers of tumour cells over a short period of time. It is possible that in due course when treatments are attempted, this may become a more recognizable complication. Where treatment is attempted in cases of equine lymphoma, pre-emptive measures may be helpful; these might include maintaining urine output and carefully monitoring and correcting metabolic abnormalities that develop during the treatment period.

Hypercalcaemia/hypocalcaemia

Overt, clinically relevant hypercalcaemia (increased ionized calcium concentration) in the horse is probably the most recognized paraneoplastic syndrome in horses; it has been recognized in 25% of horses diagnosed with gastric carcinoma.[14] Hypercalcaemia is a detectable feature in a variety of equine tumours, including lymphoma, plasma cell myeloma and disseminated squamous cell carcinoma case and less commonly in other tumour types.[1,15–24] In contrast to most other species, hypercalcaemia can be confused by renal failure in which this is also a feature.[22]

The elevation in circulating ionized calcium in cancer patients is usually attributable to the tumour-derived parathyroid hormone-related protein (PtHRP). This protein has a portion of the molecule that resembles natural parathyroid hormone. Although the protein is produced by normal cells, such as keratinocytes, muscles and bone, the amounts are minute and clinically insignificant. It is only when the amount produced by tumour cells is excessive that clinical effects appear. PtHRP leads to significant bone resorption and elevated calcium concentration. However, the likelihood is that hypercalcaemia has a much more complex aetiopathogenesis that may involve several other factors including tumour-derived prostaglandins, osteoclast activating factors, interleukin-1 (IL-1), transforming growth factor beta (TGF-β) and possibly tumour necrosis factor (TNF). Abnormal forms or induced abnormality of function of vitamin D may also be involved. Hypercalcaemia is seldom associated with bone metastasis or with bone neoplasia.

Hypercalcaemia may result in gastrointestinal, neuromuscular and cardiovascular signs and sometimes also in renal abnormalities. Intestinal stasis resulting in recurrent obstipation and anorexia are often present but can easily be overlooked. Hypercalcaemia also causes decreased neuromuscular function resulting in one or more of the following: lethargy, weakness, muscle fasciculation and twitching and behavioural changes including depression, stupor, coma and even seizure. Myocardial function is also affected, sometimes with evidence of increased myocardial excitability manifest as ventricular systole, syncope and weakness. Polyuria and polydipsia arise from decreased renal concentration ability as well as direct damage to the tubules from high circulating calcium concentration.[12]

Possible differential diagnoses for hypercalcaemia in horses are listed in Box 6.1.

Pyrexia

Recurrent undulant or persistent pyrexia of unknown origin (PUO) is a relatively common paraneoplastic effect of internal cancers of horses. It is likely that the pathogenesis is relatively simple; pro-inflammatory cytokines such as interleukin-1 and -6 (IL-1, IL-6), tumour necrosis factor alpha (TNF-α) and various interferon forms released from expanding tumours or from areas of necrosis within the tumour would usually explain the presence of fever. Concurrent elevations in inflammatory acute phase proteins may be present in the latter circumstance, but would probably not be significant in the former. Secondary infections arising from immunosuppression can also cause fever and, in this case, antibiotics and anti-pyrexic drugs will usually reduce the fever, at least temporarily.

Possible differential diagnoses for PUO in horses are listed in Box 6.2.

Anaemia

Anaemia is a prominent paraneoplastic feature of many equine internal neoplasms and in particular carcinomas and tumours affecting the lymphoid system. There are several ways in which anaemia can develop in a tumour case:

1. *Direct haemorrhage*: In this case there may be major arterial bleeding or chronic persistent blood loss resulting in clinically detectable anaemia. The blood loss anaemia is not itself then a paraneoplastic effect,

Box 6.1 Some possible differential diagnoses for hypercalcaemia in horses

- Chronic renal failure
- Hypervitaminosis D
- Plant toxicosis (e.g. *Cestrum diurnum*)
- Primary hyperparathyroidism.

Box 6.2 Possible differential diagnoses for pyrexia (of unknown origin) (PUO) in horses

- Viral, bacterial and protozoal infections / internal abscess
- Other inflammatory conditions
- Autoimmune disease.

but it may be complicated by paraneoplastic thrombocytopaenia, clotting factor deficits and developing disseminated intravascular coagulopathy (DIC). If this haemorrhage can be stopped, the anaemia will resolve. It may be possible to identify the bleeding, but in other cases it is far more problematic. From a haematological perspective, it might be possible to conclude that the anaemia is a primary event, by laboratory investigations; primary chronic blood loss anaemia is usually mildly progressive (unless there is a catastrophic bleed or a major bleed into a body cavity or externally).

2. *Bone marrow suppression*: Bone marrow suppression can be a paraneoplastic effect but possibly it is more often associated with the anaemia of chronic inflammation arising from altered iron metabolism. It is not clear whether paraneoplastic effects result in direct bone marrow malfunction, but it is reasonable to suppose that at least some cell series might be affected.
3. *Haemolytic anaemia*: Intravascular haemolysis and red cell destruction (through splenic and other functions) have been identified as relatively frequent occurrences in adult horses with neoplastic disease and it is likely that anaemia in cancer cases will have some component of this. Indeed, in adult horses presented with unexplained haemolytic anaemia, internal tumours and lymphoma in particular can be justifiably suspected.[25,26] The pathophysiology of the haemolytic state is uncertain but it may be a result of abnormal paraprotein depositions on red cells, which may result in 'physiological' destruction in the spleen. However, in many cases, the spleen may not be enlarged. Concurrent icterus is a common feature of this state and there may also be a persistent or intermittent fever.
4. *Bone marrow obliteration (myeloproliferative disease)*: Progressive and extensive tumour invasion of the bone marrow is termed 'myeloproliferative phthisic disease' and in its advanced stages this will cause a profound and progressive anaemia. Blood-forming elements of the bone marrow are unable to reproduce normal blood cells due to overgrowth of tumour cells. This state is singularly rare in horses.
5. *Coagulation dysfunction*: Clotting abnormalities are not often recorded in neoplastic disease in horses, but they do occur. Autoimmune thrombocytopaenia, however, does occur with some frequency – often in sufficient severity to result in detectable haemorrhages in mucous membranes and micro-haematuria and intestinal bleeding (with melaena). Where no other explanation can be found, this can be considered in the differential diagnosis.

Erythrocytosis (polycythaemia)

A number of neoplastic states have been identified that induce erythrocytosis/polycythaemia.[12]

Erythrocyte production is normally under the control of erythropoietin, and primary polycythaemia is a bone marrow problem in which the number of erythrocytes produced is largely independent of the erythropoietin response. Secondary erythrocytosis occurs in the face of abnormal amounts of erythropoietin; the commonest cause for this is the physiological response to sustained hypoxia or to the unnatural overproduction of erythropoietin or the production of abnormal pseudo-mediators that have the same effects. Paraneoplastic erythrocytosis is a result of tumour production of erythropoietin or a tumour production of a prostaglandin mediator, which is suggested to enhance the effects of natural erythropoietin (or both).[27,28]

The cause of the recognized erythrocytosis of neoplastic disease (polycythaemia) (abnormally elevated total erythrocyte count with haematocrit readings often in excess of 55 L/L) encountered in some neoplastic states is suggested to be the abnormal production of erythropoietin[29]; it is not certain if the erythropoietin stimulus is due to the natural hormone or an analogue that may derive directly from tumour-transformed cells. Both circumstances could arise quite understandably. The hormone erythropoietin is normally secreted by the kidney and is responsible for increasing red cell production. Abnormal production would necessarily induce excessive red cell production. In horses, renal tumours, some forms of lymphoma and hepatic tumours are recognized as being potential exogenous sources of erythropoietin.[27] This can arise, at least in theory, in cases of neoplastic damage to the kidneys and in hepatic carcinoma.[22]

The possibility of erythrocytosis should be considered when a horse has a detectable tumour and 'redder than normal' mucous membranes, with a slightly prolonged capillary refill time (Fig. 6.2). Circulation can be sluggish as result of increased red cell volume – haematocrit values of >60 L/L might occur in some cases.

The syndrome is reported in a number of equine conditions including primary hepatic tumours (hepatoblastoma and hepatic carcinoma) and metastatic carcinoma with hepatic involvement and myosarcoma.[12,27,28] Since the effect is genuinely paraneoplastic it is unlikely to be controlled long term without resolving the underlying tumour but it appears that a significant improvement (reduction) in the haematocrit can be achieved through the per os use of hydroxyurea (15 mg/kg q 12 h).



Figure 6.2 Polycythaemia/Erythrocytosis. This 12-year-old gelding was diagnosed with secondary metastatic hepatic carcinoma. His haematocrit was in 68 L/L and was considered to be a likely the result of profound erythrocytosis. His oral mucous membranes and his conjunctivae were dark (fiery) red and quite different to the colour that is associated with endotoxaemia. His erythropoietin concentration was 11 μ/mL (reference <6 μ/mL). No attempt was made to treat or manage the horse.

Box 6.3 Possible differential diagnoses for elevation of haematocrit or erythrocytosis in horses

- Primary polycythaemia
- Dehydration (for whatever reason)
- Renal failure
- Endotoxaemia.

Possible differential diagnoses for elevation of haematocrit or erythrocytosis in horses are listed in Box 6.3.

Thrombocytosis/thrombocytopaenia

There is little information on the characteristics of platelet alterations in neoplastic disease in horses, but alterations of platelet numbers and function is a feature of neoplastic disease in most (if not all) other species. Hyperthrombocytosis and thrombocytopaenia are both recognized. However, the significance of platelets in oncological disease may relate more to their function than their pure numbers.[27]

It is important to realize that significant thrombocytopaenia can arise directly from the use of chemotherapeutic drugs but in horses, as opposed to many other species, an immune-mediated thrombocytopaenia can occur as a direct paraneoplastic effect. This may arise from excessive platelet destruction/consumption or decreased production from direct bone marrow suppression. Little is known about this response in horses apart from the fact that lymphomas and, in particular, splenic lymphoma and some haemangiosarcoma cases are more often responsible.

Given its putative immune-mediated origin, corticosteroids (at doses in excess of 1–2 mg/kg q 24 h) and possibly azathioprine (1 mg/kg q 24 h) can be helpful measures in controlling the problem. One of the major difficulties is getting reliable platelet counts – ideally, citrated blood is better than EDTA samples and counts need to be performed promptly.

Thrombocytosis is relatively common in other species but there are few reports of this in horses.

Hypoglycaemia

Reduced circulating blood glucose concentrations are rare in adult horses and are commonly the result of poor technique and collection. Hypoglycaemia in cancer cases has been reported with some frequency associated with renal carcinoma,[30,31] hepatocellular carcinoma[27] and mesothelioma.[13] Explanations for this finding include possible failure of compensatory mechanisms, hepatic dysfunction/failure, elevated circulating TNF-α and increased basal metabolic rate. Paraneoplastic hypoglycaemia has been reported in a 12-year-old Shetland pony; this was a direct effect of hyperinsulinaemia derived from an active functional insulinoma.[32] Non-islet production of insulin-like peptides can also cause hypoglycaemia in other tumours; the majority of non-islet tumours that produce insulin-like peptides are hepatocellular carcinomas.[27] It is also reasonable to suggest that tumours that are metabolically very active would have a consumptive effect on circulating glucose. An additional effect might be exerted by direct metabolic suppression of the glucogenic and gluconeogenic pathways in the liver.[33] Additional factors that may be associated with a reduction in circulating glucose include concurrent infection/sepsis (especially in foals), starvation or liver dysfunction. Since these are all possible secondary effects of serious neoplastic disease, the primary cause of hypoglycaemia is often hard to establish. However, the role of insulin-like peptides is likely to be the only mechanism that can override the normal glucose homeostatic processes; severe or prolonged hypoglycaemia is most likely therefore to be associated with the peptide release.[34]

Box 6.4 Possible differential diagnoses for hypoglycaemia in adult horses

- Poor collection technique
- Exhaustion
- Enteritis/impending enteritis/colitis
- Small and large intestinal strangulation/endotoxaemia
- Hyperlipaemia/hypertriglyceridaemia
- Other inflammatory conditions.

Possible differential diagnoses for hypoglycaemia in adult horses are listed in Box 6.4.

Hypercupraemia

In human cancer patients, elevated serum copper and ceruloplasmin concentrations have been reported[35] and this has also been identified in a horse diagnosed with renal adenocarcinoma.[35,36] These parameters might be used for both early diagnosis and for prognostic guidance. The suggestion is that these two assays might be of significant help in cases of equine neoplastic disease but little is known about either substance in the horse and, in any case, they are rarely measured in clinical practice. There are few suggestions as to the basis for the elevations associated with malignancy, but there is interest in developing methods that reduce plasma copper and ceruloplasmin.[37,38]

Hyperfibrinogenaemia, hyperglobulinaemia and monoclonal gammopathy

Elevated tumour production of interleukin-6 (IL-6) stimulates the production of acute phase reaction proteins, including fibrinogen (and possibly serum amyloid A) from the liver. This response is probably best regarded as genuinely secondary, since it can arise also from infections and other inflammatory foci, which may be independent or associated with neoplastic disease. For example, horses with intestinal lymphoma are often complicated by ulceration and infection (both locally and systemically) and these can result in an acute phase protein response.[12] Typically, most/all paraneoplastic signs can be resolved if the tumour focus can be removed.[1]

Monoclonal gammopathy is common in horses with cancer and, as a group, are termed 'M-component disorders'. The hyperglobulinaemia as a paraneoplastic syndrome arises from excessive production of proteins from a monoclonal line of immunoglobulin-producing cells – either plasma cells (most often and most profoundly) or

lymphocytes. Although any protein-producing tumour can induce a 'monoclonal gammopathy', this is usually the preserve of immune cell lines, such as lymphoma or more commonly, plasma cell tumour (myeloma) (p. 92, Fig. 7.8 and p. 536). Plasma cells are naturally responsible for the production of the M component of immunoglobulins, which may include various components of the immunoglobulin molecules or the entire immunoglobulin. Plasma cell malignancy invariably derives from clonal expansion of a single abnormal cell line and these produce para-proteins of various sizes – usually IgG isotype, which cause significant elevations in serum globulins.[1,23,39]

The clinical effects of extreme hyperglobulinaemia arise as result of significantly increased plasma viscosity (reflected in an abnormally slow erythrocyte sedimentation rate), which can result in ataxia, behavioural changes including coma and seizure, and cardiac/circulatory compromise, which results in tissue hypoxia, clotting problems and even ocular changes (including retinal detachment and papilloedema).

The abnormal proteins are readily recognized by routine biochemical analysis but electrophoresis is required to identify whether the changes are monoclonal or polyclonal.

Multiple myeloma is rare in horses, but occurs from time to time. Significantly, it seems that the characteristic short-chain globulins encountered in other species (Bence Jones proteins) are not routinely found in the urine of affected horses.

Possible differential diagnoses for hyperfibrinogenaemia and gammopathy in horses are listed in Box 6.5.

Paraneoplastic pruritus

Pruritus is a relatively common equine paraneoplastic syndrome from internal neoplasms and it may be an early indicator of tumour development – often being a major clinical presentation long before any obvious tumour can be identified. This may be accompanied by primary (paraneoplastic) or secondary (self-trauma-related) alopecia.

Results of gross evaluation of the skin and microscopic evaluation of skin scrapings are often inconclusive or nonspecific. Skin biopsies may show vasculitis but the changes are easily confused by the effects of self-trauma. Since various types of lymphoma have a greater tendency to induce these changes, this and renal carcinoma in particular should be considered in the differential diagnoses when examining horses with generalized pruritus for which another cause cannot be identified (Fig. 6.3).[40]

Various aetiological mechanisms have been observed in other species, ranging from direct tumour invasion of the skin, distant metastases to paraneoplastic inflammatory skin diseases and paraneoplastic phenomena. It is suggested that this is primarily a result of T-cell destruction arising from abnormal cytokines produced by the tumour itself.

Pruritus has also been encountered during treatment of cancer cases and so this might represent side-effects of therapy. It may also be possible that as-yet unidentified mechanisms or metabolites released by the cancer tissue or dying cancer cells contribute to the origin of the pruritus.

Pruritus in cancer may also be caused by nerve compression, tumour growth or bile duct compression with cholestasis. The latter may be mistaken for the even rarer state of hepatocutaneous syndrome in horses. Toxic substances and necrotic tumour cells have also been

Box 6.5 Possible differential diagnoses for hyperfibrinogenaemia and gammopathy in horses

- Viral, bacterial, protozoal and parasitic infections
- Other inflammatory conditions
- Autoimmune disorders.





Figure 6.3 Paraneoplastic pruritus. This horse presented with acute-onset, severe, generalized pruritus. He was diagnosed clinically with renal carcinoma and this was confirmed at necropsy. In the complete absence of any other convincing cause of the pruritus, it was considered to be a paraneoplastic syndrome. **(A,B)** His persistent itching resulted in extensive hair loss over large areas of his body, face and legs. **(C)** He occasionally had episodes of much more severe pruritus, which resulted in skin erosions and bleeding that particularly affected his buttocks and upper forelimbs. There were areas that were spared and remarkably few other signs of serious underlying disease.

suggested as possible causes in pruritus of cancer patients. It is not clear whether all the mechanisms depend on progression of the carcinoma and metastasis.

It is usually believed that paraneoplastic pruritus disappears or diminishes after tumour resection/treatment and that is certainly reported in many species. Relapse of pruritus may constitute the only sign of reactivation and progression of a carcinoma and, as such, is an important sign. However, there is no clear evidence for these criteria according to clinical studies. One explanation for this circumstance is that pruritus is mostly not recorded as a symptom in cancer studies, especially in non-dermatological fields.

Paraneoplastic pemphigus and other dermatological paraneoplastic signs

Paraneoplastic pemphigus (PNP) is an autoimmune blistering disease that occurs in association with underlying neoplasms and it represents a unique clinical, histological and immunological disease characterized by autoantibody production to desmoplakin I and desmoplakin II, bullous pemphigoid antigen and, possibly, other antigens in the desmosomal complex. The occurrence of paraneoplastic cutaneous autoimmune bullous disease (pemphigus foliaceus or more rarely pemphigus vulgaris or bullous pemphigoid) is very unusual in horses but it does occur (Fig. 6.4).

The basic histological features, including epidermal acantholysis, suprabasal cleft formation, dyskeratotic keratinocytes, vacuolar change of the basilar epidermis and epidermal exocytosis of inflammatory cells, may well be indistinguishable from the naturally occurring disease, so it is difficult to be sure that the condition is not a concurrent disorder. However, an unusual combination of suprabasal acantholysis and dyskeratotic keratinocytes throughout the epidermis is a reasonable marker of the paraneoplastic form of the disease. The histological features correspond to those of the characteristic clinical lesions of pemphigus and erythema multiforme. However, immunohistochemical analysis in other species, including man, has shown that 'atypical' pemphigus-like autoantibodies occur and it is concluded that these are a result of paraneoplastic changes.[41] Recognition of the histological features should prompt immunopathological confirmation and evaluation for an occult neoplasm.

Renal carcinoma is the most frequent culprit for the development of the condition in humans and the limited numbers of cases that the authors have encountered also involve a significant proportion of renal and other internal major organ carcinoma cases.[42]



Figure 6.4 Paraneoplastic pemphigus. This Welsh cross gelding was presented with classical generalized signs of pemphigus foliaceous with extensive scaling and alopecia over his entire body **(A–D)**. He was reported to have lost weight significantly over the previous 3–6 months without explanation. There was a proliferative coronary band inflammation with extensive alteration of the hoof capsule of all four limbs and an inflamed margin around the ergots and chestnuts. There was no positive response to immunosuppressive doses of corticosteroids. A histological diagnosis of pemphigus was established but was not considered to be 'typical' in all features. He was diagnosed with intestinal adenocarcinoma and whilst the possibility remains that the pemphigus could have been a concurrent/independent event, we considered it most likely to be a case of paraneoplastic pemphigus. The histology was consistent with the paraneoplastic forms of the disease. The lack of steroid response might be a significant diagnostic feature.

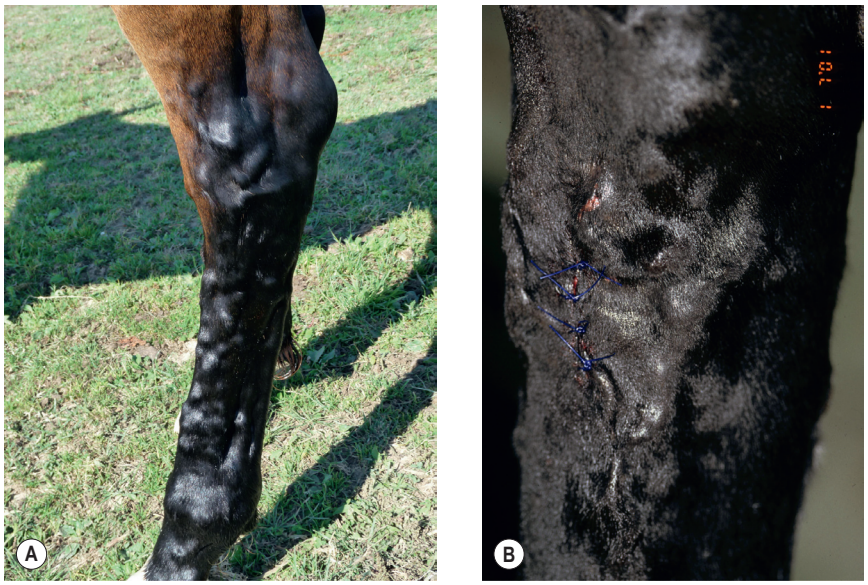


Figure 6.5 Multicentric leukaemic lymphoma. This 16-year-old horse was diagnosed with multicentric leukaemic lymphoma. **(A,B)** Biopsy of the nodules on the limbs showed dense collagen and only very few cells. This may have been equivalent to the nodular dermal fibrosis that is sometimes encountered in other species.

Concurrent evidence of a tumour condition should be sought in middle-aged or older horses that present with typical histological and clinical evidence of pemphigus. From a therapeutic perspective, the authors have found that the response to corticosteroid administration is less effective in reducing the signs than in the non-paraneoplastic forms of pemphigus. Combinations of immunosuppressive agents are usually required to obtain even partial control of the skin lesions. Characteristically, lesions occurring on the mucous membranes appear to be even more refractory to treatment.

A nodular dermatofibrosis occurs in small animal cancer patients but has not been recorded in the equine literature. However, the authors have encountered a case of multicentric lymphoma that showed all the characteristics of this syndrome (Fig. 6.5). In this case, it was assumed that the nodules in and under the skin, predominately on the legs, were due to lymphocytic nodules but biopsy confirmed that they were composed of dense collagen only.

Ulcerative coronitis

Severe swelling and ulceration of the coronary bands, and sometimes the margins of the ergots and chestnuts may also occur as a result of neoplastic disease (Fig. 6.6). Most frequently, this is associated with various forms of lymphosarcoma and in particular, alimentary lymphosarcoma.[43] Typical of many of the paraneoplastic signs, this may be the primary presenting sign and it is often mistaken for other forms of coronitis and the severity of the changes may easily divert the attention away from the possibility of a serious underlying disorder. From a histological perspective, the changes include a perivascular infiltration of mature lymphocytes and some eosinophils alongside a more general inflammatory response that may accompany secondary infection, necrosis and repeated trauma. It seems likely that this response is immunologically mediated.



Figure 6.6 Internal lymphosarcoma. A proliferative and ulcerative coronitis that affected all the feet of this horse was assumed to be associated with internal lymphosarcoma. This form is quite distinctive from other forms of coronitis and coronary band dystrophy. The characteristic lymphoid perivascular infiltration with some eosinophilic component is typical and suggests that there are immunological responses that may arise as paraneoplastic effects. *(Figure courtesy of Eva Perkonig.)*

Paraneoplastic bullous stomatitis

This is a rare autoimmune subepidermal clefting epithelial condition associated with neoplasia. It is well recognized in humans, but has been reported only rarely in horses.[2] Haemangiosarcoma is the most likely tumour associated with the condition. The feature of the condition is its failure to respond to immunosuppressive doses of corticosteroids, but its resolution following removal of the primary tumour.

Protein-losing enteropathy

Protein-losing enteropathy is easily recognized in horses but confirmation of the diagnosis of major large bowel tumour

involvement is not easy. For the most part, loss of protein into the bowel lumen in any part of the intestinal tract can be due to tumour changes. Indeed, the so-called malabsorption syndromes of diffuse tumour involvement through the wall of either small or large intestine, or both, has a profound inhibitory effect on nutrient and water absorption. Additionally, this is complicated by protein (usually albumin) loss and the induction of osmotic diarrhoea.

Renal failure

Renal failure arising from non-renal tumours is a well-recognized aspect of serious internal cancers in most other species but is poorly recognized in horses. Electrolytic crises and acid–base balance abnormalities are entirely possible but it is hard to extrapolate potential causes and the likely effects to the horse from other species. Usually, this is a result of tumour lysis syndrome (see p. 74) but it can be a result of tumour-induced/paraneoplastic haemolysis, myopathy or electrolytic or endocrinological changes.

Amyloidosis

Amyloid depositions in horses may be found as an unsuspected anatomic change without any clinical implication or it may cause death when it causes localized functional disturbances or when it is extensive enough to affect major organs. In horses, the common forms are identified in the skin, nasal cavity, conjunctiva and mouth. Oral and possibly nasal cavity amyloidosis can sometimes be regarded as a sign of plasma cell dyscrasia in particular; it is associated in humans with multiple myeloma and non-Hodgkin's lymphoma.[44] However, little is known about its relevance either in the paraneoplastic state or in its other manifestations. Systemic light chain amyloidosis has been reported in horses diagnosed with multiple myeloma, plasmacytoma lymphoma and adrenocortical adenoma.[45–48] From a clinical perspective, it is probably wise to consider neoplastic disease wherever amyloid is identified in the horse but it may be a primary condition in many cases and most of the neoplastic diseases in which it is found are difficult to diagnose at best.

Hypertrophic (pulmonary) osteopathy (Marie's disease)

This disabling and debilitating disorder is characterized by development of symmetrical painful periosteal new bone formation in the connective tissue and subperiosteal bone along the diaphysis and metaphyses of the limb bones, usually in horses without joint involvement.[49] Somewhat in contrast to other species, such as the dog and man, most cases of hypertrophic osteopathy (HO) in horses occur secondarily to some inflammatory process (granulomatous inflammatory diseases, abscess/infection trauma or other non-neoplastic masses). However, it is one of the commoner reported paraneoplastic signs in horses.[12] Although 'masses' within the thorax are by far the most common primary disorder, the syndrome can also arise from abdominal masses. It should be noted that thoracic neoplasia is in fact quite rare in horses compared with other species.[12,50] In horses it can, however, be a genuine paraneoplastic syndrome associated with squamous cell carcinoma (primary and metastatic), granular cell tumour (Fig. 6.7) and thymic lymphoma.[51] HO from extra-thoracic tumours has been reported in cases of pituitary adenoma and ovarian neoplasia.[51,52]

The cause of the unique and peculiar distribution of the pathology is hard to understand. Initially, it was proposed that it was a result of 'irritation of the periosteum and synovial membranes' by circulating toxic products from the pulmonary lesion. In support of this concept, there is the observation of round cell infiltration in the outer fibrous layer of the periosteum prior to the deposition of new bone by the cambium layer of the periosteum. Inflammatory changes in the synovial membrane of swollen painful joints have also peripheral vascular supply induced indirectly by the underlying pulmonary disease. Increased peripheral blood flow is usually present but the excess blood, which is poorly oxygenated, passes through arterio-venous shunts, bypassing the capillary bed. This type of blood flow would probably tend to produce local passive congestion and poor tissue oxygenation; in this event proliferation of the various connective tissues, including the periosteum and the synovial membrane, might be stimulated. Since the condition is also encountered (possibly more frequently) in non-cancerous inflammatory and space-occupying conditions of the thorax and abdomen, it is hypothesized that it is in fact a consequence of pulmonary vascular shunting. This is thought to result in the non-fragmentation of large megakaryocytes within the lung: fragmentation is a normal event when large megakaryocytes become trapped in the pulmonary microcirculation. Intact unfragmented megakaryocytes may then be sequestered into distal capillary beds, where they may activate endothelial cells and release growth factors that increase deposition of collagen. In this event, it is not really classified as a paraneoplastic state and is probably more a general reflection on the pulmonary circulation, i.e. it is a physical problem rather than a paraneoplastic one. However, elevated platelet numbers or platelet damage may be a feature of some equine neoplasia and that might explain the involvement of abdominal masses rather than just thoracic, space-occupying lesions. Surgical experiences in humans, dogs and horses consistently confirm that removal of primary lung lesions, lobectomy and rib resection all result in a prompt and permanent regression of the clinical signs of hypertrophic osteopathy and regression of the bone lesions.[53] Such a rapid and lasting depression in blood flow would indicate that the most likely aetiology for hypertrophic osteopathy is a nervous reflex. It has been postulated that the afferent fibres of this reflex originate in the thorax and probably leave the affected lung in the neighbourhood of the bronchus to join the trunk of the vagus nerve high in the mediastinum. An alternate pathway of the afferent fibres may be from the parietal pleura and along intercostal nerves. Thus, according to this theory, the prompt regression of hypertrophic osteopathy as a result of the above procedures probably relates either to the removal of the locus of afferent impulses or section of the afferent pathways themselves. Neither the nature of the stimulus generating these afferent impulses nor the efferent pathway of this reflex has as-yet

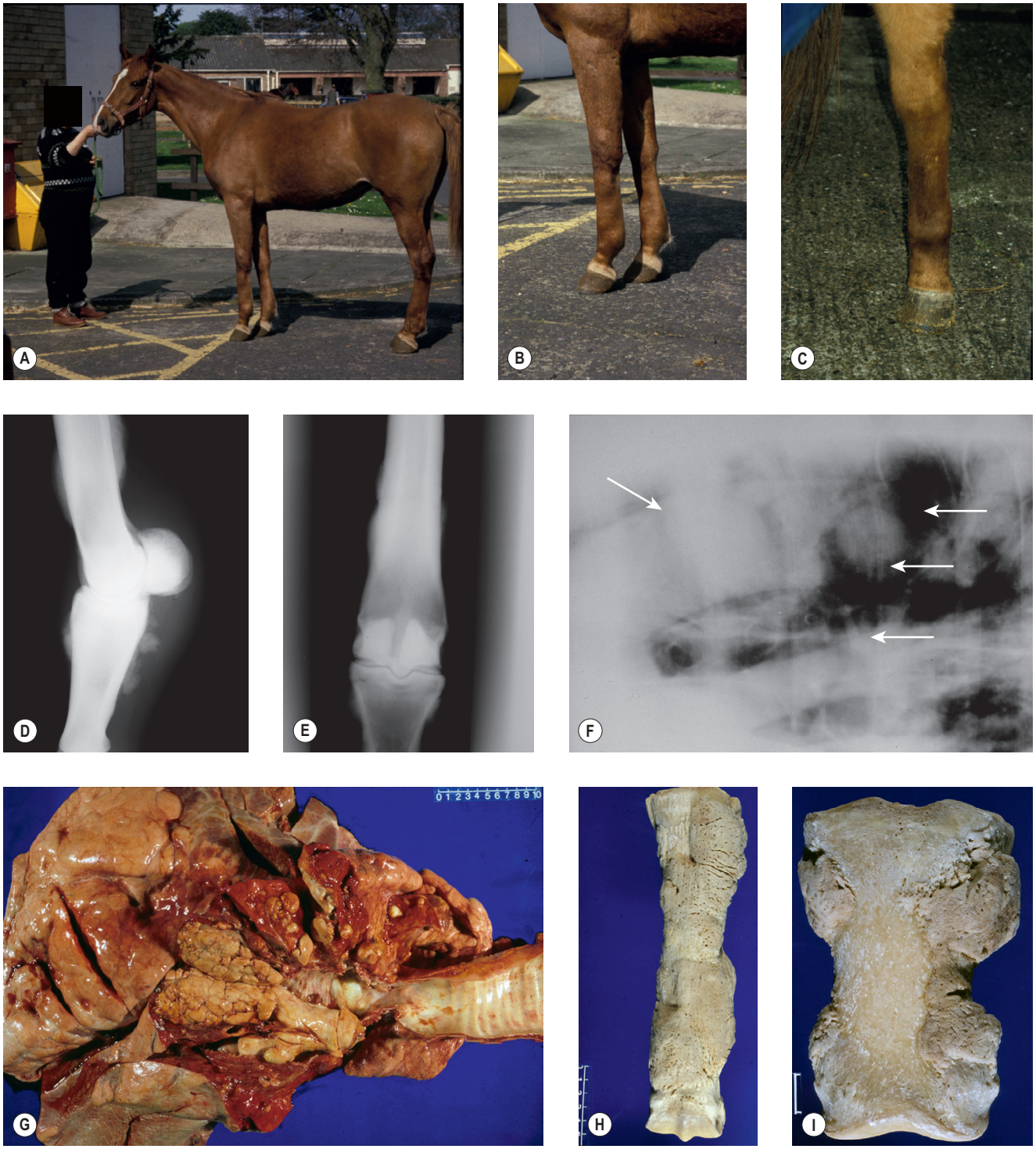


Figure 6.7 Hypertrophic osteopathy. This 7-year-old chestnut part-bred mare was presented with clinical and radiographic signs consistent with hypertrophic osteopathy. **(A–C)** She had painful, warm, oedematous enlargements of the diaphysis of all her long bones. **(D,E)** Radiographically, she showed palisading subperiosteal new bone formation without significant joint involvement. She had a history of a chronic deep, harsh cough and was diagnosed endoscopically and histologically with a bronchial granular cell tumour. **(F)** Thoracic radiography revealed several well-defined space-occupying masses in her chest associated with main stem bronchi (arrows). **(G)** At necropsy, the extent of the problem became very much clearer. This case was singularly unusual in that most bronchial granular cell tumours (see p. 500) are solitary and remain within the bronchial wall; they are seldom extensive, and extension to the mediastinal lymph nodes is even less common. **(H,I)** The extent of periosteal new bone formation in the diaphysis of the metatarsal and first phalanx of another horse with the same paraneoplastic signs.

been determined. More recent clinical studies have suggested that overproduction of vascular endothelial growth factor (VEGF) takes place in a variety of malignant tumours and this may be a significant aspect of the pathophysiology.[54]

Although most cases of osteopathy are associated with an underlying thoracic disorder, a significant number have been reported with primary disease in other locations. Such extra-pulmonary lesions are thought to follow the distribution of the vasopharyngeal and vagus nerves. These cranial nerves carry fibres that innervate vascular tissues, and they have a common nucleus of termination in the grey matter that is closely associated with their efferent dorsal nuclei. It has been suggested that this might account for a common afferent arc that forms a basic part of the mechanism responsible for osteopathy.

Any hypothesis on the aetiopathogenesis of HO needs to account for the diversity of primary conditions, since it is surely not exclusive to neoplastic conditions; endocrinopathic, hypoxic, vascular shunting and neurological (autonomic) mechanisms have all been suggested and it is possible that more than one of these is involved in most cases.

From a pathological perspective, there is endothelial cell activation and vascular hyperplasia. Distal limb swelling develops as a result of oedema and abnormal collagen deposition within the bone vascular hyperplasia and sub-periosteal bone proliferation.

However, the characteristic proliferative monolayer changes in the diaphyseal and metaphyseal periosteum of long bones is a rare but well-recognized outcome in horses with pulmonary and, in some cases, abdominal neoplasia. Significantly, there is usually no joint involvement in horses (*cf.* human). Periosteal proliferation can result in significant limb oedema both at the sites of the most extensive changes and distally; this is probably a result of circulatory interruption but may also be caused by autonomic nerve pathology. In around 25% of cases, the limb swelling is painful on palpation to some degree and in some cases the horse is noticeably lame and pain can be very significant. Although the joints do not exhibit any bony changes, there may be significant (multi) joint distension and limited joint flexibility.

Somewhat in contrast to the similar condition in other species, maxillary, nasal and mandibular bone changes also occur in some horses.[55] Depending on the primary condition, there may be a significant ventral oedema, fever and even coughing.

Diagnosis of hypertrophic osteopathy is relatively straightforward, with a combination of clinical assessment and imaging techniques (radiography, computed tomography and ultrasonography are all helpful). The primary objective of the clinician has to be to establish the primary condition, since there are profound differences in the outlook for inflammatory or infections disease and neoplastic disorders.

Removal of the causal mass, if this is feasible, is usually curative, although the modelling of periosteal changes may be limited in long-standing cases. The difficulty with the condition is largely related to the fact that the tumours are usually inaccessible, are too small to be identified or are too large to be a surgical candidate. The severity of the pathological changes is not proportional to the size of the tumour, however, and neither is it dependent on the type of disease responsible. It is therefore important to establish whether neoplastic disease *is* in fact responsible before any critical decisions are taken about the life of the patient.

References

1. Ogilvie GK. Paraneoplastic syndromes. Vet Clin N Am Equine Pract 1998; 14:439–449.
2. Williams MA, Dowling PM, Angarano DW, et al. Paraneoplastic bullous stomatitis in a horse. J Am Vet Med Assoc 1995; 207(3):331–334.
3. Auchè M. Des nevrites peripheriques chez les cancereux. Rev Med 1890; 10:785–807.
4. Brain R, Norris FH, eds. The remote effects of cancer on the nervous system. New York: Grune & Stratton; 1965.
5. Whiteside TL. Immune suppression in cancer: Effects on immune cells, mechanisms and future therapeutic interventions. Semin Cancer Biol 2005; 16(1):3–15.
6. Bennani-Baiti N, Walsh D. What is cancer anorexia-cachexia syndrome? A historical perspective. J R Coll Physicians Edin 2009; 39(3):257–262.
7. Argilés JM, Moore-Carrasco R, Fuster G, et al. Cancer cachexia: the molecular mechanisms. Int J Biochem Cell Biol 2003; 35:405–410.
8. Martignoni ME, Kunze P, Hildebrandt W, et al. Role of mononuclear cells and inflammatory cytokines in pancreatic cancer-related cachexia. Clin Cancer Res 2005; 11:5802–5805.
9. Durham WJ, Dillon EL, Shelfield-Moore M. Inflammatory burden and amino acid metabolism in cancer cachexia. Curr Opin Clin Nutr Metab Care 2009; 12:72–77.
10. Davidson MB, Thakkar S, Hix JK, et al. Pathophysiology, clinical consequences and treatment of tumour lysis syndrome. Am J Med 2004; 116(8):546–554.
11. Flombaum CD. Metabolic emergencies in cancer patients. Semin Oncol 2000; 27:190–192.
12. Axiak S, Johnson PJ. Paraneoplastic manifestations of cancer in horses. Equine Vet Educ 2012; 24:367–376.
13. LaCarrubba AM, Johnson PJ, Whitney MS, et al. Hypocalcemia and acute tumor lysis syndrome associated with peritoneal mesothelioma in a horse. J Vet Intern Med 2006; 20:1018–1022.
14. Taylor SD, Haldorson GJ, Vaughan G, et al. Gastric neoplasia in horses. J Vet Intern Med 2009; 243:1097–1102.
15. Esplin DG, Taylor JL. Hypercalcemia in a horse with lymphosarcoma. J Am Vet Med Assoc 1977; 170:180–182.
16. Meuten DJ, Price SM, Seller RM, et al. Gastric carcinoma with pseudohyperparathyroidism in a horse. Cornell Vet 1978; 68:179–195.
17. McCoy DJ, Beasley R. Hypercalcemia associated with malignancy in a horse. J Am Vet Med Assoc 1986; 189(1):87–89.
18. Fix AS, Miller AD. Equine adrenocortical carcinoma with hypercalcemia. Vet Pathol 1987; 24:190–192.
19. Marr CM, Love S, Pirie HM. Clinical, ultrasonographic and pathological findings in a horse with splenic lymphosarcoma and pseudohyperparathyroidism. Equine Vet J 1989; 21:221–226.
20. Mair TS, Yeo SP, Lucke VM. Hypercalcemia and soft tissue mineralisation associated with lymphosarcoma in two horses. Vet Rec 1990; 126:99–101.
21. Rosol TJ, Nagode LA, Robertson JT, et al. Humoral hypercalcemia of malignancy associated with ameloblastoma in a horse. J Am Vet Med Assoc 1994; 204:1930–1933.
22. Cook G, Divers TJ, Rowland PH. Hypercalcemia and erythrocytosis in a mare associated with metastatic carcinoma. Equine Vet J 1995; 27:316–318.
23. Pusterla N, Stacy BA, Vernau W, et al. Immunoglobulin A monoclonal gammopathy in two horses with multiple myeloma. Vet Rec 2004; 155:19–23.
24. Taylor SD, Haldorson GJ, Vaughan G, et al. Gastric neoplasia in horses. J Vet Intern Med 2009; 243:1097–1102.
25. Mair TS, Taylor FG, Hillyer MH. Autoimmune haemolytic anaemia in eight horses. Vet Rec 1990; 126:51–53.
26. Reef VB, Dyson SS, Beech JJ. Lymphosarcoma and associated immune-mediated hemolytic anemia and thrombocytopenia in horses. J Am Vet Med Assoc 1984; 184:313–317.
27. Roby KA, Beech J, Bloom JC, et al. Hepatocellular carcinoma associated with erythrocytosis and hypoglycaemia in a yearling filly. J Am Vet Med Assoc 1990; 196:465–467.
28. Lennox TJ, Wilson JH, Hayden DW, et al. Hepatoblastoma with erythrocytosis in a young female horse. J Am Vet Med Assoc 2000; 216:718–721.
29. Ogilvie GK. Paraneoplastic syndromes. In: Withrow SJ, McEwen EG, eds. Clinical veterinary oncology. Philadelphia: JB Lippincott; 1989: 29–42.
30. Baker JL, Aleman M, Madigan J. Intermittent hypoglycaemia in a horse with anaplastic carcinoma of the kidney. J Am Vet Med Assoc 2001; 218:235–237.
31. Swain JM, Pirie RS, Hudson NP, et al. Insulin-like growth factors and recurrent hypoglycaemia associated with renal cell carcinoma in a horse. J Vet Intern Med 2005; 19:613–616.
32. Ross MW, Lowe JE, Cooper BJ. Humoral hypoglycaemic seizures in a Shetland pony. Cornell Vet 1983; 73:151–169.
33. Brennan MD. Hypoglycemia in association with non-islet cell tumours. In: Service FJ, ed. Hypoglycemic disorders. Boston: GK Hall Medical; 1983: 143–151.
34. Sakamoto T, Kaneshige H, Takeshi A, et al. Localised pleural mesothelioma with elevation of high molecular weight insulin-like growth factor II and hypoglycaemia. Chest 1994; 106:965–967.
35. Vaidya SM, Kamalakar PL. Copper and ceruloplasmin levels in serum of women with breast cancer. Indian J Med Sci 1998; 52:184–187.
36. Owen RA, Haywood S, Kelly DF. Clinical course of renal adenocarcinoma associated with hypercupraemia in a horse. Vet Rec 1986; 119:291–294.

37. Aldave AJ, King JA, Kim BT, et al. Corneal copper deposition associated with chronic lymphocytic leukemia. Am J Ophthalmol 2006; 142:174–176.
38. Khan G, Merajver S. Copper chelation in cancer therapy using tetrathiomolybdate: an evolving paradigm. Expert Opin Investig Drugs 2009; 18:541–548.
39. Edwards DF, Parker JW, Wilkinson JE, et al. Plasma cell myeloma in the horse. A case report and literature review. J Vet Intern Med 1963; 170:169–176.
40. Finley MR, Rebhun WC, Dee A, et al. Paraneoplastic pruritus and alopecia in a horse with diffuse lymphoma. J Am Vet Med Assoc 1998; 213:102–104.
41. Anhalt GJ, Kim SK, Stanley JR, et al. Paraneoplastic pemphigus – An autoimmune mucocutaneous disease associated with neoplasia. N Engl J Med 1990; 323:1729–1735.
42. Klein T, Rotterdam S, Noldus J, et al. Bullous pemphigoid is a rare paraneoplastic syndrome in patients with renal carcinoma. Scand J Urol Nephrol 2009; 43:334–336.
43. Wilson RG, Sutton RH, Groenendyk S, et al. Alimentary lymphosarcoma in a horse with cutaneous manifestations. Equine Vet J 1985; 17:148–150.
44. van der Waal RI, van de Scheur MR, Huijgens PC, et al. Amyloidosis of the tongue as a paraneoplastic marker of plasma cell dyscrasia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002; 94:444–447.
45. Kim DY, Taylor HW, Eades SC, et al. Systemic AL amyloidosis associated with multiple myeloma in a horse. Vet Pathol 2005; 42:81–84.
46. Linke RP, Geisel O, Mann K, et al. Equine cutaneous amyloidosis derived from an immunoglobulin lambda-light chain. Immunohistochemical, immunochemical and chemical results. Biol Chem Hoppe Seyler 1991; 372:835–843.
47. Gliatto JM, Alroy J. Cutaneous amyloidosis in a horse with lymphoma. Vet Rec 1995; 137(3):68–69.
48. Van Andel AC, Gruys E, Kroneman J, et al. Amyloid in the horse: A report of nine cases. Equine Vet J 1988; 20:277–285.
49. Mair TS, Dyson SJ, Fraser JA, et al. Hypertrophic osteopathy (Marie's disease) in Equidae: a review of twenty-four cases. Equine Vet J 1996; 28:256–262.
50. Davis EG, Rush BR. Diagnostic challenges: Equine thoracic neoplasia. Equine Vet Educ 2011; 25(2):96–107.
51. Leach MW, Pool RR. Hypertrophic pulmonary osteopathy in a Shetland pony attributable to pulmonary squamous cell carcinoma metastases. Equine Vet J 1992; 4:247–249.
52. Godber LM, Brown CM, Mullaney TP. Polycystic hepatic disease, thoracic granular cell tumour and secondary hypertrophic osteopathy in a horse. Cornell Vet 1993; 83:227–235.
53. Holman C. Osteoarthropathy in lung cancer: disappearance after section of intercostal nerves. J Thorac Cardiovasc Surg 1963; 45:679–681.
54. Martinez-Lavin M, Vargas A, Riverna-Vinas M. Hypertrophic osteoarthropathy: A palindrome with a pathogenic connotation. Curr Opin Rheumatol 2008; 20:89–91.
55. Enright KE, Tobin E, Katz LM. A review of 14 cases of hypertrophic osteopathy (Marie's disease) in horses in the Republic of Ireland. Equine Vet Educ 2010; 23(5):224–230.

7

Principles of diagnosis

Clinical investigations and specialized tests/imaging methods 86
Tissue sampling 87
Ultrasonography 93
Abdominocentesis/thoracocentesis 97
Total protein assay 98
Cytological assessment 99
Radiography 101
Scintigraphy 104
Laparoscopy/pleuroscopy/endoscopy 104
Tumour markers 104

The range of tumours and their location is wide. This means that whilst in most cases skin tumours can be visualized, any other type of tumour will rely for diagnosis on a different set of diagnostic tools. In some cases, inferences can be drawn from appearance, location and the way in which the tumour grows. However, there is no substitute for an exhaustive investigation – it is easy to be diverted to an obvious tumour in an accessible site, but if there are more or different tumours at other less obvious sites, the outlook may be very different. Since therapy for different types of tumours varies, a diagnosis is vital. Diagnosis should be enhanced by establishing the likely pathological and clinical effects of a tumour. Only when the whole picture has been established and understood can a sensible judgement be made on treatment options and prognosis. A good example may be shown by a horse that has nodular masses on its skin – a biopsy might confirm a lymphoma and the temptation might be to assume that this is a cutaneous form only. A closer inspection might reveal very serious effects in other locations within the chest and abdomen that have more subtle symptoms. The outlook clearly becomes very different; this simply illustrates the need to employ clinical acumen and sensible further diagnostic methods before any attempt is made to provide a prognosis.

The clinical examination of a suspected tumour patient needs to be very precise and exhaustive since, often, the first signs that are reported in serious internal tumour states are the paraneoplastic ones; this means that it is easy to overlook the possibility of a neoplastic disease, but, by the same token, the nonspecific signs might encourage the casual clinician to make a diagnosis of neoplastic disease when there is none. The early presentation of cancer cases is usually focussed on subtle signs that an astute and observant owner notices. Quite frequently, the veterinarian is unable to pinpoint the problem at all and then it is easy to disregard the evidence. In general, few neoplastic states will be so rapidly progressive that an immediate decision has to be made. Even though many equine cancer patients are initially presented very late in the course of disease, there is usually time to undertake a careful physical examination and to obtain a really good history. It is probably wise to keep an open mind until the diagnosis can be made with some certainty, since the word 'cancer' usually strikes fear into the owners.

A physical examination may be more than adequate for a presumptive diagnosis. Since many of the commonest tumours involve the skin, direct examination and 'intuitive supposition' are usually enough to reach a terminative diagnosis, especially when considered alongside the history of the horse. Where there is no clinical doubt at all, the diagnostic process can justifiably be concluded at that point on purely economic grounds. However, in many cases, the prognosis will vary and so some sort of extra diagnostic tests will need to be performed. For example, a destructive, ulcerated mass on the penile area and glands of an older gelding can reasonably be assumed to be a squamous cell carcinoma, but the pathological behaviour and degree of differentiation may make an enormous difference to the treatment options and the prognosis. A benign, well-differentiated state might mean that treatment can be undertaken with a good outlook, whereas a highly undifferentiated aggressive and invasive histological appearance may mean that treatment is specifically contraindicated. Additional information can be gleaned at the outset from a thorough clinical assessment; enlarged sub-iliac lymph nodes might be identified by rectal examination, for example, or the horse may have respiratory signs consistent with pulmonary metastases. The horse may have paraneoplastic signs that are at a least as significant, but simply dealing with these symptomatically will rarely solve the problem. In other cases, the clinical signs may be suggestive but a further test of some sort has to be undertaken to confirm the diagnosis. A good example of this is the relatively common granulosa (thecal/sex cord-stromal) tumour of the ovary. The affected horse may have signs of male virilism that suggest a diagnosis but a rectal examination with an ultrasonographic study and a confirmatory blood sample measuring increased concentrations of testosterone and anti-Mullerian hormone will enable a categorical diagnosis to be made. In the large majority of tumours, some sort of definitive test can be performed. This increases job satisfaction for the veterinarian, informs the owner fully and enables informed decisions to be taken, based on categorical evidence.

The range of clinical tools that is available now means that there is little excuse to miss significant aspects of a tumour state, although some sophisticated methods may only be available at local or regional referral centres.

Clinical investigations and specialized tests/imaging methods

Inevitably, since the majority of the clinically useful information is provided by a combination of the history of the horse and the detailed clinical examination, clinical acumen is a fundamental 'diagnostic test'. However, although experience is helpful and intuitive, supposition is common practice, a precise, confirmed and definitive diagnosis is the objective of any clinician. Many of the major cancer conditions affecting horses involve the skin, either primarily or secondarily. Surveys of tumours in horses confirms that the large majority of tumours are primary cutaneous conditions, such as sarcoid, melanoma, cutaneous/histiocytic lymphoma and squamous cell carcinoma. Even when the diagnosis can be readily surmised from clinical information alone, it is often satisfying and prognostically useful to confirm a diagnosis using further procedures.

Diagnostic tests are indicated when a definitive diagnosis cannot be reasonably achieved clinically and when extra information is required. For example, it might be of vital prognostic significance to know whether a 'melanoma' on a cremello or bay horse is malignant or not and it might be difficult to differentiate a melanoma from a sarcoid on a grey horse's eyelid. In many internal cancers, diagnostic tests are clearly essential.

From a practice and client–relationship perspective diagnostic tests should be used wisely and not just included without genuine justification. The moment a further diagnostic test is pursued, the costs of the investigation will start to rise rapidly and although most horse owners will respect the clinicians' judgements that the tests are necessary, the clinician has to justify each and every one in terms of its clinical value. If a test is not going to alter what is done in any way, then the justification for the test is clearly much less. From a professional perspective, however, and from the perspective of the need to provide owners with genuine evidence-based advice, sampling of every tumour could be fully justified. It is important from the outset to recognize, however, that sampling of tumours is not without hazard. Even the collection process can be a risk; for example, a simple peritoneal fluid collection might cause bowel perforation and fatal peritonitis. Introduction of infection into the pleural space or into a joint can have huge implications. Not every tumour can be subjected to an accessible diagnostic test, but using a panel of tests that are sensibly and properly carried out, most tumours can be definitively diagnosed.

Direct and indirect tests can be used in suspected tumour cases. For example a piece of an organ suspected of having a neoplastic disease can be specifically sampled by biopsy (collection of a small representative sample of the tumour); by excisional biopsy (removal of the whole mass); or by direct cytology of cells aspirated from the bulk of the tumour (fine-needle aspiration). Sampling of tissue is the gold standard and usually provides a definitive diagnosis, provided that the sample is truly representative. There are inevitable problems however with accessibility and the appropriateness of the sampling. For example a biopsy of a gastric or duodenal mass using an endoscopic biopsy instrument will often only 'harvest' superficial tissue and may then not be diagnostic. A bigger biopsy sample may, however, compromise the integrity of the bowel wall and threaten the life of the horse. Techniques may have to be adjusted to suit the particular tumour, tissue, location and operator experience (Fig. 7.1).

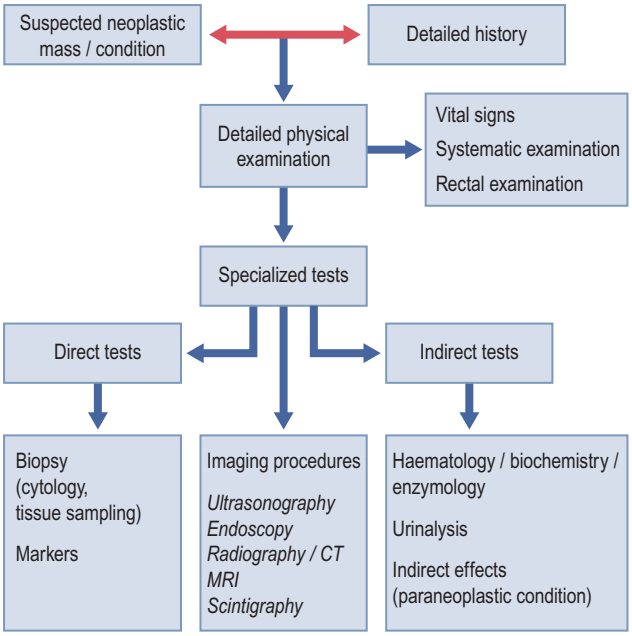


Figure 7.1 A broad schematic for the investigation of a suspected cancer case. Note that clinical examination and history are primary events that are absolutely essential in every case (whether neoplastic or not). Diagnostic tests should be performed logically and in sequence and it is clear that the circumstances for selection of tests will vary widely from case to case with some stages beyond the clinical examination being bypassed because they are specifically not required. Note: In equine oncology, markers can be taken to mean any parameter that provides strong supporting evidence for a particular type of tumour: for example testosterone and inhibin production from a granulosa (thecal) cell tumour or BPV virus positive PCR for sarcoid.

Furthermore, there is general understanding that sampling of some particular tumour types is in itself potentially hazardous – the tumour might be exacerbated by the process or the tumour might be 'spread' by the procedure either locally or it might allow tumour cells to gain access to the blood vessels and so, in theory, biopsy or surgical interference may be a potential cause of tumour dissemination. However, whilst a great deal is known in other species, little is known about the true risks in horses. A good example of this is the general fear of inducing metastatic malignancy in melanoma cases through biopsy or during surgical excision/tumour reduction procedures. In fact, opinion is strongly divided in quantification of the risk even in that tumour type. The sarcoid is another tumour that has a reputation for exacerbation following biopsy or partial excision. Most equine practitioners will recognize the veracity of that statement and that is certainly the authors' experience, although there is currently no published evidence for that opinion. However, if there is no intention to 'use' the results of the further tests for any clinical decision-making, then the justification for the procedure can properly be questioned.

Typically, the quality of the results is highly dependent on the quality of the collection of the samples – whether that is blood, tissue or other material. Diagnostic tests for cancer

are very varied and include all the basic and supportive procedures, such as blood sampling, biopsy of tissues, radiography, endoscopy, etc. As practice becomes more sophisticated, there is a strong bias towards technology – the concept of 'a good test is the latest and most expensive technology' is not helpful. Every single test applied to a clinical case, whether that is neoplastic or not, has to be directed towards some clinically or scientifically defined objective. In the end, by far the best diagnostic equipment in the world is the human brain connected to good sensory organs, such as the eyes, ears, hands and nose. It is also the cheapest diagnostic aid.

Tissue sampling

There are several different mechanisms for sampling tissue. Tissue 'accessibility' is important if representative tissue is to be obtained – tumours on the skin and external structures are usually easily accessible but sampling from masses and tissues within the body adds complication to the collection. Most tumour masses, however, can be sampled if enough care is given to the selection of the best-available method and due attention is paid to the sampling process.

Biopsy

Overview

Biopsy or tissue sampling is the removal and examination of tissue, cells or fluids from the living body for diagnostic purposes. In actual practice, the term biopsy is usually applied to the collection of tissue specimens/cells rather than aspiration of fluids, such as blood or pleural, abdominal, cerebrospinal or synovial fluids, so this section includes the sampling of solid tissues only. Other aspirations and samplings are described individually.

Biopsy is the gold standard for diagnosis, since almost all tumours can be recognized histologically with some form or another of additional tests and stains applied to the sections and smears. The value of a biopsy cannot be overstated but, typically, the sampling of tissues has to be precise and the results are a reflection of the care of collection. The most fundamental aspects of the biopsy of tissues are:

1. *Identification of the most representative tumour (if there are several) and the most representative area within the tumour being sampled*. Where a tumour is to be biopsied, the best results are likely to be achieved by sampling the most diagnostic tissue. This can be a hazard to the operator because there is strong temptation to 'avoid interference' with a tumour in a case that results in either a local exacerbation or dissemination of the tumour, i.e. the concept of iatrogenic interference resulting in a critical change in the tumour and a reduction in prognosis. There may also be a strong temptation to sample the 'middle of the tumour', since that might reflect the most advanced area of the mass and would avoid or at least minimize the risks of exacerbation. However, many tumours have degrees of tissue compromise in the middle of the mass. Tissue necrosis and inflammation may be present and this may make the interpretation difficult at best and impossible at worst. In general, the active marginal tissues are usually used but unless the particular requirements of the physician/surgeon demand information about the margin of the tumour (its extent of invasion, surgical margins of excision and so on), there is seldom any material advantage in removing 'normal tissue', so the pathologists can compare the tumour with that. Pathologists *know* what normal tissues look like and so do not probably need to be reminded. It is far better to collect a sample of an appropriate size and representative tissue to get the best chance of definitive diagnosis that can be achieved. Some samples will have to be small for one reason or another but in general a larger sample will be better than a smaller one, provided of course that the sample is correctly collected and handled from the best, most representative, site. Sometimes the pathologist will provide useful advice on the best site to sample. This clearly applies most to easily accessible tumours.
2. *Correct and appropriate selection of the biopsy technique to be used*. The type of biopsy needs to be considered carefully – tissue can be collected in many ways (see below) and individual tumour types may have particular requirements (Fig. 7.2). In considering the collection method, accessibility is a key factor. Tumours that are hard to access are usually hard to sample correctly. A good example is the sampling of a gastric carcinoma via a flexible endoscope – the biggest biopsy that can be collected using endoscopic biopsy 'grabs'/forceps is usually only a few millimetres in size. Therefore, sampling can often 'miss' the most useful pathology; tissue showing a superficial ulceration with some inflammation and infection may be all that is harvested. In some cases, the site is only accessible using ultrasonographic or radiographic or magnetic resonance imaging and they add to the complication but also to the accuracy and appropriateness of the sampling site.
3. *Correct handling of the samples*. The handling of the samples collected is clearly fundamental to success. For the most part, tissue samples are best placed in 10% formal saline when routine histology is to be performed and this is the commonest handling method. It is important however to realize that special tests/immunostaining and some physiological tests may require other handling methods. Pathologists are more than willing to provide advice in advance to maximize the value of the procedure.
4. *Provision of the required details about the case*. Pathologists are frequently frustrated by the lack of supportive information when tissue is submitted. Full clinical details about the horse and its history are essential if a good result is to be achieved. A full clinical description, including the signalment of the horse and its history, provide excellent background information for the pathologists. A careful (photograph enhanced) clinical description of the site being sampled and a list of potential differentials that are being considered will also support the diagnostic process. Inclusion of any significant further testing results, such as haematology, biochemistry and imaging modalities used, adds useful information. The point about this is that the pathologist is there to help and support – submission of specimens

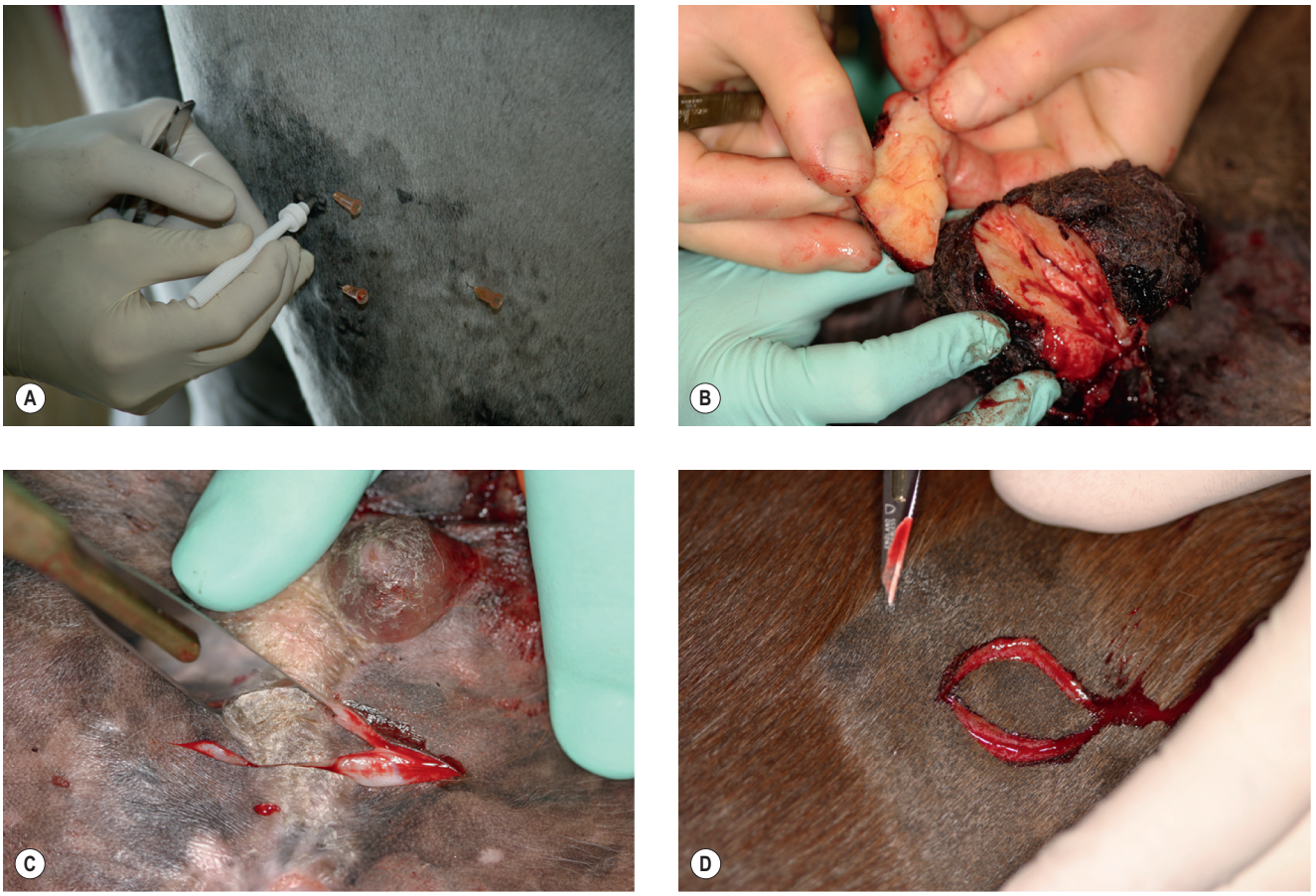


Figure 7.2 Four different methods of tissue biopsy. These examples are from skin tumours, but the same techniques can be used for almost any tissue of a suitable type and accessibility. Each method has its advantages and disadvantages. The figures illustrate the common biopsy methods that are used in practice circumstances. **(A)** Punch biopsy takes from a diffuse sarcoid in the caudal right thigh; note the needles that were used to place the bleb of local anaesthetic solution to remain in situ until the sample is taken. **(B)** A large portional biopsy of an exophytic subcutaneous mass on the skin, in this case, the overlying skin was also included in the biopsy since it was also abnormal; a histological diagnosis of fibroblastic sarcoid was made. **(C)** A larger tissue sample being taken across the width of a linear mass in the skin, extending from normal skin to normal skin across the lesion. **(D)** An excisional biopsy leaving a 0.5 cm margin around a skin mass that was diagnosed histologically as a mast cell tumour.

should not be a 'challenge' to the pathologist to 'come up with a definitive diagnosis'. The process should be a team effort with a common goal.

Biopsy methods

Punch biopsy

A column of tissue is removed with a commercially available disposable biopsy punch (see Fig. 7.2A). These are usually used for sampling skin masses, but they can be used at any site, where appropriate, such as the cornea, conjunctiva and any other accessible tissues. The instruments can be used to take samples of any organ under appropriate conditions. They are available in several different sizes, but specimens of <6–7 mm diameter are probably less useful than larger ones. Pathologists are often significantly hindered by having very small specimens, which may not be fully representative of the diseased tissue.

The punch is used to incise the skin using a single direction push-turn action. The punch should be rotated in one direction. This will minimize the stretch artefacts. Back-and-forth movements should not be used as this increases stretch artefacts.

The specimen can be easily (and significantly) traumatized by rat-tooth forceps or by excessive pressure/squeezing by forceps and these should therefore not be used.

The sample is rapidly transferred to fixative.

Suturing is not usually required and, indeed, in view of the lack of sterile technique, suturing can in fact be a disadvantage; closing a small site like this may increase the chances of infection. Leaving the site open invariably results in a rapid natural healing without complication. A dressing may be helpful in limiting the risks in some sites (e.g. on the lower leg region).

A specimen of adjacent normal skin may be obtained in a similar fashion for comparative purposes.

Wedge biopsy

A wedge of tissue is obtained by full-thickness incisions (see Fig. 7.2B). This is a standard approach that is widely used in equine practice, but it is easy to collect the wrong tissue. An outward-facing wedge with only a small amount of normal tissue may be more sensible in most circumstances. Conventionally, the clinician aims to include some normal tissue in the biopsy but this should not dictate the extent or location of the biopsy. It is seldom helpful in any case. The

pathologist requires a carefully taken representative sample of the lesion – if normal tissue is included, it should certainly not be the larger portion of the biopsy. In cases where a piece of normal tissue is considered essential, this should usually be taken separately from an adjacent piece of normal tissue.

The important portion is the abnormal tissue, and the small segment of normal tissue serves to provide the pathologist with an orientation of the lesion and an example of the normal tissue for comparison. In oncological biopsy, the margins can be significant tissue. If a diagnosis alone is being sought, the pathologist needs a truly representative sample of the tumour tissue without all the abnormal tissue that is available; usually, midway between the centre and the outer apparent margin is a good place to sample. A separate biopsy of adjacent normal tissue may be sent if requested by the pathologist.

Portional biopsy

Removal of a portion of a suspected tumour is a common technique in equine practice (see Fig. 7.2C). The method will clearly vary, depending on the site of the mass. Masses in more inaccessible sites will require special procedures, including celiotomy, laparoscopy, pleuroscopy or other imaging systems, such as ultrasonography.

Biopsy of nasal, pharyngeal or endometrial masses can be performed using an endometrial biopsy instrument with relative safety; there are important technical requirements and limitations, so these must be understood before proceeding. The sample is a more suitable size than samples taken using endoscopic biopsy channel forceps.

Rectal biopsy is also a standard procedure in diagnostic equine practice. There have been published reports of the correlation between rectal biopsy findings and the more generalized pathology in respect of intestinal neoplasia and lymphoma and adenocarcinoma in particular.[1–3] The procedure inevitably carries risks and the correlation with serious intestinal neoplasia is poor, so the technique is usually limited to non-neoplastic disease investigation.

Excisional/ablative biopsy

This technique is used when normal and abnormal tissues are required in the sample or when the lesion is so small that biopsy of a portion is difficult (Fig. 7.3). It is also used when the lesion present is likely to be adversely affected by partial biopsy or when malignancy and dissemination of tumour may follow partial biopsy.

An excisional biopsy is similar to a wedge biopsy but involves the removal of the whole lesion, which may involve rather more surgery if it is large. An elliptical incision with an appropriate margin for the type of tissue and the probable tumour type is made with a scalpel to include all tissue down to the cutaneous muscle. This method should have a reasonable expectation of total mass removal, although the pathologist will clarify that aspect retrospectively; it is in effect a combination of biopsy and surgical tumour ablation.

For wedge and excisional samples, closure of the site with sutures or staples or n-butyl cyanoacrylate adhesives may be required, depending on the size and nature of the defect. An accurate diagrammatic orientation (or preferably a photograph) of the biopsy should be made immediately to assist the pathologist.

Fine-needle aspiration

This minimally invasive technique is used to obtain a sample of cells or fluids from a lesion. Interpretation of cells obtained in this way is a specialized technique, often requiring an experienced cytological pathologist (Fig. 7.4). The method of obtaining the cells is important as tumour cells are easily damaged beyond recognition or mixed with irrelevant inflammatory cells, which can be very misleading, blood and necrotic tissue. The pathologist should be consulted on the correct sampling and preservation methods if there is any doubt.

Hollow-needle biopsy

The hollow needle (Tru-Cut®) biopsy is the mainstay for the sampling of solid tumours that are either difficult to reach or visualize or where direct access is specifically contraindicated. For example a mass in the kidney, liver or lung can really only be sampled using the hollow-needle approach and, even though the thyroid gland or a subcutaneous melanoma are accessible, minimal trauma is required and the hollow-needle approach is ideally suited (Fig. 7.5).

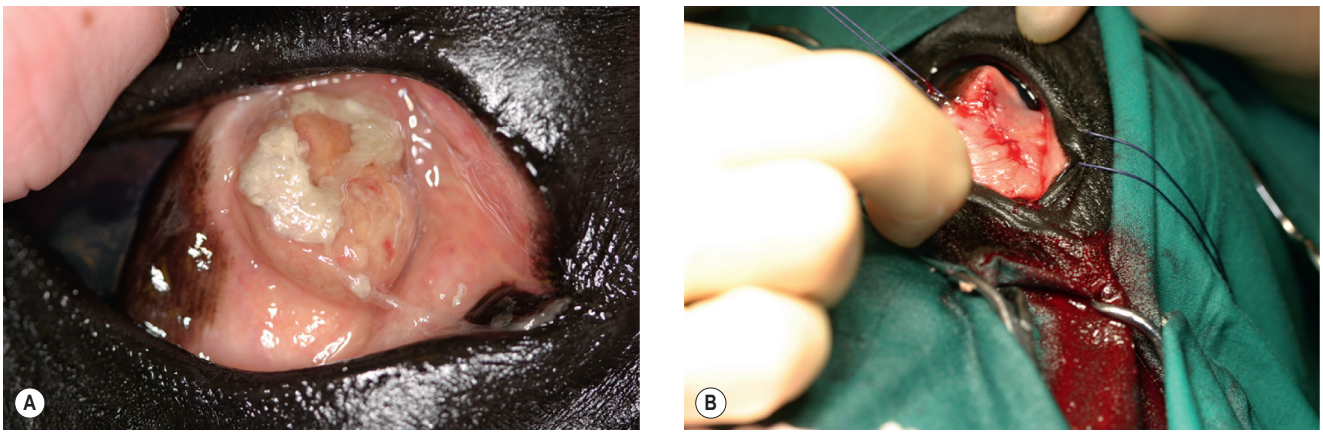


Figure 7.3 A mast cell tumour. (A) This mass was suspected clinically to be a mast cell tumour. The evidence is that mast cell tumours are not invasive and a narrow margin could probably be justified. **(B)** An excisional biopsy was performed with removal of the whole tumour and a small margin. It was submitted for histology, where the diagnosis was confirmed and the margin was proclaimed 'safe' (see also Fig. 4.17, which shows the histology of this tumour). The tumour did not recur and the third eyelid itself was preserved.



Figure 7.4 Fine-needle aspiration. Fine-needle aspiration does exactly what the name implies. A needle no larger than 21 G attached to a 2 or 5 mL syringe (*not bigger*) is introduced into the tumour so that the tip of the needle lies midway between the centre and the periphery. Whilst the best samples are probably taken without any aspiration (i.e. just the passage of the needle into the tumour), it is common practice to apply two or three sharp suctions on the syringe and then withdraw the needle. The policy of multiple needle drives into the lesion before harvesting is not recommended, since this causes bleeding and distortion within the tissue. The harvested cells are 'jetted' out onto a pre-prepared slide as quickly as possible and the slide is dried in air. Large volumes of aspirate are not helpful usually in oncological sampling. The slide is identified with a pencil (not an ink/marker pen), since the slide will be fixed in alcohol. Staining will be carried out according to the requirements. Several samples can be obtained quite safely – the procedure is minimally invasive. The best sample is a few perfectly typical cells from which a definitive conclusion can be drawn.

The main advantages of the hollow-needle approach are that it is usually possible when it is used in conjunction with an imaging system (usually ultrasonography) to sample tissues precisely and that it is minimally invasive.

There are various lengths and sizes available and the modern systems have spring-loaded mechanisms that make sampling a great deal more reliable, safer and easier than the old manual instruments. The samples should again be taken from the midway point between the centre and the margin of the tumour.

The single disadvantage of the method is that the sample size is sometimes too small for the pathologists to get a good diagnosis. However, usually it is enough, provided that it has sampled the required tissue.

Impression smears

These have limited value but they can be useful in some circumstances. Many skin lesions have surface bacterial contamination (which may or may not be of clinical significance). Exfoliative and inflammatory cells are regularly encountered and, again, they may or may not be of significance. Interpretation is particularly difficult and it is a very specialized procedure.

Tissue fixatives

The correct handling of tissues samples (whether cells or tissues) is essential if a good diagnosis is to be achieved. Prompt immersion of tissue in an appropriate fixative (formalin or glutaraldehyde if electron microscopy is required) is essential. Fixatives require a finite time to exert their effects. This may be dependent on the type and size of the specimen (and the extent of penetration required) but is seldom <24–36 h. Pathologists are justifiably reluctant to process specimens at an earlier stage and more rapid results may require frozen sections.

Notes on sample submission in fixatives:

- Buffered, neutral formol–saline is used routinely. At least 10% volume of fixative to specimen must be present
- Michel's medium was formerly used to preserve specimens for immunohistochemical investigations. This is now no longer required in many cases and consultation with the pathologist will establish its value in any particular case
- Glutaraldehyde is the preferred fixative for electron microscopy. Tissue must be cut into very small cubes (1–1.5 mm) and fixed as soon as possible
- The volume of fixative should be at least 10 times the volume of the tissue submitted – lesser volumes result in poor/unreliable uniformity of fixation
- Tissue 'cages' are helpful in maintaining the tissue shape, and orientation within the cage can be recorded for the information of the pathologist
- Following fixation, tissue becomes very rigid and inelastic – large specimens forced into narrow-neck bottles often cannot be removed for processing without breaking the container. Wide-neck containers of a suitable size must therefore be used at all times. Large samples should be subdivided or sectioned and submitted with an appropriate description
- Samples to be sent in the post that are not urgent can be fixed for 4–5 days and then the formalin can safely be poured off to allow easier, cheaper and safer posting
- Frozen sections are sometimes used to obtain a very rapid result. They require particular circumstances and handling of the specimen. Where this is required, a pathologist or technician must be present to handle the tissue. There are few circumstances when frozen sections are used in horses
- A photograph of the biopsy site before and after the biopsy has been taken may be appropriate in some circumstances (mostly the skin and surface tissues).

The requirements for biopsy of a tissue mass/suspected tumour will clearly vary with the anatomical location and the implication of interference with the organ and/or the tumour concerned. Suitable restraint with tranquillization or even general anaesthesia if necessary should be used to allow safe handling of the horse and for the safety of the surgeon so that the best possible sample can be taken. Combination of an α_2-adrenoreceptor agonist (such as romifidine or detomidine) and an opiate analgesic (such as butorphanol) often allows biopsy of the skin and other external masses or hollow-needle biopsy of accessible organs within the body. Local anaesthetic agents are irritant to tissues and so, where possible, regional analgesia or infiltration well way from the site should be used.

Haematology and biochemistry

The haematological and biochemical effects of the various tumours of the horse are extremely variable. The commonest tumours are those of the skin and include the sarcoid, melanoma, squamous cell carcinoma and mast cell tumour,

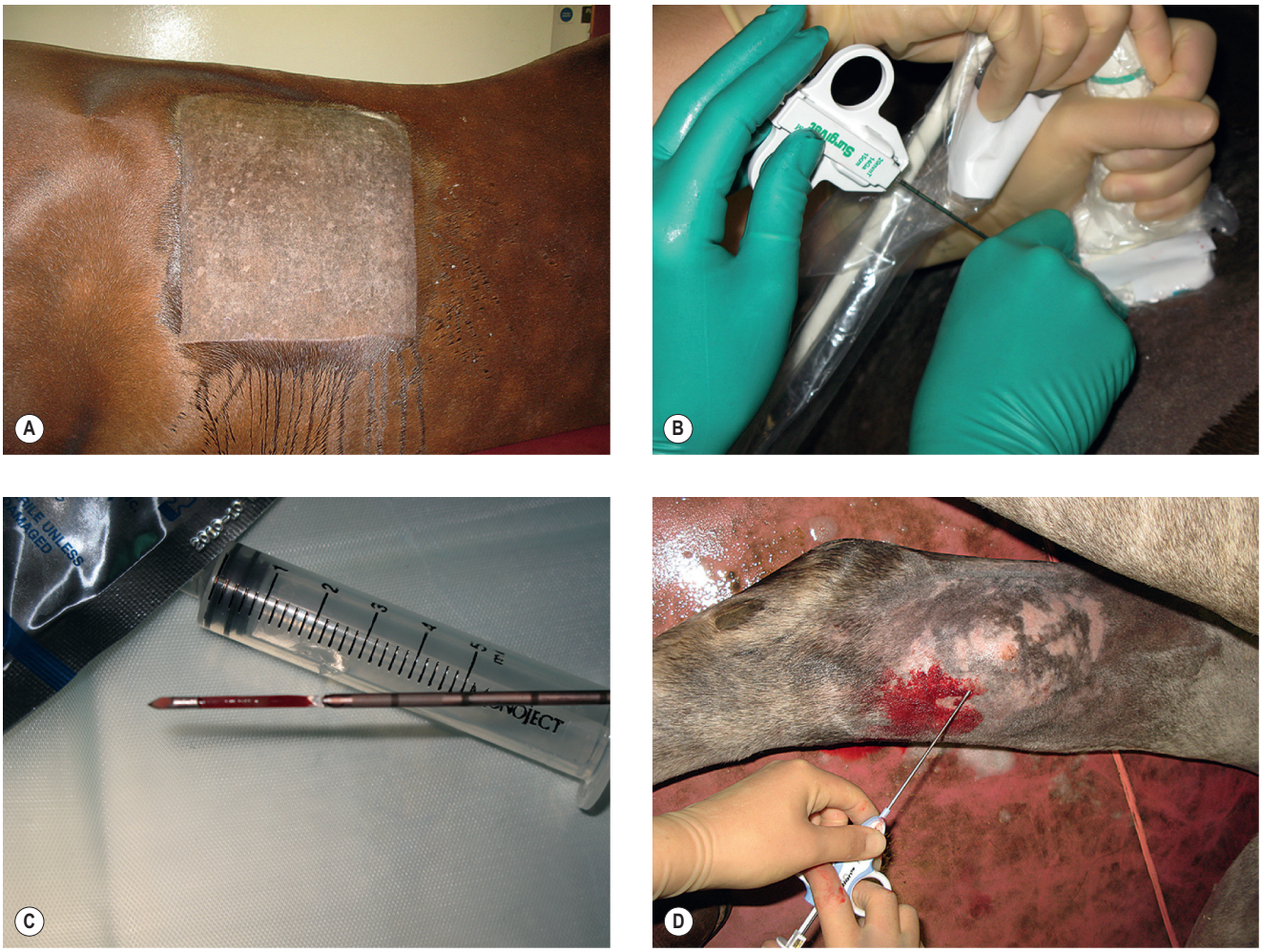


Figure 7.5 Ultrasound-guided hollow-needle biopsy. (A–C) Ultrasound-guided hollow-needle (Tru-Cut) biopsy of a focal mass within the right kidney that was identified as a renal lymphoma. Ultrasonographic guidance is a particularly useful technique for sampling of internal organs using aspiration, fine-needle aspiration or hollow-needle biopsy techniques. **(D)** Sampling a mast cell tumour in the medial distal tibial region under short-term general anaesthesia.

and in all of these there are usually no significant haematological, biochemical or enzymatic changes in the broad spectrum of measured parameters in routine laboratory profiles. Secondary changes can occur however and reflect the possible chronic loss of blood or plasma proteins, or the effects of chronic inflammation (usually manifest as normochromic or hypochromic, normocytic or microcytic anaemia) or other more direct tumour effects.

As soon as the more severe internal tumours are mentioned, there are often more obvious systemic effects and consequent changes in blood profiles. The most profound changes are usually biochemical and haematological in nature; these are usually viewed as paraneoplastic events (p. 70), but profound direct effects can be encountered. The main features of internal neoplastic disease include:

1. *Progressive anaemia or thrombocytosis*. These changes are frequently detected in cancer cases. However, apart from the recognized paraneoplastic thrombocytosis, changes are usually secondary or at least nonspecific. Causes of anaemia include direct blood loss in some cases, anaemia of chronic inflammation and possibly some degree of direct suppression of red cells by tumour obliteration of bone marrow (myelophthisic tumours).
2. *Thrombocytopaenia/thrombocytosis*. Profound changes can be encountered – the most common feature is a thrombocytopaenia, possibly of immune-mediated origin, in some forms of lymphoma and plasma cell myeloma. The clinical effects will reflect as a bleeding crisis and in the laboratory there will be evidence of low platelet counts and altered clotting profiles (Fig. 7.6).
3. *Elevated total white cell counts*. Leukocytosis is relatively common, but absolute counts should always be provided by the laboratory and each cell type should be interpreted separately first so that the correct profiles can be constructed before a diagnosis can be supported or ruled out. The various cell types are not interdependent – they are largely independent, so recognition of subtle changes in numbers (raised or lowered) as well as changes in cell morphology are important in the investigation of cancer cases. Perhaps the best example of this is in the various forms of lymphoma where the circulating mononuclear lymphocytic series can show variations ranging from



Figure 7.6 Plasma cell myeloma. A 7-year-old gelding developed recurrent episodes of mild epistaxis, which varied from bilateral to unilateral. **(A)** His mucous membranes were pale and mildly icteric. His platelet count was 22×10^9/L (reference $125–175\times10^{12}$/L). **(B)** A sample of his blood was left to stand alongside a sample from a normal horse for 15 min and this simple test demonstrated the anaemia and the lack of normal erythrocyte sedimentation that is a marker of possible hyperproteinaemia. His blood protein concentration was 143 g/L and his albumin was 23 g/L. This plasma protein distribution is a cardinal feature of plasma cell myeloma. Less dramatic elevations are a common feature of lymphoma (see Figs. 30.12 and 30.13).

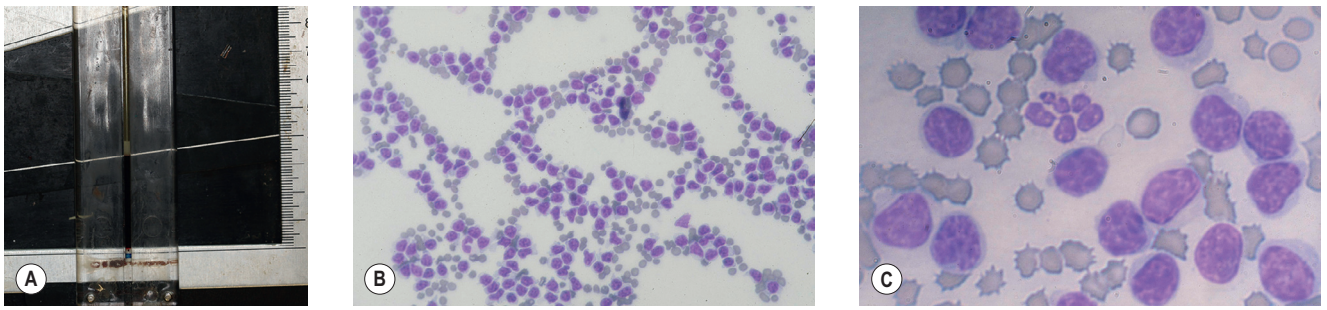
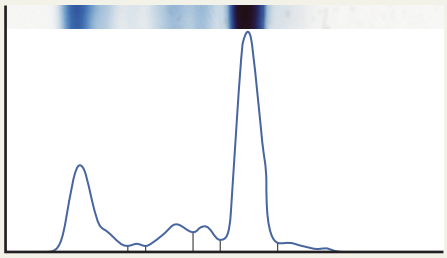


Figure 7.7 Leukaemic (B-cell) lymphoma. A 13-year-old Welsh pony gelding was presented with a 3-month history of progressive weight loss, lethargy and inappetence. On clinical examination, generalized lymphadenopathy was identified quickly and a blood sample was taken. This showed a total white cell count of 175×10^9/L (reference $6–12\times10^9$/L), of which 172×10^9/L were abnormal lymphocytes. **(A)** The haematocrit gave the first clue to his condition with a very wide buffy coat, and a significantly elevated total protein (82 g/L) was measured by refractometer; only 31 g was albumin. **(B,C)** A diagnosis of leukaemic (B-cell) lymphoma was confirmed.

lymphopenia to severe leukaemia. The changes in numbers may be accompanied by evidence of inflammatory responses (cellular and biochemical), so that where a tumour has become necrotic and/or results in systemic inflammatory responses, the neutrophil count may be markedly elevated. In some cases, however, the bone marrow production of the granulocytic series can be impaired and neutropenia may be present. Where there are both suppressive and stimulatory events, the overall counts can be relatively 'normal' but, in these circumstances, detailed cytological examination will usually show significant – often very obvious – changes (Fig. 7.7).

4. *Clotting abnormalities*. Defects of coagulation occur in cancer cases for a number of reasons. They can reflect paraneoplastic changes in clotting factor production, secondary disseminated intravascular coagulopathy as a result of systemic inflammatory response or blood loss or endotoxaemia, or can arise as result of bone marrow suppression of thrombocytes.
5. *Hypoglycaemia/hyperglycaemia.* Blood glucose concentrations are commonly abnormal in serious neoplastic diseases and again can arise as part of paraneoplastic changes or as result of derangement of glucose metabolism for other secondary reasons (p. 77). More significant causes of hyperglycaemia include pituitary pars intermedia dysfunction and equine insulin resistance (metabolic) syndrome.
6. *Protein variations.* These are common, but the variety of responses mean that the changes are usually nonspecific (Fig. 7.8). The exception to that rule is in certain types of lymphoma or in the particular circumstance of plasma cell myeloma when monoclonal gammopathies are encountered as a result of active abnormal antibody-producing cells. The latter is extremely rare in horses, but cases have been recorded with some regularity. The use of specific immunohistochemical stains can be used to identify the true nature of the tumour in some cases. Lymphoma is the best understood and documented of these.[4] As might be expected, many internal tumours do have significant implications either directly or indirectly in terms of plasma protein concentrations. Debilitating tumours may result in low serum albumin



Values below are g/L of proteins found in the case shown on the left.
The concentrations are calculated from the proportional 'area under the graph' from the total plasma protein concentration.

Alpha1 globulin	1.46	(NR: 1.1–2.1)
Alpha2 globulin	10.68	(NR: 5.5–7.9)
Beta1 globulin	7.04	(NR: 6.8–11.4)
Beta2 globulin	76.55	(NR: 3.5–7.2)
Gamma globulin	3.26	(NR: 8.3–14.4)
Total globulin:	99	(NR: 29–39)

Figure 7.8 Electrophoresis and densitometer scan of the plasma from a case of multiple myeloma. Electrophoresis can provide useful information in cancer cases. Plasma cell myeloma and lymphoma in particular are characterized by elevations of the total plasma proteins; specifically, this affects the globulin fraction and electrophoresis, such as is shown here, reveals that there is usually some form of monoclonal spike ('sky-rocket') in the scan. Often this is accompanied by alterations in alpha and beta globulins as well but these are more nonspecific evidence of a serious inflammatory response. *(Figure courtesy of Beaufort Cottage Laboratories.)*

concentrations with independent variations (either elevated or reduced) globulin concentrations. Electrophoresis is an excellent mechanism for identification of monoclonal gammopathies, which are characteristic features of some lymphoma and most plasma cell myeloma cases.

7. *Serum enzyme variations.* Animals that are losing body mass rapidly: usually as a result of cancer cachexia (p. 95), raised basal metabolic rates and fever, they may have elevations of muscle enzyme concentrations, including creatine kinase (CK) and aspartate transaminase (AST), as well as lactate dehydrogenase.
8. *Triglyceride concentration elevations.* These may rise significantly in horses that are losing weight rapidly or who become abruptly inappetant. They are usually regarded as a secondary consequence of changes in intake but there is no specific information as to whether triglyceride concentrations are altered as a paraneoplastic sign.
9. *Endocrinological variations.* There are a number of well-recognized endocrinological variations that can be detected in circulating blood and which have a definitive/pathognomonic implication. For example the finding of testosterone or oestrone sulphate in horses with suspected granulosa cell tumour (p. 641) is a definitive diagnostic test. Functional insulinoma is an extremely rare tumour in horses but a functional adenoma that resulted in hypoglycaemia has been recorded.[5] In some conditions, the functional hormones produced by a tumour are either very hard to measure (e.g. catecholamine concentrations in phaeochromocytoma of the adrenal medulla) or are not 'proper' hormones and may therefore not be estimated by the normal methods (e.g. parathormone-like peptide in some cases of lymphoma).
10. *Tumour marker detection.* In addition to the normal haematological profiles, tumour markers may be detected in circulating blood. However, few of these are used in equine practice as yet. The advantage of these specific or strongly implicative parameters is that they would enable an early diagnosis to be made with a better degree of confidence. Whether this might improve the outlook for the horse is regrettably dubious.

Since the analysis of blood samples is a routine early step in the investigation process, signs may be subtle. There are also important reasons to ensure that horses undergoing surgery, chemotherapy or radiation of any sort are as healthy as possible. Drugs may have adverse effects when the animal has significant concurrent disease (whether that is primarily due to the neoplastic disease or not). More significantly perhaps, paraneoplastic signs are often detected in cases of serious internal neoplastic disease.

Some of the main variation in the common haematological and biochemical parameters of the horse are shown in Tables 7.1–7.5.

Ultrasonography

Modern ultrasonographic equipment is versatile and sophisticated enough to be very useful in the investigation of many cancer cases. High-quality imaging systems, possibly with additional Doppler resources, are usually widely available in practice and specialist centres. Ultrasonography can provide significant diagnostic help in tumour cases; some tumours have very characteristic ultrasonographic features and some have characteristic ultrasonographically distinctive secondary effects such as fluid accumulation in the chest in cases of thoracic lymphoma. For example, granulosa cell tumours of the ovary have a pathognomonic honeycomb ultrasonographic appearance but not every such tumour has this appearance (Fig. 7.9). Mast cell tumour and melanoma often have a characteristic speckled appearance and, in the former, echodense areas are indicative of calcification (Fig. 7.10).

Most soft tissue tumours have only subtle ultrasonographic differences but it is often possible to define the extent of the mass, establish its blood supply and detect areas of necrosis or variations within the tumour mass itself (see Fig. 5.6). Clearly, a well-defined encapsulated tumour with a limited blood supply has a significantly different implication to a large, poorly-defined, invasive and highly vascularized tumour, and demonstrating this kind of difference is one of the strongest features of ultrasonography.

Ultrasonographically-guided biopsy removes the guesswork from the procedure and renders it far safer – even in complex internal locations (Fig. 7.11). For example, it can be possible to define a biopsy site that is more

Table 7.1 The relative significance of the major measured haematological parameters in the horse in respect of benign and malignant tumours

Parameter (units)	Benign tumours	Malignant tumours		Paraneoplastic effects
		Primary	Secondary	
Haemoglobin (Hb; g/L)	–	***	****	Reduced
Haematocrit (PCV; L/L)	–	**	****	Reduced
Red cell count ($\times 10^{12}$/L)	–	*	***	Reduced
Mean cell volume (fl)	–	***	***	Elevated
Mean cell Hb concentration (%)	–	*	*	Reduced
Platelet count ($\times 10^{9}$/L)	–	***	****	Elevated/reduced
White cell count ($\times 10^{9}$/L)	*	****	****	Nil
Neutrophil count	*	***	****	Nil
Morphology	*	**	***	N/A
Eosinophil count	–	–	*	Nil
Basophil count	–	–	*	Nil
Monocyte count	*	**	***	Nil
Lymphocyte count	*	****	****	Nil
Morphology	*	****	****	N/A

This generality is probably not very helpful but blood tests are invariably used during investigation of cancer cases, and so it is important to understand their limitations. Most of the changes are secondary or paraneoplastic. N/A, not applicable. The relative diagnostic value is shown by the number of stars. High value corresponds to 4 stars and low value to one star.

Table 7.2 The relative significance of the major measured biochemical parameters in the horse in respect of benign and malignant tumours

Parameter (units)	Benign tumours	Malignant tumours		Comments
	Primary	Primary	Secondary	
Total protein	NIL	***	****	Important metabolically and diagnostically
Albumin	*	**	**	
Globulin Alpha-1 Alpha-2 Beta-1 Beta-2 Gamma	*	**** NIL * * * ****	*** * * * ***	Globulin changes are common either as a primary effect or a secondary consequence of tumour activity, inflammation or necrosis. Infection is a common comorbidity in cancer cases
Urea/creatinine	NIL	**	**	Secondary effects may be paraneoplastic
Glucose	NIL	***	***	Paraneoplastic hypoglycaemia
Triglycerides	NIL	*		Secondary effects only
Bilirubin (total) Conjugated	NIL	*** **		Haemorrhage/erythrolysis/Clotting defects/immune-mediated haemolytic anaemia and/or thrombocytopaenia
Serum amyloid A (SAA)	*	***		If necrosis or secondary infection is involved
Fibrinogen (Fib)	*	***		If necrosis or secondary infection is involved

This generality is probably not very helpful but blood tests are invariably used during investigation of cancer cases, and so it is important to understand their limitations. Most of the changes are secondary paraneoplastic. The relative diagnostic value is shown by the number of stars. High value corresponds to 4 stars and low value to one star.

accessible and with lesser risk of major vascular or other complication and so the process of diagnosis of tumours is improved significantly through careful and accurate ultrasonography.

Ultrasonography can provide surgical guidance and its non-invasive nature means that it is well tolerated and is extremely safe as a diagnostic procedure. Ultrasonographic assessment of tumour size and density can be used to monitor the therapeutic progress in both external and internal tumours.

Combinations of diagnostic tests can be applied so that ultrasound and rectal examination, for example, can be used

Table 7.3 The relative significance of the major measured electrolytic parameters in the horse in respect of benign and malignant tumours

Parameter (units)	Benign tumours	Malignant tumours		Comments
	Primary	Primary	Secondary	
Sodium (Na^+)	NIL	*	*	Little effect
Potassium (K^+)	NIL	***	***	Elevated if cell lysis is present
Calcium (Ca^{2+}) ionized	NIL	****	**	Hypercalcaemia is a significant indicator of tumours of defined types
Chloride (Cl^-)	NIL	*	*	Little effect
Bicarbonate (HCO_3^-)	NIL	*	*	

This generality is probably not very helpful but blood tests are invariably used during investigation of cancer cases, and so it is important to understand their limitations. Most of the changes can be ascribed to paraneoplastic effects on the kidneys and to cell destruction in advanced cases involving tissue/tumour necrosis. The relative diagnostic value is shown by the number of stars. High value corresponds to 4 stars and low value to one star.

Table 7.4 The relative significance of the major measured blood enzymatic parameters in the horse in respect of benign and malignant tumours

Parameter (units)	Benign tumours	Malignant tumours		Comments
	Primary	Primary	Secondary	
Aspartate dehydrogenase (AST)	NIL	*		Muscle or liver damage
Alkaline phosphatase (ALP)		**	***	Nonspecific elevations
Intestinal ALP	NIL	****	**	Intestinal cell damage
Creatine kinase (CK)	NIL	**	***	Muscle haemangiosarcoma or nonspecific catabolic states in malignancy (cancer cachexia)
Glutamate dehydrogenase (GLDH)	NIL	Liver	Liver	Liver nuclear enzyme that is released as a consequence of cellular necrosis. Can be elevated in serious hepatic primary or secondary tumours
Lactate dehydrogenase (LDH)	Largely nonspecific when measured in total concentration			
Isoenzyme-1 Isoenzyme-2 Isoenzyme-3 Isoenzyme-4 Isoenzyme-5	NIL	Organ-specific changes	Organ specific-changes	Many organs have LDH isoenzymes and the interpretation of elevations in one or more can be a problem

This generality is probably not very helpful but blood tests are invariably used during investigation of cancer cases, and so it is important to understand their limitations. Most of the changes can be attributed directly to the cell destruction that occurs in serious or rapidly growing tumours. Others are attributed to secondary damage from hypoxia or local compressive or catabolic effects. The relative diagnostic value is shown by the number of stars. High value corresponds to 4 stars and low value to one star.

Table 7.5 The significance of some endocrinology tests in neoplastic disease

Parameter (units)	Benign tumours	Malignant tumours		Comments
	Primary	Primary	Secondary	
Insulin	***	***	N/A	Primary insulinoma
Testosterone	***			Granulosa cell tumour
Anti-Mullerian Hormone	***	N/A		Granulosa/thecal cell tumour
Oestradiol	*	*	N/A	Not reliable
Progesterone	NIL	NIL	NIL	Not useful
Calcitonin	*			Thyroid C cell tumour
Parathormone	NIL	(***)	(***)	Common analogue secreted by malignant tumours
ACTH	****	***	N/A	Pituitary adenoma/hyperplasia

As might be expected, specific functional hormone-producing tumours will have strong diagnostic sensitivity and specificity. The relative diagnostic value is shown by the number of stars. High value corresponds to 4 stars and low value to one star.

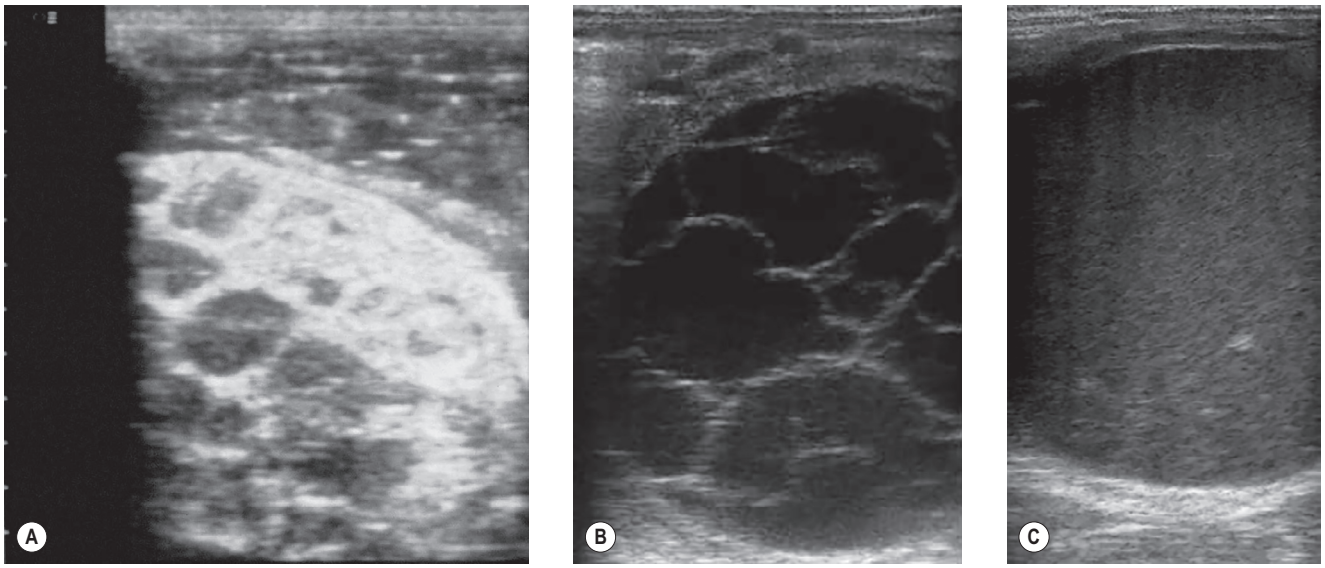
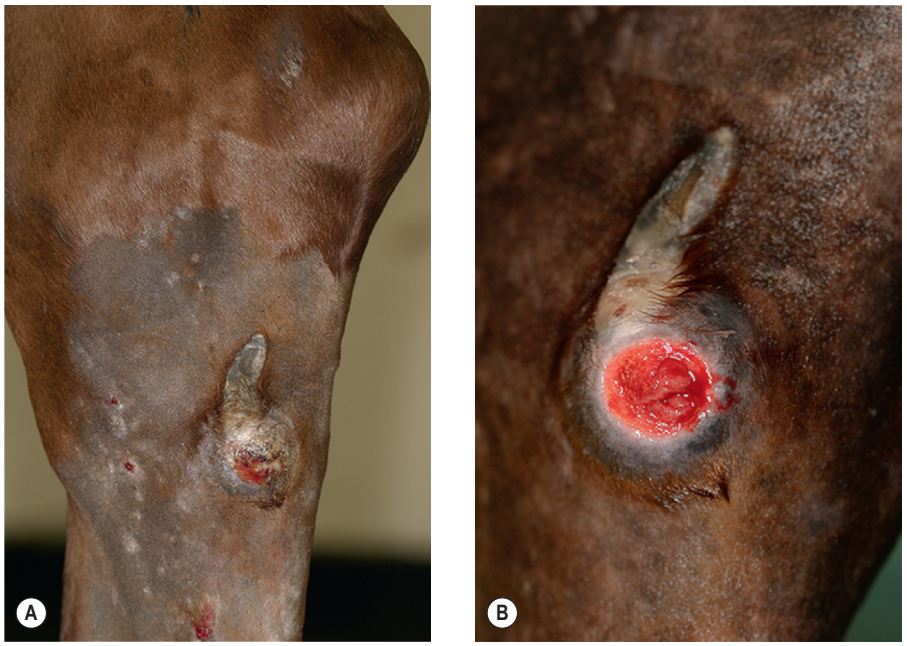


Figure 7.9 Variations in the ultrasonographic appearance of granulosa theca cell tumours. (A) Not every case has the well-recognized honeycomb appearance. **(B)** They can have wider more fluid filled-loculi. **(C)** In some cases, there can be a degree of uniformity when they are filled with blood (see p. 641). *(Figures B and C courtesy of Jon Pycock.)*



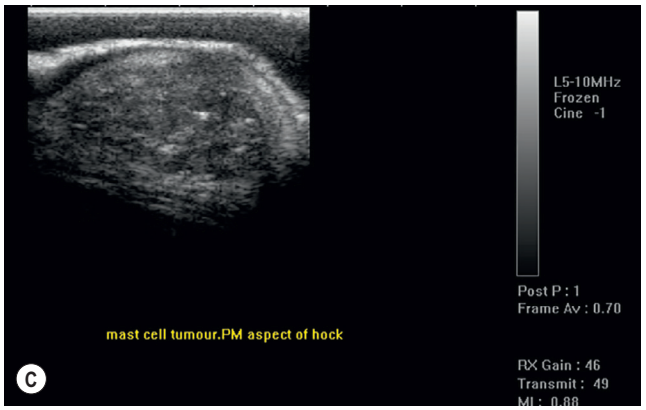


Figure 7.10 The advantages of ultrasonography. (A,B) This pruritic mass on the medial proximal metatarsal region was diagnosed as a mast cell tumour by biopsy but its location meant that there were potential surgical challenges and so ultrasonography was used to inform and guide the choice of treatment. **(C)** The encapsulated nature of the tumour suggested that surgery would be possible and that was completed without incident and without any recurrence after 8 years. The advantages of ultrasonography cannot be overstated – it is a non-invasive, simple but very useful diagnostic aid.

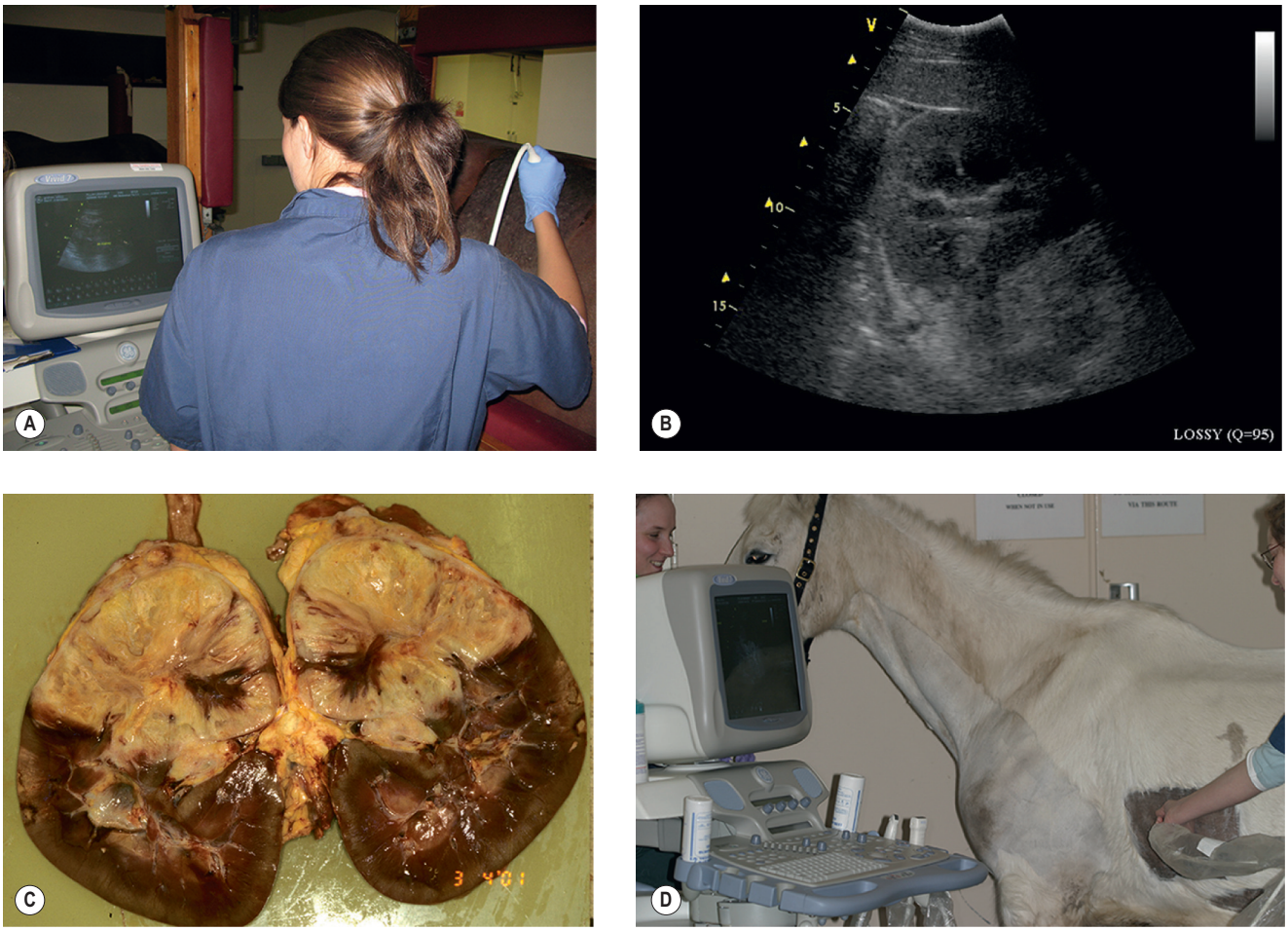


Figure 7.11 Ultrasonographic examination of external and internal tumours provides very useful diagnostic information and also allows guided biopsy of selected specific safe/suitable sites. **(A)** Ultrasonographic examination of the right kidney in a horse that was presented with unilateral ureteral haemorrhage (diagnosed with the help of cystoscopy using a flexible endoscope). The kidney was grossly enlarged and anatomically abnormal **(B)** and an ultrasound-guided biopsy was taken, which confirmed a renal carcinoma which was confirmed at necropsy **(C)**. **(D)** This horse was presented with acute weight loss, lethargy and polypnoea. A large volume of pleural fluid was identified and drained (see p. 504) and then tumours were identified within the pleural cavity **(E)**. A mediastinal lymphoma was identified at necropsy.

together to identify and characterize an abdominal mass, which can then be biopsied using an ultrasound-guided hollow-needle biopsy instrument.[6]

Abdominocentesis/thoracocentesis

Accumulation of fluid in body cavities occurs for many reasons and neoplastic disease is simply one of the possibilities.[7] Significant effusion arising as result of neoplastic disease in the thorax or abdomen carries a grave prognosis, because significant generalized neoplastic disease of the major body cavities remains untreatable.[8,9]

Suitable care and precaution must be taken during collection of fluid from either the chest or abdomen. The value of concurrent ultrasonography cannot be overstated, since it enables the identification of fluid pockets that can be sampled without undue complication.

Sampling of fluid from a cavity is a routine process in equine practice and the technique for the procedure can be found in most clinical texts. However, there are some important principles that have to be adhered to (Fig. 7.12):

1. The procedure must be performed aseptically at a 'productive' location that is identified ultrasonographically.

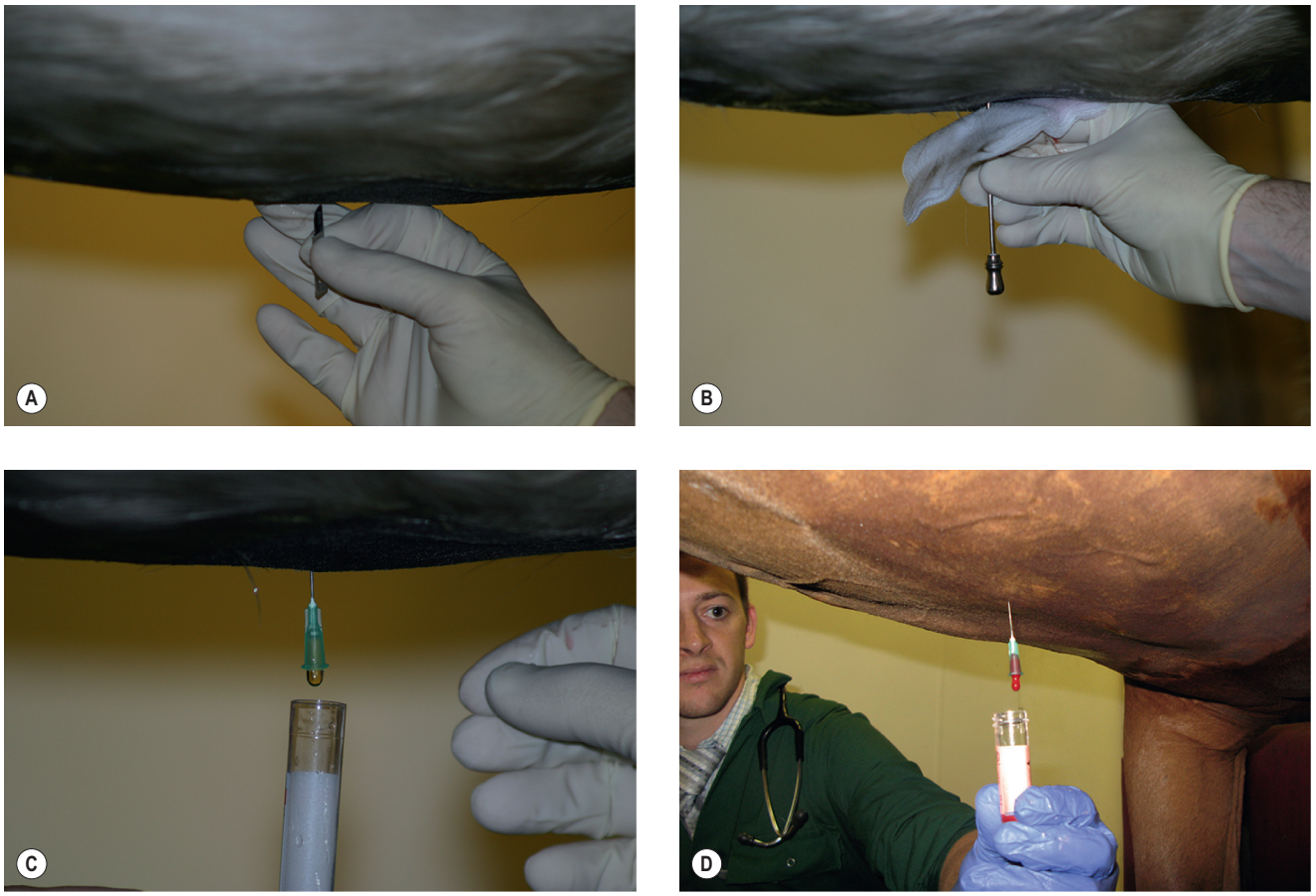


Figure 7.12 Abdominocentesis (peritoneocentesis). This is a routine procedure in equine practice that is performed either using a teat cannula **(A,B)** or a 21G×5–6.5 cm hypodermic needle **(C,D)**. **(A)** Where a teat cannula is used, local anaesthetic is used and a stab incision is made in the midline through the skin and into the linear alba. **(B)** A sterile teat cannula is protected with a sterile swab (this will prevent blood contamination of the sample by preventing blood running down the cannula), and using controlled but firm pressure the cannula is driven into the abdominal cavity. **(C)** A sample of fluid is obtained relatively quickly with this method, since it is a wider bore than a needle. Where a needle is used, there is no need for local anaesthesia in most cases. **(D)** Fluid usually appears quickly at the needle hub and can be examined directly; in this case haemorrhagic fluid was obtained from the abdomen of a 12-year-old mare with a bleeding haemangioma in the spleen; no neoplastic cells were identified in the sample. Each method has its advantages and disadvantages but the procedure is not without hazard and should only be performed when there is a justifiable clinical indication. However, it is performed when collection of the fluid is the objective. Even when the fluid appears clear **(C)**, cytological examination is essential in cases of suspected neoplastic disease. This fluid appeared clear but contained abnormal mononuclear cells consistent with intestinal lymphoma – the tumour was suspected following rectal palpation and ultrasonography – multi-modality diagnostics helped.

2. Pneumothorax must be avoided by suitable precautions, such as staggered needle entry.
3. Damage to the underlying organs should be avoided by careful technique and the use of purpose-made thoracocentesis/abdominocentesis cannulae.
4. The pleural cavities of horses may be separated or continuous, so sampling (or at least examination) of both sides of the chest should always be considered; ultrasonography will rapidly identify whether both sides have suitable effusion to sample.
5. The amount of fluid that accumulates in most cases of thoracic neoplasia is large and the fluid is usually slightly bloodstained and has a higher cell count and protein than normal fluid.
6. The cytological examination is critical even though some tumours are not exfoliative into the pleural fluid.

Centesis of fluid samples should provide direct evidence or implied support for a diagnosis of neoplastic disease, but cytological examination is not simple and requires specialist skill and experience. Often the cytological interpretation is confused by concurrent inflammation and secondary changes, such as haemorrhage (Table 7.6).

Visual examination of the fluid is performed immediately and then it can be subjected to a more detailed analysis. The protein and cytological features of the fluid will almost always assist in differentiating between neoplastic and non-neoplastic (inflammatory or non-inflammatory) accumulations.

Total protein assay

An approximate total protein concentration can be quickly obtained by the use of a refractometer (so long as the fluid is free of cells), but a proper chemical assay is important. Most neoplastic pleural or peritoneal fluid is what is conventionally termed 'a modified transudate' – the protein is usually only marginally elevated (in contrast to the characteristically high protein of inflammatory exudates).

Table 7.6 The differential features of fluid aspirated from body cavities in various conditions

	Volume	Colour	Odour	Nucleated cell count	Cytology	Total protein (g/L)
Neoplastic	High*	Bloodstained	Nil	High	Abnormal cells	Elevated
Non-inflammatory	Moderate	Clear	Nil	Nil	N/A/normal	Low (<1–2)
Exudate/infection	Low	Cloudy	Fetid	Very high	Neutrophils	Very high
Chylous	High	Yellow/beige	Nil	Low	Normal/few	Low
Differentiating value	****	**	****	*****	*****	****

Consideration of the visual, cytological and clinical features can be a strong support for neoplastic disease.[9] The characteristic feature of fluid arising as result of neoplastic disease is the speed with which it is replaced; upwards of 30 L may be present in each hemithorax and this can be replaced within hours of drainage. The relative value for the parameter is shown by the number of stars. Excellent diagnostic relevance is shown by 5 starts and moderate value is shown by 2 stars.

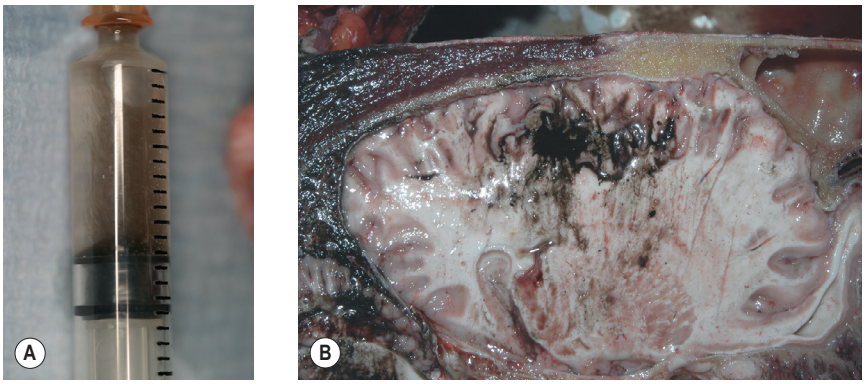


Figure 7.13 Cerebrospinal fluid. A middle-aged grey gelding was presented for orthopaedic examination as a result of his 'weakness and ataxia' (see also Fig. 5.3). **(A)** Cerebrospinal fluid sampled from his lumbosacral space was clearly brown/black and a smear confirmed the presence of malignant melanocytes. **(B)** At necropsy, there was extensive cerebral melanoma and further tumours were found within his spinal cord.

However, abnormal accumulations of fluid within the cavities may itself induce inflammation and so the position may be more complicated than it first appears.

Cytological assessment

Interpretation of the cells present in the fluid can however be difficult, as some tumours are not exfoliative; for example lymphoma tumours may show significant cells in the pleural cavity where exfoliation is more common and more prominent, but many cases of abdominal lymphoma have no diagnostically significant cells present. Some tumours, such as gastric carcinoma, may have very diagnostic cytology but the number of pathognomonic cells may be very low, and thus considerable skill, experience and patience is often required in interpretation. It is not always easy to differentiate activated inflammatory cells from neoplastic cells, so the value of a good cytologist cannot be overstated. Mesothelioma (p. 474) has probably the most distinctive exfoliative cytology but, again, the identification of tumour cells as opposed to activated mesothelial cells is not always simple.

Cerebrospinal fluid sampling

Collection of cerebrospinal fluid has proven useful in the diagnosis of some cases of primary and secondary neoplasia of the central nervous system.[10] Sampling of CSF provided significant diagnostic and prognostic information in 7 out of 12 cases of non-pituitary tumours. The most likely tumours that will be detected in this way include melanomas (although it appears that melanocytes and melanophages are very rarely encountered). Whilst it appears that nonspecific pleocytosis is likely to be the usual response, diagnostically specific cells, such as lymphoblasts, can be found.[11]

The practical difficulties of collecting cerebrospinal fluid should not be a strong deterrent to its use as a diagnostic tool. The technique for sampling from the cisterna magna in the standing horse has been described.[12] The changes would probably reflect uniformly in the CSF, so a lumbosacral sample should be attempted first (Fig. 7.13).

Bone marrow biopsy/aspiration

It is important when considering the collection of bone marrow (whether from aspiration or biopsy) that the marrow usually becomes less active in many sites as the horse ages. Thus, the medullary cavity of many long bones becomes filled with labile fatty tissue and so care should be taken in selecting a suitable site; the wing of the ilium and the sternum are the two generally accepted sites and are the preferred sites for aspiration. The ribs are theoretically acceptable as well, but the medullary cavity is shallow and the ribs are less amenable to penetration without risks to the chest. A bone marrow biopsy is best obtained from a rib.

The techniques are usually performed under sedation in the standing horse.[13] There are commercially available bone marrow needles and biopsy instruments and these make the procedure easier, faster and more reliable (Fig. 7.14). Biopsy usually requires a purpose-made drill.

Bone marrow aspiration

Bone marrow aspiration is relatively easy in horses from any number of sites; usually the sternebrae, the ribs or the wing of the ilium are chosen for their ease of access as well as the availability of reliably representative bone marrow.

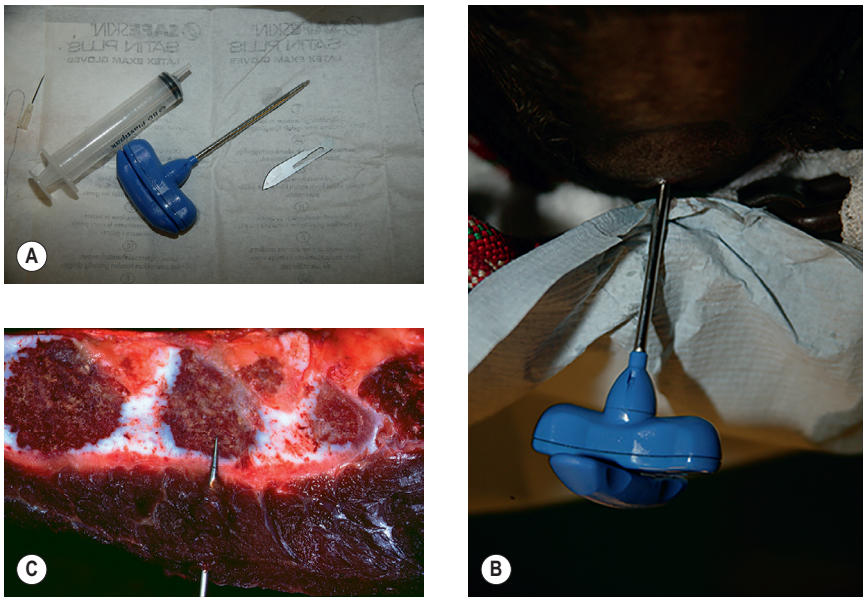


Figure 7.14 Bone marrow biopsy. Bone marrow biopsy can be performed easily in most horses and sampling is indicated in all cases suspected of lymphoproliferative disease. **(A)** A dedicated equine biopsy instrument is available. **(B)** A sternal site is probably the best in most circumstances. The procedure is performed under standing restraint/sedation and the technique is described in standard texts. **(C)** The operator needs to be aware that the outer cortex of the sternebrae is very thin and the depth required to obtain either a biopsy or an aspirate is not great – this specimen shows the sampling technique in cross-section. Typically, the care that is taken reflects the quality of the result. The technique is indicated in any cancer cases that have haematological implications. Again, bone marrow cytology requires experience, patience and attention to detail.

Table 7.7 Indications for bone marrow aspiration/biopsy in cancer patients

Indication	Comment	Precautions
Anaemia	Non-regenerative	Peripheral blood sample should be collected at the same time for routine haematology and biochemistry
Thrombocytopaenia	Function tests also helpful	
Leukopaenia	Differential count is important	
Abnormal circulating cells	Careful cytological assessment	
Hypoproteinaemia	Liver enzyme tests concurrently	Plasma protein electrophoresis is wise in all cases
Hyper-gammaglobulinaemia	Gammopathy (mono/polyclonal)	
Hypercalcaemia	Paraneoplastic	Check renal function carefully also since this is the other major cause of hypercalcaemia
Iron profiles	Anaemia of chronic inflammation	Horses with anaemia of chronic inflammation and/or neoplasia seldom benefit from iron supplementation – it can also be extremely dangerous. Iron profiles are a diagnostic aid only

Bone marrow biopsy

Although bone marrow biopsy is technically a simple technique, it does have the special requirements that justify its description as a separate diagnostic test for some forms of cancer in horses. The technique is indicated in all cases of lymphoma and plasma cell myeloma in particular. Additionally, it is also a useful aid to the investigation of paraneoplastic anaemia, anaemia of chronic inflammation and thrombocytopaenia.

Aspiration and biopsy are very different in technique and tissue handling:

- Aspiration is probably easier than biopsy and is less invasive.[14]
  - Aspiration also provides probably better cytology, but it is easier to obtain non-representative samples and heavy blood contamination, which makes the interpretation much more problematic. In theory, at least, it is also possible to cause cardiac puncture or pneumothorax when inappropriate or incorrect sampling technique is performed from the sternum or the ribs.
- Biopsy provides a better sample of all the cells that are present, including the more adherent cells that may not be collected by aspiration. Detailed cellular interactions and numbers can be estimated more accurately. Morphological features may be less obvious. It is surely much more invasive, since a core of marrow is removed and so bleeding can be more significant. The wing of the ilium is a safe site for biopsy and this is the preferred site in most cases.

Technique

The technique for bone marrow aspiration and biopsy is described in most equine medicine textbooks.[15] The technique for aspiration is significantly different from biopsy. Aspiration collects cells from the medullary space in a mixture with blood, whilst biopsy collects a core of marrow – usually with the outer cortex of the bone intact. Sometimes it helps to drill the outer cortex of the chosen site, but in the case of sternal biopsy the outer cortex is very thin and easily penetrated with a core bone marrow biopsy instrument. Generally speaking, core biopsies are taken from the ribs. The technique is as follows:

1. The required equipment is laid out carefully in a sterile manner. It is useful to ensure that several 10 mL syringes are available for collection with a few drops of heparin saline (this will stop the sample from clotting in the syringe during collection).
2. For sternal aspiration, a small area of skin in the ventral midline at the midline crossing point of an imaginary line between the left and right point of the elbow is located. The clipped area is prepared aseptically.
3. A bleb of local anaesthetic solution is injected subcutaneously and into the area of muscles beneath the site.
4. A short 1–2 cm longitudinal (stab) incision is made in the skin with a scalpel blade over the chosen site.
5. A bone marrow (Jamshidi) instrument or a 90 mm × 1.2 mm stilted spinal needle is then inserted vertically into the sternebral cortical bone; the external cortex is not thick (Fig. 7.14) and is relatively easily penetrated and there is no loss of resistance as the medullary cavity is entered.
6. A syringe is attached to the open needle hub after withdrawal of the stylet and using sharp, repeated application of 10 mL negative pressure until blood is seen at the hub of the syringe. As soon as blood is seen at the hub, the pressure must be released. The needle and the syringe are then removed together and a smear is made immediately by expelling a drop of the collected material onto a slide.
7. If no sample is obtained, the procedure should be repeated.
8. Bone marrow has a fatty/gritty texture and good marrow will usually remain as a drop on the slide.
9. The smear should be made using two slides to 'squash out' the marrow. Residual marrow in the syringe can be placed in heparinized saline and submitted along with the smears.



The marrow sample must be processed correctly if diagnostic quality is to be maintained. The smears should be prepared immediately on collection to preserve the cell structure.

Although bone marrow biopsy or aspiration has limited diagnostic use in many equine neoplasms, it can be useful in others. It is helpful in confirming a diagnosis in some forms of lymphoma, but is also useful as an aid in the investigation of anaemia associated with neoplastic and paraneoplastic states. Interpretation is really challenging and there may be very subtle variation in serious disease.

A bone marrow analysis is indicated where any abnormal circulating cells have been identified and where anaemia or biochemical alterations are clinically or haematologically evident (Table 7.7).

Radiography

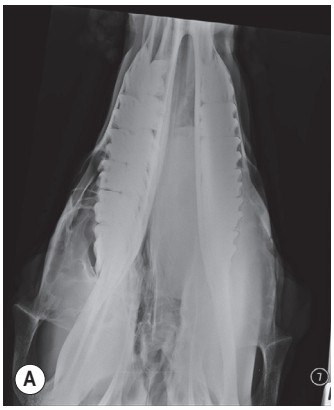
Radiography is a routine procedure in most equine veterinary practice situations. There are, however, significant limitations in most primary care practices through the size of the horse and the need for very high-output machines. The development of digital radiography (DR), where the images are captured digitally on a plate and then processed digitally, or computed radiography (CR), where the image is captured directly to a computer without the need for a separate plate and screen, have significantly improved the value of radiography. It is now possible to obtain useful images of the lungs of medium-sized and small horses using portable machines. However, there is still much value in using sophisticated equipment with grids to enhance the value of the technique.

Radiography is valuable in identifying solid tumours, tumour masses in soft tissues, such as primary or secondary lung tumours (Fig. 7.15), and can also be very helpful in identifying secondary effects of the tumours, including hypertrophic pulmonary osteopathy (p. 81).

Radiography techniques will vary according to the site of the problem, but in most circumstances helpful information can be obtained. As an example of the value of radiography it may be possible to identify the accumulation of pleural fluid – this would appear as a distinct fluid line in the affected hemithorax in a standing lateral projection. After draining the fluid, a tumour might be visible radiographically. Mediastinal tumours are not easily appreciated with ultrasonography, and pleuroscopy is a major surgical challenge.

X-ray computed tomography (CT)

Computed tomography uses X-ray beam technology to primarily create an anatomical imaging modality in which a large number of 'detectors' (up to 64) are used to acquire



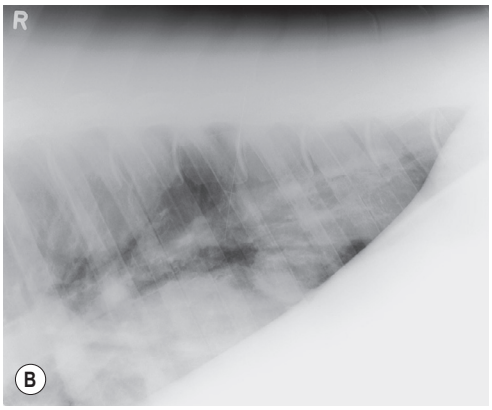


Figure 7.15 Radiography. (A) A 7-year-old gelding was presented with a 3-month history of a mild but progressive facial swelling over the left caudal maxillary sinus. A presumptive diagnosis of a sinus cyst was made but, radiographically, the mass was denser than expected and this was confirmed as a sinus lymphoma by surgical biopsy via a maxillary sinus flap. **(B)** Radiography was used to diagnose the presence of large multifocal radiodense, soft tissue masses in the mediastinum and lungs of a 16-year-old part-bred Arabian gelding with a 3-year history of increasing respiratory compromise; thoracic lymphoma was diagnosed through pleurocentesis and confirmed at necropsy. *(Figure A courtesy of Alexandra Imshaly.)*

radiographical 'slices' of a body or body part. It provides many advantages over radiography in evaluating many accessible anatomical regions of the horse (Fig. 7.16). It is becoming more widely available and many good practices and almost all referral hospitals have the equipment or access to the procedure.[16] Therefore it is one of the commoner modalities used in equine oncology. Additional spiral scanning allows extensive imaging to be collected within a very short period of time. CT is one of the best combined temporal and spatial resolutions of all tomographic modalities. Rapid 3-dimensional acquisition limits movements and results in clear images; the information obtained from all the 'images' is combined together by computer to create a volume of data that can be reconstructed in sagittal, dorsal or oblique imaging planes. Three-dimensional imaging reconstructs the volume of tissue into an image that is familiar to a clinician and therefore is ideal for surgical planning. Decisions as to the true extent of a tumour and its anatomical relations can be made with an enhanced degree of confidence. CT is best suited to evaluation of bony or solid structures and has superior contrast resolution to standard radiographs in evaluating soft tissue structures. Some soft tissue structures such as melanoma can also be imaged usefully. When iodine contrast agents are used, the method also provides useful information on tumour vasculature and blood distribution

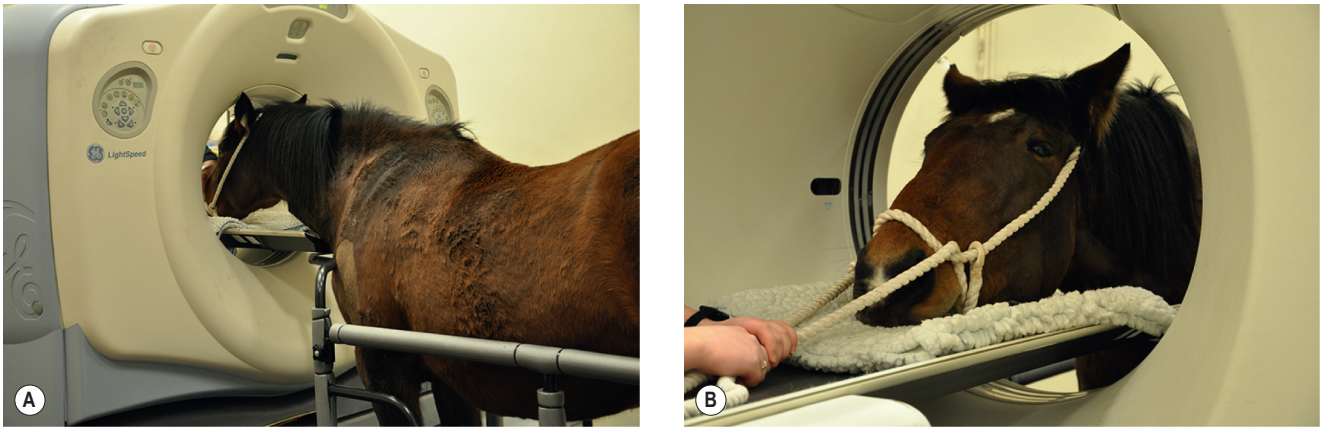


Figure 7.16 Computed tomography (CT). (A,B) Acquisition of CT images from horses presents logistic challenges, since the patient has to move slowly and precisely relative to the generator. Head CT is the easiest procedure, but limbs and neck can be imaged if the horse can be anaesthetized and positioned appropriately.

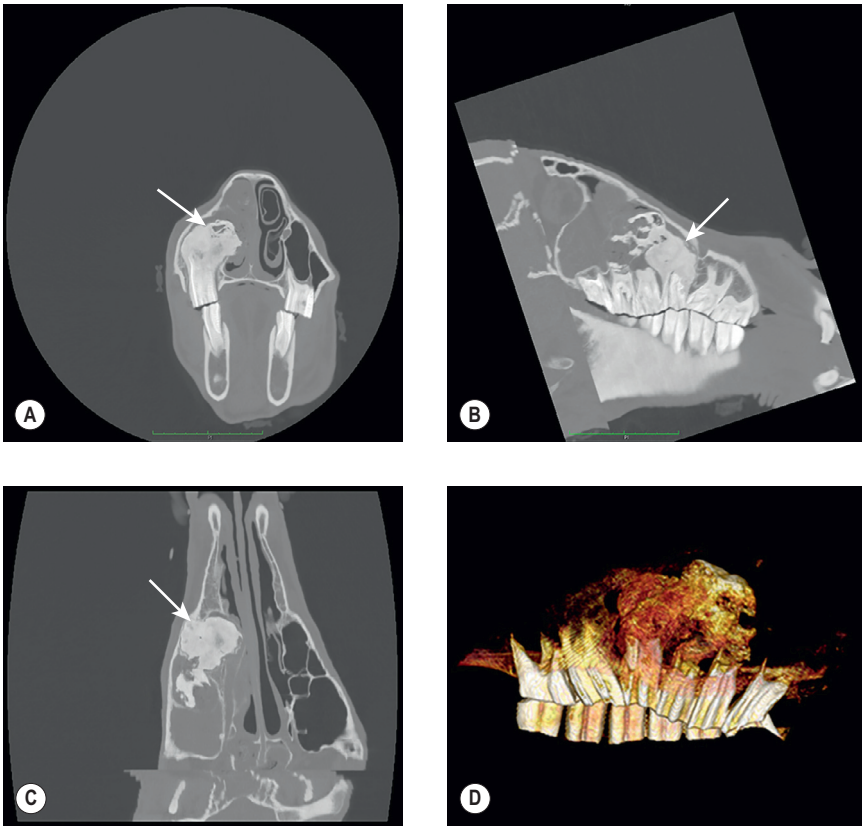


Figure 7.17 A standing CT scan. A 21-year-old Welsh cross gelding had a 4-year history of progressive right-side nasal occlusion and stertor. He had a fetid mucopurulent right-sided nasal discharge with occasional flecks of blood. **(A–C)** A standing CT scan was performed and this confirmed a dental tumour (subsequently identified as an odontoma) (arrows) that originated from the reserve root of 108 (third upper right premolar/third cheek tooth). **(D)** Information from standard radiographic projections was not surgically helpful but a full 3D reconstruction suggested that the tooth could be removed safely. This was done and the pony returned to normal use. Note the complete occlusion of the right nasal chamber.

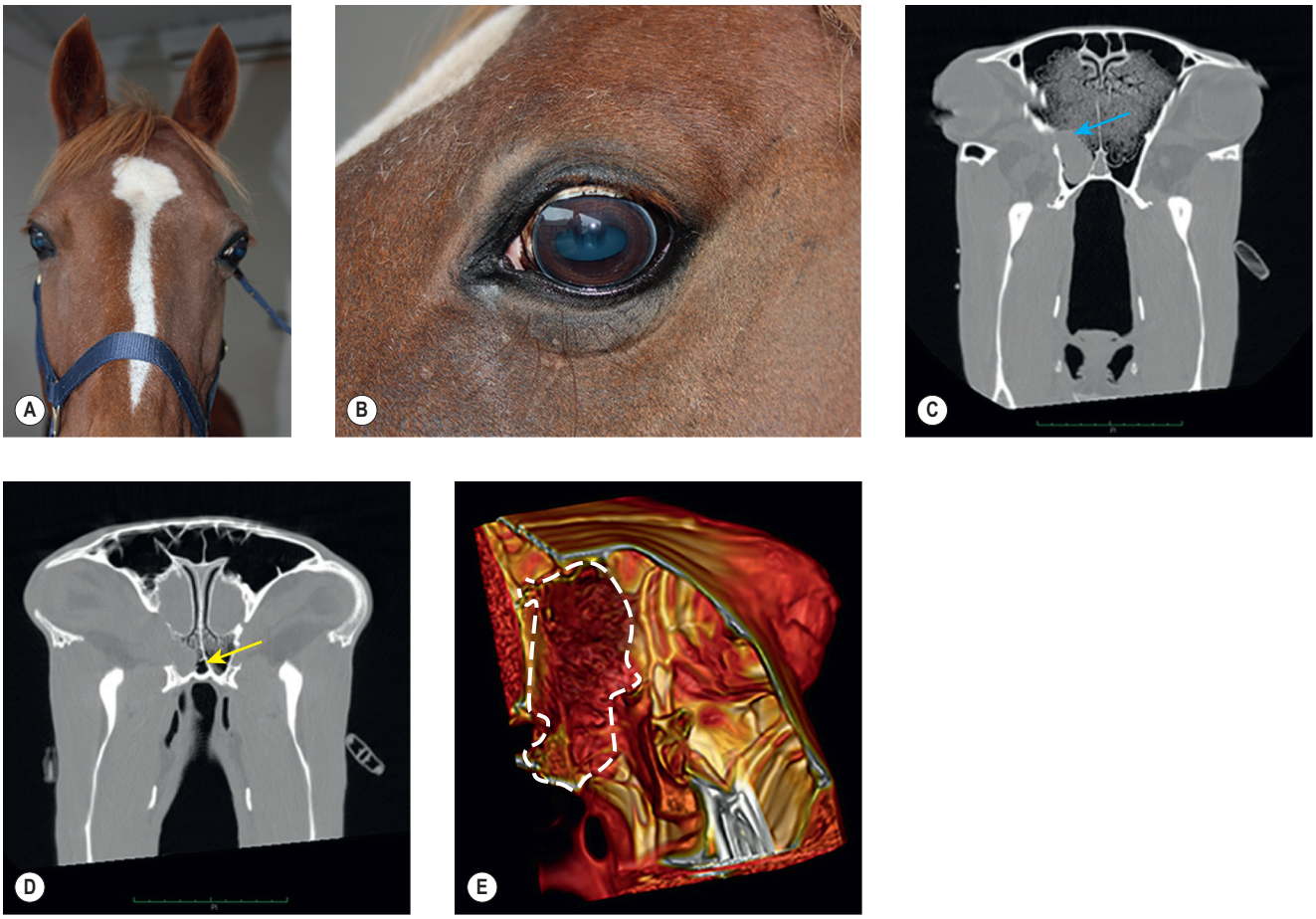


Figure 7.18 A full spiral CT scan. (A,B) A 12-year-old Thoroughbred mare was presented with a 14-month history of progressive, painless left-side exophthalmos, with occasional mild ipsilateral epistaxis. Ophthalmic examination was unremarkable. **(C,D)** Standard radiography and ultrasonography could not identify any significant pathology but a full spiral CT scan confirmed the presence of an invasive soft tissue mass within the orbit that had broken through the orbital part of the frontal bone and the lacrimal bone into the ethmoidal region (blue arrow) (probably the origin of the epistaxis) and into the sphenopalatine sinus (yellow arrow). **(E)** A colour 3D reconstruction confirmed that this tumour, which was subsequently diagnosed as an extra-adrenal paraganglioma, was not operable and so a decision could be taken to simply let the mare continue as long as her welfare was considered acceptable. The mare deteriorated rapidly some 3 months later and was humanely destroyed. Since this tumour type (see p. 595) carries a reasonable surgical prognosis if diagnosed early, a much earlier CT scan might have saved her life. CT surely saved her from having an unnecessary very difficult surgical procedure without hope of success; the prognosis for this condition is established as 'good' provided that the tumour has not invaded the bone (see p. 595).[17]

patterns. Contrast-enhanced CT using iodine-based agents intravenously can also be used to distinguish between malignant and benign tumours, and in some cases can also differentiate between high- and low-grade tumours.

The limitation of the use of CT is simply a matter of size and technology and the operator. The currently available machines are, however, limited in their 'window size' and so the head and neck and the limbs are the current limits of its use in adult horses. In foals, the whole body can be examined. On the positive side, both hard (Fig. 7.17) and soft tissue tumours (Fig. 7.18) and their associated bony and soft tissue alterations can be elegantly displayed, allowing very useful surgical/therapeutic information to be gained.

Magnetic resonance imaging (MRI)

A very powerful magnetic field is used to align the magnetization of some atomic nuclei in the body, and radio frequency is used to systematically alter the alignment of this magnetization. This causes the nuclei of the cells to produce a rotating magnetic field, which is detectable by the scanner; this information is processed to provide an image of the scanned region of interest. Magnetic field gradients cause nuclei at different locations to rotate at different speeds. By using gradients in different directions, 2D images or 3D volumes can be obtained in any arbitrary orientation. In contrast to other imaging modalities, such as radiography and computed tomography, MRI provides excellent soft tissue differentiation and this makes it particularly useful in imaging soft tissues and it is therefore an extremely useful imaging technique for many cancers. Unlike CT scans or traditional radiography, MRI does not use ionizing radiation and is therefore extremely safe as a procedure (although the power of the magnet may have implications).

Whilst the physics employed by the system is highly complex, in veterinary medicine MRI should probably be viewed as an anatomical imaging modality. In human medicine, there are also physiological applications. It has been expanded to provide elements of molecular imaging. In contrast to CT imaging, anatomical MRI has the advantage of good differentiation between soft tissues without bone artefacts.

Scintigraphy

Gamma scintigraphy involves the injection of radioisotopes (usually called 'radiopharmaceuticals') into the bloodstream that actively seek bone that is irritated or is being destroyed or re-built, or tissues that are inflamed or necrotic. Attached to this substance is a radioactive 'isotope' that emits gamma rays. Once the radiopharmaceutical has distributed through the relevant tissues, the emitted radiation can be captured by a gamma camera to form a standard 2-dimensional image showing the distribution of the radioactivity in the tissues; modern computer equipment is used to 'remove' the inevitable background radiation that arises out of natural whole-body distribution. These gamma rays can be detected using a specially designed 'gamma camera', which then conveys this information to a computer. Sophisticated computer software then enables the areas of uptake within the areas of the horse that have been imaged to be assessed. Images of a particular area of the horse can be obtained shortly after injection to examine the soft tissue structures or at 2–3 h after injection to examine the bony structures.

Different radionuclides travel through the blood to different organs and are held in normal and abnormal tissues differentially. The properties of the radiopharmaceuticals can be altered to distribute to different tissues and to different types of pathological changes. Multiple projections can be used to obtain more detailed 3-dimensional information. The technique produces images ('gamma scans') of areas where the radiopharmaceutical is deposited and different radioisotopes can be used to target different tissues, such as bone and nervous tissue but in equine practice, the most commonly used material is ^{99m}Tc-pertechnetate (technetium). An area of primary abnormal accumulation of the radiopharmaceutical takes place in active tissues and this includes cancer lesions.[18] However, it is important that the dynamics of the materials are considered before undertaking the scan. Soft tissue sites such as sarcomas will normally 'wash out' within a relatively short time, whilst bone, for example, may retain the radiopharmaceutical for much longer. Therefore when the technique is used to detect soft tissue structures, a 'soft tissue' scan is performed within 1 h of injection, whilst bone phase scans that detect bony changes (these can be cancerous also of course) are usually performed after 3–5 h.

Apart from its diagnostic role, scintigraphy can also be used to stage and monitor neoplastic disease. In equine practice, the techniques are particularly used in bone tumours and thyroid tumours, but since they are inherently rather crude in their current form in equine medicine they are not widely used in equine oncology. There are, however, some obvious indications where the technique might be very useful such as bone tumours (Fig. 7.19A), central nervous system neoplasia and liver and kidney neoplasia. This is also a very useful technique for investigating multiple myeloma, since each lesion will be detected and then radiography or ultrasonography can be used to further examine the 'hot spots' (Fig. 7.19B,C).

Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are similar nuclear medicine tomographic imaging techniques to conventional gamma scintigraphy but are able to form 3-dimensional information. This information is typically presented as cross-sectional slices through the patient, but can be freely reformatted or manipulated as required. This is not used widely in equine diagnosis at present.

Laparoscopy/pleuroscopy/endoscopy

Direct visualization of a tumour or an organ with a tumour can often be achieved using some form of endoscopic equipment. Flexible and rigid endoscopic equipment have different applications (Fig. 7.20). In the former case, a flexible endoscope is inserted into a hollow structure and the surface of the region can be examined. Good examples are the endoscopic examination of the airway, gastrointestinal tract or the urinary tract. The system is easy to perform in most circumstances with suitable equipment and very good images can be obtained.

Technique

Laparoscopy (and arthroscopy to a somewhat lesser degree) is a routine procedure in modern equine practice that has been developed to a high degree of versatility. Dedicated equine equipment and suitably sized laparoscopic instruments are now available; they are economic and robust. There are, however, some complications that can arise. For example in neoplastic disease, the mass may be inaccessible both to the instruments and the surgeon or the tumour can be too large to access therapeutically.

Where feasible and clinically appropriate, laparoscopy can be performed on the standing, sedated horse or can be performed under general anaesthesia: in the former, the upper parts of the abdomen and thorax can be accessed (and lesions can be sampled); in the latter, the ventral aspects of the cavities can be examined (provided that the operating table can be positioned accordingly).

Limitations

The limitations are becoming less significant as new techniques and equipment are developed, but the horse is a large creature and so there are size and anatomical limitations that are simply unavoidable.

Tumour markers

In the quest for a simple, convenient, rapid, reliable and definitive diagnostic test for early cancer detection, tumour 'markers' are an obvious target. Tumour markers are substances that can be found in the body when cancer is present. They are most often found in the blood or urine, but they can also be found in tumours and other tissue. They can be products of the cancer cells themselves, or made by the body in response to cancer or other conditions. Tumour markers are substances, usually proteins, that are produced by the body in response to cancer growth or by the cancer tissue itself. There are many different tumour markers; some are found only in a single type of cancer, while others can be found in many types of cancer and, occasionally, even in non-cancerous conditions.

The ideal tumour marker is a unique, pathognomonic metabolic substance that is produced only by the tumour

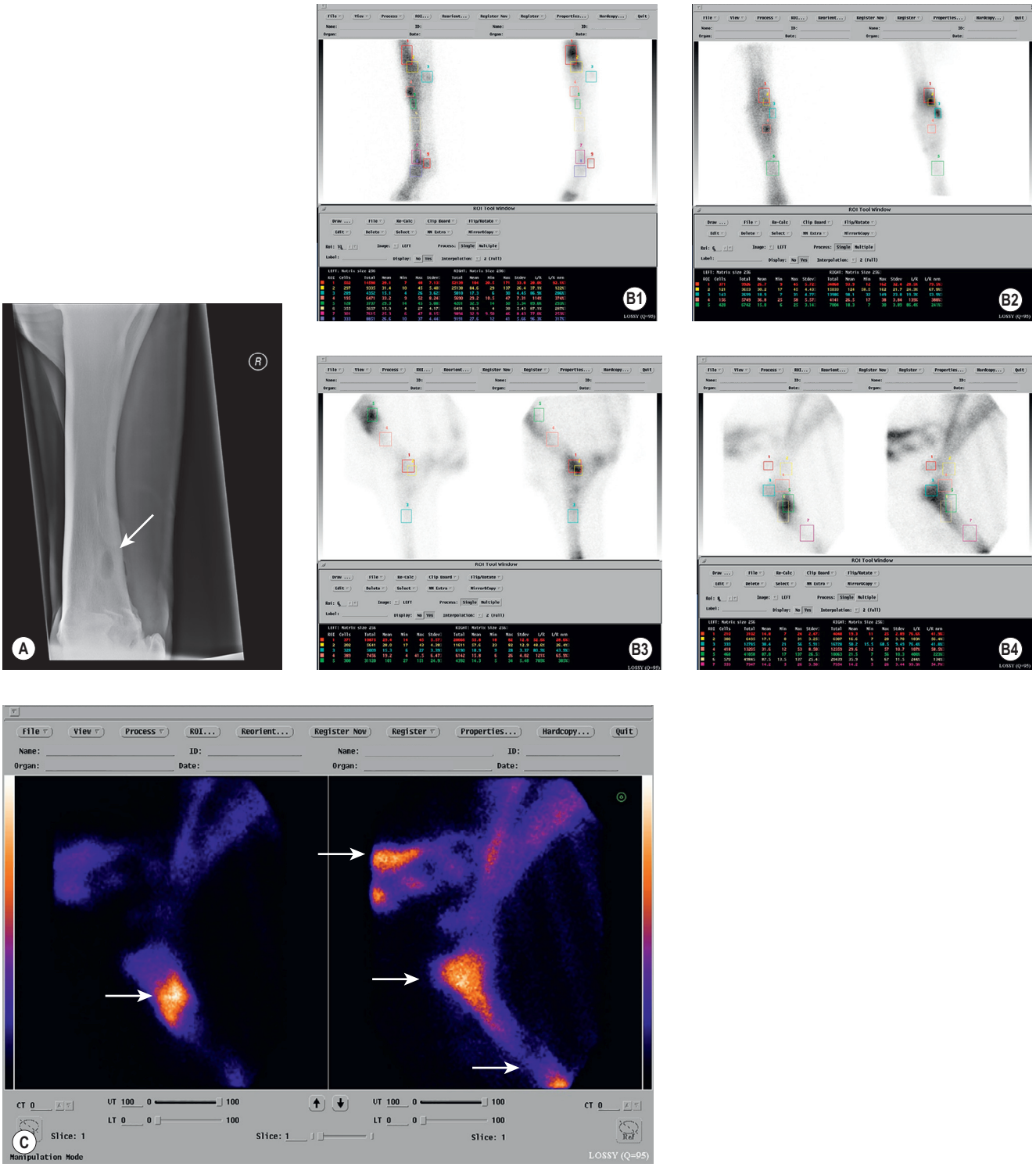


Figure 7.19 Gamma scintigraphy. A 9-year-old Irish Sport cross gelding was presented with depression, multiple site lameness and a recurrent fever of unknown origin. Haematology findings included a monoclonal hypergammopathy, suggestive of multiple myeloma. **(A)** Radiographs were inconclusive but did show small areas of bone lysis (arrow). **(B,C)** A gamma scintigraphy study showed very high radiopharmaceutical uptake in many sites, including the long bones and the pelvis and cervical vertebrae. Acquisition of high-quality images using a high-definition gamma camera can be very useful in such cases, and inform the prognosis and enable therapeutic monitoring where that is undertaken.

cells and which can be detected in an easily collected body fluid (usually blood). A tumour marker is (ideally) a tumour-specific substance found in the blood, urine or body tissues that can be elevated in cancer; these markers are used in oncology to help detect the presence of cancer.

The alteration in genetic behaviour in cancer cells implies that abnormal metabolites will be an inevitable occurrence, but not only are the substances produced in minute quantity but also they may be rapidly metabolized or also they may not be able to leave the tumour cells. Furthermore, some of the substances that could potentially be used as markers are

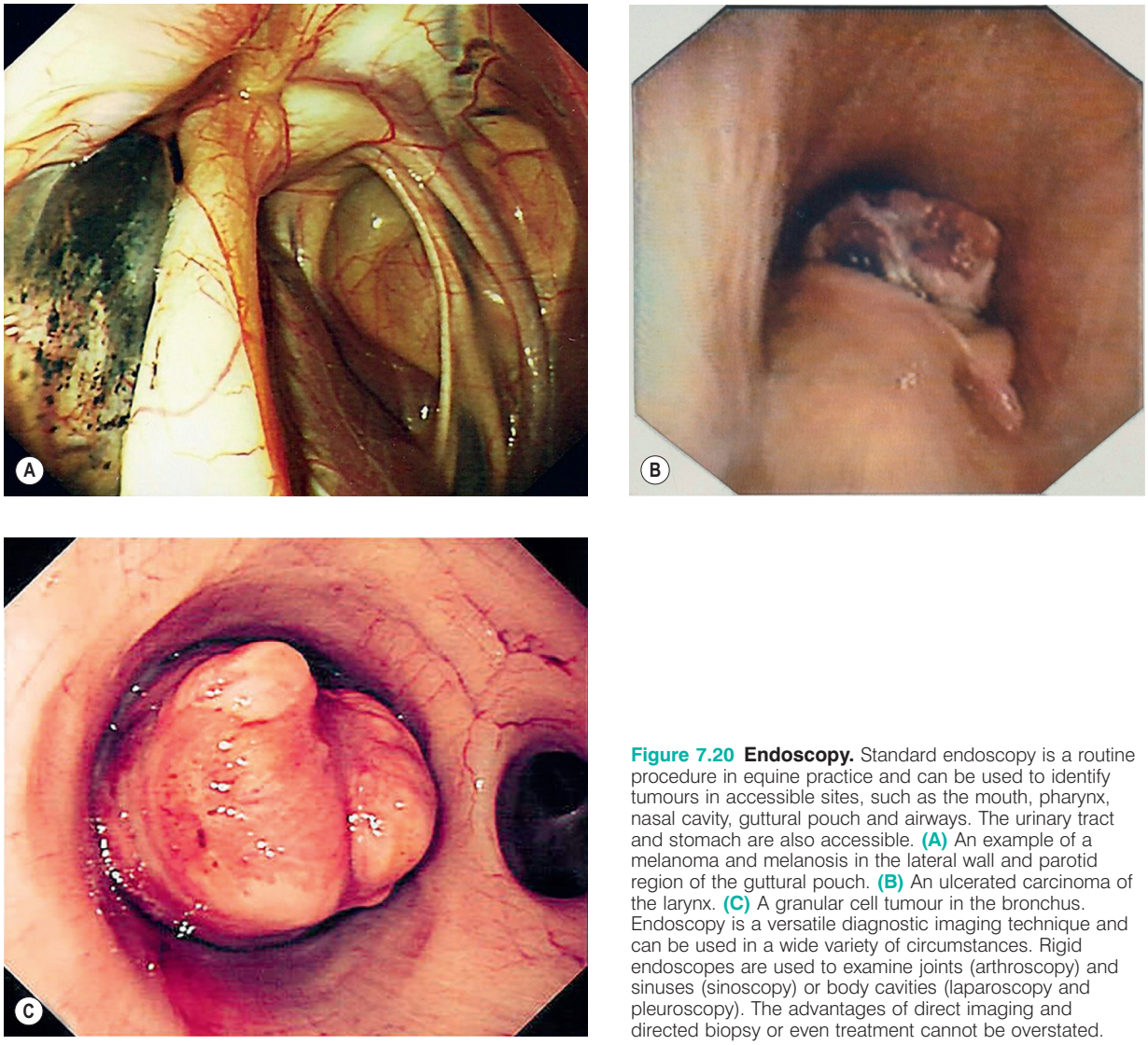


Figure 7.20 Endoscopy. Standard endoscopy is a routine procedure in equine practice and can be used to identify tumours in accessible sites, such as the mouth, pharynx, nasal cavity, guttural pouch and airways. The urinary tract and stomach are also accessible. **(A)** An example of a melanoma and melanosis in the lateral wall and parotid region of the guttural pouch. **(B)** An ulcerated carcinoma of the larynx. **(C)** A granular cell tumour in the bronchus. Endoscopy is a versatile diagnostic imaging technique and can be used in a wide variety of circumstances. Rigid endoscopes are used to examine joints (arthroscopy) and sinuses (sinoscopy) or body cavities (laparoscopy and pleuroscopy). The advantages of direct imaging and directed biopsy or even treatment cannot be overstated.

also produced by non-cancerous metabolic processes and so these cannot be used on their own as specific evidence of a cancerous condition. Some tumour markers are specific for one type of cancer, while others are seen in several cancer types. Since there is a significant overlap between the many different tumour tissue types and the markers they produce, these markers might not be specific in making a diagnosis. In some cases, two or more metabolites can be identified and then the body of evidence is far stronger. However, there are some significant substances for which there are few other explanations. They can, however, be useful in the follow-up of treated patients to describe progress of the disease or response to treatment.

Probably the best-known examples of tumour markers are in human oncology, where either a metabolite is produced or leaked in abnormally high amounts or a very specific (abnormal) metabolite is detected. In the former case, a quantitative measure is required, whereas in the latter, the detection of any of the markers is a definitive diagnostic test. Although prostate specific antigen (PSA) is produced by the normal prostate, only very small amounts leak into the circulation in normal circumstances. Enlarged prostate glands and cancerous prostate glands leak more substantial amounts and these increased concentrations can be detected and acted upon. This is an example of a quantitative marker. In this case, because the abnormal amount of the antigen can be a result of non-cancerous pathology, a final definitive biopsy will then usually be performed.

In the horse, there are few similar quantitative markers but probably the best examples are the endocrinologically active tumours. The most common of these is probably the pituitary adenoma in which abnormal concentrations of a 'normal' metabolic product (adrenocorticotrophic hormone/ACTH) is produced. The metabolic consequence of this means that endogenous cortisol also rises and so there are two (or more) quantitative markers that can be used for diagnosis (p. 585). A second good example of the quantitative marker is the detection of abnormal concentrations of the sex hormones testosterone or equilin in mares with granulosa (thecal) cell tumours (p. 641). The abnormal hormones are usually secreted in sufficient amounts to result in easily recognized reproductive and fertility abnormalities. The mare may be acyclic or may have overt androgenism with a strong stallion-like behaviour pattern.

Further examples of similar marker systems include catecholamines in phaeochromocytoma (p. 593), pancreatic islet cell tumours (insulinoma), thyroid carcinoma and C–cell tumours.

Quantitative tumour indicators can be used to diagnose the abnormally low function of an organ. Again, this is largely confined to the endocrinology tumours. In this circumstance, the metabolic evidence may be strongly supportive of the diagnosis and that can be confirmed by the detection of abnormally low endocrine secretions. There is little information available on these circumstances in equine species.

In the event that a tumour marker exists for a specific tumour, their variations may be used as an indicator of the success or otherwise of the treatment being applied. In a rather crude example, equilin elevations in a mare with a granulosa cell tumour will fall effectively to zero when the tumour is successfully removed. Where tumour metastasis has already occurred, the remote tumours may still produce the markers, so that removal of the primary tumour may not alter the presence of a marker.

The concept of a test for tumour that involves no necessity to biopsy the mass has been exploited in the case of the equine sarcoid, although the polymerase chain reaction (PCR) can also be used to detect the genome of the bovine papilloma virus (BPV) by using swabs submitted for PCR for bovine papilloma virus (BPV).[19]

In vitro cell culture assessment

There are two main methods that are being developed in veterinary oncology from similar techniques used in human medicine:

1. Tissue collected by biopsy from a tumour can often be cultured and the cells examined closely for morphological variations and cell replication rate variations. Replication rates are quantified by measuring the rate of uptake of tritiated thymidine or 5′-bromodeoxyuridine. Of course, the tests rely heavily on the availability of suitable culture techniques for the individual cell types. Currently, equine fibroblasts, squamous cells (keratinocytes) and vascular endothelial cells can be cultured easily and melanocytes and others are less effective at present.
2. Monoclonal antibody technology enables similar information to be gleaned from standard formalin-fixed biopsy specimens. In these procedures antibodies are directed at proliferating intracellular proteins – simplistically, the amount of antibody uptake is a direct indicator of the rate of replication. The test is rapid and has been used for equine squamous cell carcinoma assessment in particular.[20]

Whether these assessments influence the clinical approach and therefore improve the prognosis is not yet certain, but any extra information that can be derived that improves our understanding of oncological disease has to be a step forward.

References

1. De Bowes RM. Standing rectal and tail surgery. Vet Clin North Am Equine Pract 1991; 7:660–661.
2. Lindberg R, Nygren A, Perrson SG. Rectal biopsy diagnosis in horses with clinical signs of intestinal disorders: a retrospective study of 116 cases. Equine Vet J 2010; 28:275–284.
3. Ricketts SW. Rectal biopsy – a piece of the diagnostic jigsaw puzzle. Equine Vet J 1996; 28(4):254–255.
4. Kelley LC, Mahaffey EA. Equine malignant lymphomas: morphologic and immunohistochemical classification. Vet Pathol 1998; 35:241–252.
5. Ross MW. Hypoglycemic seizures in Shetland pony. Cornell Vet 1962; 52:133–145.
6. Ramirez S, Seahorn TL. Ultrasonography as an aid in the diagnosis of renal cell carcinoma in a horse. Vet Radiol Ultrasound 1996; 37:383–386.
7. Sweeney CR. Causes of pleural effusion in the horse. Equine Vet Educ 1992; 4:75–77.
8. Mair TS, Hillyer MH, Brown PJ. Mesothelioma of the pleural cavity in a horse: diagnostic features. Equine Vet Educ 1992; 4:59–61.
9. Mair TS, Sweeney CR. The investigation of pleural effusions in the horse. Equine Vet Educ 1992; 4:70–74.
10. Paradis MS. Tumours of the central nervous system. Vet Clin North Am Equine Pract 1998; 14:543–561.
11. Shamis LD, Everitt JI, Baker GJ. Lymphosarcoma as a cause of ataxia in a horse. J Am Vet Med Assoc 1984; 184:1517–1518.
12. Pease A, Wismer S. Ultrasound guided standing cervical cerebrospinal fluid centesis in ataxic horses. Proceedings of the 51st Congress of the British Equine Veterinary Association, Birmingham; 2012: 192.
13. Savage J, Jeffcott LB, Melsen F, et al. Bone marrow biopsy in the horse: 1 Method using the wing of the ilium. Am J Vet Res 1991; 38:776–783.
14. Savage CJ. Lymphoproliferative and myeloproliferative disorders. Vet Clin North Am Equine Pract 1998; 14:573–575.
15. Mayhew IG, Rosdale PD. A technique for bone marrow aspiration in foals and adult horses. Equine Vet Educ 1992; 4:96–98.
16. Kinns J, Pease A. Computed tomography in the evaluation of the equine head. Equine Vet Educ 2009; 21:291–294.
17. Miesner T, Wilkie D, Gemensky-Metzler A, et al. Extra-adrenal paraganglioma of the equine orbit: six cases. Vet Ophthalmol 2009; 12(4):263–268.
18. Lamb CR, Koblik PD. Scintigraphic evaluation of skeletal disease and its application to the horse. Vet Radiol 1988; 29:16–27.
19. Martens A, De Moor A, Demeulemeester J, et al. Polymerase chain reaction analysis of the surgical margins of equine sarcoids for bovine papilloma virus DNA. Vet Surg 2001; 30:460–467.
20. Theon AP, Metzger L, Griffin S. In situ analysis of cellular proliferation in canine, feline and equine tumours by immunohistochemistry: a comparison of bromodeoxyuridine, proliferating cell nuclear antigen and interchromatin-associated antigen immunostaining techniques. J Vet Diagn Invest 1994; 6:453–560.

8

Pathological methods in equine oncology

Biopsy 108
The concept of 'review' 112
The concept of 'follow-up' 112
Immunostaining/immunohistochemistry 112

Biopsy

Handling biopsy and processing

'The result is only as good as the submission' is a sentiment that many equine pathologists will recognize. Often, inappropriate samples are taken and stored and reported inappropriately and when this is compounded by a lack of clinical information the pathologists are inevitably severely hampered. The results will be compromised and the pathologist is usually then regarded as the 'inadequate' gear in the machine! It is vital that a team approach is made, since that ensures everyone plays their part in the diagnosis and the outcome.

Improving the diagnostic value of biopsy

If a clinician or surgeon wants to make the best use of both the procedure of biopsy and the experience and knowledge of the pathologists, the pathologist must be supplied with an appropriate typical specimen submitted in the correct manner and all the correct background information; the best results are obtained when a team effort is applied.

The owner needs to provide an honest and straightforward history, including admission/declaration of all procedures that have been applied. This includes admission of any other opinions that may have been given from any sources.

The veterinarian needs to carry out a full clinical examination and record the findings carefully for the pathologist (as well as for the clinical notes). The type, distribution, number and extent of the lesions should be stated (photographs can be very helpful). The results of any further tests, such as radiographic and endoscopic findings, should be stated fully. The more information a pathologist has, the better the interpretation of the histological examinations.

The correct samples are taken and handled/submitted correctly in a timely fashion. The results are only as good as the samples – some samples may require specific handling. For example, immunohistochemistry or electron microscopy may require special fixatives or special handling of the tissues. It is helpful if the pathologist is consulted prior to the collection of samples in case there are special requirements or in case the pathologist can identify a suitable site for biopsy. The pathologist must also handle the specimens carefully and interpret the findings correctly.

Regrettably, some clinicians seem to prefer to offer the challenge to the pathologists by providing misleading or incomplete information or, sometimes, even by failing to provide anything at all! There is an unhelpful concept that the pathologist can and will reach a diagnosis, regardless of the history, because the patterns of disease are always 'distinctive and pathognomonic'. This is absolutely not the case! The pathologist needs to become an integral part of the diagnostic team and he/she cannot provide a comprehensible and helpful report based on misleading or absent information.

Selecting the best biopsy site and maximizing the return

The best biopsy is obtained by careful selection of the site and consideration of the possible conditions being investigated. The differential diagnosis may include several different pathological processes that may present as 'tumour-like'. For example, focal lymphadenopathy could be a result of localized infection or a local progressive cancer.

A truly typical representative lesion (free of secondary changes or previous trauma/interference) should be selected.

It might be feasible to harvest the whole lesion (excisional biopsy); however, this might be impossible or unwise.

A piece of ostensibly normal adjacent tissue can be included if the condition is suspected as being neoplastic but there are risks with some tumour types if this is done. It is probably better to harvest a truly typical piece of the lesion, so that a diagnosis is achievable in one procedure (p. 87).

Where there are variations in the morphological appearance of the condition, all the variations that are present should be sampled and submitted separately – with a photograph, if possible, showing the lesion and the site of biopsy/sampling.

Multiple biopsies can be helpful if the tumour has patently/recognizably different areas – some changes can be secondary and of course there is no reason at all why a particular patient has to have only one condition present. A good example is afforded by the general similarity between some neoplastic and some inflammatory conditions. The sarcoid can resemble granulation tissue or even dermatophytosis or alopecia areata and carcinomas can be mistaken for cysts and granulating or infected wound sites. Lymphadenopathy can be reactive, inflammatory or neoplastic.

If possible, it is usually better to avoid the use of local anaesthetic agents at the site of biopsy.

Information that should be supplied to the pathologist

The following information should be included (Fig. 8.1):

- Veterinarian's name and contact details
- Owner's name and address (helpful also for follow-up reports)
- Name/Chip or passport identification number
- Signalment (age, breed/type, sex, colour)
- General history
- Disease/treatment history
- Concurrent related or unrelated disease problems (Problem list)
  - Any evidence of systemic involvement
- Suggested clinical differential diagnoses
- Responses to previous treatment

UNIVERSITY NAME
DEPARTMENT NAME

Request for:
Necropsy ☐
Surgical pathology ☐
Cytology ☐

For hospital use only
University Clinician .....
University Hosp. No. .....
Insurance Co. request? Y/N

For laboratory use only
Pathology Lab. No. .....
Histology Ref. No. .....
Vet. Code .....
Date Received .....
Date of Necropsy .....
Interval between Death & Necropsy .....
Tissue(s)

Owner ..... Ref. No. .....
Owner's Address .....
Species ..... Breed .....
Age ..... Sex ..... Body Weight .....
Date & Time of death/euthanasia/surgery .....

Referring Veterinary Surgeon .....
Practice Name & Address
Tel. No.
E-mail Fax. No.

Photographs

Clinical Features (including anatomical site of surgical specimen) Previous Path. Lab. No.

Differential Diagnosis/Clinical Impression

Please remember - it is a legal requirement that all specimens must be securely packaged

Please send samples to: Department Address
Tel No. Fax No. E-mail

Figure 8.1 Submission form. A suitable submission form to accompany any surgical specimens submitted for histological or cytological examination. *(Figure reproduced with permission from the School of Veterinary Science, University of Liverpool.)*

- Confirmation that the sample submitted is typical of the condition
- Photograph of the lesion biopsied with a second picture or indication of where the biopsy was taken from. Pathologists sitting American and European board-certification examinations in anatomical pathology are specifically trained to recognize and diagnose lesions in digital images, and will find these useful. It is important to take the photograph with the lesion in the centre when possible, in context (i.e. such that the location can be recognized), and with adequate lighting (indoor or outdoor). Closer images may also be appropriate, although these will often require use of a macro-lens to be of sufficient quality. Pathologists or necropsy room assistants will usually be able to provide advice on medical photography.

The more information (in terms of history and clinical signs) that is provided to the pathologist, the better the outcome. There is merit in supplying detailed close-up photographs of any obvious lesions before and after the biopsy with the documentary notes, so that the pathologist can see exactly where the biopsy was taken from; sometimes the pathologist can even be present and can then select the sites most likely to be diagnostically useful. In this way, the pathologist makes a meaningful contribution to the diagnosis. He/she might also come to appreciate the difficulties that the clinician faces when selecting material to sample. By the same token, clinicians could usefully spend some time with a pathologist to gain an improved understanding of the limitations they face. It is also very useful for the pathologist to understand the clinical context in which decisions are being made, e.g. emotional and economic considerations, access or willingness to refer to a specialist if necessary (in the case of primary opinions) and general health of the animal concerned. By the same token, clinicians could usefully spend some time with a pathologist to gain an improved understanding of the limitations they face. Pathologists do desire to be a part of the case management and will generally welcome this type of interaction, as frequently the reports are prepared and sent out with little real contact with the clinicians involved.

The decision to obtain tissue samples (of any sort) is only the first step in the process. The specimens need to be taken in the correct way, handled in the correct way and then processed correctly. These technical aspects do require some thought and careful sampling will always yield better, more meaningful results.

Helpful aspects of tissue sampling include:

- Samples submitted should be as large as possible
- Minute samples are frequently non-diagnostic. However, it is not always possible to obtain large specimens (e.g. corneal biopsy)
- Inclusion of a normal edge or a sample of unaffected skin from an adjacent area is helpful, but this should not be extensive – it is better to collect a bigger area of abnormal tissue and a smaller area of normal than vice versa. The pathologists will surely know what the normal structure of the tissue is like
- Careful biopsy technique to minimize the risks of artefacts and iatrogenic damage (p. 87)
- Correct handling of the samples to avoid artefactual damage to the tissue
  - Crushed and stretched artefacts are disappointing; this appears histologically as cellular smearing
  - Prolonged delay between collection and placing in fixative can create drying and even autolysis in some circumstances
  - Tissue frames and baskets can be useful. Pathology laboratories are usually happy to provide plastic tissue cassettes of various types. These should be labelled with a pencil not a pen or marker pen (the latter is removed by fixatives)
  - Appropriate containers are essential. A large sample pushed into a narrow-necked container might mean that the sample cannot be removed without breaking the bottle and/or the sample, and this might also mean an inadequate volume of fixative is used. Purpose-made screw top containers should be used rather than urine sample containers, blood tubes or jam jars, to avoid loss of fixative when mailing specimens. Laboratories may provide labelled containers pre-filled with fixative on request
- Selection of the correct fixative: usually for most routine circumstances, 10% formalin is the best option. The correct relative volume of fixative should be used; at least 10× the volume of the tissue. Spatial orientation of the sample in respect of the surrounding tissues is an important factor for the pathologist; sometimes a fine suture placed in one end of the biopsy can be used to orientate the specimen.

In return for the clinical effort, the pathologist needs to provide a full report on the findings, including details of any histological changes. The report should be as helpful as possible to the clinician and to another pathologist. Whilst many clinicians will actually only be interested in the 'bottom line' (diagnosis), it is very important that this is supported by credible histological information that can be interpreted by another pathologist, should this become necessary. In legal circumstances, the pathologist's report must be signed and dated (Fig. 8.2).

Information the clinician can reasonably expect

- A comprehensive and comprehensible report (properly signed and dated) covering the pattern/distribution of the pathological changes, the cellular elements involved and a morphological diagnosis
- A suggested diagnosis (whether this agrees with the clinical impression or not) with a constructive comment on the rule-outs that were suggested by the clinician on the submission forms
- Information on the possible cause and the likely prognosis.

In the case of neoplastic lesions, the pathologist will usually provide:

- A diagnosis or a presumptive diagnosis, along with a morphological description of the lesion that can be understood by another pathologist at least. The description should provide useful information, including assessment of tumour cell pleomorphism

University of Glasgow

School of Veterinary Medicine

Sample No 312213

PATHOLOGY REPORT
Biopsy

Veterinary Diagnostic Services, School of Veterinary Medicine
College of Medical, Veterinary and Life Sciences
University of Glasgow, Bearsden Road, Glasgow G61 1QH, UK
Tel: +44 (0)141 330 5777 Fax: +44 (0)141 330 5748

email: vet-sch-vds@glasgow.ac.uk Website: www.glasgow.ac.uk/vds
University of Glasgow, charity number SC004401

XXXXX Xxxxxxx Xxxxxxx Xxxxxxxx XXXXXXX 6879	Your Ref. Owner XXXXXXX Animal DOBBIN Species HORSE Breed THOROUGHBRED Age 9 y 12 m Sex M

Sample No.	312213	Sent	14/11/2012
Clinical Diag.		Received	15/11/2012
Slides	12/3041 1-4	Report Date	15/11/2012

Clinical History
This 10-year-old Thoroughbred gelding presented with multiple (20–30) well-demarcated nodular masses in the skin of the shoulders, neck and ventral thorax that have been growing over the past 2 months and are not pruritic. The masses vary in size but measure up to 10 cm in diameter. The skin overyling some masses is alopecic and ulcerated; many appear to be in the subcutis and are not firmly attached to the overlying dermis. A wedge biopsy specimen from a non-ulcerated mass on the neck is submitted for histological examination.
Received is a wedge biopsy specimen of skin and subcutaneous tissue measuring 7x5x2 cm, in formalin fixative. The subcutis is occupied by pale tan, soft, homogeneous tissue that has poorly defined margins. This tissue extends up to deep and lateral surgical margins.

Histopathology
Within, occupying and expanding the subcutis is an extensive, densely cellular, infiltrative, unencapsulated, poorly demarcated neoplastic mass that is subdivided by thick bands of collagenous tissue. The tumour cells are loosely scattered or arranged in small clusters, supported by a fine (pre-existing) fibrovascular stroma. The tumour cells are round with a moderate amount of homogeneous eosinophilic cytoplasm that has well-defined margins. Nuclei are ovoid or cleaved with finely stippled chromatin and 1–4 large, central or paracentral, deeply eosinophilic nucleoli. There is marked anisocytosis and anisokaryosis, and an average of 12 mitotic figures are noted per 10 high-power (x400) fields. There are large numbers of small, well-differentiated lymphocytes between tumour cells, with the latter only comprising 10% of the total population.

Tumour cells and associated lymphocytes are infiltrating the surrounding adipose tissue, and extend to deep and lateral surgical margins in these particular sections.

Immunohistochemistry
The neoplastic cells show diffuse, strong positive cytoplasmic membrane labelling for CD79a (a B-cell marker). The neoplastic cells do not stain positively for CD3 (T-cell marker). However, all of the small infiltrating lymphocytes show strong positive cytoplasmic membrane labelling (internal positive control). No labelling is noted in negative control sections (from which primary antibody was omitted).

Morphological Diagnosis
T-cell-rich B-cell lymphosarcoma, subcutaneous tissue of the neck.

Comment
The histological appearance and immunohistochemical labelling characteristics of this mass are consistent with the diagnosis of a T-cell-rich, B-cell lymphosarcoma. This is a subtype of large B-cell lymphosarcoma in which tumour cells only comprise a small proportion of the total cellular population, the remainder being small, mature, reactive T lymphocytes. Lymphosarcoma occurring in the subcutis and skin may occur exclusively in those sites (i.e. purely subcutaneous), but may also be part of multicentric disease. If subcutaneous only, it is relatively non-aggressive with survival times of 5 months to 11 years reported.

Prof Janet Patterson-Kane
BVSc PhD Dip ACVP MRCVS

Figure 8.2 Pathologist's report. An example of a pathologist's report for a biopsy specimen; the animal details and text are a mock-up to illustrate the type of information usually provided. *(Figure reproduced with permission from the School of Veterinary Medicine, University of Glasgow.)*

and infiltrative behaviour, and any evidence of vascular invasion. The morphological diagnosis describes what was actually seen, and does not imply anything in terms of the cause. For neoplasms, this simply takes the form of the type of neoplasm and the site involved, e.g. lymphosarcoma, spleen and liver. There may also be some modifiers, e.g. lymphosarcoma, diffuse, spleen and liver or carcinoma, metastatic, multifocal, lung.

  - Any grading should also be supplied if appropriate (although this is usually not the case for neoplasms in horses)
- Some indication as to the adequacy of excision (tissue margins)
- The prognosis and any reported information on the clinical behaviour of the tumour type that is likely to be helpful in terms of prognosis. There is some debate as to what should be addressed by the pathologist. An

opinion on prognosis again is most useful when the relevant clinical information has been provided. Whether this is commented on may depend on the type of neoplasm seen.

When a pathologist reports that the tumour extends to the margin of excision, this is a helpful piece of information for the clinician; it is not the pathologist's fault that the tumour was not excised completely and neither should the clinician necessarily be criticized – the mistake would have been not sending the sample in the first place. This finding means that extra measures, such as a repeat excision with a wider margin may be required or at least the prognosis adjusted accordingly. In any case, the owner of the horse should be told immediately, so that there is no future scope for recrimination. The reality is that for malignant tumours, at least, the margins by definition are poorly-defined and may be exceedingly difficult to recognize at the macroscopic level. It is recognized that there may be false-negative margins resulting from the nature of sectioning and processing of the tissue; this can be minimized by correct fixation and a standardized sectioning process within the laboratory, and the risks of missing the margin are generally thought to be less for skin tumours. Additionally, with at least some tumour types, there may be morphologically normal tumour cells at margins that nevertheless contain oncogenic mutations and may therefore initiate tumour recurrence.

Advice on treatment is not in most cases the realm of the pathologist; however, it may be appropriate to indicate results from the scientific literature for tumours that are rare, although this is not intended to imply that the pathologist is the clinical expert. Whilst some suggestions can be made on treatment, there are significant dangers in pathologists proffering advice to clinicians. It is an unfortunate truth that, often, treatment is suggested that is either totally impractical or inappropriate. For example, 'wide surgical excision should be curative', when the lesion involves the whole upper eyelid. Similarly, opinions of generality that are given for very rare, or even once in a lifetime cases, such as 'These very rare tumours usually respond to radiation treatment or wide surgical excision', are usually unhelpful. Whilst any information is helpful, the clinician must interpret it with care and the pathologist should construct the report with similar care, to avoid giving impractical or unproven, gratuitous advice. Most pathologists will vary the detail of the comment depending on their knowledge of the referring clinician's expertise (if they have such knowledge), e.g. general practitioner versus equine specialist, or specialist in a referral clinic, and will try simply to provide supportive information.

The concept of 'review'

The concept of review has not been widely grasped in equine clinical practice but from a pathologist's perspective it is one of the most important ways of establishing genuine defensible evidence on outcomes and prognosis. In some cases, the pathologist's report may not 'fit' with the clinical situation. Usually, if enough clinical information has been provided, the pathologist will already have sought other opinions if there is obvious conflict between the clinical description and the pathology but a clinician should not hesitate to ask for a review of the sample and its resulting specimens. Pathologists are usually very receptive to suggestions on differential diagnoses and, in particular, they welcome discussion on the case. It helps to obtain the e-mail address of the pathologist and to let them know the outcome; this improves prognostic accuracy in future, similar cases. It also significantly improves 'job satisfaction' and professional reputation.

The concept of 'follow-up'

One of the most neglected aspects in equine oncology is the concept of 'follow-up' (Fig. 8.3). The presumptive diagnosis or simply the pathological information may be helpful or it may not. The pathologist and the clinician need to cooperate to encourage dialogue and follow-up to establish whether the diagnosis led to a successful treatment or to failed treatment. Follow-up is often performed by pathologists in an attempt to improve their services and their knowledge. This can only help the clinician. Professional satisfaction and progress in knowledge would be much helped by having follow-up information at relevant times after the diagnosis and treatment has been provided.

Clinicians and pathologists can, and should, cooperate to get the maximum value from a biopsy of equine neoplastic lesions. This will lead to improved diagnosis and management in individual cases and the development of confidence and competence through shared experience of cases over time. The concept of evidence-based medicine must be the objective and only by accumulation of accurate data will progress be made. The value of a cooperative team effort cannot be overstated.

Immunostaining/immunohistochemistry

Whilst the laboratory diagnosis of most of the recognized neoplastic conditions is usually straightforward, there are circumstances when there are diagnostic difficulties. For almost every neoplastic disease we have included in this book, pathologists have characterized variants and subcategories of the condition that have very subtle variations that may blur the boundaries between behaviourally distinct tumour types. For example, there may be little gross evidence to differentiate true fibrosarcoma, neurofibroma (schwannoma) and sarcoid; the tumours may be clinically indistinguishable and the basic histological spindle cell morphology can also be very similar. The implications for prognosis and management can, however, be profoundly different.

Immunohistochemical staining is widely used in the diagnosis of abnormal cells, such as those found in cancerous tumours. The techniques are also used in basic research to understand the distribution and localization of biomarkers and differentially expressed proteins in different parts of a biological tissue.

Immunohistochemistry is the term used to describe the process of detecting antigens such as proteins within, on or around cells of a histological tissue section using antibodies with specific affinity for antigens in biological tissues.[1] This is particularly important when the tumour is

VETERINARY SURGICAL BIOPSY FOLLOW-UP REPORT

Address

Dear

We examined and reported on the following specimen from your practice and would be grateful if you would fill in the follow-up sheet and return it to the above address as soon as possible. A stamped addressed envelope is included for your reply.

Lab. Reference ..... Your Reference .....

Species & Breed .....

Specimen .....

Date Received .....

Diagnosis .....

Follow-up .....

Alive or dead? .....

Unable to trace .....

Destroyed (Give reasons. If animal was not destroyed in your practice, do you know where it was destroyed?)

Was post-mortem performed? YES/NO

If post-mortem was performed, what were the findings?

Were any more specimens retained/submitted? YES/NO

Figure 8.3 The follow-up approach. A good example of a simple 'follow-up' approach that can be made to the clinician. This may stimulate the clinician also to approach the client for information that helps all parties. *(Figure reproduced with permission from the School of Veterinary Science, University of Liverpool.)*

undifferentiated and so may have characteristics that do not allow direct differentiation.

Pathologists usually identify recognizable differences between benign, malignant tumours and reactive tumour-like conditions, but they often are unable to confirm the exact diagnosis from basic histology alone. In these circumstances, specific immunostains can be used to investigate the presence of abnormal or normal cellular and extracellular components that are typically expressed by certain types of tumour.

The availability of specific monoclonal antibodies has significantly improved the identification of cell products and cell-surface markers. This process has significant advantages in identification of the normal cell types, in determining the lineage of histologically unrecognizable malignancy, as well as in the identification of abnormal proteins that may be produced or expressed by tumour cells. Specific molecular markers can identify particular cellular events, such as Ki-67 marking cells in the S-phase of cellular proliferation.

It is very important to keep in mind that antibodies produced commercially are not made specifically to react with equine antigens; more usually they are raised against human or murine antigens. As a result, the range of antibodies available in veterinary laboratories providing this service is very limited compared with medical laboratories. In many reports in the literature on equine neoplasms and other lesions, the antibodies used have not been sufficiently validated for use on equine tissue, and all must be interpreted with caution. Additionally, protocols including the specific antibodies used and their validation are not standardized between different veterinary laboratories.[2]

It is important to determine that the antibody is detecting the correct antigen in equine tissue (i.e. specificity): in the

simplest iteration this can be done by demonstrating a band of the correct molecular weight in a Western blot made from a biological sample.[3] A Western blot involves lysing a sample and using electrophoresis to separate proteins out, depending on their size; they are transferred to a membrane and stained using the antibody in question. Other steps of the validation, which can be laborious, include determining cross-reactivity, incubation times, primary antibody concentrations, and antigen retrieval processes necessary, and staining positive and negative control specimens.[2,4]

Visualizing an antibody–antigen interaction can be accomplished in two ways.

The direct method

This is the simplest method and is a one-step process in which the antibody is conjugated to a reporter molecule, e.g. sarcoids that look like peripheral nerve sheath tumours but are S100 negative; and epithelioid haemangiosarcomas that may resemble carcinomas but will be cytokeratin negative and factor VIII-related factor positive. The antibody binds only to its specific target antigen and after binding to the antigenic site is completed, unbound or excess of the antibody removed. The substrate that is chromogenically altered by the enzyme is then applied. The location of the granular chromogenic product of the reaction marks the location of the antigen in the tissues.

A counterstain of the background tissue will enable precise localization of the site of the antigen expression within the cells and of its relationship to adjacent cells and tissue. Antigens may be expressed in a number of cellular locations, including bound to cell membranes, such as epithelial membrane antigen (EMA), cytoplasmic bound, as with vimentin, or nuclear bound, such as with oestrogen receptors (ER). It is therefore a highly accurate method of detecting which cells and which components of individual cells express a particular antigen. This also makes it is possible to identify individual cells within a population of normal/abnormal cells: for instance, marking scattered metastatic malignant melanocytes within a reactive lymph node.

The positive chromogenic change is a direct and specific marker for the antigen. The validity of the result should be controlled by reference internal tissue controls, such as peripheral nerves and native melanocytes in skin adjacent to the lesion for S100 protein, or normal epidermis for cytokeratin. In certain cases, it may give a semi-quantitative value based on the amount of antigen present.

For instance, a calculation of the number of ER-positive cells combined with the intensity of the stain can be used to determine the Hope Score indicating the oestrogen receptor status of breast carcinomas in humans. Lymphoma subtypes can be identified from their antigenic phenotype as B cell (CD20) or T cell (CD3). Proliferation markers such as Ki-67 can additionally indicate the grade of the lymphoma and its likely rate of progression. The antibody can also be tagged to a fluorescent compound such as fluorescein or rhodamine and the section examined under suitable incident or transmitted light when the marked cells will fluoresce in an otherwise dark field. The obvious disadvantage is that the precise relationship of the positive reaction to the adjacent normal and abnormal cells is more difficult to identify in a dark field.

The indirect method

This approach uses an initial unlabelled antibody. The unlabelled antibody binds directly to the antigen under investigation and any excess unbound antibody is then removed. The primary (usually monoclonal) antibody is usually produced in laboratory rabbits. When a labelled anti-rabbit antibody produced in another animal, such as a goat (i.e. goat anti-rabbit antibody), is applied as a secondary antibody, the amount of binding is exponentially increased. The binding of the secondary antibody introduces a further open or unbound receptor site available for binding on the goat anti-rabbit antibody. Excess unbound antibody is removed and the third stage of binding uses a labelled antibody (usually conjugated to a peroxidase enzyme antibody) that recognizes both the peroxidase and the antigen. The effect of this pyramid of antigen–antibody reactions is a multiplication at each level and a substantial enhancement of the end signal. The final stage can involve the use of an enzyme such as peroxidase or a fluorescent compound (Fig. 8.4).

The choice of which method to use depends on the antibodies available and the sensitivity of the required testing. The direct method has the advantages that it is simpler to perform, any positive staining can be directly related to sequential histological sections and there is a wide range of commercially available antibodies. Amplification is not possible with the direct technique, but the sensitivity can be enhanced by two simple laboratory techniques. The first is to increase antigen retrieval or exposure of any existing antigens to binding. This involves a pre-treatment of the tissue section with trypsin and is a routine process, which has been widely validated and is routine in most diagnostic laboratories. The second is to increase the titre of antibody used, although vigilance is required to avoid diagnosing 'diffuse' background false positivity from true 'granular' positivity.

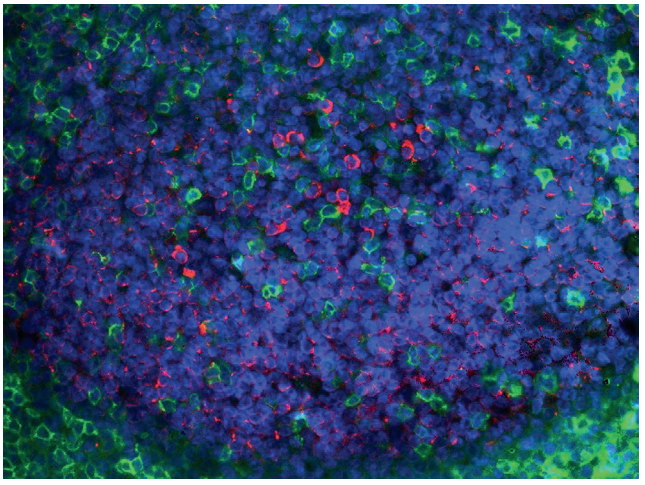


Figure 8.4 A formalin-preserved section of a T-cell lymphoma. The multispectral image was acquired using a Nuance FX multispectral imaging system (PerkinElmer, Waltham, MA). This is an interesting system that is able to remove background fluorescence, so it allows fluorescent labelling of formalin-fixed, paraffin-embedded sections. Blue, DAPI; red, CD3 (tumour cells); green, CD79a (infiltrating/remnant B cells).

The indirect method involves multiple reasonably intricate steps that might add to the potential errors, but the resulting amplification of the signal makes it more attractive as a diagnostic test if the level of antigen expression is very low. The direct method is easier to perform but is less sensitive than the indirect method.

Fluorescent immunohistochemistry

This is a sophisticated way of differentiating cells within a tumour, but this is not commonly employed in equine diagnostic pathology. Here different antibodies are used to identify different cell types and then the retained antibody is identified with a fluorescent antibody to the monoclonal antibody (Fig. 8.5).

Advantages of immunochemistry

The application of this technique allows the identification of specific markers within particular cell types and the identification of undifferentiated malignancy.

Immunohistochemistry is useful in the identification and classification of tumours. Broadly, in routine surgical pathology it is useful to identify tumours within a minimum of four major groups, based on their immunohistochemical profile:

1. Haematopoietic neoplasms/lymphomas: leukocyte common antigen (LCA) or CD45
2. Carcinomas: epithelial membrane antigen (EMA); broad-spectrum cytokeratin (AE1/AE3)
3. Sarcomas: vimentin. Many subtype-specific antibodies are also available
4. Melanomas: S100 protein; HMB45; Mel A.

Antigenic markers are also well-documented for germ cell tumours of testis/ovary, neurological tumours and endocrine tumours.

Whilst most tumour types can be differentiated simply on normal haematoxylin/eosin (H&E) section, many malignant tumours of diverse origin closely resemble each other histologically, since the cells are poorly-differentiated. Tumours such as anaplastic carcinoma, malignant lymphoma, melanoma and myxosarcoma may be hard to differentiate simply from normal H&E sections. Since the prognosis and therapeutic options are significantly different, it becomes important from an oncological perspective to be sure of the diagnosis. Antibodies against components of the individual tumour types can prove valuable in establishing the true nature of a particular tumour. In some cases, multiple immunohistochemical staining can be done to maximize the differentiation. A single stain may be enough, but in other cases a panel of stains is used, which improves the discrimination between the cell types (Table 8.1).

Determination of the original tissue type of metastatic tumours

Where a patient presents with metastatic tumours, the primary site of origin may already be obvious. For example, the primary source can be reasonably identified when a

Table 8.1 How a tumour can be differentiated by the use of immunohistochemical staining (see Fig. 8.4, Fig. 8.6)

Tumour type	Cytokeratin CK/ AE1/AE3	Leukocyte common AG(LCA) CD45	S100 protein	Smooth muscle antigen (SMA)	Vimentin
Sarcoid	NEG	NEG	NEG	POS	POS
Melanoma	NEG	NEG	POS	NEG	NEG
Carcinoma	POS	NEG	NEG	NEG	NEG
Lymphoma	NEG	POS	NEG	NEG	NEG[a]

[a]*Vimentin is positive in histiocytic malignancies.*

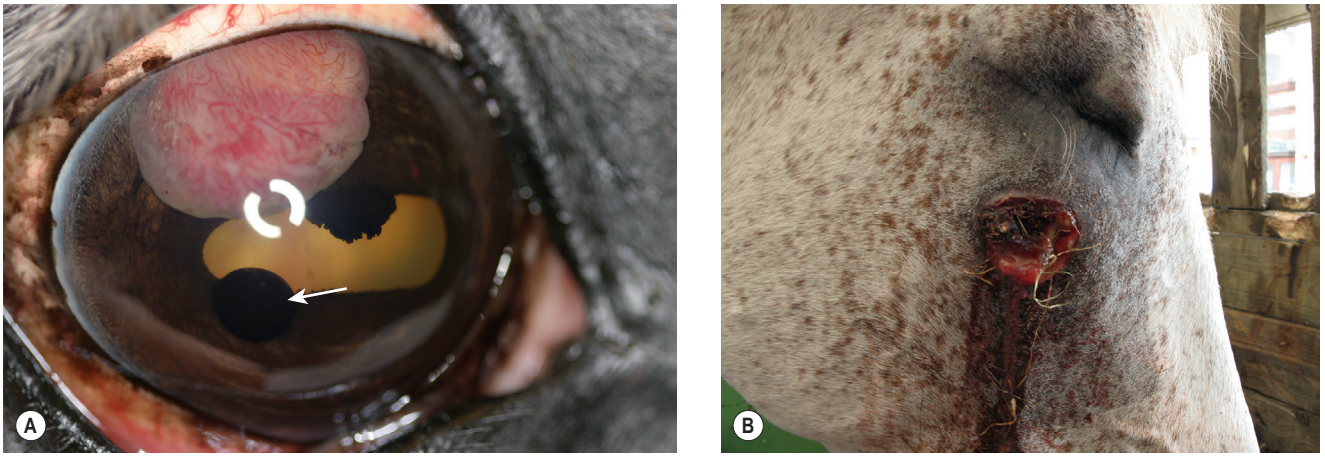


Figure 8.5 Differentiating immunohistochemistry. (A) This 9-year-old flea-bitten grey mare developed an asymptomatic intraocular tumour. Clinical examination revealed that she was blind in this eye and that the posterior segment was filled with tumour – this was confirmed ultrasonographically). The tumour was biopsied and diagnosed by differentiating immunohistochemistry, as retinoblastoma (see Figure 8.6 below). **(B)** Immediate exenteration was not enough to save the horse – some two years after exenteration secondary tumours extended widely into the maxillary sinus and regional lymph nodes. The prognosis, however, was fully understood from the outset as a result of the accurate diagnosis. Note the insignificant/incidental 'tumour like' iris cyst (arrow).

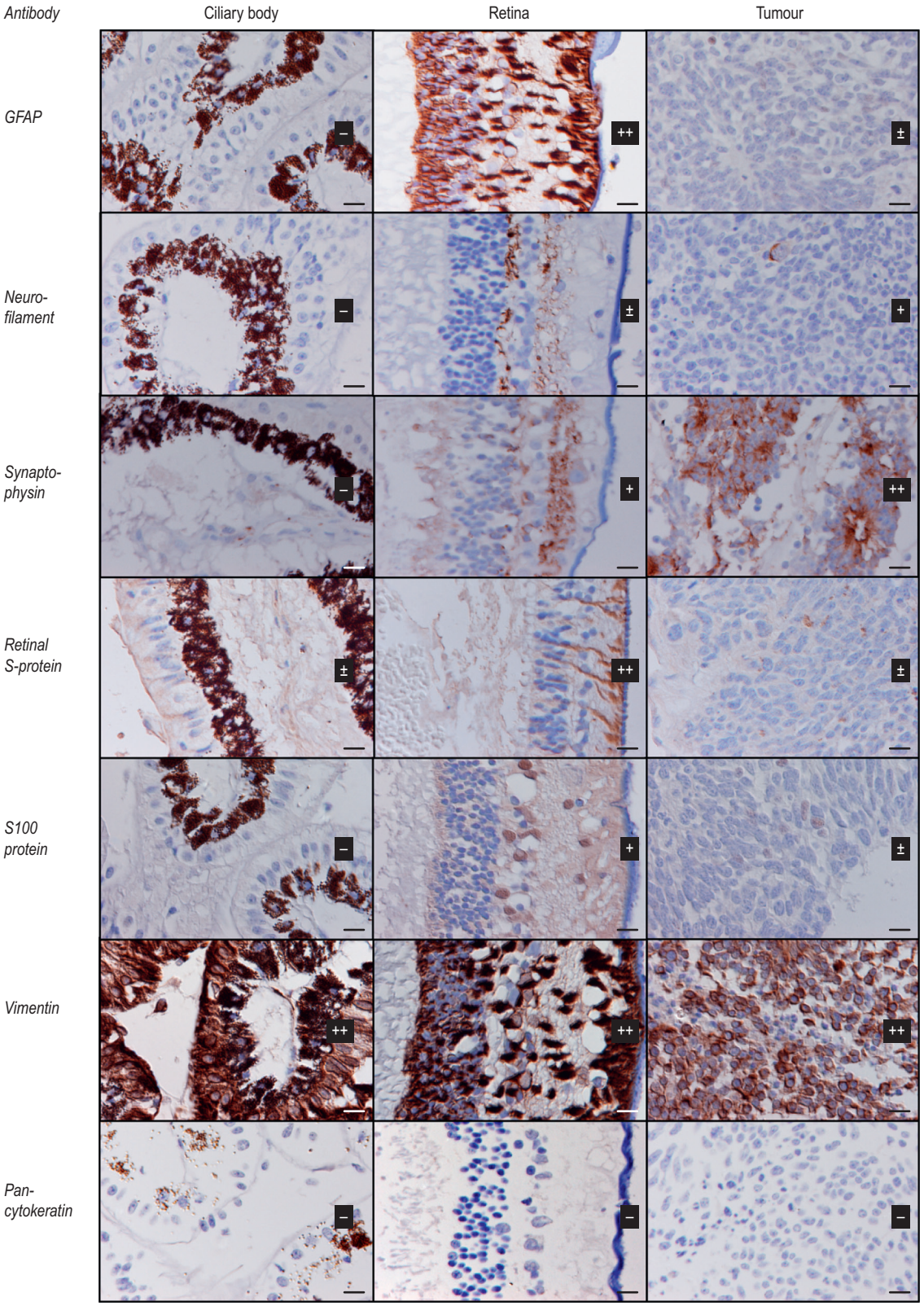


Figure 8.6 The value of immunostaining using antibodies selectively chosen to differentiate the various tumour origins and types cannot be overstated. The relatively new technology allows definitive identification of the tumour type and tissue of origin. Here, the response to the seven different antibodies (immunostains) is used to investigate the nature of an intraocular mass (see Figures 8.5 and 34.8 and p. 623). The responses are classified as strongly positive (++), positive (+), negative (–) or equivocal (±). The panel of antibodies was applied to non-pigmented ciliary body epithelium (NPE), retina and tumour cells. In this way, this tumour was identified as a retinoblastoma. GFAP, glial fibrillary acidic protein. *(Figure reprinted from Knottenbelt DC, Roberts VR, Hetzel U. Unilateral primitive neuroectodermal tumour (retinoblastoma) causing blindness in a horse. Veterinary Ophthalmology 2007; 6:348–356, with permission from Elsevier.)*

gelding with a long history of palpebral carcinoma subsequently develops tumours within the ipsilateral guttural pouch and then the lungs. In other circumstances, it can be much more difficult; where the origin of the tumour is obscure, immunohistochemical detection of tissue-specific or organ-specific antigens in a biopsy specimen taken from the metastatic tumour site can identify the primary site of the tumour or inform a short list of the most likely sites from which the clinician can track down the primary tumour. There are numerous specific markers for this use in many human tumours. Examples include prostate (PSA, PSAP), thyroid (TTF1, thyroglobulin), lung (PE10) and endocrine tumours. While few specific antibodies have been validated for horses, provided care is taken to ensure there are adequate positive and negative controls (preferably within the internal specimen tissue), a positive result is scientifically valid. An insulinoma was diagnosed in a Thoroughbred horse on the basis that the islets of Langerhans in the normal adjacent pancreas were negative for a tumour-specific antibody and provided an 'internal' control and this confirmed to insurers that the antibody for insulin production was valid (C. Temple-Camp, pers. comm.).

A case of an intraocular tumour has been described that relied heavily for diagnosis on the use of discriminatory immunohistochemical stains.[5] In order to define the true nature of the tumour in this case, the various anatomic structures were subjected to immunohistochemical examination using a panel of antibodies applied to sections of each structural component (Table 8.2 and Fig. 8.6). This leads to an unequivocal diagnosis of retinoblastoma.[5] The prognosis was poor and in spite of very prompt exenteration of the eye, tumour development in the orbital region developed over 2 years and terminated in euthanasia. The immunohistochemical analysis had predicted the tumour type, and the few available literature reports confirmed a very poor prognosis and so the owner was aware of the likely outcome from the start. Whether earlier intervention would have led to a different outcome is another matter.

Table 8.2 The immunohistology profile derived by using a panel of antibodies applied to non-pigmented ciliary body epithelium (NPE), retina and tumour cells

	Ciliary body (NPE)	Retinal cells	Tumour cells
GFAP	–	++	±
Neurofilament	–	±	+
Synaptophysin	–	+	++
Retinal S-protein	±	++	±
S100 protein	–	+	±
Vimentin	++	++	++
Pan-cytokeratin	–	–	–

++, strongly positive; +, weakly but definitely positive; ±, equivocal; –, negative.

Detection of molecules that may have implications for targeted therapy

The detection of receptors for hormones, for example in a tumour, may inform at least a part of the therapeutic approach. If a tumour were, for example, to be oestrogen- or progesterone-dependent, then suitable countermeasures might be taken, as is standard practice in human breast carcinomas. A number of human cancers now require immunohistochemical confirmation of antigen expression before appropriate therapy is instituted. For instance, cErb-2 oncogene overexpression status in breast carcinoma predicts a positive response to Herceptin; CD117 (or c-Kit) status in gastrointestinal stromal tumours (GISTs) predicts response to imatinib mesylate (Glivec®; US Gleevac®, Novartis), a relatively low-potency tyrosine kinase (KIT) inhibitor used in the treatment of Philadelphia-positive chronic myeloid leukaemia and KIT-positive gastrointestinal stromal tumours. It is one of several examples of where understanding the steps in carcinogenesis has allowed targeting of specific molecular targets.

In the case of horses, however, there is little information that is available on whether such circumstances exist. It has been suggested that certain types of cutaneous histiocytic lymphoma are sensitive and enhanced by the presence of abnormal hormone profiles in horses with granulosa cell (thecal cell) tumours, so markers on the lymphoma cells may help significantly to direct therapy towards removal of the source of the tumour drivers of tumour progression.

References

1. Ramos-Vara JA. Technical aspects of immunohistochemistry. Vet Pathol 2005; 42:405–426
2. Ramos-Vara JA, Kiupel M, Baszler T, et al. Suggested guidelines for immunohistochemical techniques in veterinary diagnostic laboratories. J Vet Diagn Investig 2008; 20:393–413.
3. Signore M, Reeder KA. Antibody validation by Western blotting. Meth Mol Biol 2012; 823:139–155.
4. Lin F, Jianhui S. Technique and troubleshooting of antibody testing. In: Lin F, Pritchard JW, eds. Handbook of practical immunohistochemistry: frequently asked questions. New York: Springer Science+Business Media; 2011: 17–21.
5. Knottenbelt DC, Hetzel U, Roberts V. Primary intraocular primitive neuroectodermal tumor (retinoblastoma) causing unilateral blindness in a gelding. Vet Ophthalmol 2007; 10(6):348–356.

9

Principles of oncological therapy

With contributions by Youssef Tamzali and Jeremy Kemp-Symonds

Ablative therapy	120	Photodynamic therapy	160
Cytotoxic/medical therapies (chemotherapy)	129	Safety issues in chemotherapy	163
Drugs used in equine chemotherapy	144	Radiation therapy/radiotherapy	165
Electrochemotherapy (ECT)	158	Cancer immunotherapy	186
		Gene therapy	192

It's not the successes that are the problem, it's the failures.

In order to establish a complete and correct diagnosis, the pathologist and the clinician must work closely together. Effective and safe therapy for all tumour types is a clinical goal for all species. Surgery, chemotherapy and radiotherapy remain the most effective modalities for tumour treatment in all species (Fig. 9.1). In the horse, radiation is much less common and it is easy to visualize that the logistic and safety issues associated with this form of treatment would be limiting, simply on the basis of the size and temperament of the horse. Nevertheless, increasing numbers of radiation facilities are being developed in specialist centres. It is entirely logical that this method should be limited to specialist centres where the expensive equipment can be justified and safety of patient and operators can be assured. It is the responsibility of the clinician to consider all of the potential treatment options for any particular tumour type and the associated evidence on efficacy and complication.

The goal of all therapy for tumours is to destroy the tumour cells and preserve the normal ones. Failure to kill 100% of the tumour cells will usually result in recurrence – often with exacerbation of signs and a more aggressive tumour. This is suggested to be because the surviving cells are less sensitive to the chemotherapeutic measures applied and therefore the faster growing ones will develop faster, thus biasing the tumour towards greater replicative rate or malignancy. At the same time, it is also a primary goal to minimize the damage to normal cells in any case treated and to absolutely avoid the risk of inducing neoplastic/malignant transformations in normal cells.

Cancer therapy relies heavily on the premise that normal cells have an inherent and highly efficient ability to repair minor cell damage or to induce apoptosis if the damage is sufficiently strong when subjected to chemical or radiation insult. In contrast, cancer cells are much more susceptible to chemical and/or radiation insult, since they are inherently less stable and have, usually, far less ability to self-repair.

There are inevitable constraints that will have to be considered and many clinicians will have their own more successful approaches. Inevitably in every case, there are factors that will have to be considered however, since few tumours are either predictable or identical. Constraints that have to be considered include: the tumour type (and its particular pathological and clinical behaviour); the anatomic location; the extent and duration of the tumour; and the extent of previous interferences. In some circumstances it may be, for example, just as important to remove the local lymph node as to remove the primary tumour. Similarly, where multiple tumours are present, or where metastatic spread has already occurred, the removal of a single 'troublesome' tumour can be justified on the grounds of palliative care, so as to improve the quality of life for the patient and reduce the emotional and therapeutic burden on the owner.

A summary of the factors that need to be considered in every case is shown in Table 9.1. One of the most important issues is the availability of facilities to carry out treatment and the experience of the veterinarians in the exploitation of the facilities available. Excellent surgeons have better results than poor ones and individuals with extensive experience usually perform better than those with less experience. What works for one person might be much less effective for another oncologist in another clinic. Results need to be clinically audited to maximize the chances of a good outcome. Often, significant benefits accrue from very small alterations in technique. Clinics and individuals need to be open to internal and external audit – there is generally no disgrace in failure, unless the failure is predictable through clinical evidence. The best clinical decision-making on the choice of treatment to be used is the one that takes account of all the factors that influence the outcome. Once the decision is made, usually with the full cooperation of the owner of the animal, the process must be followed through to its conclusion. However, clinical decisions may need to be altered in the light of changes in the clinical position. For example, a case that is being treated with corticosteroids as part of its treatment regimen may develop laminitis; that will mean that the steroid has to be withdrawn. That, in turn, may mean that the doses of other drugs may need to be adjusted or another regimen applied altogether.

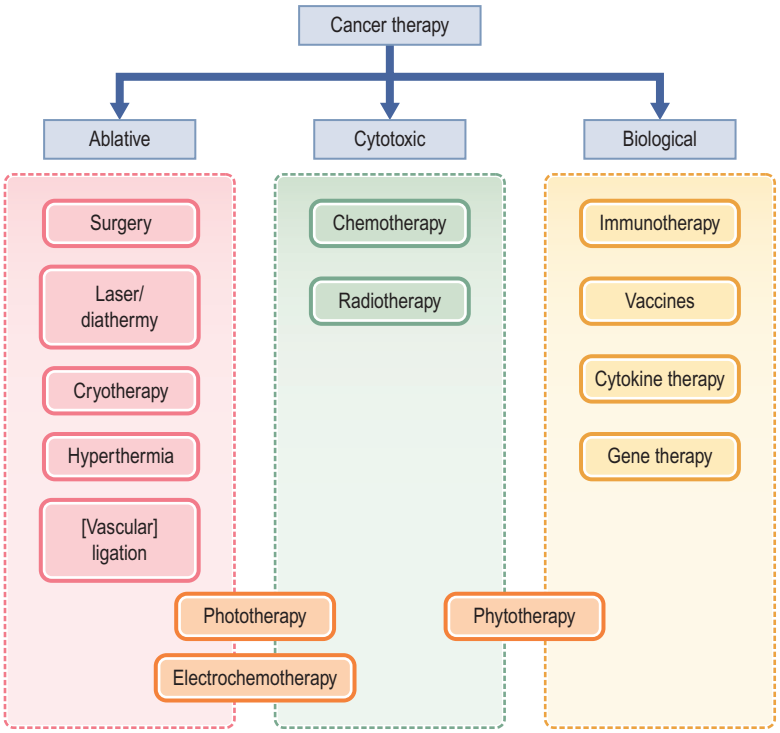


Figure 9.1 The principal methods of cancer therapy. Three basic approaches can be used. Combinations are frequently better than a single method. Usually, surgical options are combined with chemotherapy or radiotherapy.

Table 9.1 The main constraints on successful tumour treatment in equine practice that must be considered before any clinically important decisions are made

Factor	Comment
Tumour type/pathological behaviour	Partial removal of tumours is usually undesirable Malignant tumours require margins and may be inoperable
Tumour location	Anatomical constraints on therapeutic options
Tumour extent	Large tumours usually mean major therapy; surgical wounds can be large, access difficult, large overall doses of chemotherapy
Duration of tumour	Cases that require repeated or prolonged therapy can be difficult and this impacts on owner/horse compliance and treatment costs/logistics
Previous history of treatment	Previous unsuccessful treatment is usually a bad prognostic event. Failures may result from inadequate or inappropriate treatment and then the correct treatment may be effective. The reasons for failure of efficacy need to be considered carefully
Logistics of treatment	Treatment may require specialist centre facilities or may require repeated visits and possibly isolation. Chemotherapy might result in difficulties with housing and disposal of faeces/urine and bedding
Relative value of horse/cost of treatment	In some circumstances, the cost may be irrelevant because the horse is emotionally important, but in others the costs may be a major constraint. The ideal treatment option could be very expensive and, if so, a cheaper, less effective method may need to be tried
Duration of treatment/time to return to work	Treatments that require prolonged/repeated interferences result in delays and breaks in training and work
Animal compliance	Inevitably, the horse has to be able to tolerate whatever the treatment involves
Owner compliance	The owner has to play/his/her part in the programme so that accurate timings and supportive measures are possible. Owner compliance also involves aspects of logistics and cost
Facilities/operator experience	The facilities available will inevitably constrain the method of treatment. The ideal treatment may simply not be possible. Operator experience is key to success. What works for one person may not work as well for another
Other issues	Where horses are regarded as a 'human food animal', there may be severe constraints on treatment with most of the agents used in chemotherapy. Animals that have received chemotherapy should be identified as such for that reason

It is unusual for only one of these to be significant and there are some confounding factors that conflict in each case with others.

Ablative therapy

Many patients diagnosed with neoplastic disease will require some form of surgical intervention; this may be simply to obtain a biopsy for diagnostic purposes or more usually for treatment of the condition. In some circumstances, tumours can be managed completely or partially by surgical excision, but in others the removal of some or part of the tumour may provide palliative management only. As might be expected, in some cases the surgical approaches are simple because of the small or defined size of the mass, an accessible location and the benign nature of the tumour, but in other cases, radical surgery is indicated. Typically, a surgical 'dose' can be estimated – the extent of the surgery required for the particular circumstances. The surgeon may elect for a localized excision with limited margins (i.e. a low 'surgical dose') or may opt for a wide and radical excision (i.e. a large 'surgical dose'). In many cases, the surgeon will need to bear in mind the compromise in requirement between preserving tissues to allow closure (or the reconstructive measures that are anatomically feasible) and the need to remove the whole tumour. Often the 'best laid plans …' will be changed significantly during the surgery – surgical adaptability is a key requirement for a cancer surgeon. Inevitably, the surgeon has to remain constantly aware of the need to consider the animal as a whole not just the tumour – future side-effects or complications from surgery can confound the very best surgeon – 'Cancer does what cancer wants'.

Ablative therapy results in the physical removal of tumour tissue in bulk and this usually involves some form of surgical interference. Surgical removal requires of course that the tumour is accessible and that total removal is anatomically and physiologically feasible. With the advent of new surgical techniques, the scope for surgical intervention has increased dramatically. Laparoscopic methods are now commonplace procedures and abdominal, thoracic and airway tumours can be removed with greater confidence. Laser and diathermy equipment and the use of endoscopic instruments also improve the outlook in many cases that were previously thought of as impossible challenges.

There are many reports of surgical procedures in the management of skin or other accessible tumours in horses. Apart from the obvious and commonplace removal of skin tumours, there are many individual and small series reports of successful surgical excision of localized tumours, such as lymphoma and haemangiosarcoma, from within the alimentary tract,[1] upper airway[2] and reproductive tract of mares in particular. Focal iridal melanoma lesions may also be amenable to surgical removal.[3]

Ablative therapy can be used to remove some or the entire tumour; in the former case it is useful in reducing the bulk of the tumour and so allowing the use of an adjunctive treatment, which in itself might have dangers of toxicity or inadequacy on the larger tumour bulk. This is commonly used when tumours are subjected to local, topical or intralesional chemotherapy or immunotherapy. Radiation is another method that significantly benefits from partial ablative treatment. Where ablative surgery is successful in removing the entire mass, there is of course the justified expectation that there will be no recurrence at the site. This is clearly the best possible circumstance. Whether the wound that results from either partial or total ablative therapy can be closed is a different matter, even where the tumour removal results in a wound that cannot be closed and the challenges are very different from when there is residual tumour tissue in the site.

Surgical methods

The first requirement for effective surgical treatment of a tumour is a definite diagnosis. Prior biopsy or cytology will provide important information and possibly several biopsies may be required to give a true representation of the pathological behaviour of the tumour (p. 87). Notwithstanding the need to define the true nature of the tumour, many equine cutaneous tumours have a definitive clinical appearance that may reduce the need for a biopsy – indeed in some cases, biopsy can be considered to be contraindicated, e.g. in sarcoid tumours. In the latter cases, there is usually enough evidence available on the likely surgical indications and requirements for the surgeon to make considered decisions. It is important to realize that many tumours cannot be diagnosed without a biopsy or surgical/excisional biopsy; even though tumour may be familiar, not every lesion that looks like a sarcoid or a melanoma is in fact that. As an example, sarcoids can closely resemble neurofibromas and fibrosarcomas but the implications of the differential diagnoses are often profound.

A biopsy should always be considered when the appearance of the tumour is not 'typical' of a specific and definable tumour type. It should always be performed if the outcome of the histological findings will alter the approach and management of the case. A biopsy should *NOT* be performed if it is not going to alter the management of the tumour or if the information is not going to help an owner to come to an informed decision about the options for treatment and the prognosis. The specific methods for biopsy are described on page 87.

Sharp excision

The surgical excision of a tumour mass serves several purposes. The major intention is of course to remove the tumour totally and, where the tumour has the properties that support this approach, the effects are very positive. Clearly, there are constraints upon the method in terms of the location of the tumour but also in terms of the tumour type and its pathological behaviour. Well-defined easily accessible tumours that have little anatomic implications are generally viewed as ideal cases for surgical intervention. Some tumour types are better suited to the surgical approach than others (Fig. 9.2).

There are obvious advantages in surgical approaches that include:

- *Speed of result*: the tumour is removed at a single surgical intervention and there is possibly less overall pain. Modern reconstructive techniques often allow even large defects to be repaired completely
  - Rapid healing is probable if the wound can be closed or even if the site is left to heal by second intention. Again, reconstructive methods can be singularly helpful
- *Anatomical precision*: Removal of the tumour in its entirety will usually result in cure (unless of course

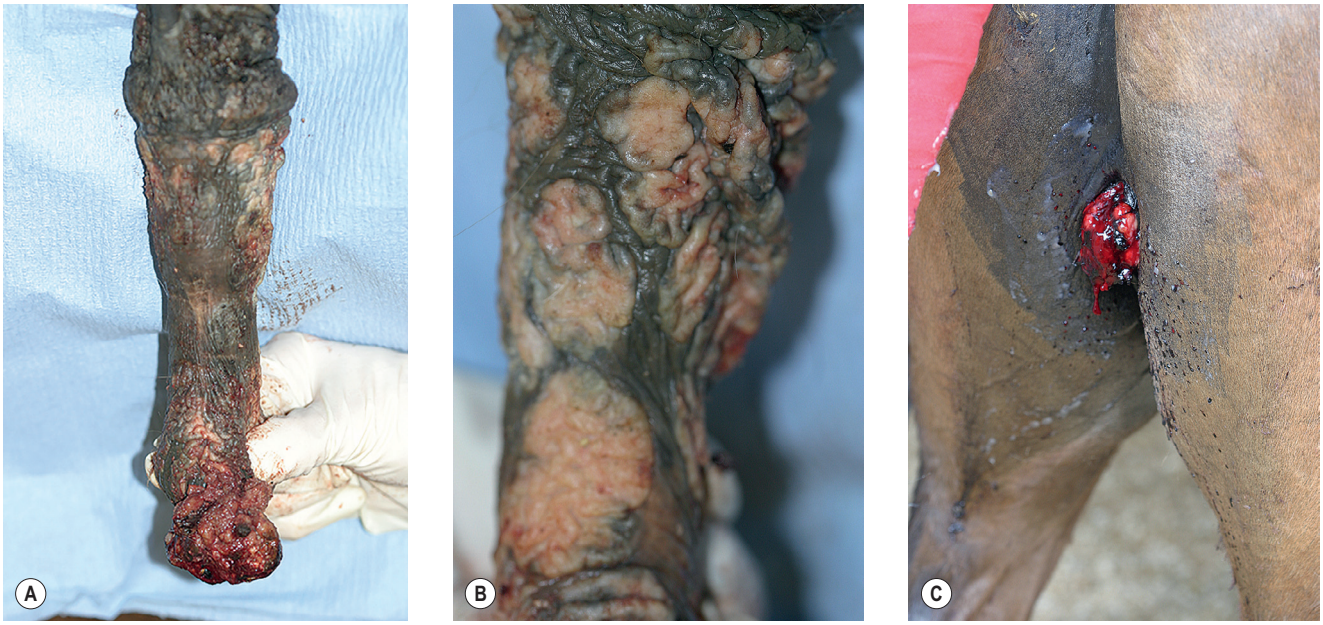


Figure 9.2 A penile carcinoma. **(A)** A penile carcinoma that required surgical ablation through an *en bloc* resection with retroversion was felt to be the only way to help the horse. **(B)** There were extensive pre-carcinomatous plaques in the proximal skin of the penis which precluded a more conservative approach. During the procedure, the regional lymph nodes were removed and found to have tumour. **(C)** The horse managed well with his perineal urethrostomy and survived a further 5 years before succumbing to unrelated orthopaedic issues.

micro-metastasis has already taken place). Surgical removal also provides information about the margins and the extent of a safe margin and this provides the surgeon with really useful information – whether a margin is achieved or not. A second (or even a third) intervention or an additional adjunctive chemotherapy or radiation might be considered if a tumour has not been removed completely. There is maximal scope for precise surgical decision-making.

Set against these, are clear disadvantages:

- The tumour may have already undergone micro- or even macro-metastasis; then even an impression of surgical success may have little influence on the outcome of the case – treatment becomes palliative
- Where the margins of the tumour cannot be defined, the opportunities for complete excision are limited by the availability of a suitable 'safe margin'
- Failure to remove the whole tumour will necessarily result in recurrence or the need for a second procedure or adjunctive therapy and so it is common practice to combine the surgical approach with chemotherapy or radiotherapy. Of course, the surgical debulking of a tumour will mean that less radiation or less chemotherapeutic agent can be used. A second procedure is usually going to carry a reduced prognosis.

Malignant tumours necessarily require a wider surgical margin – a wide margin usually means a 2–3 cm margin, but even this will have limitations. Even for equine sarcoid a margin of 1.5 cm only gives a 65–70% chance of a successful surgical margin. Removal of a wide margin (in depth and area of the tumour) will result in a massive increase in the area of the deficit and a corresponding increase in the reconstructive and healing requirements.

An additional problem associated with surgery is the restricted anatomical environments. In many cases, it is simply impossible to remove the whole tumour in any case without serious secondary effects. An example of this is afforded by a hemi-mandibulectomy to treat a mandibular osteoma or ameloblastoma. An additional good example of the problem is an upper eyelid mass; removal would result in a tissue deficit and probably functional difficulties associated with scarring and destruction of important tissue. Of course, the surgeon naturally has to have a detailed anatomical knowledge of the affected region but within the constraints of cancer surgery, the more tumour that is removed, the better the outlook will be and the more effective any concurrent chemotherapy or radiation will need to be to eliminate the residual tumour cells. As a general principle, the fewer the cells left behind, the less the overall risk but any residual tumour cell (even a single one) will probably result in recurrence.

The first objective has to be the removal of the tumour, including any local spread (including the local lymph nodes where indicated); the second goal is to close the defect. Surgeons may feel constrained by the thought that the surgical defect has to be closed afterwards and so may be less determined to reach the margins of the tumour. There is perverse logic to having a surgical team to remove the tumour and a second reconstructive team who can be called in after the tumour has been removed to close and reconstruct the wound site. The surgeon can then feel less inhibited and the tumour has a greater chance of being successfully removed. It is entirely possible that the secondary functional and anatomical deficits that ensue after surgical excision can be addressed later on by use of reconstructive surgery.

One of the problems that particularly seems to apply to the equine sarcoid is the potential for seeding of the operative site with cells desquamated from the open surface of an ulcerated tumour or from inadvertent incision of the tumour mass or the tumour extensions (roots).[4,5] In theory, this can occur with any tumour type, since the cells may be

completely viable once released into the healing wound bed, but it is a recognized problem with sarcoid in particular. In the case of the equine sarcoid, recurrence following sharp surgery occurs in 50–80% of lesions (Fig. 31.16).

The problem of seeding of a surgical wound site can be minimized by taking a number of precautions prior to and during the surgery; these are broadly grouped under the title 'smart surgery' (or minimal contamination surgical procedure), which is described below.

Surgical planning is fundamental to success in surgical oncology. All the required equipment and instruments, as well as any adjunctive drugs or procedures, should be readily to hand. It will often be necessary to alter the plan as the procedure advances and so every eventuality should be planned for from the outset.

Smart surgery

Method

- *Make a proper assessment of the tumour* (Fig. 9.3A): This way the roots and extent can be identified or at least predicted. Failure to excise any part of any tumour will likely result in recurrence and probable exacerbation. The required 'safe margin' of excision should be defined as far as is possible using every available imaging means, prior to surgery after a close examination of the tumour itself and its true pathological nature established. The margins of a diffuse, poorly-demarcated, non-encapsulated tumour will be more difficult to define than a localized, well-defined mass. The variation in tumour behaviour from site to site and from horse to horse makes the prediction of the margins very difficult in all tumour types. Whilst the likely safe margins have not yet been defined for each tumour type, a rough guideline has been established for the equine sarcoid. Investigations using polymerase chain reaction (PCR) analysis of the surgical margins of equine sarcoids for bovine papilloma virus DNA of tumour cells as an indicator of the tumour margin[6] found PCR evidence of sarcoid tumour cells at 4, 8, 12 and 16 mm in 95%, 73%, 39% and 33% of the examined sarcoids, respectively. The conclusion from this study was that in equine sarcoid surgery, an excisional margin of 8, 12 or 16 mm gave a likelihood of total excision of 27%, 61% and 67%. This is still far from 100% and to achieve that level of success in every case would probably require impossible excisional margins. The 'likely' surgical margins of the tumour can be defined by drawing on the site with an indelible (surgical) pen immediately prior to the surgery taking place. This will provide good guidance for the surgeon once the site is draped and prepared, but once the surgery is in process, this may have to be altered. It is simply not good enough to stick to the predetermined boundaries without regard for the tumour itself.

Plan carefully: Make a thorough examination and assessment of potential complications and establish the boundaries if possible. This is still a fundamental requirement for any cancer treatment (Fig. 9.3A,B).

- *Cover or isolate any open/ulcerated tumour*: Covering or masking the open tumour is done to minimize the possibility of desquamated cells gaining entry into the wound site during surgery and is a basic component of 'smart surgery'. Cells can be transferred by the surgeon's gloves, swabs or even instruments and so isolation of the tumour and meticulous care during the procedure can be an important aid to successful surgery. This isolation can be achieved by using a plastic aerosol dressing, such as 'OpSite' (Smith and Nephew, Hull, UK) or by incorporating the tumour in a dressing/swab or even within a surgical glove (Fig. 9.3C) during preparation. After initial preparation and prior to aseptic preparation, a theatre assistant applies a firm, second, now sterile wrap (Fig. 9.3D).
- *Prepare for aseptic surgery*: At this point, the site can be prepared for surgery and draped. In most circumstances (apart from sarcoid, possibly), surgical draping is performed in standard fashion. It is important to recognize that draping may need to be adjusted since tumours may extend beyond their previously visible or palpable margins and that possibility must always be considered during surgical preparation and draping. A second (sterile) wrap is placed over the tumour by a surgeon's assistant (Fig. 9.3E) and then gloves are changed.
- *Isolate the tumour base*: The assistant lifts the tumour mass in its wrap away from the body wall and a pair of suitably sized haemostats is applied across the base of the tumour as far down as feasible (Fig. 9.3F). It is important to ensure that there is enough skin below the clamps to be able to complete the next stage, which is the placement of a series of interrupted horizontal mattress sutures parallel to the clamp(s) (Fig. 9.3G). The sutures should be pulled firmly enough just to appose the two sides of the skin. Over-tight sutures will cause necrosis and that will delay healing and increase the risk of dehiscence. A useful 'trick' in the placement of the sutures is to use a new 3 cm 19G needle for each suture passage and a new length of non-absorbable suture material for each suture. This enables accuracy and it is possible then to ensure that the suture line is parallel to the clamps with a suitable safe margin to allow excision along the undersurface of the clamps.
- *Surgical excision is performed*: The tumour can now be removed using sharp or laser surgery running along the body side of the clamps, taking care to avoid cutting any of the sutures (Fig. 9.3H–J). Bleeding with either excision method is very limited with this system and swabbing is not usually necessary at all when a laser is used (Fig. 9.3K). The tumour is removed from the theatre and despatched to the pathologist to examine for a safe margin. Meticulous haemostasis is of course essential, since the surgical wound site must be carefully checked throughout the procedure; a surgical site that is continually bleeding heavily is almost impossible to assess in detail. Careful ligation or diathermy coagulation of major and minor blood vessels will have significant benefit both on the surgery itself and on the prognosis.
- *Final closure* of the site using a sub-cuticular or interrupted sutures is a matter of surgeon's choice (see Fig. 9.3). It is important to recognize that healing margins are cauterized when laser or diathermy is used and so healing will be slow (p. 124). Finally, the wound is dressed suitably or stented as appropriate for the site.

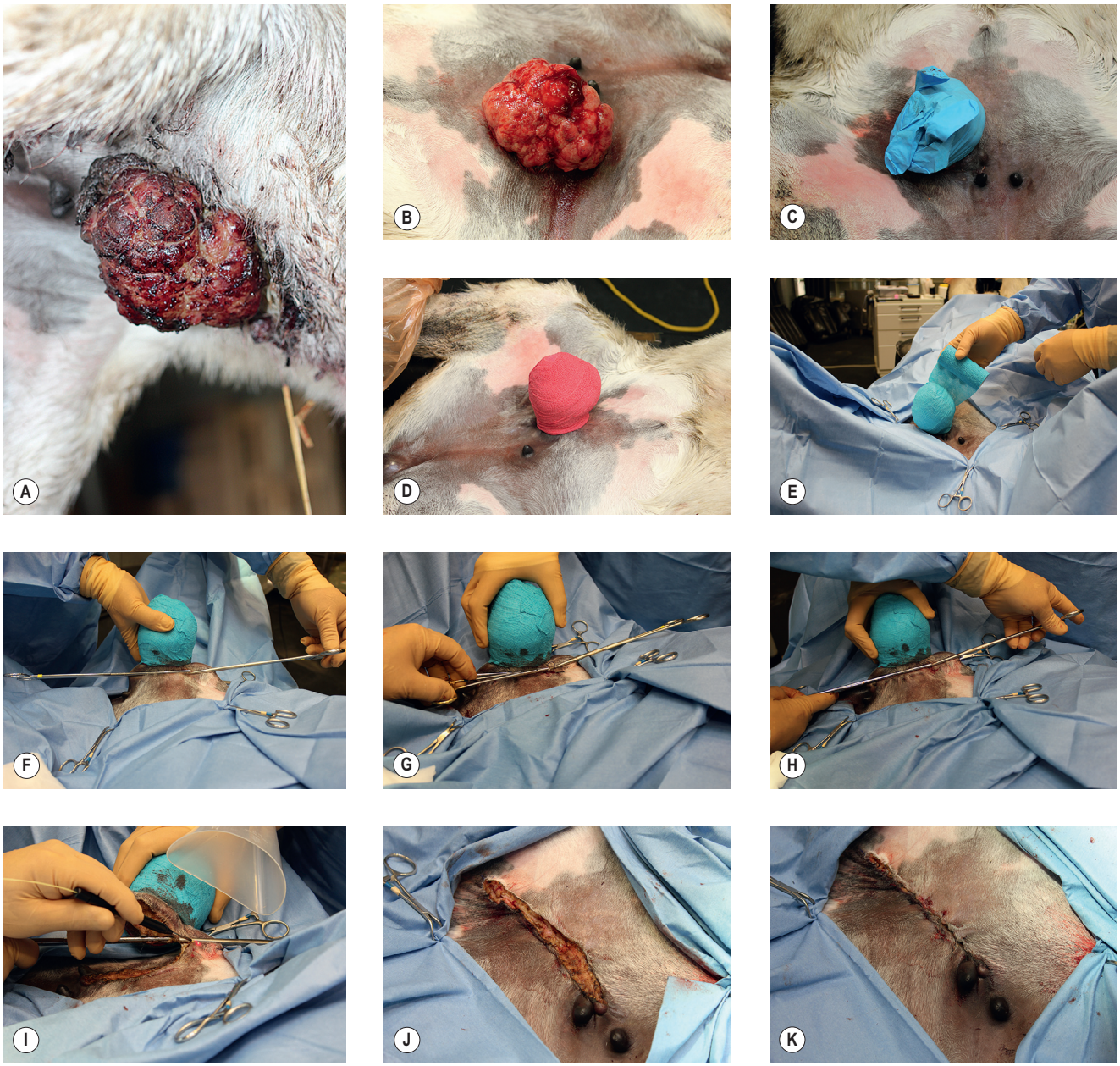


Figure 9.3 The technique for smart surgery performed to remove a fibroblastic sarcoid on the ventral abdomen. (A) The tumour is assessed carefully by all appropriate means, and the diagnosis confirmed histologically. This provides support for the likely required margins of excision. **(B)** The site should be properly prepared for aseptic surgery as far as is feasible. Careful preparation of the surgical site is essential so that the surgeon is not constrained by the preparation. Tumours should always be regarded as potentially wider than they look. Wide clipping and draping is wise. **(C)** Protection of the site during surgical preparation should be carried out by enclosing it in an impermeable wrapping (a glove is used in this case). **(D)** Prior to final aseptic preparation, a further sterile dressing is placed over the site **(E)**. After draping, etc., a further sterile dressing is placed over the site **(F)**. The tumour is lifted away from the body wall and, if possible, a large clamp (haemostat or bowel clamp) is placed under the tumour. **(G,H)** A row of horizontal mattress sutures is placed at a safe margin below the clamps. **(I)** The tumour is removed with a scalpel or preferably a laser, by incising along the margin of the clamp(s), i.e. under the clamps and outside the suture line. **(J)** Upon removal of the mass, the incision remains closed – there is no open wound site. **(K)** Sutures or staples can be placed to close the incision fully and/or a dressing can be applied as appropriate. *(Pictures courtesy Gabor Bodo.)*

Due note must be taken of complicating anatomical features throughout the procedure. Adjacent vital structures, such as major blood vessels, synovial structures and body cavities, etc., must be considered during the planning stage, as well as during the surgical procedures. Again, planning is a fundamental aspect of successful oncological ablative surgery and a detailed anatomical knowledge is essential.

- *Apply any adjunctive measures*: Concurrent/adjunctive measures, such as cryotherapy, chemotherapy, immune therapy or even radiation, may be performed prior to final wound closure or termination of the procedure. This can be useful in reducing the chances of residual tumour or tumour 'seeding'. Crude methods such as cryosurgery or direct thermal cautery can in fact be a significant help. Defocussed laser scanning over the

surgical site is also useful in the same way. Perilesional chemotherapy can be used: usually a single application at the time of the surgery is helpful, e.g. emulsion of cisplatin or mitomycin C or 5-fluorouracil.
  - Where radiation or immunotherapies (such as BCG) are used, surgical debulking is particularly useful. The use of a strontium plaque (beta emitter), for example, significantly improves the outcome of superficial keratectomy in the management of corneal intraepithelial carcinoma (carcinoma in situ).
- *Advantages and disadvantages*: The smart surgery technique has several major advantages but also some clear disadvantages. First, the wound stays closed throughout the procedure and wound closure is not a problem. Bleeding is minimized and wound site contamination by cells is virtually impossible. Set against that, it is impossible to examine the wound bed for further tumours and extensions from the parent tumour, so it is not applicable in all cases by any means. Haemostasis could theoretically be an issue but it is not a common problem.

The procedure is not applicable at all sites. Careful assessment is a fundamental part of the decision-making process in all treatment and smart surgery is no different.

Precautions and hazards

The main precaution is always to be aware of the limitations of the procedure being performed. Concurrent precautions include being aware of the extent of the tumour and the likelihood of recurrence. Being aware of the need to remove all the tumour cells often encourages the use of adjunctive therapy and this can significantly improve the prognosis. Smart surgery adds significantly to the prospects of a good outcome, even though it is rather tedious and unglamorous. The lack of bleeding and the closed wound site throughout the procedure helps with closure, so time spent in preparation is saved in closure. Anatomical knowledge is a vital aspect of the work of any surgeon.

Laser surgical excision

LASER is an acronym for Light Amplification by Stimulated Emission of Radiation. A laser is an opto-electronic device that produces highly concentrated light rays of defined wavelengths that are capable of causing tissue damage. There are several types of lasers available for medical/surgical use, including the carbon dioxide (CO_2) laser, the neodymium-doped yttrium aluminium garnet (Nd:YAG) laser and the diode laser. The former is expensive and generally more powerful and more versatile, whilst the latter is easy, convenient and relatively inexpensive but has less power and versatility. Although it is used widely in human oncology, laser surgery has been used to a limited extent for many years in veterinary surgical oncology.[7,8]

In laser surgery, a highly focussed laser beam can efficiently *ablate* (either vaporize or 'chip away') the living tissue. At the same time, it *seals* capillaries, small blood vessels, lymphatics and nerve endings which, consequentially, produces a significant benefit. However, the surgeon needs to be aware of the scope of the particular laser equipment available and must assess whether it is likely to be an advantage in any particular circumstance. The possible fine accuracy may be a disadvantage when speed is important and certainly removal of large tumours can be time-consuming when using equipment with limited power, such as diode lasers.

Advantages

- *Surgical accuracy*: Laser has the singular advantages of being both very precise and extremely controllable. The focal size of the laser beam may be adjusted to a small fraction of a millimetre, or can be defocussed to give much wider coverage. The laser power may be set at a higher level for the rapid removal of relatively large tissue amounts, or adjusted to allow the measured removal of only one cell layer at a time. Laser surgery improves many surgical procedures by making them simpler and reducing risk, enabling surgeries that are not practical with conventional methods.
- *Accessibility*: Lasers that utilize a fibre, such as the Nd:YAG, or diode laser, can be used via an endoscope allowing laser surgery to be conducted within the airway of the horse, for example, with considerable accuracy.
- *Reduced bleeding*: As it cuts, the laser seals small blood vessels, greatly improving visibility within the surgical site. This results in a much clearer and drier surgical site and, therefore, often a significant reduction in surgical time. Additionally, improved haemostasis significantly reduces the need for tissue handling with crushing or clamping instruments, which is normally a significant contributor to postoperative oedema, swelling and pain. The reduction in bleeding means that there is also less chance of inadvertent transfer of neoplastic cells within the surgical site by the surgeon's gloves, swabs and instruments.
- *Less pain*: The laser beam seals nerve endings and lymphatics, resulting in less oedema, less swelling and reduced pain. Hence, many procedures can be conducted under standing restraint/sedation alone, both obviating the need for potentially hazardous general anaesthesia and postoperative hospitalization, thereby reducing overall costs. In addition, patients typically require less analgesia postoperatively, reducing the need for medication and producing further cost benefits for the owner.
- *Reduced risk of infection*: CO_2 lasers cut the tissue at over 95°C, so the beam efficiently kills bacteria, producing a sterilizing effect with less risk of infection being associated with the site. Again, this results in reduced postoperative cost and hospitalization.
- *Quicker recovery time*: Reduced risk of infection, less bleeding, less pain and less swelling often allow the patient to recover more quickly after the surgery. Wounds are typically left open to heal by second intention, and cosmesis postoperatively is generally favourable compared with sharp surgery (Fig. 9.4). However, there is a major problem with the wound margins, of course, since they are effectively cauterized. When wound sites are closed at the time of surgery, dehiscence is more common with laser surgery than it is with sharp surgery.
- *Reduced cell contamination*: Laser ablation of tissue vaporizes cells and so there is less opportunity for neoplastic cells, in particular, to 'seed' back into the surgical site; there is less chance of recurrence.

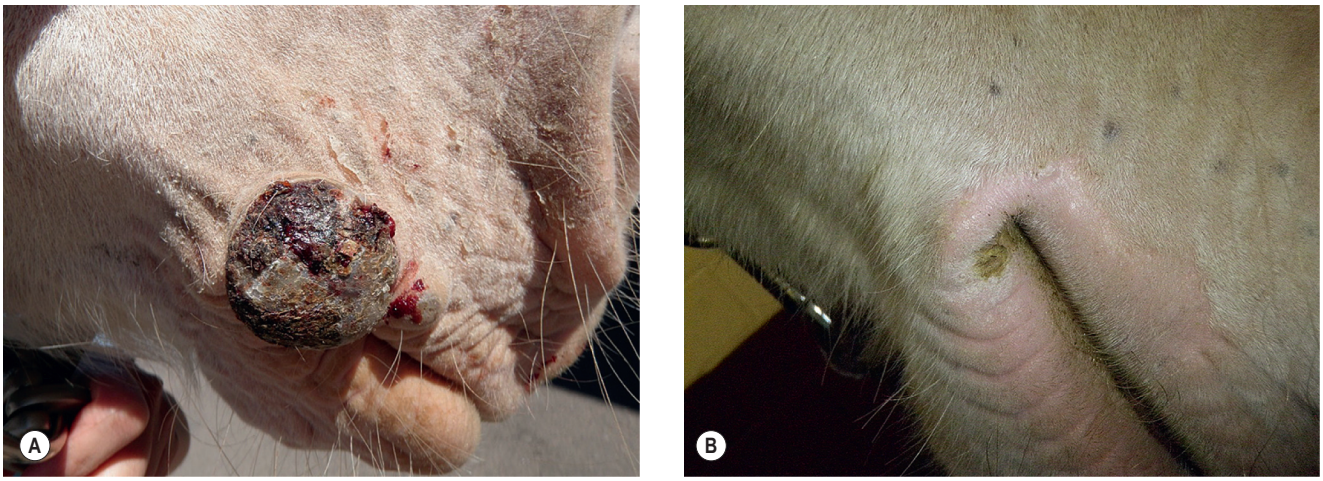


Figure 9.4 Laser surgery can be performed under standing restraint or under general anaesthesia. The results are usually clinically and cosmetically very satisfactory. **(A)** A large complex (multiple focus) histologically confirmed melanoma was removed from the lip of a cremello gelding. **(B)** There was no recurrence after 3 years. *(Figures courtesy of Jeremy Kemp-Symonds.)*

Disadvantages

- *The constraints to the use of CO_2 or Nd:YAG laser machines*: The basic expense of the equipment and the very high running costs involved in maintenance are usually the biggest constraint. Moreover, the equipment CO_2 systems are bulky and delicate. The diode lasers are cheaper, smaller and more portable; they also have minimal maintenance costs and have an inherent robustness that can be an advantage in equine practice.
- *Accessibility*: Laser beams are potentially very dangerous and most countries have licensing requirements that stipulate where and under what circumstances laser equipment can be used. Special eye protection is essential for all theatre staff at all times.
- *Wound breakdown/dehiscence*: This is much commoner than in sharp surgical excisions simply because the wound margins are also compromised and have to slough. Suture placement needs to take this into account.
- *Toxic by-products*: The smoke that is created when tissues are subjected to laser incision can contain toxic gases and vapours, such as benzene, hydrogen cyanide and formaldehyde, together with bioaerosols, dead and live cellular material (including blood fragments), viral DNA, bacteria, carcinogens and irritants, and so a smoke evacuation system should be used routinely (see Fig. 9.3H–J).

Methods

The methods and principles that apply to laser surgery are largely similar to those that apply to the use of sharp surgery. The tumour should be carefully assessed and the settings of the laser equipment should be adjusted to take account of any particular tissues that are involved, or likely to be involved. Familiarity with the system available is essential.

Precautions and hazards

Dedicated laser eye protection is essential for all theatre staff and access to the operating theatre should be restricted while laser surgery is being conducted. In addition, the use of a smoke extraction system is obligatory due to the potentially harmful smoke that is produced during surgery.

Surgical diathermy ('electrosurgery')

Surgical diathermy is usually better known as 'electrosurgery'. It is also referred to occasionally as 'electrocautery' but, strictly, this refers to direct current whereas electrosurgery uses alternating current. Electrosurgery uses high-frequency AC electrical current in either a cutting modality or a coagulation modality; the latter is used to cauterize small blood vessels to stop bleeding. In electrosurgery, the patient is included in the circuit, letting the current enter the patient's body. In contrast, during electrocautery, the current does not enter the patient's body. Only the heated wire comes into contact with tissue.

Electrosurgical cutting divides tissue with electric sparks that focus intense heat at the surgical site. By sparking to tissue, the surgeon produces maximum current concentration. To create this spark, the surgeon should hold the electrode slightly away from the tissue. This will produce the greatest amount of heat over a very short period of time, which results in vaporization of tissue.

The technique cuts tissue by burning and damage, the zone of which is controlled by the frequency and power of the settings on the device. Most diathermy equipment is set-up with options for 'cutting' and 'coagulation' or both combined.

The use of diathermy is a standard approach in veterinary practice. It has singular advantages in being fast and relatively bloodless; there is significantly less blood loss when it is employed. Attention to haemostasis takes on a different emphasis compared with sharp surgery.

In order to use the equipment correctly, a remote electrode has to be placed on the patient.

Electrosurgery and diathermy is generally rapid and the simultaneous cautery of small and large blood vessels means that surgery time is further shortened and the surgical site is kept clearer.

Methods

The variations in equipment make the use of diathermy equipment difficult to describe. In general, the monopolar methods are easier but the bipolar electrosurgery probably has better control and therefore better results. This means, however, that the earth electrode must be suitably placed in the horse – adhesives are not particularly effective and so when the horse is anaesthetized the earth electrode should be placed on the dependent side on a suitably clipped and alcohol-washed site.

Precautions and hazards

Surgical smoke is created when tissue is heated and cellular fluid is vaporized by the thermal action of an energy source, including electrosurgical and laser methods (see above). This smoke can contain toxic gases and vapours, such as benzene, hydrogen cyanide and formaldehyde, bioaerosols, dead and live cellular material (including blood fragments) and viral DNA, bacteria, carcinogens and irritants, and so a smoke evacuation system should be used.

Cryotherapy/cryonecrosis/cryoablation

Cryosurgery (cryotherapy) is the term used to describe the application of extreme cold to destroy abnormal or diseased tissue. Cryosurgery has been used since the late nineteenth century to treat a variety of benign and malignant skin tumours.

The treated tissue has to be reduced to a sufficiently low temperature to form intracellular ice crystals and then the thawing process that follows results in cell disruption/death. Tissue destruction occurs by several mechanisms:

- Formation of ice crystals within cells, thereby disrupting membranes and interrupting cellular metabolism among other processes
- Coagulation of blood, thereby interrupting blood flow to the tissue and, in turn, causing ischaemia and cell death
- Induction of apoptosis, the so-called programmed cell death cascade.

The most common application of cryotherapy/cryoablation in equine practice is to ablate solid tumours in the skin, such as squamous cell carcinoma, basal cell carcinoma, melanoma and sarcoid. It is, of course, necessary that the tumour can be defined and can be suitably accessed.

Cryoablation is used in a variety of clinical applications using hollow needles (known as 'cryoprobes') through which cooled, thermally conductive, fluids are circulated. Cryoprobes are inserted into (or placed) adjacent to the diseased tissue, so that when the probes are in place, the cryogenic freezing equipment cools from the tip of the probe and, by extension, from the surrounding tissues.

Since the speed of the freeze is a critical issue in the efficacy of the method and since the blood supply to the tumour acts as a persistent heat sink, carrying away the 'cold' and preserving tissue warmth, measures that restrict the circulation during the treatment will have a significant benefit. Temporary vascular occlusion, using a tourniquet, for example, can be really helpful in cryosurgery in horses and can significantly enhance the accuracy of the 'tissue destruction'.

Cryosurgery is a minimally invasive procedure and is often preferred to more traditional kinds of surgery because of minimal pain, scarring and relatively low cost. However, as with any medical treatment, there are risks involved. These primarily revolve around damage to adjacent healthy tissue and the importance to the local function of that damage. Damage to nerve tissue is of particular concern. Minor-to-moderate localized pain and redness, which can be alleviated by oral administration of analgesics, such as phenylbutazone or meloxicam usually occur. Blisters may form, but these usually slough within several days.

After a few hours, the treated area shows colour changes due to tissue destruction; the treated area usually becomes dark or red and swollen. A blister is formed, which later turns into an eschar (a firm necrotic plaque that is firmly adhered to the wound bed). Over the following 1–3 weeks the necrotic tissue is demarcated and sloughed, leaving a normal granulating wound bed that heals in the normal way. Multiple sessions of cryosurgery may be required to bring about a full resolution in some cases. Recurrence will occur unless every tumour cell is destroyed.

Methods of application

The method of application relies upon a fast freeze and slow thaw, which causes cell destruction.

There are several methods available, each having different features, advantages and disadvantages. The process of inducing three freeze–thaw cycles in many circumstances can be very time consuming and, whilst there are some very crude methods, the most sophisticated ones also struggle to cause therapeutic cell damage. It is said that the horse has a particularly efficient ability to resist freezing and, so, in some circumstances, it can be very hard to get a good result.

The use of tissue thermocouples strategically placed around the treatment zone will usually ensure that a suitable temperature is achieved throughout the area. Although this is a theoretically essential aspect of cryosurgery, they are rarely used in equine practice and this may explain why the method still has a relatively poor reputation.

Liquid nitrogen

A common method of freezing skin and other accessible tumours is by using liquid nitrogen at –196°C as the cooling solution. This is used either directly in a crude direct application or through the use of heat sinks that are cooled by immersion (Fig. 9.5). The super-cooled liquid may be sprayed on the diseased tissue using a commercially available canister and spray nozzle system; alternatively, the liquid can be circulated through a cryoprobe. Crude cryosurgery can be effective in practice, using a suitable heat sink and liquid nitrogen. With care, this can be very effective and demands minimal cost and equipment.

Direct application of liquid nitrogen causes uncontrolled freezing and it is impossible then to limit the freeze to the required area. The cooling is certainly fast and highly destructive but quite frequently there is run-off and collateral damage. A wide range of liquid nitrogen sprays are available. These deliver a fine mist of liquid nitrogen to the tumour site and they certainly do have a greater degree of control and accuracy.

One the main keys to successful cryosurgery using heat sinks is to ensure good cryo-adhesion between the probe and the tumour. This can be ensured by the application of a suitable water-soluble gel (KY jelly, Johnson and Johnson).



Figure 9.5 A liquid nitrogen spray being used to freeze a fibroblastic sarcoid on the neck of a horse. *(Figure reprinted from Knottenbelt DC. Pascoe's principles and practice of equine dermatology, 2nd edn. Edinburgh: WB Saunders; 2009: 124 (Fig. 4.23); copyright 2009, with permission from Elsevier.)*

Carbon dioxide and acetone

Less frequently used is carbon dioxide 'snow' formed into a cylinder or mixed with acetone to form a 'slush' that is applied directly to the treated tissue. This is not widely used in equine practice, since it is usually ineffective. Carbon dioxide systems are also available that run off a small soda siphon cartridge. Again they are, for the most part, far too weak for most circumstances but very small focal tumours can be treated in this way.

Dimethyl ether with propane

A mixture of dimethyl ether and propane is used in some commercial preparations. The mixture is stored in an aerosol spray-type container at room temperature and its temperature drops to –41°C when dispensed. The mixture is usually dispensed into a straw with a cotton-tipped swab.

Precautions and hazards

Special precautions required in the use of cryosurgery include the need to restrict the freeze to the defined tumour limits. Thermocouples are probably essential in most circumstances but small localized tumours can be 'frozen' effectively (if crudely) without their help. The use of a cryo-coupling material is also essential. When freezing tissue, it is important to try to protect deeper tissues that are not involved. Freezing of bone or tendon is a potential disaster.

Three freeze–thaw cycles is usually regarded as the minimum acceptable level of procedure for any meaningful tumour and a fourth can be added with advantage.



Although cryosurgery is widely used throughout the world, in the USA, it is regarded as 'below the minimum accepted standard of care for cancer treatment in horses' and its use can therefore be cause for client complaint and litigation when used for lesions other than benign or preneoplastic lesions or in situ carcinoma lesions (A. P. Theon, pers. comm.).

Hyperthermia

Hyperthermia (also referred to as thermal therapy or thermotherapy) involves tissue destruction through tissue exposure to controlled high temperatures; by killing cancer cells, damaging proteins and structures within cells, hyperthermia may shrink tumours.[9] Since cancer cells appear to have a greater sensitivity to raised temperatures, high tissue temperatures (up to 70°C) can damage cancer cells, usually with minimal injury to the more temperature, tolerant normal tissues.

The use of hyperthermia in equine practice has not gained the recognition it perhaps deserves and there are few reports of its use.

In other species, including man, hyperthermia is usually used with other forms of cancer therapy, such as radiation therapy and chemotherapy. Hyperthermia may render cancer cells more sensitive to radiation or it may damage cancer cells that radiation cannot damage on its own.[9] When hyperthermia and radiation therapy are combined, they are often given within an hour of each other. Hyperthermia may also enhance the effects of some anti-cancer drugs.

Safety measures

Most normal tissues are not damaged during hyperthermia if the temperature remains under 70°C. However, due to regional differences in tissue characteristics, higher temperatures may occur in various spots. This can result in burns, blisters, discomfort or pain.

No significant hazards or precautions are reported in horses.

Vascular or tumour ligation

Since tumours over 1–2 mm in size have to have a dedicated blood supply, ligation is an attractive option for treatment (Fig. 9.6). Deprivation of blood supply will necessarily mean necrosis of the deprived tissue; this might of course include the adjacent normal tissue if its blood supply is also interrupted. Although vascular ligation alone is a procedure that is used in human medicine a great deal, in the horse, it has very limited applications. The one site where such an approach may be used is in the management of carcinoma in situ of the cornea (intraepithelial carcinoma), where major vascular components can be subjected to cryoablation (p. 126) or laser ablation (p. 124). The same effect is provided by plesiotherapy (p. 184), which has a profound effect on vascular cells.

Historically, ligation with string, even horse tail hairs, has been a regular approach to sarcoids in particular. In spite of the ease of the process and the reports of some successes, it is in general an unreliable method of treatment. More often skin tumours are ligated rather crudely with tight elastic bands or Lycra® tape (Fig. 9.7).

This results, simply, in a complete isolation of the tumour mass, provided, of course, that all tumour tissue is distal to/outside the ligating band. The method is very effective in localized Type A1 and B1 sarcoids (p. 127). It can also be applied to any pedunculated benign tumour (such as a melanoma) or any tumour with a significant accessible margin.

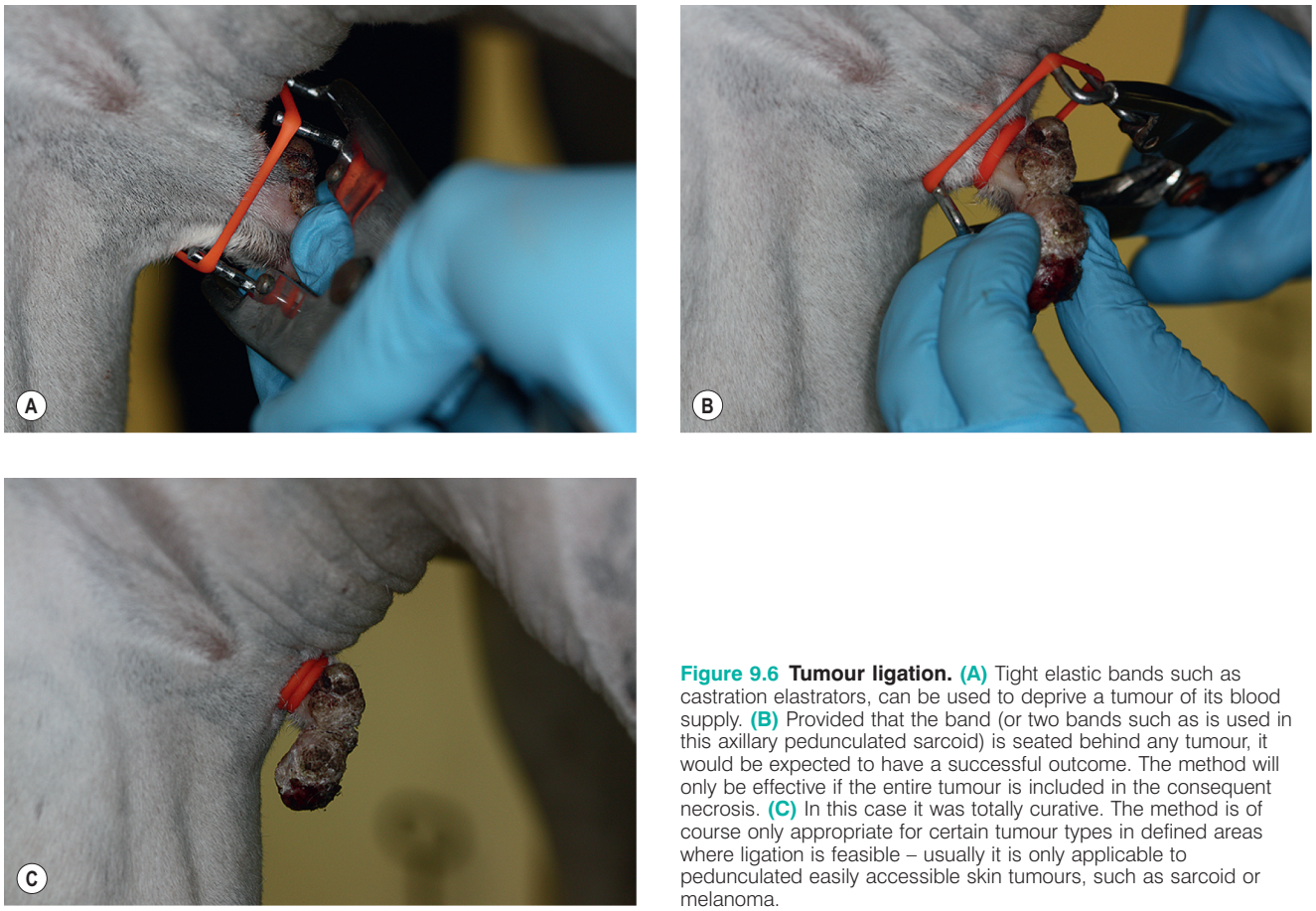


Figure 9.6 Tumour ligation. **(A)** Tight elastic bands such as castration elastrators, can be used to deprive a tumour of its blood supply. **(B)** Provided that the band (or two bands such as is used in this axillary pedunculated sarcoid) is seated behind any tumour, it would be expected to have a successful outcome. The method will only be effective if the entire tumour is included in the consequent necrosis. **(C)** In this case it was totally curative. The method is of course only appropriate for certain tumour types in defined areas where ligation is feasible – usually it is only applicable to pedunculated easily accessible skin tumours, such as sarcoid or melanoma.



Figure 9.7 Ill-advised partial ligation is usually counterproductive but it can be used to debulk accessible tumours. **(A)** In this case, the method was applied to a broad-based fibroblastic sarcoid on the face of a donkey but it served no useful purpose and was in any case far too loose to cause significant ischaemia. **(B)** Here, an attempt had been made to ligate the fibroblastic (rooted Type 1b) sarcoid with tail hairs from the horse itself. This is clearly a hopeless approach but it is attempted very commonly. Notice the very big blood supply to the tumour.

Restrictive ligation of pedunculated sarcoids and melanomas can also be combined with various topical chemotherapeutic agents (p. 139). Ligation coupled with intralesional chemotherapy is also practiced, but this should only be required if there is any suspicion of tumour extending beyond the ligation point.

It is important to assess the tumour carefully first to ensure that the ligator is placed safely (without causing significant concurrent/collateral damage) and suitably to ensure complete inclusion of the tumour. Failure to ligate the whole tumour may serve to debulk it, which may be an advantage in some circumstances; the accessible crown of the mass may be simply destroyed without significant blood loss but, under those circumstances, a suitable plan of action has be available to deal with any residual tumour. As a rule, it is most unwise in the majority of equine tumours to

perform partial removal by any means, without addressing the issue of the base or root of the mass; exacerbation can be expected in most such circumstances.

Temporary occlusion of blood flow to a region or specifically to a tumour can be a useful adjunctive measure when combined with chemotherapy. The singular advantage is that the blood supply is disrupted and so the concentration of the drug remains higher – there is no or minimal 'wash-out' and relative hypoxia of the cells may result in improved cellular penetration of the chemotherapeutic drug.

Regional intravenous or arterial perfusion of a body region can result in a significant increase in the delivery of chemotherapeutic drugs to the isolated area. The technique is similar to that commonly employed for antibiotic delivery and local regional anaesthesia techniques, but it has not been well described for use in horses as yet.

Cytotoxic/medical therapies (chemotherapy)

Chemotherapy is the term applied to the treatment of cancerous cells through the use of cytotoxic medications. Chemotherapy drugs typically prevent tumour cells from multiplying by interfering with their ability to replicate DNA. Individual chemicals and combinations of chemicals can be used to maximize the beneficial effects of the treatment whilst attempting to minimize the almost inevitable harmful effects of the drugs on normal, non-cancerous tissues. A significant aspect is the higher genomic sensitivity of tumour cells to the effects of many of the drugs than the normal cells and this is the basis of chemotherapy. Broadly, the treatment of tumours using antineoplastic drugs can be divided into systemic and local chemotherapy.

The use of chemotherapy in horses has increased recently, as more understanding of the drugs has developed. However, there have been major concerns, including the overall relative costs, the poor prognosis in patients with advanced disease, the late diagnosis and the wish not to cause unnecessary suffering, that inhibit their widespread use in equine practice. The increasingly positive demands of owners for the best possible medical management for their horses, and the availability of cheaper generic forms of many of the medications and chemicals, has made treatment much more feasible. It is important to consider that for equine patients the quality of life is more important than 'tumour control at any cost'; the human circumstance is 'tumour control no matter how high the welfare or economic cost'. The extreme measures that are commonly taken in human chemotherapy means that the risk of treatment complications in humans is far greater than in horses; unfortunately for the horse, there is an inevitable price to pay, however, through a much reduced chance of success.

The majority of the chemotherapeutic drugs work by impairing mitosis (cell division), effectively targeting fast-dividing cells and preferentially killing the cells of tumours with high growth fractions that are dividing rapidly. Since in most common and important cancers the cell proliferation rate is usually higher than that of surrounding normal cells, this provides a clinically useful window of opportunity (see Fig. 9.8). Inevitably, however, the chemicals are non-discriminatory and so there may be significant harmful effects on the exposed normal cells as well; understandably, these effects will be greater in exposed cells that are naturally

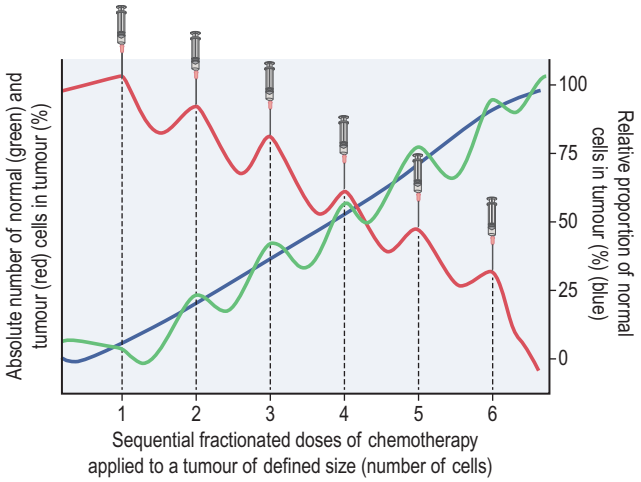


Figure 9.8 The fundamental premise of chemotherapy is to cause more damage to tumour cells than to normal cells. The beneficial effects of chemotherapy depend in turn on the greater genetic instability and lack of reparative mechanism that is a common feature of tumour cell physiology. Sequential doses of chemotherapy administered to a tumour, either through the bloodstream or intralesionally or topically, therefore harms the population of pathological cells more than the normal ones and so, as the numbers of tumour cells drop, the adjacent normal cells increase both proportionally and absolutely. Importantly, chemotherapy does have a harmful effect on the normal cells but this should be far less than the effect on the tumour cells for any drug that is selected as a chemotherapeutic agent. The ultimate theoretical objective is to destroy all cancer cells and restore a 100% normal cell population.

dividing fast; these might include bone marrow and lymphoid cells, testicular cells, hair follicle cells and enterocytes. The side-effects of chemotherapy therefore mostly relate to their effects on these cells and include reduced production of blood cells, immunosuppression, diarrhoea and weight loss and alopecia (hair loss). (Immunosuppression is defined in medical dictionaries as 'suppression (as by drugs) of natural immune responses'.) Since the intensity of chemotherapy protocols in veterinary medicine is limited, the risk of serious complication is low; a 5% risk of morbidity resulting directly from chemotherapy is considered acceptable.

The term 'cytotoxic' is applied to those chemicals that result in fatal damage to cells whether by interfering with cell division or through direct effects or through induction of apoptosis (p. 29). Clearly, there would be significant advantages to be gained from targeted chemotherapeutic agents that would have a specific effect on tumour cells alone and no effect on normal cells. This is an objective of the oncological drug industry but, currently, there are very few agents that have such a focussed effect and certainly none for horses. However, some drugs do have fewer side-effects than others, and where these can be selected there are significant benefits. Since many of the chemotherapeutic agents are also metabolically harmful, the level at which toxicity occurs is a fundamental aspect of chemotherapy. The objective has to be to maximize the effect of the drug and minimize its side-effect profile. Where two drugs have complementary activity with different cellular targets, or affect the cell at different phases of the cell cycle, or where the drugs target different, but related cell functions, it may be possible to combine them and so reduce the overall dose of each one and this forms the basis of multi-drug chemotherapy.

The basic premise is that chemotherapy works best in rapidly dividing cells and less well in slow tumours with lower growth fractions and lower mitotic indices. Additionally, chemotherapy drugs have a greater effect on the cells of earlier tumours; the best therapeutic opportunities are present when the cell replication rate is highest (see Fig. 4.34). Younger tumours are also more sensitive because there are less cells to kill and therefore a tolerable dose of chemotherapy (or radiation) might be more likely to destroy them. This represents the early stages of the development of a tumour and the best stage to actually treat a solid tumour is (at least theoretically) likely to be before the tumour is actually visible.

Typically, as the cells pass through succeeding generations and, particularly if they undergo sequential mutations, differentiation is lost and there is progressively less regulation in cell behaviour; in solid tumours the tumour cells become progressively less responsive to most chemotherapeutic agents. Additionally, the deepest cells within the tumour mass core might be physically protected from the effects of topical chemotherapeutic drugs because the drug is resorbed before it can reach the deepest layers of cells. This is also true for systemic chemotherapy before a tumour outgrows its blood supply, i.e. before the distance between tumour cells and neo-microvasculature is not adequate to maintain cell viability. Additionally, chemotherapeutics administered intravenously often cannot reach cells deep inside large tumours because there is no lymphatic drainage within tumours, and because the tumour interstitial pressure may be higher than vascular oncotic pressure, and so there is a pressure barrier to diffusion of the drug into the centre of the tumour. Cells towards the centre of a solid tumour may have a particularly slow replicative rate and so these may be much less sensitive to the agents – additionally, of course, the deepest cells might be physically protected from the effects of topical chemotherapy drugs. Tumour cells that become necrotic in the centre of the mass as a result of avascular or thrombotic necrosis are usually irrelevant in terms of the chemotherapy.

In most chemotherapy regimens, doses are administered in courses at various intervals to allow normal cells to recover from the adverse effects of the anti-cancer medicines between doses. However, during this period, cancer cells will also recover and start to replicate again. Successful treatment depends on the administration of the next course of therapy before the cancer has regrown to its previous size and the net effect is to decrease the amount of cancer with each successive course. The fractional kill hypothesis of chemotherapy proposes that in the absence of drug resistance and metastatic development and provided that all cancers are equally responsive, and are growing exponentially (represents only 5–10% of cells in solid tumours and is not true for non-dividing cells), only a defined proportion of the tumour cells will be killed by a single course of chemotherapy. The outcome of the hypothesis is that, ultimately, chemotherapy cannot reduce the number of cancer cells to zero. The hope is that with successive chemotherapeutic courses, the tumour burden will drop and the host's immune responses will be able to recognize the last cell(s) and so bring about a total resolution.

Tumour stem cells are one of the most important aspects in chemotherapy and may, in part, explain initial response and eventual treatment failure. Tumour stem cells are considered the most relevant clinical targets for chemotherapy but, unfortunately, are not affected by most chemotherapy drugs because they rarely divide as opposed to daughter tumour cells that divide regularly and are sensitive but are irrelevant for total tumour control. Tumour stem cells have been identified in human, canine and equine tumours.

Chemotherapy is by no means totally effective in all cases. The replicative rate of a tumour also has another consequence that might reduce the effects of a drug. Over time, cancer cells frequently become more resistant to chemotherapy treatments; by virtue of mutation, cells can become less sensitive to the precise effects of the drug being used. This evolutionary resistance to drugs is not new and neither is it confined to antibiotics since it is a major constraint in cancer chemotherapy.

Where chemotherapy fails to reach the core of a tumour, for whatever reason, alternative methods of cell destruction, such as radiation or hyperthermia or even high-frequency ultrasound ablation may be required. Surgery remains the best way to reduce the bulk of any solid tumour and this provides the biological and clinical basis for combination treatments of solid tumours. Obviously, for a range of reasons surgical tumour reduction is more likely to be effective when a tumour is small/and early.

There are methods that can be used to enhance the effects of some chemotherapy agents. These include concurrently administered medications that support the movement of the agents into or out of the cell: for example, by suppressing the activity of P-glycoprotein, which actively 'pumps' chemicals out of the cell, the chemotherapeutic drug is retained within the cell and so has a significantly greater effect. Similarly, it has been shown that electrochemotherapy has an enhancing effect when compared with direct chemotherapy. In this method (p. 158) passage of an electric current across the tumour enhances cellular uptake of the chemicals and so less drug can be used to create a greater effect. This is true for large or polar molecules that require an energy-dependent membrane transport because they cannot diffuse freely but it does not affect drug efflux (P-glycoprotein pump) and the net effect is usually unchanged because the cells adapt and excrete the drug as fast as it enters.

Strategies for the use of chemotherapeutic drugs vary. Chemotherapy may be given with a curative intent or it may solely aim to prolong the life of the patient or to palliate the clinical effects, e.g. bleeding, pain or the perceived discomfort or functional disability associated with the tumour. The intent may be to bring out a total cure or, more realistically in most cases, the drugs are used to reduce the rate of deterioration of the patient and the rate of expansion of the tumour. Palliative chemotherapy is a well-recognized approach in other species but this is seldom applied in horses, since once an individual animal is accepted as being incurable and in an unacceptable medical or welfare state, it is justifiably euthanized.

Since only a fraction of the cells in a tumour die with each treatment (fractional kill), repeated doses are invariably required if the effects are to be sustained (Fig. 9.8). Current chemotherapy regimens usually apply drug treatment in cycles, with the frequency and duration of treatments limited by toxicity to the patient. In horses, systemic chemotherapy has very limited application but there are a

reports of successful outcomes. There are some circumstances when significant long-term benefits can be gained.

Where the chemotherapeutic drug has no or few material side-effects, there is clearly much more scope for sustained use. The best example of that approach is the report that cimetidine (an H_2-receptor blocking drug used in treatment of gastric ulcers) had a significant effect on some melanoma cases (p. 146).[10] This drug has no apparent side-effects at the prescribed dose – the suggested dose is far lower than any value as a gastroprotectant. There are however, mixed reports of its efficacy and the dose is singularly low in respect of its normal anti-ulcer regimen. Whilst cimetidine is reported to have no unwanted side-effects, the overall consensus is that it does not have any clinical or physiological benefit on melanoma or any other tumour in horses. The same could be said for the recently published report of the successful treatment of equine sarcoid with aciclovir.[11] The therapeutic effects of the drug in treatment of herpes virus infections requires very frequent applications and high concentrations, whereas the by-stander anti-cancer effects appear to require single daily medication with a very low tumour volume proportional dose. There is no rationale in using a drug that has no positive effect, simply because it has no side-effects that preclude its use as a chemotherapeutic agent. This perhaps illustrates the concept that anti-tumour effects of drugs may be very different from the effects on other disease systems and also highlights the need to use evidence-based results to formulate treatment protocols. Evidence for credible efficacy has to be obtained from solid evidence-based data from carefully planned trials with adequate sample size, histological confirmation and adequate follow-up, rather than internet-based anecdotal reports that have not been scrutinized and corroborated by other investigators (p. 416).

Most cancers are now treated using various combinations of drugs and methods with the intention of minimizing the effects of any single compound. 'Combination chemotherapy' is a similar practice that involves treating a patient with a number of different drugs simultaneously. Synergies and additive effects are recognized, but there is also the potential for conflicts of effect with consequent negation of any expected benefit from any individual drug. The drugs differ in their mechanism and side-effects. The biggest advantage is minimizing the chances of resistance developing to any one agent.

Selection of drugs

Before selecting any chemotherapeutic modality, some basic points need to be addressed. First, it is essential that the mechanisms of action for the drugs are understood and the pharmacodynamics are fundamental to their appropriate use in all circumstances. This should include knowledge of the mechanisms of action and the positive or negative physiological effects of the agents. Figure 9.9 shows the sites of action of the common anti-cancer drug groups. The majority of the currently available cytotoxic and antimitotic drugs used in chemotherapy of all types act primarily on some aspect of cell synthesis, repair or function, i.e. on the function of DNA or on DNA or other intracellular proteins. There is therefore considerable overlap in the functions of the various drug compounds. This can be used positively, but can also be a hazard when drugs are used in combination. The choice of chemotherapeutic agent for a particular tumour type is usually based on clinical evidence, even though that is not well established in horses for any particular tumour.

Since single agents are, with a few notable exceptions, unable to effect a complete cure in most cancer conditions, multiple agent chemotherapy is often used. This can be administered or applied concurrently or sequentially. Since this approach targets different aspects of the function of tumour cells, it maximizes the chances of tumour cell death whilst at the same time, minimizes the proliferation of drug resistant tumour cells. Additionally, the choice of drugs with non-overlapping toxicity will significantly reduce the overall adverse effects of the drugs (see Fig. 9.9). Several points need to be actively considered during drug planning:

1. Only drugs with known (preferably evidence-based) activity against the particular tumour type should be selected. The difficulty is that there is little known about the specific use of many of the drugs whether used topically or systemically in horses. Most drugs used in chemotherapy have some potential to do harm as well as good. However, safe therapeutic doses are not known for most agents. Underdosing may lead to the conclusion that the drug is not effective, whilst overdosing may also create an unfair and biased outcome.
2. Drugs that differ in their mechanism of action should be used in combinations that maximize the likelihood of tumour cell kill.
3. Drugs with different toxicity profiles and different target organ toxicities should be combined, so that overall organ and tissue toxicity is minimized. It is, however, difficult to avoid cell toxicity in organs with a very high tissue turnover, such as the bone marrow, the intestinal epithelium and the testes, since most of the drugs will target them adversely anyway.
4. The correct dosages and intervals must be used at all times, since the principles of chemotherapy are based around allowing adequate recovery from toxicity in the most sensitive non-tumour tissues between doses. Avoidance of overdose is clearly vital but it is also important to point out that underdosing for fear of toxicity may cause harm whilst having no positive effect on the tumour itself.

Combined modality chemotherapy

Rather than just relying on chemotherapy drug treatment, it is common practice to 'ask less of the drug' by combining the use of drugs with other cancer treatments, such as radiation therapy or surgery. A good example of this is the use of (0.02%) mitomycin C ophthalmic drops or 1% 5-fluorouracil drops in the treatment of ocular or conjunctival carcinoma (Fig. 9.10). For example, applying local chemotherapy to a lesion which has a temporary suspension of the blood supply to the mass might bring significant benefit. The combination of chemotherapy and cryotherapy can be significantly better in some circumstances. However, although there is considerable controversy over the value of cryotherapy (p. 126) in cancer medicine, the method has been widely used in many superficial tumours.

In some cases, a reduction in the tumour size derived by chemotherapy, or other methods such as surgery, may provide the clinician with a better target for the second stage of treatment. Surgical reduction of the tumour means that

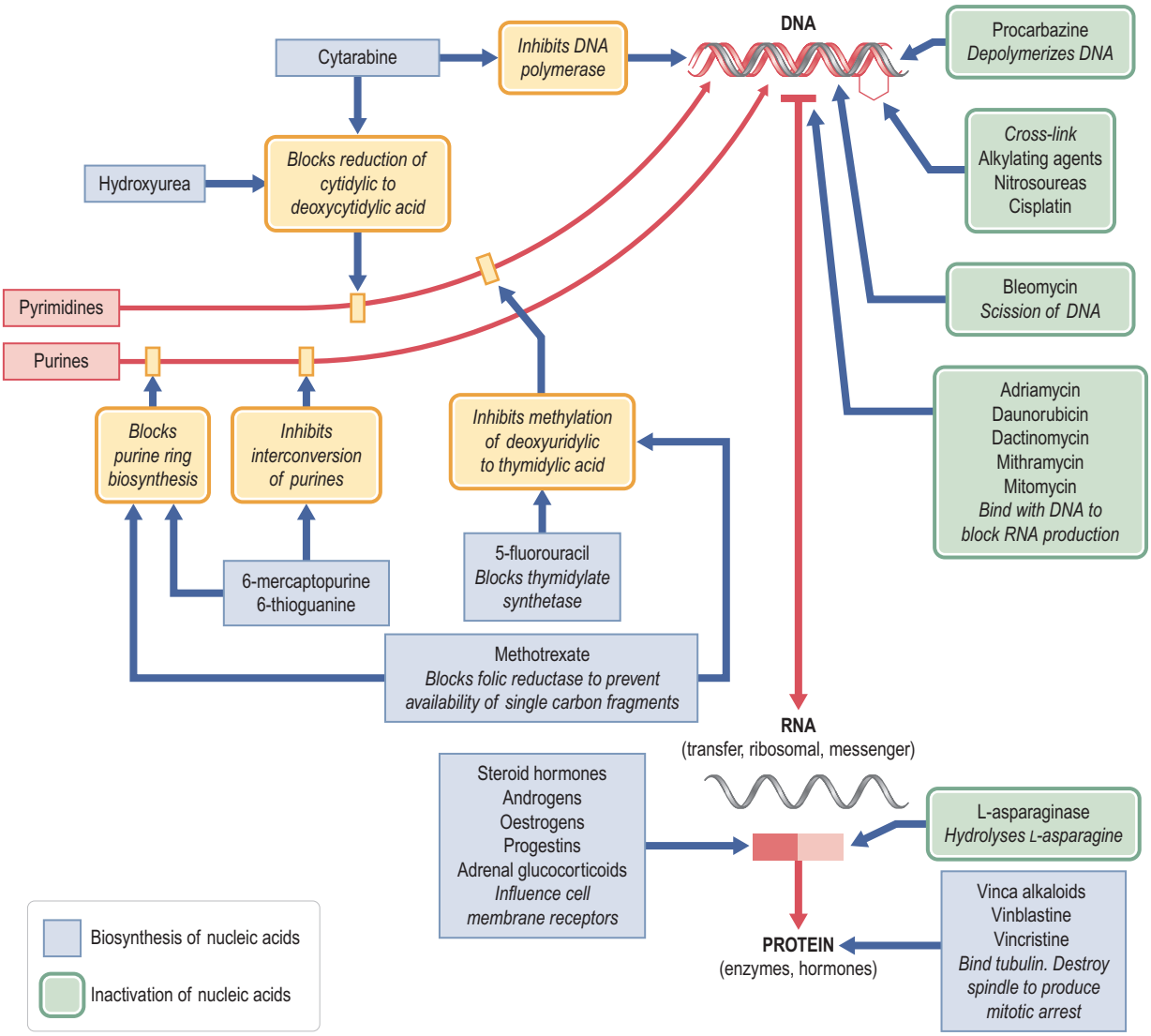
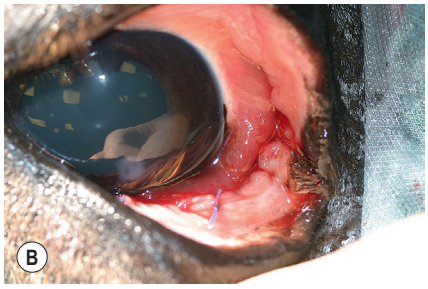


Figure 9.9 Sites of action of antineoplastic drugs. *(Figure reprinted from Krakoff IH. Systemic treatment of cancer. CA Cancer J Clin 1996; 46:137, copyright 2008, John Wiley and Sons.)*





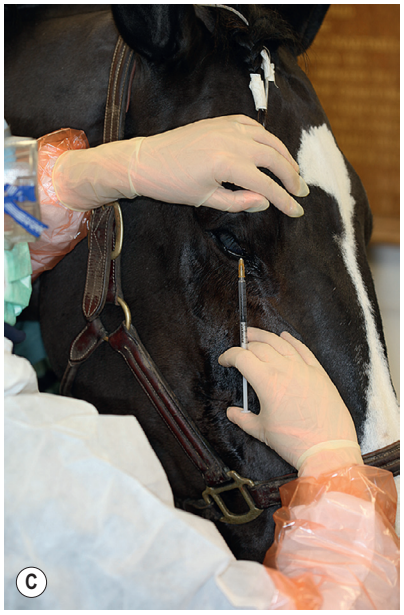


Figure 9.10 The histology report identified tumour cells at the margin of excision. **(A)** This 12-year-old Welsh cross gelding developed a carcinoma of the right nictitans. **(B)** The tumour was removed by radical excision of the third eyelid but the histology report identified tumour cells at the margin of excision. **(C)** Therefore, adjunctive 0.02% mitomycin C was administered topically q 8 h over a period of 2 weeks and then this was repeated following a 3-week 'rest period'. Note the operator protection and the use of a *broken off* 23G needle to administer the material safely and effectively. No recurrence of the tumour developed over the following 6 years at least.

less drug/radiation will have to be used – there will consequently be fewer harmful secondary effects and a greater therapeutic advantage. By the same token, a chemotherapeutically induced reduction in tumour size may facilitate subsequent surgical removal.

Adjuvant (intraoperative or postoperative) chemotherapy

When there is risk of recurrence because there is microscopic evidence of residual cancer or when the clinician does not know whether the tumour has been removed in its entirety or not, adjuvant chemotherapy can be an effective mode of treatment. An example of this is the use of intraoperative cisplatin emulsion (p. 146), beads (p. 151) or mitomycin C infiltration (p. 157) into the surgical site from where a sarcoid or a carcinoma has been removed. This approach is often beneficial, since any newly growing tumour cells are likely to have a high replicative rate and therefore would probably be more susceptible. Additionally, this can help reduce the chances of developing 'drug' resistance if the tumour does recur. However, as in all such cases, the benefit of adjunctive chemotherapy depends on the correct delivery of the drug to the site. In the case of cisplatin biodegradable beads, it is difficult to uniformly treat the microscopic invasion of tumour cells in surrounding normal tissue or in the central part of the wound site. The chemotherapy remains in the locality of the beads when they are used, so very careful thought on how they can be distributed needs to be taken. The same applies to all forms of adjunctive chemotherapy and failure to distribute the agents correctly commonly results in marginal recurrences.

Palliative chemotherapy

Where there is no possibility of a cure being achieved, it is possible to alleviate at least some of the signs of some cancers by using palliative chemotherapy. The objectives in this case are simply to decrease the tumour load and improve the welfare of the horse. If that also brings an increased life span, then that is an added benefit. Probably the best examples of this approach in horses are in management of severe melanoma or sarcoid states. Bleeding, open tumours can be medicated with chemotherapy and possibly adjunctive surgery, to try to improve the wellbeing and reduce the secondary effects of plasma and blood loss in particular. However, since the welfare of the horse is the paramount concern that overrules all other considerations, palliative care should not result in the transfer of welfare and wellbeing concerns to some other part of the horse – there is no point in inflicting painful or distressing palliative treatment on a horse without a significant welfare gain.

Since all chemotherapy regimens have at least some undesirable secondary effects, it is essential that before any chemotherapy is applied at any level by any means, the animal must be fully assessed for its ability to tolerate the treatment. The patient must be capable of undergoing the treatment. In the case of horses, tolerance has somewhat different issues from other species. It is accepted that systemic chemotherapy is poorly tolerated in some species, but fortunately it appears that the horse is remarkably tolerant of many of the drugs that create problems in other species. It appears that horses can receive doses of most chemotherapy drugs twice as high as dogs and slightly higher than human patients. Cisplatin is the exception, because horses cannot vomit, but otherwise they do not have any of the problems encountered with this drug in other species. Additionally, horses may have a much greater bone marrow reserve than most other species.

Toxicity in chemotherapy appears to relate to two fundamental rules:

1. The smaller the patient, the higher the dosage for an anti-tumour effect (exponential variation) and so the greater the opportunity for toxicity.
2. The lesser the bone marrow reserve (exponential variation), the greater the overall toxicity.

In the case of local chemotherapy, pain is a significant issue for horses. In the case of donkeys it is well known that they do not show the same external signs of pain as a horse and so it might be easy to overlook the effects of the treatment on a donkey. The haematological and metabolic status of the horse is often used as a measure to determine whether the patient can receive chemotherapy, or whether dose reduction is required, but this is probably over-simplistic, since there are many other adverse effects that are not easily assessed or quantified.

Chemotherapy can be applied in a variety of ways. The specific method chosen for a particular case should take account of the needs of the case, the practicality and the extent of secondary, unwanted, side-effects. There are additional health and safety issues for the operators and handlers of the horse since the most effective chemotherapy agents are also potentially carcinogenic. The associated problems are from their effects on DNA and cell-cycle processes, as well as via metabolic effects on the cell function. Since most are not discriminatory in any way (notwithstanding the variable effects on cells with high or lower cell replication rates), operators must ensure the safety of the handlers and owners of the horse as well as taking personal precautions to avoid any personal exposure. Repeated exposures are probably particularly dangerous. Often owners will not understand the significance of using a drug that can *cause* cancer, as a means of treating it. This means that detailed counselling is essential before embarking on any chemotherapy.

Note

In all chemotherapy protocols, in order to avoid the possibility of human safety problems, the basic and fundamental rule is *NO EXPOSURE* because complete protection is possible; this is not the case for radiation (p. 171) when an 'As Low as Reasonably Achievable' (ALARA) rule is applied.

Dose calculations

The use of cytotoxic chemotherapy at doses close to the maximum tolerated dose (MTD) is an established tenet of conventional oncological practice and the determination of MTD remains the primary objective of early-phase clinical evaluation. It has been shown in humans that most chemotherapy drugs have a narrow therapeutic range and display a steep dose–response curve gradient at doses below the MTD; therefore it is desirable to treat with doses as high as the patient can tolerate (Fig. 9.11).

Dose calculations for many chemotherapeutic agents and particularly those that are administered systemically either

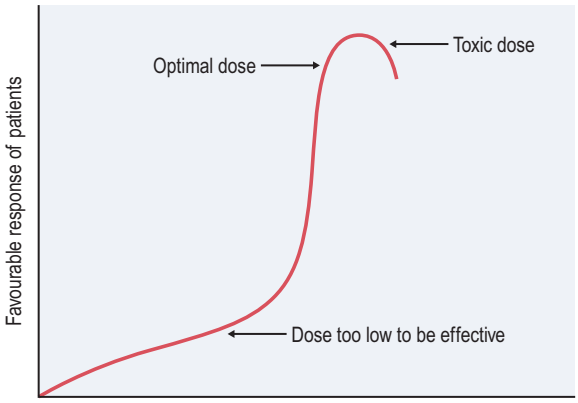


Figure 9.11 The narrow range of chemotherapeutic safety in some circumstances. The number/proportion of patients that will respond to treatment is shown on the y-axis and the dose of the drug required in shown on the x-axis of this figure. The required dose rate to induce a favourable chemotherapeutic response requires to be above the minimum effective dose and below the toxic dose. In fact, the optimal dose usually lies very near the toxic dose, when a high proportion of the patients will respond. The clinical objective is to use the highest dose of the drug that can be administered safely. In the horse, there are specific complications with some of the drugs used in chemotherapy and, as might be expected, some are extremely toxic when administered by some routes.

by injection or orally, as opposed to those administered intralesionally or topically, have the potential for unwanted systemic effects. In veterinary practice, doses are usually calculated on a per kilogram body weight basis. This is relatively easy, but in fact it is a crude mechanism. The preferred method involves the calculation of dose per square metre of body surface area. This is a more complex calculation and very few drugs apart from the chemotherapeutics are dosed in this way. In order to determine the dosage regimen that will most likely accomplish these goals, similar drug concentrations must be achieved in all patients dosed according to a specific regimen. Dosing based on body surface area (BSA) is generally used in an effort to normalize drug concentrations. This is because it is well recognized that measures of many physiological parameters that are responsible for drug disposition, including renal function and energy expenditure, can be normalized by use of BSA. Dose calculations are therefore critical to achieving a positive result whilst minimizing the adverse effects. Since many cancer drugs have a narrow safety margin between effect and toxicity, it is important to achieve therapeutic concentrations in tumour tissues at the same time that concentrations in non-target tissues are minimized.

However, there is substantial evidence that drug disposition is not always proportional to BSA. Differences in distribution, metabolism and excretion pathways may preclude dose extrapolation among species or among individuals within a species based on BSA. Moreover, genetic differences in drug metabolism are well recognized in humans and in laboratory animals; it is likely that similar differences exist among breeds of horse, in particular the variable management that horses have.

The body surface area of the horse can be calculated using the following formula:

$$\text{Body surface area } (m^2) = \frac{Wt(g)^{2/3} \times 10.5}{10^4}$$

A calculator is highly recommended. First, square the weight in grams (g), then take the cube root of the value that's given, or take the cube root of the weight in grams first and square the resulting value, whichever is more convenient. For example, 27 to the power 2/3 is 9; 8 to the power 2/3 is 4, and so on. Most calculators will allow that to be done relatively easily. The top of the power fraction represents increasing by raising to that power, the lower part represents reducing by taking the root; either can be done first. Most 150 cm horses will have a surface area of around 6–7 m^2, but the precise area is important, since that allows the precise dosage of a drug to be calculated; this is important as a basic principle of chemotherapy if efficacy is to be balanced against actual or potential toxicity. The safety margin of many cancer drugs is not wide, so overdosing can be dangerous but, also, underdosing will usually mean failure. There is also no point in underdosing, since that may simply waste the potential beneficial response.

This calculation is a fundamental aspect of chemotherapy in the horse. Doses of drugs that are used in cancer therapy must be given and calculated in doses/m^2 if failure or overdose are to be avoided. It is also true that many horses with serious neoplastic disease have concurrent problems and so are liable to be more sensitive to the potential dangers of overdosage.

The administration of a drug to a patient carries with it the implicit assumption that the drug will have a positive effect on a defined disease condition. The drug may have a directly positive clinical benefit and be effective but it may also have toxic and undesirable effects. The objectives of chemotherapy are to maximize the likelihood of producing a therapeutic response while minimizing the likelihood of producing unacceptable toxicity. The dosing variables available to achieve this goal include the amount of drug delivered and the interval or frequency at which the drug can be given. Under ideal circumstances, these variables are based on a sound knowledge of the relationship between the dose and the concentration of the agent, the likelihood of therapeutic and toxic consequences resulting from its delivery and the duration of drug effects. Unfortunately, such precise information is lacking for most anti-neoplastic chemotherapeutic agents. Moreover, not all patients are the same. As a result of genotypic and phenotypic differences, the same dose of drug will be likely to produce a range of concentration-vs-time profiles in any given group of patients, with the resulting range of therapeutic and toxic responses corresponding to that pharmacokinetic variability. An additional problem occurs when the animal is patently ill – low blood protein status, anaemia and secondary disease arising usually as a result of a combination of poor nutritional status and immunocompromise, and these will add to the potential dangers of using anti-cancer drugs. In the horse, the side-effects of most systemic chemotherapeutic agents are regarded as unacceptable, but this is probably an irrational over-simplification because there are effective methods of administering chemotherapy under some circumstances. The issue is basically that no drugs of this nature have zero side-effects and those have to be balanced against their potential benefit.

Restrictive chemotherapy support

Methods of retention of chemotherapeutic agents in a localized area are widely used in oncology in general.

Temporary vascular occlusion to retain the chemotherapeutic agent in a localized site is an effective way of ensuring exposure of the tumour cells to a longer action of the drug. For example a proximally placed tourniquet can allow an intravenous regional perfusion to be performed and so deliver a prolonged exposure to a drug that will then enter the circulation in allowed concentration and so avoid systemic toxicity. A further example of the benefit of circulation reduction is afforded by the incorporation of adrenaline in the formulation of cisplatin (p. 146). This causes vasoconstriction and so stops bleeding and limits reabsorption of the agent from the tumour site, at least until the effects wear off. It also helps to limit loss of the agent from the treated site if the tumour bleeds significantly. Similarly, it is suggested that drug uptake into cells can be significantly enhanced by concurrent cryotherapy (p. 126), hyperthermia (p. 127) or by electrochemotherapy (p. 158). However, freezing tumour tissues may actually decrease drug uptake by both intravenous and intratumoral routes. Cryosurgery does not increase cellular uptake because the cells are lysed by freeze-and-thaw cycles. While destroying all cells (normal and tumour) in the site, it also destroys blood vessels that supply the tumour. This may produce two outcomes: first, the tumour blood supply may be reduced and so the tumour will be 'harmed', and it will reduce the diffusion of the drug into the circulation, so keeping the drug localized. Second, it will reduce the delivery of drug to the tumour via the circulation and the resulting scarring may significantly impair the penetration of chemotherapeutic drugs into the tumour site. Overall, it is suggested that cryotherapy has a negative prognostic influence for intralesional therapy (A. P. Theon, pers. comm.).

The main cytological targets for chemotherapy drugs are illustrated in Figure 9.12. The various chemotherapy options available to equine practitioners and their relative advantages and disadvantages are shown in Figure 9.13.

Chemotherapy drugs can be broadly divided, in respect of their mode of action, into four 'families' (Fig. 9.14):

1. *Antimetabolites*: These drugs (such as 5-fluorouracil and methotrexate, see below), act as false substances in the biochemical reactions of DNA synthesis. The drugs therefore prevent cell division by incapacitating their ability to construct new DNA. As is always the case, when a cell is unable to replicate, it will eventually die.
2. *Topoisomerase inhibitors*: Some drugs (such as doxorubicin) inhibit topoisomerase enzymes, which are

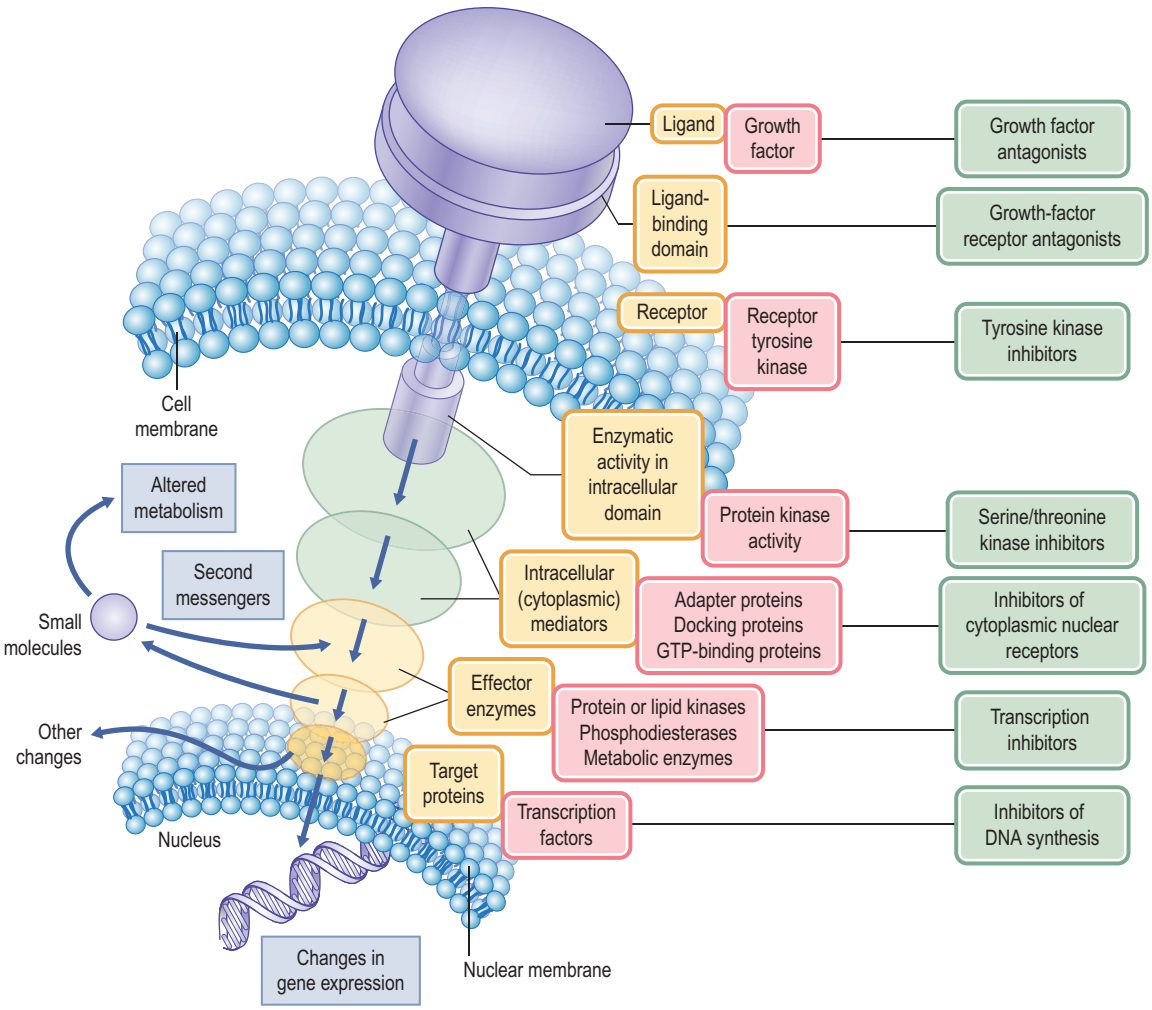


Figure 9.12 All therapeutic anti-cancer drugs interfere with one or more aspect of cell function or replication. Processes such as transcriptional activation, DNA replication, intracellular protein synthesis and cell-cycle progression. *(Figure reprinted from Downvard J. The ins and outs of signaling. Nature 2001; 411:759, with permission from Macmillan Publishers Ltd.)*

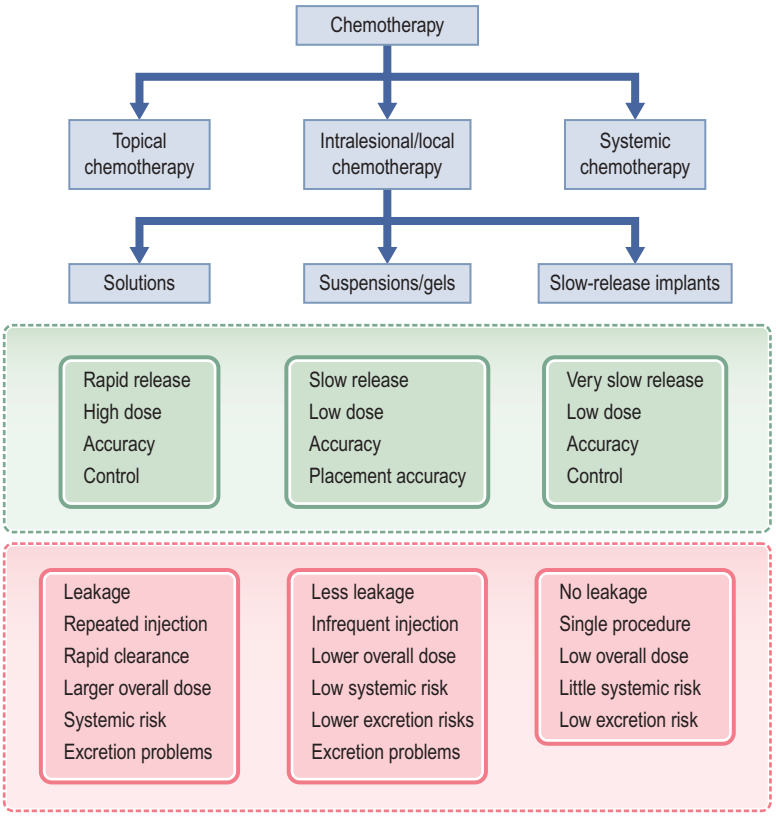


Figure 9.13 The various chemotherapy options available to equine practitioners. Their relative advantages and disadvantages.

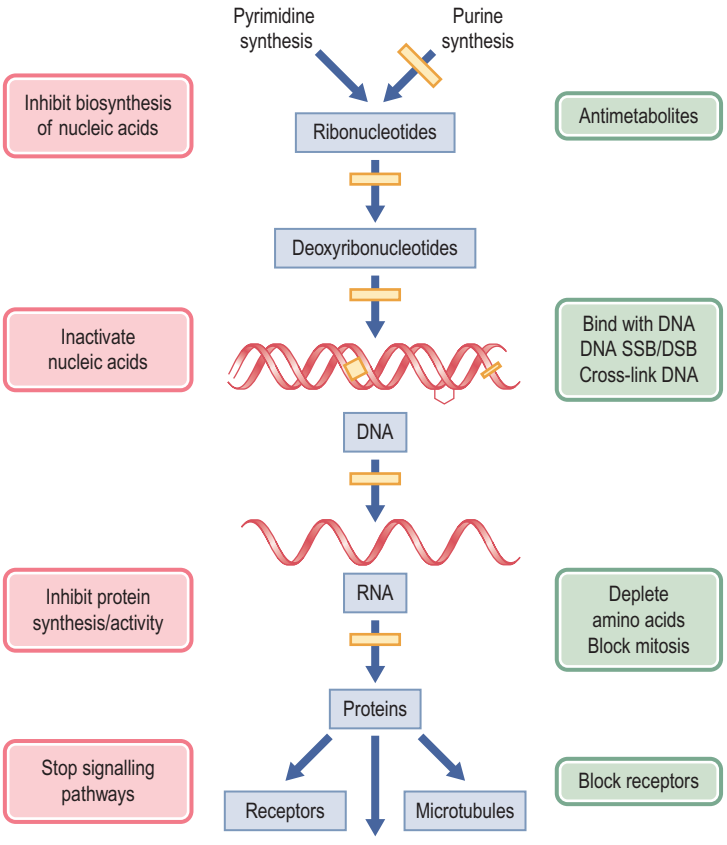


Figure 9.14 The basic functions of the main groups of chemotherapeutic agents used in cancer treatment.

responsible for pulling apart the DNA strands for replication. They prevent re-attachment of the broken ends after DNA replication – this results in cell death during mitosis.

3. *Alkylating agents*: These drugs form chemical bonds with particular DNA building blocks and induce breaks or lethal cross-linking within the normal DNA molecule. If this damage cannot be repaired, they are prevented from cell replication and eventually die. Typical examples of drugs with this action that are used in horses include cyclophosphamide and chlorambucil.
4. *Plant alkaloids*: Plant-derived substances such as vincristine and vinblastine can prevent cell division by binding to the microtubular fibres that draw duplicated chromosomes to either side of the dividing parental cell. In preventing the assembly/disassembly of these fibres, the cell cannot successfully divide and that will result inevitably in cell death.

Alternative classifications of chemotherapeutic drugs are based on the metabolic targets (DNA, RNA, proteins, microtubules, growth factor receptors, endothelium) because each drug has several mechanisms of action. In addition, drugs are classified according to their spectrum of activity in respect of the type of tumours they target (carcinomas, sarcomas, etc.) and their cell kinetics. For example doxorubicin works well whether the cells are dividing or not, and can therefore be used on slow-growing sensitive tumours, while 5-fluorouracil acts only on actively dividing cells and, in particular, on carcinomas.

Intravenous (systemic) chemotherapy

Intravenous chemotherapy is very restricted in use in equine practice; this is regrettable because at least the horse seems to be more tolerant than other species of the newer chemotherapeutic agents, such as doxorubicin. There are several valid reasons for this however, including the scarcity of suitable patients, the reluctance of owners and veterinarians to subject horses to the rigors of the treatments, the logistics of the process of treatment and the overall costs involved and the late presentation of cases; the early stages of most internal cancers are not detected either by owners or by veterinarians and so by the time the tumour is diagnosed definitively, there is often little to be gained from heavy systemic chemotherapy.

Most systemic chemotherapy protocols rely on the use of a single agent, but inevitably, this approach carries extra risks of high-dose-related toxicity. Combined therapy (p. 137) using lower doses of multiple drugs will often carry less overall toxicity, whilst maximizing the potential synergistic or additive effects of the drugs used. However, the use of combined chemotherapy in which drugs are combined at their individual maximum tolerable dose is still being developed in equine oncological practice. There is very little evidence-based information, however, of the use of combined chemotherapy in horses.

The objective of any chemotherapeutic regimen would necessarily mean that a maximal 'safe' dose was the best approach, whether a single drug or combined drugs were used.

Drugs that have been used in systemic chemotherapy in horses include:

- Corticosteroids
  - Prednisolone
  - Dexamethasone
- Doxorubicin
- Cyclophosphamide
- Vincristine
- Cytarabine (cytosine arabinoside).

By far the commonest clinical approach is the rather basic, but pragmatic use of high doses of corticosteroids. Set against the rather marginal and temporary effects on serious internal tumours, this approach can be helpful in improving the wellbeing of the patient, as well as having a generally anti-inflammatory effect that is often valuable. However, steroids are largely feared in equine medicine due to unwanted side-effects of laminitis (whether this is a genuine concern or not is another matter) and the fear of immunosuppression.

The only combination therapy that has proven efficacy for multicentric lymphoma is known as CHOP (see Box 9.2). The acronym is used to describe a protocol involving: cyclophosphamide, doxorubicin, vincristine and prednisolone. Use of the drugs is not a trivial process and requires suitable medical training for drug preparation and administration, with continued monitoring of possible drug-induced toxicities. Coordination of treatments is essential to take account of the risks of simultaneous administration.

The first multiple-agent, combined chemotherapy has been reported to be successful in the management of lymphoma.[12,13] This protocol involves the careful administration of several agents, as shown in Box 9.1.

Cyclophosphamide at 200 mg/m^2 can be used intravenously every 14 days as an alternative to the chlorambucil. In the event that a positive response (in terms of the tumour itself) is not achieved after 2–4 weeks, *vincristine* can be added to the regimen at 0.5 mg/m^2 once weekly by intravenous injection (Box 9.2). Since haemorrhagic cystitis

Box 9.1 A proven multiple drug chemotherapy protocol for equine lymphoma

- *Cytarabine* at a dose of 200–300 mg/m^2 administered once subcutaneously or intramuscularly every 7–14 days is described as the theoretical approach. However, it only seems to work in horses if administered repeatedly as a slow intravenous infusion. The subcutaneous administration is probably not equivalent to slow intravenous infusion and, therefore, the most effective method is to administer the dose intravenously over a 6 h period every 3 weeks.
- *Chlorambucil* at a dose of 20 mg/m^2 orally once every 14 days. The cost of this component is usually prohibitive.
- *Prednisolone* at a daily dose of 2.0 mg/kg orally once daily or on alternate days over the whole period of treatment. If steroids are used alone, dexamethasone, at 0.1–0.2 mg/kg q 24 h administered orally for 2 weeks and then tapered back to 0.05–0.1 mg/kg over a further week, is both safe and sometimes efficacious.
  - It is important to note that oral prednisone has no effect at all in horses. Horses lack the enzyme systems that metabolize prednisone to the active prednisolone.
  - The risks of laminitis associated with corticosteroid treatment are extremely low and probably irrelevant in oral regimens.

Box 9.2 The CHOP chemotherapy protocol

The *CHOP chemotherapy protocol* is found to be effective in some multicentric lymphoma cases:

1. *Cyclophosphamide* (200 mg/m^2 i.v. weekly × 4–6 treatments)
2. *Doxorubicin* (70 mg/m^2; 6 cycles at 3-week intervals)
3. *Vincristine* (0.5–0.75 mg/m^2; i.v. weekly for 6 weeks)
4. *Prednisolone* (1 mg/kg q 24 h am only for 7 days, then taper gradually over 4–8 weeks).

is a recognized complication, fluid intake should be encouraged (possibly even by 2× maintenance infusion) and furosemide may be administered to maintain effective diuresis.

Other reported chemotherapy regimens include the use of *L-asparaginase* at 10 000–20 000 IU/m^2 every 2–3 weeks by intramuscular (i.m.) injection. This material is extremely expensive and it cannot be administered more than twice because the patients develop allergic reactions. Various other combinations of cytarabine with cyclophosphamide and/or prednisolone have also been reported.

The drug cycle is usually continued until a suitable degree of clinical remission is achieved – usually around 2–3 months is required. A second cycle of treatment is then applied using an extra week interval to each drug as a maintenance therapy. Animals that are treated successfully appear to require a total of 6–8 months of treatment.[14]

Corticosteroid use

For many years, corticosteroids have been the mainstay of systemic chemotherapy. Whether this was born out of a lack of 'anything else to do' or a philosophy of 'no horse should die without the benefit of steroids' is not certain. However, since the early availability of corticosteroids, they have been categorically shown to have antimitotic and clinical effects. They also have profound effects on the immune system that have been recognized for many years. Adrenal corticosteroids will sometimes cause striking regression of disease in human patients with lymphomas or leukaemias.[15]

Large doses of corticosteroids have profound effects on normal tissues through their glucocorticoid and mineralocorticoid effects. In addition to their well-known effects on salt and water balance, intermediary metabolism and connective tissue, they produce atrophy of thymic and other lymphoid tissue, lymphopenia, eosinopenia and neutrophilia. Corticosteroids may exert a direct lymphocytolytic effect, as well as suppression of mitosis of lymphocytes. Following the exposure of lymphocytes to adrenal steroids in vitro, destructive changes become evident within 15 min, consisting of budding and shedding of cytoplasm, nuclear pyknosis and karyorrhexis.[16]

Corticosteroids are broadly useful anti-tumour agents in malignant lymphomas and are also valuable in treating paraneoplastic (immune-mediated) haemolytic anaemia and thrombocytopaenia that are sometimes associated with these diseases. In equine practice, there is much anecdotal evidence of a significant benefit in some serious lymphoma and infiltrative bowel tumours in particular. It is likely that some of these benefits are due to effects on the inflammatory process, which are characteristically activated in many serious neoplastic conditions.

Corticosteroids in equine chemotherapy

Corticosteroids are a foundation treatment of many serious internal tumours of horses. It is adjunctive and is usually used as part of a structured combination chemotherapy with other antimitotic drugs. Topical betamethasone or dexamethasone can be a useful aid to management of some localized tumours. It can be assumed that the effects of local corticosteroids are similar to the effects of the systemic drugs (Fig. 9.9). There is little information on the reason why corticosteroids have a significant anti-tumour effect. There may be direct effects, but there are also indirect anti-inflammatory effects.

There are a number of reasons why steroids might help in cancer treatment:

- There is a significant antimitotic effect on some cell types in particular and it may sensitize the tumour cells to the effects of other cancer chemotherapeutic drugs
- Corticosteroids reduce inflammation and so may reduce the metabolic systemic and local effects of cell necrosis and tumour-induced inflammation. A tumour might decrease significantly in size when the local (intra- and peritumoral) inflammation is reduced. This might make surgery more feasible in some cases. Additionally, they may also reduce pain through reduction of inflammatory mediators
- Corticosteroids have a strong immunosuppressive effect, but it is not certain whether this might be a harm or a benefit – to reduce the immune response, for example, after a transplant
- To help relieve depression and boost appetite.

Despite the fact that dexamethasone, a synthetic glucocorticoid, has pro-apoptotic effects on lymphoid cells in vitro, it has also been suggested that it has added properties in reducing apoptosis resistance towards chemotherapy. In a study carried out in 2011, a research group found evidence that dexamethasone can decrease cancer cell sensitivity to drug-induced cell death by preventing cell apoptosis.[17] It may not therefore always be helpful. There is no information on the definitive value of corticosteroids in horses apart from the dogma that includes it in almost all chemotherapy protocols.

Heavy metal therapy

Arsenic compounds (and particularly arsenic trioxide/As_2O_3) have been reported to be active anti-cancer agents in clinical trials on some forms of human lymphoma where it results in clinical remission (CR) rates of 85–93% when given by intravenous infusion for 2–3 h at a dose of 10 mg/day diluted in 5% glucose saline solution. The benefits of the treatment are detectable after 28–42 days. CR rates can be 98% and 84.9%, after administration of Composite *Indigo Naturalis* tablets containing arsenic sulphide and of pure tetra-arsenic tetra-sulphide, respectively. At higher concentrations (1–2 μmol/L), arsenic induces apoptosis, while at lower concentrations (0.1–0.5 μmol/L), it triggers cell differentiation in vitro. Arsenic trioxide-induced apoptosis has been observed in many human cancer cell lines, including oesophageal carcinoma, gastric cancer, neuroblastoma, lymphoid malignancies and multiple myeloma. Its effectiveness was confirmed in the treatment of multiple myeloma. Arsenic compounds appear

to be a potentially effective alternative that has not been exploited in horses thus far.[18] The logistics of administration in horses would be a major challenge in any case.

Topical arsenic trioxide has been an anecdotally reported method for caustic ablation of equine skin tumours for many years and particularly for management of sarcoid and melanoma. In this circumstance, it is a simple cautery that delivers its anti-tumour effect; in effect it is an escharotic. A similar effect can be gained topically by the use of other metal chlorides, including zinc chloride, which has been the main functional component of some commercially available sarcoid treatments that also incorporate plant extracts that may have immune-modifying effects (p. 195).

Local chemotherapy

Local chemotherapy, including topical, intratumoral and peritumoral therapy, has been developed to improve both the safety and the clinical effects of treatment and to reduce the costs of the treatment. It is clearly applicable only when direct access can be gained to the tumour (Fig. 9.15).

Since the main targets of local chemotherapy are 'inacessible' skin tumours and since the metabolic effects of systemic chemotherapy are difficult to control and the costs of treating a horse systemically are so high, greater interest is often taken to devise ways to apply the chemotherapeutic agents to localized lesions only. This approach enables high local concentrations of the drug to be used without the risk of significant toxicity and minimizes the costs. However, in many cases special delivery devices have to be constructed to achieve a positive result. The same mechanism is commonly used in treating skin and surface tumours in other species, so suitable creams and gels are available commercially in some cases.

Topical (surface) chemotherapy

Topical treatments based on ointment formulations are an attractive option for accessible skin tumours or those on easily accessible mucous membranes. For the most part, these methods are simple and usually less expensive than many others. However, there are definite constraints upon their use. Safety issues with human handlers, pain and patient resentment make owner compliance less predictable.

Topical treatments have, however, been used extensively and to considerable effect in equine practice. The history of topical treatment of equine skin tumours includes the widespread use of topical arsenic trioxide, mercuric chloride and antimony sulphate. These materials are clearly highly toxic and strongly caustic. Lesser caustics, including potassium permanganate crystals and copper sulphate crystals, have also been used for many years.

Examples of the materials that are currently in use in this way include AW4-LUDES (p. 558) (a specially formulated material containing heavy metals and fluorouracil for treatment of equine sarcoids produced exclusively by the University of Liverpool Sarcoid Service); 5% 5-fluorouracil cream, which is also used for superficial sarcoid and some carcinomas (Efudix™, ICN); tazarotene (a retinoid gel marketed as Zorac™, or Tazorac™, Allergan Ltd.) (p. 558), which is retinoid used adjunctively to treat superficial occult or verrucose sarcoid; and imiquimod (p. 154), which uses its anti-tumour/anti-viral properties to deliver activity against superficial forms of the equine sarcoid (p. 559).[19] Additionally, a number of other materials including an extract of the plant *Sanguinaria canadensis* with 25–30% zinc chloride (XXTERRA™/SARC-OFF™/Newmarket Blood Root Ointment™) (p. 195) is widely used as a topical treatment for sarcoid that the owners can both acquire and apply themselves; whether this is a sensible approach or is ethically acceptable in cancer treatment is debatable. For most of these substances, there are no evidence-based publications.

Topical applications of anti-tumour medications have also been used successfully to treat superficial intraepithelial carcinoma (carcinoma in situ) of the conjunctiva of horses. The materials that have been reported for this purpose include mitomycin C (p. 157) and 5-fluorouracil (p. 153). Additionally, corticosteroids are useful in many cases when early dysplastic changes are present. It is important to remember that corticosteroids also have anti-mitotic effects.

Set against the obvious advantages of convenience and relatively low cost, there are some important difficulties and constraints. These include:

- *Spread/run-off*: The risks of spreading the material over the skin around the lesion (called 'spread' or 'run-off') are significant. Even when an operator is meticulous about applications, the material will often 'melt' and

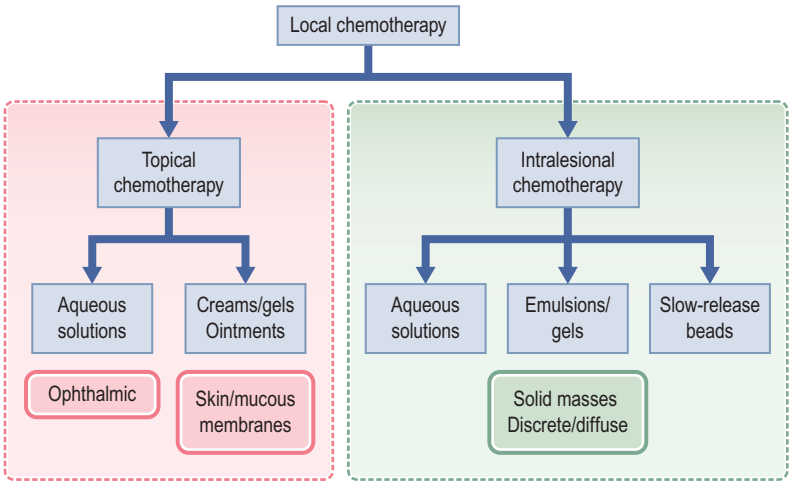


Figure 9.15 The main chemotherapeutic drug types and the routes by which they can be applied in horses. Local chemotherapy is a mainstay of equine cancer medicine for cutaneous tumours at least.

run away from the lesion itself. This can cause some problems in adjacent skin. Additionally, if the material is in any way irritant, the animal may rub the site and so cause spread of the material. Any excessive spread away from the treated site will not only cause secondary (unwanted) local damage, but of course also results in less efficacy for the treated site. An additional source of lowered efficacy arises if the animal licks the site (there may be secondary effects from that in addition of course) or if the material is washed off by rain or by rubbing on grass, etc., during eating. For example, topical treatment to a tumour on the muzzle or lip will almost inevitably be severely compromised by 'licking' or natural rub-off against grass or hay or wash-off in water. Where such constraints exist, due attention must be paid to the likelihood of success. Strategies may need to be adjusted or changed to alternatives in many cases. It might, for example, be possible to combine surgical excision/debulking with local infiltration or the burying of some slow-release chemotherapeutic drug, such as cisplatin beads or gel (p. 151). Persistence and additional applications may be contraindicated for reasons of potential systemic harm or environmental biohazard. In some cases, the horse might rub the material onto a stable door or a bucket and so the material might gain access to human handlers, to their potential detriment. Advice should always be given in respect of human safety when these chemicals are being used, even when the materials themselves are human drugs, because they inevitably have an effect on cells that they contact.

Notes

- In the USA, application of antineoplastic ointment has to be carried out by a veterinarian because of the potential biohazard and potential contamination of the owner.
- In France, no cancer treatment is permitted in horses apart from cisplatin on the grounds of possible food chain contamination.

- *Shallow/limited absorption and poor or uncertain intralesional distribution within the tumour*: It is suggested that topically applied materials are limited to 5 mm of penetration ability/absorption of the chemicals before they are absorbed into the bloodstream and therefore they may only be effective in superficial tumours. Creating a tumour-free surface can give a false sense of security, but where repeated applications can be performed conveniently it is certainly possible to treat some quite large masses and even some highly invasive ones. The inadequacy of penetration and distribution can be compensated by persistence in many cases. Good examples of this are provided by the use of AW4 and imiquimod in particular, where persistence and repeated courses can bring very pleasing results.
- *Poor cosmesis/functional outcome*: Topical materials often induce an uncontrolled response, especially if they are applied in a casual manner. In some cases, this results in failure of treatment and the need to repeat the course. In others the response may be stronger and in any case the effects are usually rather uncontrolled and unpredictable. However, set against that they are usually applied at intervals and common sense usually dictates that the treatment is either increased or decreased to provide a good degree of control. Very good cosmetic outcomes can be achieved, particularly with combined treatment protocols.

Caustic or other cytotoxic chemicals will inevitably affect normal cells as well as the tumour cells and any resulting functional problems will be a product of the extent of the damage and the tissue concerned as well as the locality. For example, a severely cytotoxic chemical application on the upper eyelid may result in significant direct damage and then a functional problem with blinking that could have profound secondary effects on the eye. Careful case selection should preclude the risk of significant problems – some sites are much more tolerant than others. Taking the local anatomical constraints and the effects of the chosen chemotherapeutic material, it should be eminently possible to make sensible clinical judgements. There is no point in application of a strong caustic material to the side of the face, since there may be a significant risk to the facial nerve or the parotid duct for example. In contrast, the belly wall is much more tolerant of a stronger more aggressive approach. The medial thigh is probably a midway point since the skin is thin and there is risk of run-off, which could cause more extensive damage.

Scarring in a vital structure, such as on the eyelid or the cheek region, can cause serious functional problems and an unacceptable scar.

A good example of local chemotherapy is in the use of a topical 5% 5-fluorouracil ointment in the treatment of superficial sarcoid and some forms of localized carcinoma, such as those on the penile skin or vulvar margins.[20–22]

Unsurprisingly, different tumours in different sites may require different regimens of application and the clinical appraisal during treatment is a fundamental requirement of all oncological therapy, not just when topical therapy is being performed. Typical of the topical anti-tumour medications, repeated applications are essential if the effects are to be maximized. For example, AW4-LUDES (p. 139) and imiquimod (p. 154) are applied over a 10-day and 3-month period, respectively, using one of several protocols. Topical 5% 5-fluorouracil cream (p. 153) and 0.1% tazarotene gel have considerable effects on surface forms of sarcoid (occult and verrucose types) when applied at 12 h intervals for 10 days. Genital squamous cell carcinoma may require much less frequent applications. Using a careful clinical assessment at each application, it is entirely feasible to bring about a good resolution with minimal cosmetic and functional problems.

Intralesional/intratumoral chemotherapy

The concept of intralesional chemotherapy has gained considerable attention in recent years and has focussed on ways of improving drug distribution within the tumour and the tumour bed, whilst using a much smaller overall dose of the drug itself. The expectation is that this will limit the systemic toxicity for the patient and the associated biohazards for operators and owners alike. The overall dose of the drugs is often low enough to be trivial; it is suggested that only 2% of the systemic dose would have to be administered

to have the same effect. It also has cost and convenience benefits.

The main criteria for selection of a drug to be administered intralesionally are that it will have a defined clinical effect on the tumour cells (preferably without damaging the non-tumour cells).

The specific formulation of the intratumoral medications will also have an influence on the need to repeat the treatments. Drugs placed within a tumour bed probably only diffuse away from the site through 5–10 mm before the active ingredients are diluted and cleared from the site into the bloodstream. This is a significant constraint to their use and dictates that repeated injections may have to be made. Water-soluble materials probably clear rapidly from the site – possibly even within minutes – and so usually require repeated injections at shorter intervals than drugs formulated to provide slow release of the drug from a stable depot delivery system or formulation. Mitomycin C (p. 157) has been used in the management of some intraepithelial (in situ) carcinomas of the conjunctiva and corneal epithelium.[23,24]

In order to overcome some of the limitations associated with unwanted cytotoxicity and danger to the operators, chemotherapeutic drugs may be formulated into slow-release forms either in stable emulsions, R-gels or biodegradable beads. A common example of the use of a slow-release formulation is the use of cisplatin in both emulsion and biodegradable bead forms (p. 151). There is a form of cisplatin that is used for intravenous use in human oncology that contains 1 mg/mL solution. *cis*-diamminedichloroplatinum (cisplatin) is available as a 50 mg/50 mL solution (Oncovertin™, Baker, UK) but this is not an effective dose and a 20 mg/mL solution must be used. This means that the raw cisplatin must be used to make the primary solution for use as an emulsion. This can be injected into a tumour bed, but since the diffusion into local blood vessels will be rapid, the injection would need to be repeated frequently; the rate of clearance from an injection of this material is too fast to allow cellular effective cellular concentrations to be built up. Furthermore, as is the case with this particular solution, delivery of a suitable dose of drug is difficult – the volume of solution required is greater than the volume of the tumour. There are devisable strategies that make the best use of such formulations and these involve the use of restrictive circulation or electrochemotherapy (p. 158).

Three methods have been devised to deliver a drug in a depot, slow-release form:

1. *Emulsions*: Emulsions that delay the delivery of a chemical have been developed. This is particularly applicable to the treatment using oily emulsions of cisplatin (p. 151) in management of accessible (surface) tumours, and the relatively low overall dose of drug means that frequently repeated injections are not required.[25] Intervals of up to 2 weeks have been suggested as being an ideal interval for cisplatin in sesame oil.[26] Similar formulations have been reported for 5-fluorouracil and mitomycin C.
2. *Biodegradable beads*: Slow-release biodegradable beads containing cisplatin made up with calcium sulphate and dextran sulphate can be implanted into the tissues either following surgical debulking or directly into the tumour bulk.[27] Whilst the material with the greatest veterinary evidence-based information is cisplatin in bead form, there is definite scope for this type of delivery with other chemotherapeutic drugs as well. The advantages of the system are the use of smaller overall amounts of the drug, accuracy of placements and sustained delivery of the chemicals. The main limitation in the use of this form of medication is their limitation in drug distribution when there is microscopic disease spread into surrounding tissues; since drugs will not diffuse more than 5 mm in normal tissue no matter how it is loaded, it is probably better to use tracing injections of a viscous-fluid formulation.
3. *Stable R-Gel systems*: These delivery systems are currently being developed as a means of slowing the delivery of a therapeutic drug from a depot site within tissues. There are currently no reports of studies into their use in oncological medicine in horses.

Only a few comparative studies have been made comparing different modalities of intralesional chemotherapy.[28] However, there are plentiful reports of various different treatments that are used in topical chemotherapy and cisplatin is a common reported intralesional agent.

Adjuvant chemotherapy

This term is used to describe the delivery of chemotherapy after a definitive surgical (usually) procedure intended to remove the whole tumour. The rationale for this usage is to restrict the chances of recurrences in patients having a moderate to high risk of subsequent relapse; for example, some particularly aggressive tumours and those cases where the tumour removal has been compromised by anatomic or other constraints. Relapses, recurrences or even, in some circumstances, remote dissemination of the tumour may occur as a result of failure to eliminate every single tumour cell; the surgeon may be anatomically constrained or may simply be unable to define a safe margin or cells may have desquamated from the tumour bulk into the wound bed prior to removal of the tumour. Additionally, the principle of adjuvant or adjunctive chemotherapy relies on the theory that chemotherapy for most large or extensive cancers is not capable of curing the patient when there is a large tumour bulk, but it is capable of a cure when there are few cancer cells; therefore, the best time to deliver chemotherapy with curative intent is when the tumour burden is least, i.e. immediately after a tumour reductive ('debulking') or excisional procedure has been carried out.

Drug resistance and failure of expected efficacy

The literature of chemotherapy in all species is bedecked with accounts of successes and rapidly improving prognosis for many cancer disorders in all species. Improvements in chemotherapeutic programmes involving multimodality treatments using combination chemotherapy and those that combine chemotherapy with radiation, surgery and other ablative methods have resulted in an improved outlook for many patients. However, there are inevitably failures; these are often given undue attention, but the reasons for failures often provide a key to alternative approaches. In most cases, failure of therapy is manifest as expansion of the tumour.

Reasons for failure of chemotherapy include natural and acquired resistance to the chemicals. The relationship between the dose of the drug and its anti-tumour effects, its side-effects and the desired outcome is highly complicated, and since there are seldom any identical tumours in identical patients, the careful planning of all chemotherapy is fundamental. A degree of flexibility has to be inherent in the process of treatment as the patient's condition may improve or deteriorate; alternatively, the drug may show increasing or decreasing efficacy.

Since relatively few chemotherapeutic agents are used in horses and since there are relatively few reports on the efficacy and the failure of expected efficacy, little is known about the specific problems of drug resistance in equine chemotherapy.

Possible reasons for failure of chemotherapy include the following.

Pharmacological and physiological mechanisms

Inadequate drug dosage

An inadequate dose or concentration of the drug (either as a result of underdosing or failure of delivery of the drug to the site) will result in a weak or even a zero effect. This means that, traditionally, chemotherapeutics have been administered at the maximum (or near-maximum) tolerable concentration based on toxicities to normal tissues and organs.

Suboptimal drug administration schedules

The efficacy depends on the delivery of the drug to the tumour cells themselves and that may vary. For example, aqueous solutions of cisplatin may be cleared from the substance of a sarcoid tumour within 20 min and that may not be sufficient time for a therapeutic concentration to be acquired within the tumour cells. That would mean that such a solution might have to be administered every few hours at least, in order to have an equivalent therapeutic effect to a depot form of the chemical, such as an emulsion or a biodegradable bead containing the drug. Generally, drugs with short half-lives and those which are cell-cycle phase specific are typically more effective when used with continuous delivery systems or rapidly repeated doses. Good examples of these drugs include 5-fluorouracil, cisplatin, bleomycin and mitomycin C.

Drug sanctuary sites (protected by blood–tissue barriers)

There are physiological barriers that inhibit certain drugs from entering specific target organs. These barriers are largely related to endothelial cell expression of the multidrug transporter P-glycoprotein. The eye, the brain and the testis are examples of organs that have significant barriers to chemotherapeutic agents (and other drugs of course). Where these exist, they act as protective mechanisms against the action of the drug and so alternative strategies have to be developed to deliver the drug to the tumour. In effect, these barriers simply block the access of the drug to the tumour.

Poor/impaired drug diffusion into cancer tissues

The distribution of a drug into a tumour will largely depend on the ability of the drug to gain access to the tissue concerned. Where a drug is delivered systemically via the bloodstream, the delivery will clearly be very dependent on the extent and efficiency of neovascularization of the tumour. Where the tumour is poorly vascularized, whether because of the particular characteristics of the tumour or because the angiogenesis is not adequate, the drug will probably fail to achieve its therapeutic dose. A good example is the failure of systemic chemotherapy to treat the solid forms of sarcoid. The blood supply is poor, the tissue density is high and there is a histologically recognized paucity of vascular distribution within the tumour. The other mechanism for failure to distribute the systemically administered chemical into the tumour is tumour necrosis. A necrotic tumour is, by definition, largely avascular and so individual cells may survive whilst the drug is not distributed into the tissue adequately.

Cellular mechanisms of drug resistance

It should be no surprise that drug resistance is an issue with chemotherapy, just as it is with antibiotics. Increasing numbers of cells with an ability to survive in the face of the drugs biases the overall tumour cell population towards resistance. The fact that genomic instability is a fundamental aspect of cancer medicine means that resistance is almost inevitable; fortunately, it is rare.

The basic mechanisms of resistance are based on several cell functions (Fig. 9.16), with the main aspect being intrinsic resistance (usually no alterations in this take place, i.e. the population of cells is inherently resistant and will not acquire sensitivity to the drug) and acquired or flexible resistance, which is mutation dependent.

Acquired and inherent/intrinsic drug resistance

There are certain drugs that simply do not have any therapeutic effect on certain types of cell – this is inherent (or intrinsic) drug resistance. This is constitutively expressed therefore in the cells from the outset and is a result of the pre-existing cellular defence mechanisms present in normal tissues. Although this lack of response limits the use of drugs for specific tumours, it is relatively easy to establish and is invariably predictable.

The more challenging resistance is that which is acquired by mutation of the tumour cells. The mechanisms for this are simply a result of evolving pressures on populations of cells in contact with a drug. As in the case of acquired antibiotic resistance, there is usually a genetic basis for this change. The genetic basis of this relies on the inherent instability of the genome of cancer cells. This tends to create populations of cells with slightly differing characteristics, one of which may be a resistance to a drug to which it is exposed. Once that population survives, whilst the others do not, the overall tumour will acquire a significant resistance to the drug. The dose rate and treatment schedule used may also influence the rate of development of the resistance and this is also a reason why high doses, that border on systemic toxicity, are usually used. Low (sub-lethal) doses of drugs given at irregular or inadequate time intervals also create a circumstance when resistance development is likely.

Drug efflux transporters

The mechanisms for the elimination of drugs from the cytosol of a cell involve specific efflux transporter processes (Fig. 9.16). The most dominant and the most widely studied drug resistance transporter is P-glycoprotein, which is specifically encoded from the genome of the cell. Where these transporter mechanisms exist they can actively naturally expel small molecules from the cell, so a drug may not be effective. Cancer cells of certain types commonly have

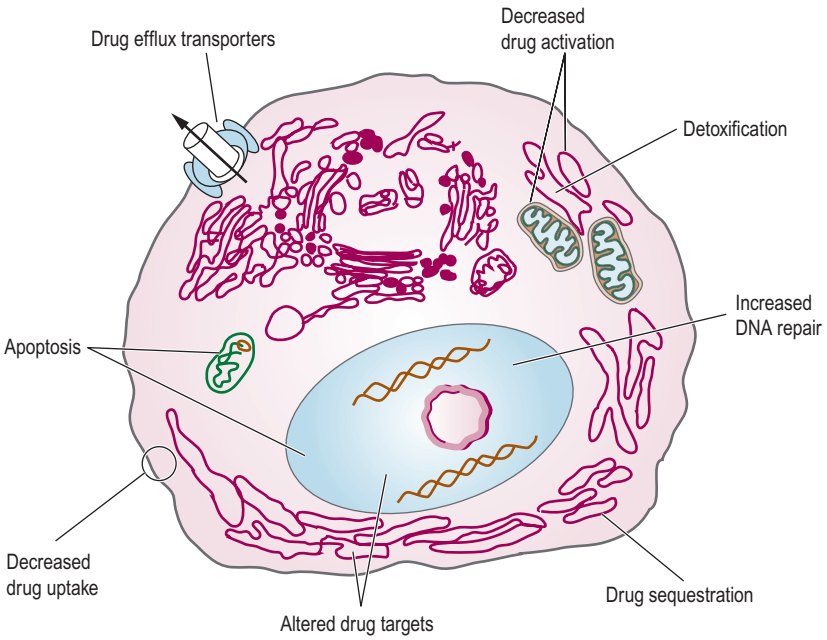


Figure 9.16 The mechanisms and sites of drug resistance to cancer chemotherapeutic drugs. *(Figure reprinted from Sikic BI. Natural and acquired resistance to cancer therapies. In: Mendelsohn J, Howley PM, Israel MA et al., eds. The molecular basis of cancer, 3rd edn. Philadelphia: WB Saunders; 2008: 254 (Fig. 19.2); copyright 2008, with permission from Elsevier.)*

P-glycoprotein overexpression; this results therefore in a multidrug resistance phenotype. Since the mechanism has very wide substrate specificity, the cells are resistant to (or at least unaffected by) a range of drugs; up to one-third of the anti-cancer drugs (as well as many other drugs used in other areas of medicine) are actively expelled from the cells, with a consequent adverse effect on prognosis.[29] Currently, a number of trials are being undertaken to try to block the effects of the efflux processes and so enhance the effects of the chemotherapeutic drugs. There is no material information on these aspects specifically in horses, but the mechanisms are broadly similar in many species and so it is likely that some cancers in horses will have upregulated transport protein molecules.

Impaired drug uptake

Most drugs gain entry to cancer cells via passive diffusion. A few drugs have active transport mechanisms and in these cases the effects of the drugs will be heavily dependent on the expression of the activity of these active processes. Cancer cells may have decreased transport mechanisms, and so where this is present the drugs will not gain normal entry into the cells and so will be seen clinically as ineffective. The diffusion of drugs into cells can be improved/increased by higher concentrations (such as might be achieved by local infiltrations or with additional mechanisms such as hypoxia, prolonged contact and electropermeabilization (p. 158). It is important that clinicians should understand the particular mechanisms of action of the various drugs and, at the same time, define factors that might reduce the expected theoretical activity of the drug.

Molecular target alteration/mutation

Alteration of drug targets is an important aspect of drug resistance in cancer chemotherapy. The specific target of the drug's activity may be altered in the unstable genetic status of the cell. Clearly where a molecular target is altered, the drug may have to be altered as well to be functional. Additionally, cellular changes that involve metabolic alteration in both the chemical and the mechanism of its action may be altered by mutational changes and, again, this may adversely influence the efficacy.

Intracellular drug redistribution

Sequestration of the drug into defined locations ('vault proteins') within a cell, in such a way that it has no therapeutic effects, is recognized in human myeloid leukaemia where it is a potential reason for drug failure.[30] It is not certain that the vault proteins that are responsible for this isolation of the drug are involved in any equine cancer.

Metabolism of drug or its active metabolites

Metabolic inactivation of a drug is a relatively common explanation for drug 'resistance'. Specific intracellular and extracellular metabolic processes can be a major mechanism for converting the drug into non-efficacious metabolites. For example, the DNA-binding glycopeptide drug bleomycin (p. 145) may be inactivated by a peptidase enzyme that has been named 'bleomycin hydrolase'. Similarly, the effects of 5-fluorouracil can be catabolized by a dihydropyrimidine dehydrogenase enzyme.[31] Again, there is no information on the role that this has in cancer therapy in horses; 5-fluorouracil is rarely used anyway, but that is probably a reflection of a failure to recognize its value, and when its use becomes more widespread these mechanisms will need to be considered and researched.

Enhanced DNA repair mechanisms

As might be expected, DNA repair pathways are important determinates of the efficacy of alkylating agents and platinum drugs. Evidence for the involvement of several DNA repair genes in response to radiation- or chemotherapy-induced DNA damage is accumulating. Where the DNA repair mechanisms are intact, drug actions may be overcome and the drug may not be effective. This may apply to different drugs at different sites in different tumours and so multimodal or combined chemotherapy can often overcome this inhibition of drug effect.[32]

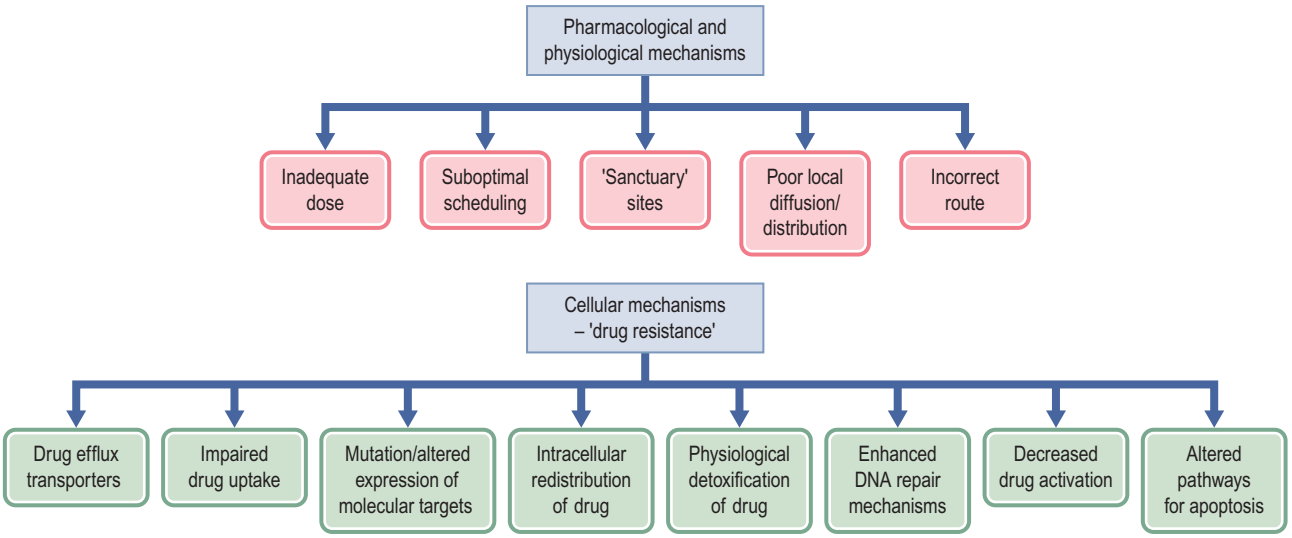


Figure 9.17 Some causes for failure of systemic or local chemotherapeutic drugs. The red outline boxes are factors that are entirely within the control of the physician and therefore should not arise in normal clinical circumstances.

Decreased drug activation

Many of the antimetabolite group of drugs (such as cytarabine, 5-fluorouracil and cyclophosphamide) require metabolic activation to an 'active' derivative. In the case of 5-fluorouracil, it requires to be converted into 5-flourodeoxyuridine monophosphate. Where the process of activation/metabolic conversion is inhibited by any intracellular mutation, the drug will be inhibited and the tumour will appear to be 'resistant' to it.[33]

Altered pathways for apoptosis

The pathways for the planned cell death (apoptosis) are fundamental to cancer therapy and of course for the processes of oncogenesis. It is probably impossible to discuss any aspect of apoptosis without reference to the p53 family of genes. Normal p53 function is essential for the normal functioning of DNA repair that arises as a result of mutation or ionizing damage. It is also essential for the reparative processes that could accompany drug-induced cell damage. The concept of reparability of cells following exposure to alkylating agents or radiation is a basic tenet of the restoration of normal tissue after treatment. Normal cells with a normal p53 gene structure will repair far better than a tumour-mutated cell in which the p53 function is significantly damaged. Thus, following treatment, normal cells are inclined to repair, whilst tumour cells are not. Where there is any compromise in the p53 function therefore, the damage to normal cells may be significantly higher. Similarly where p53 is 'functional' in cancer cells, the drugs may be negated by the efficient reparative mechanism; so it can be seen that the pathways for apoptosis are a major determinant of clinical outcome following either radiation or chemotherapy (Fig. 9.17).

Drugs used in equine chemotherapy

The use of most chemotherapeutic agents in horses has been poorly reported. There are usually many anecdotal reports of treatments that have seemed to be successful, but the variability of the presentations and the individual variations in treatment regimens has meant that few chemotherapeutic regimens have any established credibility. Frequently, the published results are later found to be unrepeatable and this is invariably due to the unique pressures on equine practice. Most owners expect a 'rub-on' treatment with a resolution within days, if not hours, and such an unrealistic approach to cancer is singularly counterproductive. As might be expected, the best evidence-based information is derived from the treatment of the common external/skin tumours including melanoma, sarcoid and squamous cell carcinoma. There is some evidence also for the management of certain forms of lymphoma. Future properly conducted clinical trials should be encouraged and supported.

Additional constraints on the use of systemic chemotherapy are the cost of the materials required to treat such large animals and the late presentation of cases. It is an unfortunate fact that many treatable tumours, even those of the skin, are presented so late that curative treatment is unrealistic.

Aciclovir

Although aciclovir has no reported anti-cancer properties it has been reported to be effective in the topical treatment of some equine sarcoid tumours.[11] Although it is hard to understand the logic of such an approach, in this study 5% aciclovir ointment was applied daily directly to a total of 47 sarcoid lesions in nine horses over a period of 2–6 months. All 47 of the sarcoids showed a positive response to treatment, with complete tumour regression observed in 68% of the lesions. Incomplete resolution was observed for 15 (32%) lesions, which the authors attributed to as 'probably due to their thickness'. No recurrences were reported over a relatively modest follow-up period. The authors conclude that aciclovir may therefore be used for the treatment of 'mild-type' sarcoids and as an adjuvant therapeutic agent in combination with surgery. Most other clinicians have not reported any successes with this treatment.

It is not clear whether this material is exerting anti-viral or by-stander anti-tumour properties, but there are no convincing corresponding studies in any other species.

A clinical trial testing the potential tumour effects of valganciclovir, a drug with known in vitro activity against Kaposi sarcoma (KS)-associated herpesvirus (KSHV), in humans showed no convincing benefits.[34] Interestingly, herpes simplex virus thymidine kinase (TK) is a widely studied enzyme used for suicide gene strategies, for which the prodrug is ganciclovir (GCV).[35] Somewhat in contrast, there is some evidence of by-stander anti-cancer effect of ganciclovir, which has been shown to upregulate the suicide genes in some tumour states in human patients.[36] It is not established whether this is an important aspect of the clinical justification for the use of aciclovir.[37] So far, this has only been tested in treatment of equine sarcoid.

Procedure

Aciclovir (5%) is applied once daily for 2–3 months directly to the surface of the sarcoid mass. No therapeutic complications are recorded. Other specialists have shown no benefit from this method and it would seem to be irrational with our current knowledge.

Further long-term studies will no doubt follow.

Bleomycin

Bleomycin is an anti-tumour glycopeptide antibiotic produced by the bacterium *Streptomyces verticillus* (comprising a group of structurally related compounds). When used as an anti-cancer agent, the chemotherapeutical forms are primarily bleomycin A_2 and B_2. Bleomycin acts by causing single- and double-stranded DNA breaks, which lead to inhibition of DNA and RNA synthesis.

Bleomycin for injection is available commercially as a sterile, white to off-white, lyophilized powder in vials for intramuscular, intravenous or subcutaneous administration. Each 15 and 30 unit vial contains sterile bleomycin sulfate equivalent to 15 or 30 units of bleomycin, respectively. The powder is reconstituted with sterile water for injection. For intralesional injection, bleomycin can be prepared in an oily emulsion similar to the preparation of cisplatin (see Fig. 9.19).

The scientific literature based on the use of bleomycin is vast and it is clearly a major player in human oncology, but in terms of veterinary and, more specifically, equine use, there are very few reports of it. A study to compare the therapeutic benefits of intratumoral administration of cisplatin (at 1 mg/cm^3 of tissue) and bleomycin at a rate of 1 IU/cm^3 of tissue 4 times at 2-week intervals, for squamous cell carcinoma of the eyelids in horses, showed that the clinical benefits were similar.[28] The effects appear to be better in tumours with high replicative rates, but such tumours probably have a greater tendency to peripheral recurrences. Local acute reactions were similar in the two treatment groups and chronic reactions were not observed. This study concluded that, based on therapeutic benefit and treatment cost, cisplatin was, on balance, a better choice for intratumoral chemotherapy of eyelid carcinomas.

Bleomycin has been found to be equally effective as cisplatin when used in electrochemotherapy regimens in human patients.[38] Bleomycin has also been used as a chemotherapeutic agent in electrochemotherapy in a variety of tumours in horses and donkeys.[39] There are otherwise no significant studies on its use in horses and it is probably not widely used. The reported outcomes of bleomycin treatment are not really convincing enough to warrant its use at present for sarcoid therapy at least.

Procedure

Bleomycin is injected intralesionally at a dose rate of 0.5 IU/cm^2 using a 21–24G needle. The injection should be made superficially into the mass or into the remaining tumour after surgical reduction. The injections are repeated every 3–4 weeks. No unwanted side-effects are reported. In one study on equine sarcoid, 23.5% of treated cases were a complete success but 41.7% horses showed recurrence or deterioration.[40]

Carboplatin

Carboplatin (*cis*-diammine[1,1-cyclobutanedicarboxylate] platinum) is a platinum compound that cross-links DNA, thereby inhibiting DNA synthesis. All of the major chemotherapeutic platinum agents form strong chemical bonds with thiol sulphurs and amino nitrogens in proteins and nucleic acids. It is classified as an alkylating agent. It is considered a 'second-generation' platinum agent. Carboplatin differs chemically from the first-generation platinum compound cisplatin (p. 151) by being a bigger molecule, with a dicarboxylate ligand. This slows the metabolic breakdown of the agent (it stays in the body longer) and reduces the rate of formation of toxic by-products.

Typical of the majority of alkylating agents, carboplatin can be used for most types of cancer, but is usually considered of greatest value in treating slow-growing tumours. In equine medicine, this is usually directed at intralesional methods for cutaneous tumours, such as the sarcoid. Anecdotally, it is being used increasingly instead of cisplatin, but there are no significant reports of its efficacy. Carboplatin does seem however to be effective in carcinoma but has more limited effect on sarcoid and cutaneous lymphoma.

Its side-effects include bone marrow suppression and metabolic disturbances (lowered blood concentrations) of calcium, magnesium, potassium, but, in general, it has less unwanted side-effects than cisplatin and, in particular, is less nephrotoxic.

Carboplatin can be used in the same manner as cisplatin (p. 151) and may be more accessible in most countries than the latter. For the most part, the platinum compounds are used locally either as stable emulsions injected into a tumour mass (p. 149) or in biodegradable bead form. This means that the overall doses are very small relative to the size of the horse and so the risks of patient toxicity are very low. However, they are all carcinogenic and cyto-destructive and so handlers need to be aware of the required precautions, both in drug handling of the drug itself and the patient after administration.

In practical terms, however, it needs to be somewhat more concentrated when used in emulsion form (p. 149). A solution of 50 mg/mL carboplatin is best. One millilitre of this solution is emulsified with 2 mL medical grade sesame oil to which 0.2 mL SPAN-80/sodium mono-oleate is added to stabilize the emulsion. The resulting 3 mL of emulsion is injected intralesionally in orthogonal planes as shown on page 149 for cisplatin. The solution is used to deliver approximately 10 mg carboplatin per cubic centimetre of tumour.

Carmustine

Carmustine (bis-chloroethylnitrosourea) is a mustard gas-related agent that is classified as an alkylating agent, which forms active metabolites that prevent DNA replication and DNA transcription.

It has significant adverse side-effects on bone marrow and renal tissue in particular. There are no reports of its use in the horse and indeed, it should probably not be considered in horses because of the major biohazard it represents. This group of drugs is extremely carcinogenic and probably has no indication in horses for that reason alone.

Chlorambucil

Chlorambucil is antineoplastic aromatic nitrogen mustard gas analogue that can be administered by mouth. It alkylates and cross-links DNA during all phases of the cell-cycle, which causes disruption of DNA and RNA function, cell-cycle arrest and which instigate apoptosis. The major side-effect is bone marrow suppression and renal toxicity with electrolytic alterations in particular causing low circulating magnesium, calcium and potassium.

There are a few reports of its use in horses.

Cimetidine

Unlikely though it may seem, the histamine H2-receptor antagonist cimetidine has been found to be an effective chemotherapeutic agent in a variety of human (renal, colorectal and gastric carcinomas) and animal tumour conditions.

In Equidae, its use is largely restricted to treatment of melanoma. The theory behind its effects is that it blocks the histamine receptors on suppressor T cells and thereby inhibits their function. Cimetidine was reported to have a significant beneficial effect in the clinical management of progressive, multifocal melanomatosis in three adult grey horses.[10] Two of the cases that were reported had shown rapid expansion in size and numbers over some months and one case had a slow growing melanoma. All three horses were treated with 2.5 mg/kg of body weight, cimetidine PO, q 8 h for between 2 months to 1 year. During treatment, the number and size of the melanomas decreased substantially (50–90%). The progression of the disease was halted in two horses and controlled in the third horse over the long term. This report stated that the benefit was a long-term remission of both numbers and size with no increase in tumour volume over 3–4 years. A second report failed to identify any significant clinical effects using the same regimen.[41] Anecdotally, it does seem that a few cases are indeed helped by cimetidine therapy, but that the large majority are not affected in any way. The dose rates are variable and the outcome is largely disappointing when compared with the original paper, which admittedly only had three cases. A carefully constructed controlled study in 15 horses aged between 18 and 27 years, tested the efficacy of the various reported dose rates (and dose frequencies 3.5 mg/kg q 12 h and 7.5 mg/kg q 24 h) administered for 60 days could not establish any efficacious difference between control and treated horses.[42] The likelihood is that this is not a useful treatment, but since a few horses have apparently responded spectacularly well, it is possibly worth considering at least a short test period during which a specific tumour can be measured accurately. In the event of an improvement being noted, the course can be justifiably continued, but if there is no change within 3–4 weeks then it seems unlikely to be helpful over a longer period. Perceived positive results should however be viewed with considerable scepticism.

Administration of cimetidine combined with tamoxifen in immunodeficient mice with transplanted melanoma cell lines, has been reported to decrease melanoma growth, but this has not been reported in horses.

Currently cimetidine probably cannot be justified in equine melanoma treatment of any sort.

Cisplatin

cis-diamminedichloroplatinum (cisplatin/DDP) is a first-generation platinum chemotherapeutic agent based on an inorganic platinum compound; it is often called the 'penicillin of cancer drugs' because it is used so widely. Medical grade, or chemically pure cisplatin, is widely available. Although the chemical (known as 'Peyrone's chloride') was first synthesized in 1845, it was only in 1965 that its effects on biological tissues were first discovered. It was approved by the FDA in the USA in 1978, for the treatment of genitourinary tumours in people. It has become one of the standard and most successful chemotherapeutic drugs.

The antineoplastic activity occurs from DNA cross-links and adducts, in addition to the generation of superoxide radicals. Its main function is as an alkylating agent that forms inter- and intra-strand DNA cross-links and, in that way, interferes with DNA synthesis and repair. Inside cells, the chemical facilitates hydrolysis of chloride ligands and these replace cell macromolecules including proteins, DNA and RNA. DNA is accepted to be the key target responsible for the drugs cytotoxicity as a result of the enhanced sensitivity of DNA in repair-deficient cells. The resulting intra-strand and inter-strand cross-linking result in cell-cycle disruption through errors of replication and transcription. There are recognized pathways of DNA repair that are responsible for the ability of normal cells to overcome the intracellular damage. This imparts highly useful tumour-selective effects on certain tumour types that have greater sensitivity than others (Fig. 9.18).

The drug is cell-cycle nonspecific (i.e. it acts at all stages in the cell-cycle). It is a versatile agent that can be used in a variety of malignancies with several different routes of administration, including aqueous solutions for intravenous use, oily emulsions, stable R-gel formulations and slow-release biodegradable beads for intralesional or adjunctive use.

Cisplatin does have significant systemic toxicity implications. Cisplatin cannot be used systemically in horses because it is profoundly emetogenic. Nephrotoxicity is the most well-known and potentially most clinically significant toxicity. Unfortunately, the mechanism for cisplatin nephrotoxicity has not been completely clarified; many hypotheses have been suggested.[43] Other toxicities include gastrointestinal, myelosuppression, ototoxicity and neurotoxicity. Saline diuresis is currently the most accepted way to prevent cisplatin nephrotoxicity. Research has focussed on pharmaceuticals and enzyme/molecular alterations as alternatives to long-term diuresis. No agents have currently been identified that can protect from all

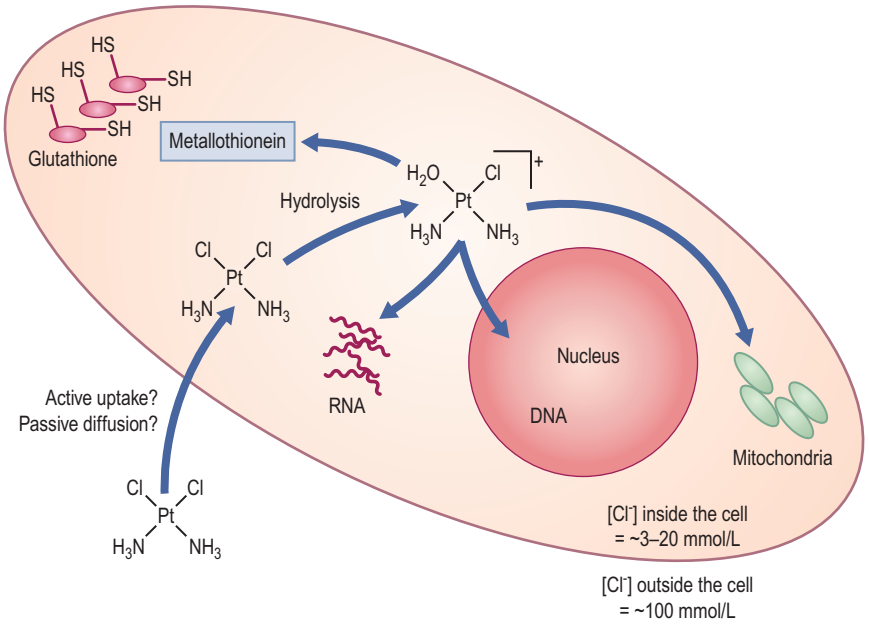


Figure 9.18 The effects of cisplatin. The effects of cisplatin are related to its efficient cellular uptake and its wider intracellular effects that are more severe/less repairable in cancer cells than normal ones.

toxicities. Since in the horse, relatively small doses are used through the restricted use as intratumoral chemotherapy, aspects of systemic toxicity do not generally have be considered in the same way as if the material was administered intravenously in large doses.

Cisplatin has shown activity against osteosarcoma, transitional cell carcinoma, squamous cell carcinoma, melanoma, mesothelioma, carcinomatosis and germinal cell tumours in the dog. In the cat, cisplatin cannot be used because of fulminant pulmonary oedema that occurs at standard doses. Intralesional cisplatin has been found to be very effective in horses for the treatment of squamous cell carcinoma, fibrosarcoma and sarcoid and most soft tissue sarcomas, solitary melanoma and lymphoma (B and T) masses. It is most effective when used in conjunction with surgical excision. It is effective in donkeys, mules and horses and is safe in breeding stallions and pregnant mares.

Particular tumours may be intrinsically resistant to cisplatin and acquired resistance to the effects of cisplatin are well recognized, particularly in human ovarian and bladder cancer. There are, so far, no reports of significant resistance in equine oncology, but increasing use of the material makes it important to recognize that resistance may become a problem. The mechanisms for this resistance are not yet established but there are several options. These include aspects of the gross tumour; the tumour may be resistant or non-responsive in vivo but susceptible in vitro. Decreased cellular cisplatin uptake through altered cell signalling pathways is another option for failure of efficacy; the drug may not rely totally on passive diffusion and so, as might be expected, cells that have a reduced uptake will be more likely to survive. Cisplatin-resistant cells have been rendered much more susceptible under hyperthermic conditions; this is assumed to be a result of increased cell membrane permeability (Table 9.2). This same mechanism may be a reason why electrochemotherapy and other adjunctive measures have been attempted in horses as well as other species. Whether any of these are really of any extra clinical value is debatable.

Table 9.2 Summary of cisplatin resistance mechanisms

1 Increased concentrations of sulphur-containing macromolecules react with cisplatin and sequester the drug within the tissues
2 Reduced cellular transport into the cell results in lower intracellular concentrations and reduced DNA damage
3 Enhanced DNA repair mechanisms eliminate the blockage to replication and transcription
4 Increased cellular tolerance of adducts on the cell DNA
5 DNA sequence modifications in critical regions that reduce the cisplatin targets and the number of adducts that occur

After Pol P, Lippard SJ. Cisplatin and related drugs. In: Bertino JR, ed. Encyclopaedia of cancer, 2nd edn. London: Academic Press; 2002: 525–543.

Practical applications of cisplatin in equine practice

Repeated injection of aqueous solution



Intravenous cisplatin is VERY DANGEROUS and MUST NOT BE USED in this way.

The commercially available aqueous solution contains 1 mg cisplatin per mL of solution. Infiltration of a tumour mass with this solution results in rapid dispersal into the bloodstream (usually <15–20 min), unless there is a temporary cessation of the circulation. This method may be applicable to some localized areas where a proximally placed tourniquet can be used to delay the diffusion of the material. It is seldom feasible to repeat aqueous injections frequently enough to be sure of sufficient uptake of the material. The uptake of the aqueous solution can be significantly improved by combining the intralesional infiltration (and circulatory interruption) with electrochemotherapy (p. 158).

Intralesional emulsion

A stable slow-release emulsion of cisplatin is made up using the raw chemical cisplatin and medical grade sesame oil to

provide 3.3 mg cisplatin/mL emulsion. The preparation of the emulsion is a fundamental requirement. The emulsion must be stable once it is formulated – the use of the aqueous intravenous form (1 mg/mL) is not effective and does not result in the formation of a suitable stable emulsion – it is also liable to leak from the injection sites during use, creating a human and environmental hazard and losing efficacy. The inclusion of SPAN-80 is a considerable help in creating the stable emulsion that is critical to its efficacious and safe use. From a patient-only perspective, there are no known contraindications for its use. It is inherently safe for all equidae and even in pregnant and lactating mares. SPAN-80 is sorbitan oleate/sorbitan (Z)-mono-9-octadecenoate a member of the polysorbates – a class of emulsifiers used in some pharmaceuticals and food preparation. It is often used in cosmetics to solubilize essential oils into water-based products. Polysorbates are oily liquids derived from PEGylated sorbitan (a derivative of sorbitol) esterified with fatty acids. Common brand names for polysorbates include Alkest, Canarcel and Tween. It is available from most formulating chemists and laboratory chemical suppliers.

Note

Carboplatin (*cis*-diammine[1,1-cyclobutanedicarboxylate] platinum) can be used in the same way with minor variations (p. 145).

Commercial preparations of cisplatin solution (1 mg/mL) that are used in human medicine for intravenous use have also been used in equine practice both in the aqueous form and in a stable emulsion.[44] This system produces an emulsion with a lower concentration of cisplatin (0.33 mg/mL) and so the overall volume used needs to be higher, but it seems that the method can be useful and it has a singular advantage in that there is no necessity to handle pure cisplatin (Box 9.3).

Box 9.3 A protocol for preparation of a stable emulsion of cisplatin

Recipe for preparation of cisplatin solution (see Fig. 9.19):

1. Apply protective gloves (double surgical gloves), mask, eye protection and suitable apron/overclothes.
2. Dissolve 10 mg cisplatin in 1 mL water for injection and draw this up into a 2–3 mL syringe (excluding any air).
3. Draw 1.8 mL medical grade sesame oil and 0.2 mL SPAN-80 into another Luer lock 2–3 mL syringe (excluding any air).
4. Connect the two syringes across a 3-way-tap with Luer locks to ensure there is no separation of the syringes during the process. It is essential to ensure that there is no air in system at all.
5. Drive the two solutions together with a pumping action from syringe to syringe until a white/yellow emulsion is formed (usually after 1–2 min). The change is quite obvious and should occur within a minute or two.
6. Test the stability of the emulsion by leaving it standing for 10 min. If stable, it should show no signs of separation. This emulsion then contains 3.3 mg cisplatin/mL.
7. Inject into the tumour in orthogonal planes as shown in Fig. 9.19).

Note: The use of the aqueous solution of cisplatin is more difficult under this method, since it is more difficult to achieve a stable emulsion and then there is a heavy leakage of the material from the entry ports. This may not then be effective and also causes unacceptable leakage and environmental contamination. (Reprinted from Theon AP. Intralesional and topical chemotherapy and immunotherapy. Vet Clin N Am Equine Pract 1998; 14:662–664, with permission.)

The placement of the emulsion within a tumour, such as a sarcoid or a squamous cell carcinoma, is critical to the success, since the diffusion of the chemical is limited to 0.5 cm from the depot. A parallel row or 'field block' pattern of injections is made so that columns of emulsion are laid 0.6–0.8 cm apart throughout the tumour. Thick tumours will necessarily require layers of injection (Fig. 9.19). Multiple planes of injection should be at right angles to each other if possible to ensure even distribution through the tumour mass. When the texture of the emulsion is correct, there should be no leakage from the sites of needle entry. It is critical to treat a margin of normal tissue both laterally and in depth to ensure that microscopic deposits of tumour cells do not extend from the gross tumour into the apparently normal surrounding of the tumour. The volume of the tissue to be treated around the gross tumour, i.e. the biological margin, is the same as the one that would have to be resected to achieve a satisfactory and histologically complete surgical excision.

Since the injections need to be carefully positioned, and since multiple injection sites have to be used, and since spillage and wastage should be avoided as far as possible, general anaesthesia may be required. In many circumstances, it is be possible to carry out the procedure understanding sedation and local anaesthesia, but it is clearly more difficult to control leakage and movement of the patient. If the emulsion is truly stable it should not separate and an ideal procedure has no significant leakage.

General anaesthesia is clearly indicated for lesions on the hind legs and sheath for safety reasons. The procedure can usually be performed on an outpatient basis.

Repeated procedures up to 4 times at 2–3 week intervals are used using the same predetermined dose of cisplatin/volume of emulsion each time, regardless of the possibility of a decrease in the size of the tumour over the course of treatment.[25,26]

Where this procedure is used as an adjunctive measure to surgical excision, treatment can be delayed for 2–3 weeks or can be used immediately at the time of surgery; there is no apparent harmful effect on healing. There is merit in treating at the time of surgery since the material can be placed accurately into the surrounding and deeper tissues; the treatment can be continued in the event there is histological evidence that no margin of excision has been achieved. In the event that a good margin is achieved, the procedure can of course be halted.

Factors that might influence the decision relating to the timing of the first cisplatin treatment include:

- Tumour location and anatomic structures involved
- Extent of surgical resection
- The method of wound closure (open or closed/first or second intention healing): Postoperative treatment is usually indicated when a large bulk of tumour has been removed and there is a significant risk of wound breakdown
- Evidence of residual tumour and the volume of residual tumour (microscopic or macroscopic) (*Is the surgeon satisfied with the margin and is there histological evidence of a safe margin?*): Immediate (frozen) section identification of tumour margin safety can be very useful, but is seldom available to veterinary surgeons. Delayed-onset treatment is usually made when there is only microscopic evidence of incomplete surgical removal.

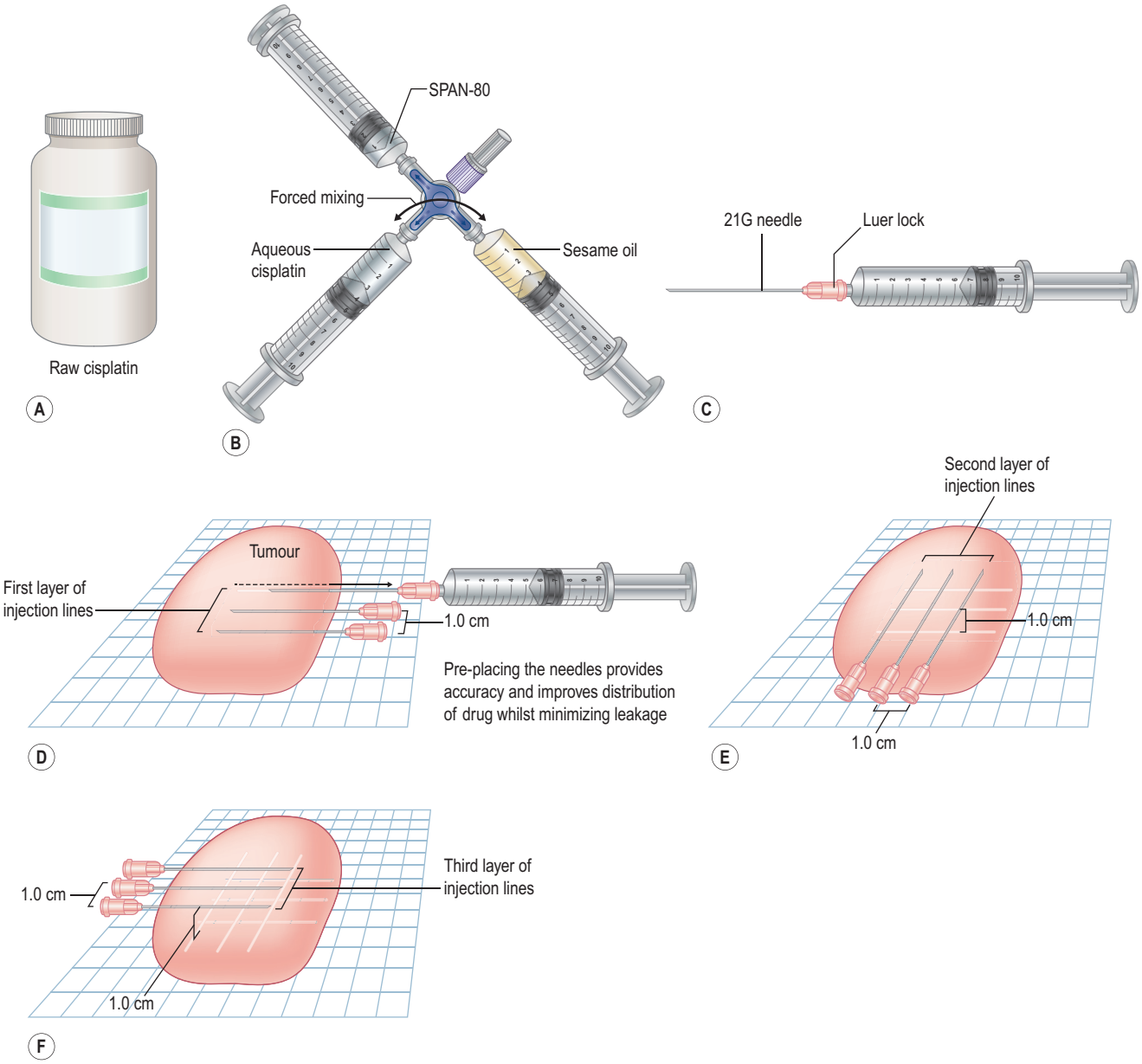


Figure 9.19 Cisplatin injection method – preparation of emulsion, injection method and pattern in solid tumour. The emulsion can be stabilized by the inclusion of SPAN-80 administration needles is a helpful procedure so the pattern of injection can be accurately defined. **(A)** The raw cisplatin is dissolved in an appropriate amount of water. A selected volume (x) of the solution is drawn into a 5 mL syringe and double the volume (2×) of medical grade sesame oil is drawn into another syringe. A third syringe *can* be prepared containing 0.5 mL SPAN-80 emulsifier. **(B)** If SPAN-80 is used, it should be mixed with sesame oil first and the two syringes are then coupled to a three-way tap with full Luer lock safety protection. ALL AIR IS DRIVEN OUT OF THE SYSTEM. The tap is opened to allow the two components to be forced from syringe to syringe until the emulsion is formed – the pressure required will suddenly increase. **(C)** The syringe of emulsion is prepared for use using a 19G needle of an appropriate length. **(D,E)** Pre-placement of the needles at 0.75–1 cm intervals in orthogonal planes provides greater accuracy of injection and planning. The material is injected with moderate pressure as the needles are withdrawn. **(F)** Deeper tumours will require injection at 1 cm depths in the right angle planes.

Where the tumour has been debulked rather than removed or where it is certain that tumour is left, immediate treatment is usually indicated

- Proven tumour behaviour (usually derived first from diagnostic biopsy material) is a strong indication for prior tissue sampling. It would be wise to start early in proven highly active tumours
- Treatment should be delayed until any overt infection at the site has been controlled. Prophylactic antibiotic treatment is possibly indicated after each treatment session in any case.

There will be circumstances when one or more of these factors conflicts with others. Then, a careful clinical judgement can be taken on the merit of starting immediately or delaying the onset of cisplatin emulsion therapy.

The effects of the treatment remain local and include localized swelling, ulceration and necrosis; all these are self-limiting and usually resolve quickly. Treatment with analgesics and non-steroidal drugs is usually undertaken in any case to try to limit the harmful effects. No treatment-related systemic effects/toxicities and no hypersensitivities have been reported. The cosmetics of treatment are

impressive. Scarring is minimal and even hair loss and hair colour changes are not prominent features of the method. Repeated treatments do not appear to have any tendency to cause any unacceptable increase in scarring or side-effects.

A study on a large number of tumour cases, including sarcoid, squamous cell carcinoma, soft tissue sarcomas, cutaneous lymphomas and melanomas, in horses, donkeys and mules treated using the oily suspension of cisplatin found an overall cure rate, defined as local control at 4 years, of 93.3%.[45] Cure rates for the individual tumour types were 96% for sarcoid and lymphoma, 88% for squamous cell carcinoma, 85% for soft tissue sarcoma and 81% for melanoma. These results are remarkably good. Treatment was reported to be well tolerated, but local reactions were more likely to occur and to be more severe after the third and fourth treatment sessions. This study confirmed that the precise treatment protocol and the tumour stage were significant prognostic factors for tumour control. Additionally, treatment efficacy was lower for large tumours, those with gross postoperative residual disease and those that had been treated previously with other modalities. A total of 14 horses with 23 sarcoids were treated with an oily emulsion of cisplatin with complete regression in 78% of the tumours. No systemic side-effects were encountered.

A slowly progressing subcutaneous periocular neurofibrosarcoma over the right supraorbital process was successfully treated using an emulsion of cisplatin injected 3 times at 2 weeks, 5 weeks and 8 weeks after surgical debulking.[46] This type of response illustrates that the intervals between injection are not yet established, but also that this aspect may be less important overall than the amount of chemical injected. In this case and others who reported using the same method, a dose rate of 1 mg cisplatin is used per millilitre of tumour volume.

There are some complications that can arise relating to both the placement of the material and the density of the tumour. Difficulties have been found with the intralesional injection technique, including difficulty in performing injections in periocular sarcoids, leakage of the cisplatin solution following injection and unpredictability in the consistency and stability of the emulsion.[20] There is also a risk of accidental injection for the veterinarian administering the cisplatin, especially if there is inadequate patient restraint or analgesia at the site of the injection, so general anaesthesia is recommended (Fig. 9.20).

In some cases, it is hard to be precise enough to ensure even distribution of the chemical emulsion through the tumour and, in any case, it is important that the injections are extended to the outer limits of the tumour and if possible 1 cm beyond any clinically detectable margin; i.e. the theoretical limit of histologically detectable tumour.[47] The use of a 21G needle of suitable length is important – in theory at least, the emulsion is injected uniformly as the

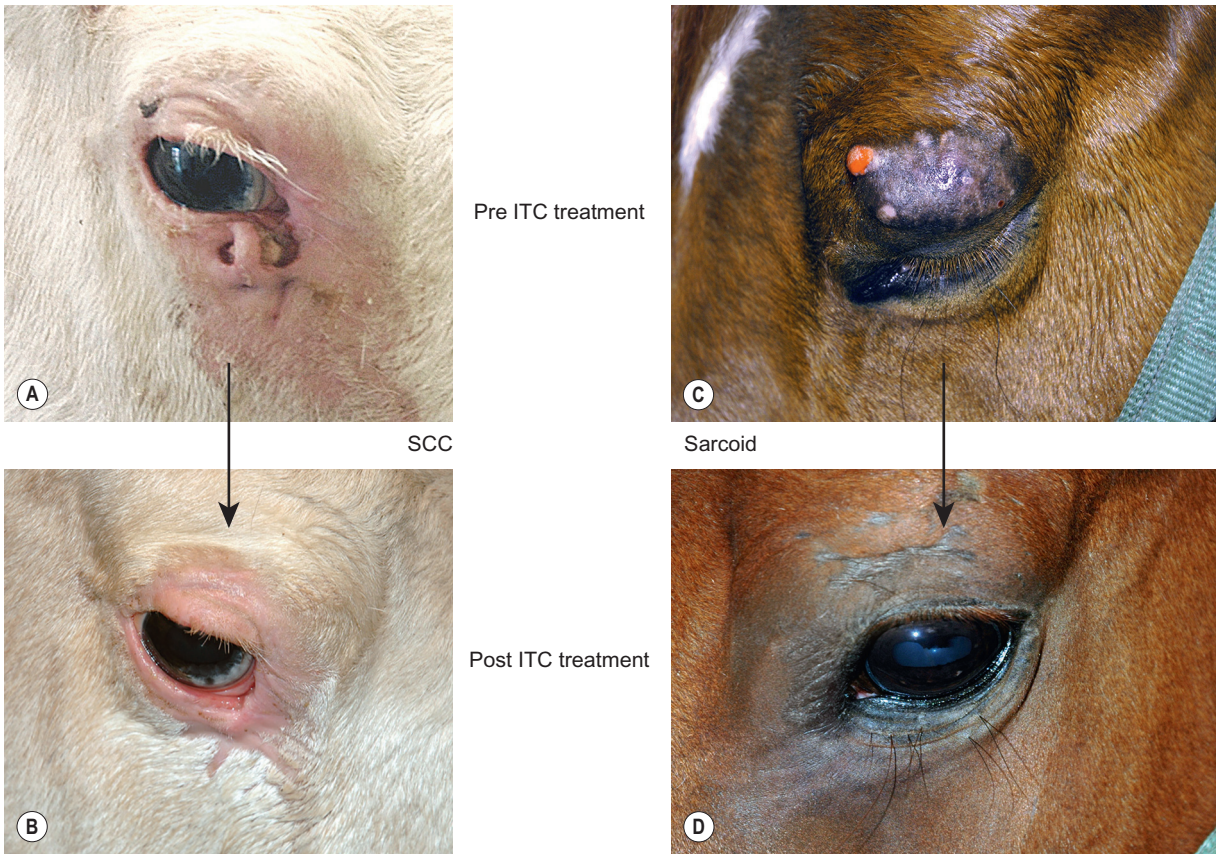


Figure 9.20 The effects of intratumoral cisplatin (ITC) emulsion chemotherapy can be very satisfying. This highly destructive, malignant palpebral carcinoma **(A)** was treated with intralesional cisplatin emulsion and this resulted in a very acceptable resolution without recurrence **(B)**. The same method can also be used with confidence in the treatment of sarcoid. Here, a large diffuse and complex sarcoid in the upper eyelid of this horse **(C)** was given a three treatment course of intralesional cisplatin emulsion and a very acceptable resolution was obtained **(D)**. Note the regrowth of hair also. This tumour also had no recurrence. *(Figures courtesy of Alain Theon.)*

needle is withdrawn from the tumour. It is probably better to start at the depth of the tumour where this can be defined by either clinical means or through other imaging modalities, such as ultrasonographic examination. In practice, however, the density of the tumour may make this less feasible and less reliable. Similarly, in soft tumours it may be difficult to contain the volume and distribution correctly. Nonetheless, with care and patience, the system is known to have a significantly beneficial effect in sarcoid, carcinomas, fibrosarcoma and some localized melanomas and lymphoma lesions. Although there are obvious constraints, the emulsion can also be used as an adjunctive measure for surgery – the material is then injected along the margins of the surgical wound bed.

The emulsion has also been used in conjunction with high-dose radiation brachytherapy (p. 179) and of course electrochemotherapy (see p. 158). In the former, it is used in emulsified form, whilst in the latter the aqueous form is preferred.

Cisplatin is mutagenic and carcinogenic, and self-protection is clearly essential. The process of injection requires that meticulous personal precautions are taken to avoid contact with the cisplatin – the raw material is particularly dangerous. There are very important health and safety issues regarding the handling of the raw material and the preparation, as well as use of the emulsion, particularly in respect of potential repeated human contact with an alkylating agent of this potency. Operators and handlers of the animal must wear masks, protective glasses, gloves and a protective suit. Urine and faeces disposal might be an issue in some circumstances and owners of horses undergoing cisplatin treatment (by any method) must be given appropriate advice. Use of the material should probably be restricted to specialist oncology centres where its use can be properly controlled.

Slow-release biodegradable beads

Slow-release biodegradable beads are available commercially from the maker (*MATRIX III*, ROYER Inc., USA) or from local agents for the company. The beads are packed in sterile containers each containing 3 × 3 mm beads. Each bead weighs around 25 mg and each incorporates 1.6 mg cisplatin.

The method of placement varies depending on the tumour type, the location and the need to debulk large lesions to minimize the amount of cisplatin (number of beads) required. In some circumstances, the beads can be safely implanted in standing sedated horses, but in others general anaesthesia may be required.

The accuracy of placement is an important aspect of the procedure if a good result is to be achieved and this is the most problematic aspect of their use. The beads should be placed 9–10 mm apart, with particular attention being given to the peripheral regions of the tumour (Fig. 9.21). Tumours over 1.5 cm in diameter may require surgical debulking (either by sharp excision or by laser surgical excision), although this clearly makes the placement of the beads more problematic unless the wound can be closed afterwards. Where tumours are surgically removed/debulked prior to placement, the beads are carefully located in stab incisions made along the periphery of the wound site at intervals of 1–1.5 cm. Each stab incision should be closed with a small absorbable suture or stapled to ensure proper retention of the bead. The material only diffuses 0.5 cm away from the bead itself and so placement is a major challenge, especially around the periphery and within the deep bed of a tumour excision site.

A variety of skin tumours in the horse, donkey, zebra and mule have been reported to respond positively to the placement of the beads. In a study involving the treatment of sarcoid, fibrosarcoma, fibroma, peripheral nerve

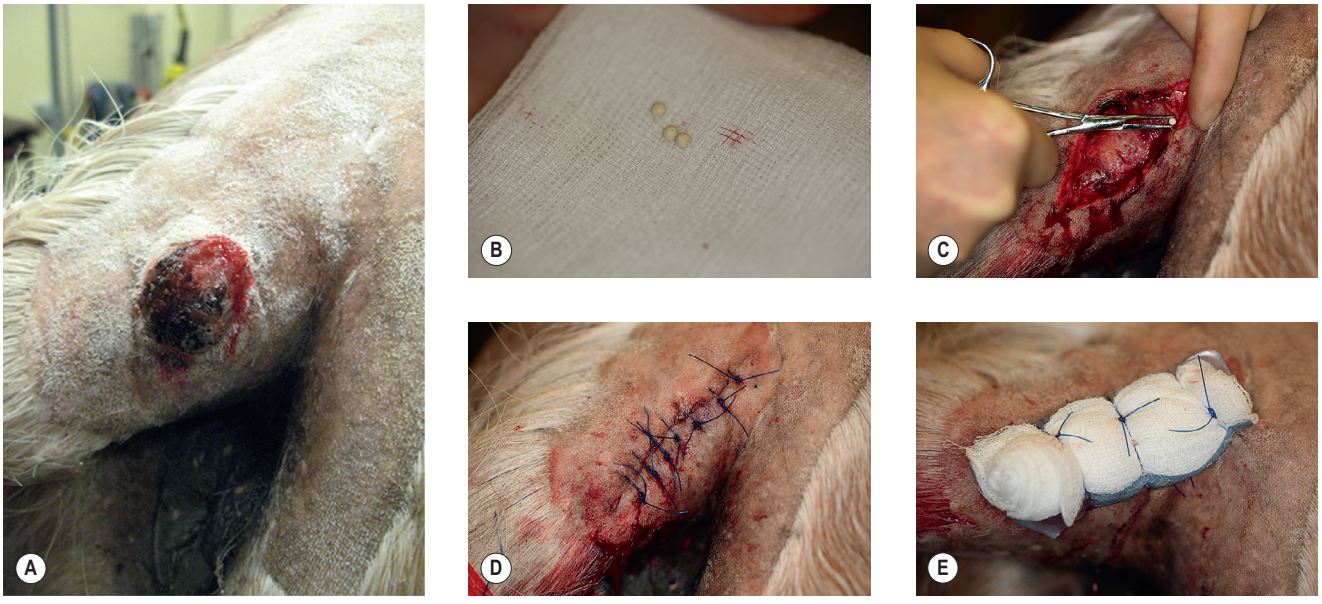


Figure 9.21 A biopsy showed a malignant melanosarcoma. **(A)** This 6-year-old cremello horse was presented with an ulcerated darkly pigmented mass on the tail. A biopsy showed it to be a malignant melanosarcoma. No evidence of metastatic dissemination was detected. **(B,C)** The tumour was removed with wide surgical margins and 22 cisplatin biodegradable beads were inserted into the periphery and base of the surgical site at 0.5 cm intervals. **(D,E)** The wound was closed and stented. Surgical pathology showed that a safe margin had been achieved overall, apart from a small area on the proximal margin. Routine follow-up at 3 months and at 4 years showed no recurrence at the site.

sheath tumour (schwannoma), squamous cell carcinoma, melanomas lymphoma, adenocarcinoma and basal cell carcinoma, outcome results suggest that implantation of cisplatin-containing biodegradable beads, with or without tumour debulking, is an effective primary and adjunctive treatment. In one study, surgical debulking by sharp excision or laser ablation was performed prior to bead implantation.[27] Over 90% of fibroblast tumours (sarcoid, fibroma, fibrosarcoma and schwannoma), 60% of carcinoma cases and over 95% of melanoma lesions were resolved and relapse-free 2 years after treatment. Adverse effects reported in this study were minimal. The results from this relatively small study suggest that implantation of cisplatin-containing biodegradable beads, with or without tumour debulking, may be an effective treatment for a variety of skin tumours in Equidae. As an adjunctive measure following surgical reduction, it can be used in either bead or emulsion forms.

Cyclophosphamide

Cyclophosphamide is a synthetic alkylating agent, chemically related to the nitrogen mustards, that has established antineoplastic and immunosuppressive activities. The main effect of cyclophosphamide is due to its metabolite phosphoramide mustard.[48] It is a pro-drug and it is converted to the active metabolites aldophosphamide and phosphoramide mustard in the liver. These metabolites impart its chemotherapeutic activity by inducing DNA cross-linkages and by binding directly to DNA, thereby inhibiting DNA replication and initiating cell death. However, the metabolites are only formed in cells that have low levels of aldehyde dehydrogenase enzymes (ALDH) and so it has a relatively narrow spectrum of indication. Although the drug is rarely used in horses, it has been used as part of a combination multidrug chemotherapeutic regimen in the treatment of some forms of equine lymphoma[49–51] (p. 524) and there are individual cases that have responded to its use as part of a combined chemotherapy programme.[49] In the horse, remission of a thoracic lymphoma was achieved by use of a chemotherapeutic protocol consisting of administration of cytarabine, cyclophosphamide and prednisolone (Table 9.3). No adverse drug reactions were encountered during treatment.

Doxorubicin

Doxorubicin is an anti-tumour (cytotoxic) anthracycline antibiotic, isolated from cultures of *Streptomyces peucetius* var. *caesius*. It exerts its anti-cancer effects by binding to nucleic acids (intercalation), and therefore is known to have strong inhibitory effects on DNA synthesis, RNA synthesis and DNA repair. DNA helicases (enzymes that support separation of duplex DNA strands for DNA processing) are significantly inhibited and this is probably one of the major reasons why the drug is so effective.[52] Doxorubicin can also inhibit topoisomerase-II, which is a crucial component of the cell-cycle. Doxorubicin promotes the intracellular formation of free radicals that oxidize DNA in mitochondria and the cell nucleus.

Cells treated with doxorubicin undergo apoptosis (p. 29). This process minimizes the secondary effects of cell death usually associated with necrosis and may be an integral component of the cellular mechanism of action relating to its beneficial therapeutic effects and to its toxicities, or both.

Animal studies have shown activity in a spectrum of experimentally induced tumours. Additionally, it has a significant immunosuppressive effect and, also, significant carcinogenic properties in rodents at least. It also has a variety of known toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and testicular atrophy to testes, in rats and dogs at least.

Notwithstanding the unwanted side-effects, there is increasing evidence of its value in clinical tumour management in horses and the drug is gaining considerable reputation for efficacy against a variety of hitherto untreatable tumour states. Doxorubicin has been used successfully in human medicine to produce regression in disseminated neoplastic conditions, such as acute lymphoblastic leukaemia, acute myeloblastic leukaemia, neuroblastoma, soft tissue and bone sarcomas, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma and malignant lymphoma. There are few reported attempts to use the substance in tumours other than lymphoma, but it does not appear to be as effective in some tumour types in horses as in other species. It was reported to fail in the treatment of an aggressive leiomyosarcoma of the genital tract of a mare.[53] Its clinical use is limited by its dose-related side-effects, including bone marrow toxicity, gastrointestinal, acute and cumulative cardiac damage and nephrotocity.[54]

An interesting use of the drug has been described in the management of neurectomy-induced 'neuroma' following surgical neurectomy of the palmar digital nerves. Whether this is a genuine tumour is another consideration but the drug had unacceptable secondary effects on the wound site, so it is probably not of value in the treatment of neuroma in horses.[55]

Doxorubicin has demonstrable dose-independent pharmacokinetics in the dose range of 30–70 mg/m^2 and this is the effective range for its clinical use in horses. Horses do seem to be somewhat more 'tolerant' of the drug than other species and there is probably a wider margin of safety in horses than in most other species. That of course does not mean either that it can be treated casually or that it will have no clinical side-effects. The latter means that full monitoring of metabolic and cardiac functions must be carried out meticulously, whenever it is used.

Table 9.3 The use of cyclophosphamide in horses for the treatment of lymphoma using a multimodality treatment regimen

Drug	Dosage (/m^2)	Route	Frequency/Interval	Regimen	
Cyclophosphamide	200 mg	i.v.	14 days	Single agent (seldom used)	
				CAP	Cyclophosphamide (200 mg/m^2) Cytarabine (1–1.5 g total dose) Prednisolone (1 mg/kg)

Practical applications of doxorubicin in equine practice

The method of use for treatment is actively being developed for the management of advanced or multicentric tumours, including lymphoma, carcinoma, melanoma and sarcoid. The recommended maximum dose of doxorubicin is 70 mg/m^2.[54]

The drug is administered under strictly controlled conditions as dictated by guidelines on chemotherapy used in veterinary oncology.[56]

1. The calculated dose of doxorubicin is drawn into 50–60 mL Luer lock syringes.
2. A downward-facing intravenous short-stay catheter is placed in the jugular vein under aseptic precautions. A continuous saline infusion is maintained throughout the procedure at approximately 400–450 drops/min to ensure continued dilution of the drug during administration.
3. An intravenous dose of flunixin meglumine at 0.5 mg/kg and an intramuscular injection of diphenhydramine hydrochloride at 1 mg/kg BW is administered 30 min before the infusion starts.
4. Using an infusion pump, the total dose is administered via the side port of the infusion set over a period of 1 h (Fig. 9.22), so that the final solution administered via the catheter is 5 mg/min at 1 mg/mL.
5. Dose-limiting side-effects include hypersensitivity reactions and myelosuppression/neutropenia (Fig. 9.23). The former usually develops 4–5 h after treatment. Adverse effects are likely dose-dependent but not schedule-dependent and so are unlikely to be a true hypersensitivity response. The visible side-effects are mitigated rather than eliminated by premedication with flunixin and diphenhydramine.
6. The procedure is repeated at 3-weekly intervals for 6 cycles.

Precautions

All urine and faeces (and soiled bedding) is handled as a biohazard for a period of 7 days. Since the procedure is performed on an outpatient basis, owners should be instructed to use gloves and, of course, pregnant women and children are not permitted to handle or touch the horse or its soiled bedding.

Outcome

Inevitably, since the procedure is largely restricted to severe advanced cases, the prognosis for any particular case remains guarded. Animals that are in good body condition seem best able to tolerate the procedure and are likely to carry the best prognosis.

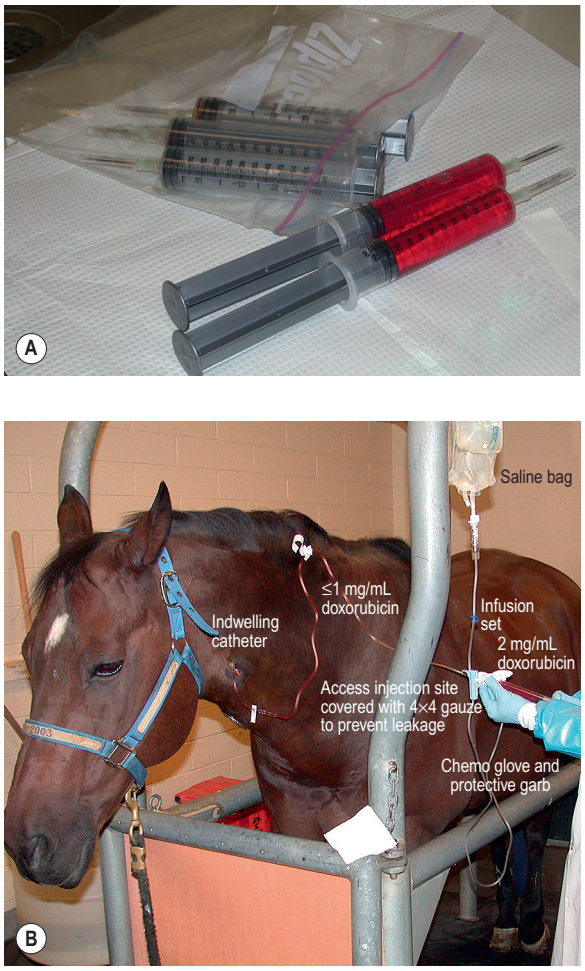


Figure 9.22 The handling, administration and disposal of the drug and the administration of doxorubicin is carried out strictly in accordance to the requirements laid down in the protocols for the use of chemotherapeutic agents in veterinary medicine. **(A)** The calculated dose of doxorubicin is loaded into Luer lock syringes with secure caps, within a biosecurity cabinet (hood) and delivered to the treatment site in a sealed bag. **(B)** The patient is securely restrained and a downward-facing, short-stay jugular catheter is inserted under aseptic precautions and secured appropriately. The drug is administered into the injection port of the three-way tap, over a 1 h period, using either slow manual injection over that period, or preferably using a powered injector, so that a concurrent saline infusion running at 450 drops per minute results in the administration of 0.2 mg/mL and a dose of 5 mg/min. The system is entirely closed with Luer locks and there is no reason for any contamination. Following infusion, the entire administration equipment is removed intact and disposed in accordance with local regulations for biohazardous materials. *(Figures courtesy of Alain Theon.)*

5-Fluorouracil

This is a fluorinated uridine compound that is metabolized intracellularly to its active form, fluorodeoxyuridine monophosphate; the active metabolite inhibits DNA synthesis by inhibiting production of thymidine and so it is classified as an antimetabolite. It is cell-cycle specific, acting in the S-phase.

It is available in an injectable solution for intravenous (and intratumoral/intralesional) use (Fig. 9.24) and as a 5% cream for topical use (Efudix). In both its forms, 5-fluorouracil is a useful treatment option for some superficial tumours and compares favourably with several other similar materials.[22]

Practical use of 5-fluorouracil

Intratumoral injection

The intratumoral use of injectable (intravenous) 5-fluorouracil (50 mg/mL) compares favourably with most other treatment modalities for sarcoids, in horses and donkeys, with a long-term successful resolution rate of 61.5%.[57] Intratumoral injections can be made once a week for up to 5–7 doses. Smaller lesions (<13.5 cm^3) that have not been subjected to previous therapeutic interference are more likely to respond favourably in the long term, than larger, more aggressive

tumours (≥13.5 cm^3) that have had been subjected to repeated (failed) treatments.

When using this method, a dose of around 5–10 mg/mL of tumour should be used at weekly intervals. If a positive response is not achieved by the seventh injection, it is unlikely to be effective. Injections must be made with care and suitable precautions, since the material is mutagenic and carcinogenic. A pressure syringe is a useful item for ensuring intralesional injection. Suitable operator protection must be afforded.

A slow-release method using a stable emulsion produced in a similar way to cisplatin (p. 141) may provide a therapeutically better and more convenient mechanism for its use.



Figure 9.23 The side-effects with doxorubicin are relatively benign in most horses when the dose is carefully calculated. However, hair loss is a prominent feature and loss of mane and tail hairs is more persistent than loss of body hairs. This picture shows a case that had received intravenous doxorubicin for treatment of lymphoma. *(Figure courtesy of Alain Theon.)*

Topical application

Three horses with superficial ulcerative squamous cell carcinoma were successfully treated with topical 5-fluorouracil.[58] Two of them remained in remission after a single course of treatment and the third case was controlled by the application of a 5% 5-fluorouracil cream for 7 days every 6 weeks. No systemic side-effects were observed, but there was a localized inflammatory reaction in the skin in each case. The topical route can also be an effective treatment of superficial verrucose sarcoid (Fig. 9.25).

Topical ophthalmic drops containing 1% 5-fluorouracil can also be used (q 8 h) to treat superficial (in situ/intraepithelial) conjunctival or corneal carcinoma or, more usually, are used as adjunctive therapy following surgical removal of bulk tumour.



5-Fluorouracil solution cannot be administered intravenously to horses since they suffer from severe intestinal side-effects that may be rapidly fatal.

Imiquimod

Imiquimod is an immune response modifier with anti-viral and anti-tumour properties. It is manufactured as a 5% cream (Aldara™, 3M Health Care Ltd., Leicester, UK). It is mainly used to treat human genital warts, solar keratoses and basal and squamous cell carcinoma, where its use has expanded recently, both as a primary anti-cancer drug and as an adjunctive treatment alongside surgery or other ablative methods.[59]







Figure 9.24 Invasive fibrosarcoma treated with a preliminary series of intralesional injections of aqueous 50 mg/ml 5-fluorouracil. (A,B) This invasive fibrosarcoma was treated using a preliminary series of intralesional injections of 50 mg/mL aqueous solution of 5-fluorouracil. A total of 500 mg was injected into the lesion every 72 h for four injections and then a stable emulsion containing 33 mg/mL was injected every 2 weeks for four injections using 0.5 cm orthogonal planes of injection. No adverse side-effects were encountered. **(C)** The tumour resolved slowly over 4 months, resulting in an acceptable cosmetic outcome without functional compromise. No recurrence of the tumour was reported.

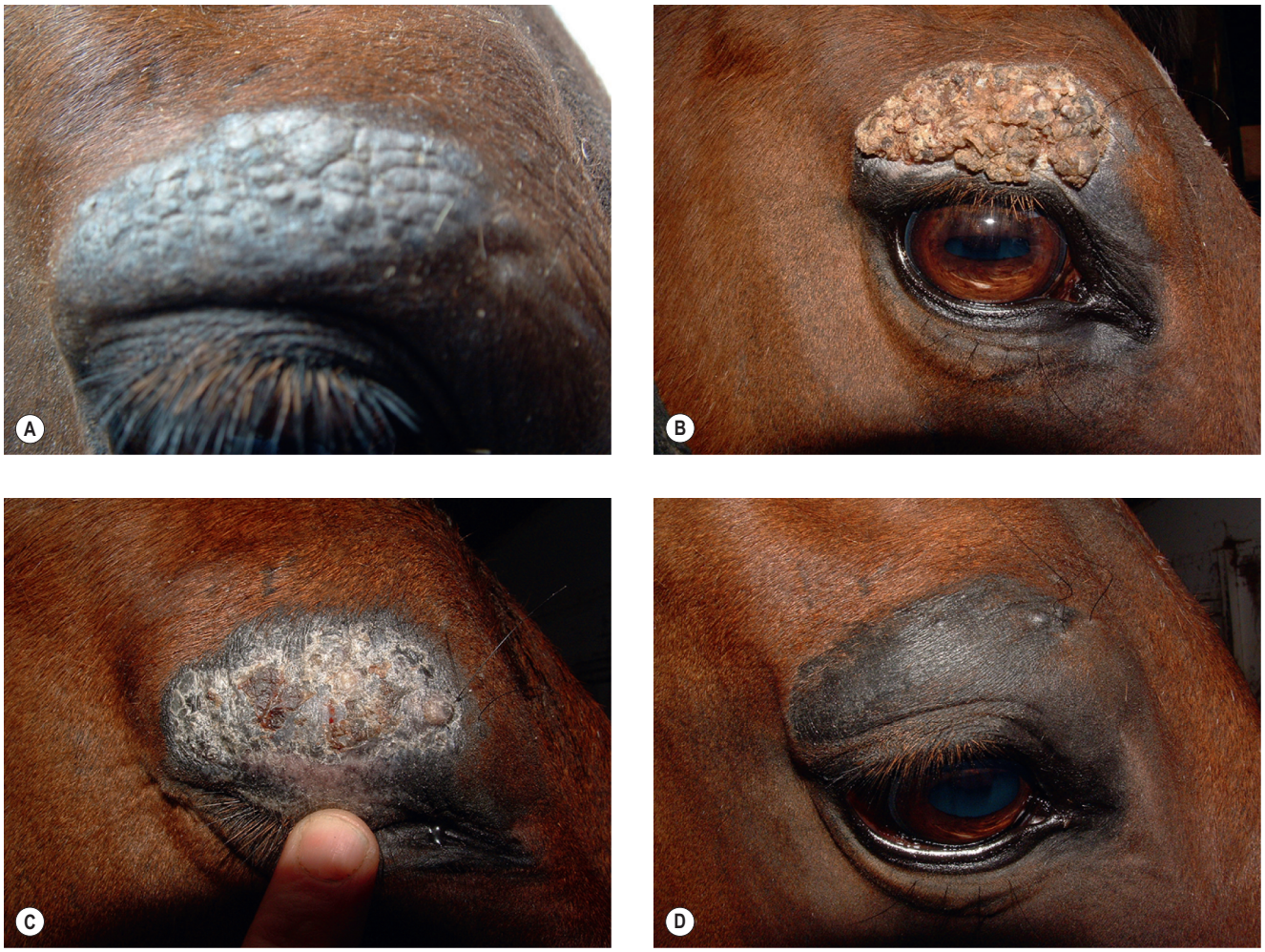


Figure 9.25 Topical treatment with 5% 5-fluorouracil cream for a diffuse verrucose sarcoid. **(A)** This diffuse verrucose sarcoid was treated topically using twice-daily applications of 5% 5-fluorouracil cream (Efudix™, Meda Pharmaceuticals, UK) for 10 days. **(B)** Following a moderate and painful exudative site, a crust developed over the following 21 days. **(C)** The crust sloughed away over the ensuing 3–4 weeks. **(D)** After 6 months, the area was hairless and visually sarcoid-free (and remained so for at least 4 years). *(Figures courtesy of Ricky Farr.)*

Several other tumour types have been reported to respond, including some haemangiosarcoma cases. However, the consensus is that it is much less effective against melanoma.

The precise mechanism of action by which imiquimod and its analogues activate the immune system is not clear. However, imiquimod probably works by stimulating the immune system to release a number of cytokines, which are important in elimination of viruses and destroying of cancer cells.[60] It is, however, clear that imiquimod activates immune cells through the toll-like receptor 7 (TLR7), commonly involved in pathogen recognition. Cells activated by imiquimod via TLR-7 secrete cytokines (primarily interferon-α (IFN-α), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α)). There is evidence that imiquimod, when applied to skin, can lead to the activation of Langerhans cells, which subsequently migrate to local lymph nodes to activate the adaptive immune system.[61,62] The imiquimod is taken up by TLR7 on certain immune cells that are found in the outside part of the skin (the epidermis); these receptors are expressed more in some individuals and in some skin lesions than in others.[63] New research has shown that imiquimod has anti-proliferative effects in vitro that are independent of immune system activation or function. Imiquimod exerts its effect by increasing levels of the opioid growth factor receptor (OGFr); blocking this with siRNA technology resulted in loss of any antiproliferative effect of imiquimod.[64] Other cell types activated by imiquimod include natural killer cells, macrophages and B lymphocytes.

When used to treat skin cancers and pre-cancerous lesions, imiquimod results in inflammation, which may destroy the lesion. The degree of inflammation is quite variable from case to case, but most horses show moderate to severe inflammation during the treatment period. There are, however, some that show less reaction and some sites are more or less likely to have a stronger response. The face and ears are usually markedly affected.

Imiquimod is particularly useful on areas where surgery or other treatments may be difficult, complicated or otherwise undesirable, especially the eyelids and ears of horses, but it does have a relatively crude effect and its spectrum of activity is relatively narrow. However, it has been shown to have a significant effect in sarcoid treatment and, since this is by far the commonest tumour in the eyelid and skin of the eye, that makes the drug a useful agent in

equine oncology.[19] As experience of its use increases, its value is becoming greater with several unusual tumours being treated successfully.[65] It has also been used in the treatment of viral plaques in the ears. Its spectrum of anti-tumour activity in horses might be found to be wider in the future.

Practical use of imiquimod (Aldara™)

Imiquimod is available commercially as a 5% cream in 1 gram sachets containing 50 mg of imiquimod in an off-white oil-in-water vanishing cream base.

A course of treatment ranges from 4 to 16 weeks; these variations add to the management requirement for the treatment method.

- The material is applied evenly and carefully over the lesion and gently rubbed until it is no longer visible – this will limit the run-off. The owners are usually quite capable of applying the material after suitable training, but regular checks need to be made in case variations in duration, frequency and interval need to be applied (Fig. 9.26).
- Excessive spread and run-off should be avoided
- Repeated applications are made every alternate day for 10 applications, then every third day thereafter for up to 12–14 weeks. It is important to apply the material to the fresh surface of the tumour site and so a careful wipe with a gauze swab moistened with diluted chlorhexidine is used to remove 'the previous application' before the new one is applied. This is a process that can be painful and resented by the horse.
- The progression of the treatment should be carefully monitored; it may be necessary to apply more or less at each application or to lengthen the period between applications depending on response.
- Once the inflammation has settled, there is generally a good or excellent cosmetic result with little scarring and hair loss is not a feature of the treatment – of course the tumour condition may leave little chance of hair regrowth, but imiquimod should probably not be blamed entirely for hair loss at a treatment site.

Melphalan

Melphalan is an alkylating agent which is, like other alkylators, not cell-cycle phase specific. It has been widely used in the management of plasma cell myeloma, in particular in humans and cats; it has been suggested that a dose of 3.5–7.0 mg/m^2 administered orally every 24 h for

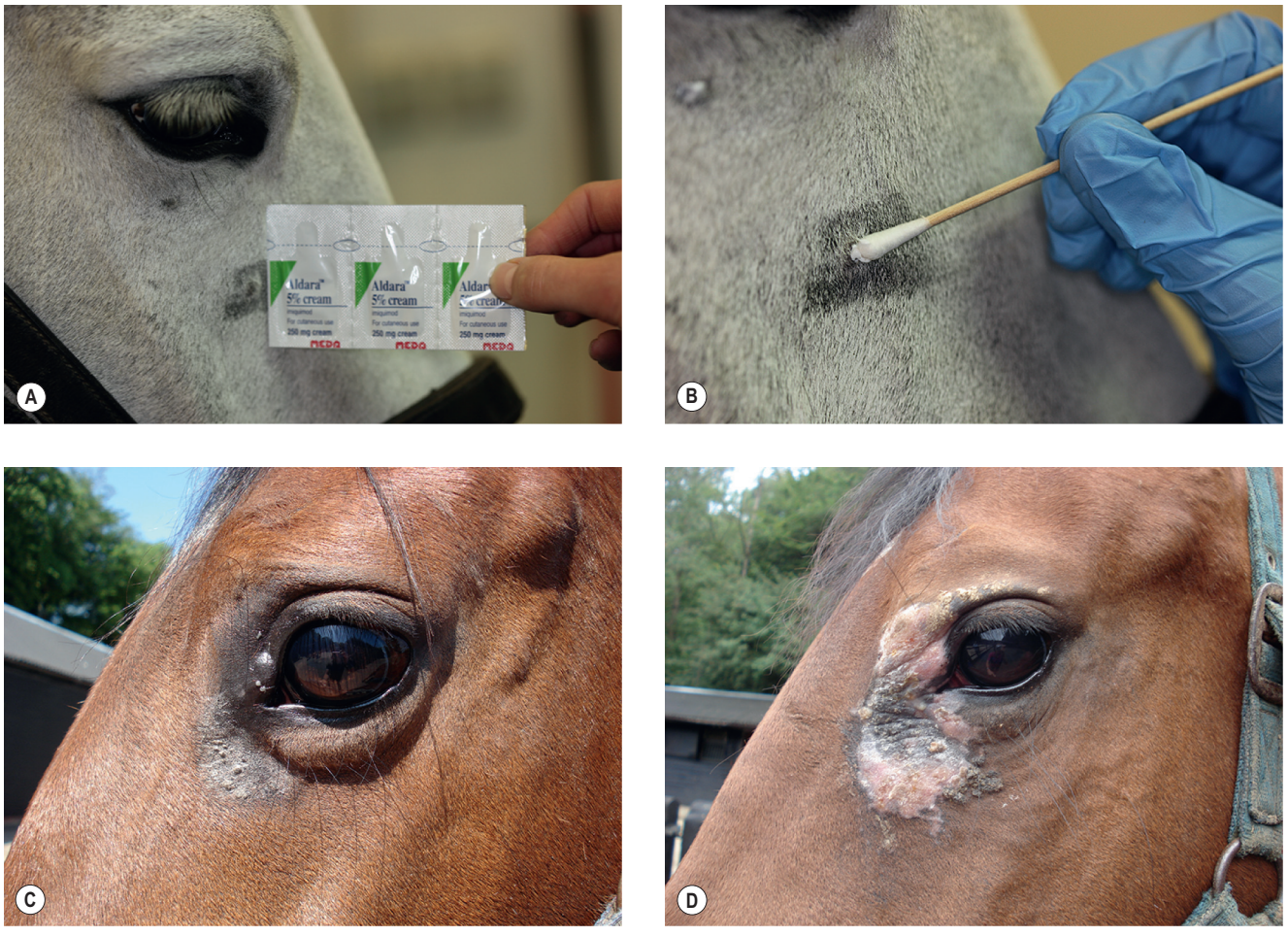


Figure 9.26 The use of imiquimod on small superficial sarcoids has gained a good reputation. It is difficult to use in sensitive areas, such as the ear and face because it does cause considerable superficial inflammation and excoriation of the epidermis in particular. **(A,B)** It is best applied as precisely as possible, even using a cotton bud to apply and rub it into the site. **(C,D)** The material and its effects are hard to keep confined and usually the 'reaction' is wider than the treatment zone as a result of spreading extension onto the surrounding skin. *(Figures C and D courtesy of Marta Ferari.)*

5–10 days and then once every 3 weeks might be an effective treatment for the equine condition[66]; the number of plasma cell myeloma cases in horses is extremely low, so there are no case series that provide any useful information beyond the anecdotal reports of 'successes' and failures.

Mitomycin C

This anti-tumour antibiotic is activated in vivo to an alkylating agent. Its action is independent of the cell-cycle stage and its effects are attributable to DNA cross-linking and consequent inhibition of DNA synthesis and function. Mitomycin C has gained a good reputation in the treatment of ocular and other squamous cell carcinoma states in horses.[23,24]

Topical mitomycin C is best regarded as an adjunctive treatment that can be used best after surgical tumour reduction has been carried out (see p. 617). It is probably not suitable as a sole treatment for dense or extensive tumours. Mitomycin C has an added benefit in inhibiting fibrosis in scars on the cornea in particular and this property could be seen to be singularly beneficial following surgical removal of corneal intraepithelial carcinoma lesions.[67]

Practical use of mitomycin C

Mitomycin C is available in 2 mg and 15 mg vials for reconstitution with water for injection. It is used in two ways:

Ophthalmic drops: (0.02 mg/mL)

To make up this solution, 10 mL of water for injection is added to the 2 mg vial. The material made up in this way will retain its efficacy for up to 3 days provided that it is kept refrigerated. Drops are applied twice daily for 14 days and a break is then taken for a further 14 days. Repeated courses may be required.

Intralesional injection

Mitomycin C can be used intralesionally in aqueous or in slow-release oil emulsion forms. The dose rates for the various tumours are not yet established but the method does appear to have some merit in the management of carcinoma and sarcoid. Side-effects include local tumour necrosis and marked pigmentary changes. The latter effect, noted serendipitously by the authors, suggests that the drug has a significant effect on melanocytes and this might have implications for the management of melanoma in the future (Fig. 9.27).

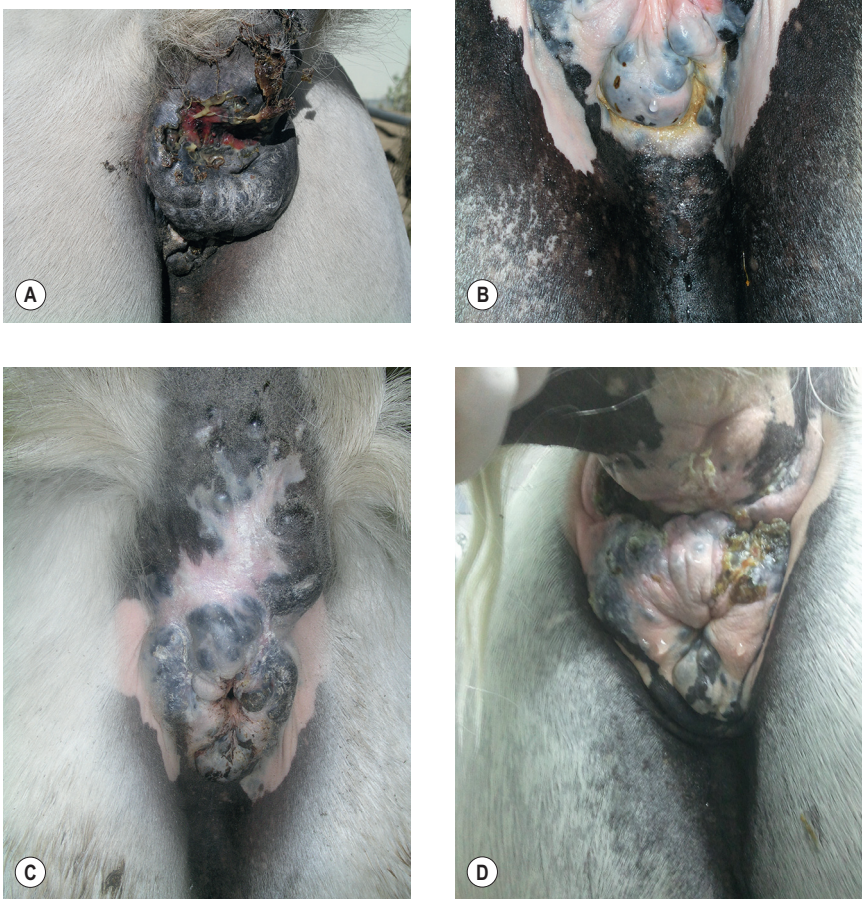


Figure 9.27 A novel intralesional mitomycin C regimen for untreatable melanoma. **(A)** A 14-year-old grey gelding was presented with very large and functionally compromising perianal melanomata that were ulcerated and histologically malignant. This was treated using a novel intralesional mitomycin C regimen with significant benefit. **(B,C)** The improvement was sustained and, although it did require some repeated procedures, the horse survived for 4 years. **(D)** Some 8 months of treatment resulted in a significant overall improvement in both the extent of the tumour and the local functionality. This is an unpublished method thus far, but it does appear to have some promise. *(Figures courtesy of Petr Jahn.)*

Piroxicam

Piroxicam is a non-steroidal anti-inflammatory drug of the 'oxicam' class used to relieve the symptoms of rheumatoid and osteoarthritis. It has also been used in small animal veterinary medicine to treat certain neoplasia expressing cyclooxygenase (COX) receptors, such as bladder, colon and prostate cancers.[68] There are few reports of its use in horses, but it would seem to be potentially valuable in the management of bladder and urethral tumours. There are reports of its adjunctive value in supporting treatment of some ocular and mucocutaneous carcinoma cases at 150 mg/kg per os q 24 h × 10, then q 48 h for several months.[69]

The possible side-effects are not established in horses.

Vinblastine/vincristine

Vinblastine is a chemical analogue of vincristine, an alkaloid derived from the Madagascar periwinkle plant *Vinca rosea* (*Catharanthus roseus*), from which it derives its name. Both vincristine and vinblastine bind to the microtubular proteins of the mitotic spindle and prevent cell division during the anaphase of mitosis. They arrest mitosis and cause cell death. The drugs are therefore M-phase cell-cycle specific and their effects are therefore limited to dividing cells. The faster dividing cells will be more affected than those with a low mitotic index.

Toxicities include bone marrow suppression (which is dose-limiting), gastrointestinal toxicity, potent vesicant (blister-forming) activity and extravasation injury (forms deep ulcers). Some immunosuppression also occurs.

Vincristine and vinblastine are an effective component of certain chemotherapy regimens, particularly when used with bleomycin, and methotrexate in chemotherapy for Hodgkin's lymphoma in humans. The inclusion of vinblastine allows for lower doses of bleomycin and reduced overall toxicity, with larger resting periods between chemotherapy cycles.

There are few reports of their use in horses and these relate to their use in combined treatment protocols for cutaneous and non-cutaneous forms of lymphoma (p. 524 and p. 533).[70] Most of the protocols for use of either of these medications employ doses that are variously prescribed at 0.01–0.025 mg/kg or 0.8 mg/m^2 every 7 days by intravenous infusion. There are few reports of the toxic effects of these drugs but they are rarely used.

Electrochemotherapy (ECT)

Contribution by Youssef Tamzali

Electrochemotherapy involves the application of two aspects of cancer treatment (i.e. chemotherapy and electropermeabilization of the cell membranes); the combinations of two known anti-cancer treatments are best treated as separate entities. The technique is based on the local application of short and intense electric pulses that transiently induce an electrically-mediated reorganization of the plasma membrane of cells (permeabilization), thus allowing transport of molecules that are otherwise not capable of crossing the cellular membrane. Electrochemotherapy combines local or systemic administration of chemotherapeutic drugs that have poor membrane permeability, such as bleomycin (p. 145) or cisplatin (p. 146), with electropermeabilization by direct application of electric pulses to the tumours. Whether this involves physical disruption of the cell membranes or alters drug efflux transporters is a debatable issue. The method overcomes some of the criticism and physiological constraints associated with the use of aqueous solutions of chemotherapeutic agents, such as rapid diffusion away from the site and poor maintenance of cell concentration of drugs. The method results in a significantly increased intracellular concentration of the chemotherapeutic agent, which in turn leads to a significant increase in cytotoxicity.

Various studies on different animal models and various tumour types have demonstrated significant benefits of electrochemotherapy.[71] There are added benefits in minimizing patient toxicity and maximizing operator safety. Clinical studies in veterinary oncology have also demonstrated that electrochemotherapy is very effective in the treatment of cutaneous and subcutaneous tumours of different histological types in cats, dogs and horses.[72] Clinical trials conducted in human patients demonstrated the pronounced anti-tumour efficacy of electrochemotherapy, with a successful outcome being recorded in 80–85% of the treated cutaneous and subcutaneous soft tissue tumours. The clinical use of anti-tumour electrochemotherapy using cisplatin has been described for treatment of equine sarcoid and for several other equine integumentary tumours; its use is, however, clearly restricted to sites where the required tumour exposure is available. Tumours on the skin surface and on accessible parts of the oral cavity are regarded as amenable sites for the procedure.

The results of these studies have also demonstrated a significant long-lasting benefit in 80% of tumours treated by electrochemotherapy. Primary tumours of different histological types have been treated and electrochemotherapy has future promise in veterinary oncology as a highly effective treatment method.[39] It could be used to treat primary or recurrent solitary or multiple cutaneous and SC tumours of different histology or as an adjuvant treatment to surgery (Fig. 9.28).

Electrochemotherapy treatment consists of delivering cytotoxic drugs with an inherently low cell permeability (usually cisplatin or bleomycin), either systemically or locally, and then applying electric pulses to the tumour when the surrounding concentration of the drug around the tumour is at its peak. The electric pulses cause defects in the cell membrane, which alter its permeability. The effects develop immediately and are sustained for some time after the procedure has been completed, so that molecules of the cytotoxic agents can diffuse more freely into the cytoplasm. In addition, local and transient vasoconstrictive effects contribute to the anti-tumour action of ECT (drug sequestration and infiltration of immune cells within tumour tissue) and may also control the metastatic dissemination of malignant cells. Multiple positioning of the electrodes and subsequent pulse delivery can be performed, so that the whole tumour can be treated during one session. Treatments are repeated at 2-week intervals. An average of four treatments is required. Larger tumours may require up to seven treatments.

The amplitude of the pulses depends on the tissues to be treated and on the shape and position of the electrodes, but in the case of the tumours, in vivo, the amplitude of the

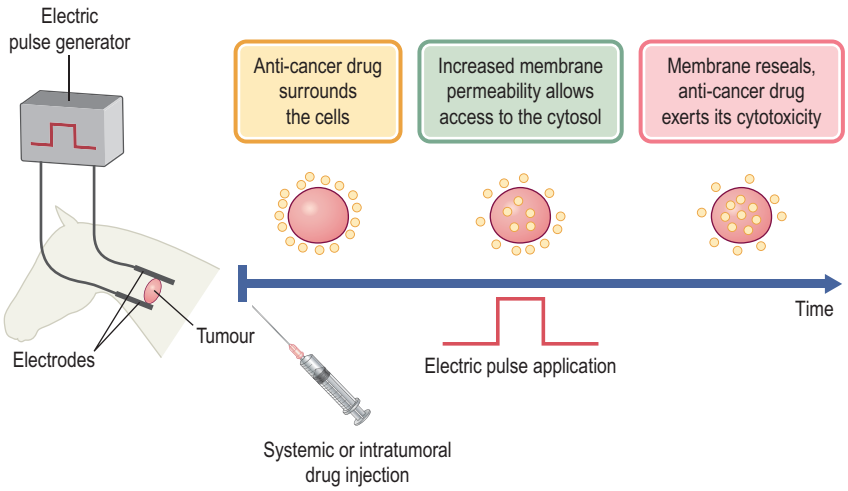


Figure 9.28 Electrochemotherapy. This involves the stimulated uptake of a chemotherapeutic drug into cells through the application of short-pulsed electric current.

electric pulses has to be high enough to establish an electrical field of 400 V/cm in the area of the tumour. The length of pulses is usually 100 microseconds. In early experiments, pulses were delivered with a period of 1 second (i.e. at a repetition frequency of 1 Hz); today, however, pulses are delivered in a much shorter time period, at a repetition frequency of 5000 Hz, resulting in much less discomfort for the patient and in shorter duration of treatment. Pulses are currently being delivered in a series of eight pulses, but can be repeated if necessary.

A retrospective study evaluating the efficacy of cisplatin ECT in the treatment of equine sarcoids has been undertaken using the protocol described above and this demonstrated that ECT, with or without concurrent tumour debulking, is an effective alternative for treatment of equine sarcoids. A total of 194 sarcoids on 34 horses, two ponies, 11 donkeys and one mule were treated with ECT. The 4-year non-recurrence rate was 97.9% for animals (47/48) and 99.5% (193/194) for tumours. When ECT was used as a single treatment, a significant influence of tumour size ($r = 0.55$) on the number of treatments required for cure was shown. When prior surgery was performed, there was a significant influence ($p < 0.001$) of the excision quality (complete or incomplete) and the healing mode (closed or open wound) on the number of treatments. The most common adverse effect is a slight local oedematous reaction, particularly for lesions located on thin skin regions.

Method

Although the chemotherapeutic agent can in theory be administered intravenously, the doses required in the horse for this approach are so high that this particular approach has not been suggested as being either practicable or sensible.

Restriction of blood flow and intralesional or perilesional infiltrations of the chosen chemotherapeutic drug provide the surgeon with an opportunity to accurately apply the electrical pulses solely to the selected tissues at a time when the local concentrations of the drug are at their peak (Fig. 9.28). Clearly, restriction of blood flow is only practicable on the limbs, ears and tail of horses.

1. The horse is carefully prepared for surgery and the tumours to be treated are defined and their volumes calculated using physical measurements.
2. All equipment is carefully checked before starting the procedure.

Table 9.4 The theoretical calculated total dose of cisplatin

Drug	Dose/cm³ of tumour (theoretical)	Volume/cm³ of tumour (theoretical)
Cisplatin (1 mg/mL)	0.3 mg/cm³	0.3 mL/cm³

3. The horse is anaesthetized and placed in a suitable position to provide direct access to the tumour.
4. Using a 1 or 3 mL Luer lock syringe and a 22G 2.5 cm needle, a 1 mg/mL solution of cisplatin is infiltrated into and around the lesion to include a 2 cm wide apparently healthy margin (Fig. 9.29). To obtain uniform drug distribution, injections are carefully spaced approximately 6 mm apart in one plane and two planes of injections are spaced 1 cm apart. The theoretical calculated total dose of cisplatin is 0.3 mg of cisplatin/cm³ of target tissue with the intention of saturating the tumour tissue as well as the margins with the solution (Table 9.4).
   - Where the procedure is used in conjunction with primary closure with complete or incomplete tumour excision, the skin is infiltrated over a 2 cm margin on both sides of the incision.

Within 5 min of the cisplatin injection, two flat, parallel, specially designed stainless steel electrodes (9 mm wide, 2 mm thick and 9 mm apart) are applied in contact with the skin on the tumour surface. Square wave electric pulses are applied using an electropulsator[73] (Betatech Unipolar, L'Union, France). Tissue contact is secured by application of an ultrasonic gel. The electric pulses are monitored by an oscilloscope or digitized and stored on a computer. Two series of eight electric pulses lasting 100 ms using 1300 V/cm to electrode gap are applied and delivered in one shot at a frequency of 500 Hz in two orthogonal directions per site. Each electric pulsing site represents almost 1 cm³ and the procedure is repeated to ensure that the entire infiltrated tumour and the marginal area of apparently normal tissue is treated.

Precautions and hazards

Since horses do not tolerate application of electric current at all well, subjects will require repeated deep general

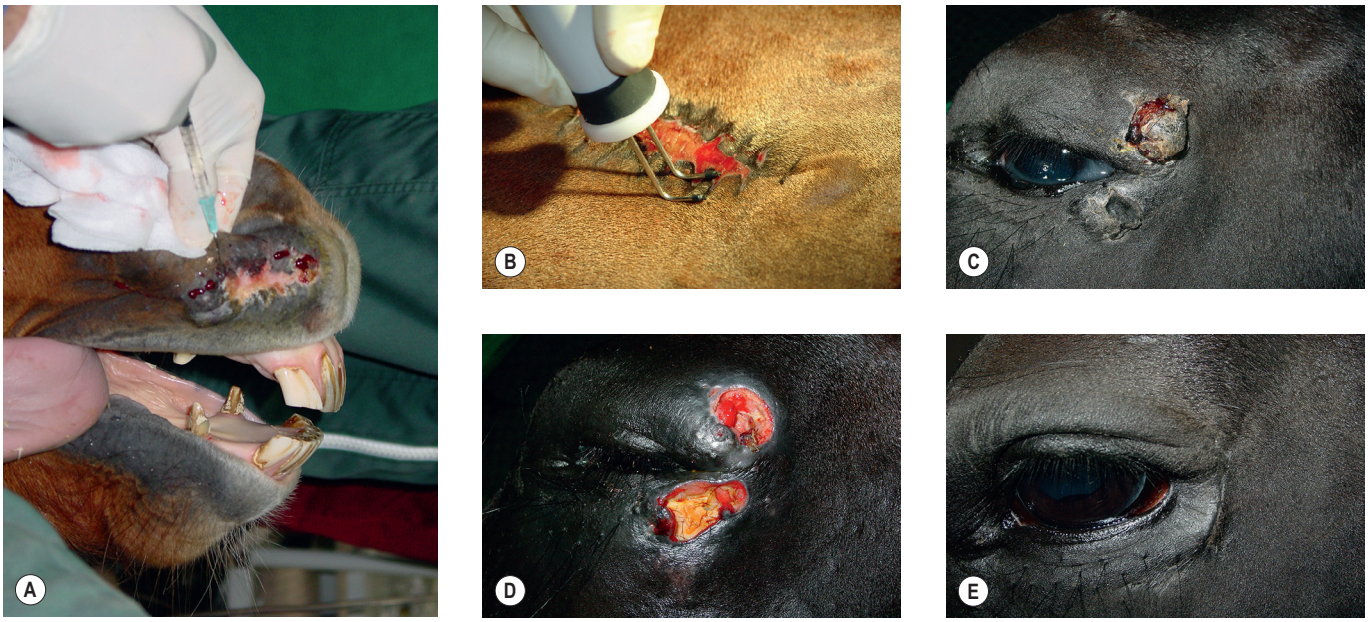


Figure 9.29 Electrochemotherapy is performed under deep general anaesthesia. It involves the intralesional injection of aqueous cisplatin (1 mg/mL) **(A)** and the application of a series of electrical pulses applied across two electrodes **(B)**. **(C)** The two periorbital sarcoids shown in this case were treated by electrochemotherapy. **(D)** The response at the site after the removal of necrotic tissue after 2 weeks. **(E)** The site 6 weeks after the treatment shows a good outcome and minimal scarring. *(Figures courtesy of Youssef Tamazali.)*

anaesthesia. This adds significantly both to the logistic and cost implications of the technique, but, in general, healthy horses seem to tolerate the procedure well. Owners will, however, be required to make an informed decision on the risks associated with the anaesthesia requirements in particular.

Appropriate facilities for safe use of the agents are essential. Suitable protection for personnel in the theatre has to be ensured. However, since local electrochemotherapy employs far lower dosages of chemotherapeutic drugs than standard chemotherapy protocols, the risks to the patient and the owner and surgical staff are usually negligible. In the clinical use of electrochemotherapy in horses, no significant side-effects related to bleomycin or cisplatin are recorded.

Provided that appropriate anaesthesia is used for alleviation of the symptoms associated with application of electric pulses and the control of the pain level during the electrochemotherapy is good, the procedure is well tolerated. Muscle contraction during electric pulse delivery is the only discomfort for the patients associated with electrochemotherapy and personnel have to be aware of the possibility of body movement during the pulses. There is also induction of a vascular lock by the type of pulses used in electrochemotherapy: for a few minutes blood flow is interrupted in the treated normal tissues. Fortunately, its duration is too short to have any significant or detectable deleterious effects due to ischaemia. In tumours, however, the vascular lock is of a longer duration and probably contributes positively to the effectiveness of the electrochemotherapy technique.

Chemical cautery

Perhaps one of the crudest, but also the cheapest and most available treatment methods for localized tumours on the skin and some other circumstances, involves the topical application of formalin pastes or other tissue destructive materials. Heavy metal salts and, in particular, the heavy metal chlorides (such as mercury and zinc) and arsenic trioxide have been used for many years in the management of superficial tumours in horses. These chemicals are highly caustic and potentially toxic. They do, however, appear to have a potential role in some circumstances.

A recently described chemical cautery method for the management of the pseudo-tumorous state of the equine progressive ethmoidal haematoma involves the use of formalin injections placed into the lesion itself. The technique is most commonly used for the progressive ethmoid haematoma, which is probably not a true neoplasm anyway, but the principle is very effective in that condition (Fig. 9.30). Intralesional formalin injections in large melanomas may also be effective, at least in reducing the size and bulk of the tumours.

Photodynamic therapy

Contribution by Jeremy Kemp-Symonds

Photodynamic therapy (PDT) uses precise beams of light of specific wavelengths to treat cancer, as part of a two-step process. First, the patient is given an inert 'pro-drug' that builds up in the body, particularly in tumours. The pro-drug is then converted to an active drug when light of a certain wavelength is shone on it. Because the light and the drug only meet each other in the patient's tumour, the drug is only activated there. This is designed to reduce damage to healthy tissue, keeping side-effects to a minimum. The German physician Friedrich Meyer–Betz performed the first study on 'photoradiation therapy' (PRT) with porphyrins in humans in 1913 by testing the effects of haematoporphyrin-PRT on his own skin. It was, however, only in 1986 that the

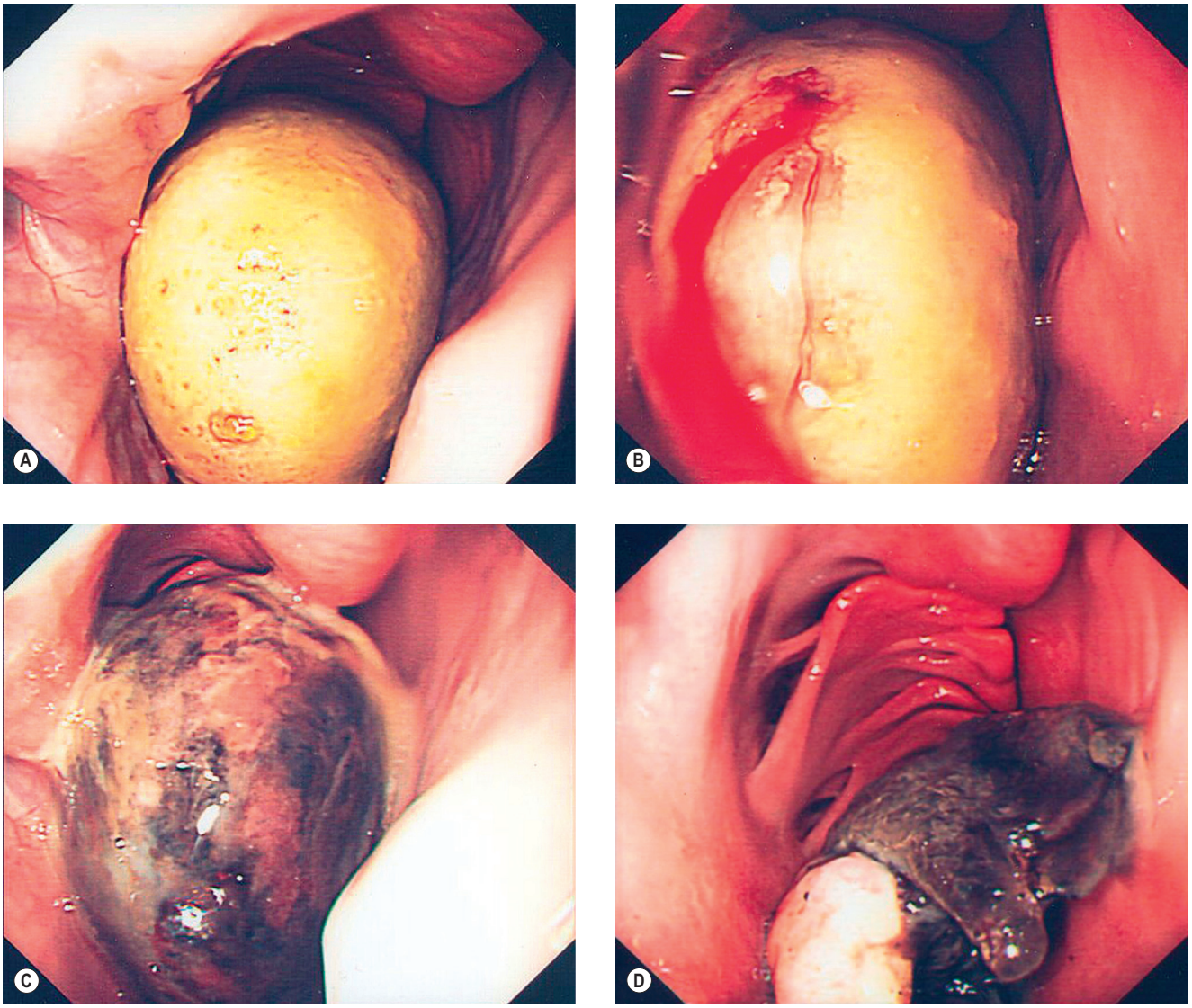


Figure 9.30 Formalin cautery of a large progressive ethmoid haematoma. **(A)** A large progressive ethmoid haematoma (a tumour-like condition affecting the nasal cavity and paranasal sinuses of the horse) had caused progressive unilateral nasal obstruction and a chronic sero-haemorrhagic nasal discharge. **(B)** An intralesional injection of 5 mL of 10% formalin was made via an endoscopic injector. **(C)** The tumour regressed progressively over the following 2 weeks. **(D)** At 12 weeks' post-treatment. There was no recurrence, although the horse did develop a second lesion in the contralateral maxillary sinus.

method was properly investigated as a treatment for cancer and, subsequently, it has been used widely in human medicine to treat a variety of conditions, including both pre-cancerous and cancerous lesions, such as Bowen's disease (an early stage of squamous cell carcinoma) and basal cell carcinoma, respectively. The use of PDT in veterinary medicine has been far more limited, although it has been applied to the treatment of carcinomas and sarcoid, in particular, in equine practice.[74,75]

A photosensitizer is a chemical compound that can be excited by light of a specific wavelength. This excitation uses visible or near-infrared light. In PDT, either a photosensitizer or the metabolic precursor of such an agent is administered to the patient. When the photosensitizer and an oxygen molecule are in proximity, an energy transfer can take place that allows the photosensitizer to relax to its ground singlet state and create an excited singlet state oxygen molecule. Singlet oxygen is a very aggressive chemical species and will very rapidly react with any nearby biomolecules. The specific targets depend heavily on the particular pharmacodynamics of the photosensitizer chosen. Ultimately, these destructive reactions will kill cells through apoptosis or necrosis. This mechanism is identical to the mechanism of the human disease erythropoietic protoporphyria, which causes blistering in response to sun exposure; this is due to a genetic defect in the same metabolic pathway that results in an endogenous photosensitizing agent.

Photodynamic therapy involves either the topical application of a photodynamic agent (the photosensitizer), or the systemic administration of a primary or metabolic derivative photosensitizing agent. The clinical benefits develop after exposure of the treatment site to light of the defined wavelength capable of exciting the photosensitizer for the specific agent. The topical (direct) application of the agent has singular advantages in being focal, but there are

inevitable limitations to the depth of tumour that can be treated in this way. Systemic administration delivers the agent to all tissues (albeit with natural variations in the uptake depending on its natural tissue distributions) and so the effect is then entirely dependent on where the 'light' is applied. This has the advantages that multiple sites can be dealt with, including some internal sites, such as the oesophagus or the vagina, when endoscopic delivery of the light can be focussed only on the lesion itself. However, it suffers a singular disadvantage in that inadvertent exposure of any body part to a suitable radiation source will cause damage; the theory that the compounds are taken up only by abnormal cells does not apply so strongly to this modality, although there are some newer agents that will target cancer cells more specifically and so there is a considerable risk of collateral damage if precautions are not properly taken. In addition, systemic administration requires relatively large doses of the photosensitizer (or photosensitizing agent), which are often costly, and so this method may not currently be economically viable for larger species such as equidae. The singular advantage of PDT in either method is the fact that the effect of the treatment can be localized.

A wide array of photosensitizers can be used for PDT. The photodynamic agents can be divided into porphyrins, chlorophylls and dyes. Examples include aminolevulinic acid (ALA), silicon phthalocyanine 4 (Pc 4), *m*-tetrahydroxyphenylchlorin (mTHPC) and mono-L-aspartyl chlorin e6 (NPe6); several of these are marketed commercially. The major difference between the different types of photosensitizers is in the parts of the cell that they target.

Unlike radiation therapy, where damage is done by targeting cell DNA, most photosensitizers target other cell structures. For example, mTHPC localizes in the nuclear envelope and does its damage there. In contrast, ALA has been found to localize in the mitochondria and methylene blue in the lysosomes.

Photodynamic agents that have been used in the horse include various forms of hypericin (extracted from the plant *Hypericum perforatum*, St John's wort) and chemical photo-activating compounds, such as 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL). However, none have been tested in horses in large-scale studies.

The specificity of treatment in PDT can be improved in several ways:

- The light source can be placed directly and exclusively onto the tissues to be treated. All other tissues are then either masked out or shielded from the light source, so that there is no activation of the photosensitizer in any other site and no tissue damage beyond the treated tissue.
- The photosensitizer can be administered in such a way as to limit its location and mobility: the more focal the material, the more focal the response. Where the agent is applied only to the area to be treated (or is bound only to the tissue by some other metabolic process), adjacent tissues will not be affected by the light radiation.
- There are some photosensitizing agents that are selectively absorbed by targeted cells. For example, ALA is taken up significantly better by metabolically active cells; since malignant cells tend to be growing and dividing much more quickly than healthy cells, the ALA therefore, at least to some extent, targets the unhealthy cells whilst sparing the normal cells. Subsequent exposure to the light source then results in focal tissue destruction. The extent of the destruction will usually be proportionate to the actual amount of the agent in the cells and so the greatest effects will be exerted on the cancer-transformed cells. There is an inevitable crudity about the method and so some normal cells are likely to be damaged to some variable extent.

Apart from the purchase of the required light sources, PDT is significantly cheaper than radiotherapy or most surgical procedures. Additionally, there is less aftercare required over the following days. Recovery is typically hours or days rather than weeks, although repeated procedures may be required in many circumstances; indeed, many of the protocols require at least two treatments at an interval of some 7 days. A major limitation of PDT is that the light needed to activate most photosensitizers cannot penetrate through more than 1 cm of tissue. The system is therefore probably not applicable to most metastatic circumstances or in large tumours. However, new high-powered LED technology is currently improving penetration and it is likely that deeper lesions will become amenable to the method. Also, hollow needles and endoscopes have been used by some units to get the light into deeper tissues, but little is known about the more advanced methods in horses since few centres are performing many procedures. The process of photodynamic therapy is becoming much more sophisticated in human oncological therapy and systemic photodynamic agents and agents bound to monoclonal antibodies are being employed for some aggressive internal cancers.

Technique

Photodynamic treatment is relatively simple to perform when tumours are accessible. Internal tumours would be much more problematic.

- The chosen photosensitizer precursor (5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL) or levulinic acid (LA) or hypericin) is applied directly to the tumour, ensuring that it reaches the margins of the tumour; in some cases the margins cannot be defined and in others the application may be difficult to restrict to the tumour itself.
- The photosensitizer is left in situ for 2–3 h under a light-occlusive dressing to allow penetration. In this period, the agent will be absorbed by cells in the treated area and will be converted metabolically into an active form (usually some form of porphyrin).
- After the incubation period, any excess photosensitizer is wiped away and the specific wavelength light source is then applied directly to the treated zone using shields to protect any surrounding tissues that are not to be treated; there is a slight risk that the chemical may have spread away from the treated zone, and so failure to afford protection may cause more widespread damage than is desirable. The light exposure usually lasts between 8 and 20 min. Different tumours with different extracellular characteristics may require longer or shorter exposures. In general, soft tissue tumours such

as squamous cell carcinoma will require shorter exposure times, while the firmer tumours such as sarcoid require longer exposure.
    - The metabolic process involved in inducing cell destruction is complex and involves production of damaging free radicals.[76]
- Within a few days, the exposed tumour (and any normal tissues involved in the treatment) will become necrotic and sloughing will take place over some weeks.
- Repeat treatments are often required, especially for deeper or extensive tumours. Given the limitations of penetration of the various photosensitizers, larger, solid tumours may require surgical debulking prior to the use of PDT.
- It is also common for the patient to experience pain or discomfort from the area treated both during the application of the light source and also in the days after the procedure. Therefore, sedation and suitable restraint of the patient should be carefully considered, while both pre- and postoperative analgesia are always indicated.
- After the treatment the patient will need to avoid excessive exposure to sunlight for a short period of time.

Safety issues in chemotherapy

In veterinary practice, the use of cytotoxic and antimitotic drugs for their anti-cancer and immunosuppressive effects is expanding. Most, if not all, the agents used in chemotherapy of any sort have some inherent risks for the handlers and some are extremely dangerous. Cytotoxic and antimitotic drugs (usually known as anti-cancer drugs) inevitably have an effect on cell replication and function and these drugs are used to alter the cancer cells and so trigger their immunological destruction. However, whilst their therapeutic effects are clearly of significant benefit to cancer patients, the drugs can produce unwanted (side)-effects in both the patient and other humans (and animals) that might be exposed to the drugs. Apart from the adverse effects on the patients themselves, there are risks to handlers, stable attendants, owners and the operating technicians and veterinarians. Therefore, whenever they are used, proper safety precautions *must* be taken. The reader is encouraged to visit: www.ecvim-ca.org/guidelines.[56]

Of course, danger is a matter of degree of risk. The benefits to the patient usually (hopefully invariably) outweigh the risks but people accidentally exposed to these drugs without any therapeutic benefits in their use, risk significant side-effects. Therapeutic doses of cytotoxic drugs induce signs of toxicity because there is a narrow margin between therapy and toxicity and because they are not discriminatory between the target cancer cells and normal cells. Careful use under controlled circumstances probably means that the risks will be minimized (though possibly never eliminated completely) whilst casual, irresponsible use will inevitably increase the risks to operators, patient and handlers. As in all medication use, the risk versus the benefit has to be weighed up. There is no equine case that warrants a human putting himself/herself at serious risk of injury or harm.

The main reasons for concern are based on:

1. The potential toxic side-effects encountered in patients. Horses appear to be more tolerant of many of the drugs that are used, but some are extremely dangerous. For example, intravenous 5-fluorouracil is regarded as contraindicated because of its emetic effects.
2. Evidence that most drugs of this class can induce chromosomal alterations and may therefore have cancer-inducing properties, reproductive abnormalities and other effects. There is ample evidence that many of these drugs cause serious unwanted effects, including induction of neoplasms and leukaemias, testicular and ovarian dysfunction including permanent sterility, cumulative chromosomal damage and additional effects on organs, particularly those with a high cell turnover, such as the intestinal epithelium and the bone marrow. Not all cytotoxic drugs are carcinogenic however; drugs such as methotrexate, 5-fluorouracil and cytarabine have no cancer-inducing properties whilst the alkylating agents are more dangerous in this respect.
3. Adverse effects in operators using the drugs that may relate to either of the above: notwithstanding the established risks, usually even long-term exposure to very small amounts of the drugs does not appear to have any relationship to developing future cancer, so the lowest possible exposure will minimize risks in handlers – clearly, zero exposure is by far the best way to ensure personal safety during use of any anti-cancer drug of any type.

Safety aspects for chemotherapeutic use

Control of exposure

The ALARA principle (*A*s *L*ow *A*s *R*easonably *A*chievable) should be followed by all persons – veterinarian, technicians, stable staff, owners) when using cytostatics or cytotoxic drugs. This principle should be foremost in the mind of every person involved.

In order to diminish, or hopefully eliminate, the risks of exposure to anyone using these drugs the European College of Veterinary Internal Medicine – Companion Animals (ECVIM-CA)[56] makes the following recommendations:

1. Only drugs with a proven evidence-based efficacy should be used. This is a problem in equine oncology because little information is available; although many protocols for therapy of all sorts have been suggested, few meaningful trials have been performed. Only one significant attempt has been made to overcome this difficulty: the use of doxorubicin has recently been tested.[54] Further trials are of course required but, otherwise, extrapolation from other species is probably the only way forward. Certainly no trial-and-error approaches can be condoned.
2. Protocols must be established that take account of the specific hazards of particular drugs that are to be used. This should involve precautions during preparation, use and disposal of the drugs. These are usually based upon the medical use of the drugs and, although there are obvious differences in the actual use of the drugs between human and small animals and horses, there should be no differences in the preparation and

disposal stages. (Guidelines for the Safe Use of Cytotoxic Drugs: adapted from ECVIM-CA Preventing occupational and environmental exposure to cytotoxic drugs in veterinary medicine 2007: www.ecvim-ca.org

All personnel involved (including any person likely to handle the patient or its excreta or other body fluids) should be appraised of the need to take precautions to avoid exposure. They need to be positively informed of:

- The known or putative risks of working with cytotoxic compounds and procedures that are to be taken in the event of accidental contact/contamination
- Preparation and handling of the chemicals in properly constructed ventilated biological safety cabinets that are designated for use with hazardous materials: Properly constructed cabinets will automatically be suitable for preparation of cytotoxic materials. Generally the raw materials (i.e. concentrated solutions and powders) are the most dangerous stage to handle these chemicals. The cabinets should have a certificate of safety and operation testing. Eating, drinking or chewing of gum, etc., is strictly forbidden. Where tablets, etc., have to be crushed, this should be performed by a qualified pharmaceutical chemist under controlled conditions
- Control/prevention of any aerosol formation that might be inhaled or ingested: Eyewash and shower facilities should be available to cope with any accidental exposures
- Methods of reducing personal contamination and environmental risk by use of protective clothing: Chemoprotectant gloves (surgical gloves or preferably double gloving), disposable suit and eye and face protection are essential. Proper signage must be used to ensure that during the procedure the minimum number of personnel is involved and that the environment is properly protectable, so that the site can be properly cleaned afterwards. Damaged protective clothing must be replaced immediately. All cleaning should be according to the local regulations for the drugs used. All areas involved should be cleaned suitably before any other personnel and horses are allowed to enter. All persons responsible for the cleaning process should be suitably protected by mask, protective clothing and eye protectors. Wipe tests may be used to establish the efficiency of the cleaning process; they are not readily available in most circumstances but they are clearly advisable
- Methods of handling spillage and accidental contamination: This should be clearly understood and there should be no 'acceptance' of spillage – every spill or suggested spill *MUST* trigger appropriate cleaning/decontamination procedures
- Appropriate administration methods that minimize the risks of accidental exposure: All syringes should be Luer lock type but closed systems are preferred where that is possible. All prepared solutions, etc., *MUST* be labelled at the point of preparation, so that they are clearly identified in respect of the case and the substance and the concentration. The date and time of preparation *MUST* be indelibly marked in the containers. The words 'CYTOTOXIC SUBSTANCE' *MUST* be used and *MUST* be clearly visible.
- The minimum number of people that is consistent with safety and efficiency should be used. Owners should under no circumstances be present in case of complications and spillages
- All administrations must be undertaken in a designated area
- The patient should be suitably calm and restrained appropriately. *Horses that are not temperamentally suited to the procedure or its safe completion should not be treated*
- All personnel involved should be clothed in proper protective gloves, suits and masks with eye protection
- Closed systems or fully Luer locked systems are suitable. Electronic pump systems are excellent ways of ensuring proper dose and flow rates but may add to the cleaning complications
- Intravenous systems should use suitable intravenous catheters with downward-facing insertion. The catheter should be removed and disposed after completion
- Methods of administration to be used: The animal should be restrained suitably and all administration equipment MUST be checked carefully before use. Checking for leakages and spillages is paramount. Upon completion, all contaminated and potentially contaminated disposable protective clothing should be bagged up and sent for appropriate disposal. The hands and face of operators should be washed with warm water and soap
- Methods of disposal: Disposal will need to be according to local regulations, but usually means that all protective clothing and equipment, such as syringes and needles and drug vials, must be disposed in hazardous waste receptacles
- Post-treatment nursing requires knowledge of the drug used and its pharmacokinetics. Suitable nursing and stable care and protection of personnel is obligatory both during and after the horse leaves the facility
  - Owners may need special advice regarding the aftercare if the horse is returning home. A written statement needs to be signed by the owner in respect of the procedure and its risks to both patient and handler
- Regular health monitoring of all personnel involved through proper medical checks by appropriate physicians
- Any persons that might have concurrent health issues or pregnant women (or those who might be trying to conceive) should avoid contact at all costs. Such persons need to be specifically and totally forbidden from any possible contact.

Drug risk classification

Drug Safety Categories for Drugs Used in Equine Chemotherapy as defined by the International Agency for Research on Cancer (IARC) are as follows:

1. Group 1: Drugs that are carcinogenic (positive evidence):
   - Azathioprine
   - Chlorambucil
   - Cyclophosphamide
   - Melphalan.
2. Group 2: Drugs that are probably/possibly carcinogenic to humans:
   - Carmustine/lomustine
   - Cisplatin/carboplatin
   - Doxorubicin
   - Bleomycin
   - Mitomycin.

Radiation therapy/radiotherapy

Radiotherapy (also called 'radiation oncology') is the term applied to the use of ionizing radiation in the treatment of neoplastic (usually malignant) disease as part of cancer treatment to control malignant cells and therefore gross tumours[77]; it can also be a useful method of treatment of benign tumours and some non-neoplastic conditions also.[78,79]

The value of radiation in treatment of cancer was suggested by Alexander Graham Bell shortly after Roentgen discovered radiographs in 1895. Bell proposed that radiation might be useful for direct implantation in malignant tumours (a technique now known as 'brachytherapy'). The first therapeutic use of radiation took place in 1896. Marie and Pierre Curie discovered radium in 1898 and that provided a basis for the development of radiation treatment of tumours that has culminated in sophisticated and highly effective treatment of many benign and malignant cancers. Radiation was first used in the treatment of equine tumours in 1906.[80] In the early days, radiation was used in the treatment of benign disease, such as orthopaedic inflammation and inflammatory skin disease, rather than malignancy.

The absence of a convincing method of measuring the applied dosage constrained the early use of radiation therapy. Probably the biggest limiting factor in early treatment was the damage that the skin could tolerate; empirical doses were prescribed that continued until the skin became erythematous, which were assumed quite wrongly to be uniform and standardized. This hurdle was finally overcome with Coutard's recognition of the value of fractionation (i.e. dividing the dose into several smaller increments rather than administering a single massive dose). The concept of the additive effects of radiation as means of sparing normal tissues (such as skin or organs which radiation must pass through in order to treat the tumour) made a massive difference to the safety and efficacy of radiotherapy. Today, 'shaped' radiation beams can be aimed from several directions to intersect at the tumour, providing a much larger absorbed dose at the focus point than in the surrounding, healthy tissue. High-energy megavoltage generators now provide the technological basis of modern radiation therapy units. Radiation therapy has developed into a recognized medical specialty, with increasing emphasis being placed on its use.

The sophisticated technological advances that have taken place over the last 50 years or so have dramatically improved radiation therapy techniques; equipment has become more precise and advanced imaging techniques are used to maximize the therapeutic effects, whilst sparing adjacent normal cells. It has become one of the most effective non-surgical treatments of localized superficial and deep-seated cutaneous tumours in particular and that is currently where the value mostly lies in horses. Radiation provides an organ-sparing approach and is particularly effective in early-stage cancers and has the potential for significant palliation of advanced or metastatic tumours. The scope for radiation treatment of horses has widened slowly as equipment and facilities have become available to equine hospitals. It is the gold standard treatment modality in many cancer conditions and there are increasing numbers of reports of the efficacy of radiation in the treatment of individual benign and malignant tumours in horses. However, in spite of the general advances in radiation therapy in other species, there are still very few centres that are either experienced or equipped to undertake radiation therapy of any sort in horses. The costs of the treatment are generally very high and, additionally, the logistics of equine anaesthesia and support nursing make it a challenging speciality. Regrettably, in spite of its elegance and increasing sophistication, which allows the sparing of organs and the specific targeting of defined tumour types with radiations that are more likely to be effective therapy whilst being less toxic to normal surrounding cells, radiation is not yet widely used in equine oncology.

The physics of radiation therapy

The fundamental principle of radiotherapy is the fact that radiation kills cancer (and other) cells. Ionizing radiation may be electromagnetic (X-ray and γ-rays or photons) or particle (electrons).[81] Regardless of its nature or how it is generated, ionizing radiation is characterized by the ionization (and excitation) of atoms and molecules in cells. When one or both DNA strand(s) are broken or damaged, the cells are unable to continue to divide and die before completing the cell replication cycle. Although radiation damages cancer cells and normal cells, the latter are able to repair radiation damage to a greater extent and they are therefore less susceptible to the effects of radiation. The difference in repair capacity between healthy and tumour cells means that radiation therapy can be used to kill cancer cells whilst preserving the contiguous and surrounding non-cancerous structures. This differential ability to eradicate a tumour without undue complication is referred to as the selective effect of irradiation. However, there is a radiation-dose limit at which normal tissues will be irreparably damaged (p. 174). This is termed the 'radiation tolerance'. For most treatments, the dose of radiation that can be delivered to a tumour is limited by the radiation tolerance of surrounding normal tissues. A radio-curable tumour is one that can be destroyed by a dose of radiation that is well tolerated by surrounding normal tissues. If the dose of radiation required for tumour control exceeds the radiation tolerance of adjacent normal tissues, radiation therapy cannot be used alone safely and other modalities, such as surgery, will be required to improve the differential margin (p. 171).

The mechanism of production of radiation of various types can be found in most physics books, but in effect, three types of radiation can be used therapeutically in medical practice and each has its own particular ability to penetrate tissues to cause a medically useful (or harmful) effect (Fig. 9.31):

1. *Alpha (α) particles (helium atoms)*. These have no recognized medical use since they have little ionizing capacity and no tissue penetrating ability.
2. *Beta (β) electrons*. These particles form a basic and important aspect of radiotherapy. Electrons have variable penetrating ability, depending on the state of excitation, but there is a characteristic rapid, depth-dependent fall off (see Fig. 9.48).
3. *X-rays and gamma (γ) ray photons are part of the electromagnetic spectrum*. They have no mass and can penetrate tissues rapidly and effectively (see Fig. 9.31). Gamma rays and X-rays are used therapeutically.

Radioactive isotopes occur naturally and can also be generated artificially. The radioactivity of a radioisotope decays over time. The key properties of isotopes include the energy spectrum, decay spectrum and the half-life (Table 9.5). A particular isotope may decay through production of α particles (helium atoms) or β particles (electrons).

Radiation can be produced directly from radioactive isotopes (see Table 9.7); this is the way in which brachytherapy and plesiotherapy are applied. The various isotopes are used in different ways for different tumour types. For example, the specific iodine-concentrating ability of the thyroid gland can be used to treat thyroid tumours. The gland can accumulate and concentrate low concentrations of radio-iodine administered by intravenous injection; once the critical concentration is accumulated, the dose of radiation emitted is enough to cause localized cytotoxicity.

External beam therapy is commonly delivered via a medical linear accelerator or cobalt-60 unit. The introduction of these megavoltage units is the basis of modern radiation therapy. These units deposit the maximum dose beneath the surface; therefore, external beam therapy spares the skin overlying the tumour. Photons traverse the entire tissue thickness, but deposit less of the dose as the depth increases.

Many modern linear accelerators are also capable of producing electrons, which can be used for treatment situations where the limited depth penetration of these particles is useful, as in cases where deeper tissues must be spared (Fig. 9.32).

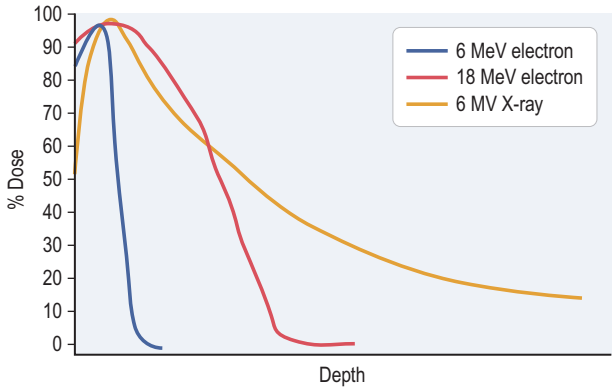


Figure 9.31 The different types of radiation have relatively different tissue-penetrating capabilities and properties. Thus, alpha particles have zero penetration capability and so have no ionizing effects and cannot therefore be used for radiotherapy. Beta particles (electrons) will penetrate tissue depending on their energy: higher energy (red) gives greater penetration than low energy (blue), but a rapid fall off is characteristic of this type of radiation. Electromagnetic (gamma or X-ray) radiation has a much higher penetrative capacity and lesser fall off with depth (orange).

The molecular basis of radiation therapy

The precise manner by which radiation induces cell death (apoptosis) is still uncertain. However, it is generally accepted that double-stranded breaks of nuclear DNA are the most important cellular effect of radiation. This necessarily leads to irreversible loss of the replicative capacity of the cell and eventual cell death. It is thought that whilst radiation can cause direct ionization of the DNA, it is probably more likely that it indirectly induces ionizing damage when free-radical intermediaries are formed from the ionization of cellular water. Additionally, radiation can affect the cell-cycle processes required for cell growth, cell senescence and apoptosis (programmed cell death). The therapeutic mechanism for radiation is based on the intrinsic ability of cells to repair damage and the ability of the oncologist to take advantage of any spatial separation between malignant and non-malignant and normal tissues.

Cell survival after exposure can be expressed in terms of a logarithmic curve of survival vs dose (Fig. 9.33). The curve forms an initial shoulder followed by a logarithmic decline in survival, which varies with the dose. Sub-lethal damage, which must be overcome with each fraction of radiation therapy, is thought to cause the initial shoulder.

Repeated small doses of radiation are individually less damaging to a sensitive cell than a single fraction containing an equivalent total dose and so more cells may survive.

Besides being related to intrinsic cellular radio-sensitivity, cell survival is also related to oxygen tension, the position of the cell in the cell-cycle and the applied dose rate of radiation. These features are responsible for the 4 Rs of radiobiology: repair, redistribution, reoxygenation and repopulation (p. 168).

Table 9.5 The physical characteristics of the various radioactive isotopes used in medical therapy

Isotope		Half-life	Energy (MeV)	Half-value layer (mm lead)	Exposure rate constant (R/cm²/mCi-h)
Radon	Ra-226	1600 years	0.047–2.45 (0.83 avg.)	8.0	8.25
Cobalt	Co-60	5.26 years	1.17–1.33	11.0	13.07
Caesium	Cs-137	30 years	0.662	5.5	3.26
Iridium	Ir-192	74.2 days	1.36–1.06 (0.38 avg.)	2.5	4.69
Iodine	I-125	60.2 days	0.028 avg.	0.025	1.46
Gold	Au-198	48 hours			
Strontium	Sr-90	27 years			

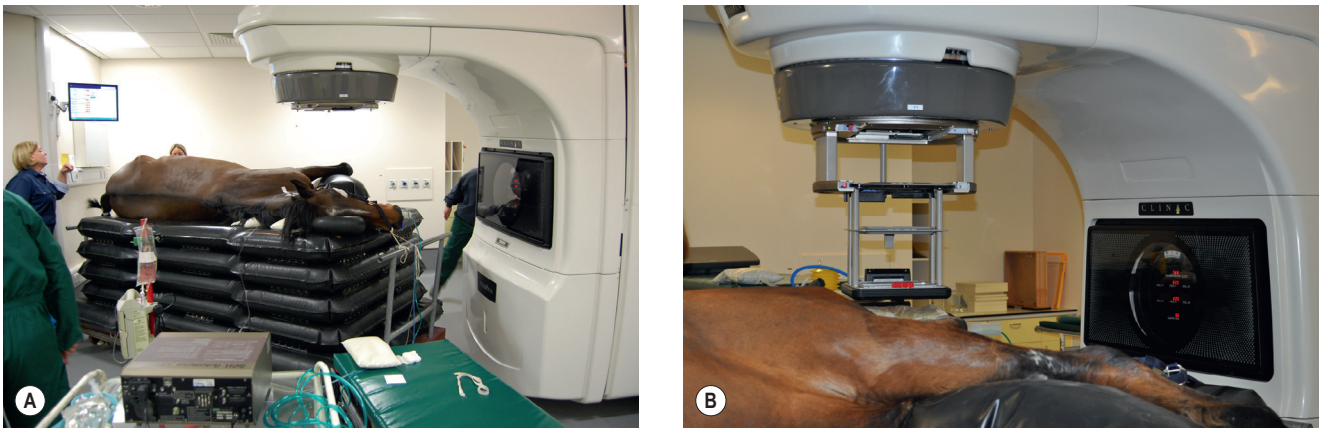


Figure 9.32 A linear accelerator is a means of generating accurately defined radiation for use in radiotherapy. The machine is linked to a sophisticated computer system that controls the beams and sets the doses accurately; detailed planning and preparation are essential. **(A)** Although the procedures are usually of short duration (often a matter of minutes), the logistics of the procedure usually dictates that the horse must be anaesthetized. **(B)** A horse being treated at the University of Cambridge in a radiation generator for a carcinoma of the mouth.

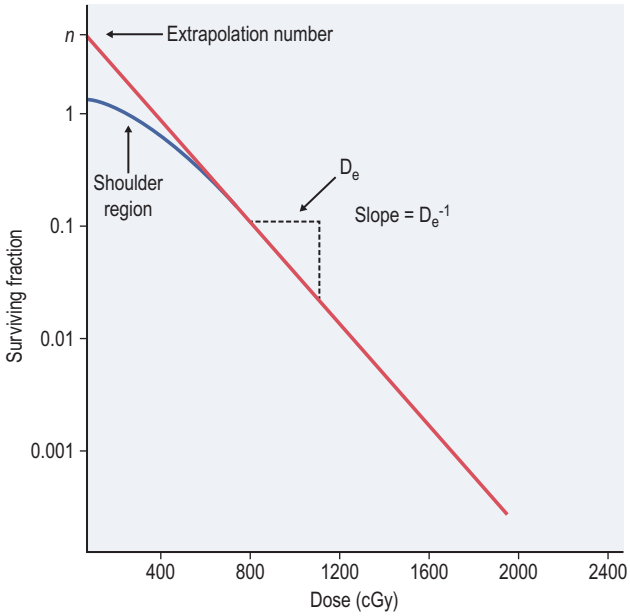


Figure 9.33 Cell survival, following a single radiation exposure/fraction. Notice the shoulder region, which probably arises as a result of sub-lethal exposure. Typical of almost all treatment options, there will be a population of cells that is less affected by the radiation – these may be harmed less severely and may survive when doses are relatively low. The lower the dose the bigger the shoulder will expect to become.

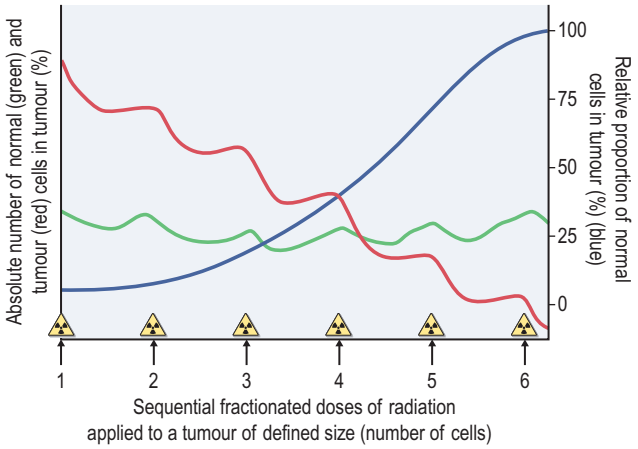


Figure 9.34 The theoretical effect of six fractionated radiation doses on the populations of normal cells and tumour cells. Note how the normal cells are less affected and recover faster than the tumour cells, resulting in an eventual near 100% kill out. If 100% can be killed, the tumour will of course be cured. This is somewhat oversimplified of course, and the differential effects can be enhanced by reducing the overall number of tumour cells by reduction surgery or the sensitivity of the tumour cells can be increased by use of enhancing drugs or higher doses of radiation. The ultimate objective is to 'replace' the tumour cells with normal cells derived from the normal population, i.e. to restore the 100% normality.

When repeated doses of radiation are administered, most of the tumour cells will be killed or irreparably damaged each time. Since it takes a relatively longer time for the surviving tumour cells to recover, reoxygenate, redistribute and repopulate than normal cells, which are less affected by the radiation, an increasing proportion of normal cells will be left in the site after each radiation exposure. This means that there is an increasingly beneficial effect as the population of abnormal cells is reduced and the recovery of the normal tissue takes place (see Fig. 9.34).

Radiation therapy, including intensity-modulated radiotherapy (IMRT), stops cancer cells from dividing and growing, thus slowing or stopping tumour growth. In many cases, radiation therapy is capable of killing all of the cancer cells and resulting in tumour shrinkage and a cure. There is compelling evidence, however, that many solid cancers are organized hierarchically and contain a relatively limited and possibly, small population of cancer stem cells (CSCs). It is reasonable to suggest that a cancer cure can only be achieved if this population is eliminated. Unfortunately, there is also increasingly convincing evidence that CSCs are inherently more resistant to radiation and perhaps also to other cancer therapies.

Tumour cells in a hypoxic environment are up to 2–3 times more resistant to radiation damage than those in a normal oxygen environment; high tissue oxygen increases the efficacy of radiation by forming DNA-damaging free radicals within the cells. Solid tumours can outgrow their blood supply, causing localized tissue hypoxia, and, since oxygen is a strong radio-sensitizer, this is one of the major limitations of photon radiotherapy of solid tumours.

The faster-growing tumours are the most likely to have significant hypoxia. Therapeutic measures that overcome the intralesional hypoxia, such as the use of hyperbaric oxygen, blood substitutes that carry increased oxygen and hypoxic cell radio-sensitizer drugs, such as metronidazole, will necessarily therefore improve the radio-sensitivity of a solid tumour.

The cytological effects of irradiation

Radiation therapy works by damaging the DNA of abnormal (cancer) cells; it is also true to say that normal cells will also incur damage. In order to understand the cytological effects tradition and the rationale for the use of radiobiology in medical practice, it is important to understand the mechanism for radiation damage. DNA damage can be induced by one of two types of energy:

1. Electromagnetic/photon (X-rays and γ-rays, photon)
2. Charged particle energy (electrons).

Irrespective of the type of radiation or the way in which the radiation is produced, ionizing radiation is characterized by the mechanisms of energy dissipation in tissues: namely, ionization (and excitation) of atoms and molecules in cells. Radiation-free radicals within the cells that react with intracellular cellular DNA and this is generally assumed to be the main mechanism of action. However, indirect ionization occurs from the free radical release, as a result of the ionization of water, and these hydroxyl radicals also cause significant damage to the DNA.

Since cells have very effective mechanisms for repairing single-stranded DNA damage, double-stranded DNA breaks will inevitably cause the most significant cell death. Tumour cells have less ability for DNA repair than healthy cells. Thus, between fractionation doses of radiation, healthy cells have a significantly greater ability to repair any damage. With each subsequent mitosis, the cumulative effects of unrepaired DNA result in apoptosis (cell death) of the tumour cells.

The positive effects of radiotherapy rely on the fact that cancer cells are generally undifferentiated and, being more stem cell-like, they have a diminished ability to repair sub-lethal damage compared with most healthy differentiated cells. Single-stranded DNA damage can be passed on through sequential generations of stem cells and the accumulating damage ultimately results in their death or at least a significant retardation of their replicative rate.

The four Rs of radiotherapy

Radiobiology defines the interrelationships between cells and radiation exposure in four major categories – all starting with the letter 'R' (the four 'Rs'):

Repair

It is assumed as a fundamental tenet of radiotherapy that tumour cells are less able to repair DNA damage than normal cells, although this is not always true in vitro where tumour cells and normal cells usually have largely the same repair capability. However, in vivo tumour cells are often oxygen and nutrient deficient and this makes them more liable to radiation damage. Remarkably, in the face of radiation damage or chemotherapy for that matter, normal tissues repair damage more efficiently than tumours. This in particular provides the basis for the successful use of radiation as a therapeutic agent. Following radiation, exposure cells may repair the resulting DNA damage in-between radiation treatments (fractions/doses).

It needs to be remembered that with larger radiation doses, radiation sensitizers (e.g. concurrent chemotherapy) partly overcome the repair processes and so increasing numbers of normal cells can be damaged. It becomes a balance between the need for a faster more aggressive 'kill-out' and the inevitable damage to normal cells.

Redistribution

Cells are more sensitive to radiation during some phases of their cycle than others. A radiation fraction will kill mainly the more sensitive (tumour) cells. The remaining tumour cells will be somewhat 'synchronized' within the cell-cycle (i.e. all at the same part of the cycle). Cells 'redistribute' from radio-resistant phases (e.g. S-phase) of the cell-cycle to more radio-sensitive cell-cycle phases, such as the M-phase, in-between radiation treatment sessions/fractions. Then, at a later time these synchronized cells will move synchronously into a more sensitive phase and this is the most effective time to deliver the next fraction of radiation.

Hyperfractionated radiotherapy (increased number of fractions) increases the probability of cells being in M-phase during a treatment.

Reoxygenation

Tumour cells are unrestrained by the natural homeostatic mechanisms that control the cell division and death and proliferate in an uncontrolled manner; they divide and proliferate as rapidly as they are able to without apparent destruction and are limited only by their own inherited characteristics and the availability of an adequate blood supply. This uncontrolled expansion means that the tumour is inclined to outgrow its own blood supply and areas of necrosis or at least hypoxia are frequently present within the tumour mass; often up to 15% of the total viable tumour cells will have enough nutritional or oxygen restriction to result in various degrees of necrosis.

As the tumour outgrows its blood supply, rapid cell proliferation near capillaries displaces other cells into regions away from a blood supply, where there is an inadequate concentration of oxygen and other nutrients. These cells will die, giving rise to a progressively enlarging necrotic zone; this is usually at its most obvious in the central core of the tumour. The hypoxic state of the viable cells reduces the number of cells that can pass the various checkpoints in the cell-cycle. This means that hypoxic cells have a slower cell-cycle and therefore a greater sensitivity to radiation damage. Cells may pass from a hypoxic (and thus radio-resistant) environment to a well-oxygenated state as a course of treatment proceeds.

Repopulation

Radiation often stimulates cell division ('accelerated repopulation') and at least some of this response is due to the death of adjacent cells. In normal tissues, this is kept under control by normal intracellular homeostatic mechanisms, but this is not true for tumours. Accelerated radiotherapy kills off cells before they gain the opportunity to repopulate. Therefore another dose of radiation is administered to counteract the repopulation by tumour cells.

Repopulation by normal cells, that recover faster, is likely to result in an improving clinical position with overall

tumour size reduction and restoration of normal appearance and possibly function. Repopulation with tumour cells will inevitably have the opposite effect – the tumour will persist and possibly get bigger and the cosmetic appearance and functionality of the tissue will be harmed.

Normal surrounding cells will have a normal blood supply and therefore be less radio-sensitive and can therefore repopulate faster than the radiated cells. Another manifestation of the overstretched vascular supply is that only a portion of the viable cells are actually proceeding through the cell-cycle and multiplying. This is the foundation of fractionation of radiation. The normal cells are not as badly affected as the tumour cells and recover faster with a faster replicative rate. This means that each time a dose of radiation is given, the relative proportion of normal cells increases.

Much of the effort that goes into treatment planning (p. 176) is directed at minimizing the effects of treatment on normal tissue. The effects of radiation on normal tissues can be divided into acute and chronic (late) effects. The acute effects can be uncomfortable for the patient, but they generally resolve. The chronic effects usually have less distressing effects, but can result in devastating, permanent and progressive side-effects. Human and small animal patients are usually most concerned by the acute effects; it is hard to know if horses are adversely affected at all by the acute effects. However, veterinarians should be at least equally concerned about the chronic effects. In reality, it seems that the horse is fairly tolerant of even quite high doses of radiation with few acute or chronic side-effects being reported. However, it has to be said that, for many reasons, very few horses are subjected to heavy radiation treatment courses.

Acute effects are usually encountered during the actual course of therapy and during the immediate post-therapy period (approximately 2–3 weeks after the completion of a course of irradiation). Tissues with a high natural cell turnover (e.g. bone marrow, testicular cells and cells lining mucous membranes) respond acutely to radiation and are responsible for much of the acute morbidity of the treatment. For example the mucous membranes of the mouth and pharynx respond quickly to fractionated radiation; erythema may progress to generalized inflammation, ulceration and superficial necrosis after 1 week of treatment at conventional doses. Radiation probably induces early melanocyte death, which manifests as leukotrichia and leukoderma at sites of even low-level radiation, and it is likely that this is an acute effect (even though the manifestation may be a longer-term feature).

Chronic effects can manifest from weeks to years after the treatment. Other therapies, such as surgery and chemotherapy, can increase the probability and severity of radiation-related long-term morbidity. Two major suggestions are used to explain long-term/chronic injury. In either case, late effects can be a source of ongoing morbidity after a course of radiation therapy:

- Chronic injury might arise from damaged microvasculature; localized necrosis and tissue devitalization with fibrous metaplasia can occur
- Stem cell depletion is a second long-term harmful effect. As in acute effects, the chronic effects are related to site, dose, volume and time
- Radiation-induced cancers are, fortunately, very rare subsequent to therapeutic doses of radiation. Probably, a greater risk of a second malignancy is posed by the original aetiological and genetic mechanisms that were responsible for the primary tumour.

Other structures in the region of the radiation should be considered during treatment and, in particular, the ocular tissues. Exceeding the tissue tolerance of the lacrimal gland can result in dry-eye syndrome (see Fig. 9.35 and Fig. 31.18). The cornea and the lens are highly sensitive to radiation, and direct irradiation of the lens may result in cataract formation even with the most commonly used therapeutic doses (see Fig. 31.18). The retina and optic nerve must also be respected during treatment planning in some circumstances (Fig. 9.36).



Figure 9.35 A mixed invasive periocular sarcoid. (A) This mixed invasive periocular sarcoid had failed to respond to surgical excision and BCG immunotherapy. It was treated using low-dose iridium brachytherapy to deliver a total of 65 Gy over a 10-day period. The immediate effects included swelling and some local discomfort and discharge. By around 3 months, however, swelling had reduced and the tumour had almost cleared. Leukoderma, leukotrichia and alopecia at the site developed but the functional outcome was excellent. **(B)** After 12 months, the sarcoid had largely resolved with a very acceptable outcome, although two small recurrences were noted. These were treated successfully using intralesional chemotherapy. The long-term legacy of the treatment included clinically impaired eyelid function over the nasal half of the upper eyelid and a loss of tolerance to windy conditions when ocular lubricants were required in the treated eye; the latter was possibly a result of altered tear film formation.

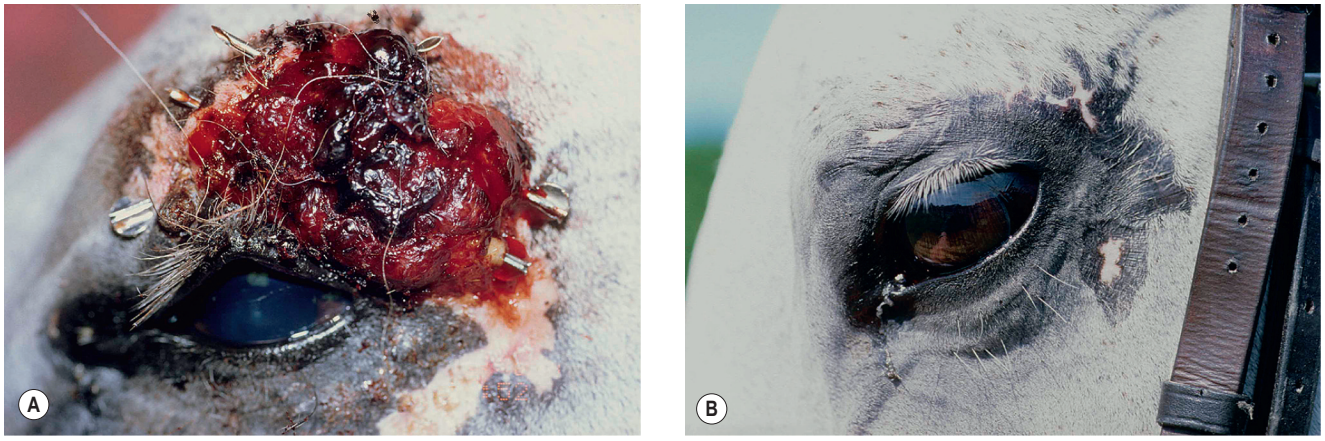


Figure 9.36 Low-dose iridium brachytherapy. (A) This horse had received multiple unsuccessful surgical attempts to remove sarcoid tumours around its eye. They were followed by several rather desperate attempts at cryosurgery and repeated intralesional injections of cisplatin emulsion. Finally, a course of BCG immunotherapy was attempted. This also failed. Low-dose iridium brachytherapy was finally used and the outcome was very successful. **(B)** At 12 months post-treatment. However, the dose that was required was higher than it might have been when the tumour was smaller and 'younger'.

Delayed wound healing can be a consequence of high-dose preoperative or postoperative radiation and sites subjected solely to radiation, such as the use of brachytherapy in the management of sarcoids may also heal slowly and with complications, such as scarring and contraction. Ulceration and bone exposure may develop. If serious injury to the underlying bone occurs, bone necrosis may follow. Fortunately, this complication is rare, but it can arise when high doses of radiation are required to treat a tumour with poor radio-sensitivity, such as dense nodular sarcoid on the face (p. 560). Where the tumour has no 'tolerant' cushioning supporting tissue, the risks to vital structures that are in direct contact are significantly greater. A nodular sarcoid or a melanoma over the facial bones, over a joint, tendon, ligament or over a long bone may prove to be difficult to treat with any form of radiation without risk of causing damage. The hope is that the tumour is more sensitive to the radiation than the surrounding or contiguous structures. When concurrent damage does occur, management of the condition may be difficult. Although patience is important, some cases clearly necessitate intervention, including antibiotic therapy, hyperbaric oxygen treatment and resection.

Fractionation

Since the effects of radiation exposure are accumulative (or additive) the total dose of this type of radiotherapy is usually fractionated by spreading it out over time. This is done for several important reasons:

1. Fractionation allows normal cells to recover before subsequent doses are applied: tumour cells are generally less efficient in repair between fractions and so are less liable to repair. The overall damaging effect is therefore minimal on normal cells and maximal on tumour cells.
2. Fractionation also allows tumour cells that were in a relatively radio-resistant phase of the cell-cycle during one treatment to cycle into a more sensitive phase of the cycle before the next fraction is administered.
3. Tumour cells that were in a chronically or acutely hypoxic state (and therefore would be more radio-resistant) have a chance to reoxygenate between fractions, improving the killing effect of the radiation.

A variety of methods have been used in equine radiation therapy units to correlate different dose-fractionation schemes and to establish best practice for the various equine tumours. These methods are based on an understanding of the dose–response curves and the association (or lack of association) between the acute tissue reactions and the long-term sequelae of treatment.

One of the early attempts at altered fractionation was the use of split-course therapy. The aim was to achieve comparable (or better) levels of tumour control by allowing re-oxygenation with reduced acute toxicity to take place following radiation exposure. A 2–3-week interval between treatments was often employed. However, this prolonged rest period resulted in a poorer long-term tumour control because repopulation and accelerated repopulation dominated the inter-treatment pathology.

Other fractionation schemes include hyperfractionation, hypofractionation and accelerated fractionation. These probably have no material advantages in horses and are largely impractical at the present time. Developing radiation methods for horses may enable some of them to become more feasible in the future.

Hyperfractionated regimens deliver higher tumour doses while maintaining a level of long-term tissue damage that is clinically acceptable. The daily dose is unchanged or slightly increased while the dose per fraction is decreased and the overall treatment time remains constant. Hyperfractionation allows radio-sensitization through redistribution. With a greater number of fractions, it is more likely that the tumour will be in a sensitive phase of the cell-cycle at some time during the treatment. This strategy invariably results in more intense acute reactions when compared to conventional treatment. This is probably impractical in most equine circumstances.

In the accelerated fractionation schemes, the dose per fraction is unchanged while the daily dose is increased and the total time for the treatment is reduced.

Continuous hyperfractionated accelerated radiation therapy (CHART) is an intense schedule of treatment in which multiple daily fractions are administered within an abbreviated period. An intense acute reaction develops in most patients. This reaction usually limits the total dose.

In a concomitant boost technique, the first fraction of the day is administered in a larger volume and the second fraction is targeted to a reduced-boost field of treatment. The boost may be administered early in the course of therapy or toward the end of treatment. This regimen is based on the recognition that the treatment can induce an accelerated repopulation of the tumour cells, so that reduction of the overall treatment time results in improved control.

Fractionation can be used in all forms of radiotherapy. In the case of teletherapy (external beam radiotherapy) (p. 169) fractionation can be very accurately tuned or adjusted to ensure that tumour cells are destroyed while normal cells damaged during the process can recover between doses (p. 169). Fractionation can also be applied with brachytherapy – the source is applied directly to the surface of the tumour (in the case of plesiotherapy) or embedded for short periods within the tumour tissue (interstitial brachytherapy, p. 181). Radiation implants can be fractionated over minutes or hours, or they can be permanent or temporary seeds or linear 'wires', which continue to deliver low, but sustained (decreasing) radiation doses until they become inactive. This is the principle of the use of radio-gold pellets or iridium beads or wires (p. 182). Where a radiation source is embedded within the tissue and left in situ the radiation is maintained persistently and this also allows the accumulation of the total dose of radiation; this is not strictly viewed as fractionation, since every cell in the surrounding area will be subjected to the radiation and there is no pause during which normal cells can recover.

Unfortunately, typical ('standardized') fractionation schedules for horses are not yet established since there are so few centres undertaking this type of treatment. As clinical evidence emerges, it will surely become clear what fractionating is best suited to the individual tumour states in horses. In human radiotherapy, a concomitant boost regimen or hyperfractionation is used in some cases near the end of a course of treatment. This involves two fractions per day used in tumours that regenerate more quickly when they are smaller. Again it is not clear yet if the same cell behaviour applies in equine tumours, but it is reasonable to suppose that it might.

General principles of the application of radiation

The choice of radiation technique is dependent on several major factors, which vary considerably according to the special characteristics and the limiting factors of a particular tumour in terms of tumour type, location, extent, pathological behaviour and patient tolerance and compliance. There are a few additional constraints that apply to radiation therapy in particular, relating to its accessibility and the safety precautions that are required for operators.

Patient factors include:

1. *The tumour type and its particular characteristics and pathological and clinical behaviour*: The particular radio-sensitivity of the tumour is inevitably a significant factor – there is no point in attempting to treat a tumour when it is far less radio-sensitive than any vital tissues around it that will necessarily be harmed by the procedure. Disseminated tumours are not treatable by radiation. The best tumours are those that have relatively high mitotic index and which are reasonably confined to an accessible site. Accessibility will vary of course for the different radiation treatment methods, with superficial tumours being the most accessible to all forms of radiotherapy (see below).
2. *The location of the tumour and its relationship to other surrounding tissues and organs*: Where the tumour is very superficial and accessible, radiation may be more effective and there may be fewer constraints. Some tumours are inaccessible or are surrounded by tissues that will be susceptible to radiation damage.
3. *The extent/size of the tumour*: Larger tumours carry a notably lesser prognosis when treated with radiation. This can be mitigated somewhat by tumour reduction surgery or chemotherapy, but these are not always feasible. Widely disseminated tumours are not usually amenable to radiation therapy. Confined, accessible tumours with high radio-sensitivity are the best candidates for treatment.
4. *The duration of the tumour*: Long-standing tumours have a reduced radio-sensitivity (p. 165). Ideally, every tumour should be treated when it is very small and early in its course (Fig. 9.36). This seldom occurs in fact!
5. *The extent of secondary tumour effects* (paraneoplastic and other effects): Tumours with severe metabolic or physical effects are less treatable by any means. For example a gastric carcinoma has a singularly poor prognosis in spite of the theoretical sensitivity of the tumour to radiation – it is simply not feasible to treat it and by the time it is recognized the tumour is usually so advanced, and the secondary effects are so profound, that radiation is out of the question.
6. *Previous interferences and treatment attempts*: Any prior failures result in a significant reduction in prognosis for any method of treatment, including radiation. Prior attempts to treat a tumour inevitably result in delays and worsening pathological behaviour. It is far better to embark on a coordinated approach to any tumour – this gives the best possible outcome and it is far better to avoid ill-advised interference or panic interventions. Combination therapies can often help to minimize the side-effects. The best possible treatment should be used first – there is no point in holding the best treatment as a 'back-stop'!

External/other important constraining factors include:

1. *The availability of facilities for radiation*: These are regrettably few and far between, but as more is known about equine cancer medicine and equipment becomes relatively cheaper, it is likely that centres will be set up that are capable of carrying out radiotherapy in horses at some level or another. One of the major constraints on the development of equine oncology centres is the capital costs of the units. Radiation protection requires that human safety is paramount and so the facilities are usually extremely expensive to build. The equipment used is probably financially manageable in most circumstances, but running costs are high and case throughput would need to be significant to justify the costs. The logistics of radiation treatment often means that the patient is treated under general anaesthesia; this creates additional logistic complications.

2. *The availability of expertise in equine radio-oncology*: Most radiologists with veterinary experience work in specialist small animal practices or university faculties and the exposure to equine cancer medicine is therefore very remote. There is a clear need to develop equine radio-oncology specialists.
3. *Patient compliance*: Radiation therapy is usually physically demanding on the horse. Some methods require repeated general anaesthesia and others require isolation for extended periods. If, for behavioural, medical or other reasons, the horse cannot tolerate such a challenge, then radiation treatment cannot be used. This aspect is probably overstated in most circumstances, since with care and common sense (and some chemical assistance in terms of sedations and analgesics) most cases can in fact be handled well. Nevertheless, there are some cases where the required procedure would be impossible to carry out safely.
4. *Owner compliance*: Embarking on a course of radiation therapy demands that the owner understands the method that is being used, the logistic implications (some may require repeated long-distance transport to a centre for treatment), the prognosis and the costs involved, which are often considerable. There is little evidence-based medicine available for most tumour types so whilst there is a general optimism about radiation efficacy, the owner has to be aware of the lack of meaningful evidence that might temper the initial optimism. It is singularly unwise under any circumstances to promise 100% success. Nevertheless, radiotherapy is usually highly efficacious when it is properly conducted and planned on a tumour that is sensitive to that method of treatment.
5. *The limitations of cost for the owner*: Although radiation for some particular common equine tumours such as carcinoma and sarcoid carries a high rate of success, the cost is often prohibitive and this biases the treatment away from early intervention. It leads to the late presentation of cases and a corresponding reduction in prognosis. The concept that radiotherapy is a useful 'long-stop', which can be applied in the event of failure of other treatment is not the best way to use it. Typically, for all cancer medication methods, radiation is best applied when the tumour is early and when it is used in direct conjunction with other methods such as surgical tumour reduction. Where a case is presented with a history of several (often well-meaning) failed previous treatments, the chances that radiation will 'solve the problem' are not as high as they would be had the case been presented for radiation at the outset but usually if the treatment plan is calculated with all factors being considered, the outcome can still be remarkably good.

Effect of radiation on different types of cancer

Different tumours respond to radiation therapy in different ways. Some are faster and more sensitive, whereas others are slower and less sensitive to the effects. The specific response of a cancer to radiation is described by its radio-sensitivity and usually different tumours of the same type respond in a broadly similar fashion (whether on the same animal or on different animals). There may however be subtle differences that relate to the specific nature of an individual tumour. For the most part, tumour cells with a high radio-sensitivity are rapidly killed by modest doses of radiation. Good examples of this type of tumour include most lymphomas and germ cell tumours. Regrettably, because the majority of equine tumours are of epithelial origin, the majority of epithelial cancers are only moderately radio-sensitive; these tumours inevitably require significantly higher radiation doses of 60–70 Gy to achieve a cure. It is important to realize that some types of cancer are recognized as 'radio-resistant', i.e. much higher doses are required to produce a radical cure than may be safe in clinical practice. Renal carcinoma and melanoma are generally considered to be radio-resistant; there is no information on the value of radiation in renal carcinoma in horses and although equine melanomas have been shown to be sensitive to radiation in some cases, the majority have low radio-sensitivity.

There is an important conceptual difference in actual clinical practice between the radio-sensitivity of a particular tumour, which to some extent at least is a laboratory measure, and its radiation 'curability'. A good example of this is the multicentric lymphoma complex in horses – whilst a single focal lymphoma can be effectively treated with radiation, the widespread dissemination of the tumour makes the theoretical radio-sensitivity of the tumour largely irrelevant; the tumour is clinically and practically incurable. Similarly, it may be possible to treat an isolated melanoma with radiation, even though it has a low radio-sensitivity – it may be more treatable by virtue of its defined nature and its accessible location.

Therapeutic ratio

The 'therapeutic ratio' is the relationship between radiation dose and the probability of control of a particular tumour type. This relationship is a sigmoidal one that defines how many tumour cells are destroyed as the radiation dose increases until ultimately 100% of tumour cells are destroyed and a cure can be achieved. The same ratio, however, also applies to normal cells and so the probability of normal tissue damage and tumour cure are similar (Figs 9.37, 9.38).

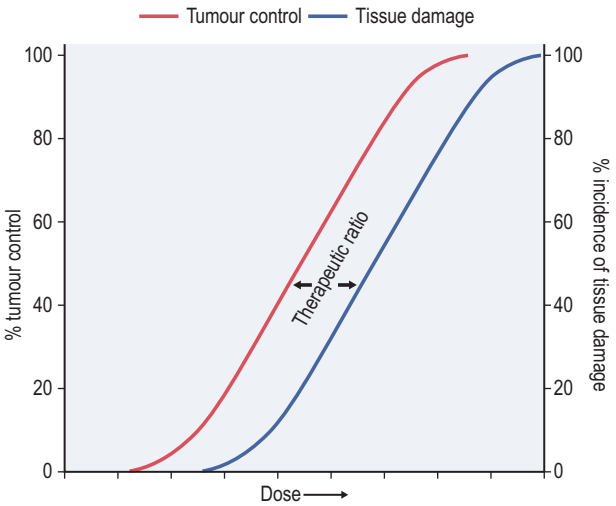


Figure 9.37 Therapeutic ratio. The response curves of both tumour cure and normal tissue complication are sigmoidal. The differential in dose to achieve these effects is the therapeutic ratio. *(Figure reprinted from Rubin P, Williams JP. Clinical oncology: a multidisciplinary approach for physicians and students, 8th edn. Philadelphia: WB Saunders; 2001 (Fig. 6.3); copyright 2001, with permission from Elsevier.)*

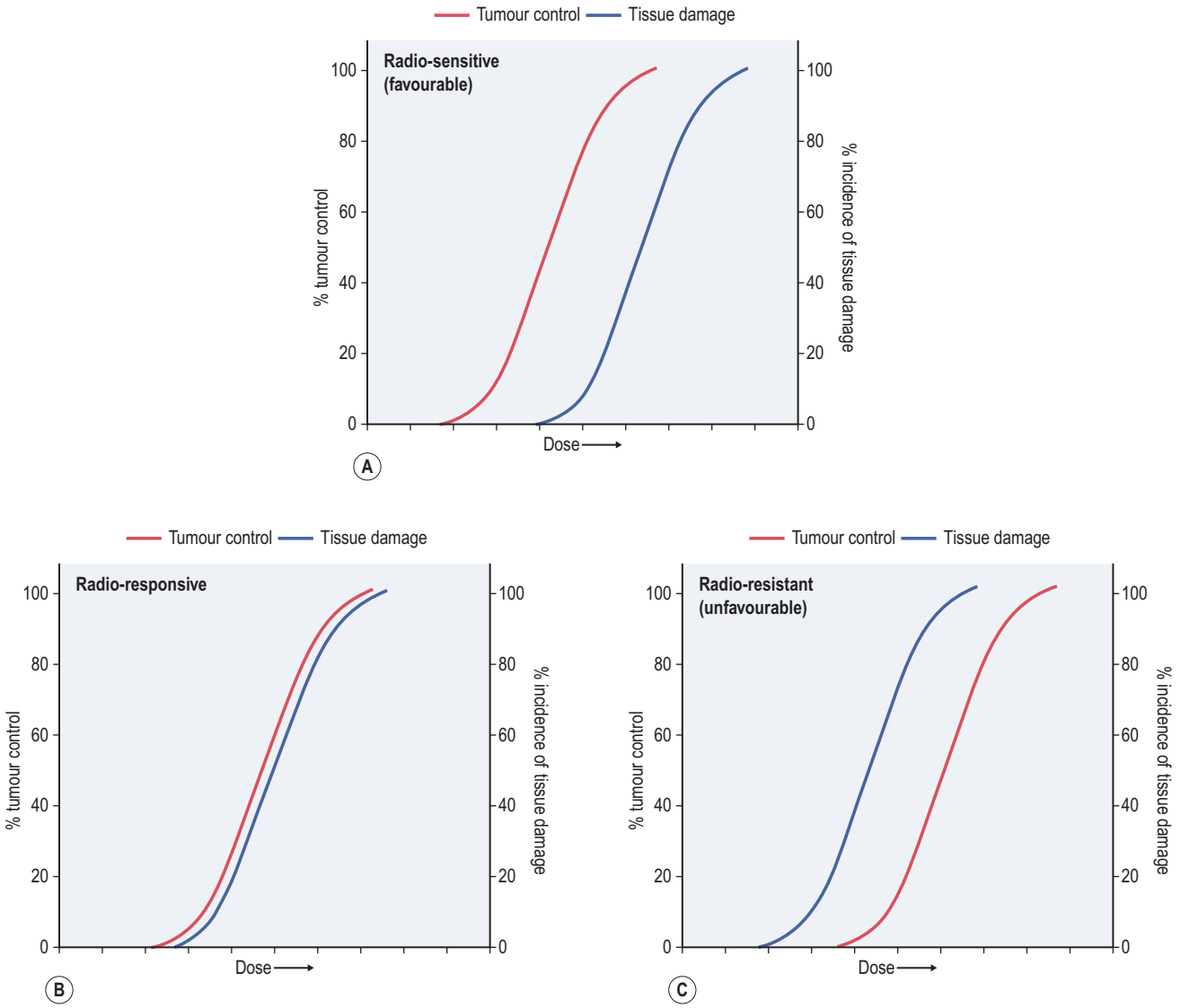


Figure 9.38 Different therapeutic ratios exist in different clinical circumstances, depending on the relative radio-sensitivities (dose–response curves) of tumour vs the critical normal tissue in the treatment field. These figures show **(A)** a favourable ratio, **(B)** a less favourable ratio and **(C)** an unfavourable ratio. *(Figures reprinted from Rubin P, Williams JP. Clinical oncology: a multidisciplinary approach for physicians and students, 8th edn. Philadelphia: WB Saunders; 2001 (Fig. 6.4); copyright 2001, with permission from Elsevier.)*

There are probably over 100 tumour types in horses and around 50 different normal tissue types, so there is ample scope for overlap between the curative dose of radiation and the unwanted damage to normal tissues. It is the relationship between normal tissue tolerance and tumour lethal dose that defines the 'therapeutic ratio'. When the tumour curve is set to the left of the normal tissue (the tumour is radio-sensitive, see Fig. 9.38A) the therapeutic ratio is favourable – the tumour can be destroyed without excessive damage to the normal tissues. However, when the tumour curve is set to the right of the normal tissue dose–effect curve, the tumour is radio-resistant (see Fig. 9.38C), and there is likely to be more damage than is acceptable to the normal tissue and a cure is unlikely unless the normal tissue can be sacrificed. The situation becomes unfavourable. The middle ground is termed 'radio-responsive', where there is little difference in sensitivity between the tumour and the normal tissues (see Fig. 9.38B). In order to 'push' the curve to the left to create a safety margin between the tumour and the normal tissue, adjunctive therapy, including surgical or chemotherapeutic reduction, may be required. An example of this is in the treatment of a palpebral sarcoid; here the ratio will vary for the various adjacent tissues. The cornea may have a dose–effect curve to the right of the tumour curve, whilst the eyelid skin may have a dose–effect curve to the left – the cornea will suffer whilst the skin will not (Fig. 9.39). This case also illustrates the fact that within an organ or structure, individual cells may have greater or lesser radio-sensitivity. In the example shown in Figure 9.39, melanocytes and hair bulb germinal cells have been irreparably damaged/destroyed by the radiation, whilst keratinocytes and fibroblasts, etc., have survived and remained (relatively) normal.

Early developing tumours are recognized as being more sensitive to all forms of chemotherapy and radiation treatment; if a tumour can be identified and categorized

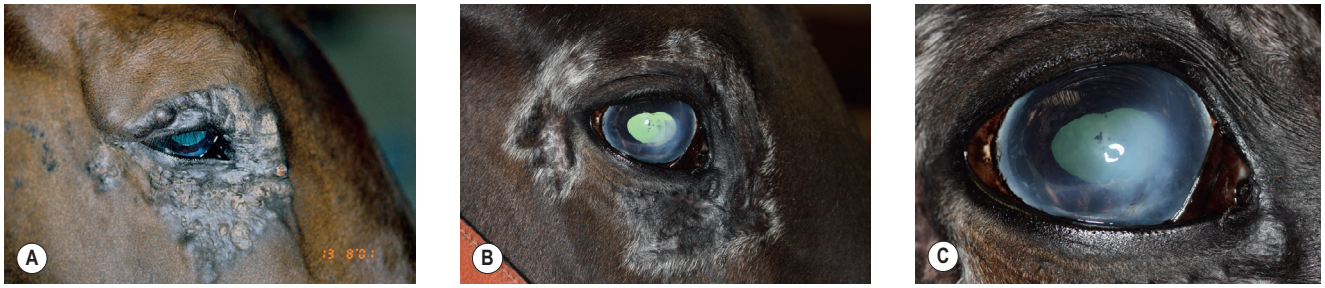


Figure 9.39 This case clearly demonstrates the differences in therapeutic ratio with radiation treatment. (A) An extensive and invasive periocular sarcoid was treated with iridium brachytherapy. **(B)** The effect on the tumour was correctly predicted with a really satisfactory long-term resolution of the tumour complex. **(C)** However, since the dose–effect curve for the cornea and iris were slightly to the right of that for the tumour itself, there was an undesirable effect of these structures in the long term (see close-up illustration). Recurrent episodes of sub-acute uveitis and corneal ulceration occurred over 2 years following the treatment but then settled into a static position.

very early in its progression, radiation may be an extremely potent therapeutic measure with a high treatment success rate – the same tumour in an advanced state will likely be much less sensitive.

Metastatic cancers are generally best regarded as being incurable with radiotherapy because it is not possible to treat the whole body; chemotherapy and immune methods are far more potent in that circumstance.

Palliative radiotherapy can be used, but in the equine species, it is not generally accepted; the welfare of the horse and the availability of humane euthanasia mean that under such circumstances, radiation is simply not offered. However, there are some circumstances where such an approach may be offered.

A severe and untreatable sarcoid could possibly be reduced by radiation and thereby permit the horse to live an active useful, if limited, life. Whether the long-term outlook might be better following radiation therapy than benign neglect is another matter, if the horse is not really markedly affected itself by the mass.

The response of a tumour to radiotherapy is also related to its size; large tumours respond less well to radiation than smaller tumours or microscopic disease. The most common technique to mitigate this problem is surgical resection/reduction prior to radiotherapy. The tumour can also be reduced by chemotherapy or immunotherapy prior to radical radiotherapy. An interesting additional technique is to enhance the radio-sensitivity of the tumour by administering radio-sensitizing drugs that enhance the effects of radiation, such as cisplatin, metronidazole, nimorazole and cetuximab. These drugs enhance the sensitivity of the tumour cells to the radiation and so widen the 'safety' index and improve the therapeutic ratio between the tumour control and the incidence of undesirable tissue damage (Fig. 9.40). This is likely to become a significant aspect of equine radiation therapy, particularly in tumours refractory to chemotherapy alone, but, as yet, there is little published evidence on the procedures for horses.

In some forms of radiation, sophisticated imaging mechanisms, including MRI (p. 178) and CT (p. 102), need to be used to identify the true extent of the tumour and its relationships with surrounding normal structures. For tumours of the head and limb extremities, a cast can be made that will allow the respective region to be fixed in a repeatable manner so fractionated doses of radiation can be given over several occasions to an identical location in an identical fashion. Fiducial markings on the skin and the cast are used to guide the placement of treatment fields. The more precise the radiation, the better the effects will be and the more satisfying the outcome. In the management of radiation therapy in equine (or other species) cancer, there is little that is totally certain and it is important to consider the case holistically.

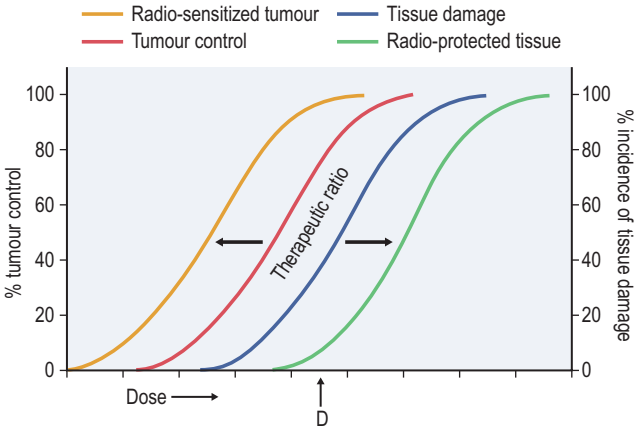


Figure 9.40 Although radio-sensitizers are not used in equine radiation therapy at the present time, their value should not be underestimated. The use of radio-sensitizers means that the tumour sensitivity is increased and the differential between the tumour and the normal tissue responses to the radiation is widened. This widening of the therapeutic ratio may mean that a higher dose of radiation can be used or that the same radiation dose will have a lesser harmful effect on surrounding tissues that might be of a vital nature. *(Figure after Rubin P, Williams JP. Clinical oncology: a multidisciplinary approach for physicians and students, 8th edn. Philadelphia: WB Saunders; 2001:119 (Fig. 6.5); copyright 2001, with permission from Elsevier.)*

Dose and tolerance

Oncologists use radiation administration in the same way as physicians use prescriptions of conventional drugs, and radiotherapy planning and decision-making is based firmly on its biological properties. Radiation doses or exposures are expressed in units of absorbed radiation per unit of tissue. The gray (Gy) represents 1 J/kg of tissue and this has replaced the roentgen and the rad (radiation absorbed dose). Although conversion is irrelevant nowadays, 1 Gy = 100 rad and 1 rad is therefore equivalent to 1 cGy (0.01 Gy).

The exposure and dose rate of radiation are governed by the inverse square law, so that the exposure decreases by four when the distance increases by two. This is the fundamental basis of safety measures taken to avoid unwanted exposure. The shorter the time of exposure and the greater the distance separating the radioactive source and the target (or accidental living tissue), the less the radiation exposure; the inverse square law.

The amount of radiation varies depending on the type and stage of tumour being treated. Every tissue and every tumour type will have its 'ideal' dose, although there is little that can be defined categorically about these in most equine circumstances, simply because of the paucity of evidence-based data. In human and pet animal radiation practice, the parameters are well established within ranges. In general, however, connective tissue, muscle, bone and nerve tissue are most tolerant of radiation exposure. High turnover glandular epithelial cells (such as intestinal mucosal cells), bone marrow cells, lymphoid tissue (in all sites including the gut wall), ovaries, testes and the lens are the most sensitive. Squamous epithelial cells and glandular tissues have an intermediate radio-sensitivity (Fig. 9.41).

Radiation therapy requires careful pre-treatment planning. Dosimetry is the science of the calculation of the required amount of radiation for a particular tumour under the prevailing circumstances and defines how that dose will be delivered spatially and temporally. Treatment planning is generally performed on dedicated computers using specialized treatment planning software. Depending on the radiation delivery method, several angles or sources may be used to summate to the total necessary dose. The skill lies in designing a plan that delivers a uniform prescription dose to the tumour whilst minimizing the dose of radiation applied to surrounding healthy tissues and organs.

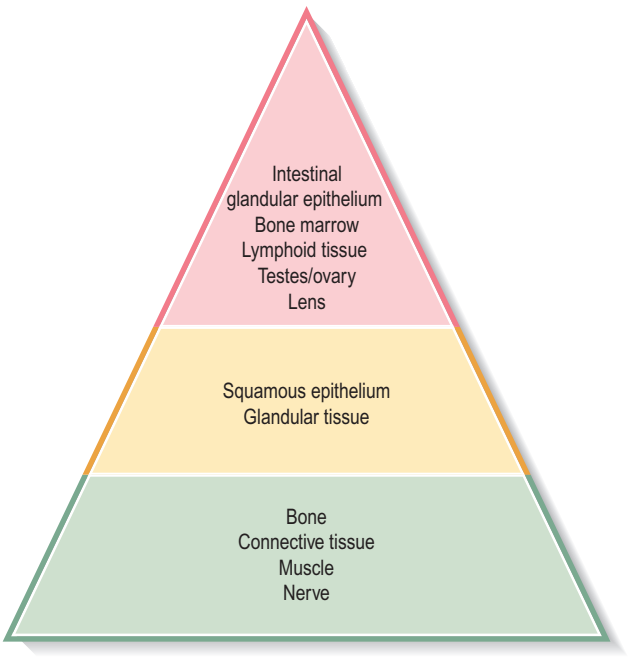


Figure 9.41 The relative radio-sensitivity of the various tissues. Tissues with the highest radio-sensitivity tend to be those with a high replicative rate and metabolic turnover. The densest tissues with low metabolic rates and turnovers usually have the lowest radio-sensitivity. There are, however, some exceptions to the rule.

Many factors need to be considered when selecting a dose of radiation, including whether the patient is receiving concurrent chemotherapy, patient comorbidities, whether radiation therapy is being administered before or after surgery and the degree to which any supportive surgery has reduced the tumour cell count. Additionally, there are some newer techniques that involve the concurrent use of radiation sensitizing drugs (p. 167).

The dose of radiation required to effect a cure is calculated for each tissue type involved and is set at a level that will result in the death of a high proportion of the cells, so that repeated high radiation doses (or in the case of some forms of interstitial brachytherapy sustained/persistent low-level radiation) result in progressive destruction of the tumour cell population. The objective has to be to set the dose in such a way that there is a positive therapeutic effect with minimal effect on normal structures, organs and tissues. However, in practice, there is little that is known about the various tumours of the horse even for the few major important tumours. Furthermore, the dose is not 'fixed' and will vary somewhat in respect of precise tumour type, grade, differentiation and clinical behaviour, tumour size, tumour location (in respect of adjacent vital or non-vital tissues) and its tumour-specific individual radio-sensitivity. For example, a typical dose for a solid epithelial tumour, such as an equine sarcoid, ranges from 60 to 80 Gy, while lymphomas may only require 20–40 Gy. Preventative (adjuvant) doses are typically around 45–60 Gy in 1.8–2 Gy fractions. All these facts are taken into account to try to define a tumour lethal dose that has a 9% probability of killing the tumour (achieving control). In humans, and to some extent in small animal species, practical guides for tumour radio-curability have been defined, but little is known about the horse in these respects. To some extent at least, tumour size is a critical factor in radiation planning and here again there is an unfortunate clinical problem in horses. Tumours that are very small are usually overlooked or ignored and many are presented in an advanced state.

Clearly, there are many limiting factors that can apply under any particular circumstances. The location, the tumour type, the size and the accessibility of the tumour are major issues, but there are other patient and logistic aspects that have to be considered carefully:

- The overriding consideration is the *availability of the facilities* for radiotherapy for horses. Necessarily, there are severe health and safety controls on the use of ionizing radiations. Special facilities and special monitoring systems have been in force and most countries have licensing authorities that govern the physical requirements and the actual procedures that can be carried out.
- Having the right facilities for radiotherapy is only a fraction of the logistic requirement. *A specialist radiologist* who is equipped to calculate the dose of radiation to be administered and the precise planning of the radiation treatment is essential.
- *The availability of the radiation materials* is also a significant limiting factor in most circumstances.

The clinical basis of radiation therapy

Radiation therapy is used to treat cancerous tumours because of its ability to control cell growth and replication.

Ionizing radiation damages DNA in the cells of the exposed tissue, leading to cell death. Radiation therapy may be curative in a number of types of cancer if they are localized to one area of the body. It may also be used as part of curative therapy to prevent tumour recurrence after surgery and to remove a primary malignant tumour (see below). Radiation therapy can also be used synergistically with chemotherapy (see below). Additionally, greater understanding of the molecular cellular effects has allowed radiologists to define treatment protocols using a variety of radiation types so that the targeted cells will be subjected to a maximum 'harm' whilst adjacent cells are spared.

The objective of radiation therapy is the obliteration of tumour cells whilst preserving the normal tissues and functions in surrounding areas. Radiation has several singular benefits in cancer treatment:

- It carries an improved overall survival rate in all species in which it has been used.
- Its efficacy can be enhanced by the use of fractionation (p. 169) and multi-beam radiotherapy (p. 178). New and more precise mechanisms are being devised for human and small animal cases, whereby radiation delivery is focussed either by use of multi-beam delivery (p. 178) or by the use of immunological or non-biological delivery methods, so that tumour cells are fatally harmed whilst sparing the surrounding and adjacent normal tissues.
- Radiation can be used to enhance and support concurrent use of chemotherapy ('radiation-chemotherapy') (p. 129) and surgical tumour reduction.

Many recent advances have been made with increasing understanding of the biological processes involved in radiation therapy. There are probably no differences in the tissue responses to radiation in horses when compared with other species and so it is likely that radiation will become a regular procedure in equine cases as well. The only limitations to its use at the present time are the costs and the availability of the required equipment and facilities. There are few individuals with the ability to offer specific equine radiation treatment, but that probably reflects the other limitations to its use.

Radiation itself causes no systemic toxicity and therefore has none of the side-effects of chemotherapy. It is also free of the constraints that limit surgery.

It is appropriate practice to include a margin of normal tissue in the radiation beam to allow for uncertainties in location and function. Radiation may also be directed at the draining lymph nodes if they are clinically, histologically or radiologically involved with tumour, or if there is thought to be a risk of subclinical malignant spread. No matter what method is used to deliver the radiation and no matter how carefully the treatment is planned (p. 177), there are always degrees of uncertainty. These uncertainties can be caused by several factors:

- Individual tumours of the same broad histological type (even possibly being histologically indistinguishable) may respond very differently in some circumstances.
- There may be some internal movement of tissues or organs (e.g. respiration and bladder filling) and there may be movement of external skin marks relative to the tumour position.

In general, success or failure of standard clinical radiation treatment is determined by the 4 Rs of radiobiology (p. 168).[82] These are:

1. Repair of DNA damage
2. Redistribution of cells in the cell-cycle
3. Reoxygenation of hypoxic tumour areas
4. Repopulation.

Radiotherapy in horses

There are very few scientific papers relating to radiation therapy procedures in horses and these usually involve limited numbers or at least single or few tumour types and so radiation remains a rather under-utilized and under-appreciated approach to cancer therapy.

In the horse, radiation therapy is currently only used to treat focal defined tumours in accessible sites because tumour cells are destroyed only in the anatomical area being irradiated; the accessibility of the tumours is, however, improving as increasingly sophisticated radiation techniques develop. It is not effective, at this time, for treatment of distant metastases or generalized neoplasia.

Tumours that are confined within a limited anatomical site and which are locally invasive are the best candidates for radiation treatment. Tumours that cannot be completely removed by surgical excision because this might result in an unacceptable functional or cosmetic defect, or tumours that have recurred after a previous surgical attempt, bare also reasonable prospects for radiation therapy. A significant reduction in the effects of radiation, and therefore the prognosis, is encountered when tumours have been subjected to previous ineffective treatment; the more times a tumour has been treated (whether by surgery or other means), the more difficult the tumour will be to control. This is a general principle for oncological therapy, but applies to radiation as much as anything else. Radiation should not really therefore be thought of as a 'fail-safe' approach to be used when all other options have failed. It is far better to apply it at the outset and so the availability and compliance issues (client and patient) have to be considered *a priori* at the outset of discussion.

During the planning stages of radiotherapy, the physical findings and diagnostic imaging information are considered carefully alongside the regional anatomy, the pathology and natural history of the particular tumour type. Initially, it is important to decide *if* radiation can play a significant part in the treatment of the patient. Once that has been decided, consideration must be given to whether the radiation will be prescribed as definitive, palliative or adjuvant therapy and whether it will be integrated with surgery and chemotherapy.

The three most important prognostic factors are:

1. *Tumour type*: For a given tumour size, the response of the tumour to radiation is a direct function of the pathological behaviour of the tumour (its histological type and its growth/replication rate). The radio-curability of the most common tumours in decreasing order is: squamous cell carcinoma/papilloma, sarcoid, soft tissue sarcoma (neurofibrosarcoma, fibrosarcoma, haemangiosarcoma) and melanoma. To some extent at least, the variability of the responses can be explained by variations in the cellular susceptibility to radiation

damage. In the case of melanoma, for example, the cells appear to be largely resistant to damage by radiation. The growth rate of individual tumours also affects the response to radiation; for example, a rapidly expanding fibroblastic sarcoid may be as responsive as (or more responsive) than a slow-growing carcinoma.

2. *Tumour location*: When they occur in different anatomical locations, tumours of the same histological type and approximately the same pathological behaviour may respond quite differently to radiation (and other treatment also, it has to be said). However, there is little information as to the variations that might be inherent in the various tumour types of horses simply because very few cases have been treated with radiation.
3. *Tumour volume*: The likelihood of a successful outcome from irradiation is inversely proportional to the tumour volume. Larger tumours have a worse prognosis and large tumours with metastatic extension are hopeless in most cases. Multiple considerations affect the prognosis and the likely benefits of radiation.

Radiation can be used as the sole method of treatment, in combination with surgery or other methods. The objectives of the combined approach are to improve the efficacy and reduce the morbidity of the treatment. The fundamental objective of using a combination therapy of surgery and radiation is that conservative surgery and adjuvant irradiation is as effective as radical surgery and results in less functional and cosmetic deficit. When given after surgery, radiation therapy is usually used to eradicate residual tumour cells within the surgical site – put simplistically, radiation has 'less to do' and 'can do it better'. It also may reduce the extent of margin contamination because, in the circumstances, radiation can be widened to include a margin that is likely to be present; the margins may effectively be sterilized of tumour cells.

Whilst it is clear that surgical tumour reduction can significantly improve the overall efficacy of irradiation, the quality of the surgical procedure has a profound bearing on the outcome. There is no point in accepting a poor surgical procedure on the basis that 'it does not matter, since radiation is going to be used alongside'. Since radiation therapy is much more effective for microscopic disease ($<10^8$ cells) and is more often much less effective for bulk tumour ($>10^{10}$ cells), surgical tumour reduction carried out prior to radiation, should aim to reduce the tumour to microscopic levels; this will require very careful surgical planning. Surgical excision, leaving visible tumour ($>10^9$ cells), gives very little therapeutic advantage; gross residual tumour is probably less treatable by radiation. For example, if 99% of a tumour containing 10^{10} tumour cells (10 grams of tissue) is removed surgically, there will be 10^8 ($10^{10} \times 0.01 = 10^8$) residual tumour cells and this number can easily be killed with radiation therapy. In contrast, surgical excision of 90% of a tumour with 10^{10} tumour leaves a significant tumour cell burden ($>10^9$ cells) and this is associated with a low probability of a cure with radiation therapy.

Radiation therapy can also be used as a cytoreductive measure prior to surgery. The tumour can be 'shrunk' by the radiation and so the surgery may become less challenging and so improves the prospect of an effective surgical resection. Residual tumour cells might reasonably then also be significantly harmed and would be less liable to survival.

The therapeutic benefit is also decreased by the number of previous unsuccessful surgeries and so a careful history is a fundamental aspect of the planning of radiation. Tumours such as sarcoids are frequently presented because they have failed to respond to several other modalities and radiation is then viewed as the 'long-stop' or fall-back position. This is absolutely not the way to use radiation. However, it is a fact of life that since radiation therapy is usually very expensive and logistically difficult, it is entirely understandable that previous attempts will have been made; owners may wish to explore every available option first before embarking on radiation. The way in which this attitude can be countered is by evidence-based information on the overall efficacy. Most clients will prefer a 90% chance of success that costs twice as much as a cheaper option with a 50% chance of resolution.

Planning of radiation fields (Fig. 9.42)

Clinical and imaging techniques are used to establish the physical dimensions of the tumour and its relationship to contiguous and adjacent tissues. The gross tumour volume (GTV) and the clinical tumour volume (CTV) are calculated using 3-dimensional imaging methods and these are then used to define the safe and effective radiation fields, ensuring adequate therapeutic 'cover' whilst sparing or minimizing the dose to the non-target healthy tissues (see Fig. 9.42).

The delivery of radiation to a tumour requires that the area remains stationary and fractioning the radiation into different treatment episodes requires that the same position is achievable on each occasion. Usually this involves the construction of a thermoplastic mould that will recreate the original planning position. The logistics of the procedure in horses are a considerable challenge.

Radiation treatment is prescribed in the same way as pharmaceutical drugs in terms of overall treatment type (electrons/beta or electromagnetic/gamma), total radiation dose and dose intervals (or when referred to in radiation prescription dose fractionation pattern) and duration (time). Based upon clinical evidence of large numbers of cases these aspects are calculated carefully using all the known factors relating to radio-sensitivity, location, size, tumour type, behaviour. Other aspects that are taken into account include the history and treatment history and the clinical status of the patient. It is neither sensible nor correct to simply prescribe an overall dose and pattern of delivery that ignores all the ancillary considerations apart from the type of tumour itself. There may be constraints on the number of general anaesthetics that the horse can tolerate and there may comorbidity. There are also usually cost and logistic implications for the owner.

Fractionation of the total prescribed dose of radiation to be delivered is important, particularly for the treatment of large tumours because it allows the use of large/maximal total dose without exceeding the tolerance of surrounding normal tissues. Conventionally, fractionation in humans and small animals is considered to be 1.8–2 Gy/day, administered 5 days each week for 5–7 weeks, depending on the particular clinical situation. However, in horses, such an approach would be almost impossible to carry out. Alterations to this scheme need to be considered for various reasons, including time constraints, staff constraints,

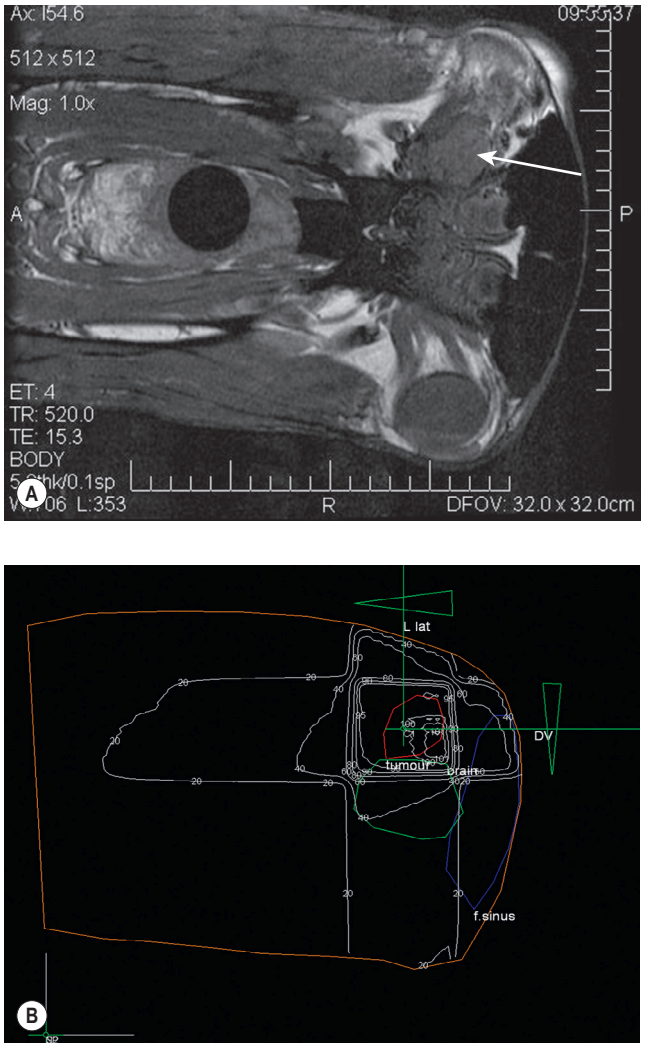


Figure 9.42 The generation of treatment plans is reliant upon computer programs that enable the radiologist to target the tumour accurately and completely without causing unwanted effects on adjacent structures. (A) MRI imaging of an orbital paraganglioma (arrow) that generated a radiation treatment plan **(B)** that would ensure that the external beam radiation treated only the targeted tumour tissue. Clearly, there is a temporal dissociation between the planning and the execution of the fractionation procedures and so it is vital that the target organ is very carefully orientated to ensure reliable, repeatable and accurate delivery to the tumour on each occasion. *(Figures courtesy of Rachel Murray and Merry Smith, Animal Health Trust, Newmarket.)*

machine availability and patient convenience. Although horses appear to tolerate repeated general anaesthesia for short-term procedures very well, the few centres performing equine radiation therapy usually try to deliver the prescribed total dose in as few fractions as possible. There is then an inevitable conflict between safety and efficacy; fewer fractionations are delivered with a higher power and this has dose-safety implications. In horses, the total dose of radiation (36–75 Gy) is usually administered in 6–12 fractions of 4–8 Gy each given at 14- or 21-day intervals over 3–4 weeks.

Associated/adjunctive chemotherapy

Numerous chemotherapy agents have been used either sequentially or concurrently to enhance the effects of radiation therapy. Most studies suggest that the concurrent use of radiation and platinum-based chemotherapy (using cisplatin or carboplatin) is likely to give the best results (p. 146). The concurrent use of chemotherapy also intensifies the acute toxicities of treatment; patients may require metabolic support during therapy. Other agents that are used in small animals and humans include fluorouracil, paclitaxel, docetaxel and hydroxyurea.

Biological agents are being studied that may reduce some of the toxicities of combined chemotherapy and radiation or may enhance the effect of radiation therapy. Keratinocyte growth factor (KGF) has been found to be useful in reducing mucosal toxicity in human and small animal patients undergoing total-body irradiation and may also be useful in other applications.

Safety aspects

Whilst radiation is used in diagnostic methods and in the management of a variety of non-cancer diseases, its use is usually inhibited by the threat of inducing cancerous changes in the treated cells. Radiation is one of the most potent carcinogens known (p. 44).

Principles

There are two main methods by which radiation therapy is delivered. The first is 'teletherapy', also called 'external beam therapy', in which the beam of radiation is delivered from an external radiation-generating source. The second is 'brachytherapy' where sealed radioactive sources are used to deliver radiation by being directly applied to the surface area of treatment (plesiotherapy) or by being implanted within the tumour itself (interstitial brachytherapy).

Teletherapy

In teletherapy (external beam radiotherapy) the radiation dose is beamed into the treatment site from an external generating source some distance from the patient. Radiation-generating machines used for teletherapy emit high-energy X-, γ- or β-rays, which can be regulated in both power and radiation type and therefore the depth of penetration can be controlled. The beam can be collimated to protect surrounding normal tissues. This means that precision treatment can be undertaken for deeper tumours as well as superficial ones. The method spares normal overlying skin and adjacent normal structures; treatment that avoids the possibility of skin or bone necrosis is clearly advantageous. In the case of the horse, megavoltage machines provide the best overall versatility and applicability. Inevitably, the cost of the generators is high and the dangers of radiation mean sophisticated facilities are essential; this means that there are few facilities that can handle horses. Additional costs are incurred through the use of sophisticated imaging systems and repeated general anaesthesia. Generally, superficial tumours are therefore more often treated with brachytherapy (p. 179) or plesiotherapy (p. 184).

The treatment plan is based on factors relating to the tumour type itself and its location and size. A sophisticated computer system is used to plan the delivery of the radiation accurately so that the tumour receives its computed maximal dose whilst the surrounding tissues are largely (or preferably completely) spared. Since the effects depend on accurate dosimetry of the whole tumour on several occasions through fractionation, the precise positioning of the tumour site is

fundamental to success. Even though the treatment times are usually only a matter of minutes, the horse usually needs to be under general anaesthesia; this adds to both the logistic and cost implications.

Method

Treatment is prescribed in much the same way as any pharmaceutical drug in terms of total (radiation) dose, duration of treatment (time) and administration pattern (frequency). Typically of any treatment that is prescribed, it needs to be carefully planned and accurately administered. The science behind radiation treatment is such that it really does require specialist involvement.

Once the horse is positioned accurately, the external beam radiotherapy is triggered as a series of small, equally-sized doses of radiation; these are referred to as dose fractions. In this way, the surrounding or overlying tissues are spared the strongest effects of radiation, whilst the tumour itself receives the maximal calculated dose overall.

For logistic reasons, radiation is applied to horses in as few treatment sessions as possible. Whilst in small animals and humans treatments may be delivered daily for 5 days over several weeks, in the horse this would be impossibly complicated. Horses usually receive the full dose (35–45 Gy) over 6–9 dose fractions of 4–5 Gy each twice or three times a week over 3–4 weeks. Even more aggressive courses can be used, although, inevitably, as the dose is increased the risks of unwanted effects also increase.

Radiation of this type is most suitable for treatment of deeper tissues involving bone, for example, and most reported cases involve oral/nasal tumours such as oral/nasal carcinoma, osteoma/osteosarcoma of the mandible, ossifying fibroma or ameloblastoma (Fig. 9.43). Limb tumours involving soft tissues of the limb (carcinoma, haemangiosarcoma and sarcoid) and tumours of bone and cartilage are also reported to respond positively. Clearly in circumstances when the tumour can be surgically reduced, the effects of radiation are likely to be significantly better and it can add positively to the overall prognosis of tumour surgery when it is used to prevent post-surgical recurrence. External beam radiotherapy is seldom used for superficial tumours, except when these are clearly inoperable or not amenable to any other treatment by virtue of location, size or number.

Since teletherapy has good palliative capabilities, palliation (non-curative treatment that results in tumour control as opposed to elimination) by radiation can be justified in some circumstances. However, inevitably, the question will be asked as to whether the treatment is ethically justified on welfare grounds when the outlook is extremely poor and the horse is required to undergo multiple major procedures. It seems that many owners are willing to subject their horses to the rigors of palliative radiotherapy for sentimental or commercial reasons. The ethical dilemmas have to be faced in individual circumstances.

The results of teletherapy treatment of equine tumours are largely dependent on the usual factors that affect outcome. In many circumstances, tumours are presented so late that palliation is the only way forward, but where tumours are identified in a timely fashion and are managed correctly from the outset, the results can be very acceptable (Table 9.6).

Brachytherapy

Brachytherapy (internal radiotherapy) is delivered by placing radiation source(s) directly inside or next to the area

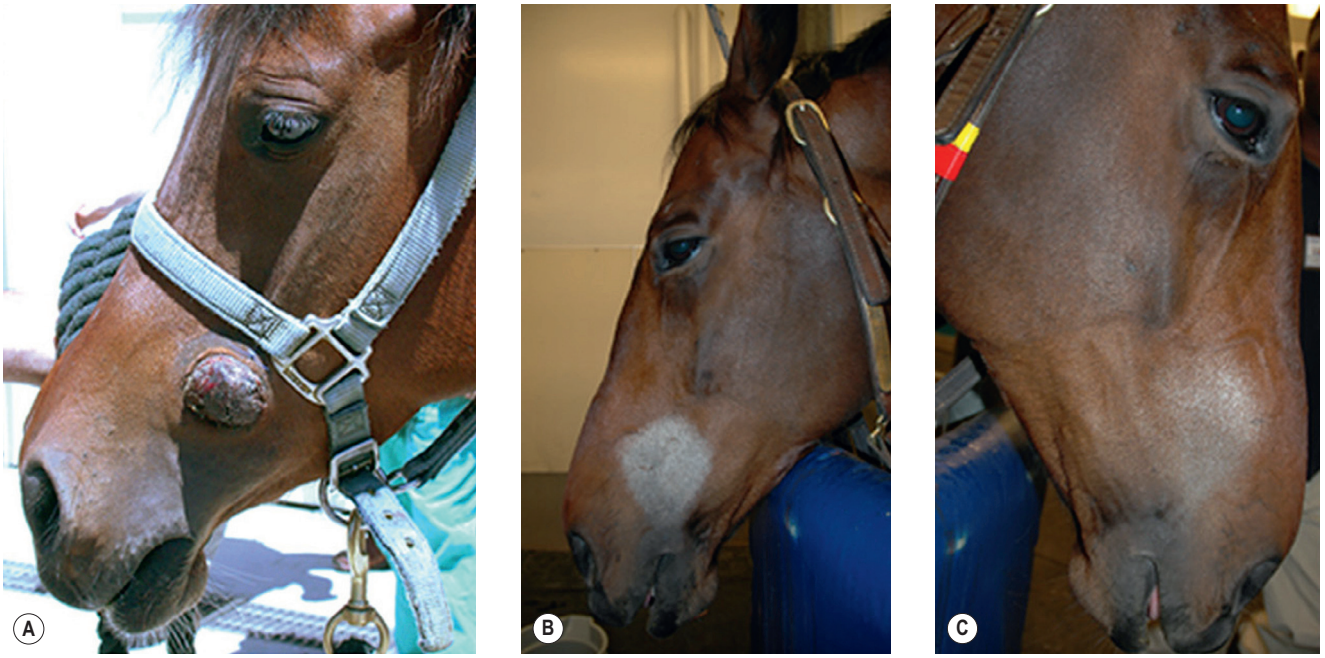


Figure 9.43 Even when radiation is strictly controlled, some collateral effects are still likely to occur – whether they are clinically significant or not. **(A)** This 5-year-old Dutch Warmblood gelding was diagnosed with ameloblastoma that had extended through the buccal wall onto the side of the cheek. The tumour was radiated using 12 dose fractions of 4 Gy each on Monday, Wednesday and Friday for 4 weeks, delivering a total dose of 48 Gy. **(B)** The tumour site at 4 years' post-radiation showing some loss of hair and pigmentation but functionality and cosmesis was excellent. **(C)** Mild hair coat and skin changes on the contralateral (unaffected) cheek were present as a result of exit beam exposure.

Table 9.6 Results of external beam radiation (teletherapy) in 27 horses (University of California, Davis, CA)

Tumour location	Tumour type	Number	Remission period (months)
Mouth	Squamous cell carcinoma	1	4 (euthanasia regional metastasis)
Mandible	Osteoma	2	34/26
	Fibroma	1	22
	Ameloblastoma	3	34/42/54
	Squamous cell carcinoma	5	2 (euthanasia regional metastasis) → 21
Larynx	Squamous cell carcinoma	2	3 (euthanasia regional metastasis)
Orbit	Squamous cell carcinoma	2	2 (euthanasia regional metastasis)/12
Parotid	Melanoma	3	24→48
Nasal cavity	Myxosarcoma	1	6 (recurrence)
	Lymphoma	1	32
	Squamous cell carcinoma	2	8/11 (both recurrence)
Metatarsus	Squamous cell carcinoma	1	34
Hoof capsule	Squamous cell carcinoma	3	3→16

Reprinted from Theon AP. Radiation therapy in the horse. Vet Clin N Am Equine Pract 1998; 14:673–688, with permission.

Table 9.7 The physical characteristics of some of the radionuclides used in brachytherapy

Isotope	Form	Half-life	Emissions	Equine use
Radium-226	Wires/needles	1620 years	Gamma (2.45 MeV)	Not reported
Caesium-137	Afterloading seeds/wires	30 years	Gamma (0.662 MeV)	Not reported
Cobalt-60	Tubes afterloading	5.3 years	Gamma (1.3 MeV)	NO[a]
Iridium-192	Wires/seeds	74 days	Gamma (0.38 MeV)	YES
Iodine-125	Seeds	60 days	Gamma (30 MeV) X-rays (36 keV)	YES
Gold-198	Seeds	3 days	Gamma (0.4 MeV)	YES
Strontium-90	Plaque	29 years	Beta (2.3 MeV)	YES
Ruthenium-106	Plaque	1 year	Beta (3.54 MeV)	NO

Only iridium, gold and strontium have been used with any degree of regularity.
[a]*Cobalt teletherapy has been reported and has a high success rate.*
Reprinted from Theon AP. Radiation therapy in the horse. Vet Clin N Am Equine Pract 1998; 14:673–688, with permission.

requiring treatment (see Fig. 9.46). This is an ideal method of using radiotherapy, since the dose can be accurately delivered to the tumour only over a relatively short period of time. The most common radioisotopes used in equine brachytherapy are iridium-192 and iodine-125 but others, such as gold-198 have also been used (Table 9.7). The latter has some advantages in having a very short half-life (48 h) and so the gold 'seeds' can be left in situ after placement. However, in order to deliver an effective 50–60 Gy, the handling of the seeds is a serious risk to operators. Gold-198, iodine-125 and iridium-192 emit γ-rays. They are available in wire or seed forms. Iridium-192 is usually used in wire forms that are sheathed in platinum, whilst the latter are incorporated into plastic tubing in a pattern that is pre-planned for the tumour shape and size.

The effects of the radiation remain local to the tumour and the surrounding tissues are largely or completely spared. Interstitial brachytherapy is used either on its own or in conjunction with surgical debulking. Typically of all forms of radiation, the extent of the treatment will depend on whether it is to be used to treat a gross solid tumour, a partially excised tumour with macroscopic residual tumour or as an adjunct to tumour excision to ensure elimination of microscopic tumour residues. Where it is used in conjunction with surgery, it can be used intraoperatively, i.e. at the end of surgical tumour reduction or where primary wound healing can be achieved 2–3 weeks following surgery, when the site has had some chance to heal. As might be expected, radiation will have its best effects when the tumour burden is at its lowest and so it is best applied in the early or immediate postoperative period. The possibility of radiation harm to healing is important, but there is delicate balance between the treatment efficacy and the harmful effects on wound healing. It is important to recognize that there is very likely to be *some* residual effects on healing.

Generally, implantation of all brachytherapy sources requires careful planning and accurate dosimetry that may involve sophisticated imaging techniques and computer-assisted dose calculations. For these reasons, implantation is therefore usually performed with the patient under general

anaesthesia. However, the horse is probably more generally tolerant of the use of radiation, with few side-effects being reported. Since most treatments involve superficial skin tumours (such as sarcoid, melanoma and squamous cell carcinoma), insertion can be practically achieved in many cases in standing, sedated patients.

The process of insertion of the radioactive sources is called 'implantation'. Where implantation is carried out under general anaesthesia, this does often result in increased personal exposure because the horse has to be monitored during recovery and then has to be moved to its isolation facility. In some circumstances, such as is carried out at Liverpool University, the procedure is carried out under standing sedation and local nerve blocks. The process is extremely fast and efficient, with far less human exposure risk than the overall amount when general anaesthesia is used. Clearly, there will be circumstances when a general anaesthetic is unavoidable.

Permanent implants are not usually preferred for safety reasons; the one exception is the use of radio-gold (gold-198) where the half-life is very short (48 h) and decay therefore occurs rapidly. It is important however to realize that even in this circumstance, there will be some residual radiation for a very long time – whether that is significant or not in terms of human exposure hazards.

Temporary implants have the singular advantage in that once they have been removed when the calculated dose has been delivered, the patient is totally safe and no residual radiation hazard will exist. Temporary implants can be afterloaded manually, which inevitably entails a degree of operator hazard, or mechanically through more sophisticated equipment and facility, which demands a far greater degree of patient restraint and zero operator exposure hazards.

The implantation of the radioactive sources can be carried out in several ways:

Manual implantation

Traditionally, implants are loaded into preplaced introducers with the aid of long-handled forceps. Once the sources are correctly located, the introducers are removed and the wires are locked into place either with sutures or with lead beads and washers. In this circumstance, the sources can be left in situ for as long as is required to deliver the radiation dose. This low-level persistent radiation exposure does have implications for normal tissues of course. However, low emission sources can be used; the advantage of this process is that operator hazard is very low, provided that distance and time are manipulated correctly during implantation. Fast insertion of a low-emission source using long-handled instruments results in minimal exposure.



It is still exposure, however it is viewed, and therefore carries an inherent risk that can be a significant problem in some circumstances. Careful monitoring of exposure using finger dosimeter rings, personal dosimeters and other safety precautions will enable the operator(s) to remain within the legal and sensible safe limits of radiation exposure.

Following insertion, the horse is moved immediately to a radiation protection loose box and is fed and watered remotely. Observation through lead glass windows or camera technology allows the horse to be checked. Although the horses are isolated, there is seldom any behavioural problem. In some circumstances, a pre-treatment customization period in the confined facility is used to test the horse's ability and willingness to remain isolated.

During the treatment session, the sources emit a constant stream of radiation over the required period – usually between 5 and 10 days with a low-dose rate (LDR) radiation source; 0.3–0.5 Gy/h is usually the target. Overall, the dose that is required will vary for different tumour types and different clinical circumstances; 35–70 Gy is the common range, with the lower-end doses being used when responsive soft tissue tumours (e.g. superficial squamous cell carcinoma) are being treated or when radiation is being used to 'sterilize' a surgical excision site. The higher-end doses are prescribed for intact gross tumours and when there is macroscopic postoperative residual tumour.

Hazards/precautions

One of the major complications of LDR temporary implantation techniques is the lack of detailed control. Whilst the case is held within the radiation isolation facility, the horse is a radioactive hazard and so if the horse were, for example, to develop some other problem, such as colic, or becoming cast in the box or to injure itself, the sources have to be removed immediately prior to any other clinical assessment. This will inevitably add to exposure risks.

The second hazard is dislodging of the implants either within the tumour (so rendering the dose calculations invalid and the efficacy lowered) or when the implant falls out of the tumour and into the bedding. In the former circumstances the outcome might be adversely affected or there might be more significant effects on normal adjacent tissues since they might be exposed to far more radiation that was planned. In the latter circumstances the tumour will of course receive no further radiation and so will not be treated effectively. In the event that the source was to drop into the bedding, it can be found relatively easily and quickly with the aid of a Geiger counter. After removing the horse from the facility (and of course after removing any other sources), the stable is rapidly scanned to identify the quarter where the source lies. Once the general location is known, the counter is used to subdivide the area down until the source is located and placed in a safe container. In the event that the source does become dislodged, it is wise to scan the horse itself, in case the source has been eaten or is stuck to the horse. In the event that the source has been eaten, there is a long-term serious radiation hazard for operators and the horse has to remain in radiation isolation until it shows no radiation at all either through decay or through passage of the sources down the alimentary tract and into the faeces, from where they can be retrieved. Such circumstances are very rare but suitable plans have to be in force to cope with the special needs of the system. These emergency plans have to be clearly understood by all parties involved in the process and by the owner of the horse from the outset.

Remote afterloading

A new technique that improves operator and patient safety in every area and improves overall dosing accuracy is known as 'remote afterloading'. In this method, there is no operator exposure risk and the horse remains radiation free during the whole course of treatment apart from the

exposure days when high-dose rate (HDR) radiation is actually in the tissue. This method also shortens treatment times and so has major advantages; it is possible to deliver the full radiation dose in a matter of minutes. There is no direct handling of the radioactive sources. It does, however, have major disadvantages in that it requires special equipment and a very secure radiation facility that will enable an anaesthetized horse to be treated.

In this method, the applicators are inserted according to the plan created from imaging techniques and the treatment dosing is planned for each part of the tumour. Once these calculations and plans have been completed, a computer-controlled system is used to drive high-activity (10 Ci nominal activity) iridium-192 sources from a shielded safe into each introducer for a pre-calculated time period, in turn, according to the treatment plan. Different parts of the tumour might require different radiation doses and so the computer applies and withdraws the sources according to the pre-treatment plan. On completion, the sources are withdrawn back into the shielded container and the horse is allowed to recover from its general anaesthetic. Treatments are usually carried out on an outpatient basis, with the horse returning home between treatments. Two or three dose fractions are usually prescribed to deliver the total required dose of between 25 and 40 Gy; note that this overall dose is somewhat less than the dose for LDR methods. Deep-seated tumours can also be treated using this method – the constraints are usually set by the imaging methods available and the enthusiasm and care of the operator. The method is far cheaper to perform on each case and is far safer from operator and management perspective, but requires much more sophisticated facilities, and so this is not yet in widespread use in equine oncology units. The system is very economical, since the radiation sources last a very long time and are stored in a totally safe environment within the machine. The results are impressive and so it is expected that this method will become the standard approach to equine brachytherapy.

- The introducers are placed according to the treatment plan and left in situ
- The horse is then restrained suitably (usually under general anaesthesia) in an isolation facility and the introducers are then connected to the delivery equipment
- When the operators are satisfied that everything is ready and all personnel have withdrawn from the treatment room, the machine is activated and very high-output iridium-192 sources (10 Ci nominal activity) are delivered from a safe unit into each of the introducers for a predetermined time period that delivers the calculated fractionated radiation dose. Different parts of the tumour might require different radiation doses and so the computer applies and withdraws the sources in each introducer according to the pre-treatment plan.

The system is very economical, since the radiation sources last a very long time and are stored in a totally safe environment within the machine. The procedures are usually of short duration (5–10 min), during which time the required dose (25–35 Gy) is administered in two dose fractions 1 week apart. The procedure is well-tolerated, even in standing horses, although more usually, it is performed under a short-duration general anaesthesia. Although the procedure has to be carried out in a very protected/shielded facility, there is no risk of human exposure at all. The treatments are usually performed on an outpatient basis at 1-week intervals. A set of 2 or 3 treatments are usually all that is required (Figs 9.44–9.46). The horse is obviously not radioactive when it leaves the facility.

Brachytherapy sources

Iridium-192

Most modern brachytherapy systems are based on the use of iridium-192. The high specific activity of iridium-192 permits a high activity source to have small dimensions and it is therefore ideally suited to use as in brachytherapy and, in particular, to afterloading systems. Lead shielding has limited protective effects.

Iridium is usually used in the form of wires or seeds for low-dose rate (LDR) manual implants. The central radioactive core of the pellets or wires is usually surrounded by a platinum sheath. The wires can be obtained in coils or in hairpin configurations in two thicknesses. The thin section wire (0.3 mm) is usually delivered in coils and is cut to the

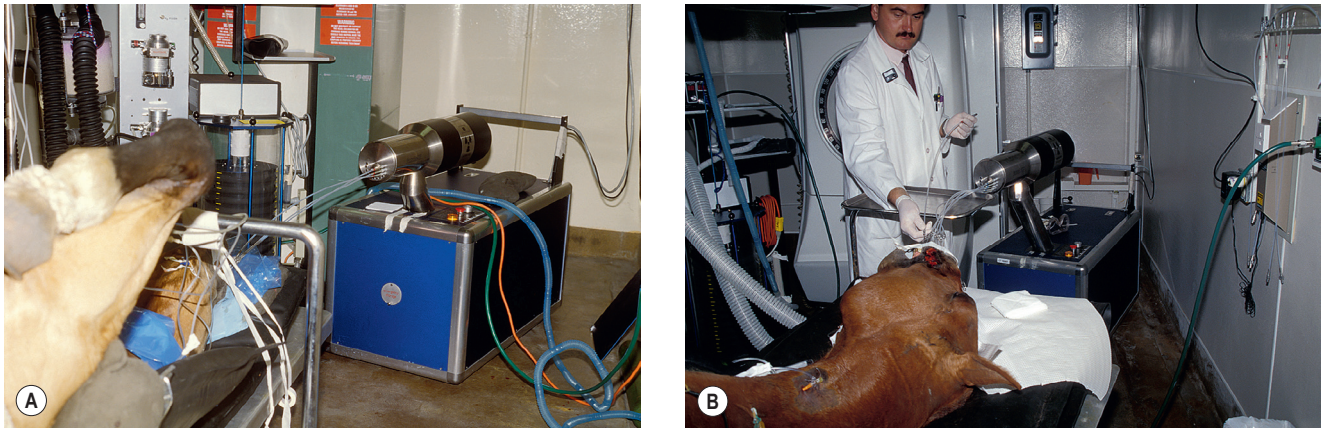


Figure 9.44 Remote afterloading of high-intensity brachytherapy using iridium-192 seeds is undertaken in strictly controlled facilities with the patient under general anaesthesia. Note that the system is completely safe while the sources remain within the machine itself. The duration of treatment is usually short, so the procedure is entirely suited to short-duration anaesthesia. If an organ or structure is accessible and the tumour is of a suitable size and type to respond to the radiation amount that can be given, the method is probably applicable. In these two cases **(A,B)** facial carcinomas are being treated. *(Figures courtesy of Alain Theon.)*

required length by the user but is less useful in equine circumstances than the 0.6 mm wires, which are less liable to bending and breakage. The hairpin configuration has two 'legs' of 60 mm length, with a crosspiece that measures 12 mm. Iridium seeds are in effect short lengths of iridium in a platinum sheath.

For high-dose afterloading brachytherapy systems (Fig. 9.47) higher activity sources are used.

Iodine-125

Iodine-125 is a daughter product of xenon-125, which has a half-life of 60 days. The emitted γ-ray has an energy of 35.5 keV. This low energy means that lead shielding is highly protective. For brachytherapy, iodine-125 is incorporated into implantable seeds and there are several different commercially available types. They are only rarely used in horses but are reported to be effective.[83]



Figure 9.45 Accessibility to the tumour is clearly fundamental to the efficacy of high-dose radiation (HDR). A penile sarcoid is being treated. As imaging becomes more sophisticated, the opportunities to use HDR systems becomes wider. The benefits are worth the development of innovation in terms of gaining access and, as a result, more challenging tumour states are being treated. *(Figure courtesy of Alain Theon.)*

Gold-198

Gold-198 decays by beta emission to an isotope of mercury with a half-life of 2.7 days. The isotope emits a 0.412 MeV γ-photon radiation (plus a few insignificant amounts of other energies).

Grains consisting of gold-198 encapsulated in platinum have been used as permanent implants in horses, especially around the eye.[84] Typical of all other radiotherapy techniques, radio-gold has been used adjunctively with other tumour reducing methods, such as hyperthermia, where it has a synergistic effect.[85] However, at least in the UK, gold seeds are no longer available.

In one report,[85] a single horse with a unilateral ocular squamous cell carcinoma was treated effectively with a combination of repeated radiofrequency hyperthermia and interstitial radiotherapy. Gold-198 implants were used to deliver a total dose of approximately 50 Gy over an area of 1 cm^2. Hyperthermia was repeated three times, and radiotherapy was used twice. The case was reported to have a complete cure with no complications.

The results of interstitial brachytherapy on equine tumours have been consistently excellent, no matter what system is used (Table 9.8), and range from 75% to 100% non-recurrence at 12 months. Most studies confirm the better long-term outcome for smaller tumours (<2–3 cm). Larger tumours clearly need higher doses but this risks concurrent/collateral damage to normal tissue. As a result, the benefits of adjunctive effect of surgical tumour reduction, preferably to microscopic extent, are well recognized. Dose rates of around 30 Gy for HDR methods and 50 Gy for LDR methods appear to be well-tolerated by horses, with little untoward effects, and are capable of producing cosmetically very good cures. Concurrent chemotherapy with cisplatin or 5-fluorouracil can be helpful in reducing the overall required dose of radiation and improving the prognosis.[86]

One of the main aspects of client communication during radiotherapy is the information provided regarding the progression of the treated site following the treatment. Radiation is not a 'quick-fix'; the benefits develop

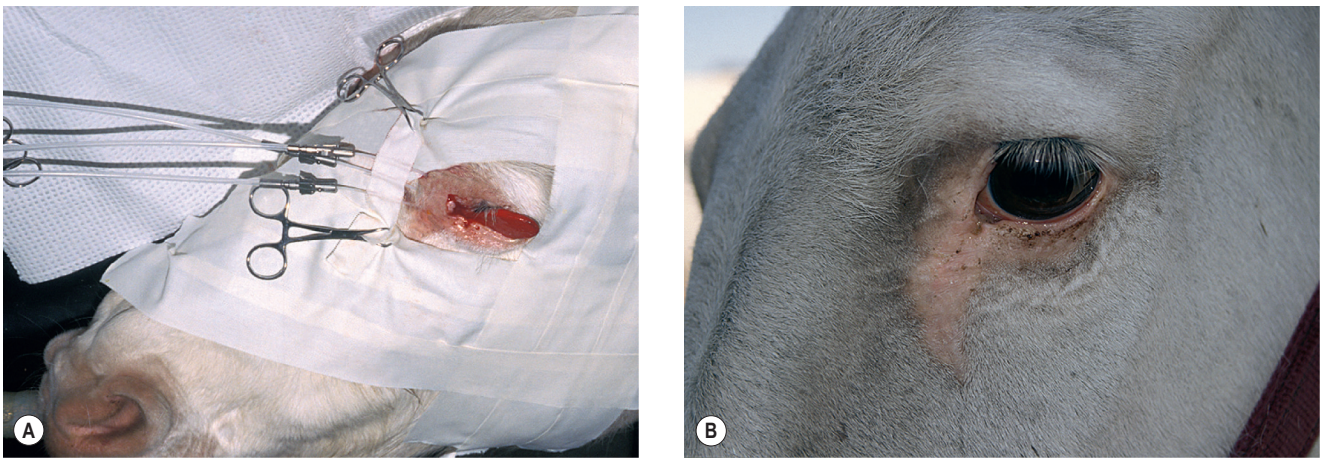


Figure 9.46 A palpebral carcinoma involving the caruncle and the medial palpebral conjunctiva was treated using HDR. **(A)** Typically the process is carried out under general anaesthesia, as in this case. The introducers are pre-placed and then connected to the delivery apparatus; this delivers the radiation sources to predefined sites for predetermined periods so that the required precise dose of radiation is administered accurately to the tumour and not the surrounding normal tissue. **(B)** After 18 months, the cosmetic results are extremely satisfying, with normal function and no recurrence or new carcinoma.

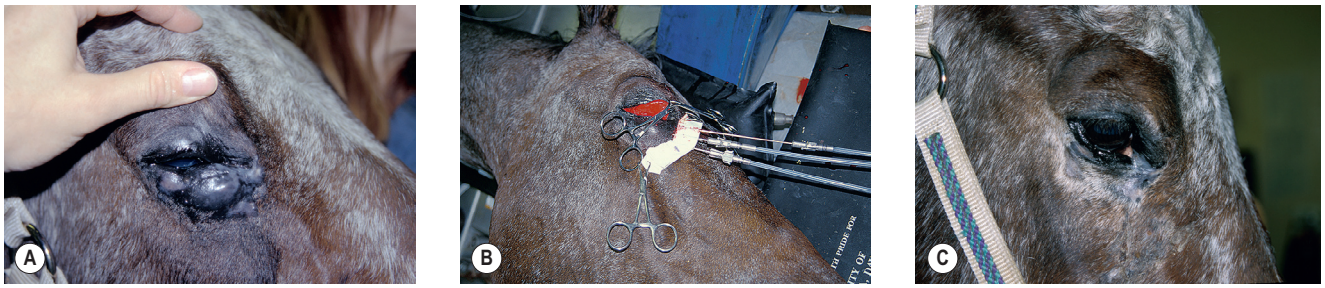


Figure 9.47 Management of an aggressive complex sarcoid. (A) This aggressive complex sarcoid was probably untreatable without radiation. **(B)** Preliminary surgical tumour reduction was followed immediately by HDR with afterloading; high-activity iridium-192 sources were used to deliver high-dose rate (HDR) radiation. The afterloading HDR system was performed under short-duration general anaesthesia at the University of Davis, California Equine Oncology Unit. Whilst this method requires far more sophisticated technology and facilities, the outcome is excellent **(C)** and the operator and patient hazards are eliminated; personal exposure to radiation using this method is zero. *(Figures courtesy of Alain Theon.)*

Table 9.8 The published outcomes of brachytherapy involving the major isotopes that have been reported in equine oncology to date

Isotope	Source	Tumour type	Cases (*n*)	Location	Dose (Gy)	No recurrence (%)	
						12 M	24 M
Iridium-192	a	Sarcoid/SCC	26	Periocular/skin	70	100	–
	b	Sarcoid	66	Periocular	65–78		95
	c	Sarcoid	8	Periocular	35–55	100	
			15	Non-periocular		87	
	d	Sarcoid		Periocular/skin	54–93	92	89
	e	Sarcoid/SCC	115	Periocular	60	84	77
Iodine-125	g	SCC	17	Ocular/ periocular	36–100	76	60
Gold-198	f	Various	19	Fibroma/ sarcoid/SCC	70	87	

SCC, squamous cell carcinoma.

a. Wyn-Jones G. Treatment of equine cutaneous neoplasia by radiotherapy using iridium-192 linear sources. Equine Vet J 1983; 15:231–363.

b. Knottenbelt DC, Kelly DF. The diagnosis and treatment of periorbital sarcoid in the horse: 445 cases from 1974 to 1999. Vet Ophthalmol 2000; 3:169–191.

c. Byam-Cook KL, Henson FM, Slater JD. Treatment of periocular and non-ocular sarcoids in 18 horses by interstitial brachytherapy with iridium-192. Vet Rec 2006; 159:337–341.

d. Turrel JM, Stover SM, Gyorgyfalvi J. Iridium-192 interstitial brachytherapy of equine sarcoid. Vet Radiol 1985; 26:20–24.

e. Theon A, Pascoe JR. Iridium-192 interstitial brachytherapy for equine periocular tumours; treatment results and prognostic factors in 115 horses. Equine Vet J 1994; 27:117–120.

f. Wyn-Jones G. Treatment of periocular tumours of horses using radioactive gold-198 grain. Equine Vet J 1979; 11:3–5.

g. Walker MA, Goble D, Geiser D. Two year non-recurrence rates for equine ocular and periorbital squamous cell carcinoma following radiotherapy. Vet Radiol 1986; 4:146–148.

progressively over some months and many reports note that the full benefit is not achieved before 7–12 months following treatment. Furthermore, during the postoperative period, there may be periods of time when there is considerable tissue reaction and possibly even localized tumour necrosis. Clearly, this is far more likely when a gross tumour is being treated rather than a microscopic sterilization in a healed surgical site.

Overall, radiation is the treatment of choice for smaller and many larger accessible tumours in horses. At particular sites, it has singular advantages. Where tumours are large, they will benefit from surgical tumour reduction to the best possible level and concurrent chemotherapy may be a singular advantage in terms of long-term prognosis.

The non-recurrence rates for radiation treatment of sarcoid and squamous cell carcinoma and a few other tumour types are excellent.

Note

Radiation is probably the 'gold standard' for treatment of most localized superficial and deep tumours in horses against which other methods should be measured.

Plesiotherapy

Plesiotherapy (surface brachytherapy) is the procedure when radioactive sources are applied directly onto the surface of a tumour. In veterinary medicine, this is currently largely restricted to the use of a strontium wand/plaque. The source is mounted on a stainless steel shaft with a protective β-radiation shield to protect the operator. The active surface is applied directly to the tumour to deliver a stream of high-energy electrons. Since β-radiation is particulate, it has no therapeutic effects beyond 2–2.5 mm in tissue. Fractionation can be used by repeated applications to

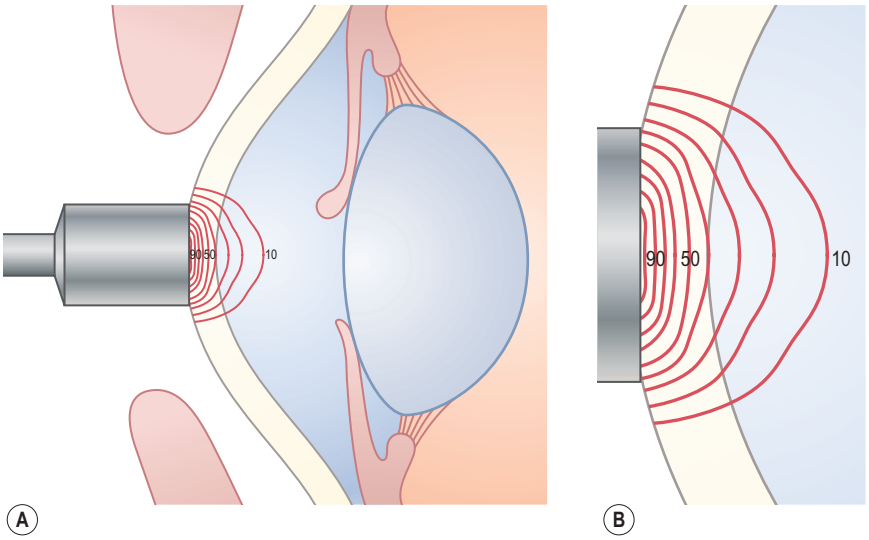


Figure 9.48 Placement of a strontium-90 applicator (wand or plaque) on the cornea results in therapeutic doses of radiation within the cornea but a rapid fall off beyond, so that no significant radiation reaches the iris or lens.
(A) Radiation dose restricted to the cornea. **(B)** Dose iso-curves for the strontium wand used at the University of California, Davis. *(Figure redrawn from Theon AP. Radiation therapy in the horse. Veterinary clinics of North America Equine Practice 1998; 4:687, with permission).*

achieve a therapeutically effective overall dose over a period of time. In some circumstances, a single dose of around 200 Gy is adequate. Since the penetration is low, it is obviously only applicable to superficial tumours and its particular applications are in the management or corneal, palpebral and conjunctival squamous cell carcinoma. Commonly, since beta radiation only penetrates 2 mm of tissue, surgical tumour reduction is commonly used (Fig. 34.2), where it can be a significant benefit.

Strontium-90

Strontium-90 is used in plesiotherapy as a beta emitter for superficial treatment of tumour conditions and some benign inflammatory states (Fig. 9.48). It decays by beta emission with a half-life of 28.7 years to yttrium-90. The beta emission from the strontium-90 is in fact too weak for any practical use in radiotherapy but the daughter yttrium-90 (half-life 64 h) decays with a useful beta emission of 2.27 MeV. The combination therefore provides a source of 2.27 MeV beta particles with an effective half-life of 28.7 years.

Strontium-90 has been used for surface applicators and in particular for ophthalmic use, where the beta particles provide the required surface dose with a rapid fall-off beneath the surface (Fig. 9.49). The applicators are constructed with a silver and steel back-plate that provides a complete radiation shield and is available in a number of shapes and forms. The surface dose rates mean that treatments usually take 4–10 min. Fractionation can be used by repeated applications to achieve a therapeutically effective overall dose over a period of time. In some circumstances, a single dose of around 20 Gy is adequate. Since the penetration is low, it is obviously only applicable to superficial tumours and its particular applications are in the management or corneal, palpebral and conjunctival squamous cell carcinoma (see Fig. 9.49). A retrospective study, involving 38 horses diagnosed with ocular squamous cell carcinoma that involved the limbal conjunctiva and/or cornea, concluded that treatment involving strontium-90 irradiation immediately after keratectomy and conjunctival graft surgery was effective in at least 83% of the horses. Side-effects were very rare in this study.

Strontium wands/applicators are no longer available in the UK but are still used in some equine radiation units; their place in human radiotherapy has been taken by ruthenium-106; there is no information available on the value of ruthenium in horses.[87]



Figure 9.49 A strontium plaque/wand being used to apply radioactive therapy to the cornea of a horse diagnosed with carcinoma in situ. Note that the treatment is carried out under general anesthesia in these cases after surgical tumour reduction. It is feasible to apply the wand to the conscious sedated horses with suitable precautions. Note the protective shield and the extension grasper for the handle – all measures are designed to minimize the risk of operator exposure. *(Figure courtesy of Alain Theon.)*

Hazards and safety

The dangers of personal exposure to radiation cannot be overstated. Every effort must be taken to minimize and hopefully eliminate the risk of any exposure. It should be possible in most circumstances to avoid it completely but, otherwise, minimal exposure and careful monitoring of exposure must be carried out.

All radiation sources are potentially dangerous and due care has to be taken with their use. An understanding of the physics of radiation and the biology of exposure to radiation of any sort should be gained before any handling or use is made.

The strontium wands/plaques are robust but they can be damaged and they do need to be cleaned and regularly tested carefully in such a way as to totally avoid operator exposure.

Cancer immunotherapy

Immunotherapy refers to the techniques that alter the relationship between the host's immune system and the tumour and therefore utilize the immune system to specifically recognize and destroy tumour cells. Since the immune system responds to the environmental factors it encounters on the basis of discrimination between self and non-self, tumour cells are tolerated by the patient's own immune system; the tumour cells are essentially the patient's own cells that are growing, dividing and spreading without proper regulatory control. Cancer vaccination has considerable potential based upon the ability of T cells and antibodies to recognize cancer antigens and kill cancer cells expressing these antigens. In spite of this desirable expectation, there have not yet been any successful approved multiple phase 3 clinical trials. Prophylactic vaccines given before exposure to potential oncogenic infectious agents (usually viruses) have a very different immunological implication, in so far as they target an immunologically naive immune system through generation of neutralizing antibodies that prevent the initial stages of infection or neutralize toxins the microbes might produce. To be successful, therapeutic cancer vaccines must break tolerance to generate therapeutically meaningful responses and so most cancer immunotherapy seeks to activate and expand tumour-specific T cells in vivo.

Notwithstanding the general status of an individual in respect of its immune system, it is certainly true that cancer cells adversely affect the host's ability to recognize them as non-self. The main concept of cancer immunotherapy is to 'force' the patient's immune system to attack the tumour cells. The main beneficial effects arise because the immune system can actively recognize any cell that has a 'recognizable' signal that identifies it as foreign or damaged sufficiently to warrant destruction by one or more of the pathways for cell elimination. This can be either through immunization of the patient, for example by administering a 'cancer vaccine' that encourages the patient's own immune system to recognize tumour cells as targets to be destroyed, or through the administration of therapeutic antibodies in a similar way to drugs, in which case the patient's immune system is recruited to destroy tumour cells by the therapeutic antibodies.

Tumour cells differ from their normal counterparts in both antigenic composition and biological behaviour that derive from mutational changes, deletions, amplifications and chromosomal rearrangements. Many, but by no means all, tumour cell types express recognizable antigens that are either inappropriate for the cell type and/or its environment, or are only normally present during fetal development. Examples of these antigens include GD2, a glyphosate disialoganglioside, normally only expressed on the outer surface membranes of neuronal cells, where its exposure to the immune system is limited by the blood–brain barrier. These antigenic differences are the basis of the development of therapeutic vaccines for cancer. These differences introduce the possibility of supporting specific recognition of the tumour cells by T cells. In the human at least, GD2 is expressed on the surfaces of a wide range of tumour cells including neuroblastoma, medulloblastoma, astrocytoma, melanoma, small-cell lung cancer, osteosarcoma and other soft tissue sarcoma. This is therefore a convenient tumour-specific target for immunotherapy and provides an access point for intervention. There are also other tumour cells with cell surface receptors that are rare or absent on the surfaces of healthy cells, which are responsible for activating cellular signal transduction pathways that cause the unregulated growth and division of the tumour cell.

Cancer cells commonly have at least some local immunosuppressive effects through T-cell malfunction, antigen presenting cell (APC) deficiencies and induction of regulatory T cells. Immunosuppression by tumours is also possibly mediated by soluble cytokines and enzymes and, in those circumstances, the immunosuppressive effects can be more widespread. The type of immunosuppression dictates the choice of the most appropriate immunotherapy.

To be successful, the chosen immunotherapy must contain a substance designed to interfere with one or more mechanisms of tumour-induced immunosuppression. This may range from the use of co-stimulatory antibodies to rescue tumour-specific T cells, to the use of depleting antibodies to eliminate regulatory T cells. It is clear that in later/advanced cancers, immunosuppression is more severe compared with that in early-stage cancer. Immunotherapies administered in very early disease, or even better, as immune prevention in high-risk individuals, could result in very effective protection from cancer.[88] Such early stage interventions are already standard in chemoprevention.[89]

The process is easily misinterpreted as 'boosting of the immune system', but it is far better viewed as the mechanism that maximizes or restores the ability of the host to recognize tumour tissues. Notwithstanding that concept, most opinion suggests that the effects are due to either augmentation of the immune system or restoration of immunological activity. Since most tumour-affected animals have a fully functional immune system and since tumour progression is a result of immune evasion rather than immune suppression (p. 33), the techniques usually work through restoring immunological recognition or redirecting the immune system to allow it to recognize tumour cells specifically as non-self.

Various attempts have been made to employ or persuade the host's immune system to control or eliminate tumour cells. This approach is an extremely attractive one, since it would have the best possible outcome with the least possible clinically adverse effects. The concept of tumour 'vaccination' or immunomodulation remains the target of many research programmes. For example, 21 horses with sarcoid tumours were treated by bio-immunotherapy using autogenous vaccines. The base of the tumour was left in the skin after the bulk had been removed surgically and 'autovaccines were made from extirpated tumour tissue by polymerization'.[90] One of 12 horses having a primary tumour and four of nine horses suffering recurrent tumours, prior to bio-immunotherapy, developed single recurrences. Four of these five horses suffering recurrence were re-treated, leading then to remission. Disease-free intervals were significantly longer for primary and recurrent sarcoids than for conventional surgery alone.

Active immunotherapy refers to the 'stimulation' of the host's intrinsic immune system through forcing recognition of antigens on tumour cells. In this way, the immune system is encouraged to recognize the tumour cells and therefore destroy them. Restorative immunotherapy means the reinstatement of a compromised immune system or a

supressed host immunological response. In passive immunotherapy, previously sensitized immunological agents, in the form of cells or antibodies, are introduced to the host in an attempt to stimulate an immunological anti-tumour response.

Cell-based immunotherapy is a further mechanism used in cancer immunotherapy. In this method, immune cells such as the natural killer cells (NK cells), lymphokine activated killer cell (LAK), cytotoxic T lymphocytes (CTLs), dendritic cells (DC), etc., are either activated in vivo by administering certain cytokines, such as interleukins, or they are isolated, enriched and transfused back into the patient to destroy cancer cells.

Alteration or modification of the immune system does have some drawbacks of course that mostly relate to the less specific alterations that for example might suppress recognition of bacterial or viral pathogens.

Identified tumour antigens provide immunologists with candidate immunogens for vaccine development. Most vaccines that have been used thus far are employed as 'therapeutic' interventions in patients suffering with the tumour and perhaps, understandably, have therefore had moderate or low positive effects only.

Passive/adoptive immunotherapy

Monoclonal antibody therapy

The development of technology that could produce monoclonal antibodies (mAbs) that could target specific molecules gave rise to hopes that antibodies directed to tumour antigens could be used as therapeutic reagents to specifically target and therefore destroys the tumour cells. Initial optimism, however, gave way to realism and this proved far more complex than was first thought. The idea was attractive, but the execution was clearly problematic, since antibodies were produced in animals other than the host and the host developed a rapid immunity to the antibody therapy. Further complications arose from the inability of antibodies to penetrate sufficiently into the tumour mass and their inherently short half-life in the circulation, which required frequent administration and more practical issues of the cost of production and thus the cost of therapy. Advances in recombinant DNA technology revived interest in monoclonal antibody therapy. New 'chimeric' antibodies were generated that retained the tumour antigen specificity while being much less immunogenic to the patient's own immune system.

A good example of a therapeutic antibody is the chimeric antibody rituximab, specific for the CD20 antigen, commonly found on B-lymphoid malignancies. Rituximab has been used to treat non-Hodgkin's lymphoma in man, chronic lymphocytic leukaemia and small-cell lymphocytic leukaemia. It has been used alone (or coupled to radioisotopes) with maximal clinical responses occurring when the antibody therapy was combined with conventional chemotherapy.[91]

Several mechanisms have been suggested to account for the anti-tumour effect of antibodies. These include complement-dependent lysis of tumour cells, antibody dependent cell-mediated cytotoxicity and possible inhibition of the function of the target antigen.[92] Growth factors and their receptors, adhesion molecules and angiogenic molecules are all potential targets for antibody therapy. No information is available at the present time on the use of these methods in treatment for horses.

T-cell therapy

There have been significant investigations into the use of sensitized T cells in tumour elimination. Clinical studies have confirmed that adoptive transfer of highly selected tumour-reactive T cells can result in tumour regression.[93] Major difficulties in the method include competitive naturally occurring T cells that inhibit the beneficial effects of the 'engineered' cells – this can to some extent be overcome clinically by lymphoreduction techniques. Additionally, there appear to be difficulties relating to the trafficking of the transferred lymphocytes to the targeted tumour site. No information is available at the present time on the use of these methods in horses.

Mediator therapy

An interesting therapeutic option is the administration of specific cytokines and mediators that have a targeted anti-tumour effect. This approach is very early in its development but there have been equine studies that use the technology. Local interleukin-2 (IL-2) is effective in a number of experimental animal models and in veterinary and human cancer patients without discomforting side-effects. A study comparing the intratumoral administration of 5–10 low doses of IL-2 with those of a combination of cisplatin and a single high dose of IL-2 in the treatment of equine sarcoids found that a single high dose of IL-2 was significantly better than the combined effect of cisplatin and low doses of local IL-2 administered daily over 5 or 10 days (80% and 43%, respectively).[94]

Endogenous interleukin production has also been used in treatment of equine melanoma using cytokine-encoding plasmid DNA in horses with metastatic melanoma to induce immunological anti-tumour effects. Interleukin-18-encoding plasmid DNA, interleukin-12-encoding plasmid DNA or empty plasmid DNA (control group) injected intratumorally were compared. Significant tumour regression occurred in both the treatment groups receiving IL-18 and IL-12-encoding plasmid DNA, whereas placebo-treated control patients showed tumour growth over the course of the treatment. In addition, 7 of 10 tumours from horses treated with IL-18 or IL-12 showed peritumoral and/or intratumoral inflammatory infiltrates after treatment compared with one of the six in the control group. The treatment, as assessed by serial blood draws and clinical investigation, was safe and well tolerated.[95]

It is likely that these approaches will become more common, more sophisticated and more widely used in horses, but properly conducted trials are required before they will become clinically useful.

Active (specific) immunotherapy

Active immunotherapy refers to the 'stimulation' of the host's intrinsic immune system through either forcing recognition of antigens on tumour cells or recognition of a metabolic component of the cancer cells. In this way, the immune system is stimulated to recognize the tumour cells and therefore destroy them. Unfortunately, cancer cells have

a tendency to develop mechanisms that escape immune detection (p. 33). Cell vaccines are an attractive option but it is obviously far more complicated than it seems and most attempts to 'vaccinate' horses using modified cells of the tumours (so far largely restricted to melanoma and sarcoid) have failed.[41] Recent reports of a vaccination system involving the autologous grafting of 'frozen blocks' of sarcoid tumour into the subcutis of the neck have been controversial. The original report suggested a very high success rate but this has not been corroborated subsequently. Such a crude mechanism is unlikely to be either effective or logical in the management of any cancerous condition.

Most systems employ the harvesting of cancer cells from an individual, which are then cultured in vitro and are altered in such a way that they would be identified by the immune system usually through activation of cytokine genes.[96] These genes then produce molecules that promote systemic inflammation. The modified cells are then grown in a controlled environment and destroyed and the remaining contents of the cells are combined to produce a cancer vaccine (Fig. 9.50).

The identification of tumour antigens provides immunologists with candidate immunogens for vaccine development. Most vaccines that have been used thus far are employed as 'therapeutic' interventions in patients suffering with the tumour and perhaps understandably have therefore only had moderate or low positive effects. The better approach of therapeutic vaccines is to control tumour growth and prevent tumour recurrence. There have been some trials, primarily in humans diagnosed with melanoma, lung, breast and prostate cancer. In none of these trials, however, have major clinically measurable benefits been reported. Given that vaccines for other diseases are seldom effective therapeutically and that the majority of tumour patient are immunosuppressed, small benefits can be seen to be a positive outcome.

Vaccination against cancer can involve administration of whole tumour cells, or tumour cell preparations (whether live or altered) or synthetic recombinant proteins/tumour antigens. In contrast to vaccination against infectious disease, cancer vaccination is usually applied after the tumour has developed and is a strategy to encourage the immune systems to detect and destroy the cancer cells which up to that point will have been 'non-recognizable'.

Vaccines that can be administered in advance of the cancer condition have clearly a somewhat different approach. Vaccination is also a strategy that can be applied prospectively when an infectious agent is known to be responsible for later tumour development. A good example of this is the use of a vaccine against HPV types 6, 11, 16 and 18 (the known cause of some forms of human cervical cancer).[97] In this circumstance, the causative infection is prevented immunologically; similarly, hepatitis vaccines have been used to reduce the overall incidence of hepatic carcinoma, which probably arises at least in part from chronic viral hepatitis.

The commonly held dogma for a causative role of bovine papilloma virus (BPV) type 1 or type 2 in the development of sarcoids has led to the search for immunological methods of treatment focussed on the virus itself. Chimeric virus-like particles (CVLPs) of BPV-1 L1–E7 have been tested as a possible mode of immunotherapy for equine sarcoid, with some promising early results.[98]

In terms of the horse, immunological tumour treatment is largely confined to the sarcoid. Several approaches have been made. The most commonly used methods are reliant upon the use of mycobacterial cell-wall fractions, live lyophilized *Bacillus Calmette–Guérin* (BCG) or *Propionibacterium* cell-wall extracts. In order to have any beneficial effects, these materials have to be injected intralesionally on repeated occasions. The benefits of these materials is suggested to be a result of cell-mediated immunity, leading to enhanced recognition of tumour cell-specific antigens and consequent tumour cell destruction. Since the effects are dependent to some extent, at least, on the actual amount of antigen injected relative to the amount of tumour, surgical cytoreduction is commonly undertaken. Success rates are relatively high for smaller fibroblastic and nodular sarcoid tumours and, in particular, for those around the eye. As might be expected, since the materials have to be injected intralesionally, the effects on superficial verrucose and occult sarcoids are poor. There are no recognized remote effects on tumours at untreated sites.

However, new vaccine technologies are being explored, but so far none has given any significant benefit. In a single study in which 21 horses with sarcoid tumours were treated by bio-immunotherapy; the base of the tumour was left in the skin and autovaccines were made from extirpated tumour tissue by 'polymerization'.[90] Only one of 12 horses had a primary tumour and five of nine horses suffered recurrent tumours, prior to bio-immunotherapy. Four of these five horses suffering recurrence were retreated, leading to remission. Disease-free intervals were longer for primary (p = 0.0005) and recurrent sarcoids (p = 0.0156) than for

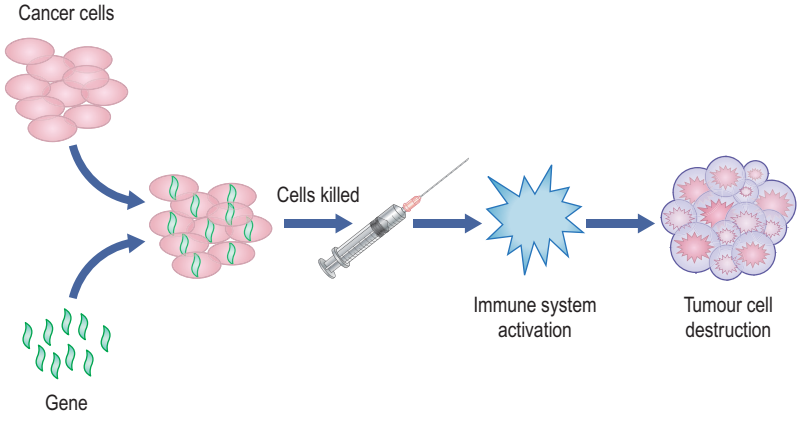


Figure 9.50 The process of active specific immunotherapy using altered cancer cells.

conventional surgery alone. The method has not been widely adopted and there are no follow-up studies using the method. The results of the original study were, however, suggestive of a potential value. In a study of histologically confirmed equine sarcoid cases in Cape mountain zebra in South Africa, affected zebras were treated with surgical excision, 5-fluorouracil, allogenous vaccine or a combination of 5-fluorouracil and allogenous vaccine.[99] After 2 years, all treated sarcoids had resolved. The efficacy of the three treatment methods in Cape mountain zebra was viewed as encouraging, but, since all recovered completely, it is hard to know what was a naturally occurring immunological response and what was a result of the chemotherapy or immunotherapy.

BCG immunotherapy in practice

This method relies on the induced intense immunological response following local injection of protein cell-wall extracts from mycobacterial organisms, killed or live mycobacteria, usually (BCG). Cell-wall extracts can be crude (usually 'milky' in appearance) or refined and are available commercially. Viable freeze-dried BCG reconstitutes to a clear aqueous solution whose concentration and volume can be varied by appropriate dilution.

Several other forms of mycobacterial protein have been developed in response to the concept that the viable (live) bacillus is likely to cause an anaphylactic response that may be fatal. The alternative approaches, said to be 'free of adverse effects', include purified cell wall extracts (*Regressin-V*®, Vetrefarm Research Inc., USA; *Ribigen-E*®, Ribi Immunochemical Research, USA) and protein-free extracts of cell skeleton (*Nomagen*®). Other bacterial extracts (including a heat-killed protein preparation of *Propionibacterium acnes* (*Eqstim*®, Neogen, USA) have been developed to exploit the effect for treatment of certain cutaneous neoplasms, including the equine sarcoid and squamous cell carcinoma. However, there are limitations to their use in both conditions and most of the commercial products have fallen into disuse or been withdrawn after problems with production or use.

The therapeutic benefits of these materials rely on specific and nonspecific effects; they have no direct effect on the tumour cells themselves. Simplistically, the nonspecific effects occur when probably the protein material binds to cells directly and a delayed hypersensitivity response is mounted locally. The proteins are also intensely immunogenic. Ingress of T cells, neutrophils, macrophages and NK cells results in tumour cells being killed 'incidentally' or nonspecifically in a massive inflammatory response. T-cell recognition of the tumour cells may result in a longer effect. Therefore, the method is restricted to individually treated lesions – there is usually no detectable effect on untreated lesions on the same animal. Furthermore, it is probably only applicable to discrete tumours – diffuse surface sarcoids of the occult and verrucose types, for example, respond poorly, while nodular lesions show a good effect (particularly around the eye). Treatment of multiple lesions is therefore difficult and requires a large volume of the protein. The material has little or no effect if injected around a lesion and requires to be injected truly intralesionally.[100] There is also a reported risk of anaphylactic reactions following repeated injections. Ideally, therefore, it should be injected intralesionally after suitable premedication has been given to prevent untoward systemic reactions.

This method has a good record against periocular nodular sarcoid, somewhat less effect on fibroblastic sarcoid and is probably impractical for verrucose or occult sarcoid.[20] Sarcoids away from the periocular region have a poorer response and those on the limb may be exacerbated by the procedure. The method has a poor record against squamous cell carcinoma in horses (whereas in cattle it has a significant if somewhat unpredictable beneficial effect). BCG and the related immunological methods are not effective against many of the other tumours, including melanoma and neurofibroma.

Several protocols are commonly used. Intralesional injection seems to be vital for satisfactory results with sarcoids and it is virtually impossible to inject a significant volume of the material into the skin surface of the verrucose and occult lesions. A McClintock type (TB-Testing Automatic 0.1 mL dose) or a dental syringe can be used to spread the material within the lesion (Fig. 9.51).

It is important that the needle is *not too* fine since the pressure in the syringe will usually result in failure and leakage; a 21/22G needle is usually ideal (Fig. 9.51).

Attempts to treat equine sarcoid lesions with an undefined 'immunostimulant' failed to show any convincing benefit beyond a placebo effect.[101]

Surgical debulking of sarcoid lesions, in particular, prior to administration of BCG has been reported to improve the overall results. In general, however, it seems unwise to use debulking with a sarcoid in particular.[100]

Indications

The method has a good reputation for treatment of nodular and fibroblastic sarcoids around the eye but, somewhat surprisingly, is much less reliable elsewhere. Indeed, there is some suggestion that its use away from the head may induce a more aggressive growth of the tumour mass.[102] There is no apparent effect on lesions away from the injected ones; each lesion requires its own tumour-volume-related injection, making it a tedious and very expensive procedure for general use for sarcoid. Additionally, the risks of the procedure could significantly increase the dangers and the reluctance to use the method.[20,103,104]

Note

Treatment of squamous cell carcinoma with BCG has a poor overall success rate; in the author's experience, less than 20% of squamous cell carcinoma tumours will respond at all and even fewer will be 'cured'.

Method

Several different methods have been advocated and the chosen one will reflect the material used and the type of lesion being treated. In most protocols, it is usually necessary to use up to 4–10 injections, although there are reports of single or two injections giving rapid, total resolution. Although it has been suggested that the effect is dose-related (larger tumours need more material), the proper placement of the reconstituted proteins seems equally or more important; nevertheless a dose appropriate to the size of the tumour is the most rational approach.

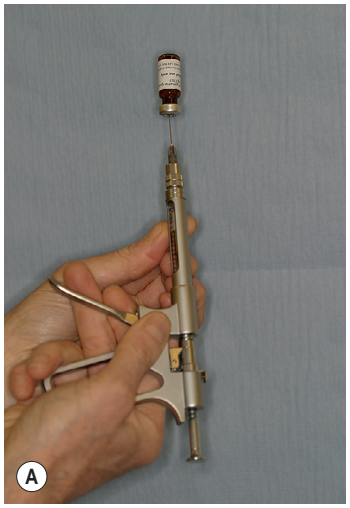




Figure 9.51 Bacillus Calmette-Guérin (BCG). (A) Live lyophilized Bacillus Calmette-Guérin (BCG) is reconstituted with an appropriate volume of diluent according to the requirements and volume of the tumour. **(B)** The solution of BCG is injected intralesionally into the tumour using a pressure volume-limited syringe that dispensed 0.1 mL with each click (KRUUSE™, UK); in this case, a nodular sarcoid in the upper eyelid. Similar equipment is used to perform intradermal injections during TB testing in cattle. Note the Luer lock needle attachment, which prevents the system from bursting when very high pressure is applied.

There is also a genuine finite risk of anaphylaxis, although this can be minimized by careful placement of the material and by suitable steroid and non-steroidal premedication (see Box 9.4 below).

- Lesions may be injected with reconstituted BCG vaccine or purified cell-wall extracts at 7–10-day intervals.
- The protocol used by Liverpool University employs intralesional injection of the reconstituted freeze-dried, live BCG organisms at *intervals* of 7, 14, 21, 28, 28, 28 days; the protocol is referred to as the expanding week interval method. Thus, the second injection is administered 1 week after the first. The third injection is given after a further 2 weeks and the fourth after a further 3 weeks and so on up to a maximum interval of 28 days. This protocol is described fully in Box 9.4 below. The advantage of this method is that fewer doses are used and the risks of anaphylaxis are minimized. It is also far cheaper than many of the other weekly regimens that use much larger doses of the BCG itself.

Notes

- True intralesional injection is critical to the success and the avoidance of dangerous systemic/anaphylactic responses.
- The material is injected into the lesion with a fine needle and infiltrated to avoid reflux of the fluid. The volume of injectate should be adjusted to permit maximal antigen delivery into the tumour mass and the tumour–tissue interface.
- Injection is sometimes highly problematic due to the density of the tumour (especially in the case of nodular sarcoid or neurofibroma).

Box 9.4 University of Liverpool protocol for periocular, nodular (and some fibroblastic) sarcoids

(This method is not considered valuable for other types of sarcoid or for other neoplastic disorders.)

1. Evaluate the history, size and type of tumour to be treated.
2. At 30–45 min prior to every single injection (including the first) the patient is premedicated intravenously with corticosteroids (e.g. dexamethasone at 0.05–0.1 mg/kg) and flunixin meglumine (at 1.1 mg/kg).
   An alternative method should be considered if there is a history of use of the same method, or if the horse is known to have had an adverse reaction previously. Antihistamines are of dubious value and are not used routinely.
3. Sedate and restrain the horse.
4. Perform careful surgical preparation of the site of injection.
5. Dilute one ampoule of lyophilized BCG viable bacillus into an appropriate volume of water (for small tumours <0.5 cm diameter, the contents are diluted in 0.5 mL of water; for larger tumours, one ampoule can be reconstituted with 1–1.5 mL) and injected intralesionally. A 1 mL tuberculin-type syringe (or a dental pressure syringe with a Luer lock needle) and 24–26G needle of an appropriate length should be used.
6. Repeat injection after 7 days (second dose after 1 week).
7. Repeat injection after 14 further days (third dose after a further 2 weeks).
8. Repeat injection after 21 further days (fourth dose given after a further 3 weeks).
9. Repeat injection after 28 further days (fifth dose after further 4 weeks).
10. Further doses are repeated at 4-week intervals.
11. Up to 9 or 10 injections may be required (5 is 'average').

Responses observed

- Local swellings are common.
- Repeated injections result in either exaggerated responses with further swelling or progressive shrinkage of the mass and sometimes immediate swelling followed by rapid shrinking.
- Some nodular and fibroblastic sarcoids react by abscessation and discharge of purulent material; this may result in a chronic discharging sinus tract requiring surgical curettage.
- Anaphylaxis has been reported following repeated use of attenuated live BCG in particular. The first injection is probably safe (provided that the method has not been used previously on the present lesion or on another lesion); thereafter, appropriate precautions should be taken. The danger may be further minimized by premedication with corticosteroids (e.g. dexamethasone at 0.05–0.1 mg/kg intravenously) and flunixin meglumine (at 1.1 mg/kg intravenously) at least 30 min before the injection is given. Antihistamines, such as tripelennamine hydrochloride (at 1 mg/kg intramuscularly), have also been used to premedicate horses prior to BCG injection, but the value of antihistamines is doubtful. True intralesional injection is essential and also minimizes the risks of anaphylaxis.

Dosing should not stop until a suitable response is evident. Significant reactions developing after 3–5 injections indicates that treatment can be either stopped or delayed to allow assessment of the responses. Some cases will require up to 8 treatments. A few cases suddenly resolve some months after the method has been abandoned due to lack of efficacy. The reasons for this are not clear.

Localized abscessation can develop and can be alarming, with a persistent discharging sinus developing for over 12 months. Total surgical excision of the abscess may be the only reliable treatment to resolve this problem. In other cases, the tumour gradually shrinks, with the full effect taking up to 12 months. BCG treatment of sarcoids results in a very acceptable cosmetic effect and is generally safe for both operator and patient.

- Best results are obtained in nodular sarcoids in and around the eyelids. There is no detectable effect on untreated sarcoids on a horse on which one or more individual lesions are treated with BCG.
- It is imperative that the entire contents are injected *intralesionally*. Subcutaneous injection in the vicinity of a sarcoid is to be avoided as far as possible; this may increase the risk of anaphylaxis and certainly reduces the prognosis (Box 9.4).

Advantages

- Convenient/simple and little equipment required
- Cheap (for single or few lesions). For larger numbers and bigger tumours the procedure is more hazardous and a lot more expensive
- Can be administered to a standing, sedated horse
- Effective in over 70–100% of palpebral nodular sarcoids.

Disadvantages

- Risk of anaphylaxis. This is a serious, if very rare, complication. True intralesional injection using a suitable proportionate volume/concentration of BCG will minimize the risk
- Repeated injections are required (increasing the risk of anaphylaxis and adding to the overall cost)
- Volume/mass-dependent (larger lesions need more material). However, this may be less important than the distribution of the material within the lesion. Over-diluted solutions created by adding too much diluent reduces efficacy significantly
- No effect is detected on lesions remote from the injected one, i.e. every lesion requires specific injection. This may be highly problematic and very expensive if there are many lesions
- Must be injected intralesionally. This largely precludes its use in verrucose and occult lesions, where intralesional injection is either impossible or very difficult
- Limited efficacy range (not effective for squamous cell carcinoma or melanoma); little effect on sarcoids of verrucose or occult types or tumours of all types away from the periorbital region
- This method is probably contraindicated for sarcoids on limbs. The reason for this is not clear, but exacerbation is relatively frequent and the overall benefits are marginal at best.

Treatment of anaphylaxis

Careful preparation must be made prior to the injection of any BCG or similar product, to permit immediate treatment of an untoward response. The reactions may develop instantly upon injection or within 20–40 min afterwards, so the operator should be ready in either case to deal with the emergency.

The emergency preparations should include instantly accessible:

- Adrenaline solution for injection (1:10 000 is usually available in 1–3 mL ampoules)
- Oxygen with delivery/demand valve
- Dexamethasone solution for intravenous injection (2 mg/mL) (treatment may require a dose of around 0.2 mg/kg).

Notes

- The treatment method has much to commend it, but there are a significant number of failures and definite (however small) risks.
- The attending veterinarian should remain with the horse for 1–2 h after the injection, with adrenaline readily available.

(Fig. 9.52)

Notes

General notes on treatment using immune methods

- Autogenous vaccines in horses are strictly limited at this time to the 'viral wart' or viral papilloma. Most of these cases will resolve spontaneously in around 8 weeks in any case, whereas it takes about 2 months with the vaccines.
- The use of crude autogenous vaccines for neoplastic lesions is almost certainly entirely illogical – if it were as simple as this, there would be no neoplasia. Furthermore, the use of autogenous vaccines in sarcoid therapy may be dangerous – this approach is contraindicated and it should probably never be used with the current 'autogenous vaccine' technology.
- Injections of freshly prepared BCG must be made for each administration and the dose should be related to the size and type of tumour.
- Squamous cell carcinoma in horses is much less responsive to BCG injections in all its forms than in cattle.
- *Corynebacterium parvum* can also be used effectively, but is less predictable and is less available.

Autologous grafting

Autologous grafting of frozen blocks of tumour tissue is an additional 'immunological' method that has been recently described as an effective treatment for equine sarcoid tumours. In this method, 1 cm cubes of excised tumour are frozen in liquid nitrogen and then individually implanted into pockets under the skin of the neck. The published results are impressive, but there are difficulties with the concept and the execution and there are anecdotal reports of poor outcomes. There are quality issues associated with



Figure 9.52 Intralesional treatment with a 5-injection course of BCG. (A) This complex Type B nodular sarcoid was treated intralesionally with a 5-injection course of BCG (Danish Strain 1331™, SSI, Denmark), at intervals described in the Liverpool University BCG protocol (see p. 189) A single ampoule (equivalent to ten 0.1 mL human vaccination doses was used) **(B)** After the course, only a small verrucose component remained and this was treated with topical 5-fluorouracil cream (see p. 153). No further recurrences were reported after 6 years but the horse had a multiple sarcoid problems elsewhere. **(C)** This large invasive fibroblastic sarcoid received eight intralesional treatments with BCG (Danish Strain 1331, SSI, Denmark) at intervals described in the Liverpool University BCG protocol (Box 9.4, above). Four ampoules were used in a total volume of 3 mL diluent. BCG injections were carefully distributed through the lesion. **(D)** The appearance of the treated site 12 months later. No further sarcoid developed for at least 2 years.

the degree of cell death that follows the freezing procedure, and unless the cells are non-viable the results will be singularly disappointing and tumours may emerge from the graft sites (Fig. 9.53). Repeating freezing/thawing 3 times before use is a way of ensuring cell death is complete.

Further properly conducted clinical trials need to be carried out before this method can be recommended in practice.

Gene therapy

Gene therapy has shown some success in animal models and human patients. A randomized double-blind, placebo-controlled study was conducted to investigate the immunological anti-tumour effects of treatment with cytokine-encoding plasmid DNA in 26 horses with metastatic melanoma. Intratumoral interleukin-18 and interleukin-12-encoding plasmid DNA showed a useful anti-tumour effect in metastatic melanoma in grey horses.[95] The study suggested that intratumoral treatment with IL-18 and IL-12-encoding plasmid DNA has anti-tumour effects in the treatment of patients with metastatic melanoma.

Gene therapy is a technique used in the treatment of malfunctioning genes (whether these cause cancer or other morbidity), in which a deficient or defective gene is replaced by a working gene, so that the body can make the proper enzyme or protein and, as a result, eliminate the origin of



Figure 9.53 Autografting. Autografting was attempted in this case without proper killing of the cells and, as might be expected, tumours grew at the graft sites and proved extremely difficult to resolve. This method of treatment for equine sarcoid is not only ill-advised, it is totally irrational. *(Figure courtesy of Christoph Koch.)*

the disease. This means that gene therapy is directed specifically at genetically-based diseases, in which a known and identifiable faulty gene causes an enzyme to be either absent or ineffective. Gene therapy has shown some success in animal models and human patients. There are several approaches for correcting defective genes:

1. The most common approach is inserting a gene into a nonspecific location within the genome, replacing a non-functional gene.
2. Through selective reverse mutation, the malformed gene can be repaired to regain its normal role.
3. Via homologous recombination, the normal gene is exchanged for the abnormal gene.
4. Alteration of the regulation of a particular gene.

Considering the established pivotal role of genetics in cancer and the profound effects of mediator and cytokine variations in the progression and growth of cancers, it is not surprising that gene and mediator therapies are being sought. This is a rapidly expanding field of cancer medicine. The complexity of the genome and the consequences of alterations of gene function initially proved almost insurmountable obstructions to the concept of gene therapy for cancer. However, the first truly effective gene transfer vectors based on rodent retroviruses were developed in 1981.[105] Since then, many new vectors and associated trials have taken place and a few clinically significant outcomes have been reported.

In order to insert the corrected gene into the patient's targeted cell, a carrier molecule, called 'a vector' is used; 'harmless' viruses are the most common form of vector. The virus is genetically modified to contain DNA of the target species within it by replacing the deformed gene with the genes encoding for the desired effect. Thus, the virus can be used as a 'vehicle' to carry the good genes into the targeted 'damaged' human cell (Fig. 9.54). Once incorporated into the target cells, the viral vector transfers the 'therapeutic gene' into the target cell's genome. The therapeutic gene then generates the production of functional proteins and restores the cell to its normal state.

Gene transfer methods involving retroviral vectors were the first to be explored and remain the current focus of most of the technology. The retroviral genome comprised two identical copies of a single-stranded RNA molecule and are divided into oncoviruses, lentiviruses and spumaviruses. Additionally, adenoviruses and herpes simplex and vaccinia are also being explored, amongst several other candidate viruses.

There are inevitably some significant problems associated with gene therapy:

1. Viral vectors can trigger immune and inflammatory responses and result in significant morbidity. In theory at least, the viruses may develop a pathological strain and so might cause significant disease.
2. Gene therapy is short lived, since there are problems with integrating the therapeutic DNA into the patient's genome and so there are significant constraints on the duration of a beneficial effect. In most circumstances, therefore, patients have to undergo a series of treatments. In order for gene therapy to become a permanent cure for a disease, the DNA would need to be completely and permanently integrated into the genome and remain functional and stable within the target cell. This is a major problem that confronts the researchers in this field.
3. There is a risk of initiating an immune attack when inserting the therapeutic gene into the patient, since the immune system recognizes the vector as a foreign protein. The natural immune recognition of the vector means that gene therapy cannot usually be repeated in the patient – a least using the same vector.
4. Where multiple gene damage occurs, it becomes less feasible to use gene therapy and that is a significant event in cancer medicine, given that most advanced or serious cancers have multiple genetic mutations. Tumours that arise from single mutations are the best candidates for gene therapy.

Mediator therapy employs the natural protective abilities of specific mediators that may be either absent in a cancerous state or in insufficient amounts to bring a beneficial change. Mediator therapy therefore involves the direct administration of naturally occurring (but usually recombinant) anti-tumour cytokines or it may involve the production of higher amounts of a 'beneficial' cytokine by indirect stimulation. Many specific and nonspecific cellular interactions cause release of large numbers of cytokines and some of these have been explored for anti-tumour effects. Interleukins and interferons are usually accepted as the most likely candidate cytokines for anti-tumour effects.

The main focus of this approach in equine cancer medicine has exploited the metabolic effects of the interleukins and several clinically significant attempts have been made to treat cancerous states in horses by this method. One study involved a properly conducted double-blind, placebo-controlled trial using interleukin-18 and interleukin-12 encoding plasmid DNA in the management of metastatic melanoma in grey horses.[95] In this randomized double-blind, placebo-controlled study in 26 adult grey horses with spontaneously occurring metastatic melanoma,[95] treatment consisted of interleukin-18-encoding plasmid DNA, interleukin-12-encoding plasmid DNA or empty

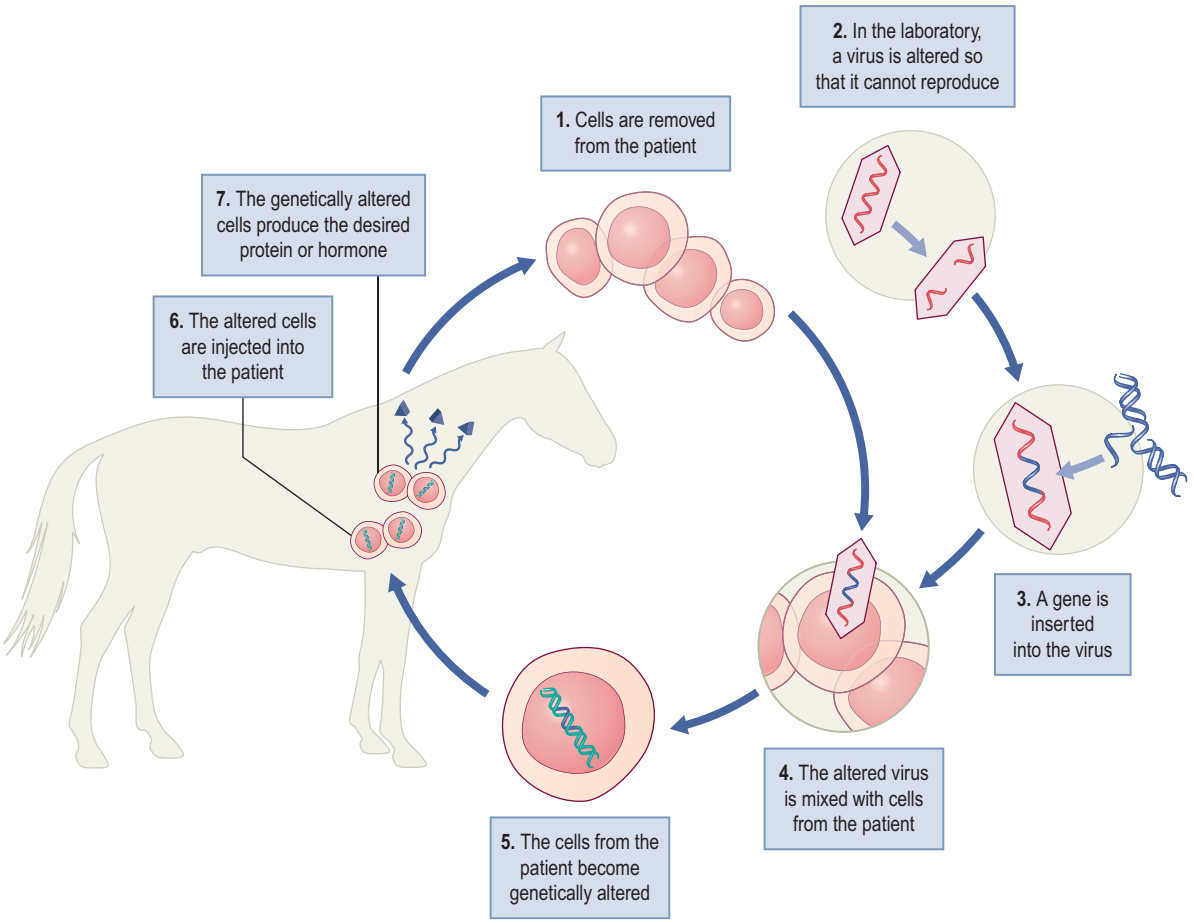


Figure 9.54 Gene therapy. The mechanism for gene therapy for cancer is a relatively simple process that sounds and looks easy when summarized in simple steps, but this belies the complexity and elegance of the method.

plasmid DNA (control group), injected intratumorally, respectively. Significant tumour regression could be shown in both the treatment groups receiving IL-18 and IL-12-encoding plasmid DNA, whereas placebo-treated control patients showed tumour growth over the course of the treatment. In addition, 7 of 10 tumours from horses treated with IL-18 or IL-12 showed peritumoral and/or intratumoral inflammatory infiltrates after treatment, compared with one of the six in the control group. The treatment showed no apparent adverse effects and the conclusion was that the intratumoral treatment with IL-18 and IL-12-encoding plasmid DNA had clinically valuable anti-tumour effects.

Phytotherapy

Many plant and other medications have been used for managing some types of tumour in horses. For the most part, this usually relates only to the equine sarcoid and most of the reports are uncontrolled, non-blinded and often even anecdotal. However, there has been a study of 53 horses (see below), with a total number of 444 sarcoid lesions of various, largely superficial types, in a prospective, randomized, blinded, clinical trial using an extract of the mistletoe plant (*Viscum album austriacus* extracts – VAE; Iscador® P, Weleda, CH-Arlesheim).[106]

Viscum album austriacus

This is suggested as a possible sarcoid treatment and there is no information on its potential value in other tumour types in horses. A total of 42 cases were treated with extract of *Viscum album austriacus* – (VAE; Iscador® P, Weleda)[106] or placebo alone; 11 cases were treated with intralesional injections of the extract or a placebo after surgical tumour reduction. No significant adverse effects were observed except for mild oedema at the injection site in a few cases. Complete or partial regression was observed in 13 horses of the treatment group (41%); three of the control horses (14%; $p<0.05$) also improved significantly. Some 27 sarcoid lesions disappeared completely in the VAE group (38%), compared with nine in the control group (13%). The authors concluded that VAE (Iscador® P) was a safe and effective treatment for equine sarcoid. The remarkable thing about this study is the number of cases that improved or were 'resolved' by placebo use. It was a properly conducted trial and so the conclusions are probably justified.

Procedure

The material is injected subcutaneously at a remote site to the tumours following a strict 3 days per week treatment schedule for up to 15 weeks (Table 9.9). A slight local swelling is all that is reported and an expected resolution is suggested to occur in up to 66% of cases (Fig. 9.55).

Sanguinaria canadensis

Extracts of the plant *Sanguinaria canadensis* (Blood Root) and its related plant species are widely used under various commercial names, such as *Xxterra*™ (Larson Ltd., Fort Collins, CO), Blood Root Ointment and Newmarket Blood Root Ointment in the management of equine sarcoid (p. 195). For equine use, the material is conventionally combined with an escharotic zinc chloride (10–30%). *Sanguinarine*, the principal alkaloid found in extract of bloodroot (*Sanguinaria canadensis* and other plants of the same family) has escharotic properties[107] and other properties that may be of value in cancer therapy including:

1. Inhibition of the nuclear transcription factor, NK-κB[108]
2. Induction of apoptosis in human epidermoid cancer cells[109]
3. Inhibition of mitogen-activated protein kinase phosphatase[110]
4. Inhibition of survivin, an inhibitor of apoptosis[111]
5. Antiproliferative, anti-angiogenic and anti-invasive effects in carcinoma.[112,113]

There is plentiful evidence, however, in peer-reviewed journals of the specific properties of the alkaloid(s) in modifying tumour cell behaviour (in several different tumour types, including carcinoma and melanoma) that may explain its specific equine efficacy in sarcoid treatment. There is no report of its use in other neoplastic conditions in horses but there are reports of use in human cancer cases.

Like all other materials, without exception, there are cases that are more appropriate than others and like all cancer therapies, there are bound to be failures along with the successes.[107]

Table 9.9 The suggested ideal protocol for the use of extract of *Viscum album austriacus* extract (VAE) in the treatment of equine sarcoid tumours

Treatment week	VAE dosage per injection (mg/mL)		
	Monday	Wednesday	Friday
Week 1	0.1	0.1	0.1
Week 2	0.1	1.0	1.0
Week 3	1.0	1.0	10.0
Week 4	10.0	10.0	10.0
Week 5	10.0	10.0	–
Week 6	1.0	1.0	1.0
Week 7	1.0	10.0	10.0
Week 8	10.0	10.0	20.0
Week 9	20.0	20.0	20.0
Week 10	20.0	20.0	–
Week 11–15	20.0	20.0	20.0

Homeopathy

The author's view on homeopathy is that it is universally useless. In humans, homeopathy relies upon gullibility, vulnerability and disillusionment and its credibility is gained by application of 'mystery, magic and voodoo', coupled with a nonsensical application of bamboozling jargon and mumbo-jumbo. The philosophy behind homeopathy is reliant upon the concept that no matter what outcome is delivered, it is considered to be successful – this is a system that by manipulating what it considers to be 'success' to its own advantage, it delivers 100% success.

Fortunately, horses are not susceptible to placebo effects (as far as we know) and are not influenced by mumbo-jumbo and there is no scientifically proven effect in any species that can possibly justify the use of homeopathy in cancer medicine in horses or indeed in any veterinary species. It is far better to simply tell the truth and apply evidence-based medicine deriving from properly conducted clinical trials and scientifically-based experience.

However, it is likely that homeopathy at least does no harm and, in that respect, it might be a better approach than a patently harmful one, but, by the same token, the use of homeopathic remedies delays the application of proper therapy – often to the point when proper therapy has no chance of success. This is then used as evidence that the homeopathy was at least controlling the cancer and that conventional evidence-based medicine has failed. It is disingenuous and dishonest and, as such, cannot be justified at all.

Palliation

Inevitably, given the slow presentation of cancer cases in most equine practices, there are a high number of cases that are presented in an untreatable state. An added subset of



Figure 9.55 Remote injection of *Viscum album austriacus*. (A) This 7-year-old horse was presented with a thick verrucose/fibroblastic sarcoid in the skin just rostral to the medial canthus. Remote injection of *Viscum album austriacus* (Iscador® P, Weleda) was administered by subcutaneous injection at a site remote to the tumours 3-times weekly over a period of 15 weeks. **(B)** Day 74 of treatment course. **(C)** The tumours underwent gradual regression over the treatment period, to resolve completely by day 395. *(Figures courtesy of O. Christen-Clottu.)*

cases that would often benefit from palliative treatments is the group of cases with slowly advancing tumours that have no really effective therapy. Procedures such as colostomy and tracheostomy can be used in some circumstances to improve the useful and distress-free life span of a patient. In one recorded case with severe and perianal carcinoma, a permanent end-on colostomy resulted in a stable, pain-free horse for 14 months before euthanasia was considered unavoidable.

Provision of palliative care for horses affected by cancerous conditions will inevitably come into conflict with the concepts of animal welfare that are foremost in the minds of most veterinarians but it is also true to say that many horses are destroyed earlier than they strictly need to be on humane grounds, mostly for fear of rapid deterioration or development of pain.

References

1. Dabareiner RM, Sullins KE, Goodrich LR. Large colon resection for treatment of lymphosarcoma in two horses. J Am Vet Med Assoc 1996; 208:895–897.
2. Burba D, Jahn H, Confer A. Surgical reduction of a laryngeal lymphosarcoma mass causing dyspnea in a horse. Equine Practice 1991; 13:14–18.
3. Rebhun WC, del Piero F. Ocular lesions in horses with lymphosarcoma; 21 cases (1977–1997). J Am Vet Med Assoc 1998; 184:313–317.
4. Ragland WL, Keoen GH, Spencer GR. Equine sarcoid. Equine Vet J 1970; 2:2–5.
5. Diel M, Vingerhoets M, Stornetta D. Specifische Methoden zur Entfurnung des Equinen Sarkoides. Tierartztiche Praxis 1987; 7:14–17.
6. Martens A, De Moor A, Demeulemeester J, et al. Polymerase chain reaction analysis of the surgical margins of equine sarcoids for bovine papillomavirus DNA. Vet Surg 2001; 30:460–467.
7. Crane SW. Lasers in medicine and surgery. Vet Clin Small Anim Pract 2002; 32:11–12.
8. McCauley CT, Hawkins JF, Adams SB, et al. Use of a carbon dioxide laser for surgical management of cutaneous masses in horses: 32 cases (1993–2000). J Am Vet Med Assoc 2002; 220:1192–1197.
9. Hildebrandt B, Wust P, Ahlers O, et al. The cellular and molecular basis of hyperthermia. Crit Rev Oncol Hematol 2002; 43:33–56.
10. Goetz TE, Ogilvie GK, Keegan KG, et al. Cimetidine for treatment of melanomas in three horses. J Am Vet Med Assoc 1990; 196:449–452.
11. Stadler S, Kainzbauer C, Haralambus R, et al. Successful treatment of equine sarcoids by topical aciclovir application. Vet Rec 2011; 168:187.
12. Byrne BA, Yvorchuck SK, Couto CG, et al. Successful management of lympho-proliferative disease in two pregnant mares. Proceedings of the 28th Annual Conference of the Veterinary Cancer Society, Seattle; 1991: 8–9.
13. Couto CG. Lympho in the horse. Proceedings of the 12th Annual Veterinary Medical Forum; 1994: 865.
14. Schneider DA. Lymphoproliferative and myeloproliferative disorders. In: Robinson NE, ed. Current therapy in equine medicine. Philadelphia: Saunders; 2003: 359–362.
15. Karnofsky DA, Clarkson BD. Cellular effects of anticancer drugs. Annu Rev Pharmacol 1963; 3:357–428.
16. Dougherty TF. Kinetics of cellular proliferation. New York: Grune & Stratton; 1959: 264–274.
17. Yang N, Zhang H, Si-Ma H, et al. Dexamethasone decreases hepatocellular carcinoma cell sensitivity to cisplatin-induced apoptosis. Hepatogastroenterology 2011; 58:1730–1735.
18. Wang ZY. Arsenic compounds as anticancer agents. Cancer Chemother Pharmacol 2001; 48: S72–S76.
19. Nogueira SA, Torres SM, Malone ED, et al. Efficacy of imiquimod 5% cream in the treatment of equine sarcoids: a pilot study. Vet Dermatol 2006; 17:259–265.
20. Knottenbelt DC, Kelly DF. The diagnosis and treatment of periorbital sarcoid in the horse: 445 cases from 1974 to 1999. Vet Ophthalmol 2000; 3:169–191.
21. Fortier LA, MacHarg MA. Topical use of 5-fluorouracil for treatment of squamous cell carcinoma of the external genitalia of horses: 11 cases (1988–1992). J Am Vet Med Assoc 1994; 205:1183–1185.
22. Van Den Top JG, Ensink JM, Gröne A, et al. Penile and preputial tumours in the horse: literature review and proposal of a standardised approach. Equine Vet J 2010; 42:746–757.
23. Rayner SG, Van Zyl N. The use of mitomycin C as an adjunctive treatment for equine ocular squamous cell carcinoma. Aust Vet J 2006; 84:43–46.
24. Malalana F, Knottenbelt DC, McKane S. Mitomycin C, with or without surgery, for the treatment of ocular squamous cell carcinoma in horses. Vet Rec 2010; 167:373–376.
25. Theon AP, Pascoe JR, Carlson GP, et al. Intratumoral chemotherapy with cisplatin in oily emulsion in horses. J Am Vet Med Assoc 1993; 202: 261–267.
26. Spoormakers TJ, Klein WR, van Weeren PR. Treatment of equine sarcoids with cisplatin in arachid oil: a useful alternative? Tijdschr Diergeneeskd 2002; 127:350–354.
27. Hewes CA, Sullins KE. Use of cisplatin-containing biodegradable beads for treatment of cutaneous neoplasia in Equidae: 59 cases (2000–2004). J Am Vet Med Assoc 2006; 229:1617–1622.
28. Théon AP, Pascoe JR, Madigan JE, et al. Comparison of intratumoral administration of cisplatin versus bleomycin for treatment of periocular squamous cell carcinomas in horses. Am J Vet Res 1997; 58:431–436.
29. Sikic BI. Natural and acquired resistance to cancer therapies. In: Mendelshonne JM, Howley PM, Israel MA et al., eds. The molecular basis of cancer. Philadelphia: Saunders; 2008: 585–586.
30. List AF, Spier CS, Grogan TM, et al. Overexpression of the major vault transporter protein lung-resistance protein predicts treatment outcome in acute myeloid leukaemia. Blood 1996; 87:2464–2466.
31. Millano G, McLeod HL. Can dihydropyrimidine dehydrogenase impact 5-fluorouracil based treatment? Eur J Canc 2000; 36:37–41.
32. Olaussen KA, Dunnant A, Fourtet P et al. DNA repair by ERCC1 in non-small cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 2006; 355:983–987.
33. Spiers CP. Clinical resistance to antimetabolites. Hematol Oncol Clin North Am 1995; 9:397–413.
34. Krown SE, Dittmer DP, Cesarman E J. Pilot study of oral valganciclovir therapy in patients with classic Kaposi sarcoma. J Infect Dis 2011; 203:1082–1086.
35. Schwarzenberger P, Byrne P, Gaumer R, et al. Treatment of mesothelioma with gene-modified PA1STK cells and ganciclovir: a phase I study. Canc Gene Ther 2011; 18:906–912.
36. Wang C, Natsume A, Lee HJ, et al. Neural stem cell-based dual suicide gene delivery for metastatic brain tumors. Canc Gene Ther 2012; 19: 796–801.
37. Redaelli M, Franceschi V, Capocefalo A, et al. Herpes simplex virus type 1 thymidine kinase-armed bovine herpesvirus type 4-based vector displays enhanced oncolytic properties in immunocompetent orthotopic syngenic mouse and rat glioma models. Neuro Oncol 2012; 14:288–301.
38. Mali B, Jarm T, Snoj M, et al. Antitumor effectiveness of electrochemotherapy: A systematic review and meta-analysis. Eur J Surg Oncol 2013; 39:4–16.
39. Cemazar M, Tamzali Y, Sersa G, et al. Electrochemotherapy in veterinary oncology. J Vet Intern Med 2008; 22:826–831.
40. Monika Fürst, Klinische Studie über den Einsatz von Bleomycin bei der Behandlung von equinen Sarkoid. Dissertation aus Zürich, 2011.
41. MacGillivray KC, Sweeney RW, Del Piero F. Metastatic melanoma in horses. J Vet Intern Med 2002; 16:452–456.
42. Laus F, Cerquetella M, Paggi E, et al. Evaluation of cimetidine as a therapy for dermal melanomatosis in grey horses. Isr J Vet Med 2010; 65:48–52.
43. Barabas K, Milner R, Lurie D, et al. Cisplatin: a review of toxicities and therapeutic applications. Vet Comp Oncol 2008; 6:1–18.
44. Ueno, Y, Tamura N, et al. Application of topical injection of cisplatin to squamous cell carcinoma (SCC). J Equine Sci 2012; 23:15.
45. Théon AP, Wilson WD, Magdesian KG, et al. Long-term outcome associated with intratumoral chemotherapy with cisplatin for cutaneous tumours in Equidae: 573 cases (1995–2004). J Am Vet Med Assoc 2007; 230: 1506–1513.
46. Strubbe DT. Periocular neurofibrosarcoma in a horse. Vet Ophthalmol 2001; 4:237–241.
47. Theon AP, Pascoe JR, Meagher DM. Perioperative intratumoral administration of cisplatin for treatment of cutaneous tumours in Equidae. J Am Vet Med Assoc 1994; 205:1170–1176.
48. Burns T, Cauto C. Systemic chemotherapy for oncologic diseases. In: Robinson NE, Sprayberry K, eds. Current therapy in equine medicine. St Louis: Saunders; 2009: 15–18.
49. Saulez MN, Schlipf JW Jr, Cebra CK, et al. Use of chemotherapy for treatment of a mixed cell thoracic lymphoma in a horse. J Am Vet Med Assoc 2004; 224:733–738.
50. Gollagher R, Ziola B, Chelack B, et al. Immunotherapy of equine cutaneous lymphosarcoma using low dose cyclophosphamide and autologous tumour cells infected with vaccinia virus. Can Vet J 1993; 34:371–373.
51. Tainter J, Schleis S. Equine lymphoma. Equine Vet Educ 2011; 23:205–213.
52. Bachur NR. Anthracyclines. In: Encyclopaedia of cancer, 2nd edn. Amsterdam: Elsevier; 2002: 57–61.
53. Hurcombe SD, Slovis NM, Kohn CW, et al. Poorly differentiated leiomyosarcoma of the urogenital tract in a horse. J Am Vet Med Assoc 2008; 233:1908–1912.
54. Théon AP, Pusterla N, Magdesian KG, et al. Phase I dose escalation of doxorubicin chemotherapy in tumor-bearing Equidae. J Vet Intern Med 2013; 27:1209–1217.
55. Fubini SL, Cummings JF, Todhunter RJ. 1988 The use of intraneural doxorubicin in association with palmar digital neurectomy in 28 horses. Vet Surg 17:346–349.
56. ECVIM-CA. Preventing occupational and environmental exposure to cytotoxic drugs in veterinary medicine, 2nd edn. 2007. http://www.ecvim-ca.org/guidelines.
57. Stewart AA, Rush B, Davis E. The efficacy of intratumoral 5-fluorouracil for the treatment of equine sarcoids. Aust Vet J 2006; 84:101–106.
58. Paterson S. Treatment of superficial ulcerative squamous cell carcinoma in three horses with topical 5-fluorouracil. Vet Rec 1997; 141:626–628.
59. Naylor M. Imiquimod and superficial skin cancers. J Drugs Dermatol 2005; 4:598–606.
60. Hemmi H, Kaisho T, Takeuchi O, et al. Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. Nat Immunol 2002; 3:196–200.
61. Sauder DN. Imiquimod: modes of action. Br J Dermatol 2003; 149:5–8.

62. Miller RL, Gerster JF, Owens ML, et al. Imiquimod applied topically: a novel immune response modifier and a new class of drug. Int J Immunopharmacol 1999; 21:1–14.
63. Zagon IS, Donahue RN, Rogosnitzky M, et al. Imiquimod upregulates the opioid growth factor receptor to inhibit cell proliferation independent of immune function. Exp Biol Med 2008; 233:968–979.
64. Urosevic M, Oberholzer PA, Maier T, et al. Imiquimod treatment induces expression of opioid growth factor receptor: a novel tumour antigen induced by interferon-alpha? Clin Cancer Res 2004; 10:4959–4970.
65. Cihocki LM, Divers TJ, Johnson AL, et al. A case of multiple epitrichial sweat gland ductal carcinomas in a horse. Vet Dermatol 2007; 18:134–137.
66. Savage CJ. Lymphoproliferative and myeloproliferative disorders. Vet Clin North Am Equine Pract 1998; 14:563–578.
67. Buss DG, Sharma A, Giuliano EA, et al. Efficacy and safety of mitomycin C as an agent to treat corneal scarring in horses using an in vitro model. Vet Ophthalmol 2010; 13:211–218.
68. Knottenbelt C, Chambers G, Gault E, et al. The in vitro effects of piroxicam and meloxicam on canine cell lines. J Small Anim Pract 2006; 47:14–20.
69. Moore AS, Beam SL, Rassnick KM, et al. Long-term control of mucocutaneous squamous cell carcinoma and metastases in a horse using piroxicam. Equine Vet J 2003; 35:715–718.
70. Riggott JM, Quarmby WB. Treatment of fibrosarcoma in a horse. Equine Vet J 1980; 12:193–196.
71. Rols MP, Tamzali Y, Teissié J. Electrochemotherapy of horses: A preliminary clinical report. Bioelectrochemistry 2002; 55:101–105.
72. Tamzali Y, Borde L, Rols MP, et al. Successful treatment of equine sarcoids with cisplatin electrochemotherapy: A retrospective study of 48 cases. Equine Vet J 2012; 44:214–220.
73. Mazères S, Sel D, Golzio M, et al. Non invasive contact electrodes for in vivo localized cutaneous electropulsation and associated drug and nucleic acid delivery. J Control Release 2009; 134:125–131.
74. Ota J, Giuliano EA, Cohn LA, et al. Local photodynamic therapy for equine squamous cell carcinoma: evaluation of a novel treatment method in a murine model. Vet J 2008; 176:170–176.
75. Giuliano EA. Equine periocular neoplasia: current concepts in aetiopathogenesis and emerging treatment modalities. Equine Vet J Suppl 2010; 37:9–18.
76. Garg AD, Krysko DV, Vandenabeele P, et al. Hypericin-based photodynamic therapy induces surface exposure of damage-associated molecular patterns like HSP70 and calreticulin. Canc Immunol Immunother 2012; 61:215–221.
77. Weaver MP, Dobson JM, Lane JG. Treatment of intranasal lymphoma in a horse by radiotherapy. Equine Vet J 1996; 28:245–246.
78. Dixon RT. Radiation therapy in horses. Aust Vet J 1967; 43:508–510.
79. Pommer A. X-ray therapy in veterinary medicine. J Am Vet Radiol Soc 1964; 5:58–63.
80. Eberlein R. Röntgentherapie bei Haustieren. Adv Vet Sci 1958; 4:97–98.
81. Schrieber GJ, General principles of radiation therapy. http://emedicine.medscape.com/article/846797-overview#a1.
82. Pajonk F, Vlashi E, McBride WH. Radiation resistance of cancer stem cells: the 4 Rs of radiobiology revisited. Stem Cells 2010; 28:639–648.
83. Walker MA, Goble D, Geiser D. Two year non-recurrence rates for equine ocular and periorbital squamous cell carcinoma following radiotherapy. Vet Radiol 1986; 4:146–148.
84. Wyn-Jones G. Treatment of periocular tumours of horses using radioactive gold-198 grain. Equine Vet J 1979; 11:3–5.
85. Wilkie DA, Burt JK. Combined treatment of ocular squamous cell carcinoma in a horse, using radiofrequency hyperthermia and interstitial ^{198}Au implants. J Am Vet Med Assoc 1990; 196:1831–1833.
86. Theon AP. Radiation therapy in the horse. Vet Clin North Am Equine Pract 1999; 14:673–688.
87. Plummer CE, Smith S, Andrew SE, et al. Combined keratectomy, strontium-90 irradiation and permanent bulbar conjunctival grafts for corneolimbal squamous cell carcinomas in horses (1990–2002): 38 horses. Vet Ophthalmol 2007; 10:37–42.
88. Lollini PL, Cavallo F, Nanni P, et al. Vaccines for tumour prevention. Nat Rev Cancer 2006; 6:204–216.
89. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. J Am Med Assoc 2006; 295:2727–2741.
90. Kinnunen RE, Tallberg T, Stenbäck H, et al. Equine sarcoid tumour treated by autogenous tumour vaccine. Anticancer Res 1999; 19:3367–3374.
91. Cheson BD. Monoclonal antibody therapy of chronic lymphocytic leukemia. Canc Immunol Immunother 2006; 55:188–196.
92. Levene AP, Singh G, Palmieri C. Therapeutic monoclonal antibodies in oncology. J R Soc Med 2005; 98:146–152.
93. Morgan RA, Dudley ME, Wunderlich JR, et al. Cancer regression in patients after transfer of genetically engineered lymphocytes. Science 2006; 314: 126–129.
94. Spoormakers TJ, Klein WR, Jacobs JJ, et al. Comparison of the efficacy of local treatment of equine sarcoids with IL-2 or cisplatin/IL-2. Cancer Immunol Immunother 2003; 52:179–184.
95. Müller J, Feige K, Wunderlin P, et al. Double-blind placebo-controlled study with interleukin-18 and interleukin-12-encoding plasmid DNA shows antitumor effect in metastatic melanoma in gray horses. J Immunother 2011; 34:58–64.
96. Finocchiaro LM, Riveros MD, Glikin GC. Cytokine-enhanced vaccine and suicide gene therapy as adjuvant treatments of metastatic melanoma in a horse. Vet Rec 2009; 164:278–279.
97. Denny L. Cervical cancer: prevention and treatment. Discov Med 2012; 75:125–131.
98. Mattil-Fritz S, Scharner D, Piuko K, et al. Immunotherapy of equine sarcoid: dose-escalation trial for the use of chimeric papillomavirus-like particles. J Gen Virol 2008; 89:138–147.
99. Marais HJ, Page PC. Treatment of equine sarcoid in seven Cape mountain zebra (Equus zebra zebra). J Wildlife Dis 2011; 47:917–924.
100. Theon AP. Intralesional and topical chemotherapy and immunotherapy. Vet Clin North Am Equine Pract 1998; 14:659–671.
101. Studer U, Marti E, Stornetta D, et al. The therapy of equine sarcoid with a non-specific immunostimulator – the epidemiology and spontaneous regression of sarcoids. Schweiz Arch Tierheilkd 1997; 139:385–391.
102. Lavach JD, Sullins KE, Roberts SM, et al. BCG Treatment of periocular sarcoid. Equine Vet J 1985; 17:445–448.
103. Vanselow BA, Abetz I, Jackson AR. BCG emulsion immunotherapy of equine sarcoid. Equine Vet J 1988; 20:444–446.
104. Owen RH, Jagger DW. Clinical observations on the use of BCG cell wall fraction for treatment of periocular and other equine sarcoids. Vet Rec 1987; 120:548–550.
105. Wei C, Gibson M, Spear PG. Construction and isolation of a transmissible retrovirus containing the SRC gene of Harvey murine sarcoma virus and the thymidine kinase gene of herpes simplex virus type 1. J Virol 1981; 39:935–944.
106. Christen-Clottu O, Klocke P, Burger D, et al. Treatment of clinically diagnosed equine sarcoid with a mistletoe extract (Viscum album austriacus). J Vet Intern Med 2010; 24:1483–1489.
107. Cienki JJ, Zaret LJ. An Internet misadventure: bloodroot salve toxicity. J Altern Complement Med 2010; 16:1125–1127.
108. Chaturvedi MM, Kumar A, Darnay BG, et al. Sanguinarine (pseudochelerythrine) is a potent inhibitor of NF-kappaB activation, I-kappa B-alpha phosphorylation, and degradation. J Biol Chem 1997; 272:30129–30134.
109. Adhami VM, Aziz MH, Mukhtar H, et al. Activation of prodeath Bcl-2 family proteins and mitochondrial apoptosis pathway by sanguinarine in immortalized human HaCaT keratinocytes. Clin Cancer Res 2003; 9: 3176–3182.
110. Vogt A, Tamewitz A, Skoko J, et al. The benzo[c]phenanthridine alkaloid, sanguinarine, is a selective, cell-active inhibitor of mitogen-activated protein kinase phosphatase-1. J Biol Chem 2005; 280:19078–19086.
111. Sun M, Lou W, Chun JY, et al. Sanguinarine suppresses prostate tumor growth and inhibits survivin expression. Genes Cancer 2010; 1:283–292.
112. Tsukamoto H, Kondo S, Mukudai Y, et al. Evaluation of anticancer activities of benzo[c]phenanthridine alkaloid sanguinarine in oral squamous cell carcinoma cell line. Anticancer Res 2011; 31:2841–2846.
113. De Stefano I, Raspaglio G, Zannoni GF, et al. Antiproliferative and antiangiogenic effects of the benzophenanthridine alkaloid sanguinarine in melanoma. Biochem Pharmacol 2009; 78:1374–1381.

10 Introduction

Many pathologists and clinicians, if asked to discuss the importance of equine neoplasia, would probably say that such lesions are not common. However, many veterinary pathologists do not deal with a high equine caseload, making this difficult to judge. When considering equine cases only, and in biopsy specimens in particular, neoplasms will often comprise a significant proportion; it has been estimated that up to approximately 30% of biopsy specimens from equines fit into this category.[1] If all neoplastic lesions (both benign and malignant) occurring in horses and other equine species are included, the prevalence is even greater, i.e. lesions that are not likely to be excised and/or submitted for diagnosis (e.g. 'warts') and those that are clinically silent (e.g. thyroid adenomas) and therefore only likely to be found incidentally at post-mortem examination. Many neoplasms diagnosed involve the skin, as would be expected in terms of owners noticing their presence and/or the ability of the clinician to excise or sample them. However, it is noticeable that, increasingly, improvements in technology are resulting in clinicians being able to sample internal neoplastic (and non-neoplastic) lesions for histological diagnosis. Some of the histological images in the following chapters are from such samples.

I would have counted myself among the pathologists who regarded neoplasms in horses as an infrequent occurrence, prior to thinking about the topic and reviewing the literature. What I expected to take a few months turned into a gruelling experience that occupied more than a year, and this literature extended a long way back, perhaps not surprising, given the history of our interest in horses not only as companions but also as working (and competing) animals. With the exception of the lack of access to more modern diagnostic techniques, including immunohistochemistry, much of the earlier literature was thorough and accurate, and particularly in the North American journals, the language used for gross and histological description had not altered significantly. A notable exception to this was the literature for sarcoids, which have been variously diagnosed (particularly less recently) as fibromas, fibrosarcomas, fibropapillomas, granulation tissue and granulomas. Some of this misdiagnosis related to rigid application of histological criteria, including 'typical' hyperplastic epidermal changes that are now known not to necessarily be present in all lesions. However, despite being the most common type of neoplasm in horses, sarcoids are still a common source of frustration for the pathologist and submitting clinician, due to their frequent complication by granulation tissue and their tendency to arise in wounds. A recent paper documenting bovine papillomavirus DNA in large numbers of inflammatory lesions in horses and in normal skin specimens further complicates the issue, perhaps in terms of thinking we could resort to polymerase[2] chain reaction (PCR) techniques to make an easy diagnosis.

What is also unfortunately evident is that with the exception of a few types of neoplasm, most notably sarcoids, equine neoplasia has not been the subject of significant research and/or documentation. The literature does reveal that there is most likely a depth in the variation of types and subtypes of neoplasms similar to that being determined for dogs and cats (and as for human patients), but their full description, documentation and correlation with useful clinical information is sadly lacking. In the absence of any central reporting system for horses that specifically includes neoplasia, this is going to be difficult to advance, particularly given the fact that neoplasms are still less common in horses than in the small animal domestic species.

On a positive note, some of the larger surveys now being conducted are at least updating our knowledge on the frequency of occurrence of various tumour types, including risk factors,[3,4] and in some cases, advancing our knowledge of the pathophysiology of disease in a scientifically rigorous manner. Highlights include: the dogma-breaking detection of bovine papillomavirus DNA in the epidermis of sarcoids (and non-sarcoid lesions), and in peripheral blood mononuclear cells that is beginning to explain some of the epidemiological findings for this disease condition[1,5,6]; identification of genetic mutation (in the syntaxin-17) gene that has been selected to provide the highly attractive grey coat colour but also causes susceptibility to melanomas[7]; and the discovery of *Equus caballus* papillomavirus-2 in papillomas, papillomatosis and in situ and invasive squamous cell carcinomas of the penis, i.e. evidence of an aetiological role of yet another virus in the development of a common neoplasm of horses.[8–10] More firmly in the diagnostic field, there have been some very elegant papers by veterinary pathology specialists, including definition of histological variants of melanocytic naevus, neurofibroma, haemangiosarcoma and sarcoid.[11–14] This work is introducing a greater degree of sophistication to diagnosis even with access to only small numbers of cases; it will now need to be extended by collection of greater numbers of cases inclusive of follow-up information. However, the problems in terms of collecting sufficient numbers of examples correlated with useful prognostic information are by no means isolated to equine species.

In the review that follows, wherever possible, gross and histological descriptions have been provided from the existing literature, even where reports have been infrequent. For some types of neoplasm, more general descriptions are provided and some subtypes included, even if they are not yet found in horses. Immunohistochemical labelling is included wherever possible, but, for diagnosis of equine neoplasms, this is not as advanced as for dogs and cats; the literature needs to be interpreted cautiously as many authors have not sufficiently validated the antibodies for use in this species. For some neoplasms, antigens that might be expected to be positively labelled are indicated. A recent paper documenting the use of immunohistochemistry to diagnose sarcoids that had the histological appearance of peripheral nerve sheath tumours (schwannomas) illustrates the importance of continuing to advance its use to avoid case mismanagement.[14]

Due to the infrequent reports of many types of neoplasm in horses, not all have been illustrated with macroscopic and/or histological images. However, veterinary colleagues throughout the world have been extremely generous in taking the time to locate and send images and/or slides, and this could not have been put together without their input.

References

1. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
2. Wobeser BK, Hill JE, Jackson ML, et al. Localisation of bovine papillomavirus in equine sarcoids and inflammatory skin conditions of horses using laser microdissection and two forms of DNA amplification. J Vet Diagn Invest 2012; 24:32–41.
3. Schaffer PA, Wobeser B, Martin LE, et al. Cutaneous neoplastic lesions of equids in the central United States and Canada: 3,351 biopsy specimens from 3,272 equids (2000–2010). J Am Vet Med Assoc 2013; 242:99–104.
4. Valentine BA. Survey of equine cutaneous neoplasia in the Pacific Northwest. J Vet Diagn Invest 2006; 18:123–126.
5. Brandt S, Tober R, Corteggio A, et al. BPV-1 infection is not confined to the dermis but also involves the epidermis of equine sarcoids. Vet Microbiol 2011; 150:35–40.
6. Brandt S, Haralambus R, Schoster A, et al. Peripheral blood mononuclear cells represent a reservoir of bovine papillomavirus DNA in sarcoid-affected equines. J Gen Virol 2008; 89:1390–1395.
7. Rosengren Pielberg G, Golovko A, Sundström E, et al. A cis-acting regulatory mutation causes premature hair graying and susceptibility to melanoma in the horse. Nat Genet 2008; 40:1004–1009.
8. Scase T, Brandt S, Kainzbauer C, et al. Equus caballus papillomavirus-2 (EcPV-2): an infectious cause for equine genital cancer? Equine Vet J 2010; 42:738–745.
9. Knight CG, Munday JS, Rosa BV, et al. Persistent, widespread papilloma formation on the penis of a horse: a novel presentation of equine papillomavirus 2 infection. Vet Dermatol 2011; 22:570–574.
10. Lange CE, Tobler K, Lehner A, et al. EcPV2 DNA in equine papillomas and in situ and invasive squamous cell carcinomas supports papillomavirus aetiology. Vet Pathol 2013; 50:686–692.
11. Schöniger S, Summers BA. Localised, plexiform, diffuse, and other variants of neurofibromas in 12 dogs, 2 horses, and a chicken. Vet Pathol 2009; 46:904–915.
12. Schöniger S, Summers BA. Equine skin tumours in 20 horses resembling three variants of human melanocytic naevi. Vet Dermatol 2009; 20:165–173.
13. Warren AL, Summers BA. Epithelioid variant of haemangioma and haemangiosarcoma in the dog, horse, and cow. Vet Pathol 2007; 44:15–24.
14. Bogaert L, Heerden MV, Cock HE, et al. Molecular and immunohistochemical distinction of equine sarcoid from schwannoma. Vet Pathol 2011; 48: 737–741.

11 Sarcoids

Cellular origin	203	Biological behaviour	210
Profile	203	Gross pathology	211
Oncogenesis	203	Histopathology	213
Commonly affected sites	209	Differential diagnoses	217

Cellular origin

There is considerable evidence that the most important aetiological factor in the oncogenesis of equine sarcoids is bovine papillomavirus (BPV) infection. Dermal fibroblasts comprise the majority of proliferating cells in these neoplasms. However, epidermal hyperplasia may add to the mass-effect in many cases, and recently the associated BPV DNA has been found in epidermal cells in addition to dermal fibroblasts.[1,2] The incidence of sarcoid formation is very low for a viral infection, implying the involvement of other factors, as discussed below.

Profile

Sarcoids were first formally described in 1936, but they had been recognized for centuries; the name *sarcoid* means 'flesh-like'. Sarcoids are now known to be the most common neoplasms affecting equines worldwide (see p. 545).[3,4] In addition to horses, donkeys and mules, they have also been reported in wild and captive zebra.[5] The economic loss associated with this high morbidity can be substantial.

The documented prevalence of equine sarcoid, i.e. the total percentage of cases, has varied widely in published surveys. In horses presented to large referral clinics in Canada, the USA and Europe, these estimates have ranged from 0.7% to 6%.[6–8] Such figures, taken from highly selected clinical populations, may exceed the actual prevalence in the general equine populations from which these horses are derived; for example, sarcoids were reported in only 0.7% of Swiss Warmblood and 0.4% of Freiberger horses in a Swiss study.[9] Particularly high prevalences of 25–53% have been reported in some inbred wild zebra populations in South Africa, sometimes as outbreaks.[10,11] When only skin neoplasms or tumours are considered, prevalence figures of 13–69% have been reported.[4,12–16] Remarkably, in one study at the University of Bern in Switzerland, 90% of horses with skin neoplasms had sarcoids.[7] Sarcoids have also been estimated to comprise up to 51% of skin lesions in total (i.e. both neoplastic and non-neoplastic) and 8–38% of ocular neoplasms.[17–19] There is geographical variation in the occurrence of equine sarcoid in horses; for example, surveys conducted in the USA suggest a higher prevalence in the Pacific north-west compared with north-eastern regions.[13,19] This is likely to relate to complex differences in various risk factors that may include numbers of cattle in proximity to Equidae, breed compositions of the equine populations or density of vectors (see below).[19]

Sarcoid incidence (the risk of development of this type of neoplasm within a defined time period) has also been measured. In a UK population of 4126 donkeys, a crude incidence of 0.6 cases per 100 animal years was estimated. There was a peak incidence of 15.2 cases per 100 animal years in animals in their fourth year of life.[20] Similar data are not available for horses.

Sarcoids are usually reported to develop first in horses 3–6 years of age of any breed or colour, although younger and older horses are commonly affected; the youngest reported age is 1 month.[4,14,21] In a Kansas State University survey of 153 sarcoid cases, the mean age was 3.8 years, and 89% of affected horses were ≤7 years of age.[14] In a UK referral hospital study of 51 cases, the affected horses were younger (mean age 5.8 years) than unaffected horses, but their gender distributions did not vary.[22] Similarly, in a Canadian study there was no difference in the risk of sarcoid development between geldings, stallions or mares.[23] In a retrospective case–control study of 503 sarcoid cases at Cornell University, geldings were at a higher risk than stallions, but there was no significant difference between stallions and mares.[24] In the same study, the risk increased with age up to 15 years and then declined. Young male donkeys (in the UK at least) appear to have an increased risk of sarcoid development.[20]

Oncogenesis

Bovine papillomavirus: a cross-species infection

There is a well-known association between equine sarcoid development and bovine papillomavirus (BPV)-1 and/or -2 infection, and numerous studies have suggested that these viruses have a causative role.[25] In a study conducted in Brazil, a sarcoid from one horse contained sequences showing 99% homology with a newly proposed BPV type, 'BR-UEL-4', recently identified in that country.[26] These are the only known examples of natural cross-species papillomavirus infection in domestic animals.[27]

There is no association between equine sarcoids and any of the equine papillomaviruses. Sarcoid cell lines (MC-1) spontaneously release an inducible endogenous retrovirus found in normal equine cells, but this virus has no proven role in sarcoid development.[28,29] Similar genotypes obtained from matched sarcoid and non-neoplastic DNA samples in horses and donkeys do not support the possibility that sarcoids are caused by allografts of infectious cells, as occurs for canine transmissible venereal tumour and Tasmanian devil facial tumour disease.[30]

Evidence of BPV in sarcoids

In studies performed in the UK, Germany, Switzerland, Austria, Italy, USA and Australia, up to 100% of examined sarcoids in horses, donkeys and captive and wild zebras have contained BPV DNA sequences.[5,27,31–40] Interestingly, sarcoids containing BPV-1 DNA have also been found in the pinnae of two (related) captive tapirs (*Tapirus bairdii*) in Costa Rica, consistent with a further cross-species BPV infection. These animals were kept in an area where cattle were housed in an adjacent facility, and a horse at the same location was also diagnosed with a sarcoid.[41]

There have been geographical differences in the BPV type identified. In Europe ≤20% of sarcoids are associated with BPV-2. In eastern regions of the USA, BPV-1 and BPV-2 have been detected with approximately equal frequency in some (but not all) studies.[36,38,39,42,43] In a study conducted in western Canada, BPV-2 DNA was present in 80% of lesions for which a PCR product was obtained, with 19% BPV-1 positive.[23] Similarly, 63% of sarcoids in a western USA study were BPV-2 positive.[38] In one Australian analysis of 14 sarcoids, 12 contained BPV-2 DNA; BPV-1-related DNA was found in one derived cell line.[35] A small number of horses and zebras have DNA from both BPV-1 and -2 in their lesions, or two sarcoids each with a different BPV type.[23,36,38,40,43] In a UK study of 18 donkey sarcoids, greater viral sequence homology was found with BPV-1 than between BPV-1 and BPV-2: i.e. the donkey sarcoid-associated virus was considered to be a subtype of BPV-1.[44]

The causative role of BPV is supported by evidence of viral transcription in sarcoids.[39,45,46] The papillomavirus genome is separated into early (E) genes encoding non-structural proteins and late (L) genes encoding structural (viral capsid) proteins. E1 and E2 are required for viral replication and transcription regulation, respectively. Of the other early genes, E4 codes for cytoplasmic proteins, and E5, E6 and E7 are known to play roles in neoplastic transformation. In addition to the L1 and L2 genes there is a non-coding long control region (LCR) that provides cis-regulatory elements required for viral replication and transcription.[47] In analysis of 20 sarcoids (19 from donkeys) containing BPV-1 DNA, mRNA for E2, E5, E6, E7 and L1 was identified in sarcoids; although not all transcripts were found in all neoplasms, most were positive for E5.[48] In other studies, evidence of E6 transcription was found in 72% of 30 sarcoids, and E5 in 85% of 41 specimens.[46,49]

No evidence of BPV has been found in non-sarcoid neoplasms in equines including papillomas, squamous cell carcinomas (SCC) and melanomas, with the exception of recent reports of BPV E5 DNA and BPV-1 DNA in periocular and head/neck SCC, respectively.[38,50–52] In the latter case, there was co-presence of BPV and *Equus caballus* papillomavirus 2 DNA in the neoplastic tissue.[52]

Sarcoid oncogenesis: the cellular pathways

Much of the information on BPV-induced transformation of equine cells has come from fibroblastic cell culture experiments. In cell culture, BPV-1 DNA has been used to transform equine primary fibroblasts, and this is reversible by knockdown of oncogene expression using small interfering RNAs.[53,54] Neoplastic transformation induced by BPV in cattle is largely mediated by E5, with other early genes playing more minor roles.[48,55]

The E5 protein

This oncoprotein is expressed in most sarcoids, sarcoid cell lines and BPV-1-transformed equine fibroblasts.[27,48,49] The main mechanism underlying BPV carcinogenesis is proposed to be binding of E5 protein to platelet-derived growth factor-β receptor (PDGFβ-R). The E5 protein, localized in the endoplasmic reticulum and Golgi apparatus of the host cell, forms a stable complex with this receptor, causing dimerization, activation and recruitment of cell signalling and proliferative proteins. Dual expression of E5 and PDGFβ-R proteins has been demonstrated in sarcoids, with evidence of receptor phosphorylation, expression of the P13K-AKT-cyclin D3 molecular pathway (commonly dysregulated in a variety of human neoplasms and allowing cell-cycle progression) and activation of specific transforming factors.[27,56] Activation of PDGFβ-R can in turn trigger activation of p38 mitogen-activated protein kinase (MAPK), an enzyme involved in multiple processes including the cell-cycle, cell motility and invasive behaviour; however, it appears that in BPV-1-infected equine fibroblasts it is E6 rather than E5 that enhances proliferation via p38 activation.[57]

Other effects of E5 in bovine cells, not all of which have been investigated in equine systems, include:

- Isolation of infected cells by downregulation of gap junctional intercellular communication[58]
- Intracellular retention of MHC class I (ELA) molecules to evade the immune system.[59] Inhibition of MHC I heavy chain transcription, and intracellular retention of the MHC I complex has been demonstrated in equine fibroblasts transfected with BPV-1 E5, with the end-result of downregulation of the MHC I complex on the cell surface[60]
- Disruption of protein processing and sorting and, (potentially) recycling of undegraded growth factor receptors (including PDGFβ-R, as above)[61,62]
- Activation of numerous kinases, resulting in disruption of normal cell-cycle control and signal transduction cascades.[61]

Oncogenic pathways in BPV-infected bovine and equine cells cannot always be presumed to be similar. For example, BPV-1 E5 can upregulate the cell-cycle proteins cyclin A and cyclin-dependent kinase 2 (CDK2) in bovine cells but this has not been demonstrated in sarcoids.[46] This may be due to differences in E5 proteins found in sarcoids versus those in bovine neoplasms; i.e. the particular BPV E5 sequence variants that have been detected in sarcoids may influence the mechanisms of oncogenesis.[49]

p53 and the E6 protein

The p53 protein loses normal tumour suppressor properties in a wide variety of neoplasms in both humans and animal species. Mutations in the *p53* gene have not been found in

sarcoids from horses ($n=20$) and donkeys ($n=36$).[48,63] Despite this, it is considered likely that the p53 protein is involved in sarcoid oncogenesis: abnormal cytoplasmic and nuclear expression has been found; and it was shown to have lost the ability to activate the transcription of the *mdm2* gene in a sarcoid cell line.[46,64] In 44% of 50 sarcoids, p53 levels were increased, as measured by immunohistochemical labelling in perinuclear regions.[65] These findings are interesting as p53 is a nuclear protein and should be inactivated in a cytoplasmic location. It has been suggested that loss of function of the p53 protein could be caused by the BPV E6 protein, as occurs in human papillomavirus infections. The E6 protein is a transcriptional activator that can inhibit p53 function by interfering with the transcriptional co-activator CBP/p300.[66] The E6 protein can therefore have anti-apoptotic activity and interfere with the normal anti-proliferative signalling system within cells.[63] Expression of the E6 protein has been found in most sarcoids tested, however only a subset of sarcoids show abnormal cytoplasmic p53 expression.[46,65]

The E7 protein

The E7 protein has been detected in sarcoid neoplasms: in human papillomas it is known to complex with retinoblastoma protein (pRb). The lack of an E7 pRb-binding domain in artiodactyl papillomaviruses including BPV-1 and -2 has been suggested to be important in development of fibropapillomas rather than papillomas, i.e. targeting of fibroblasts.[67] E7 also cooperates with E5 and E6 in cellular transformation, and E7 and E2 may assist in evading innate immune responses by downregulating Toll-like receptor 4.[54,61,68]

The E2 protein

The E2 protein is the viral transcription regulator.[55] It may play additional roles in sarcoid oncogenesis by transactivation or repression of transcription of other BPV early genes, and it is also required for stable extrachromosomal maintenance of the viral genome.[69,70] If *E2* gene expression is interfered with in infected sarcoid fibroblasts using small interfering RNA (siRNA), most lose their viral genomes and there is an increase in apoptotic cell death.[71] The LCR is regulated by various cellular factors and by the E2 protein. There is now evidence that BPV-1 viruses with certain LCR and E2 sequence variations are associated with sarcoid development. For example, the LCR II variant was found in 66% of equine sarcoids ($n=35$; 9 British and 26 Swiss) but was not identified in bovine neoplasms ($n=14$).[72] This variant strain showed higher transcriptional activity in equine than in bovine cells. E2 also appears to play an important role in expression of matrix metalloproteinases (MMPs). The MMPs are zinc-dependent endopeptidases that break down surrounding matrix proteins, and therefore play critical roles in neoplastic cell invasion. Downregulation of *E2* gene expression in sarcoid fibroblasts using siRNA treatment reduced the expression of some of the MMPs (MMP-2 and -9, i.e. gelatinases), and invasion of gels composed of basement membrane proteins by those cells.[73] Further research demonstrated that expression of MMP-1, a collagenase, is enhanced by other viral oncoproteins, i.e. E5, E6 and E7.[74] It should be noted, however, that although neoplastic progression and MMP expression are often correlated, the MMP enzymes are not always produced by the cancer cells themselves. They may also be expressed by host-derived cells, including fibroblasts, myofibroblasts, endothelial cells and inflammatory cells[75]; all of these cells types are present in sarcoids and require further investigation. There may also be induction of enzymes other than MMPs that contribute to local invasion by cancer cells.[54]

Other oncoproteins

In a study of the Fragile Histidine Triad (FHIT) tumour suppressor gene in equine sarcoids, the oncosuppressor protein expression was significantly reduced in neoplastic tissue and sarcoid-derived cell lines.[76] This alteration in gene expression could not be related to differences in DNA methylation, i.e. there was not an epigenetic mechanism. Aberrations in the *FHIT* gene have also been identified in human papillomavirus-associated cervical carcinomas.

Telomerase

Telomeres are repeated nucleotide sequences found at the ends of chromosomes, that lose 100–200 nucleotides every time the chromosomes are copied during cell division (see pp. 31–34). Telomerase is an enzyme that can replace those short DNA sequences to maintain chromosome length, resulting in cellular immortality. This enzyme is activated in approximately 90% of human cancers, but such activity has not been found in equine sarcoids.[77]

Note

Despite the above findings, it is generally agreed that BPV infection alone is not sufficient for neoplastic transformation in vivo.

Genetic risk factors

Genetic factors clearly play an important role in sarcoid development, although there will always be horses belonging to low-risk groups who still develop the condition. In two studies involving analysis of hundreds of sarcoid cases, Quarter Horses, Appaloosa horses and Arabian horses were at greater risk of sarcoid than Thoroughbreds, while Standardbreds were at lower risk.[16,25] Other researchers also documented a lower prevalence of sarcoids in Standardbred horses compared with Thoroughbreds.[78] It is possible that breed susceptibilities to some extent relate to the types of horses more likely to be kept on cattle farms, e.g. Quarter Horses.[16] A Canadian study of sarcoid specimens submitted to diagnostic laboratories ($n=802$) found that the relative risks of developing sarcoid were lowest for Warmblood horses and only significantly elevated for donkeys (3.1× more likely).[23]

There is also evidence for higher sarcoid prevalence in certain equine families; in one highly inbred family, four out of five animals were affected.[79] Sarcoids were reported at 18–24 months of age in all descendants of one mare who had highly aggressive, repeatedly recurring neoplasms.[80]

Particular equine leukocyte antigen (ELA) haplotypes are associated with sarcoid susceptibility at the population level. The ELA proteins are the gene products of the equine major histocompatibility complex (MHC) (see pp. 34–35); this is one of the strongest MHC associations with disease that has been documented in any species.[8] Class I genes

encode proteins expressed on the surfaces of all nucleated cells, while class II genes encode those that are only expressed by antigen-presenting cells and lymphocytes. Sarcoid-associated haplotypes frequently include the class II allele ELA W13 (B1). Of 44 sarcoid cases 41% were W13-positive.[7] The W13 antigen has been linked with susceptibility in a number of breeds including the Thoroughbred, Swiss Warmblood, Irish Sporthorse, Selle Français and Swedish Halfbred.[78,81–83] There are significant similarities between different studies of Swiss, Irish, French and Swedish Warmbloods, as they are related and have an appreciable genetic contribution from the Thoroughbred.[83] In studies of Swiss Warmblood and Swedish Halfbred horses, the relative risk of sarcoid development for animals with the W13 antigen was calculated to be approximately three times that of the respective reference populations for both breeds.[7,83] In Swedish horses, W13 was associated with an increased likelihood of recurrence following surgical removal. Additionally, the combination of W13 and the class I antigen A3 (see below) was associated with increased prevalence; horses with the A3 haplotype often also carry W13.[83,84] The A3 and W13 haplotypes in Swedish Halfbreds were considered to be associated with the aetiology of 28% and 37% of sarcoid cases, respectively, i.e. at least 40% of the total number (because they are often expressed together).[83] The W13 antigen is not expressed in Standardbreds: i.e., a breed at a lower risk (see above).[78] Freiberger horses lack both A3 and W13; however, one study horses of that breed with sarcoids showed an increased frequency of a breed-specific class I antigen, Abe108.[82]

In 207 Swiss Warmblood horses, the relative risks for sarcoid development were found to be approximately 2 for each of the class 1 antigens A3, A5, A16, A20 and the class 2 antigen W21.[7] The A3 antigen in Swedish Halfbreds was similarly associated with a relative risk of 2.[83] The A3 and A5 antigens also occurred more frequently in sarcoid-affected French horses.[82,83] In Swedish horses, A5 was associated with early onset of sarcoid development.[84] The W11 and W5 antigens have been associated with sarcoids in Irish Warmbloods, and Swiss and French Warmbloods, respectively.[81]

The ELA antigens are most likely breed-dependent markers for genes more directly involved in sarcoid oncogenesis. The precise 'sarcoid susceptibility gene' or genes linked to the MHC region have yet to be identified. Associations between class II MHC antigens and papillomavirus-induced disease have also been reported for cervical cancer in women and cutaneous neoplasms of rabbits.[85,86] It is possible that specific MHC class II alleles are associated with an impaired immune response to BPV and/or sarcoid tumour-associated antigens, e.g. inadequate cytotoxicity of 'killer' cells.[51,81] However, the majority of horses with the alleles mentioned above (of either class) will never develop sarcoids. This indicates the importance of other factors that may be genetic, epigenetic and/or environmental. For example, in Arab horses there is a significant correlation between sarcoid development and heterozygosity for the defective catalytic subunit of the DNA-dependent protein kinase (DNA-PKcs) allele that is responsible for severe combined immunodeficiency.[87] The normal DNA-PK may act as a tumour suppressor by assisting in maintenance of chromosomal stability.[87]

The key role of trauma

Sarcoid development is a recognized serious complication of equine skin wounds; this is particularly likely if the horse has sarcoids at other sites.[88] Sarcoid development may occur in any type and size of wound, including micro-trauma due to injections (Figs. 11.1 and 27.8A) or potentially even insect bites. It is thought that sarcoids involving the limbs (distal to the stifle or elbow joints) only occur following wounding.[88] The timing of neoplastic transformation is variable, and this may occur from very early during the healing process to months or years following apparent complete healing.[88] Trauma is thought to contribute not only to neoplastic initiation but also to progression in severity of the disease. Mechanisms could include allowing access of BPV or BPV-infected cells to epidermal basal layers and/or sub-epidermal fibroblasts, and induction of various growth factors and cytokines as part of the normal wound healing process.[89,90] It has been proposed that transformed fibroblasts enhance fibroplasia and angiogenesis in wounds, and inhibit epithelial proliferation, via direct and/or indirect alterations in the cytokine milieu.[88] The role of trauma as a co-factor is also supported by some of the inoculation studies discussed below.

What happens when horses are experimentally infected with sarcoid material or BPV?

Early studies of sarcoid transmission included autologous transfer to a mule, reported in 1939.[91] In a 1948 study, cell-free material did not induce lesions, but topical application of fresh pulverized sarcoid tissue to the scarified skin of a mule resulted in development of non-regressing tumours. This method could not be successfully repeated with the same mule, other mules or other horses.[92] In later studies horses developed sarcoid-like masses following autologous or homologous transfer of whole sarcoid tissue, or following inoculation of scarified skin with minced sarcoid suspension or cell-free supernatant.[90] Autologous transfer had a greater success rate than homologous transfer (80% vs 17%) and a



Figure 11.1 Sarcoid development at a site of trauma. An extensive sarcoid (with focal nodule formation) at an injection site. Micro-trauma due to injections and possibly even insect bites appears to be involved in oncogenesis.

shorter latent period (57 days vs 115 days). Some regression of original and transferred masses was noted. However, that author considered that the longer than expected latent period, the failure of growth when cell-free material was inoculated intradermally or subcutaneously, and the failure of a cellular material from equine sarcoids to produce lesions in calves proved that BPV was not the cause. The need to damage the skin to produce lesions supported the role of trauma as a co-factor.

In other studies, intradermal inoculation of cell-free extracts from bovine neoplasms containing BPV, and of the virus itself, caused transient lesions resembling but not identical to sarcoids within approximately 2 weeks. The masses induced in young ponies (1–2 years old) were more aggressive and persisted for longer periods of time than those in adult horses (8–25 years old).[90,93,94] The (younger) ponies were likely to be more naive immunologically. In these ponies, there were mild inflammatory infiltrates with diffuse and slowly progressive collagen deposition. Some of these masses were histologically indistinguishable from equine sarcoids (see below) at 6 months but they did still regress by 1 year (unlike natural cases). In the horses, there was more marked inflammation with perivascular collagen deposition that progressed to scar tissue formation; in the masses that underwent earlier regression, infiltrating eosinophils were a prominent feature.[93] The experimentally infected older horses also generated anti-BPV antibodies; specific antibodies have not been identified in animals with naturally-occurring sarcoids, with the exception of donkeys.[44,93] It should be noted that even naturally infected bovines rarely generate detectable levels of anti-BPV antibodies.[55] Regression associated with inflammatory infiltrates and antibody responses in these experimental equine models could be considered evidence that other factors are required for persistence of sarcoid neoplasms. However, these early studies involved injection of crude extracts containing large amounts of bovine cellular protein in addition to unusually large amounts of papilloma virus; natural infection could potentially involve only a single virus particle.[45]

There were no detectable neutralizing anti-BPV-1 serum antibodies either pre- or post-challenge in a contemporary study in which weanling foals were injected intradermally with bovine wart-derived BPV-1 virions only. These foals developed multiple 'pseudo-sarcoids' at inoculation sites, that contained BPV-1 DNA (11–60 copies per cell). The tumours became palpable at 11–32 days, reached sizes of up to 2 cm in diameter and regressed within 6 months.[95] No lesions developed when foals were injected with either primary sarcoid fibroblasts containing viral episomes (1 copy per cell), or naked full-length BPV-1 genomes.[95] Interestingly, surgical excision of the pseudo-sarcoids that developed resulted in transient recurrence with more aggressive behaviour, this being further support for the importance of trauma.

How does BPV infection differ between cattle and horses?

Bovine papillomaviruses-1 and -2 are part of the fibropapillomavirus subgroup in the family Papillomaviridae.[61] In the natural hosts, i.e. cattle, BPV induces exophytic papillomas of the skin or mucosa.[55] Infection of cattle with BPV-1 can cause papillomatosis of the teats, udder and penis; BPV-1 and -2 can both cause cutaneous papillomas (warts).[64] BPV-1 and -2 in cattle infect both epithelial cells and fibroblasts, resulting in induction of benign fibropapillomas that regress due to cell-mediated immune responses. There are both CD4- and CD8-positive T-lymphocytes in the immune cell infiltrates.[96] Neither regression nor immune cell infiltration are characteristic of equine sarcoids.

In external sites, the papillomas/fibropapillomas of cattle rarely progress to malignancy; with this is more likely in internal mucosal sites in the presence of certain environmental co-factors including bracken fern.[51,55] BPV-2 has been associated with fibropapillomas in the oesophagus. In bovines, early (E) gene expression and DNA replication occur in epithelial (i.e. epidermal) basal and suprabasal layers. In external bovine neoplasms, the expression of late gene transcripts occurs only in terminally differentiated cells, this facilitating formation and release of virions as those cells die. In equine sarcoids, it was initially thought that BPV only infected fibroblastic cells, in particular those at the dermal–epidermal junction.[18,97] However, in recent studies in which laser micro-dissection techniques were used, BPV-1 DNA was identified in overlying epidermal tissue in all samples, with loads ranging between 2 and 195 copies per cell; BPV-5 DNA was also identified in two of the specimens.[1,2] The E5 and E7 proteins were also detected in the epidermal tissue; the E5 protein was not found in the epidermis overlying experimentally induced pseudo-sarcoids as described above and no epidermal lesions were noted in those cases (see Histopathology, below).[95] It has been hypothesized that, in horses, BPV infection may start in the epidermis, followed by shifting of viral material to the sub-epidermal fibroblasts, where full transformational activity is exerted.[98] This was supported by a study in which BPV DNA was found in micro-dissected epidermal samples in 40% of normal skin specimens and early-stage sarcoids but was only located in fibroblasts in the advanced sarcoids.[89] Interestingly, in that study, the epidermis of one normal skin specimen was BPV-2 infected and the underlying dermis BPV-1 infected. The opposite situation exists in cattle, where fibroblast transformation precedes epidermal hyperplasia and papilloma formation.

In contrast to the productive infection in cutaneous bovine neoplasms,[55] BPV infection in horses is abortive. The BPV DNA exists as free circular episomes within the nucleus rather than being integrated into the genome, and intact virions have never been detected. This is, however, similar to BPV-induced urinary bladder cancers in cattle (i.e. internal lesions); those neoplasms also contain episomal copies of viral DNA with no evidence of virion production, although the copy number is significantly lower than that documented in equine sarcoids.[99–101] The number of viral genomes per cell in equine sarcoids does vary widely (0–808 copies) and is less on average for BPV-2 than for BPV-1.[34,42,99,101] Intralesional BPV DNA loads seem to reflect the severity of the disease; in one study, horses with quiescent, slow-growing sarcoids or multiple mild lesions had a viral load up to 1.4 copies per cell.[102] However, horses with rapidly growing and/or multiple aggressive sarcoids had viral loads of 3–569 copies per cell.

How is BPV transmitted to horses?

The most common routes are presumed to be by direct contact with cattle, contaminated tack, or buildings/surfaces. As above, skin trauma, including micro-trauma, is thought to be important for this transmission.[98] The BPV virus most likely remains infective in the environment for days, on the basis of known in vitro properties.[103] BPV-1 has been shown to be extremely resistant to desiccation, retaining up to 30% of infectivity after dehydration for 7 days at room temperature.[104] The virus in cell extracts also shows significant heat resistance, surviving for 1 h at 56°C, retaining 30% infectivity at 65°C and finally being inactivated at 74°C. There is some retention of infectivity following treatment with 70% ethanol and desiccation, but autoclaving did completely inactivate the virus. In a further study, BPV DNA was not found in samples from stable walls and feed tubs where horses with sarcoids were housed; however, the stable wall of one horse living in contact with an infected cow was positive.[103] This was thought to indicate the fact that the viral infection can occur a long time before visible sarcoid development, at which time the virus may have disappeared from the surrounding environment. Such findings may also support the occurrence of viral latency (see below).[103] BPV-1 DNA LCR sequence variants II and IV (commonly found in equine sarcoids) have been detected in flies in the UK but it is not known if levels in these insects are high enough to result in equine infection.[105,106] Wounds occurring during the fly season are more prone to sarcoid development (although other factors may be involved), and flies will be attracted to ulcerated neoplasms; biting flies may be less likely to be involved, as they do not prefer to feed on ulcerated tissue.[88]

In cattle, BPV DNA has been identified in whole blood and in peripheral blood mononuclear cells (PBMCs), with some evidence for in utero transmission.[107,108] In initial studies of horses and donkeys with sarcoids, viral DNA was not found in lymphocytes and/or identified in peripheral blood.[36,42,98,109,110] However, in a more recent study, BPV E5 DNA was found in PBMCs from one sarcoid-affected individual. That finding was then repeated in an additional cohort of horses with sarcoids.[50] The BPV-1 or -2 DNA was associated with E5 gene transcription in some horses, but L1-DNA or protein was not detected, i.e. blood cell infection is not considered to be productive.[31,50] It is possible that the L1 gene is partially truncated or deleted in blood cells as observed in some sarcoids.[1,42] When foals were inoculated intradermally with BPV-1 virions, viral DNA was detected in PBMCs 2–4 weeks before skin tumours developed, from as early as day 7 post-inoculation.[95] It was suggested that infection of white blood cells is therefore an early event required for onset of disease and infection of skin, i.e. there is a viraemic phase. The viral DNA load in PBMCs of inoculated foals increased during tumour growth, and then reduced towards zero during regression.[95] It is considered to be highly unlikely that sarcoid cells would be present in the circulation.[50] While the presence of BPV DNA in the blood of affected horses suggests that in utero transmission might occur, it also provides a possible mechanism by which individuals develop multiple sarcoids at different body sites, particularly if infected PBMCs migrated to sites of inflammatory skin disease (see below).[50]

Does BPV occur as latent infections?

In a number of studies, BPV DNA and mRNA have also been found in normal skin specimens taken from horses with or without sarcoids.[38,98,103] In a study conducted in Belgium, BPV DNA was found in the normal skin of 73% of sarcoid patients, 73% of horses without sarcoids that were living in contact with infected cattle 50% of horses without sarcoids living in contact with sarcoid-affected animals and 30% of control horses.[98] The occurrence of BPV DNA in horses without disease in conjunction with extremely low levels of mRNA, was considered to be consistent with latency.[98] A latent phase of infection in the skin is another potential explanation (in addition to peripheral blood mononuclear cell infection) for why horses often develop multiple sarcoids over time that are not the result of metastasis. Another factor, such as local trauma, with the associated healing process (including growth factors) could trigger viral transcription and translation in a latently infected area.[45] In one study, a higher percentage of normal skin positive for BPV-2 DNA (38%) than BPV-2-associated sarcoids (≤20%) was found in horses living in contact with cattle.[98] This might indicate that BPV-2 infection is more likely to be cleared (than BPV-1) and therefore less likely to induce neoplastic transformation; interestingly, that study was conducted in Europe, where BPV-2 is less frequently associated with sarcoid development compared with BPV-1. A similar analysis has not been made of normal skin and sarcoid tissue in a geographical area where BPV-2 is the virus type more commonly linked with neoplasia.

The site of latent infection in equine skin has been proposed to be the epidermis, with reactivation occurring due to trauma.[61] In a 1991 study, BPV DNA was detected in equine skin affected by dermatitis, the significance of which was not certain.[42] In a further study, BPV-1 genomes with copy numbers ranging from 0.2 to 155 per cell were found in four cases of inflammatory skin disease, with E1, E2 and E5 gene expression.[111] The latter cases might have represented activation of latent infection by trauma and/or inflammation. However, it was difficult to claim on the basis of such a limited study using such highly variable lesions that inflammatory skin lesions are a reservoir of infection; in at least two of the cases described and imaged, trauma was a likely primary cause. However, in a more extensive study involving analysis of 86 skin biopsy specimens (comprising cases of dermatitis, vasculitis, dermatophytosis, pemphigus foliaceus, exuberant granulation tissue, urticaria, eosinophilic granuloma and normal skin), 41 were positive for BPV DNA; positive results were obtained for all categories, including the normal skin, with approximately equal proportions of BPV-1 and BPV-2 DNA.[2] Subsequent laser micro-dissection indicated differences in the location of BPV DNA between sarcoid and non-sarcoid specimens. The DNA was more likely to be in intact or inflamed epidermal tissue of the non-sarcoid specimens. In general, inflamed areas of both the epidermis and dermis were more likely to contain BPV DNA than non-inflamed areas. What is not known is how many of these cases do undergo neoplastic transformation, but it does suggest that inflammation in the absence of trauma in some cases could be sufficient to initiate oncogenesis and/or compromise cutaneous integrity sufficiently to allow ingress of the virus. Conversely, it is

also possible that the presence of BPV predisposes to, or is involved directly in, the development of inflammatory skin lesions.[2] Interestingly, lesions of hoof canker (chronic proliferative pododermatitis) in horses without sarcoids have also been found to contain BPVV-1 and -2 DNA variants commonly found in sarcoid isolates, with evidence of gene transcription.[112]

Can transmission of BPV occur between horses?

Many researchers consider that BPV infection is not productive in equines because intact virions have never been detected in sarcoids by electron microscopy or immunolabelling; the requisite cellular environment may only exist in well-differentiated keratinocytes of cattle.[34,45,101] Horse-to-horse transmission and donkey-to-donkey transmission does appear to have occurred in closed equine herds (see Fig. 27.7).[20,79,98] However, in those circumstances, previous exposure to cattle and latent skin infection cannot be completely excluded. More direct evidence was obtained in one study where two donkeys with BPV-1-associated sarcoids were each paired with a donkey free of infection; the latter animals developed sarcoids containing identical genetic sequences to the virus found in their companion (this was distinct between the pairs).[61]

Bovine papillomavirus-1 LI major capsid protein transcripts were detected in 50% of 20 sarcoids (19 from donkeys) in a UK study.[113] In a more recent analysis conducted in Austria, 58% of 21 sarcoid samples were positive for BPV-1 DNA, which was complexed with L1 major capsid proteins. In two of those neoplasms the complexed DNA was a full-length, circular BPV genome.[31] The results of this study did not indicate if these are pre-viral structures or fully assembled virions; however they again raised the possibility that there may be intact virions in equine sarcoids. It has been previously hypothesized that intact virions are present, but only in very low numbers, or restricted to certain development stages of the neoplasm.[31,64] Non-productive infection in many cases may explain the failure of some horse-to-horse transmission studies using sarcoid extract material.[13,93]

On the basis of the most recent research findings, BPV transmission between horses should therefore be considered possible, and appropriate hygienic measures taken when animals with sarcoids are present. Such transmission is likely to occur to a lower degree than that between cattle and horses.[98]

Commonly affected sites

The most common locations overall are:

- Ventral body
- Girth
- Head
- Neck
- Limbs
- Sites of thin skin with limited or no hair cover and a tendency to sweat including:
  - Axillae
  - Groin
  - Scrotum and penile sheath (see Fig. 35.4).[18,21]

Lesions on the head may be periocular (see Fig. 3.2D) or involve the pinnae or ear canals; pedunculated masses may occasionally arise in the ear canals.[114] It should be noted that no external site is exempt from the possibility of sarcoid development, including the coronary band (Fig. 3.3C), anal skin, mammary gland skin, and mouth (see Figs. 28.10 and 35.17). The nasal cavities and paranasal sinuses have been affected on very rare occasions.[115] Sarcoids have never been found in internal organs.

It has been suggested that UK and continental European cases show greater similarity in anatomical site distribution than those from warmer climates, such as the USA and Australia.[7] In studies conducted of horses with sarcoids in South Africa, the USA and Canada, 35–58% occurred on the head and neck; 19–52% on the limbs; 7–33% on the trunk; and smaller numbers in paragenital locations.[14,23,116,117] In Polish and Swiss studies, the distributions were 22–36% head and neck; 12–23% limbs; and 30–55% trunk.[7,118] In a UK study however, 50% involved the paragenital region (male and female); 14% the head; 26% the trunk; and 10% other sites, including the head and neck; paragenital regions were also most common in a UK donkey population, in which there was a male predilection.[20,22] The extent of variation between studies conducted in different countries and regions makes it difficult to come to firm conclusions, most likely due to the fact that environmental and various other factors (e.g. genetic/breed composition of the equine population) are involved in addition to climate.

Another important geographical difference is that horses in the UK are more likely to have multiple sarcoids, and greater numbers of them, than those in Australia, North America and continental Europe.[119] Nearly half of horses in most regions eventually develop 2–8 neoplasms, but in the UK, there may be 10 to several hundred on a single horse.[7,45,119] In a UK referral hospital study, 71% of sarcoid patients had multiple sarcoids, with males and females being equally likely to have more than one lesion; this percentage was suggested to be artificially high due to the potentially greater likelihood of more severe sarcoid cases to be referred.[22] In a study of sarcoids submitted to diagnostic laboratories in Canada (n=722) only 28% of animals had more than one neoplasm.[23] This finding might suggest there are a lower percentage of multiple sarcoids per horse in non-referral caseloads, but it is confounded by the fact that it is less likely in horses outside of the UK.

Sarcoids frequently occur at sites of current or previous injury and scarring, and this plays a significant role in determining predilection sites (see Fig. 11.1). It should be kept in mind that the wound may have been too small to be noticeable, or may have healed months to years previously. Sarcoids on distal limbs almost invariably occur at wound sites, and those in less frequent locations, including the back and upper trunk, might also be assumed to have occurred at trauma locations. However, in UK donkeys, despite a paragenital predilection site and higher risk of sarcoid development in males, the castration procedure was not identified as a risk factor.[24] Sites of sarcoid development might also be related to activity of

flies, although there is no direct proof for their involvement in this disease.

There have been more detailed analyses of locations of periocular sarcoids. They may occur as single or multiple masses, including eyelid involvement, and are the second most common periocular neoplasm (the first being SCC), comprising 8–38% of the total.[17] In 445 cases: 78% were unilateral; 67% involved the upper eyelid and adjacent skin only; 69% involved the medial canthus (only 5% involved the lateral canthus); 12% developed the periocular lesion first; and only 14% had lesions restricted to this area.[120] A mean number of 6.6 periocular sarcoids per horse was documented, with no predilection for age, breed, gender or coat colour. The frequent development of sarcoids at eyelid margins and the medial canthus where flies often congregate has been suggested to support their role in disease transmission.[120]



Figure 11.2 Recurrent sarcoid mass at a previous site of excision. Scars from the sutures can still be seen.

Biological behaviour

Single or multiple neoplasms may have a benign behaviour, remaining static or growing slowly for many years; this depends on the clinical type (see below). Horses with smaller numbers of sarcoids tend to be less susceptible to further developments and more likely to have long-term stasis of those neoplasms. Many sarcoids are locally aggressive to various degrees; some suddenly develop locally aggressive behaviour for no apparent reason although in some cases, this can be related to trauma (including that induced by pruritus). A study proposed that axillary sarcoids may be more aggressive, which again could be related to the likelihood of local trauma; see Fig. 31.7).[121] Sarcoids in periocular locations frequently invade the subcutis and deeper muscular structures.[120]

Sarcoids do not metastasize, with the exception of the recently described malignant form.

Do sarcoids regress?

Spontaneous regression of sarcoids is generally thought to be a rare occurrence, particularly for periocular masses (see Fig. 31.15).[120] However, it was reported to occur in one-third of cases in a study of 120 Swedish horses, and one-third of untreated cases in a Belgian study.[84,90,93,122] Regressing tumours appear to have lower viral activity.[39] Experimental models have indicated that regression is associated with immune/inflammatory responses.[93] This has been supported by multiple studies in which regression of spontaneously arising sarcoids has been achieved by various methods of immune system upregulation. These methods have included intralesional inoculation of BCG, application of immunomodulatory compounds and vaccination with autologous tumour cells.[123–125] The documented effects were limited to individually injected tumours.[123] However, in more recent studies, donkeys and horses vaccinated with chimeric virus-like particles composed of BPV-1 L1 and E7 proteins showed positive clinical effects, including a tendency towards enhanced regression and reduced progression, reduced numbers of neoplasms, and evidence of humoral immune responses.[100,126] Presumably, immune responses sufficient to induce sarcoid regression do not usually occur. The BPV E5 protein downregulates MHC class I molecules, potentially allowing evasion of host immunosurveillance mechanisms (see p. 204).[59,60]

There is still some evidence of cell-mediated immunity: in mixed lymphocyte-tumour cell assays using Mc-1 sarcoid line cells, lymphocytes from horses with sarcoid tumours showed an earlier maximal proliferative response and a slight increase in mean cytotoxicity against the Mc-1 cells.[127] Antibody to papillomavirus antigen has only been found in donkey sera.[44]

The likelihood and nature of recurrence

Sarcoids frequently recur post-therapy, with recurrence rates of 7–50% after surgical excision (Figs. 11.2, 31.14, 31.16).[84,122,128] This recurrence may result from failure to completely excise the neoplasm or by autoinoculation during the surgical procedure.[43] Most recurrence is seen within 4 months and the risks of this increase with early onset, long duration, large size, sarcoids, which have previously failed to respond to treatment, and localization to distal limbs.[84,122] Recurrent masses may be more aggressive, with more extensive local invasion and more rapid growth.[129] In a study conducted at the University of Liverpool, the regrowth was more aggressive in character in over 90% of cases; regrowth tended to be more rapid for larger neoplasms.[119] It should also be noted that it is possible for sarcoids to recur at the site of previous removal up to 10–15 years later.[119]

Should sarcoids be biopsied?

A number of authors have suggested that sarcoids should be diagnosed clinically and not biopsied, due to the risks of this trauma either inducing or worsening locally aggressive behaviour (see pp. 554–555). In one study, periocular sarcoids that were traumatized by a either a biopsy procedure, accidentally or by partial treatment, were all found to worsen and develop into exuberant masses.[120] As sarcoids can show significant clinical similarity to other diseases, it may not be possible to make the diagnosis without histological confirmation; on that basis, it has been

suggested taking a biopsy is appropriate as long as treatment is rapidly initiated.[130]

The results of some studies have indicated that less invasive sampling may be possible if the diagnosis is made using polymerase chain reaction (PCR) to detect BPV DNA, e.g. from superficial scrapings and swabs.[131] It was suggested that this might be particularly valuable for testing small static or quiescent sarcoid lesions or checking for recurrence. This type of diagnosis requires meticulous sampling and laboratory technique to avoid contamination.[130,131] Aside from sampling issues, identification of BPV DNA in lesions that have proven problematic to diagnose histologically might be useful, for example in cases of fibroblastic sarcoid (see below) that can have a very similar appearance to exuberant granulation tissue or masses that contain significant amounts of granulation tissue. However, the major problem in both situations, i.e. avoiding of sampling trauma and diagnosing difficult cases histologically, is that BPV DNA can be present in non-sarcoid lesions or normal skin including the epidermis (see p. 208).[1,2,38,98] In a recent study, 50% of masses composed of exuberant granulation tissue were BPV DNA-positive.[2] Therefore, even with a positive PCR result, any decision would still need to be made on a balance of the clinical and diagnostic evidence, due to the apparent ubiquity of BPV DNA in multiple types of equine cutaneous pathology and indeed in normal skin of unaffected horses.

Gross pathology

On the basis of their macroscopic appearance, sarcoids have been classified into six clinical types (see Fig. 31.1).[119,132] The reasons for these different clinical manifestations and the relationships between them are still poorly understood. However, the classification is important because each type and subtype has therapeutic individuality, making some treatments better than others for the particular type (see pp. 555–561).

Occult

This is the mildest form of sarcoid disease. Occult sarcoids usually present as slowly growing flat, ovoid or circular patches of alopecia, sometimes with hyperkeratosis or small epidermal nodules (see Figs. 31.2, 31.10). The surface may be grey and scaly. If the skin is not alopecic, there may be changes in the density, colour or length of the overlying hair; on careful palpation, small (miliary) nodules or plaques are usually detectable.[120,132] In periocular regions, this type may present as more extensive, scaly alopecia that spreads to other areas of the face.[133] Occult sarcoids have been noted in the UK to be most common on the medial thighs, sheath, neck and face, but as for other clinical forms of sarcoid may be found in most sites.[119] This sarcoid type may not progress, but can do so, with transition to either verrucose or fibroblastic forms. Fibroblastic or nodular masses can have a surrounding halo-like area with characteristics of the occult form (see Fig. 31.3). If that surrounding occult area is not also surgically excised, there may be very rapid recurrence, sometimes within days. This can present as surgical wound dehiscence and subsequent failure to heal.[119]

Verrucose

This is the 'warty' form. Verrucose sarcoids are dry, often diffuse masses with poorly-defined margins (see Figs. 9.25, 31.3). There is a papillary, alopecic and hyperkeratotic surface, with dermal and subepidermal nodules. Elevated areas of these neoplasms may alternate with flat and scaly regions.[132]

Verrucose sarcoids are generally <6 cm in diameter but can be very extensive in some cases. There may be small or larger areas of ulceration. The axillae and inguinal regions, trunk in general and the neck have been described as predilection sites for this sarcoid type.[119] Verrucose sarcoids have also been described as developing in wound sites on the head.[88] The behaviour of this sarcoid type is intermediate between that of occult and fibroblastic forms.

Note

Both occult and verrucose types are rare in North America, Australia and Africa but common in the UK.[119]

Nodular

This is the next most advanced form of sarcoid disease, with division into two types, and further subdivision depending of the extent of capsular limitation[132]:

- *Type A* nodular sarcoids are firm, well-demarcated spherical or ovoid masses in the subcutaneous tissue. The overlying epidermis is intact but may be thin. These neoplasms may be freely mobile on palpation.
  - *Type A1* nodules have well-defined capsules and can be moved freely under the skin and over the underlying tissues (Fig. 31.4).
  - *Type A2* nodules have no skin involvement but are bound down to the deeper tissues. Movement of the sarcoid relative to the deeper tissues is not possible (Fig. 31.5).
- *Type B* nodular sarcoids are similar, but there is epidermal involvement that varies in extent.[120,129]
  - *Type B1* nodules are by definition bound to the skin (there is no independent movement of the skin and the nodule) and this type can however be moved relative to the deeper tissues – the main body of the lesion is encapsulated and therefore is free to move independently) (Fig. 31.6A).
  - *Type B2* nodules are bound to both skin and sub-lesional tissues. It is impossible to move the lesion independently of either the skin or the surrounding structures (Fig. 31.6B).

Nodular sarcoids have a predilection for the eyelids and inguinal regions (see Fig. 31.5), where they may cause significant deformity.[119] Their behaviour is similar to that of verrucose sarcoids. Nodular sarcoids in the eyelids have a particular tendency to infiltrate deeply and extensively, and surgical excision is not generally advised.[119] It is possible for this sarcoid type to ulcerate, and develop quickly into the more aggressive fibroblastic form. Some nodules remain static whilst others ulcerate, and in the case of A1 nodules, ulceration can be followed by spontaneous sloughing, usually without recurrence. In the case of A2 and B1 and B2

nodules, sloughing is less common and there is a high rate of recurrence.

Fibroblastic

Fibroblastic sarcoids have a fleshy appearance with marked ulceration and serous or inflammatory exudation, and can therefore be most easily confused with exuberant granulation tissue. This type of sarcoid is prone to trauma, haemorrhage and local infection.[119] There is division into two types and the Type 1 lesions are further divided into two subtypes:

- *Type 1* fibroblastic sarcoids are pedunculated (on a stalk).
  - *Type 1a* fibroblastic sarcoids have a narrow pedunculated base but no tumour extension beyond (deep to) the pedicle (Fig. 31.7A).
  - *Type 1b* fibroblastic sarcoid has a narrow pedicle but the tumour extends beyond the pedicle into the surrounding skin and subcutis, i.e. the tumour is not limited by the pedicle and has a 'dumbbell' shape) (Fig. 31.7B).
- *Type 2* fibroblastic sarcoids have a broader base and poorly-defined margins, i.e. they are sessile and invasive.[120,132] There is swelling of the surrounding skin (see Figs. 31.9, 31.10).

In the absence of trauma, fibroblastic sarcoids are rarely found on the neck or trunk. The Type 1b neoplasms are a relatively common complication of skin wounds, particularly of the limbs.[119] However, limb wounds may develop Types a or b.[88] Fibroblastic sarcoids have locally aggressive behaviour. Occult, verrucous or nodular sarcoids can rapidly progress to the fibroblastic form, even after remaining stable for many years, and this can occur from individual tumour nodules.[39,120] If a sarcoid mass of a more indolent form is accidentally incised during removal, over 60% will regrow as fibroblastic lesions.[119]

In a study conducted in Canada, horses with fibroblastic sarcoids were significantly younger than horses with other types, suggesting (but not directly proving) that this variant does not always develop from pre-existing, less aggressive types.[23]

Mixed (verrucose, nodular and fibroblastic)

Mixed sarcoids may contain any of the above-described types, but most often nodular and verrucous.[120] Sites of involvement include the axillae, inguinal regions and face (see Figs. 9.35, 31.11).[119,132]

Note

Most sarcoids fall into this category in reality but classification is usually based on the predominant type, and a mixed classification is not used unless a predominant type is not obvious.

Malignant

Malignant sarcoids, otherwise known as malevolent or aggressive, are the most severe form of the disease. They are composed of multiple, partially ulcerated nodules and cords, typically 2–5 cm in diameter that may form an expanding ring (see Figs. 31.12, 31.13, 31.18). This form of sarcoid is thought to usually develop from a mechanically irritated fibroblastic tumour, most often on the elbow, pre-femoral flank fold or lateral face (cheek) areas.[119,132] Malignant sarcoids are less frequently found in periocular locations as opposed to other sites.[120] They generally grow more rapidly than other types of sarcoid, but this is not invariable.[120,132] Most notably, malignant sarcoids invade along lymphatic vessels and extend to local lymph nodes.[132] There is no further extension to internal sites.

Associated lesions

The association between sarcoid development and cutaneous wounds should always be kept in mind, and this may present as early wound dehiscence following surgery; delayed healing; abnormal granulation tissue; and failure of wound contraction.[88] When dealing with limb wounds in horses (but not ponies), the situation is complex, as formation of exuberant granulation tissue is a frequent complication in any case and wound contraction is not a prominent feature of healing.

In horses with periocular sarcoids, where masses may become very large and/or there can be significant distortion of an involved eyelid, associated lesions can include conjunctivitis, ocular discharge, traumatic corneal damage including ulceration, and obstruction of the nasolacrimal duct.[120,133]

Regional lymph node enlargement might occur in any sarcoid case but would be expected to be due to inflammation and/or lymphoid hyperplasia for all sarcoid types other than the malignant form.

How common are the various sarcoid types?

In various studies conducted in different geographical locations, there have been significant variations in proportions of the different clinical sarcoid types. In a German study (n=421), the most common type was fibroblastic, with a lower frequency of mixed sarcoids, and infrequent diagnosis of verrucose lesions.[18] In a Canadian study of specimens submitted to diagnostic laboratories (n=467), the fibroblastic type was also the most common (31%), with 22% nodular, 15% occult, 15% verrucose and 16% mixed.[23] In a UK referral hospital study (n=147), 46% were verrucose, 38% fibroblastic and 16% mixed.[22] It is possible that these figures do not reflect the true percentages, as more aggressive or more cosmetically unattractive sarcoid types may be more likely to be referred or biopsied. In the UK study, the sarcoid types did not differ significantly in body site distribution.[22] In a UK study of periocular sarcoids, 36% were nodular, 29% verrucose, 16% fibroblastic, 13% mixed, 3% occult and 0.1% malignant.[120] Ulcerated lesions were more frequent in the medial canthus region and upper eyelid, while those in the lateral canthus and lower eyelid were more often occult or nodular.

Is there a relationship between clinical type and viral activity?

In a European study, nodular sarcoids had a higher BPV load. This may relate to the higher proportion of blood

vessels and inflammatory cells in fibroblastic sarcoids, epithelial cells in the verrucous type, and non-transformed fibroblasts in occult sarcoids, as opposed to transformed cells.[39] The nodular sarcoids also contained the highest expression of E2, E5, E6 and E7 mRNA.[39] In the same study, no significant correlation was determined between viral load and tumour size, location, time of onset, recurrence or horse breed or gender. In a further European study the viral load estimated by quantitative real-time PCR for E2, E5, L1 and L2 genes correlated with the severity of disease as determined by considering tumour growth kinetics, lesion number and sarcoid type, but it was not related to the clinical appearance.[102] However, in an earlier study conducted in the USA, the highest quantity of BPV E5 protein was found in the fibroblastic variant.[45] All sarcoid types can express BPV-1 DNA complexed with L1 major capsid proteins, i.e. all are potentially productive.[31]

Histopathology

It can be very difficult for the pathologist to make a diagnosis of sarcoid based on examination of punch or other small biopsy specimens. Confounding factors include granulation tissue formation (which may be exuberant), inflammation, and loss of the epidermis – any of which can easily result in an incorrect diagnosis. For these reasons, and also due to the potential for the exacerbation of sarcoid disease by biopsy trauma (see above), excisional specimens are optimal. Nevertheless, the histological features of the fibroblasts and vascular distribution, as described below, are usually enough to allow a diagnosis even in the absence of any epidermal tissue.

Sarcoids have classically been described as biphasic, with both epithelial (epidermal) and mesenchymal (dermal) components. The mesenchymal component is most prominent in fibroblastic sarcoids and is infiltrative with poorly-defined margins. Proliferating fibroblastic tumour cells and their supporting collagenous stroma may be seen forming a wide variety of patterns even within the same mass, including interlacing bundles, whorls, herringbone patterns or more haphazard arrangements (Fig. 11.3). There may be arrangement of the fibroblastic cells and stromal tissue in two approximately perpendicular directions.[4] The stroma can vary markedly in abundance even within the same neoplasm, and is myxomatous in some cases. Where the collagenous stroma is very prominent, it is possible to misdiagnose a sarcoid as a fibroma (see Fig. 11.3); lack of a repetitive pattern (that occurs in many sarcoid cases), and more particularly an infiltrative margin, should allow the diagnosis of fibroma to be ruled out. In some sarcoids, the tumour cell arrangement mimics that of a peripheral nerve sheath tumour (PNST), with storiform patterns and palisading bundles, within which the nuclei are aligned (Antoni A type pattern). It has been suggested, based on immunohistochemical labelling studies, that sarcoids that have this histological appearance are of myofibroblastic origin (see p. 216).[134] On this basis, any equine dermal tumour with the appearance of a PNST should undergo immunolabelling and/or molecular analysis for BPV DNA (see below).

Fibroblastic cells forming sarcoids are spindle-shaped with a finely fibrillar eosinophilic or amphophilic cytoplasm that has poorly-defined margins. Nuclei are thin and elongate, plump and ovoid and/or irregularly shaped with finely stippled or vesicular chromatin. Cellular pleomorphism is variable; there may be marked anisocytosis (cell size variation) and anisokaryosis (nuclear size variation) in some masses or in some regions of the same neoplasm. The mitotic rate is generally low; it tends to be higher in rapidly growing tumours and in superficial or ulcerated regions.

In classical descriptions, there is epidermal hyperplasia that may be regular, irregular, papillated or pseudocarcinomatous (pseudoepitheliomatous), with orthokeratotic and/or parakeratotic hyperkeratosis. The fibroblastic cells frequently palisade with respect to the basement membrane ('picket fence' formation; Fig. 11.4) and are more densely arranged in subepidermal regions. Typically, elongate and often branching rete pegs that may be broad in some cases (often >20 cells) extend into the underlying fibroblastic component (see Fig. 11.4), and there may be formation of epidermal inclusion cysts.[4]

The histological appearance of a sarcoid is not related to the type of BPV present, but there are distinct differences between the clinical types. Nearly all verrucose and mixed sarcoids show typical epidermal and dermal changes.[134] Problems arise for the pathologist when those 'typical' lesions are not present. In one study in which the clinical type of sarcoid was not documented, epidermal hyperplasia, 'rete peg' formation and 'picket fence' arrangements of fibroblastic cells were absent in 33%, 12% and 9% of cases (n=100), respectively.[128] However (as expected), fibroblastic proliferative lesions were always noted. The epidermis may be atrophic (with or without marked hyperkeratosis), normal or even absent due to extensive ulceration (Fig. 11.5); this may result in misdiagnosis as a fibroma, neurofibroma or fibrosarcoma. Epidermal changes are particularly likely to be absent in occult and Type A nodular sarcoids. Occult sarcoids may be more difficult to diagnose than other clinical types; they are usually covered by epidermis that is either normal or shows only subtle changes (see Fig. 11.5). In BPV DNA-positive epidermal tissue of occult sarcoids and of latently affected 'normal' skin, subtle epidermal lesions may include swollen keratinocytes with a pale-staining basophilic cytoplasm and perinuclear halo (resembling koilocytes; see papillomas), and thickening of the basement membrane.[89] In the dermis of occult sarcoids the lesions are also more subtle than expected, with an increased density of sub-epidermal fibroblasts infiltrating between reduced numbers of adnexal structures (see Fig. 11.5). These fibroblasts do not show any particular pattern of arrangement (including the 'picket fence' pattern). In nodular sarcoids, epidermal thinning with only occasional, short rete pegs was noted in 50% of cases.[65] Additionally, in the Type A nodular type, the epidermal changes are not in direct contact with the underlying fibroblastic component. Fibroblastic sarcoids will usually be at least partially ulcerated, with hyperplasia of the immediately adjacent intact epidermis (see Fig. 11.5).[65]

Granulation tissue can confound the histological diagnosis by infiltrating defects due to any cause including epidermal ulceration and traumatic or surgical injury; it is also common for the wound to be the primary lesion, with sarcoids developing in wounds of horses that have sarcoids at other sites and/or are in contact with infected cattle or horses (see p. 206).[88] Experience is required to differentiate

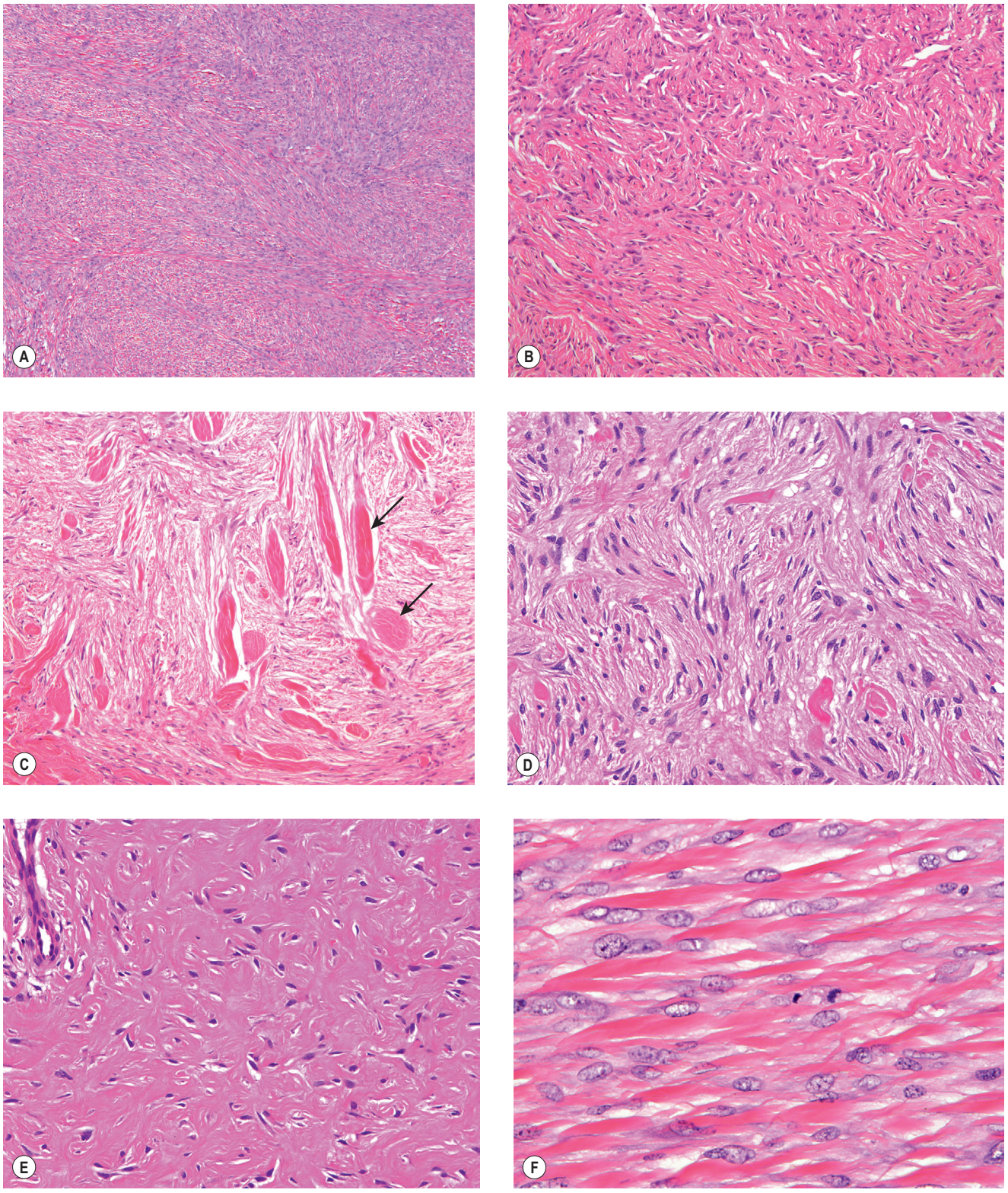


Figure 11.3 The various arrangements of fibroblastic tumour cells and their supporting stroma in equine sarcoids. **(A)** Interconnecting fascicular bundles (H&E, ×40). **(B)** Shorter bundles in a more repetitive pattern (H&E, ×100). **(C)** Infiltration between pre-existing, large collagen fibril bundles (arrows) (H&E, ×100). **(D)** Bundles showing a poorly-defined palisading arrangement; where that type of arrangement is seen, immunohistochemical labelling should be used to rule out a diagnosis of peripheral nerve sheath tumour (H&E, ×200). **(E)** A sarcoid containing prominent, dense collagenous stroma; the amount and appearance of the stroma can vary enormously both within and between neoplasms (H&E, ×200). **(F)** The fibroblastic tumour cells, with pale-staining, fibrillar eosinophilic cytoplasm and ovoid nuclei containing finely stippled chromatin. A mitotic figure is seen in this field, but in many neoplasms they cannot be found (H&E, ×400).

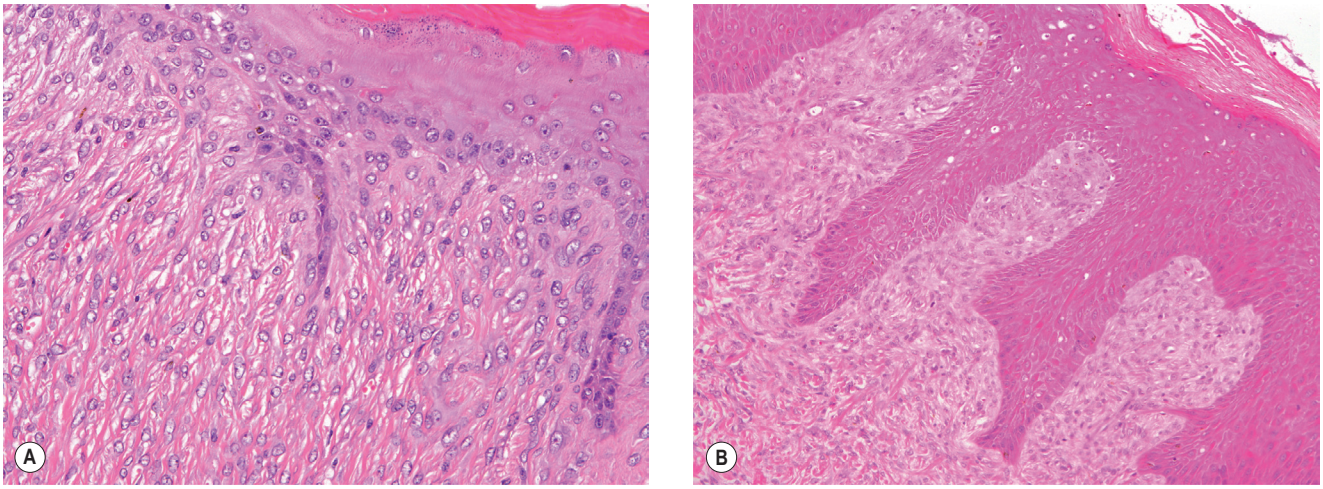


Figure 11.4 Classical epidermal changes in equine sarcoids. **(A)** Fibroblastic tumour cells palisading with respect to the overlying, hyperplastic epidermis. This epidermis is forming thin rete pegs (H&E, ×200). **(B)** The epidermal rete pegs can be broad; in this case, there is also surface parakeratosis. Again, the fibroblastic tumour cells are palisading with respect to the epidermal basement membrane (H&E, ×100).

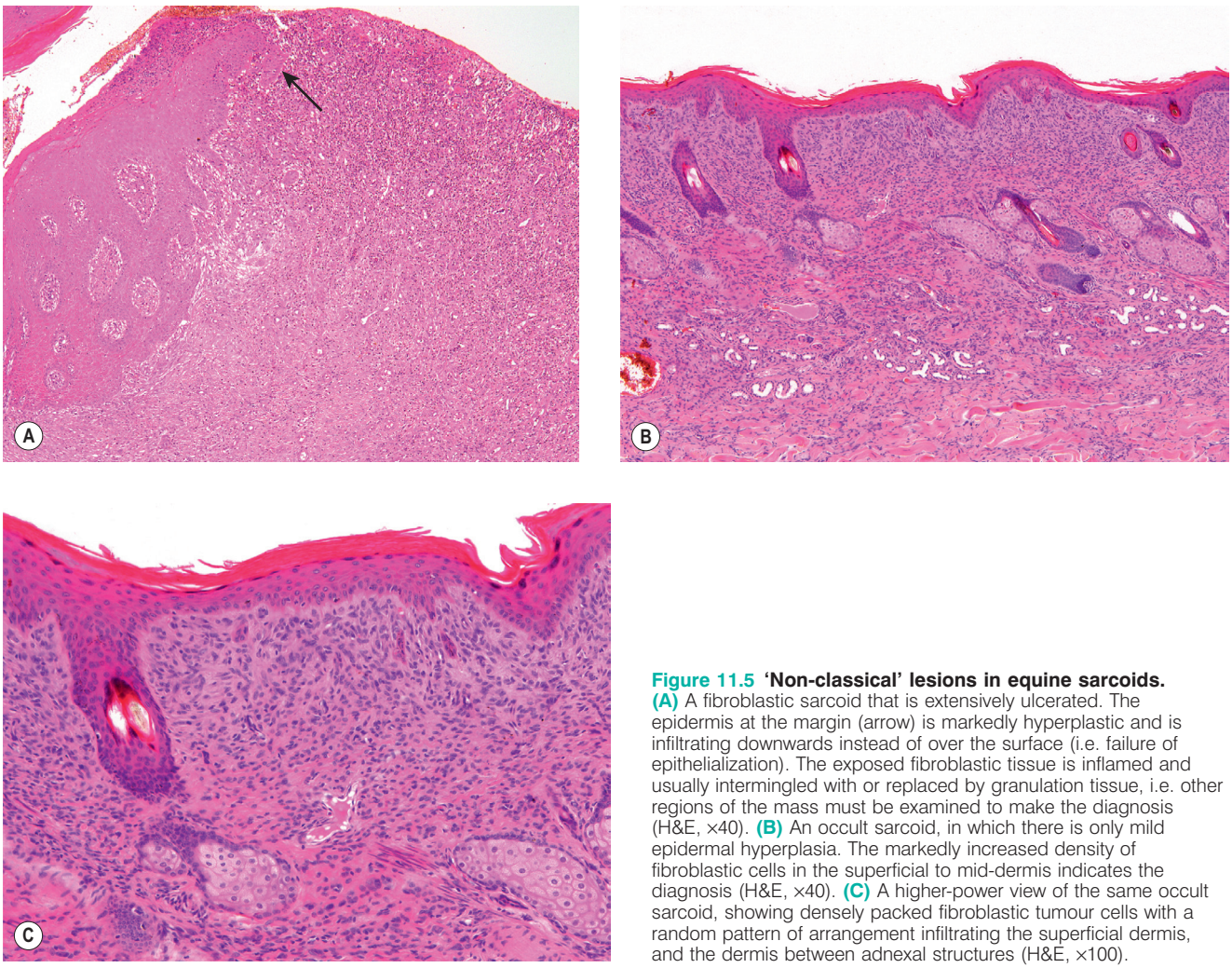


Figure 11.5 'Non-classical' lesions in equine sarcoids. **(A)** A fibroblastic sarcoid that is extensively ulcerated. The epidermis at the margin (arrow) is markedly hyperplastic and is infiltrating downwards instead of over the surface (i.e. failure of epithelialization). The exposed fibroblastic tissue is inflamed and usually intermingled with or replaced by granulation tissue, i.e. other regions of the mass must be examined to make the diagnosis (H&E, ×40). **(B)** An occult sarcoid, in which there is only mild epidermal hyperplasia. The markedly increased density of fibroblastic cells in the superficial to mid-dermis indicates the diagnosis (H&E, ×40). **(C)** A higher-power view of the same occult sarcoid, showing densely packed fibroblastic tumour cells with a random pattern of arrangement infiltrating the superficial dermis, and the dermis between adnexal structures (H&E, ×100).

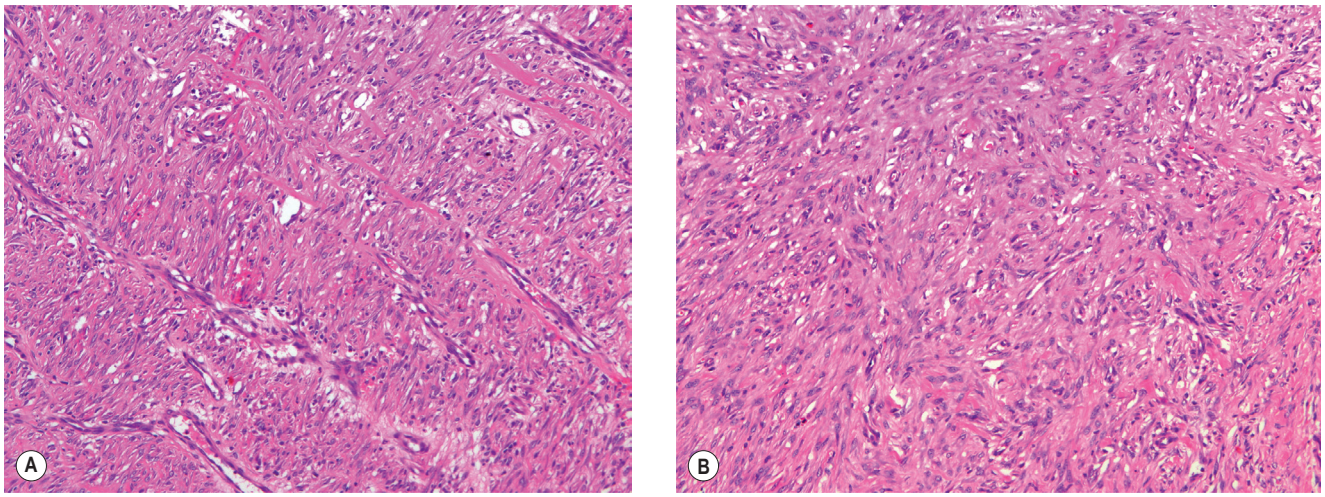


Figure 11.6 The complication of granulation tissue formation in making a histological diagnosis of equine sarcoid. **(A)** The classical appearance of granulation tissue, with large reactive fibroblasts and collagenous tissue arranged perpendicularly to the blood vessels; small numbers of inflammatory cells are also infiltrating (H&E, ×100). **(B)** An area of sarcoid tumour tissue beneath an ulcerated surface. Inflammatory cells are infiltrating, but the fibroblastic cells and blood vessels are randomly arranged (H&E, ×100).

the proliferative processes involved in cutaneous wound healing from lesions consistent with sarcoid development. Sarcoid tissue and granulation tissue may be intermixed, both grossly and histologically, and this can be a diagnostic problem; particularly when small biopsy specimens are submitted. Both clinician and pathologist should recognize that with some specimens, a histological diagnosis may not be possible. To summarise:

- Typical granulation tissue contains blood vessels arranged parallel to each other, with bundles of fibroblasts and collagen fibres oriented perpendicularly to them (Fig. 11.6). In more exuberant granulation tissue, there may be a less regular arrangement but it is usually possible, at least in a few fields, to find something approximating it.
- The blood vessels in sarcoid tissue are more randomly arranged, there is often (but not always) less collagenous tissue, and the tumour cells are not arranged in regular bundles (as described above); different but (possibly) repetitive arrangements or haphazard orientations are typical and should be sought throughout the mass where a diagnosis of sarcoid is suspected (Fig. 11.6).
- Fibroblasts in healing wounds may be relatively large and show mild to moderate pleomorphism with low mitotic rates; there is some overlap of these cellular characteristics with sarcoids. On that basis, the differentiation is usually made more easily by examining the arrangement of fibroblasts and stromal tissue at a lower magnification.

In ulcerated lesions there may also be secondary infection including bacteria, fungal elements, and parasites, e.g. *Habronema*. Inflammatory changes associated with those infections can additionally complicate the diagnosis.

When examining the surgical margins, it should be noted that even sarcoids with the most benign histological appearance may have very delicate marginal cords of tumour tissue extending outwards. These might not even be detected by examination of multiple sections at different levels; veterinary diagnostic laboratories will not routinely cut sections from different levels in the tissue block, due to time and financial constraints. This possibly accounts, at least partially, for the rather high rates of post-surgical recurrence and the need to ensure adequate surgical margins.[43]

Immunohistochemical labelling

In sarcoids immunolabelled for Ki67, a nuclear protein associated with cellular proliferation, the mean proliferative fraction has often been similar to that in normal skin (1.4–2.4%), but highest in superficial regions.[39,46,65] In the superficial regions only, fibroblastic and verrucose sarcoids showed higher numbers of Ki67-positive nuclei when compared with occult and nodular types.[134] This correlates with the results of in situ hybridization studies, in which the greatest numbers of BPV-positive cells were also located near the dermal–epidermal junction.[18,97]

In sarcoid stromal tissue, no qualitative difference was found in collagen composition versus the normal dermis; however, immunolabelled type III collagen showed pronounced organization into fibres in sarcoids only.[135]

In 10 cases of sarcoid that showed histological resemblance to PNSTs, the fibroblastic cells were strongly positive for vimentin but negative for S100.[134] Most PNSTs express S100 protein, although it is not a specific marker. There was also positive labelling for laminin and collagen type IV, suggesting the presence of a basal lamina. Such a finding could indicate Schwann cell origin; however, myofibroblasts also express those proteins in the form of fibronexus junctions and 8/10 of the sarcoids were smooth muscle actin-positive.[134] All of the PNST-like sarcoids of putative myofibroblastic origin contained BPV-1 or -2 DNA sequences.

Typical localization of E5 protein in the cytoplasm immediately adjacent to the nucleus (i.e. juxtanuclear) may be visualized by immunofluorescent labelling; this has been noted in fibroblasts of lesions induced experimentally by intradermal virion inoculation, but not the overlying epidermis.[95]

Box 11.1 Differential diagnoses for sarcoids

Neoplastic
- Papilloma
- Squamous cell carcinoma
- Fibroma
- Fibrosarcoma
- Peripheral nerve sheath tumour (including neurofibroma)
- Melanoma
- Carcinoma
- Giant cell Tumour / Histiocytoma

Non-neoplastic

Occult
- Dermatophytosis
- Alopecia areata
- Vitiligo
- Rub marks
- Traumatic lesions

Verrucose
- Dermatophytosis
- Dermatophilosis
- Traumatic lesions

Nodular and mixed
- Foreign body reaction
- Abscess
- Scar tissue
- Cyst (including dermoid cyst)
- Collagenolytic granuloma
- Bacterial pyogranuloma (e.g. *staphylococcal pseudomycetoma*)
- Parasitic granuloma (e.g. habronemiasis)
- Fungal granuloma
- Foreign body granuloma
- Inflammatory polyp (ear canal)

Fibroblastic and malevolent
- Exuberant granulation tissue.

Electron microscopy

Ultrastructurally, irregularly branching and anastomosing 25–30 nm diameter tubules have been noted within the cisternae of the endoplastic reticulum of sarcoid cells, from both tissue specimens and cell culture.[136] These tubules do not occur in sarcoids from all horses, or in the MC-1 cell line; they seem to be a nonspecific cellular response to various pathological situations including viral infection, in multiple animal species.

Molecular diagnostics

A complete, definitive diagnosis of sarcoid could be said to require both histological confirmation and demonstration of the presence of BPV DNA, although the latter is not performed routinely by diagnostic laboratories. Without histological examination, misdiagnosis based on a positive PCR result would be possible due to the fact that, as discussed above (p. 208), other types of skin pathology frequently contain BPV DNA, as can normal skin.[2] The use of PCR testing may have better clinical relevance for assessment of surgical margins of histologically diagnosed sarcoids, due to the problems in visualizing narrow marginal cords of neoplastic cells (as above). In 41 sarcoids, the tumour margin was PCR-positive at 4, 8, 12 and 16 mm (away from the histologically identified mass margin), respectively, in 95%, 73%, 39% and 33% of cases.[43] There was a greater probability of local recurrence of the sarcoid if the surgical margin was positive for BPV DNA, but for horses where the margins were negative, no such recurrences were documented.

Differential diagnoses

These are listed in Box 11.1.

References

1. Brandt S, Schoster A, Tober R, et al. Consistent detection of bovine papillomavirus in lesions, intact skin and peripheral blood mononuclear cells of horses affected by hoof canker. Equine Vet J 2011; 43:202–209.
2. Wobeser BK, Hill JE, Jackson ML, et al. Localisation of bovine papillomavirus in equine sarcoids and inflammatory skin conditions of horses using laser microdissection and two forms of DNA amplification. J Vet Diagn Invest 2012; 24:32–41.
3. Jackson C. The incidence and pathology of tumours of domesticated animals in South Africa. Onderstepoort J Vet Sci Anim Ind 1936; 6:1–460.
4. Sullins KE, Roberts SM, Lavach JD, et al. Equine sarcoid. Equine Pract 1986; 8:21–27.
5. Löhr CV, Juan-Sallés C, Rosas-Rosas A, et al. Sarcoids in captive zebras (Equus burchelli): association with bovine papillomavirus type 1 infection. J Zoo Wild Med 2005; 36:74–81.
6. Fretz PB, Barber SM. Prospective analysis of cryosurgery as the sole treatment for equine sarcoids. Vet Clin North Am Equine Pract 1980; 10:847–859.
7. Marti E, Lazary S, Antczak F, et al. Report of the first international workshop on equine sarcoid. Equine Vet J 1993; 25:397–407.
8. Goodrich L, Gerber H, Marti E, et al. Equine sarcoids. Vet Clin North Am Equine Pract 1998; 14:607–623.
9. Dubath M-L. Recherche d'Association entre le Système ELE et une prédisposition aux sarcoides equins (Thesis). Switzerland: University of Berne; 1986.
10. Nel PJ, Bertschinger H, Williams J, et al. Descriptive study of an outbreak of equine sarcoid in a population of Cape mountain zebra (Equus zebra zebra) in the Gariep Nature Reserve. J S Afr Vet Assoc 2006; 77:184–190.
11. Marais HJ, Nel P, Bertschinger HJ, et al. Prevalence and body distribution of sarcoids in South African Cape mountain zebra (Equus zebra zebra). J S Afr Vet Assoc 2007; 78:145–148.
12. Smith HA, Jones TC. Neoplasia. Veterinary pathology, 3rd edn. Philadelphia: Lea & Febiger; 1966: 269.
13. Ragland WL, Keown GH, Spencer GR. Equine sarcoids. Equine Vet J 1970; 2:2–11.
14. Strafuss AC, Smith JE, Dennis SM, et al. Sarcoid in horses. Vet Med Sm Anim Clin 1973; 68:1246–1247.
15. Pascoe RR, Summers PM. Clinical survey of tumours and tumour-like lesions in horses in south east Queensland. Equine Vet J 1981; 13:235–239.
16. Angelos J, Oppenheim Y, Rebhun W, et al. Evaluation of breed as a risk factor for sarcoid and uveitis in horses. Anim Genet 1988; 19:417–425.
17. Dugan SJ. Ocular neoplasia. Vet Clin North Am Equine Pract 1992; 8:609–626.
18. Teifke JP. Morphologic and molecular biologic studies of the etiology of equine sarcoid. Tierarztl Prax 1994; 22:368–376.
19. Valentine BA. Survey of equine cutaneous neoplasia in the Pacific Northwest. J Vet Diagn Invest 2006; 18:123–126.
20. Reid SW, Gettinby G, Fowler JN, et al. Epidemiological observations on sarcoids in a population of donkeys (Equus asinus). Vet Rec 1994; 26:207–211.
21. Lane JG. The treatment of equine sarcoids by cryosurgery. Equine Vet J 1977; 9:127–133.
22. Torrontegui BO, Reid SWJ. Clinical and pathological epidemiology of the equine sarcoid in a referral population. Equine Vet Educ 1994; 6:85–88.
23. Wobeser BK, Davies JL, Hill JE, et al. Epidemiology of equine sarcoids in horses in western Canada. Can Vet J 2010; 51:1103–1108.
24. Reid SWJ, Mohammed HO. Longitudinal and cross-sectional studies to evaluate the risk of sarcoid associated with castration. Can Vet J 1997; 61:89–93.
25. Mohammed HO, Rebhun WC, Antczak DF. Factors associated with the risk of development of sarcoid tumours in horses. Equine Vet J 1992; 24: 165–168.
26. Silva MS, Weiss M, Brum MC, et al. Molecular identification of bovine papillomaviruses associated with cutaneous warts in southern Brazil. J Vet Diagn Invest 2010; 22:603–606.
27. Borzacchiello G, Russo V, Della Salda L, et al. Expression of platelet-derived growth factor-β receptor and bovine papillomavirus E5 and E7 oncoproteins in equine sarcoid. J Comp Pathol 2008; 139:231–237.

28. Cheevers WP, Fatemi-Nainie S, Anderson LW. Spontaneous expression of an endogenous retrovirus by the equine sarcoid-derived MC-1 cell line. Am J Vet Res 1986; 47:50–52.
29. Fatemi-Nainie S, Anderson LW, Cheevers WP. Culture characteristics and tumorigenicity of the equine sarcoid-derived MC-1 cell line. Am J Vet Res 1984; 45:1105–1108.
30. Gobeil P, Gault EA, Campo MS, et al. Equine sarcoids are not induced by an infectious cell line. Equine Vet J 2007; 39:189–191.
31. Brandt S, Haralambus R, Shafti-Keramat S, et al. A subset of equine sarcoids harbours BPV-1 DNA in a complex with L1 major capsid protein. Virology 2008; 375:433–441.
32. Teifke JP, Weiss E. Detection of bovine papillomavirus DNA in equine sarcoids using the polymerase chain reaction (PCR). Berl Munch Tierarztl Wochenschr 1991; 104:185–187.
33. Reid SWJ, Smith KT. The equine sarcoid: detection of papillomaviral DNA in sarcoid tumours by use of consensus primers and the polymerase chain reaction In: Wade JF, ed. Equine infectious diseases VI. Newmarket: R&W Publications; 1991: 297–300.
34. Amtmann E, Müller H, Sauer G. Equine connective tissue tumors contain unintegrated bovine papilloma virus DNA. J Virol 1980; 35:962–964.
35. Trenfield K, Spradbrow PB, Vanselow B. Sequences of papillomavirus DNA in equine sarcoids. Equine Vet J 1985; 17:449–452.
36. Otten N, von Tscharner C, Lazary S, et al. DNA of bovine papillomavirus type 1 and 2 in equine sarcoids: PCR detection and direct sequencing. Arch Virol 1993; 132:121–131.
37. Bloch N, Breen M, Spradbrow PB. Genomic sequences of bovine papillomaviruses in formalin-fixed sarcoids from Australian horses revealed by polymerase chain reaction. Vet Microbiol 1994; 41:163–172.
38. Carr EA, Théon AP, Madewell BR, et al. Bovine papillomavirus DNA in neoplastic and nonneoplastic tissues obtained from horses with and without sarcoids in the Western United States. Am J Vet Res 2001; 62: 741–744.
39. Bogaert L, van Poucke M, de Baere C, et al. Bovine papillomavirus load and mRNA expression, cell proliferation and p53 expression in four types of equine sarcoid. J Gen Virol 2007:2155–2161.
40. Van Dyk E, Oosthuizen MC, Bosman AM, et al. Detection of bovine papillomavirus DNA in sarcoid-affected and healthy free-roaming zebra (Equus zebra) populations in South Africa. J Virol Methods 2009; 158:141–151.
41. Kidney BA, Berrocal A. Sarcoids in two captive tapirs (Tapirus bairdii): clinical, pathological and molecular study. Vet Dermatol 2008; 19:380–384.
42. Angelos JA, Marti E, Lazary S, et al. Characterisation of BPV-like DNA in equine sarcoids. Arch Virol 1991; 119:95–109.
43. Martens A, De Moor A, Demeulemeester J, et al. Polymerase chain reaction analysis of the surgical margins of equine sarcoids for bovine papilloma virus DNA. Vet Surg 2001; 30:460–467.
44. Reid SWJ, Smith KT, Jarrett WF. Detection, cloning and characterisation of papillomaviral DNA present in sarcoid tumours of Equus asinus. Vet Rec 1994; 135:430–432.
45. Carr EA, Théon AP, Madewell BR, et al. Expression of a transforming gene (E5) of bovine papillomavirus in sarcoids obtained from horses. Am J Vet Res 2001; 62:1212–1217.
46. Nixon C, Chambers G, Ellsmore V, et al. Expression of cell cycle associated proteins cyclin A, CDK-2, p27kip1 and p53 in equine sarcoids. Cancer Lett 2005; 221:237–245.
47. Campo MS. Viral and cellular oncogenes in papillomavirus-associated cancers. Br J Cancer Suppl 1988; 9:80–84.
48. Nasir L, McFarlane ST, Reid SWJ. Mutational status of the tumour suppressor gene (P53) in donkey sarcoid tumours. Vet J 1999; 157:99–101.
49. Chambers G, Ellsmore VA, O'Brien PM, et al. Sequence variants of bovine papillomavirus E5 detected in equine sarcoids. Virus Res 2003; 96: 141–145.
50. Brandt S, Haralambus R, Schoster A, et al. Peripheral blood mononuclear cells represent a reservoir of bovine papillomavirus DNA in sarcoid-affected equines. J Gen Virol 2008; 89:1390–1395.
51. Chambers G, Ellsmore VA, O'Brien PM, et al. Association of bovine papillomavirus with the equine sarcoid. J Gen Virol 2003; 84:1055–1062.
52. Kainzbauer C, Rushton J, Tober R, et al. Bovine papillomavirus type 1 and Equus caballus papillomavirus 2 in equine squamous cell carcinoma of the head and neck in a Connemara mare. Equine Vet J 2012; 44:112–115.
53. Yuan Z, Gault EA, Gobeil P, et al. Establishment and characterisation of equine fibroblast cell lines transformed in vivo and in vitro by BPV-1: model systems for equine sarcoids. Virology 2008; 373:352–361.
54. Yuan Z, Gault EA, Campo MS, et al. Different contribution of bovine papillomavirus type 1 oncoproteins to the transformation of equine fibroblasts. J Gen Virol 2011; 92:773–783.
55. Campo MS. Bovine papillomavirus: old system, new lessons? In: Campo MS, ed. Papillomavirus research: from natural history to vaccines and beyond. Norfolk: Caister Academic Press; 2006: 373–387.
56. Borzacchiello G, Mogavero S, De Vita G, et al. Activated platelet-derived growth factor beta receptor expression, P13K-AKT pathway molecular analysis, and transforming signals in equine sarcoids. Vet Pathol 2009; 46:589–597.
57. Yuan Z, Gault EA, Campo MS, et al. p38 mitogen-activated protein kinase is crucial for bovine papillomavirus type-1 transformation of equine fibroblasts. J Gen Virol 2011; 92:1778–1786.
58. Faccini AM, Cairney M, Asharafi GH, et al. The bovine papillomavirus type 4 E8 protein binds to ductin and causes loss of gap junctional intercellular communication in primary fibroblasts. J Virol 1996; 70:9041–9045.
59. Ashrafi GH, Tsirimonaki E, Marchetti B, et al. Down-regulation of MHC class I by bovine papillomavirus E5 oncoproteins. Oncogene 2002; 21:248–259.
60. Marchetti B, Gault EA, Cortese MS, et al. Bovine papillomavirus type 1 oncoprotein E5 inhibits equine MHC class I and interacts with equine MHC I heavy chain. J Gen Virol 2009; 90:2865–2870.
61. Nasir L, Campo MS. Bovine papillomaviruses: their role in the aetiology of cutaneous tumours of bovines and equids. Vet Dermatol 2008; 19:243–254.
62. Schapiro F, Sparkowski J, Adduci A, et al. Golgi alkalinization by the papillomavirus E5 oncoprotein. J Cell Biol 2000; 148:305–315.
63. Bucher K, Szalai G, Marti E, et al. Tumour suppressor gene p53 in the horse: identification, sequencing and a possible role in the pathogenesis of equine sarcoid. Res Vet Sci 1996; 61:114–119.
64. Campo MS. Animal models of papillomavirus pathogenesis. Virus Res 2002; 89:249–261.
65. Martens A, De Moor A, Demeulemeester J, et al. Histopathological characteristics of five clinical types of equine sarcoid. Res Vet Sci 2000; 69:295–300.
66. Zimmermann H, Koh CH, Degenkolbe R, et al. Interaction with CBP/p300 enables the bovine papillomavirus type 1 E6 oncoprotein to downregulate CBP/p300-mediated transactivation by p53. J Gen Virol 2000; 81: 2617–2623.
67. Narechania A, Terai M, Chen Z, et al. Lack of the canonical pRB-binding domain in the E7 ORF of artiodactyl papillomaviruses is associated with the development of fibropapillomas. J Gen Virol 2004; 85:1243–1250.
68. Yuan Z, Bennett L, Campo MS, et al. Bovine papillomavirus type 1 E2 and E7 proteins down-regulate Toll like receptor 4 (TLR4) expression in equine fibroblasts. Virus Res 2010; 149:124–127.
69. McBride AA, Romanczuk H, Howley PM. The papillomavirus E2 regulatory proteins. J Biol Chem 1991; 266:18411–18414.
70. Piirsoo M, Ustav E, Mandel T, et al. Cis and trans requirements for stable episomal maintenance of the BPV-1 replicator. EMBO J 1996; 15:1–11.
71. Gobeil PAM, Yuan ZQ, Gault EA, et al. Small interfering RNA targeting bovine papillomavirus type 1 E2 induces apoptosis in equine sarcoid transformed fibroblasts. Virus Res 2009; 145:162–165.
72. Nasir L, Gault E, Morgan IM, et al. Identification and functional analysis of sequence variants in the long control region and the E2 open reading frame of bovine papillomavirus type 1 isolated from equine sarcoids. Virology 2007; 364:355–361.
73. Yuan Z, Gobeil PAM, Campo MS, et al. Equine sarcoid fibroblasts over-express matrix metalloproteinases and are invasive. Virology 2010; 396:143–151.
74. Yuan Z, Gault EA, Campo MS, et al. Upregulation of equine matrix metalloproteinase 1 by bovine papillomavirus type 1 is through the transcription factor activator protein-1. J Gen Virol 2011; 92:2608–2619.
75. Jodele S, Blavier L, Yoon JM, et al. Modifying the soil to affect the seed: role of stromal-derived matrix metalloproteases in cancer progression. Cancer Metastasis Rev 2006; 25:35–43.
76. Strazzullo M, Corteggio A, Altamura G, et al. Molecular and epigenetic analysis of the fragile histidine triad tumour suppressor gene in equine sarcoids. BMC Vet Res 2012; 8:30.
77. Argyle D, Ellsmore V, Gault EA, et al. Equine telomeres and telomerase in cellular immortalisation and ageing. Mech Ageing Dev 2003; 124: 759–764.
78. Meredith D, Elser AH, Wolf B, et al. Equine leukocyte antigens: relationships with sarcoid tumours and laminitis in two pure breeds. Immunogenetics 1986; 23:221–225.
79. Ragland WL, Keown GH, Gorham JR. An epizootic of equine sarcoid. Nature 1966; 210:1399.
80. James VS. A family tendency to equine sarcoids. SW Vet 1968; 21:235–236.
81. Lazary S, Gerber H, Glatt PA, et al. Equine leucocyte antigens in sarcoid-affected horses. Equine Vet J 1985; 17:283–286.
82. Lazary S, Marti E, Szalai G, et al. Studies on the frequency and associations of equine leucocyte antigens in sarcoid and summer dermatitis. Anim Genet 1994; 25 (Suppl 1):75–80.
83. Broström H, Fahlbrink E, Dubath ML, et al. Association between equine leukocyte antigens (ELA) and equine sarcoid tumours in the population of Swedish halfbreds and some of their families. Vet Immunol Immunopathol 1988; 19:215–223.
84. Broström H. Equine sarcoids. A clinical and epidemiological study in relation to equine leucocyte antigens (ELA). Acta Vet Scand 1995; 36:223–236.
85. Han R, Breitburd F, Marche PN, et al. Linkage of regression and malignant conversion of rabbit viral papillomas to MHC class II genes. Nature 1992; 356:66–68.
86. Madeleine MM, Brumback B, Cushing-Haugen KL, et al. Human leukocyte antigen class II and cervical cancer risk: a population-based study. J Infect Dis 2002; 186:1565–1574.
87. Ding Q, Bramble L, Yuzbasiyan-Gurkan V, et al. DNA-PKcs mutations in dogs and horses: allele frequency and association with neoplasia. Gene 2002; 283:263–269.
88. Knottenbelt DC. Sarcoid transformation at wound sites In: Theoret C, Stashak TS, eds. Equine wound management, 2nd edn. Ames: Wiley-Blackwell; 2008: 585–608.
89. Bogaert L, Martens A, Kast WM, et al. Bovine papillomavirus DNA can be detected in keratinocytes of equine sarcoid tumours. Vet Microbiol 2010; 146:269–275.
90. Voss JL. Transmission of equine sarcoid. Am J Vet Res 1969; 30:183–191.
91. Montpellier JR, Dieuzeide R, Badens P. Greffe d'une tumeur schwannienne chez le mullet. Bull Acad Vet Fr 1939; 12.
92. Olson C. Equine sarcoid: a cutaneous neoplasm. Am J Vet Res 1948; 9:333–341.
93. Ragland WL, Spencer GR. Attempts to relate bovine papilloma virus to the cause of equine sarcoid: equidae inoculated intradermally with bovine papilloma virus. Am J Vet Res 1969; 30:743–752.

94. Olson C, Cook RH. Cutaneous sarcoma-like lesions of the horse caused by the agent of bovine papilloma. Proc Soc Exp Biol Med 1951; 77:281–284.
95. Hartl B, Hainisch EK, Shafti-Keramat S, et al. Inoculation of young horses with BPV-1 virion leads to early infection of peripheral blood mononuclear cells (PBMC) prior to pseudo-sarcoid formation. J Gen Virol 2011; 92:2437–2445.
96. Knowles G, O'Neil BW, Campo MS. Phenotypical characterization of lymphocytes infiltrating regressing papillomas. J Virol 1996; 70:8451–8458.
97. Lory S, von Tscharner C, Marti E, et al. In situ hybridisation of equine sarcoids with bovine papilloma virus. Vet Rec 1993; 132:132–133.
98. Bogaert L, Martens A, Van Poucke M, et al. High prevalence of bovine papillomaviral DNA in the normal skin of equine sarcoid-affected and healthy horses. Vet Microbiol 2008; 129:58–68.
99. Yuan Z, Gallagher A, Gault EA, et al. Bovine papillomavirus infection in equine sarcoids and in bovine bladder cancers. Vet J 2007; 174:599–604.
100. Ashrafi GH, Piuko K, Burden F, et al. Vaccination of sarcoid-bearing donkeys with chimeric virus-like particles of bovine papillomavirus type 1. J Gen Virol 2008; 89:148–157.
101. Lancaster WD. Apparent lack of integration of bovine papilloma virus DNA in virus-induced equine and bovine tumour cells and virus-transformed mouse cells. Virology 1981; 108:251–255.
102. Haralambus R, Burgstaller J, Klukowska-Rötzler J, et al. Intralesional bovine papillomavirus DNA loads reflect severity of equine sarcoid disease. Equine Vet J 2010; 42:327–331.
103. Bogaert L, Martens A, de Baere C, et al. Detection of bovine papillomavirus DNA on the normal skin and in the habitual surroundings of horses with and without equine sarcoids. Res Vet Sci 2005; 79:253–258.
104. Roden RBS, Lowy R, Schiller JT. Papillomavirus is resistant to desiccation. J Infect Dis 1997; 176:1076–1079.
105. Kemp-Symonds JG. The detection and sequencing of bovine papillomavirus Type 1 and 2 DNA from Musca autumnalis (Diptera; Muscidae) face flies infesting sarcoid-affected horses. London: Royal Veterinary College; 2000.
106. Finlay M, Yuan Z, Burden F, et al. The detection of bovine papillomavirus type 1 DNA in flies. Virus Res 2009; 144:315–317.
107. Stocco dos Santos RC, Lindsey CJ, Ferraz OP, et al. Bovine papillomavirus transmission and chromosomal aberrations: an experimental model. J Gen Virol 1998; 79:2127–2135.
108. Diniz N, Melo TC, Santos JF, et al. Simultaneous presence of bovine papillomavirus in blood and in short-term lymphocyte cultures from dairy cattle in Pernambuco, Brazil. Genet Mol Res 2009; 8:1474–1480.
109. Campo MS, Jarrett WF, O'Neil W, et al. Latent papillomavirus infection in cattle. Res Vet Sci 1994; 56:151–157.
110. Nasir L, McFarlane ST, Torrontegui BO, et al. Screening for bovine papillomavirus in peripheral blood cells of donkeys with and without sarcoids. Res Vet Sci 1997; 63:280–290.
111. Yuan Z, Philbey AW, Gault EA, et al. Detection of bovine papillomavirus type 1 genomes and viral gene expression in equine inflammatory skin conditions. Virus Res 2007; 124:245–249.
112. Brandt S, Tober R, Corteggio A, et al. BPV-1 infection is not confined to the dermis but also involves the epidermis of equine sarcoids. Vet Microbiol 2011; 150:35–40.
113. Nasir L, Reid SWJ. Bovine papillomaviral gene expression in equine sarcoid tumours. Virus Res 1999; 61:171–175.
114. Sullins KE. Endoscopically guided thermocautery and laser removal of an inflammatory polyp associated with chronic otitis externa in a pony. Equine Vet Educ 2006; 8:330–332.
115. Boulton CH. Equine nasal cavity and paranasal sinus disease: a review of 85 cases. J Equine Vet Sci 1985; 5:268–275.
116. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
117. Bastianello S. A survey on neoplasia in domestic species over a 40-year period from 1935 to 1974 in the Republic of South Africa IV. Tumours occurring in equidae. Onderstepoort J Vet Res 1983; 50:91–96.
118. Kasperowicz B, Rotkiewicz T, Otrocka-Domagala I. Pathomorphological and immunohistochemical study of selected markers of tumour cell proliferation in equine sarcoids. Pol J Vet Sci 2006; 9:109–119.
119. Knottenbelt DC, Edwards S, Daniel E. Diagnosis and treatment of equine sarcoid. In Pract 1995; 17:123–129.
120. Knottenbelt DC, Kelly DF. The diagnosis and treatment of periorbital sarcoid in the horse: 445 cases from 1974 to 1999. Vet Ophthalmol 2000; 169–191.
121. Owen RA, Jagger DW. Clinical observations on the use of BCG wall fraction for treatment of periocular and other equine sarcoids. Vet Rec 1987; 120:548–552.
122. Martens A, De Moor A, Vlaminck L, et al. Evaluation of excision, cryosurgery and local BCG vaccination for the treatment of equine sarcoids. Vet Rec 2001; 149:665–669.
123. Vanselow BA, Abetz I, Jackson AR. BCG emulsion immunotherapy of equine sarcoid. Equine Vet J 1988; 20:444–447.
124. Kinnunen RE, Tallberg T, Stenback H, et al. Equine sarcoid tumour treated by autogeneous tumour vaccine. Anticancer Res 1999; 19:3367–3374.
125. Rush BR, Flaminio MJ. Immunomodulation in horses. Vet Clin North Am Equine Pract 2000; 16:183–197.
126. Mattil-Fritz S, Scharner D, Pluko K, et al. Immunotherapy of equine sarcoid: dose-escalation trial for the use of chimeric papillomavirus-like particles. J Gen Virol 2008; 89:138–147.
127. Broström H, Bredberg-Rådén U, England J, et al. Cell-mediated immunity in horses with sarcoid tumours against sarcoid cells in vitro. Am J Vet Res 1979; 40:1701–1706.
128. Tarwid JN, Fretz PB, Clark EG. Equine sarcoids: a study with emphasis on pathological diagnosis. Comp Cont Ed Pract Vet 1985; 7:293–300.
129. Giuliano EA. Equine periocular neoplasia: current concepts in aetiopathogenesis and emerging treatment modalities. Equine Vet J (Suppl) 2010; 37:9–18.
130. Knottenbelt DC, Matthews JB. A positive step forward in the diagnosis of equine sarcoid. Vet J 2001; 161:224–226.
131. Martens A, De Moor A, Ducatelle R. PCR detection of bovine papillomavirus DNA in superficial swabs and scrapings from equine sarcoids. Vet J 2001; 161:280–286.
132. Knottenbelt DC. A clinical classification of the equine sarcoid. Clin Tech Equine Pract 2005; 4:278–295.
133. Newton SA. Periocular sarcoids in the horse: three cases of successful treatment. Equine Vet Educ 2000; 12:137–143.
134. Bogaert L, Van Heerden M, De Cock HEV, et al. Molecular and immunohistochemical distinction of equine sarcoid from schwannoma. Vet Pathol 2011; 48:737–741.
135. Williams IF, Heaton A, McCullagh KG. Connective tissue composition of the equine sarcoid. Equine Vet J 1982; 14:305–310.
136. Madewell BR, Munn RJ. Tubuloreticular inclusions in equine connective tissue neoplasms. J Comp Pathol 1989; 100:449–452.

12 Squamous cell carcinoma

Cellular origin 220
Profile 220
Oncogenesis 220
General and site-specific pathology 222

Cellular origin

Epithelial cells, with differentiation to keratinocytes.

Profile

Squamous cell carcinoma (SCC) is one of the most common equine cancers. It is often cited as the second or third most frequently reported type of neoplasm in horses, and has been estimated to comprise 7–31% of total neoplasms in various surveys.[1,2]

Horses of any age can be affected by SCC, with reports in animals as young as 1 year. However, it is most often reported in older horses, with mean ages of 12.0 and 12.4 years in two surveys conducted in the USA.[1,3]

There may be a gender predilection for SCC development; however, this has not been found in all surveys. In one study, geldings were reported to be five times more likely than stallions, and two times more likely than mares to develop SCC; this agreed with the results of another study in which this type of neoplasm occurred in twice as many geldings as mares.[4–7] Older geldings are more liable to SCC of the penis and preputial skin than entire horses.

Horses with non-pigmented skin (including white, white-grey and palomino horses) that are exposed to excessive solar radiation are also predisposed to SCC development. This includes Appaloosa, Pinto and American Paint horse breeds. The lack of pigmentation may specifically involve certain SCC-prone sites, including ocular structures and periocular skin (see Figs. 27.5 and 31.33).

In one study of cases of ocular SCC (n=147) submitted to USA Veterinary Colleges, there was a high prevalence in horses with white, grey, cremello and palomino hair colours; however, the skin pigmentation and hair colour specifically around the eye was not known.[5] In a study of corneal and corneolimbal SCC (n=38), the most commonly represented coat colours were white, chestnut/sorrel and grey.[8] Affected animals were reported to have less pigment in the periocular skin and conjunctiva, and Appaloosas were over-represented as a breed (53%). In continental Europe, Haflingers, i.e. a breed with a light chestnut coat colour, are more commonly affected than other breeds or horses with other coat colours.[6] Some breeds, including Belgians, Shires and Clydesdales that have pigmented periocular skin and eyelid margins but non-pigmented (interpalpebral) conjunctiva, are also SCC-prone. Clydesdales and Shires have been reported to develop SCC at any ocular site.[9] Belgians are also susceptible to ocular SCC in general, but in particular neoplasms arising from the conjunctiva and nictitating membrane.[10,11]

Squamous cell carcinomas can occur on any cutaneous site, and sites of wounds (including burns), where this neoplastic change can be a significant cause of incipient wound healing failure (see Aetiological factors, below). In these skin sites, again, non-pigmented regions are most often involved and many cases have a remarkable demarcation to the non-pigmented skin. Prior repeated episodes of actinic keratosis are often reported (see below).

Oral and respiratory mucosal SCC also occur in horses with some frequency.

Genetic influences on SCC susceptibility other than pigmentation may include immune determinants, for example equine leukocyte antigens. Interestingly, the incidence of SCC in donkeys and mules is very low and the reasons for this are not known.[1,12,13]

Oncogenesis

Squamous cell carcinoma is a progressive condition, with significant evidence that the most common cause is cumulative exposure to ultraviolet-B radiation. It is thought that the ensuing DNA damage leads to mutant clones within normal skin, with potential progression to in situ (intraepidermal or intraepithelial) neoplastic disease.

'Precursor' lesions

Actinic keratosis and squamous cell carcinoma in situ: intraepidermal cancers?

The veterinary and medical literature in relation to this terminology is confusing. All such lesions occur in sun-exposed skin and are confined to the epidermis, with no dermal invasion. Some pathologists consider actinic keratosis (AK) to be the earliest form of SCC, i.e. an early form of in situ SCC, some consider AK to be *pre*cancerous, and others use the terms 'AK' and 'squamous cell carcinoma in situ' (SCCIS) completely interchangeably.[14,15] By definition, SCCIS is a neoplasm, and often diagnosed when epidermal/epithelial cell atypia and disorganization extend through all layers even if only in one small focus (see Fig. 3.13). In medical pathology there is a contention that as atypia begins

in the basal layer and eventually extends to the entire epidermal thickness, the associated continuum of lesions should be recognized; grading systems have been proposed based on the extent of keratinocyte atypia within the thickness of the epidermis and associated adnexa, with the highest grade being equivalent to SCCIS.[14,16,17] These intraepidermal lesions could all (at any stage) potentially be defined as neoplastic as suggested by many authors, as they frequently contain transformed cells, i.e. epidermal cells with mutations in the tumour suppressor gene *p53* (see below).[18] Similar grading systems might be usefully applied to horses to allow determination of the risk of progression (if associated with clinical data) as intraepidermal atypia is frequently noted at surgical margins (see Histopathology, below).

Breeds with a predilection for developing lesions consistent with AK/SCCIS include American Paint, Appaloosa, Belgian, Clydesdale, Shire and Pinto horses.[19] These closely match the list of breeds predisposed to SCC. Many middle-aged to older horses with non-pigmented eyelid margins have been noted to have small AK lesions that are frequently not noticed by owners.[19] The risk of any type of intraepidermal cancer progressing to invasive SCC is not known in horses, but in humans, it is thought to be 5% to >10% depending on the site, with an even higher risk in individuals with multiple lesions. Some low-grade lesions are known to regress, but this has not been documented specifically in equines. In studies of human patients where AK and SCCIS were considered to be equivalent, i.e. all intraepidermal cancers were included, nearly all SCCs developing on sun-damaged skin evolved from them; those intraepidermal lesions were noted at margins of or within the invasive neoplasms.[20]

Penile precancerous plaque (leukoplakia)

These plaques, which only occur on the penis (see Figs. 3.8, 31.31), frequently progress to invasive SCC. The epithelium is dysplastic and hyperplastic, and may contain koilocytes. Koilocytes are enlarged epidermal cells with a clear cytoplasm and an eccentric, irregularly shaped, hyperchromatic nucleus; they can be an indicator of papillomavirus infection, as can other changes, including giant keratohyalin granules (see Fig. 14.1). Papillomavirus DNA has been amplified from these lesions.[21] As for AK/SCCIS, the epidermal basement membrane is intact.

Aetiological factors

Ultraviolet light radiation

The cumulative effect of ultraviolet light (UV)-B radiation (wavelength 290–320 nm) resulting from exposure to natural sunlight is the most well-known aetiological factor. This type of radiation causes thymidine dimer formation in DNA and RNA. A higher percentage of SCC (of total neoplasms in horses) in the Pacific Northwest of the USA, compared with Northeastern regions, may reflect greater exposure to solar radiation.[12] There is a higher prevalence of ocular SCC with increasing longitude, altitude and mean annual solar radiation, and decreasing latitude; however, there are other location-specific variables that might also affect this, including heat and wind, and breed compositions of the equine populations.[5]

Wounds and infections

Other factors suggested to be involved include chronic irritation or infection, cutaneous burns, poor wound healing and parasitic diseases (e.g. habronemiasis, onchocerciasis) (see Fig. 27.8C). In ocular sites, chronic conjunctivitis, chronic nasolacrimal duct obstruction, and congenital or acquired eyelid deformities are all possible risk factors.[9] In one study, seven horses diagnosed with ocular SCC had a documented previous eye injury.[22]

There was one report of an extensive and deeply invasive SCC (40×80 cm) that developed beneath a non-healing wound over the ilium that had resulted from burns sustained 8 years earlier.[23] A further case occurred in exuberant granulation tissue at the site of a previous injection site abscess over the gluteal region, approximately 2 years following the initial injury.[24] A SCC was also reported to develop in a chronic wound at the site of a neck laceration that had been treated topically with various chemicals; it is thought that the latter may be important in carcinoma pathogenesis.[25] As only a few cases have been specifically reported, it is difficult to know what the incidence of post-traumatic SCC is.

For SCC of the male genitalia, smegma has been suggested to be an aetiological factor, either as an irritant or due to the presence of a true carcinogen.[26] In human medicine this theory is controversial, with little experimental proof – despite the widespread belief that it causes penile, cervical and prostate cancer.[27] Injection of equine smegma into the skin of mice in a 1947 study induced the development of SCC, papilloma and fibrosarcoma at those sites;[28] however, those studies have not been repeated. Other factors suggested to predispose to penile/preputial SCC include repeated trauma and phimosis. It has been suggested that SCC of the hoof may arise as a consequence of keratoma formation. In the stomach (see p. 231–232) there has been speculation that irritation caused by parasites or diet may be involved.

Equine papillomavirus

An association between papillomavirus and SCC development appears to exist for genital lesions at least (see Fig. 31.32). Penile precancerous plaques have been demonstrated to contain papillomavirus DNA (see above).[21] In a recent study in the USA, DNA sequences from *Equus caballus* papillomavirus 2 (EcPV2) were amplified from 9 out of 20 horses with penile SCC.[29] Similarly, in a European study, EcPV2 DNA was detected in 5/6 penile SCC and one clitoral SCC from horses in the UK and 4/4 penile SCC from Austria; the virus was not detected in histologically normal adjacent tissues, smegma, scrotal skin, ocular SCC or equine sarcoids but was detected in genital carcinoma in situ lesions.[30] Both EcPV2 DNA and BPV-1 DNA were isolated from head and neck SCC lesions in a Connemara mare in Austria; EcPV2 E6 transcripts were found in peripheral blood mononuclear cells and SCC tissue.[31] In a study of genital and ocular SCCs, EcPV2 DNA was found not only in all genital SCCs, penile intraepithelial neoplasia (PIN) lesions and papilloma but also in all ocular SCC lesions.[32] The viral DNA in this study was also found in a high proportion of swabs from genitalia (including the cervix) and eyes of horses without neoplasia; positive genital swabs included those from animals never used for breeding.

These studies suggest a role for papillomavirus infection in the development of genital SCC in particular, where high ultraviolet light exposure would not be as likely and where there may be sexual or close-contact transmission of the virus between horses.[29,30,32] However, carcinoma is extremely rare in entire stallions and, in particular, in those used for breeding. Additionally, there may be involvement of this virus in development of at least some SCCs in ocular and other sites. It is not certain as yet if the EcPV2 virus can be transmitted: (i) between horses, or between different anatomical sites on the same horse; (ii) by insects; or (iii) vertically from mare to foal. It is also not known if EcPV2 is a primary cause of neoplasia or has a secondary role; the presence of latent infection suggests that the virus alone is not sufficient to induce oncogenesis.[32]

Oncogenesis: the cellular pathways

p53 mutation

The p53 protein is a tumour suppressor factor that is normally rapidly degraded, with levels being too low for detection. When cells experience genotoxic stress this protein is stabilized, functioning to arrest the cell-cycle and allow more time for DNA repair; apoptotic (cell death) pathways are engaged if the damage is too severe (see pp. 29–31). The *p53* gene is particularly susceptible to UV light-induced mutation (leading to loss of function or aberrant function), and many studies have indicated that these mutations are critical in the development of a large proportion of human cases of SCC.[33] In one study of equine SCC, two of the eight samples analysed contained missense mutations in the *p53* gene consistent with UV light damage.[34] In many cases the translated protein has a greater half-life, accumulating in the nucleus and sometimes also the cytoplasm (where it can be identified by immunohistochemical labelling). In two studies, all equine ocular SCC tumours ($n=11$) overexpressed p53 protein in the nucleus, as did associated intraepithelial lesions.[35,36] In one of those studies, 78% of penile/vulvar SCCs ($n=9$) were also positive. It should be noted that failure to detect the protein immunohistochemically does not rule out a mutation that has either abolished the protein, or not stabilized it sufficiently for detection. There may also be non-mutational p53 protein stabilization due to binding by oncoproteins or interruptions in the degradative pathway.[35]

Cyclooxygenase (COX)-2 expression

Cyclooxygenases (COX) are enzymes that convert arachidonic acid to prostaglandins, with COX-1 and COX-2 being the most biologically active. COX-1 and COX-2 have different physiological functions and are expressed by different genes; both are constitutively expressed in many healthy tissues. In other species, including humans, high levels of expression of the COX-2 enzyme in SCC and AK/SCCIS lesions are thought to increase angiogenesis, invasiveness and metastasis, induce resistance to apoptosis, and suppress anticancer immune responses. The mechanisms of COX-2 upregulation are not clear, but there is involvement of prolonged sunlight exposure, which may contribute at least partly via its action on p53 (see above). The resulting effects may largely be mediated by increased concentrations of COX-2-derived bioactive lipids including prostaglandin E_2.

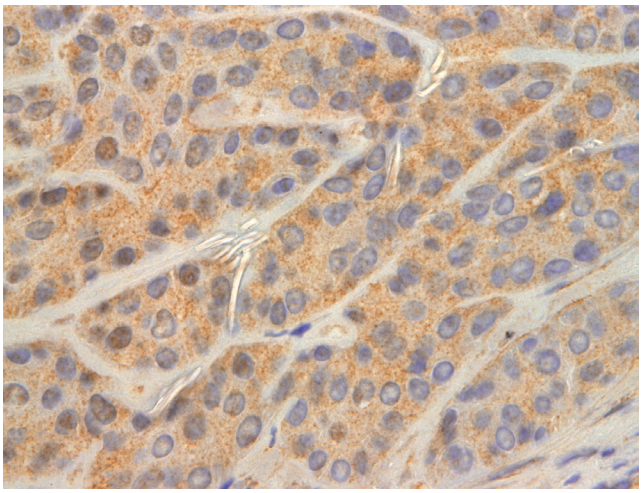


Figure 12.1 Diffuse cytoplasmic COX-2 expression in tumour cells of metastatic squamous cell carcinoma in a lymph node. The primary mass was located in the vulva (immunohistochemistry, ×400).

In non-equine species, COX-2 is not usually expressed by normal epithelial tissue. In horses, however, the epidermis, conjunctival/preputial/penile epithelium and SCC tissue do express COX-2 (and COX-1) protein (Fig. 12.1).[37,38] In 22 horses with equine ocular SCC, 27% showed positive immunolabelling for COX-2 in <10% of the cancer cells; this expression was significantly associated with the mitotic index, but not degrees of differentiation or invasiveness.[39] In another study, immunoreactivity for both COX-1 and COX-2 was greater in corneal SCC tissue than the normal cornea.[38] There was not significant overexpression in eyelid SCC in the same study; the authors did note that immunolabelling of typically variable biopsy specimens is not strictly quantitative, necessitating further analysis. In a study of 43 ocular SCC/SCCIS, approximately 60% of lesions (of either type) showed positive COX-2 immunolabelling in a small percentage of cancer cells (≤1% in 90% of the neoplasms) that was not noted in control tissue.[40] In a study of SCC from ocular, genital, alimentary, nasal and metastatic sites ($n=37$), 86% were COX-2-positive and the labelling involved 21–50% of cells in over half of them; significant differences were not noted between the anatomical sites.[41]

It has been suggested that drugs inhibiting COX-2 may therefore be of use, particularly as they only minimally affect the physiological functions of COX-1. In one case, remission of a lip SCC (with a high level of COX-2 expression) was achieved using *per os* piroxicam.[42] The universal application of such treatments is not certain however, given the equine-specific constitutive expression of COX enzymes in multiple epithelial sites, the demonstrated significant variation in COX-2 expression between different cases and the low percentage of cells expressing it in many neoplasms.

General and site-specific pathology

As in other species, equine SCCs are locally aggressive neoplasms that invade surrounding tissues and have the potential to metastasize, although they are often slow to do so.

Gross pathology

The gross appearance of SCC masses varies significantly between horses and anatomical sites; some authors classify them as productive/proliferative or erosive/destructive. The neoplasms are usually pale and firm due to significant amounts of supporting fibrous tissue. When obtaining specimens for a histological diagnosis, it is important not to scrub the involved surface, as this avoids removal of relevant superficial tissue. Cytological diagnosis may be possible for internal SCC involving the thorax or abdomen that have penetrated the serosa; however, sufficient numbers of exfoliated cells may not always be present.[43]

Histopathology

The histological appearance, regardless of site, is similar, with tumour cells arranged in infiltrating, irregularly-shaped trabeculae, islands and/or cords supported by collagenous stromal tissue that is frequently abundant (Fig. 12.2). The squamous epithelial tumour cells tend to be well-differentiated with progression from one to several layers of polyhedral basal cells with scanty amphophilic cytoplasm at the periphery of the neoplastic structures to large polyhedral cells in the centres; the latter cells have abundant, finely fibrillar, brightly eosinophilic cytoplasm with well-defined margins and they may show prominent intercellular bridges (see Fig. 12.2). Nuclei are large, central, round or ovoid, often vesicular, contain one to several prominent nucleoli, and show variable pleomorphism and mitotic rates. In cases where the tumour cells are less well-differentiated, they may be spindle-shaped on rare occasions.[44] There may be central accumulation of concentrically laminated keratin ('keratin pearls') that tends to be most prominent in well-differentiated SCC; these centres may undergo necrosis and be infiltrated by neutrophils (see Fig. 12.2). In less well-differentiated SCC, keratin pearls are not observed, but there may individual keratinized (dyskeratotic) tumour cells.[44,45] Dyskeratotic cells may be swollen or shrunken with normal or condensed, homogeneous brightly eosinophilic cytoplasm, and a normal or condensed and elongated hyperchromatic nucleus (see Fig. 12.2).[46] Contiguity with the overlying epidermis or epithelium can often be identified histologically (see Fig. 12.2), however the margins between normal and neoplastic tissue are often poorly-defined. It is not uncommon to encounter intraepithelial neoplasia (AK/SCCIS) at the margins of excised equine SCC, which should be brought to the attention of the referring veterinarian. As SCC can metastasize to regional lymph nodes, a more accurate prognosis will require formalin-fixed samples for histological examination from these structures at the time of surgical intervention or any other treatment. These should be wedge biopsy specimens to maximize the detection of micrometastases, i.e. individual or small clusters of neoplastic cells.

'Precursor' and other solar-associated lesions

In lesions confined to the epidermis or epithelium, i.e. AK/SCCIS (pp. 220–221; Fig. 3.13), cellular changes include:

- Disorganized maturation
  - Hyperkeratosis (particularly parakeratotic)
  - Dyskeratosis
  - Variation in cytoplasmic staining intensity that may include vacuolation
  - Variation in cellular shape
  - Disrupted nuclear polarity (nuclei arranged at obtuse angles rather than being perpendicular to the surface)
  - Enlarged, irregular and hyperchromatic nuclei
  - Increased anisokaryosis and mitotic rates
  - Nuclear crowding
  - Scattered to confluent anaplastic cells, some with abnormal mitotic figures (see Fig. 3.13).[17]

In one (medical) grading system, grade I lesions refer to keratinocyte atypia in basal and suprabasal layers only (lower one-third of the epidermis), while grade II and III involve up to two-thirds and more than two-thirds of the thickness, respectively; grade III lesions also involve hair follicle epithelium.[14] Immunohistochemical labelling of SCCIS lesions of human patients for the proliferation-associated nuclear protein Ki67 was positive for 40–50% of cells; this proliferative fraction exceeded that seen in invasive SCC.[16,47] Similar comparative labelling of proliferative fractions in intraepithelial and invasive SCC has not been attempted for equines. In the dermis, evidence of chronic solar damage may include superficial laminar fibrosis parallel to the epidermal surface, containing telangiectatic (dilated) blood vessels.[19] It is possible that, as in other species, the laminar fibrosis may follow or be seen in conjunction with pale-staining, altered (homogenized) collagen just beneath the epidermis; the collagen fibres are separated by pale-staining, Alcian blue-positive substance.[48]

Solar elastosis is a further potential dermal lesion that may occur with or without fibrosis.[19,48] Thick, wavy basophilic fibres are noted in the superficial dermis, being composed of degenerate elastic and/or collagen fibres; these are best seen using a van Gieson silver stain or an elastin stain, and are just below and intermingled with amorphous, slightly basophilic areas of degenerate collagen.[48] Solar elastosis was reported in association with multiple SCCs in the skin of two horses in Florida.[49] In human SCC patients, the presence of solar elastosis has been associated with a lower potential for metastasis.

Grading

Equine SCC is not routinely graded by pathologists, but grading systems have been suggested by several authors (see also pp. 18–19)[44,50]:

- *Grade I SCC*: well-differentiated with numerous dyskeratotic cells and prominent keratin pearls, and obvious intercellular bridges
- *Grade II SCC*: moderately-differentiated with frequent dyskeratosis but only occasional keratin pearls and poorly-defined intercellular bridges
- *Grade III SCC*: poorly-differentiated cells with infrequent keratinization and some atypical mitotic figures.

These grades have been associated with depth of invasion for SCC (n=19) from the penis, skin or conjunctiva.[50] The grade and presence of metastasis were not linked in a study of oropharyngeal and nasal SCC.[44]

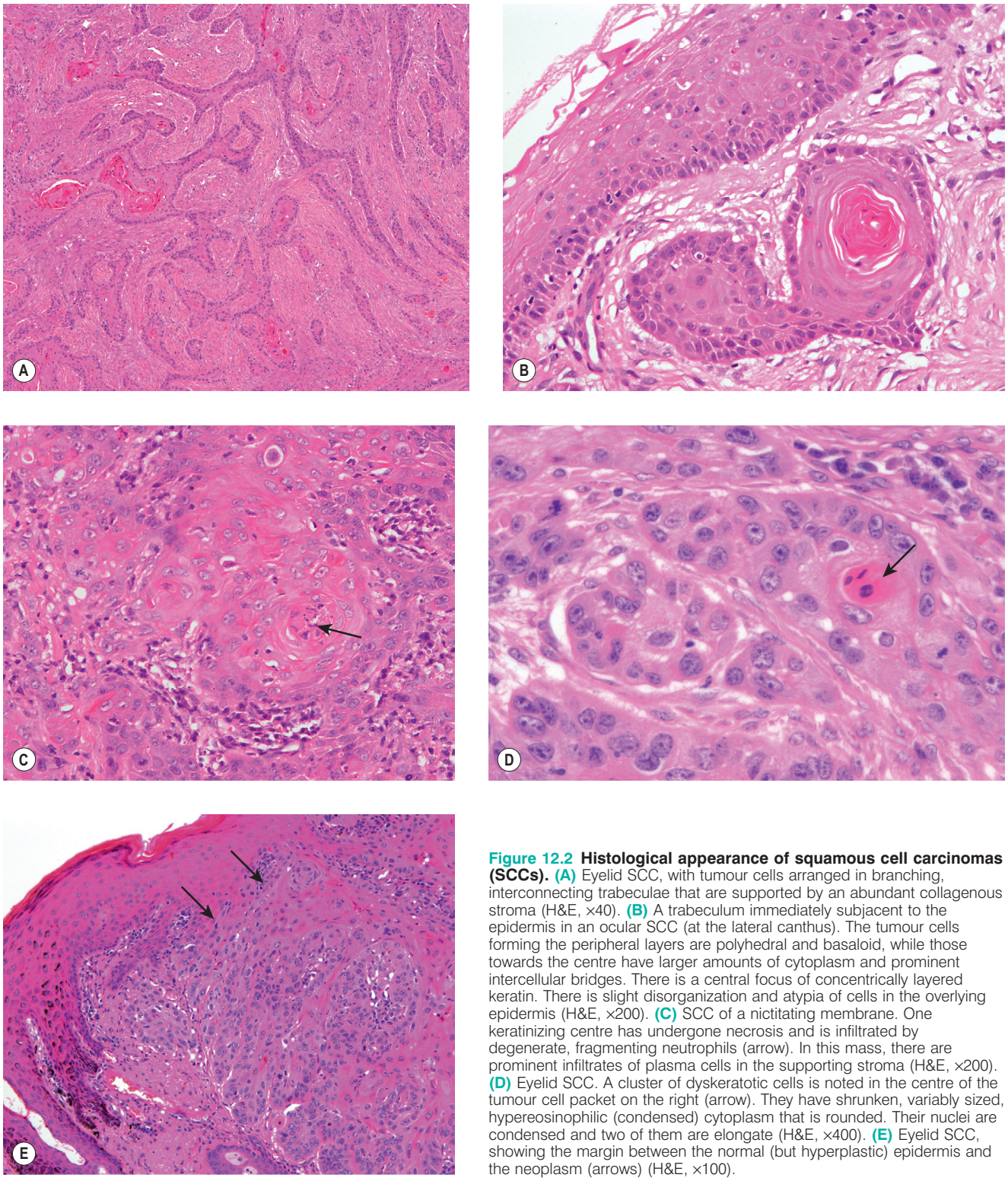


Figure 12.2 Histological appearance of squamous cell carcinomas (SCCs). (A) Eyelid SCC, with tumour cells arranged in branching, interconnecting trabeculae that are supported by an abundant collagenous stroma (H&E, ×40). **(B)** A trabeculum immediately subjacent to the epidermis in an ocular SCC (at the lateral canthus). The tumour cells forming the peripheral layers are polyhedral and basaloid, while those towards the centre have larger amounts of cytoplasm and prominent intercellular bridges. There is a central focus of concentrically layered keratin. There is slight disorganization and atypia of cells in the overlying epidermis (H&E, ×200). **(C)** SCC of a nictitating membrane. One keratinizing centre has undergone necrosis and is infiltrated by degenerate, fragmenting neutrophils (arrow). In this mass, there are prominent infiltrates of plasma cells in the supporting stroma (H&E, ×200). **(D)** Eyelid SCC. A cluster of dyskeratotic cells is noted in the centre of the tumour cell packet on the right (arrow). They have shrunken, variably sized, hypereosinophilic (condensed) cytoplasm that is rounded. Their nuclei are condensed and two of them are elongate (H&E, ×400). **(E)** Eyelid SCC, showing the margin between the normal (but hyperplastic) epidermis and the neoplasm (arrows) (H&E, ×100).

A different grading system, based on the ratios of well-differentiated to anaplastic tumour cells, has also been suggested[51]:

- *Grade 1 (well-differentiated)*: SCC with only minimal basal/suprabasal atypia
- *Grade 2 (moderately-differentiated)*: A more disorganized neoplasm with less keratinization, higher nuclear/cytoplasmic ratios, thicker nuclear membranes, moderate nuclear pleomorphism, occasional clumping of nuclear chromatin, obvious nucleoli, and higher mitotic rates
- *Grade 3 (poorly-differentiated)*: Anaplastic cells with other features that are more marked than those found in grade 2 neoplasms including increased nuclear pleomorphism and higher mitotic activity.

These grades appear to give some indication of prognosis for penile/preputial SCC at least (p. 229). Unfortunately, example photomicrographs from equine SCC for each grade under this system have not been provided in the literature to facilitate their use, including agreement between pathologists.[51–53]

Secondary lesions

Lesions associated with SCC include superficial ulceration with granulation tissue formation, suppurative inflammation and bacterial or parasitic colonization (with associated inflammatory changes; Fig. 12.3). The overlying and adjacent intact epidermis/epithelium is frequently hyperplastic with hyperkeratosis. With the exception of those that are highly anaplastic, there is frequently an intense lymphoplasmacytic infiltrate at the tumour margins (Fig. 12.3).[44] There are often mixed inflammatory cell infiltrates in the stroma. Inflammatory cell infiltrates around and within SCC and AK/SCCIS lesions were found to be largely composed of T lymphocytes, B lymphocytes, IgG-expressing plasma cells and macrophages.[50] The extent of these infiltrates did not correlate with histological grade or the degree of invasion. However, in areas of a small number of the neoplasms, in which tumour cells expressed major histocompatibility complex class II (MHCII) antigens (i.e. indicating antigen-presenting capability), there was local invasion only and numerous CD3+ T cells and plasma cells were present with evidence of tumour cell death.[50]

When lymph nodes or biopsy specimens from them are examined, there will frequently be lymphoid hyperplasia and/or inflammatory changes due to drainage of inflamed neoplasms and surrounding tissues. Such sections need to be searched carefully for metastatic lesions, and this may require immunolabelling for cytokeratin.

Immunohistochemical labelling

Tumour cells are cytokeratin-positive.

Eye and ocular adnexal tissues

See also page 578.

Squamous cell carcinomas represent 48–75% of total ocular and adnexal neoplasms.[4,54] Some 40–65% of all SCC neoplasms reported in horses involve the eye and its adnexal structures. Most are unilateral (65–84%), with single or multiple neoplasms in the affected eye, but there may be bilateral involvement either synchronously or metachronously (see Fig. 31.34).[1–4,7,55–60] Exact ocular sites have varied significantly between studies conducted in various regions of the USA, with up to 60% involving the nictitating membrane and 6–65% the eyelids.[7,22,54,55,61] Approximately 90% of neoplasms specifically involving the nictitating membrane are SCC (Fig. 12.4), and in one study this was the sole site of involvement in 50% of ocular SCC cases ($n=50$) presented to the University of Florida.[7,9,54] In two horses, SCC and haemangiosarcoma masses were diagnosed in the same nictitating membrane.[62,63] SCC is also the most common neoplasm of the equine cornea, bulbar conjunctiva and sclera.[9,54] Corneal masses tend to arise in the limbus with expansion into adjacent corneal tissue (see Figs. 12.4, 34.2).[54] The lacrimal caruncle may also be a site of origin.[64] Horses with ocular SCC may have similar primary tumours at other sites, in particular the external genitalia; in a study of 147 ocular SCC cases, 9.5% had SCC in other locations.[55]

There is an increasing prevalence of ocular SCC with age, with a mean age of 9.4 years in one survey.[4,5,65] Many horses present with SCC in ocular sites between 7 and 13 years of age, with a range of 3–26 years. The mean age of horses with ocular SCC (13 years) is less than that for genital SCC (19–21 years).[12]

Biological behaviour

Orbital and eyelid SCC have a poorer prognosis than those arising in the nictitating membrane or limbus, because they are more invasive (see Fig. 31.34).[55] Orbital SCC usually arises from the spread of ocular adnexal SCC, and may

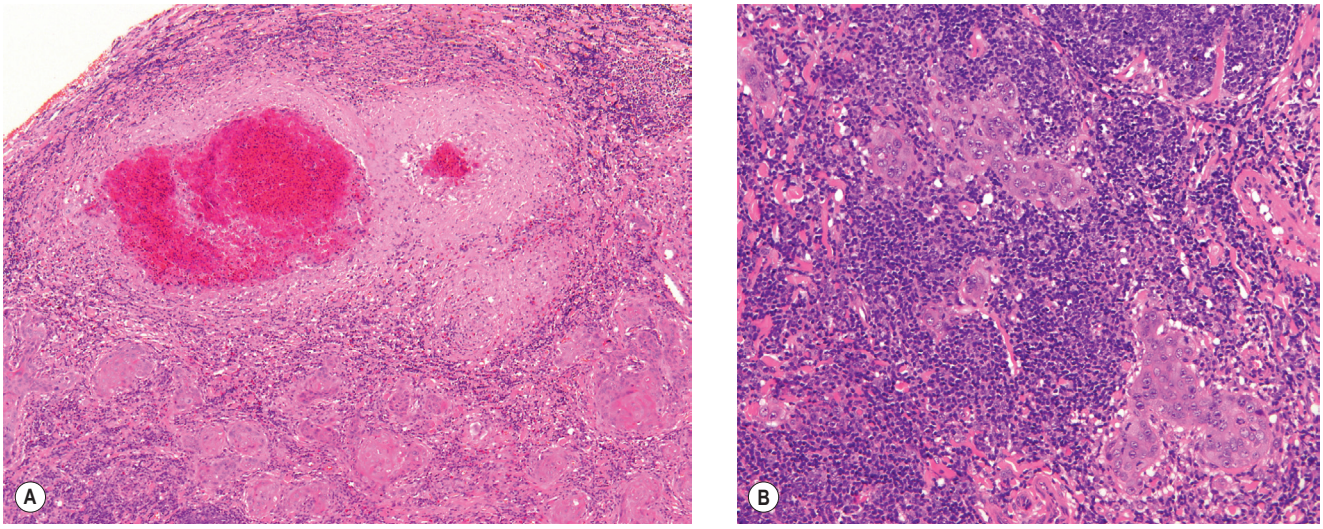


Figure 12.3 Secondary changes in squamous cell carcinomas (SCCs). (A) Large eosinophilic granulomas towards the surface of a nictitating membrane SCC. Inflammatory lesions of this type can have a number of possible causes that would include parasites and staphylococcal infection (H&E, ×40). **(B)** A prominent lymphoplasmacytic infiltrate around tumour cell trabeculae and packets, towards the margins of a nictitating membrane SCC (H&E, ×100).



Figure 12.4 Ocular squamous cell carcinomas (SCCs). **(A)** Nictitating membrane. **(B)** Extension from the limbus out into the cornea. **(C)** Lacrimal caruncle (arrow).

extend into orbital bones, sinuses and the calvarium.[9] Corneolimbal or limbal SCCs are also locally invasive but rarely infiltrate into the eye.[8] There are exceptions to this rule, with one report of a limbic neoplasm that extensively invaded the cornea, anterior chamber of the eye and uvea following cryotherapy.[60] In another case, an SCC thought to have arisen in the medial canthus extensively destroyed the orbital bone and invaded the nasal cavity.[66] Larger nictitating membrane masses may occasionally infiltrate the orbit.

Recurrence rates of 10–67% for ocular SCC in general have been reported; some reports suggest a lower likelihood for recurrence of neoplasms involving the nictitating membrane, canthus or limbus, relative to those in the orbit and eyelids.[7,55,67] In one study, 16 horses with SCC of the nictitating membrane had no recurrences or associated problems over a 41-month period, although six were euthanized for other reasons.[68] Other reports have not documented a relationship between risk of recurrence and initial location.[10] As might be expected, recurrence is also influenced by the method of treatment. In 43 cases, the rate of recurrence of ocular SCC was significant only when surgery was performed without adjunctive treatment, such as cryotherapy, hyperthermia or irradiation; the eyelids and nictitating membrane were the primary sites involved.[7] Superficial keratectomy alone for corneal or corneolimbal masses was followed by a 45% recurrence rate.[7] For SCC of the nictitating membrane specifically, treatment by surgical removal is less likely to be followed by recurrence than cryotherapy alone.[55]

Recurrence of ocular SCC generally occurs several months to some years after treatment.[8] Survival analysis of horses with ocular SCC (n=125) showed a good overall prognosis, with median recurrence time of 47 months.[55] However, one or more recurrences following treatment reduced the likelihood of survival.

Survival time is also negatively related to the maximal dimension of ocular SCC masses.[55] The prognosis in one study was more favourable for neoplasms measuring ≤1 cm in diameter and <0.2 cm in depth.[9] Similarly, other authors found horses with ocular SCC >2 cm in diameter to have a 3.5× increased risk of recurrence.[55] This is likely to relate to the ease of treatment; corneal masses >2 cm in diameter in another study were amenable to surgical excision (only) when they were limited to the cornea and bulbar conjunctiva, with 20/24 of such patients being free of recurrence long term, following keratectomy with postoperative beta radiation.[69]

Reports of the metastatic rate of ocular SCC have varied between 0.03% and 19%.[4,7,10,22,61] Metastasis occurs to the regional lymph nodes, salivary glands and, less frequently, the thorax (Fig. 12.5).[54] The lymphatic drainage of ocular structures is to the parotid, then lateral retropharyngeal and, finally, medial retropharyngeal lymph nodes.[70] Further spread may occur to cervical and cranial mediastinal lymph nodes.[4,66] Extensive involvement of the lower eyelids has been associated with metastasis specifically to the submandibular lymph nodes.[71] One author reported a

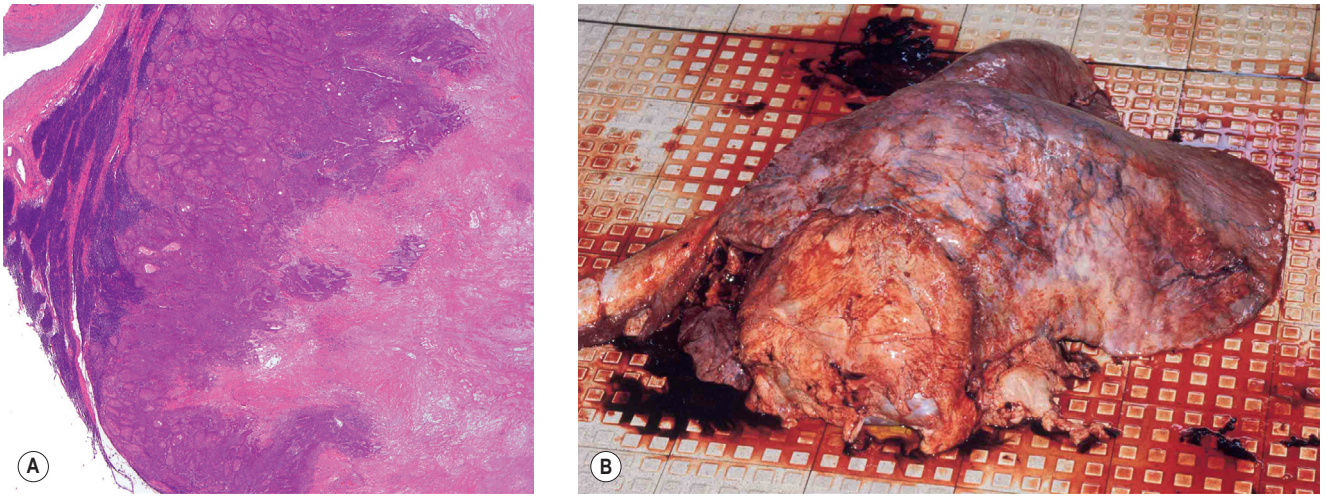


Figure 12.5 Metastatic squamous cell carcinoma lesions. (A) Histological appearance of a large metastatic mass replacing most of the normal architecture of a lyph node. Some compressed nodal lymphoid tissue is noted on the left. There is a large central region of necrosis within the mass (H&E, ×12.5). **(B)** A large metastatic mass in the lung. This stage of disease is infrequent.

metastatic rate of 10–15% to regional lymph nodes for SCC of the nictitating membrane.[61] Corneal and corneolimbic SCC have a lower probability of systemic metastasis compared with those arising from the nictitating membrane and eyelids.[72] Delayed metastasis to the parotid lymph node was reported 1–3.5 years post-treatment in two relatively young horses (4 and 8 years).[70] Metastatic lesions involving sympathetic nerves and causing bilateral Horner's syndrome have also been reported.[73]

Gross pathology

Single or multiple intraepithelial lesions may be noted in some cases, either preceding or in conjunction with invasive neoplasms. They are usually firm or soft (necrotic) white-grey, pink or red raised areas that begin with a smooth surface, become roughened or papillary and may then progress to erosion and ulceration with dark crusting.[9,67] Masses involving the nictitating membrane are typically white/pink/red with a 'cobblestone' appearance (see Fig. 34.1A), but may initially be seen as small white plaques (see Fig. 27.5B). They usually originate on the palpebral side (facing the eyelids) of the free margin and can erode through the cartilage of the membrane to involve the bulbar aspect.[9]

Eyelid, conjunctival and corneal SCC are pink or red (erythematous), often raised and irregularly-shaped, with a papillary or cobblestone surface that may be necrotic and bleeds easily (see Figs. 31.34, 34.2).[9,69] Masses near the canthus tend to be eroded or ulcerated.[9,60] There have been rare reports of pigmented SCC involving the conjunctiva or nictitating membrane; they may resemble melanoma.[74,75]

Highly invasive SCC may not bulge from the corneal or limbic surfaces.[69] An unusual variant termed 'corneal stromal-invasive SCC' (CDI-SCC) appears as a white, poorly-demarcated, thickened region of the cornea with marked vascularization and oedema. These masses grow directly and deeply into the corneal stroma, leading to underestimation of their true extent. In a Wisconsin study, CDI-SCC comprised 12% of all ocular SCC samples (n=87) submitted to that diagnostic laboratory over a 26-year period; half of these cases had a prior clinical diagnosis of stromal keratitis.[76]

Gross lesions associated with ocular SCC include:

- Chemosis, hyperaemia and/or inflammation of the conjunctiva
- Superficial corneal vascularization and inflammation
- Ulceration
- Purulent ocular discharge (see Fig. 31.34C).

Histopathology

Many ocular SCCs are referred to as low grade on the basis of nuclear morphology and low mitotic indices. In most cases of CDI-SCC, the tumour cells do not show contiguity with the overlying corneal epithelium, beneath which a zone free of neoplastic tissue is noted. There may however be direct connection to the limbus, with associated, marked lymphoplasmacytic infiltrates.[76] Changes in the overlying, intact corneal epithelium may include marked hyperplasia and disorganization of the cellular layers.

Inflammatory changes associated with SCC of the nictitating membrane and conjunctiva may include lymphoid nodule hyperplasia. In the nictitating membrane, there can also be hypertrophy and hyperplasia of the seromucinous gland surrounding the base of the cartilage, with dilation of ducts.[74] Reactive changes may also been seen in the cartilage itself (Fig. 12.6).

Differential diagnoses

These are listed in Box 12.1.

Cutaneous habronemiasis ('summer sores'): Cutaneous habronemiasis is caused by infection of wounds with larvae of the gastric parasites *Habronema* and *Draschia*; flies act as the intermediate hosts. This disease is most common in hot, humid climates in the spring and summer, and also in unsanitary and overcrowded housing conditions. The masses that develop may appear and grow rapidly and can reach >2 cm in diameter.[54] Larvae stimulate granulation tissue formation, and small, yellow caseous masses or tracts are noted grossly on cut sections.[77] Histologically, the larvae are immediately surrounded by large numbers of eosinophils with necrotic debris. Infection of neoplastic tissue including ulcerated SCC could occur.

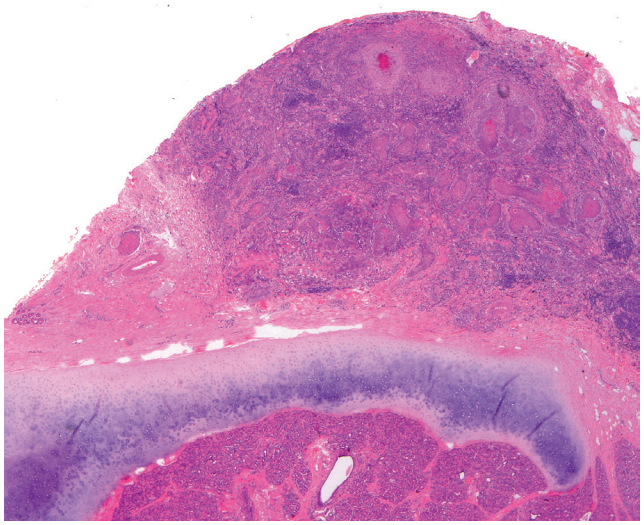


Figure 12.6 Squamous cell carcinoma of the nictitating membrane. The cartilage and associated seromucinous gland (lower margin of this image) may show reactive changes (H&E, ×12.5).

Box 12.1 Differential diagnoses for ocular and adnexal squamous cell carcinoma

Neoplastic
- Sarcoid
- Papilloma
- Eyelid adenocarcinoma
- Other cutaneous epithelial neoplasms such as melanoma, mast cell tumour and lymphosarcoma (pp. 239, 352, 357)

Non-neoplastic
- Local irritation and inflammation
- Bacterial or fungal granulomas (e.g. *Actinomyces*, Phycomycetes)
- *Onchocerca* – induced keratoconjunctivitis

Equine conjunctival 'pseudotumour': Equine conjunctival pseudotumours have been infrequently reported in 5–8-year-old horses; the masses are smooth, pink and nodular or diffuse and may additionally involve the nictitating membrane and cornea. The pseudotumours are composed of sheets or follicular arrangements of lymphoid cells, and are presumed to be immune-mediated in origin.[78]

Ocular dermoids: Ocular dermoids are anomalous skin-like masses that occur unilaterally or bilaterally.[79] They are usually non-cystic masses located in the conjunctiva, but may also involve the limbus, cornea, eyelids or nictitating membrane.[80,81] Orbital dermoids potentially develop as gradually expansile fluid-filled cystic masses that cause congenital or juvenile exophthalmos.[81] Histologically, dermoids are composed of hair follicles with associated adnexa and collagenous tissue; follicular development can be minimal, with lesions having the appearance of aberrant pigmentation.[80]

Anterior uveal cyst: Anterior uveal cysts occur in horses of various ages, but may actually be congenital with enlargement later in life. These unilateral or bilateral lesions arise in the corpora nigra (an extension of the posterior iris epithelium), along pupillary margins, in the anterior chamber, attached to the ciliary body or within the iridal stroma.[82] One author has noted that anterior uveal cysts tend to occur in older ponies with blue irides.[54] These forms are variable in size, spherical to ellipsoid, dark brown or black, smooth-surfaced and sometimes thin-walled and translucent; detachment or spontaneous rupture may occur. There is no association with inflammation.

Iridal or ciliary body cysts: Iridal or ciliary body cysts arise due to failure of the two neuroectodermal layers to completely fuse during development.[82]

External genitalia

Squamous cell carcinoma is one of the most common types of neoplasm arising in the male and female external genitalia, with males affected twice as frequently as females; it comprises 68–85% of genital neoplasms of male horses.[26,52,83,84] Some authors state that this tumour type more frequently affects geldings than stallions, possibly relating to their greater accumulation of smegma, but there is not universal agreement on this point and smegma is a controversial aetiological factor (p. 221).[26,83] In surveys in the USA and UK (with similar results) the penis and prepuce have been listed as the second most common site for development of this neoplasm, comprising 21–29% of total SCC cases.[1,22,56,57] Conversely, in one US study, 45% of equine SCC involved the male external genitalia, with ocular sites being the second most frequently affected.[3]

In a UK survey, SCC occurred twice as frequently on the prepuce and penis as squamous papilloma, and masses on the glans penis accounted for 53% of total equine male genital SCC (n=48).[83] It should be noted that 29% of horses with penile/preputial SCC also had a squamous papilloma. The coexistence of SCC and papilloma has been noted in other studies,[52] and papilloma is considered by some researchers to be a precancerous state, as evidenced by histological and PCR findings (pp. 221–222). In a study of the distribution of lesions within the male genital region, 46% involved the penis, 54% the prepuce and 4% both sites.[26] In a more detailed study of 45 horses undergoing surgical treatment for penile or preputial SCC, the glans penis was involved in 53%, the body of the penis or inner lamina of the preputial fold in 60%, and the external preputial fold in 22%.[85] Similarly, in a Netherlands study (n=77), 47% involved the glans penis, 35% extended from the glans penis to the outer lamina of the internal preputial fold and the remainder (18%) involved single or multiple segments excluding the glans penis.[52] The urethral diverticulum, urethral process or urethra was involved in almost 30% of cases in the UK study.[83] There is one report of a primary SCC of the urethral process of a stallion resulting in haemospermia.[86]

Perianal, vulvar and clitoral tumours in females comprise 5–12% of all equine cases of this tumour type.[1,57,87] They most often originate at the clitoris, with infiltration towards the vaginal vestibule.[88]

Older horses tend to be affected (9–20+ years), and in one study (n=74), the mean age was 19.8 years.[52] However, cases have also been reported in horses 3–5 years of age.[2,83] In one study, the mean age of horses with genital SCC (19–21 years) was greater than that for ocular SCC (13 years).[12]

Biological behaviour

Penile and preputial SCC are usually low grade and slowly progressive; they often remain undetected for long periods

of time, so that by the time of diagnosis local invasion and spread has often already occurred.[85] There is one report of urinary bladder rupture in an 18-year-old Quarter Horse gelding secondary to urethral stricture caused by a penile and preputial SCC that had been overlooked.[89]

In a study of 77 penile/preputial SCC conducted in the Netherlands, 44% were not successfully treated, with recurrence rates of 26% or 18% following partial phallectomy or incomplete removal respectively.[53] This was reduced to 13% by *en bloc* penile and preputial resection with penile retroversion and removal of inguinal lymph nodes.

Metastasis of genital SCC occurs slowly, but it can extend to regional lymph nodes, including superficial and deep inguinal and sublumbar, followed by more widespread dissemination to sites including the lungs, myocardium and abdominal lymph nodes.[90,91] In one UK study of penile/preputial SCC (n=41), 12% had metastasized to regional lymph nodes.[83] Regional lymphadenopathy is not necessarily an indicator of metastasis, since it can reflect drainage of secondary inflammation and infection. However, metastatic lesions are more likely to be found in enlarged nodes: in one histological study (n=82), 32% of enlarged nodes contained neoplastic cells, while only 9% of those that were grossly normal did.[52] In another study of 31 horses with genital SCC, none had enlarged superficial lymph nodes at the time of diagnosis, but within a year, four of those animals were euthanized due to abdominal metastasis.[85] They were found to have SCC invasion of the corpus callosum – histological checking of lymph nodes in those cases is essential, whether they are enlarged or not. If the lymph nodes are free of neoplastic tissue (as assessed histologically) at the time of diagnosis of the primary penile/preputial SCC, the prognosis is more favourable. The finding of iliac lymphadenopathy at rectal examination is a poor prognostic sign.

If the neoplasm infiltrates into the corpus cavernosum in males, there may also be haematogenous spread, to sites including the liver and lungs.[92] Rare sites of metastasis have included a thoracic vertebral body (resulting in pathological fracture) and the mediastinum, where a large mass perforated into the trachea and obstructed the lumen.[93,94] A Shetland pony with a primary penile SCC that had metastasized to the lungs presented with hypertrophic osteopathy.[95] Female genital SCC (see Fig. 35.8) may also metastasize, with spread to the lungs in one case where a vulval neoplasm was diagnosed.[22] Pseudohyperparathyroidism as a paraneoplastic sign was reported in a mare with a vulval/perineal SCC.[96]

Gross pathology

Horses with penile/preputial SCC frequently present with malodorous, purulent and haemorrhagic preputial discharge, or haemorrhage only.[83] Most affected horses have balanoposthitis. Intraepithelial lesions may be seen as small plaques or non-healing ulcers (see Figs. 9.2, 35.1A). Early SCC (if noticed) is small, circumscribed, nodular or papillary and the overlying epidermis/epithelium may be intact (see Fig. 35.1). In the early stages of development, ulcerative lesions may be confused with non-healing wounds, with indurated margins and granulation tissue formation.[59] Early lesions in the female genitalia include hypertrophy of the clitoris and surrounding tissue with roughening of the ventral commissure of the vulva.

Box 12.2 Differential diagnoses for external genital squamous cell carcinoma

Neoplastic
- Sarcoid
- Papilloma
- Other cutaneous epithelial neoplasia

Non-neoplastic
- Local irritation and inflammation
- Bacterial or fungal granulomas (e.g. *Actinomyces*, Phycomycetes)
- Cutaneous habronemiasis (pp. 227–228): The external genitalia are a common site for habronemiasis
- Non-healing wounds, granulation tissue

More advanced neoplasms may be single or multiple, vary in size, and are usually elevated and ulcerated (Figs. 27.4, 27.6, 35.1, 35.2). Larger SCC in these sites may be papillary or pedunculated with rough surfaces; papillary masses tend to have a broader base than would be expected in the case of a papilloma (Figs. 31.32, 35.8).[91] Neoplasms at sites prone to trauma may have extensive areas of erosion and ulceration with associated necrosis and high susceptibility to bleeding (see Fig. 35.1).[83,91] There may be severe oedema of the area, and ulcerated areas are susceptible to secondary parasitism, e.g. habronemiasis or infiltration by maggots and infection (see Figs. 35.1 and 35.2). Palpable firm thickening of the penis has been associated with infiltration of the urethra, lymphatic and blood vessels, and corpora cavernosa.[85] Regional (inguinal and iliac) lymph nodes will often be enlarged due to reactive lymphoid hyperplasia as a response to the secondary balanoposthitis, and/or in some cases due to metastatic masses.[83]

Histopathology

In a study of penile/preputial SCC (n=114) using the grading system based on ratios of well-differentiated to anaplastic tumour cells (G1–G3),[51] metastatic rates for G1, G2 and G3 neoplasms were 3%, 25% and 44%, respectively.[52] Treatment was not successful for G1, G2 and G3 SCC in 31%, 43% and 67% of cases, respectively. Based on this study, it seems that this grading system may be of use for determining the prognosis of male genital SCC at least.

Differential diagnoses

These are listed in Box 12.2.

Skin

Squamous cell carcinoma is one of the most common cutaneous neoplasms of horses, most frequently involving mucocutaneous junctions including the lips, nares, and anus (see Figs. 28.8, 31.33).[42] In some surveys, it has been reported to be the first or second most common site for SCC development.[97,98] In a South African survey of SCC (n=89; 1935–1974), 20% arose in the skin.[57] Rare epidermal sites of origin include the hoof wall, frog and sole; it is the second most common type of neoplasm diagnosed in the equine hoof and some authors consider malignant transformation of keratoma to be possible.[11,99–102] Authors of a survey of equine cutaneous neoplasms found the mean age of horses

with cutaneous SCC (15 years) was less than that for horses with genital SCC (19–21 years).[12]

Biological behaviour

Cutaneous SCC invade locally; those rare neoplasms involving the hoof wall may invade into the bone of the distal phalanx, resulting in pathological fractures.[101]

Estimates of the metastatic frequency for cutaneous SCC range between 10% and 19%.[13] As for other sites, metastasis tends to occur late in the disease course, usually first to regional lymph nodes and then distant sites with those reported including lungs, mediastinum, myocardium, liver, kidneys, internal lymph nodes, thyroid and parathyroid glands, and skeletal muscle.[26]

Histopathology

Although most SCCs in the skin arise from the epidermis, it is also possible for them to originate from hair follicle epithelium including that of follicular cysts (p. 230).

Differential diagnoses

These are listed in Box 12.3.

Follicular cysts (synonyms: epidermoid cysts, epithelial or epidermal inclusion cysts) tend to be diagnosed in older horses (6–19 years of age), are usually solitary and most frequently involve the head or distal limbs. Follicular cysts may arise from the hair follicle infundibulum, in which case they are lined by squamous epithelium with a granular layer and variable intraluminal orthokeratotic and parakeratotic hyperkeratotic debris. Those arising from the isthmus are lined by epithelium resembling the outer root sheath of the middle segment of anagen follicles and the middle and lower regions of catagen-phase follicles; there is no granular layer and keratinization is tricholemmal. Multiple follicular cysts are reported on rare occasions[103]; generalized infundibular and isthmus-catagen follicular cysts were reported in one 4-year-old stallion.[104] Epidermoid cysts have also been reported in non-cutaneous locations including the mandible, brain distal phalanx, and the deep digital flexor tendon sheath of the foot; these may arise from embryological remnants or traumatic implantation of epithelial cells (see pp. 321–322).[105,106]

Dermoid cysts are usually diagnosed in younger horses (age range 6 months to 9 years), with the highest incidence in yearlings.[2] The most frequent sites for these single or multiple lesions include the base of the ear, false nostril and dorsal midline.[103,104] They have also been reported on the ventral thorax, distal limbs, and in one case, as a retrobulbar mass causing exophthalmos.[107] Dermoid cysts are usually thought to be congenital if occurring in the midline or possibly in ocular regions, i.e. arising from primordial epithelial cells entrapped during closure of the neural tube. They may alternatively arise following traumatic displacement of epithelial tissue. The wall of dermoid cysts is similar to that described for follicular cysts but includes adnexal structures, with the central cavity containing both keratin and hair shafts; grossly they contain coiled hairs.[2] Their size varies between 2 mm and several centimetres.[108] Transformation of follicular or dermoid cysts to squamous cell carcinoma has not been reported in horses. Associated lesions may include granulomatous inflammation where keratin has escaped from the cyst lumen into surrounding tissues.

Cutaneous amyloidosis can present in horses as multiple nodular masses up to 2.5 cm in diameter in skin of the head, neck and pectoral regions. Amyloid is a toxic protein aggregate composed of bundles of fibrillar protein arranged in β-sheets. The amyloid (in the cutaneous form) involves the full thickness of the skin and the subcutis, and is also seen in enlarged regional lymph nodes but not internal organs.[109] It should be noted that cutaneous amyloidosis has been associated with internal neoplasms, including lymphosarcoma.[110] There is also a systemic form of amyloidosis in horses where skin nodules may be noted in addition to extensive deposits in internal organs.[111] Histologically, fibrillar eosinophilic material is surrounded by macrophages and multinucleate histiocytic giant cells (Fig. 12.7) and granulation tissue may also be noted.[112] When stained using the Congo red method, amyloid is orange-red and shows apple-green birefringence under polarized light. In one study, the amyloid material from nodular cutaneous lesions was identified as being derived from a monoclonal immunoglobulin lambda-light and gamma-heavy chain, with the light chain being the predominant and presumptive primary component.[113]

Box 12.3 Differential diagnoses for cutaneous squamous cell carcinoma

Neoplastic
- Sarcoid
- Papilloma (viral or non-viral)
- Other cutaneous epithelial neoplasms (pp. 251–256)
- Poorly pigmented/amelanotic melanoma
- Fibroma
- Fibrosarcoma
- Lymphosarcoma
- Peripheral nerve sheath tumour

Non-neoplastic
- Local irritation and inflammation
- Bacterial or fungal granulomas (e.g. *Actinomyces*, Phycomycetes)
- Cutaneous habronemiasis (pp. 227–228)
- Dermatophytosis
- Dermatophilosis
- Chronic non-healing wounds including exuberant granulation tissue
- Foreign body reaction
- Abscesses
- Keratoma (in the hoof)
- Collagenolytic granulomas
- Cutaneous amyloidosis
- Follicular (epidermoid) and dermoid cysts: these cysts are uncommon in horses

Alimentary tract

SCC is the most common tumour of the oral cavity of horses, and can also arise on rare occasions in the pharynx and oesophagus (see Figs. 28.9, 28.18, 28.19, and 28.24).[114–119] Most affected horses are >8 years of age.[11] In a survey of seven affected horses (11–22 years of age), the sites involved were the tongue (n=3), labial gingiva (n=1), oral mucosa (n=1) and pharynx/epiglottis (n=2).[44] Three oral SCCs

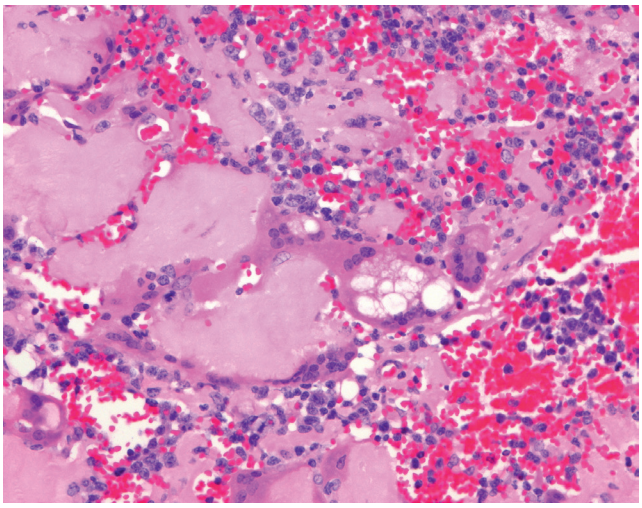


Figure 12.7 Cutaneous amyloidosis in a horse. Fibrillar eosinophilic material is infiltrated and surrounded by multinucleate histiocytic giant cells, macrophages and lymphoid cells (H&E, ×200).

were documented in an earlier study, involving the gingival mucosa around the teeth.[22] Oral SCCs may also arise from the lips, soft palate and hard palate (Figs. 28.8, 28.9).[88,120] The occurrence of this type of neoplasm in the oesophagus is more usually the result of local extension of a gastric carcinoma.[43] There have been rare cases of SCC originating in cervical or thoracic oesophageal segments (see Fig. 28.24).[115,117] One oesophageal mass originated in an oesophageal diverticulum.[121]

Squamous cell carcinoma is the most common type of neoplasm affecting the equine stomach, in which a large part of the (proximal) mucosa is composed of stratified squamous epithelium. However, gastric SCC comprises only 3–4% of total carcinomas or SCC occurring in horses.[1,122] Most of these neoplasms arise from the squamous/oesophageal region of the stomach.[123,124] Gastric SCC occurs predominately in middle-aged to older horses (6–18 years), with mean ages of 12.6 and 18 years, respectively, in two studies.[122,125–128] However, it may still be found in younger animals and in one review of 20 cases, more than one-third were ≤10 years of age.[124,129] Gastric SCC was reported to be four times more common in males than females; however, this has not been confirmed in all studies; Quarter Horses and draft breeds have also been suggested to be at increased risk.[126,130] In some early publications, it was suggested that the damage caused by *Gasterophilus* sp. larvae might be involved in oncogenesis of gastric SCC; however, there is no conclusive evidence for this. Equine populations in which large numbers of animals are infected with *Gasterophilus* sp. have not shown an associated high incidence of gastric SCC.[131,132]

Biological behaviour

As for other species, excision of oral SCC can be problematic. Metastasis of oral SCC, including those of the lips, is reported to be common.[11] One mass originating in the tongue metastasized to submandibular, retropharyngeal and rostral cervical lymph nodes, cervical facial tissue and skeletal muscle, and the skin on one side of the neck.[118] Other reported metastatic sites include the cranial mediastinal lymph nodes, lungs, vagus nerve and tracheobronchial lymph nodes.[44]

Lower down the alimentary tract, space-filling and invasive effects may have significant functional implications: a large proportion of the gastric lumen may be occupied by the mass, and in a few cases recurrent oesophageal obstruction ('choke') has been reported.[46] One Clydesdale horse with an SCC of the base of the tongue presented with dysphagia.[133] There may be evidence of hypersalivation and [micro]haemoptyalism, which has been associated with oesophageal narrowing (by neoplastic infiltration or hypertrophy) and/or gastroesophageal ulceration.[128]

Local invasion of gastric SCC can include involvement of the distal oesophagus. The distal oesophageal wall may be markedly thickened by intramural infiltration; in one case of gastroesophageal SCC, a pleuroscopic biopsy was successfully obtained for histological diagnosis.[134] If a gastric SCC penetrates the stomach wall (see Fig. 28.25), which often occurs over the greater curvature, there may be direct extension into surrounding tissues (diaphragm, liver, spleen, omentum) (see Fig. 28.25) and implantation of masses on and in abdominal organs leading to a diagnosis of peritoneal carcinomatosis.[122,128,130,135] In one study of 19 horses with gastric SCC, 89% presented with transmural extension and transcoelomic spread.[128] Recurrent oesophageal obstruction was found to be caused in one case by a transmural mass that extended from the greater curvature of the stomach, encircled the oesophagus and constricted the lumen.[130]

As a gastric SCC invades from the mucosa it may permeate along intramural blood and lymphatic vessels; however, vascular metastasis will not usually be seen in the absence of carcinomatosis.[128,136] Gastric SCCs are slow to metastasize (as is typical for this type of neoplasm) and early cases have been identified in which this has not yet occurred; in two such cases, the neoplasm was confined to the mucosa, suggesting that determining the depth of invasion into the stomach wall may be clinically important.[98,128] In the study of 19 horses, there was evidence of metastasis in 68%, all but one of which had carcinomatosis.[128] Frequent sites of metastasis include the regional lymph nodes, liver, spleen, lungs, and visceral and parietal pleura. Metastasis to the thoracic cavity is thought to occur in 50–75% of cases, although SCC comprises only 5% of total thoracic neoplasms in horses; a few horses have presented with signs referrable only to the respiratory system.[88] Spread of neoplastic cells into the thorax may occur via diaphragmatic lymphatic vessels, by direct infiltration of the gastric neoplasm through the diaphragm, or occasionally by extension along the oesophagus (as above).[126,127] Sites affected may include the pericardium and thymus in addition to the lungs and pleura.

Anaemia has been diagnosed in 37–60% of horses with gastric SCC.[124,126,128] In one such case, this was due to marked haemorrhage from the primary mass. Hypoalbuminaemia is also a common finding, and often associated with hyperglobulinaemia; the latter may be due to chronic secondary gastritis or peritonitis. Neutrophilia occurs in some horses.[126] Hypercalcaemia of malignancy was identified in 4/16 horses with gastric SCC in one study (including animals with hypoalbuminaemia) and one case of hypertrophic osteopathy has been reported.[128,135]

Gross pathology

Cases with alimentary tract SCC may be emaciated and are usually at least in poor body condition by the time of presentation.

Oral and pharyngeal SCC are multilobular, project from mucosal surfaces and are usually ulcerated. There may be extensive infiltration of surrounding tissues including bone (Figs. 28.9, 28.18, 28.19, and 29.14A).[44] In one description of an SCC of the tongue on an 18-year-old Quarter Horse mare, firm white tissue replaced the epithelium and musculature of the right side with severe dorsal and lateral ulceration.[118]

Gastric SCCs are typically advanced by the time of diagnosis, and in one study 4/5 were palpable per rectum.[126] Gastric and oesophageal neoplasms are grossly similar to those noted in external sites (see Figs. 28.24, 28.25). In many cases of gastric SCC, a variably sized (3–25 cm diameter) and usually solitary mass is noted on the mucosal surface, this being elevated, papillary or plaque-like, firm and frequently severely ulcerated (Fig. 28.25). A few horses have been found to have two or more masses.[128] The stomach wall becomes progressively and often transmurally thickened by firm white tissue, with loss of mucosal longitudinal folds, filling of the lumen and progressive ulceration of the surface and/or adjacent mucosa. Areas of ulceration are secondarily infected and coated with red and/or grey-white debris. On sectioned surfaces, the masses are variably red, white and/or brown.[124] There is often distinct demarcation of the mass from the adjacent mucosa at the level of the margo plicatus, and in some cases, most of the squamous mucosa is involved (see Fig. 28.25).[122,130] The remaining non-neoplastic squamous mucosa is diffusely thickened in some horses.[128] There may also be ulcers of the more distal glandular gastric mucosa.[128]

The stomach may be adhered to surrounding organs and tissues, including the liver, diaphragm, spleen and omentum. These adhesions can be extensive; one such adhesion between a gastric SCC mass and the diaphragm measured 30 cm in diameter and extended into the pleural cavity.[135] Metastatic masses often measure 2–4 cm in diameter (although they can vary significantly in size), are nodular and may be very numerous. The consistency of the metastatic lesions varies depending on amounts of fibrous stroma within them. Metastatic nodules involving the liver are often found on the surface of the hilus, but may also occur deep in the parenchyma.[124] In animals with carcinomatosis involving the peritoneal and/or pleural cavities, there may be sterile exudative effusion and peripheral dependent oedema (mesothelioma is a differential diagnosis). The amounts of pleural fluid can be massive in some cases and this is usually straw-coloured, but it may be red (serosanguineous) in some horses due to tissue invasion.[88,137] Some authors have suggested that the inflammatory exudates in affected body cavities are a result of increased serosal capillary permeability caused by the physical presence of metastatic masses and/or irritant effects of neoplastic cell products.[138] In some more severe cases of peritonitis, there has been transmural leakage of gastric content.[128]

Neoplastic epithelial cells might be identified in cytological smears of peritoneal or pleural fluid, but they could also be obtained from gastric lavage samples.[88,127]

Histopathology

Multiple gastric tissue samples may be obtained for histological examination by gastroscopy, although the very small biopsy sample size usually only shows peripheral inflammation or necrosis.[43] Neoplastic cells are noted in the lamina propria and may extend throughout the wall; they may produce keratin as in other sites. Sections should be searched carefully for vascular emboli, and where an antemortem diagnosis is required, finding neoplastic tissue only in the gastric mucosa with no evidence of metastasis in regional lymph node tissue may indicate a more positive prognosis.

In cases of gastric carcinoma, cytological examination of peritoneal fluid can be a significant aid; this is more likely to be useful when there is carcinomatosis.

Box 12.4 Differential diagnoses for alimentary tract squamous cell carcinoma

Neoplastic
- Gastric or intestinal adenoma or adenocarcinoma
- Lymphosarcoma
- Fibroma
- Leiomyoma
- Leiomyosarcoma
- Gastrointestinal stromal tumour
- Peripheral nerve sheath tumour
- Metastatic carcinoma
- Mesothelioma
- Sarcoid (oral)

Non-neoplastic
- Hamartomatous polyp
- Submucosal haematoma
- Chronic primary mucosal ulceration
- Leukoplakia

Differential diagnoses

These are listed in Box 12.4.

Hamartomatous polyps: Polypoid hamartomas composed of increased amounts of well-differentiated tissue would require histological differentiation. Such masses have been reported in the stomach of older adult horses, in rare cases.[139] These polyps may measure up to 20 cm in length, may have a stalk, and histologically are composed of inflamed hyperplastic gastric mucosal tissue. These lesions are not confined to the stomach – an inflammatory polyp comprised of fibrous tissue, adipose tissue and blood vessels in the small colon of an Arabian yearling filly resulted in ulceration, perforation and peritonitis.[140] A cystic hamartoma was reported in the rectum of a newborn foal.[141]

Submucosal haematoma: Submucosal haematomas of the gastro intestinal tract are uncommon but may also cause a mass-effect.

Leukoplakia: This is a condition in which multiple white plaques up to 6 cm in length occur on mucosal surfaces of the oesophagus and squamous region of the stomach.[142] The plaques are well-demarcated areas of epithelial hyperplasia and hyperkeratosis that may occur in response to chronic irritation, and in human patients are considered to be a premalignant lesion.

Respiratory tract

Squamous cell carcinoma is the most common type of neoplasm affecting the nasal and paranasal sinuses, pharynx and larynx, although total numbers of cases are small

relative to the other sites (see Figs. 7.20B, 29.1, 29.2).[57,143–145] Squamous cell carcinomas and other neoplasms are slightly more common in the nasal cavities than the paranasal sinuses, where there is a predilection to occur in the caudal maxillary sinus; the nasopharynx may also be involved.[22,44,143,146–148] Some sinusal tumours appear to have originated from gingival epithelium of the upper molars or from the hard palate, i.e. oral cavity, while others may arise from metaplastic epithelium in the sinuses.[125] Some earlier authors believed that maxillary sinus tumours were of hard palate origin, being recognized on the lateral aspect.[149]

Squamous cell carcinomas infrequently arise in the guttural pouches, and may be unilateral or bilateral.[150] One case of bilateral guttural pouch SCC was thought to originate in the middle ear with extension via the auditory tube; papillomas previously excised from right and left acoustic meati may have been precursor lesions.[151]

Sinonasal SCC tend to occur in middle-aged to older horses or ponies (7–26 years) with their highest incidence in animals ≥15 years of age.[143,148,152] There has been a report of a congenital, anaplastic SCC involving the rostral dorsal conchal and caudal maxillary sinuses in a 3-month-old foal.[153] In a survey of 11 horses with SCC of the larynx and or pharynx, the mean age was 15 years and over half were dyspnoeic.[154] There is no indication of gender- or breed-specific predilection. For pulmonary SCC, see pp. 264–265.

Biological behaviour

Sinonasal SCC tend to fill the cavity in which they originate before extending into directly communicating sinus, nasal or oral cavities, where they again undergo intraluminal expansion.[146,148] Naso-maxillary openings are slit-like and do not favour extension of a solid neoplasm, and it is also rare for nasal tumours to infiltrate caudally through the choanae into the contralateral nasal passage.[148] Sinonasal SCC can cause significant bone destruction (see Fig. 29.2), infiltrating into bones of the orbit from maxillary, frontal or ethmoidal sinuses.[11,155] In one case, compression of the optic tracts was caused by pressure on ethmoid and sphenoid bones by an extensive neoplastic mass, rather than by bony invasion.[146] Invasion of periocular tissues may in some cases disrupt optic nerves, and some horses will present with exophthalmos. Extension into the cranium can occur either through the region of the sphenopalatine sinus underlying the brain, or via the cribriform plate along lymphatic vessels associated with the olfactory nerves.[148]

Metastasis of sinonasal SCC has been reported to regional lymph nodes.[22,44,152] Most of the sinonasal area drains to mandibular and retropharyngeal lymph nodes; however, the olfactory region also drains to pharyngeal and cervical nodes. It has been suggested that more distant metastasis is rarely reported because horses with sinonasal tumours are usually euthanized soon after diagnosis.

Squamous cell carcinoma of the pharynx, nasopharynx and larynx (see Fig. 28.9D) can also be highly locally invasive, with lymphatic metastasis to regional lymph nodes; due to poor accessibility, surgery is often not possible and the prognosis is poor.[145,154]

Gross pathology

Grossly, SCC masses are often multilobulated, and are variable in consistency and colour, from firm and white/yellow/white-grey to friable and/or gelatinous. The masses fill or partially fill the nasal cavity or one or multiple sinuses and there can be distortion, osteolysis or periosteal reaction of surrounding bones, which may include alveolar bone and the hard palate (Figs. 29.1, 29.2). Molar teeth may be loosened, nasal conchae and the nasal septum eroded and distorted, and destruction of the maxillary septum has been described (Fig. 29.2).[152,155] Where there is direct pressure on bone, resorption is not balanced by bone formation due to disruption of blood supply, while adjacent to the tumour mass where the blood vessels are not damaged there may be significant reactive bone deposition resulting in facial swelling and/or deformation or asymmetry.[148]

Some masses may be malodorous with extensive necrosis (softening).[152] Surfaces projecting from mucosal surfaces may be ulcerated. There is often associated purulent or mucopurulent nasal discharge that may become sanguineous in later stages of the disease.[155]

In one study, 78% of horses with sinonasal neoplasms (n=22) had unilateral submandibular lymph node enlargement; however, this was more often due to inflammation and secondary infection than metastasis.[148,156]

Histopathology

It should be noted that superficial biopsy specimens will not usually allow a diagnosis of SCC in these locations, e.g. obtained using endoscopic biopsy forceps. This is partly due to small sample size, but also because neoplasms that do not extend into nasal cavities cannot be reached via the nose.[152,157]

Keratin pearls are thought to be a rare histological feature of equine paranasal SCC, and although some keratinization may be noted, it is generally sparse.[148,155] It has been suggested that SCC found in paranasal sinuses that are well-keratinized are actually of oral (or potentially ocular) origin.[158]

It has also been proposed that histological grading of sinonasal SCC is of little value in horses (as for human patients). In one case series a moderately-differentiated SCC had completely eroded surrounding bones, while an undifferentiated carcinoma was slow-growing and remained localized.[152]

Differential diagnoses

These are listed in Box 12.5.

Urinary bladder

Squamous cell carcinoma of the urinary bladder is thought to arise from islands of squamous epithelial cells that are a normal part of the equine urinary bladder epithelium, or alternatively from areas of squamous metaplasia; the latter is probably less likely.[159,160]

Urinary bladder neoplasms are rare in horses and tend to affect older animals (13–23 years of age), with SCC being the most common type.[160–162] Squamous cell carcinoma has also been reported in the male urethra.[56] Some authors have suggested a male predilection.[160]

The pathogenesis of urinary bladder carcinomas in horses is not understood, but as in cattle and sheep, they have been linked geographically to the distribution of bracken fern

Box 12.5 Differential diagnoses for respiratory tract squamous cell carcinoma

Neoplastic
- Adenoma or adenocarcinoma
- Fibroma
- Myxoma
- Fibrosarcoma
- Fibromatosis
- Sarcoid
- Melanoma
- Lymphosarcoma
- Mast cell tumour
- Haemangiosarcoma
- Peripheral nerve sheath tumour
- Odontogenic neoplasms
- Carcinoid
- Meningioma
- Olfactory neuroblastoma

Non-neoplastic (pp. 258–260)
- Progressive ethmoidal haematoma
- Paranasal sinus cysts
- Nasal polyp
- False nostril (epidermal inclusion) cysts
- 'Tumour-like' nasal amyloidosis
- Reactive fibrosis

(*Pteridium aquilinum*).[163] Some authors have suggested that chronic cystitis may be an instigating factor. Pyelonephritis might potentially cause chronic urinary bladder irritation with progression to neoplastic transformation; however, alternatively, the pyelonephritis might be a secondary result of cystitis caused by the presence of a urinary bladder neoplasm.[160,161]

Biological behaviour

Urinary bladder SCC are locally invasive, extending through the bladder wall to pelvic and abdominal organs and perivesicular tissue; they may also seed transcoelomically within the abdominal cavity, resulting in carcinomatosis.[160] Gross or micro-haematuria is a common clinical sign.

Gross pathology

Squamous cell carcinoma of the equine urinary bladder is usually a solitary, variably firm, and white or tan mass, often with an irregular surface, that projects into the lumen. Grossly, these neoplasms are not distinguishable from transitional cell carcinoma (see Figs. 36.4, 36.5), although they are more likely to have a larger amount of stromal tissue.[162] Mucosal erosion or ulceration frequently occurs, resulting in haematuria.[164]

Histopathology

Histologically, if there are areas of squamous differentiation but most tumour cells also show transitional cell differentiation, the neoplasm should be diagnosed as a transitional cell carcinoma rather than an SCC (see p. 274).

Differential diagnoses

These are listed in Box 12.6.

Box 12.6 Differential diagnoses for urinary bladder squamous cell carcinoma

Neoplastic
- Transitional cell carcinoma

Non-neoplastic
- Fibromatous/fibroepithelial polyp
- Chronic cystitis

Rare sites

A large SCC involving the temporohyoid region and extending through the foramen lacerum to cause marked infiltration of the pons and midbrain was diagnosed in a 20-year-old horse.[165]

References

1. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
2. Pascoe RR, Summers PM. Clinical survey of tumours and tumour-like lesions in horses in south east Queensland. Equine Vet J 1981; 13:235–239.
3. Strafuss A. Squamous cell carcinomas in horses. J Am Vet Med Assoc 1976; 168:61–62.
4. Lavach JD, Severin GA. Neoplasia of the equine eye, adnexa and orbit: a review of 68 cases. J Am Vet Med Assoc 1977; 170:202–203.
5. Dugan SJ, Curtis CR, Roberts SM, et al. Epidemiologic study of ocular/adnexal squamous cell carcinoma in horses. J Am Vet Med Assoc 1991; 198:251–256.
6. Auer U, Walde I. Retrospektive studie über das plattenepithelkarzinom im bereich des auges und seiner. Adnex beim pferd (1981–1996). Wien Tier M 1999; 86:221–229.
7. King TC, Priehs DR, Gum GG, et al. Therapeutic management of ocular squamous cell carcinoma in the horse: 43 cases (1979–1989). Equine Vet J 1991; 23:449–452.
8. Plummer CE, Smith S, Andrew SE, et al. Combined keratectomy, strontium-90 irradiation and permanent bulbar conjunctival grafts for corneolimbal squamous cell carcinomas in horses (1990–2002): 38 horses. Vet Ophthalmol 2007; 10:37–42.
9. Rebhun WC. Tumours of the eye and ocular adnexal tissues. Vet Clin North Am Equine Pract 1998; 14:579–606.
10. Schwink K. Factors influencing morbidity and outcome of equine ocular squamous cell carcinoma. Equine Vet J 1987; 19:198–200.
11. Valentine BA. Neoplasia. In: Bertone JJ, ed. Equine geriatric medicine and surgery. St Louis: Saunders Elsevier; 2006: 147–167.
12. Valentine BA. Survey of equine cutaneous neoplasia in the Pacific Northwest. J Vet Diagn Invest 2006; 18:123–126.
13. Kerr KM, Alden CL. Equine neoplasia, a ten year survey. Proc 17th Annual Mtg Am Ass Vet Lab Diagnosticians 1974; 17:183–187.
14. Röwert-Huber J, Patel MJ, Forschner T, et al. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. Br J Dermatol 2007; 156:8–12.
15. Ratushny V, Gober MD, Hick R, et al. From keratinocyte to cancer: the pathogenesis and modelling of cutaneous squamous cell carcinoma. J Clin Invest 2012; 122:464–472.
16. Arlette JP, Trotter MJ. Squamous cell carcinoma in situ of the skin: History, presentation, biology and treatment. Australas J Dermatol 2004; 45: 1–11.
17. Bhawan J. Squamous cell carcinoma in situ in skin: what does it mean? J Cutan Pathol 2007; 34:953–955.
18. Leffell DJ. The scientific basis of skin cancer. J Am Acad Dermatol 2000; 42:18–22.
19. Scott DW, Miller WH. Neoplasms, cysts, hamartomas, and keratoses, 2nd edn. Maryland Heights: W.B. Saunders; 2011.
20. Guenthner ST, Hurwitz RM, Buckel LJ, et al. Cutaneous squamous cell carcinomas consistently show evidence of in situ changes: a clinicopathologic correlation. J Am Acad Dermatol 1999; 41:443–448.
21. Vercauteren G, Bogaert L, Chiers K, et al. Equine genital carcinoma in situ resembling human genital intra-epithelial neoplasia (Bowenoid papulosis). 27th Meeting of the European Society of Veterinary Pathology and the European College of Veterinary Pathologists, Krakow, Poland 2009; 283.
22. Runnells RA, Benbrook EA. Epithelial tumours of horses. Am J Vet Res 1942; 3:176–179.
23. Schumacher J, Watkins JP, Wilson SR, et al. Burn-induced neoplasia in two horses. Equine Vet J 1986; 18:410–412.
24. Baird AN, Frelier PF. Squamous cell carcinoma originating from an epithelial scar in a horse. J Am Vet Med Assoc 1990; 196:1999–2000.
25. Fessler JF, Faber NA, Blevins WE, et al. Squamous cell carcinoma associated with a chronic wound in a horse. J Am Vet Med Assoc 1993; 202: 615–616.

26. Brinsko SP. Neoplasia of the male reproductive tract. Vet Clin North Am Equine Pract 1998; 14:517–533.
27. Van Howe RS, Hodges FM. The carcinogenicity of smegma: debunking a myth. J Eur Acad Dermatol Venereol 2006; 20:1046–1054.
28. Plaut A, Kohn-Speyer AC. The carcinogenic action of smegma. Science 1947; 105:391–392.
29. Knight CG, Munday JS, Peters J, et al. Equine penile squamous cell carcinomas are associated with the presence of equine papillomavirus type 2 DNA sequences. Vet Pathol 2011; 48:1190–1194.
30. Scase T, Brandt S, Kainzbauer C, et al. Equus caballus papillomavirus-2 (EcPV-2): an infectious cause for equine genital cancer? Equine Vet J 2010; 42:738–745.
31. Kainzbauer C, Rushton J, Tober R, et al. Bovine papillomavirus type 1 and Equus caballus papillomavirus 2 in equine squamous cell carcinoma of the head and neck in a Connemara mare. Equine Vet J 2012; 44:112–115.
32. Vanderstraeten E, Bogaert L, Bravo IG, et al. EcPV2 DNA in equine squamous cell carcinomas and normal genital and ocular mucosa. Vet Microbiol 2011; 147:292–299.
33. Brash DE, Rudolph JA, Simon JA, et al. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proc Natl Acad Sci U S A 1991; 10124–10128.
34. Pazzi KA, Kraegel SA, Griffey SM, et al. Analysis of the equine tumour suppressor gene p53 in the normal horse and in eight cutaneous squamous cell carcinomas. Cancer Lett 1996; 107:125–130.
35. Teifke JP, Löhr CV. Immunohistochemical detection of p53 overexpression in paraffin wax-embedded squamous cell carcinomas of cattle, horses, cats and dogs. J Comp Pathol 1996; 114:205–210.
36. Sironi G, Riccaboni P, Mertel L, et al. p53 protein expression in conjunctival squamous cell carcinomas of domestic animals. Vet Ophthalmol 1999; 2:227–231.
37. Elce YA, Orsini JA, Blikslager AT. Expression of cyclooxygenase-1 and -2 in naturally occurring squamous cell carcinomas in horses. Am J Vet Res 2007; 68:76–80.
38. McInnis CL, Giuliano EA, Johnson PJ, et al. Immunohistochemical evaluation of cyclooxygenase expression in corneal squamous cell carcinoma in horses. Am J Vet Res 2007; 68:165–170.
39. Rassnick KM, Njaa BL. Cyclooxygenase-2 immunoreactivity in equine ocular squamous-cell carcinoma. J Vet Diagn Invest 2007; 19:436–439.
40. Smith KM, Scase TJ, Miller JL, et al. Expression of cyclooxygenase-2 by equine ocular and adnexal squamous cell carcinoma. Vet Ophthalmol 2008; 11(Suppl 1):8–14.
41. Thamm DH, Ehrhart EJ, Charles JB, et al. Cyclooxygenase-2 expression in equine tumours. Vet Pathol 2008; 45:825–828.
42. Moore AS, Beam SL, Rassnick KM, et al. Long-term control of mucocutaneous squamous cell carcinoma and metastases in a horse using piroxicam. Equine Vet J 2003; 35:715–718.
43. Brazil TJ. Recurrent oesophageal obstruction caused by gastro-oesophageal squamous carcinoma: a diagnostic challenge for the clinician? Equine Vet Educ 2008; 20:633–634.
44. Schuh JCL. Squamous cell carcinoma of the oral, pharyngeal and nasal mucosa in the horse. Vet Pathol 1986; 23:205–207.
45. Goldschmidt MH, Dunstan RW, Stannard AA, et al. Histological classification of epithelial and melanocytic tumors of the skin of domestic animals, 2nd series In: American Registry of Pathology. Washington, DC: World Health Organization; 1998.
46. Booth TM, Marmion WJ, Cullimore AM, et al. Oesophageal obstruction in an aged pony associated with squamous cell carcinoma. Equine Vet Educ 2008; 20:627–631.
47. Baum HP, Meurer I, Unteregger G. Expression of proliferation-associated proteins (proliferating nuclear antigen and Ki67 antigen) in Bowen's disease. Br J Dermatol 1994; 131:231–236.
48. Gross TL, Ihrke PJ, Walder EJ, et al. Skin diseases of the dog and cat. Clinical and histopathologic diagnosis, 2nd edn. Ames: Blackwell Science 2005; 399–401.
49. Campbell GA, Gross TL, Adams R. Solar elastosis with squamous cell carcinoma in two horses. Vet Pathol 1987; 24:463–464.
50. Pérez J, Mozos E, Martin MP, et al. Immunohistochemical study of the inflammatory infiltrate associated with equine squamous cell carcinoma. J Comp Pathol 1999; 121:385–397.
51. Van den Top JGB, Ensink JM, Gröne A, et al. Penile and preputial tumours in the horse: literature review and proposal of a standardised approach. Equine Vet J 2010; 42:746–757.
52. Van den Top JGB, de Heer N, Klein WR, et al. Penile and preputial tumours in the horse: a retrospective study of 114 affected horses. Equine Vet J 2008; 40:528–532.
53. Van den Top JGB, de Heer N, Klein WR, et al. Penile and preputial squamous cell carcinoma in the horse: a retrospective study of treatment of 77 affected horses. Equine Vet J 2008; 40:533–537.
54. Dugan SJ. Ocular neoplasia. Vet Clin North Am Equine Pract 1992; 8:609–626.
55. Dugan SJ, Roberts SM, Curtis CR, et al. Prognostic factors and survival of horses with ocular/adnexal squamous cell carcinoma: 147 cases (1978–1988). J Am Vet Med Assoc 1991; 198:298–303.
56. Priester WA, MacKay FW. The occurrence of tumours in domestic animals. Natl Cancer Inst Monogr 1980; 54:1–210.
57. Bastianello S. A survey on neoplasia in domestic species over a 40-year period from 1935 to 1974 in the Republic of South Africa. IV. Tumours occurring in Equidae. Onderstepoort J Vet Res 1983; 50:91–96.
58. Junge RE, Sundberg JP, Lancaster WD. Papillomas and squamous cell carcinomas of horses. J Am Vet Med Assoc 1984; 185:656–659.
59. Johnson PJ. Dermatologic tumors (excluding sarcoids). Vet Clin North Am Equine Pract 1998; 14:625–658.
60. Kaps S, Richter M, Philipp M, et al. Primary invasive ocular squamous cell carcinoma in a horse. Vet Ophthalmol 2005; 8:193–197.
61. Gelatt KN. Corneolimbal squamous cell carcinoma in a horse. Vet Med Sm Anim Clin 1975; 70:53.
62. Sansom J, Donaldson D, Smith K, et al. Haemangiosarcoma involving the third eyelid in the horse: a case series. Equine Vet J 2006; 38: 277–282.
63. Gearhart PM, Steficek BA, Peteresen-Jones SM. Haemangiosarcoma and squamous cell carcinoma in the third eyelid of a horse. Vet Ophthalmol 2007; 10:121–126.
64. Moore CP. Eyelid and nasolacrimal disease. Vet Clin North Am Equine Pract 1992; 8:499–519.
65. Brooks DE. Equine conjunctival diseases: a commentary. Equine Vet Educ 2010; 22:382–386.
66. Eversole TG, Lavach JD. Primary ocular squamous cell carcinoma with metastasis in a horse. Vet Med Sm Anim Clin 1978; 73:287–290.
67. Giuliano EA. Equine periocular neoplasia: current concepts in aetiopathogenesis and emerging treatment modalities. Equine Vet J (Suppl) 2010; 37:9–18.
68. Payne RJ, Lean MS, Greet TRC. Third eyelid resection as a treatment for suspected squamous cell carcinoma in 24 horses. Vet Rec 2009; 165: 740–743.
69. Rebhun WC. Treatment of advanced squamous cell carcinomas involving the equine cornea. Vet Surg 1990; 19:297–302.
70. Elce YA, Wilkie DA, Santschi EM, et al. Metastasis or delayed local extension of ocular squamous cell carcinoma in four horses. Equine Vet Educ 2011; 23:496–499.
71. McCalla TL, Moore CP, Collier LL. Immunotherapy of periocular squamous cell carcinoma with metastasis in a pony. J Am Vet Med Assoc 1992; 200:1678–1681.
72. Kircher CH, Garner FM, Robinson FR. Tumours of the eye and adnexa. Bull World Health Organ 1974; 50:135–142.
73. Bacon CL, Davidson HJ, Yvorchuk K, et al. Bilateral Horner's syndrome secondary to metastatic squamous cell carcinoma in a horse. Equine Vet J 1996; 28:500–503.
74. Jackson C. The incidence and pathology of tumours of domesticated animals in South Africa. Onderstepoort J Vet Sci Anim Ind 1936; 6:1–460.
75. McCowan C, Stanley RG. Pigmented squamous cell carcinoma of the conjunctiva of a horse. Vet Ophthalmol 2004; 7:421–423.
76. Kafarnik C, Rawlings M, Dubielzig RR. Corneal stromal invasive squamous cell carcinoma: a retrospective morphological description in 10 horses. Vet Ophthalmol 2009; 12:6–12.
77. Schumacher J, Vaughan JT. Surgery of the penis and prepuce. Vet Clin North Am Equine Pract 1988; 4:473–491.
78. Moore CP, Grevan VL, Champagne ES, et al. Equine conjunctival pseudotumours. Vet Ophthalmol 2000; 3:57–63.
79. Joyce JR, Martin JE, Storts RW, et al. Iridial hypoplasia (aniridia) accompanied by limbic dermoids and cataracts in a group of related quarterhorses. Equine Vet J Suppl 1990; 10:26–28.
80. Turner AG. Ocular conditions of neonatal foals. Vet Clin North Am Equine Pract 2004; 20:429–440.
81. Cutler TJ. Diseases and surgery of the globe and orbit. In: Gilger BC, ed. Equine ophthalmology. St Louis: Elsevier Saunders; 2005: 63–106.
82. Hollingsworth SR. Diseases of the anterior uvea In: Gilger BC, ed. Equine ophthalmology. St Louis: Elsevier Saunders, 2005; 253–268.
83. Howarth S, Lucke VM, Pearson H. Squamous cell carcinoma of the equine external genitalia: a review and assessment of penile amputation and urethrostomy as a surgical treatment. Equine Vet J 1991; 23:53–58.
84. Burney DP, Theisen SK, Schmitz DG. Identifying and treating squamous cell carcinoma of horses. Vet Med 1992; 87:588–594.
85. Mair TS, Walmsley JP, Phillips TJ. Surgical treatment of 45 horses affected by squamous cell carcinoma of the penis and prepuce. Equine Vet J 2000; 32:406–410.
86. Bedford SJ, McDonnell SM, Tulleners E, et al. Squamous cell carcinoma of the urethral process in a horse with haemospermia and self-mutilation behaviour. J Am Vet Med Assoc 2000; 216:551–553.
87. McCue PM. Neoplasia of the female reproductive tract. Vet Clin North Am Equine Pract 1998; 14:505–515.
88. McFadden KE, Pace LW. Clinical manifestations of squamous cell carcinoma in horses. Comp Cont Ed Pract Vet 1991; 13:669–676.
89. May KA, Kuebelbeck KL, Johnson CM. Urinary bladder rupture secondary to penile and preputial squamous cell carcinoma in a gelding. Equine Vet Educ 2008; 20:135–139.
90. Edwards JF. Pathologic conditions of the stallion reproductive tract. Anim Reprod Sci 2008; 107:197–207.
91. Cramer SD, Breshears MA, Qualls HJ. Pathology in practice. Squamous cell carcinoma of the penis with multifocal metastasis to the regional lymph nodes, lungs, and heart. J Am Vet Med Assoc 2011; 238:581–583.
92. Mair TS. Management of squamous cell carcinoma of the penis. Equine Vet Educ 2004; 16:18–19.
93. Hovda LR, Shaftoe S, Rose ML, et al. Mediastinal squamous cell carcinoma and thyroid carcinoma in an aged horse. J Am Vet Med Assoc 1990; 197:1187–1189.
94. Patterson LJ, May SA, Baker JR. Skeletal metastasis of a penile squamous cell carcinoma. Vet Rec 1990; 126:579–580.
95. Leach MW, Pool RR. Hypertrophic osteopathy in a Shetland pony attributable to pulmonary squamous cell carcinoma metastases. Equine Vet J 1992; 24:247–249.
96. Karcher LF, Le Net J, Turner BF, et al. Pseudohyperparathyroidism in a mare associated with squamous cell carcinoma of the vulva. Cornell Vet 1990; 80:153–162.
97. Head KW. Neoplastic diseases. Vet Rec 1953; 65:926–929.

98. Damodaran S, Ramachandran PV. A survey of neoplasms of equidae. Indian Vet J 1975; 52:531–534.
99. Henkels P. Karzinom der phalanx tertia beim pferd – amputation der zehe-rezidiv an der amputationsstelle und metastasen-mit rücksicht auf die frühdiagnose. Dtsch Tierarztl Wochenschr 1922; 52:676–680.
100. Christopher KJ, Sastry GA. Carcinoma of the hoof of a pony. Indian Vet J 1970; 47:722–723.
101. Berry CR, O'Brien TR, Pool RR. Squamous cell carcinoma of the hoof wall in a stallion. J Am Vet Med Assoc 1991; 199:90–92.
102. Durham AE, Walmsley JP. Squamous cell carcinoma of the epidermal laminae. Equine Vet Educ 1997; 9:30–33.
103. Hillyer LL, Jackson AP, Quinn GC, et al. Epidermal (infundibular) and dermoid cysts in the dorsal midline of a three-year-old thoroughbred-cross gelding. Vet Dermatol 2003; 14:205–209.
104. Ginel PJ, Zafra R, Lucena R, et al. Multiple generalised follicular cysts in a stallion. Vet Dermatol 2007; 18:456–459.
105. Camus AC, Burba DJ, Valdes MA, et al. Intraosseous epidermoid cyst in a horse. J Am Vet Med Assoc 1996; 209:632–633.
106. Sanchez MG, Sampson SN, Schneider RK, et al. Detection of an epidermoid cyst in the foot of a horse by use of magnetic resonance imaging. J Am Vet Med Assoc 2006; 228:1918–1921.
107. Muñoz E, Leiva M, Naranjo C, et al. Retrobulbar dermoid cyst in a horse: a case report. Vet Ophthalmol 2007; 10:394–397.
108. Pascoe RR. The nature and treatment of skin conditions observed in horses in Queensland. Aust Vet J 1973; 49:35–40.
109. Jakob W. Spontaneous amyloidosis of mammals. Vet Pathol 1971; 8:292–306.
110. Gliatto JM, Alroy J. Cutaneous amyloidosis in a horse with lymphoma. Vet Rec 1995; 137:68–69.
111. Hawthorne TB, Bolon B, Meyer DJ. Systemic amyloidosis in a mare. J Am Vet Med Assoc 1990; 196:323–325.
112. Stünzi H, Ehrensperger F, Wild P, et al. Systemic and cutaneous amyloidosis in the horse. Vet Pathol 1975; 12:405–414.
113. Linke RP, Geisel O, Mann K. Equine cutaneous amyloidosis derived from an immunoglobulin lambda-light chain. Immunohistochemical, immunochemical and chemical results. Biol Chem Hoppe Seyler. Biol C 1991; 372:835–843.
114. Hensen WR. Carcinoma of the tongue in a horse. J Am Vet Med Assoc 1939; 94:124.
115. Pommer A. Carcinomstenose des oesophagus beim pferd. Wien Tierarztl Monaatsschr 1947; 34:193–197.
116. Dorn CR, Priester WA. Epidemiologic analysis of oral and pharyngeal cancer in dogs, cats, horses, and cattle. J Am Vet Med Assoc 1976; 169:1202–1206.
117. Roberts MC, Kelly WR. Squamous cell carcinoma of the lower cervical oesophagus in a pony. Equine Vet J 1979; 11:199–201.
118. Routt L, Monfort T, Betley M. Squamous cell carcinoma of the tongue in a horse. J Equine Vet Sci 1981; 1:25–27.
119. Tuckey JC, Hilbert BJ, Beetson S, et al. Squamous cell carcinoma of the pharyngeal wall in a horse. Aust Vet J 1995; 72:227.
120. Hance SR, Bertone AL. Neoplasia. Vet Clin North Am Equine Pract 1993; 9:213–234.
121. Campbell-Beggs CL, Kiper ML, MacAllister C, et al. Use of esophagoscopy in the diagnosis of esophageal squamous cell carcinoma in a horse. J Am Vet Med Assoc 1993; 202:617–618.
122. Meagher DM, Wheat JD, Tennant B, et al. Squamous cell carcinoma of the equine stomach. J Am Vet Med Assoc 1974; 164:81–84.
123. Krahnert R. Zum magenkrebs des pferdes. Mh Vet Med 1952; 7:399–404.
124. Tennant B, Keirn DR, White KK, et al. Six cases of squamous cell carcinoma of the stomach of the horse. Equine Vet J 1982; 14:238–243.
125. Cotchin E. A general survey of tumours in the horse. Equine Vet J 1977; 9:16–21.
126. Olsen SN. Squamous cell carcinoma of the equine stomach: a report of five cases. Vet Rec 1992; 131:170–173.
127. McKenzie EC, Mills JN, Bolton JR. Gastric squamous cell carcinoma in three horses. Aust Vet J 1997; 75:480–483.
128. Taylor SD, Haldorson GJ, Vaughan B, et al. Gastric neoplasia in horses. J Vet Intern Med 2009; 23:1097–1102.
129. Hertsch VB, Eidt E. Zur klinischen Diagnose des Magenkarzinoms beim Pferd. Dtsch Tierarztl Wochenschr 1976; 83:92–96.
130. Moore JN, Kintner LD. Recurrent esophageal obstruction due to squamous cell carcinoma in a horse. Cornell Vet 1976; 66:590–597.
131. Tamaschke C. Pracancerosen beim Tier unter besonderer Berucksichtgung des Magenkrebses beim Pferd. Arch Geschwulstforsch 1958; 12:205–226.
132. Becker C-H. Uber prakanzerose Vorgange in der Magenschleimhaut des Pferdes. Zentralbl Veterinarmed A 1966; 13A:270–277.
133. Hudson NPH, Dixon PM, Pirie RS, et al. Dysphagia caused by squamous cell carcinoma of the tongue. Equine Vet Educ 2000; 12:133–136.
134. Ford TS, Vaala WE, Sweeney CR, et al. Pleuroscopic diagnosis of gastroesophageal squamous cell carcinoma in a horse. J Am Vet Med Assoc 1987; 190:1562–1564.
135. Schleining JA, Voss ED. Hypertrophic osteopathy secondary to gastric squamous cell carcinoma in a horse. Equine Vet Educ 2004; 16:304–307.
136. Head KW. Tumours of the upper alimentary tract. Bull World Health Organ 1976; 53:145–146.
137. Wrigley RH, Gay CC, Lording P, et al. Pleural effusion associated with squamous cell carcinoma of the stomach of a horse. Equine Vet J 1981; 13:99–102.
138. Zicker SC, Wilson WD, Medearis I. Differentiation between intra-abdominal neoplasms and abscesses in horses, using clinical and laboratory data: 40 cases (1973–1988). J Am Vet Med Assoc 1990; 196:1130–1135.
139. Morse CC, Richardson DW. Gastric hyperplastic polyp in a horse. J Comp Pathol 1988; 99:337–342.
140. Saulez MN, Cebra CK, Snyder SP. Small colon polyp with peritonitis in an Arabian yearling filly. Equine Vet Educ 2004; 16:184–187.
141. Dunkel B, Shokek AB, Wilkins PA. Congenital cystic polypoid rectal hamartoma in a newborn foal. Vet Pathol 2004; 41:700–702.
142. Johnson JL, Hultine JJ, Cook JE, et al. Leukoplakia of the esophagus and stomach of a foal. Vet Pathol 1980; 17:638–640.
143. Madewell BR, Priester WA, Gillette EL, et al. Neoplasms of the nasal passages and paranasal sinuses in domesticated animals as reported by 13 veterinary colleges. Am J Vet Res 1976; 37:851–856.
144. Boulton CH. Equine nasal cavity and paranasal sinus disease: a review of 85 cases. J Equine Vet Sci 1985; 5:268–275.
145. Van den Wollenberg L, Van den Belt AJM, Van der Kolk JH. Squamous cell carcinoma of the larynx in a Shetland pony. Equine Vet Educ 2002; 14:60–62.
146. Gaughan EM, Gift LJ, DeBowes RM, et al. Squamous cell carcinoma as a cause of dysphagia and blindness in a horse. Cornell Vet 1991; 81:295–303.
147. Freeman DE. Sinus disease. Vet Clin North Am Equine Pract 2003; 19:209–243.
148. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 1: Review of the literature and tumour classification. Vet J 1999; 157: 261–278.
149. Weisz L. Carcinoma of the maxillary sinus of the horse. Middlesex Vet 1944; 4:16–17.
150. Trigo FJ, Nickels FA. Squamous cell carcinoma of a horse's guttural pouch. Mod Vet Pract 1981; 62:456–459.
151. McConnico RS, Blas-Machado U, Cooper VL, et al. Bilateral squamous cell carcinoma of the guttural pouches and the left middle ear in a horse. Equine Vet Educ 2001; 13:175–178.
152. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 2: A contribution of 28 case reports. Vet J 1999; 157:279–294.
153. Acland HM, Orsini JA, Elkins S, et al. Congenital ethmoid carcinoma in a foal. J Am Vet Med Assoc 1984; 184:979–981.
154. Jones DL. Squamous cell carcinoma of the larynx and pharynx in horses. Cornell Vet 1994; 84:15–24.
155. Kowalczyk L, Boehler A, Brunthaler R, et al. Squamous cell carcinoma of the paranasal sinuses in two horses. Equine Vet Educ 2011; 23:435–440.
156. Tremaine WH, Dixon PM. A long-term study of 277 cases of equine sinonasal disease. Part 1: Details of horses, historical, clinical and ancillary diagnostic findings. Equine Vet J 2001; 33:274–282.
157. Witte TH, Perkins JD. Early diagnosis may hold the key to the successful treatment of nasal and paranasal sinus neoplasia in the horse. Equine Vet Educ 2011; 23:441–447.
158. Moulton JE. Tumours of the respiratory system In: Moulton JE, ed. Tumours of domestic animals, 3rd edn. Berkeley: University of California Press; 1990: 303–346.
159. Pamukcu AM. Tumours of the urinary bladder. Bull World Health Organ 1974; 50:43–52.
160. Fischer AT, Spier S, Carlson GP, et al. Neoplasia of the equine urinary bladder as a cause of hematuria. J Am Vet Med Assoc 1985; 186: 1294–1296.
161. Traub-Dargatz JL. Urinary tract neoplasia. Vet Clin North Am Equine Pract 1998; 14:495–504.
162. Meuten DJ. Tumours of the urinary system In: Meuten DJ, ed. Tumours in domestic animals, 4th edn. Ames: Iowa State Press; 2002: 509–546.
163. Hopkins NCG. Aetiology of enzootic hematuria. Vet Rec 1986; 118: 715–717.
164. Barrell E, Hendrickson DA. Tumours of the equine bladder: what makes treating these cases so difficult? Equine Vet Educ 2009; 21:267–268.
165. D'Angelo A, Bertuglia A, Capucchio MT, et al. Central vestibular syndrome due to a squamous cell carcinoma in a horse. Vet Rec 2007; 161: 314–316.

13

Melanocytic neoplasms

Cellular origin	237	Gross pathology	240
Classification	237	Histopathology	240
Profile	237	Immunohistochemical labelling	243
Oncogenesis	238	Electron microscopy	245
Commonly affected sites	238	Differential diagnoses	245
Biological behaviour	239		

Cellular origin

Melanocytes are dendritic cells derived from neuroectodermal melanoblasts. They are mainly found in the skin, within the basal layer of the epidermis and in the outer root sheath of hair follicles.

Classification

Tumours of melanocytes may be benign or malignant; benign melanoma is sometimes referred to as 'melanocytoma'. The classification of melanocytic neoplasms of the equine skin is confusing for both clinician and pathologist, with no generally agreed system. Certain benign neoplasms have been classified as naevi (i.e. equivalent to 'moles' in humans). In one study of 57 melanocytic neoplasms from 53 horses, four categories were suggested, including one form of naevus (i.e. melanocytic naevus), dermal melanoma, dermal melanomatosis and anaplastic malignant melanoma.[1] More recently, three additional types of naevus were described that show similarity to subgroups of naevi found relatively commonly in human patients, but rarely in horses. These are the intradermal common melanocytic naevus, cellular blue naevus and combined cellular blue naevus.[2]

Profile

A total of 6–15% of cutaneous neoplasms and 2–34% of total neoplasms in horses are melanomas. The age-related predisposition of grey horses to development of melanocytic neoplasia has been recognized for centuries. It is estimated that approximately 80% of older grey horses are affected.[3] In a survey of Camargue-type grey horses (n=264) the prevalence of cutaneous melanomas was 31% for the total population and 67% for those over 15 years of age.[4]

Breeds including Arabian and Lipizzaner horses appear to have a high prevalence, and this may be related to the higher proportion of grey horses in those breeds[5]; most Lipizzaners are grey as are many Arabs, although the skin itself is invariably black. 'Greying out' of the hair coat occurs with age, from a birth colour that is often bay, chestnut or black, to completely white or 'flea-bitten' grey in older horses. The speed of greying out varies significantly between individuals. In both breeds, the depigmentation process begins around the eyes and in the perianal region, where melanomas are most commonly identified. These coat colour changes have been diagnosed as minimal partial albinism and progressive vitiligo.[6] In a study of Arabian horses in the USA, most horses were dark brown initially but began to grey at 2 years of age, becoming white by 9 years; many horses developed melanomas by 5–6 years of age, usually beginning around the anus.[6] In Lipizzaner horses in Austria and Croatia (n=296), 50% had melanomas.[7] These neoplasms occurred under the tail in 75% of horses over 15 years of age, and 76% of total cases.

While most melanocytic neoplasms are found in older horses, there have been a small number of reports of congenital or acquired cutaneous or non-cutaneous lesions in animals up to 2 years of age; some were reported as malignant, but three cases were not followed by evidence of recurrence or metastasis (see Fig. 31.26).[8–12] In one retrospective study of 18 melanocytomas (benign melanomas) from horses 3 weeks to 2 years of age that were submitted to two diagnostic laboratories in the USA, 14/15 animals for which there was follow-up information did not show subsequent evidence of recurrence or metastasis for up to 8 years.[11] These horses were of a variety of breeds and coat colours.

Some surveys have indicated a higher incidence in males,[13] but others have not supported a gender predilection.[4] Of 18 horses with congenital melanocytoma, 13 were female.[11]

Some of the apparent contradictions between different studies might be clarified by considering the more recent classification of equine melanocytic neoplasms into subtypes, as follows (p. 569).[1,2]

1. *Naevi* are not confined to grey horses or older horses. Depending on their type (differentiated histologically), they arise either from altered melanocytes ('naevus cells') in the epidermal basal layer or dermal dendritic melanocytes. The melanocytic naevus (melanocytoma) described by one author has frequent epidermal involvement, and usually occurs in horses 6 years of age or less[1]; this naevus type may also be congenital. The other types of naevi (intradermal common

melanocytic naevus, cellular blue naevus, combined cellular blue naevus) are dermal and have been reported in horses 2–20 years of age with occasional congenital lesions and a predominance in males.[2]

2. *Dermal melanomas* occur mostly in older grey horses, with 80% in one study occurring in animals over 6 years of age, and an average age of 13 years.[1] Dermal melanomas may be benign or malignant; those presenting initially as malignant may be more frequently diagnosed in younger adult horses.[14]

   By definition of some authors, the term 'dermal melanoma' is only used when the affected horse only has 1–2 discrete masses.[15] Dermal melanomatosis, where there are many lesions that coalesce, also involves grey horses over 15 years of age.[1,16]
3. *Anaplastic malignant melanomas* are rare and typically occur in non-grey horses >20 years of age (see Fig. 31.30).[1]

The occurrence of intraocular melanomas is less age-related than for many of the cutaneous forms.[17]

Oncogenesis

It has always been suspected that the development of melanocytic neoplasms is likely to involve disturbances in melanin metabolism. Some authors have suggested that reductions in uptake of cutaneous melanin pigment in grey horses during ageing results in accumulation in melanoblast-melanocyte populations, which eventually stimulates hyperplasia or neoplastic transformation.[18] Others proposed that these lesions to be a manifestation of a pigment storage disease, rather than being true neoplasms.[19]

More recent studies have begun to establish the molecular pathways by which disturbances in pigmentation and neoplastic transformation of melanocytes occur in grey horses. The grey coat phenotype is apparently associated with a duplication in intron 6 of the syntaxin-17 (*STX17*) gene.[20] Lipizzaner horses homozygous for this duplication show more rapid greying out, and are more homogeneously white in the final stages; these horses also have a significantly higher incidence of melanoma. Both *STX17* and the neighbouring *NR4A3* gene are overexpressed in melanomas from grey horses.

Syntaxins are involved in vesicle transport that could include melanosomes, but have also been shown to be localized to nuclei in some malignant cells where they may interact with *RAS* oncogenes.[21] NR4A3 is a nuclear hormone receptor that can be involved in multiple biological processes, including cell-cycle regulation and apoptosis; it has been proposed that in these grey horses, both gene products promote dermal melanocyte proliferation.[20] In the hair follicle, this melanocytic hyperproliferation may cause premature stem cell depletion, leading to loss of hair pigment. NR43A has been linked with oncogenesis for other types of neoplasm. Upregulation of one of its target genes, *CCND2* (for the cell-cycle protein cyclin D2) has also been identified in melanomas of grey horses.

In a study of six melanocytic tumours from five horses, the malignant melanomas ($n=2$) showed overexpression of p53 protein but no evidence of *p53* mutation.[22] As melanomas typically occur in areas that are not sun-exposed, ultraviolet radiation does not seem to be a risk factor as it is in many human cases.

In one immunohistochemical study of COX-2 expression (see SCC, p. 222) in 11 melanomas, seven showed moderate to strong reactions (labelling of 21–50% of cells), suggesting that this may be a therapeutic target.[23]

Although retrovirus-like particles have been found in melanoma cells from grey horses, their role in neoplastic transformation is not certain.[7]

Commonly affected sites

Skin

The skin is the most common site for melanoma development in horses. In a survey of 30 cases, 67% of melanomas were cutaneous, 13% involved ocular tissues and small numbers of masses involved the respiratory system or male genitalia.[24] Similarly, in a survey using data from the US Veterinary Medical Data Program between 1964 and 1977, 41% involved the skin, 21% other soft tissues and 14% affected the oral cavity; all of those tumours were classified as malignant.[25] The coat colour of the horses was not noted in either survey.

In ageing grey horses, there may be single or multiple masses, i.e. dermal melanoma or dermal melanomatosis, respectively.[1] For this form of the disease, primary sites considered 'typical' include the ventral tail, perineum and external genitalia (see Figs. 5.1, 31.27 and 35.3). The head (including eyelids, periocular skin (see Figs. 31.27 and 34.4) and ears), neck, parotid salivary glands (see Figs. 28.12 and 31.28) and limbs are less frequent sites of origin. Dermal melanomas presenting initially as malignant tend to occur in atypical locations.[14] Additional sites of involvement reported in cases of dermal melanomatosis include the mouth/lips (Fig. 28.11), crest, mammary gland (Fig. 35.16), and guttural pouch (Fig. 31.28); cutaneous and non-cutaneous sites can co-exist.[15] The foot is rarely involved, with only single reports in the coronary band (non-grey horse) and hoof wall, respectively.[26,27]

Naevi are not confined to what are considered typical anatomical sites for melanomas. Reported locations include the head, eyelids, neck, thorax, dorsum and hindlimbs.[1,2]

Internal sites

Less frequently, melanocytic neoplasms are reported in internal sites. One theory is that these neoplasms arise from nests of melanocytes left behind during the migration of neural crest precursor cells to the skin (i.e. embryological rests), or they may derive from melanoblasts that migrated aberrantly. Internal melanomas could also be metastatic, with primary masses not always being identified.[28] In one study, the primary origin was unknown in 3% of human patients with malignant melanoma.[29]

Internal melanomas may also occur on rare occasions in the nasal cavity, oral cavity, nasopharynx and guttural pouch (see Fig. 29.13).[30–32]

In cases of disseminated malignant melanoma (see Fig. 31.29), the primary site or sites can be particularly difficult to identify. Internal sites of origin have included the spleen, oesophagus, heart (see Fig. 30.10) and thoracic cavity.[8,33,34] A primary malignant melanoma in the right atrial wall of the heart of a Thoroughbred stallion was associated with

haemorrhage in the interventricular septum, and sudden death.[33] A thoracic melanoma in a grey Thoroughbred cross, presumed to involve the cervicothoracic ganglion, was associated clinically with signs of sympathetic denervation including a well-demarcated area of cutaneous hyperthermia and sweating on one side of the body (see Fig. 33.4).[34]

Ocular sites

Primary melanocytic neoplasms rarely occur in ocular sites, and are predominantly diagnosed in grey horses. Despite their relative rarity, it has been stated that they are the most common intraocular neoplasms in horses.[35] Locations have included the cornea, conjunctiva, limbus, nictitating membrane, choroid, iris and ciliary body (see Figs. 3.2B, 3.5B, 5.6, 31.27, 31.30, 34.3, 34.4).[36–43] One grey horse presented with bilateral iridal melanomas.[43] Only one case of retrobulbar melanoma has been reported.[44] An epibulbar malignant melanoma (i.e. originating from the limbic sclera) was reported in a 6-month-old foal.[12] An epibulbar melanocytoma (benign melanoma) occurred in a 7-year-old pony and was successfully excised.[45]

Cutaneous and intraocular melanocytic neoplasms in horses can co-exist, and may or may not be related, with histological similarity and dissimilarity both reported.[35]

Biological behaviour

Cutaneous melanocytic neoplasms

Cutaneous naevi are solitary, relatively small masses that should be resolved by surgical excision. In humans, many melanomas arise from pre-existing naevi, but there is no evidence for this in horses.

Dermal melanomas may be benign *or* malignant at the time of presentation. Some authors believe that most benign neoplasms eventually progress to malignancy as the patient ages, and may then metastasize internally.[14] In one study, 14% of 101 dermal melanomas metastasized after 1–6 years; however, these authors suggested that the true metastatic rate may be less.[46] It has also been suggested that melanomas in the parotid region are more likely to metastasize. Dermal melanomas presenting initially as malignant have been reported to metastasize rapidly and some of these horses die or are euthanized within months of diagnosis.[14]

In cases of dermal melanomatosis, i.e. multiple cutaneous melanomas, the metastatic rate to internal organs is thought to be high.[1] However, in one study of horses with dermal melanomatosis where masses were surgically excised, 9 of 11 horses were alive at the time of follow-up (from <1 year to 6 years' post-treatment) with no evidence of internal metastasis.[15] Some did develop new lesions close to the site of excision and others showed an increase in size of similar but pre-existing masses; only those causing clinical problems were removed and some developed further masses after that. Other authors do not recommend surgical excision, due to the risk of stimulation of further growth and/or metastasis.[47]

Anaplastic malignant melanomas are large and invasive, with widespread metastasis within a year of diagnosis (see Fig. 31.29).[1] In malignant dermal melanoma, dermal melanomatosis and anaplastic malignant melanoma, extensive direct infiltration of surrounding tissues and organs may cause significant problems (see Fig. 33.4). For example, when masses arise in typical perineal and tail-base sites, there may be infiltration into the vertebral bodies and paravertebral musculature of the lumbosacral spine, resulting in extradural compression of the spinal cord.[5,46,48] Post-mortem examinations of horses with perineal and/or tail-base melanomas should include inspection of the pelvis and spinal column (see Fig. 33.3). Cases of highly invasive melanoma involving the pelvic region and lumbosacral spine and resulting in posterior paresis or lameness have been reported in which no cutaneous masses were identified; they may have been primary in those sites.[28,49] Masses involving the hoof are rare, but again may cause extensive disruption through local invasion of the hoof wall, coronary band and more proximal tissues, with osteolysis and separation of the distal phalanx.[26,27]

Ocular neoplasms

Resection of corneal and/or conjunctival melanomas is often curative, but there is a sub-population of aggressively recurrent and invasive neoplasms that may ultimately lead to enucleation.[40] In one case, there was destruction of the cornea and invasion of extraorbital muscles and the anterior chamber of the eye, with posterior displacement of the lens.[36]

Limbal (epibulbar) melanomas, as in other species, are often considered to be benign, with slow growth and the possibility of curative surgery.[40,45] One case of limbal melanoma in a 6-month-old foal was highly aggressive-it appeared suddenly, grew rapidly and showed extensive infiltration of the limbus, cornea, sclera and choroid.[12] Melanomas involving the nictitating membrane are thought to typically be more aggressive.[41]

Anterior uveal melanocytic tumours are usually considered to be benign, but their progression can still result in compromise of internal ocular structures. There have been rare reports of malignant melanomas in those sites. A ciliary melanoma in a 7-year-old grey Quarter Horse extended to the posterior lens capsule, into the vitreous humour and along the vitreal face of the detached retina and was diagnosed as malignant, based on this behaviour rather than histological appearance.[37] An iridal mass occupying the anterior chamber of a 7-year-old grey Mustang gelding was diagnosed as malignant based on the histological appearance, and iridectomy was successfully performed with no evidence of recurrence or metastasis 15 months postoperatively.[42]

Metastasis

Melanomas may metastasize via blood or lymphatic vessels. Transcoelomic spread may also occur. Cutaneous melanoma often spreads first to regional lymph nodes. Reported sites for internal metastasis include lymph nodes (e.g. iliac, inguinal, mesenteric, thoracic, cervical); thoracic inlet, lungs, heart (pericardium, left atrium, right ventricle, coronary vessels); diaphragm, thoracic cavity, liver, spleen, pancreas, kidneys, peri-renal adipose tissue, adrenal glands, peritoneum, omentum, intestinal mesenteric tissue, small intestinal wall, mesometrium, uterus, skeletal muscle, bone marrow, brain, and intra- or perivascular sites throughout the body (see Figs. 4.31, 5.9, 13.1, 31.29, 36.7).[46] In some horses, metastatic lesions have been described as incidental

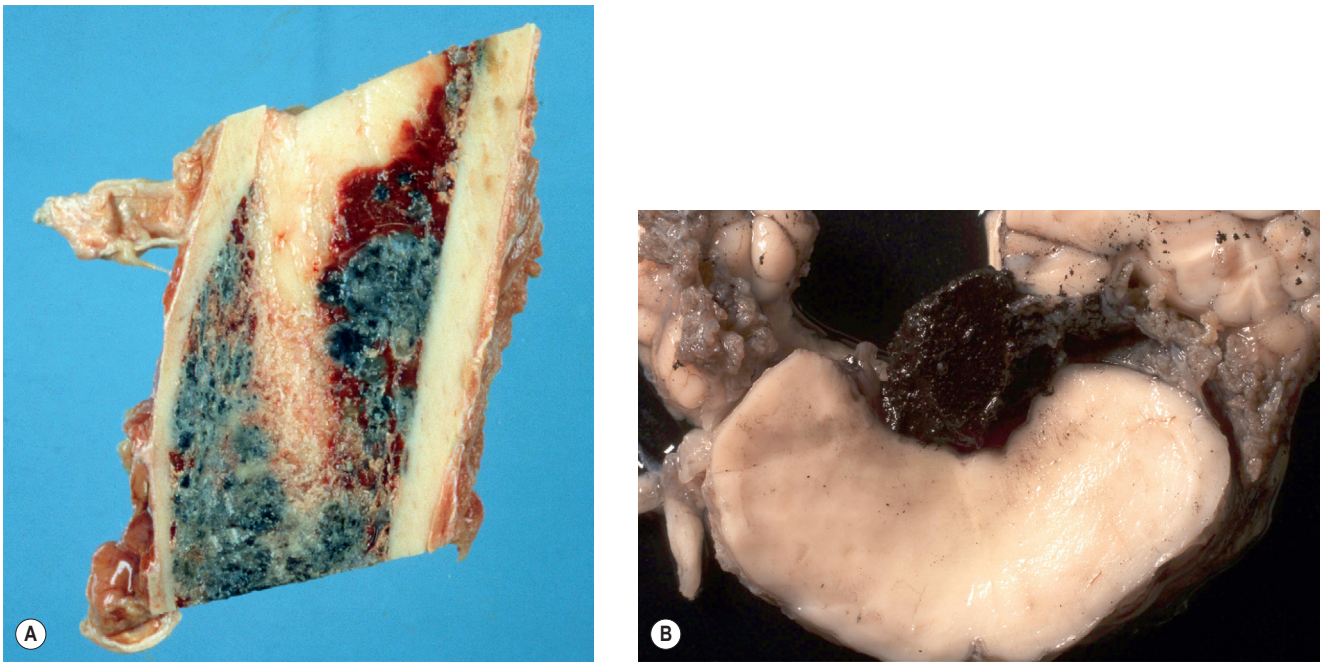


Figure 13.1 Metastatic melanomas. (A) Melanoma cells occupying the bone marrow of a long bone, seen as black-grey discoloration. This horse had disseminated disease, with tumour cells throughout medullary cavities of the axial and appendicular skeleton.[48] **(B)** A melanoma mass involving the meninges of the dorsal brainstem. This 14-year-old grey gelding presented with perianal melanomas and bilateral parotid swellings that appeared to be static; however, the horse developed progressive ataxia and weakness over a 7-day period with generalized body sweating and head pressing. This mass was found at post-mortem examination in addition to numerous other (small) metastatic melanomas in the major organs.

findings at post-mortem examination.[1] Peripheral sites may include skeletal muscle, bones, joints, tendon sheaths, mammary tissue, eyes and lymph nodes. Lameness may be the presenting complaint in rare cases where metastasis has occurred to joints or muscles, and these may include invasion of the articular cartilage and bone.[50]

There has been debate as to whether there is true vascular metastasis, or whether additional internal neoplasms arise from multifocal melanocytic neoplastic transformation.[46] Metastatic lesions may be found some distance from putative primary cutaneous masses; for example, in two older grey horses with perineal/tail-base melanomas, there was a mass at the level of the 7th cervical vertebra, causing significant spinal cord compression.[51] Neither horse showed evidence of neoplastic infiltration of the cerebrospinal fluid. Another horse with perineal and ventral tail-base melanomas presented with dysphagia and recurrent oesophageal obstruction, and was diagnosed with a dorsal brainstem melanoma (see Fig. 13.1).[52]

There have been few reports of disseminated melanoma, involving older grey horses or ponies, and usually but not always diagnosed with solitary or multiple masses in typical cutaneous sites.[48,53,54] In one such case, anaplastic melanoma cells occupied the bone marrow throughout the axial and appendicular skeleton (Fig. 13.1).[48]

Gross pathology

Cutaneous melanocytic naevi are solitary, slightly raised papular lesions that can measure up to 3 cm in maximal diameter and are likely to resemble similar lesions in humans, i.e. they could be pink, flesh-coloured or tan to brown, with a smooth or verrucous surface.[2]

Dermal melanomas may be solitary or multiple and horses with dermal melanomatosis have multiple, often coalescing masses (see Fig. 31.27). Melanomas usually measure from a few millimetres to several centimetres in diameter and are often spherical or ovoid, but may be irregularly-shaped, plaque-like, flat, polypoid or verrucous.[16,46] Coalescing masses may have a cobblestone appearance. Melanomas may be of any colour, including grey, brown, red or even dark blue, but are often firm and black, with abundant black pigment on sectioning (Figs. 5.1, 30.10, 33.3).[16] There may be alopecia of the overlying skin, and larger masses are frequently ulcerated.[11] One cutaneous melanoma of a black Appaloosa foal was surrounded by a 'halo' of depigmented skin; this feature has been seen associated with melanomas in children and young adults, some of which regress.[10]

The size and degree of pigmentation of ocular melanomas is variable (Fig. 31.27). There may be distortion and/or obliteration of intraocular structures. Secondary effects can include cataract formation, glaucoma and secondary keratitis (see Fig. 34.4).[39] If the corneal endothelium is contacted by an intraocular mass, focal corneal oedema may be seen.[42]

In horses with metastatic melanoma, common findings include weight loss and peripheral oedema, most frequently of the ventral abdomen.[46]

Histopathology

General features

Normal melanocytes do not retain melanin, packaging it in melanosomes and transferring it to surrounding epidermal/epithelial cells.[16] Melanoma cells, however, typically contain

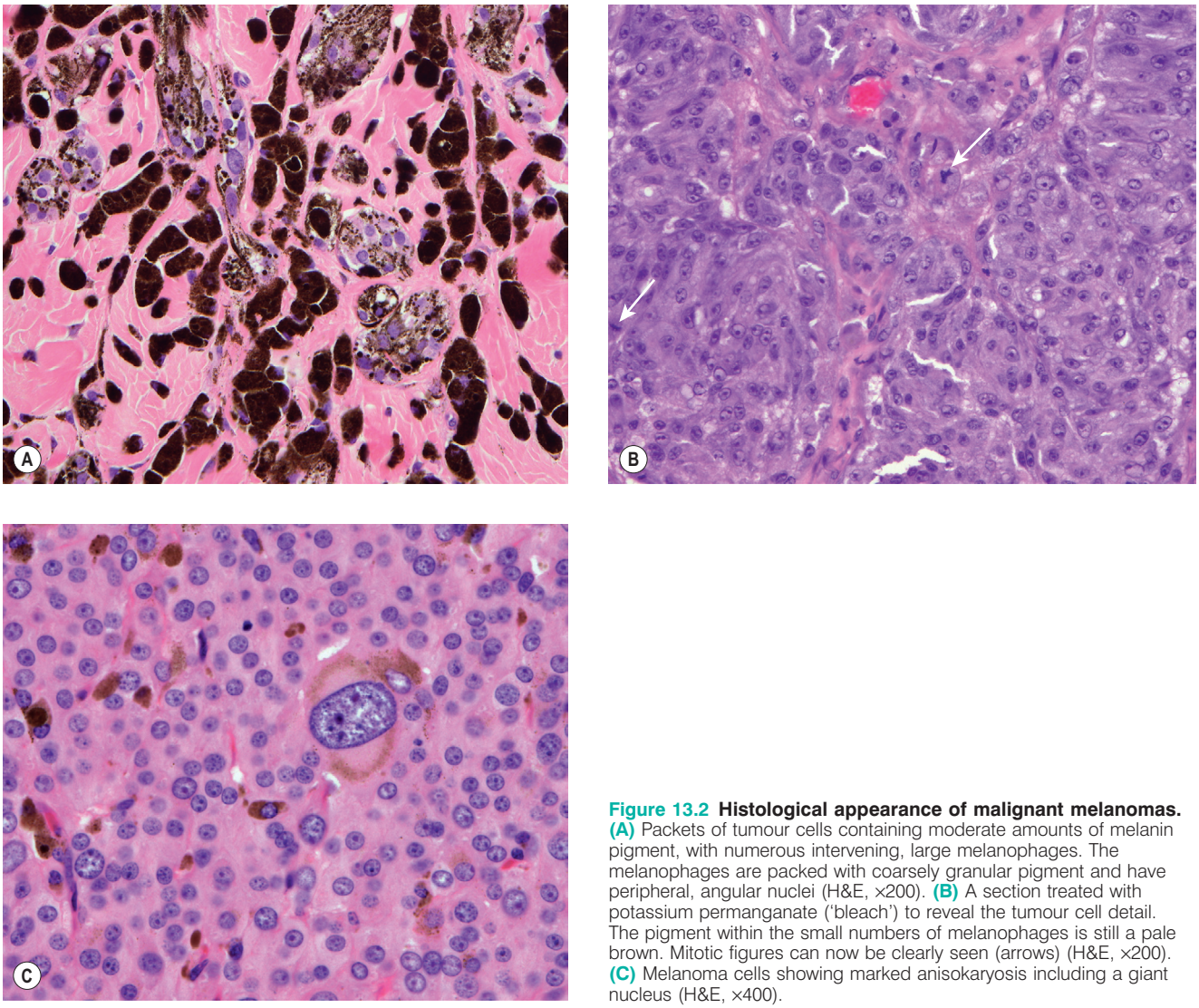


Figure 13.2 Histological appearance of malignant melanomas. **(A)** Packets of tumour cells containing moderate amounts of melanin pigment, with numerous intervening, large melanophages. The melanophages are packed with coarsely granular pigment and have peripheral, angular nuclei (H&E, ×200). **(B)** A section treated with potassium permanganate ('bleach') to reveal the tumour cell detail. The pigment within the small numbers of melanophages is still a pale brown. Mitotic figures can now be clearly seen (arrows) (H&E, ×200). **(C)** Melanoma cells showing marked anisokaryosis including a giant nucleus (H&E, ×400).

variable amounts of melanin pigment, which is usually finely granular (Fig. 13.2). There may be large numbers of associated melanophages that have a large amount of cytoplasm packed with coarsely granular melanin pigment and small, peripheral, angular nuclei (see Fig. 13.2). 'Bleaching' of sections using potassium permanganate is often necessary to allow examination of tumour cell detail and determination of the mitotic rate. Following bleaching, tumour cells will have a clear cytoplasm, while the pigment in melanophages does retain a brown colour. Mitotic figures can be confused with pyknotic nuclei of dying cells, or small hyperchromatic nuclei of stromal fibroblasts when obscured by the melanin pigment.[16]

When regional lymph nodes are examined, bleached sections are also required, as melanophages will often migrate to these structures from the neoplastic masses or associated inflamed areas, and must be differentiated from tumour cells.

Mitotic figures should be counted in areas where they are highest in number, as they do vary regionally within neoplastic masses. Classically, three or more mitotic figures per 10 high power (×400) fields in melanomas are said to indicate malignancy.[16] However, this may not always be the case in equine melanocytic tumours (see naevi, below) and both histological and clinical factors must be taken into account. Other histological evidence of malignancy can include asymmetrical contour, poor demarcation, invasive behaviour, necrosis, cellular atypia and pleomorphism (other than ancient change, p. 242), and bizarre mitotic figures (see Figs. 3.14, 13.2). The histological appearance will not always be useful in terms of predicting present or future pathological behaviour.

The histological features of previously described types of equine melanocytic tumour are provided below; however, it should be noted that some masses are not classifiable, including those showing features of both melanocytic naevus and dermal melanoma.[1]

Naevi

Melanocytic naevus

These naevi[1] are discrete masses composed of nests of tumour cells located in the superficial dermis and/or dermal–epidermal junction, with frequent epidermal involvement – i.e. nests may be seen within a hyperplastic

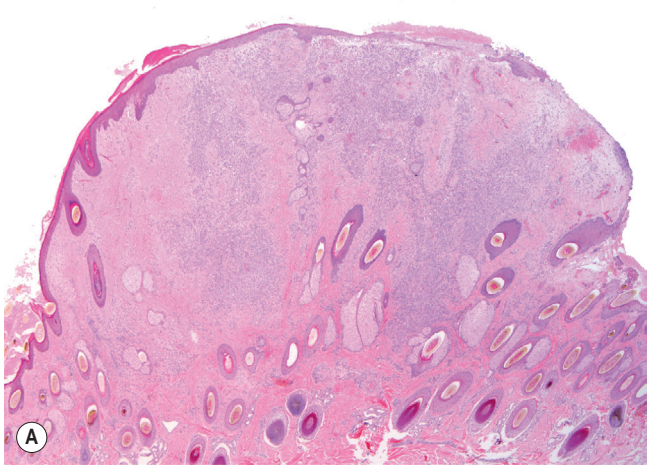
epidermis. Epidermal involvement is a significant difference from the three other types of naevus described below. The tumour cells are relatively large, epithelioid (polygonal) or spindle-shaped, and may show mild to moderate pleomorphism. Some do show features normally associated with malignancy including marked pleomorphism, variable pigmentation and high mitotic activity (see above). There are numerous heavily pigmented melanophages between the tumour cells.

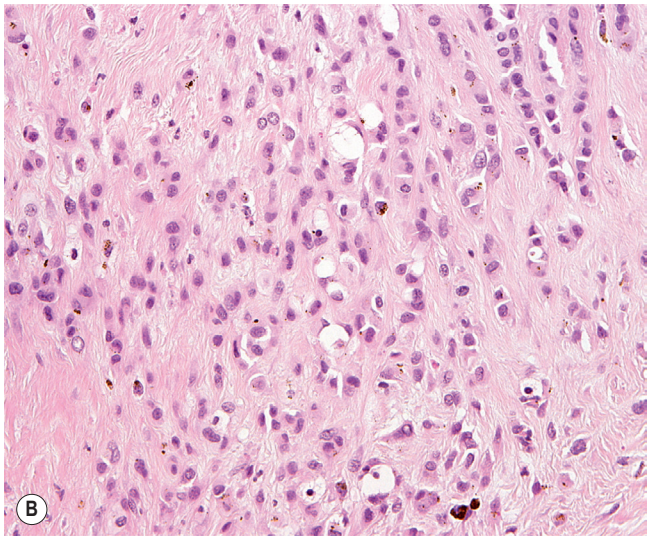
Intradermal common melanocytic naevus (CMN)

Intradermal common melanocytic naevi[2] in horses are well-demarcated, unencapsulated, and symmetrical (Fig. 13.3). They may occupy only the superficial to mid-dermis or extend into the deep dermis and surround adnexal structures. The tumour cells are arranged in dense nests within multiple islands of myxomatous stroma; the latter are separated by collagenous tissue. Two cell types have been noted, these being round cells with scanty cytoplasm occasionally containing a few melanin granules, and non-pigmented, spindle-shaped cells; in human patients, these are referred to as B- and C-type naevus cells, respectively (see Fig. 13.3). Nuclei are round or elongate with stippled chromatin, and cellular pleomorphism is not marked. Occasional cells may show variation in nuclear size or shape or multiple nuclei, these indicating senescence rather than malignancy ('ancient change'); ancient change has also been seen in peripheral nerve sheath tumours (see p. 301). The mitotic rate is highly variable; from 0 to 18 mitotic figures per 10 high power (×400) fields. The overlying epidermis may be hyperplastic, hyperpigmented, atrophic, eroded or ulcerated (see Fig. 13.3).

Cellular blue naevus (CBN)

Cellular blue naevi[2] are located in the reticular (deeper) dermis. In human patients, blue naevi are known to arise from dermal dendritic melanocytes. Tumour cells are arranged in interlacing fascicles, supported by a collagenous stroma (Fig. 13.4). They are ovoid or elongate and fusiform, with a moderate amount of eosinophilic or clear cytoplasm containing variable amounts of melanin pigment; those with less pigmentation in human patients are referred to as hypomelanotic. Nuclei are ovoid, with stippled chromatin and occasional nucleoli (1–2). Cellular pleomorphism is mild but occasional multinucleate cells may be noted ('ancient change'). The mitotic rate varies from 0 to 3 per 10 high power (×400) fields. Melanophages may be noted in the overlying (superficial) dermis or around the tumour periphery. The overlying epidermis may be hyperplastic, hyperpigmented or ulcerated.





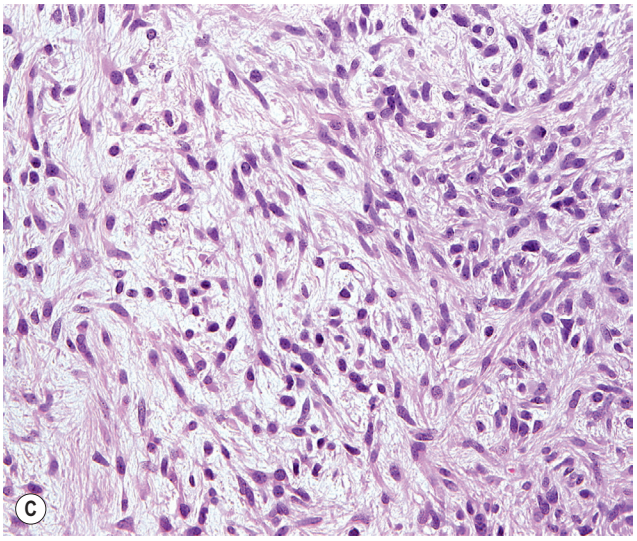


Figure 13.3 Intradermal common melanocytic naevi (CMN). **(A)** An unencapsulated, approximately symmetrical, densely cellular mass occupying the superficial to mid-dermis. There is multifocal ulceration of the overlying epidermis (H&E, ×12.5). **(B)** Round or polygonal tumour cells, some containing small amounts of (brown) melanin pigment ('B-type naevus cells') (H&E, ×200). **(C)** Predominantly spindle-shaped tumour cells that are not pigmented ('C-type naevus cells') and are surrounded by an amphophilic (myxomatous) stroma (H&E, ×200). *(Histological slides courtesy of Professor Brian Summers, Royal Veterinary College, University of London, UK.)*

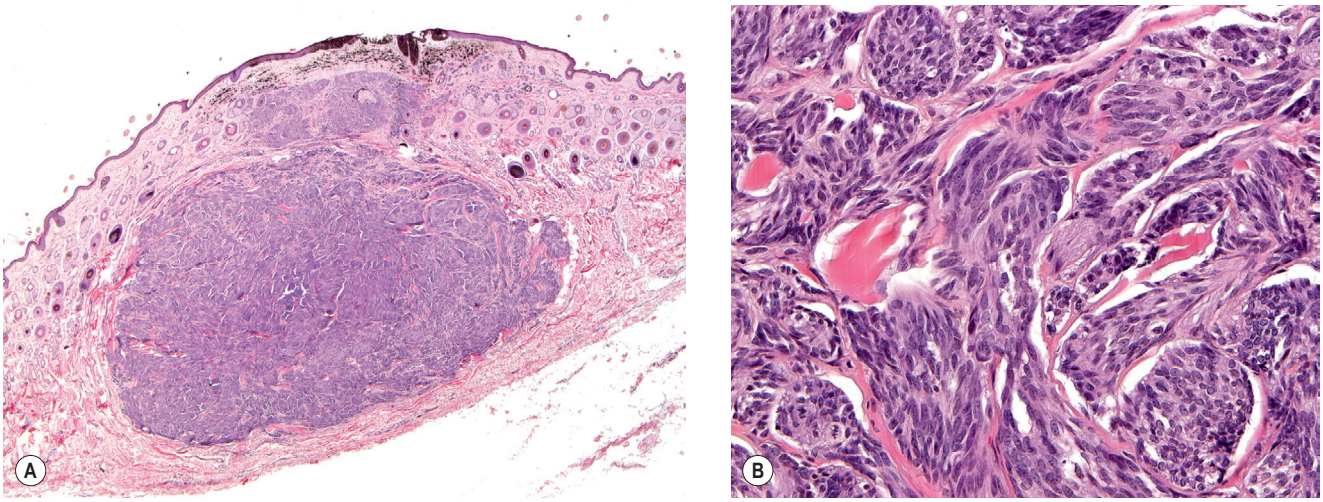


Figure 13.4 Cellular blue naevus (CBN). (A) A typical mass located predominantly in the deep dermis (H&E, ×12.5). **(B)** Interlacing fascicular bundles of spindle-shaped tumour cells (the circular fascicles are those cut in cross-section). In this case, the cells are not highly pigmented (H&E, ×200). *(Histological slide courtesy of Professor Brian Summers, Royal Veterinary College, University of London, UK.)*

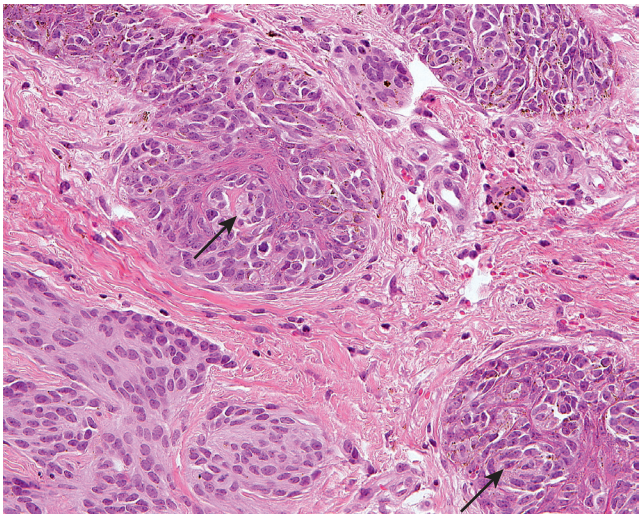


Figure 13.5 Combined cellular blue naevus (CCBN). There are numerous nests of round tumour cells within the hyperplastic epidermis (arrows) in addition to spindle-shaped to polygonal tumour cells in the underlying dermis (on the lower left) (H&E, ×200). *(Histological slide courtesy of Professor Brian Summers, Royal Veterinary College, University of London, UK.)*

Combined cellular blue naevus (CCBN)

In the one described case, the histological appearance was similar to that of CBN lesions. However, it was defined as a CBN combined with a junctional CMN-like tumour due to the presence of tumour cell nests within the basal epidermis (Fig. 13.5).[2] The intraepidermal tumour cells were round and pigmented.

Dermal melanomas and melanomatosis

These melanomas may be intradermal (deep dermal) and/or subcutaneous and have variably well-defined margins, with pseudo-encapsulation in some cases.[55] Dermal–epidermal junctional activity was not noted in one study of 27 melanomas from grey horses; however, it can occur (Fig. 13.6).[55] Tumour cells are variable in size, spindle-shaped, epithelioid, balloon-cell or mixed epithelioid and spindle-shaped, and contain variable amounts of melanin pigment; this pigmentation is often dense (see Fig. 13.6).[1,11,55] They are arranged in sheets or packets. A Fontana–Masson stain can be used to identify melanin in neoplasms that are poorly pigmented. Nuclei are round and variable in size, but may be large with a prominent nucleolus.[46] Numbers of mitotic figures are highly variable between different masses, but often most prominent at the margins.[55] Small tumour cells in some masses can be difficult to identify between large numbers of melanophages that are heavily pigmented.[1] Associated changes can include tumour necrosis, and intravascular tumour emboli (see Fig. 13.6). Assessment of malignancy should take into account multiple histological features, as discussed above.

Anaplastic malignant melanomas

Anaplastic malignant melanomas have poorly-defined margins and are infiltrative. Tumour cells are arranged in sheets, cords, nests or packets, supported by a fine fibrovascular stroma, and pseudoacini have also been noted. There may be widespread epidermal invasion by poorly-pigmented tumour cells occurring either singly or in small nests (junctional activity).[1,55] The tumour cells may be epithelioid, spindle-shaped or mixed, with a small to large amount of eosinophilic cytoplasm that is variably (including poorly) pigmented and has well-defined margins. The degree of pigmentation can vary significantly within the same mass, and rare amelanotic masses have been reported.[32] Some tumour cells may contain large intracytoplasmic vacuoles. Nuclei are large and hypochromatic, may be irregularly-shaped and may contain multiple nucleoli. There is marked pleomorphism with a variable but potentially high mitotic rate, and multinucleate tumour giant cells may be noted (see Fig. 13.6E). There may also be evidence of vascular invasion by tumour cells. Associated lesions may include lymphoplasmacytic infiltrates and epidermal ulceration.[55]

Immunohistochemical labelling

Melanoma cells should show positive labelling for the nonspecific markers vimentin and S100 but are *usually*

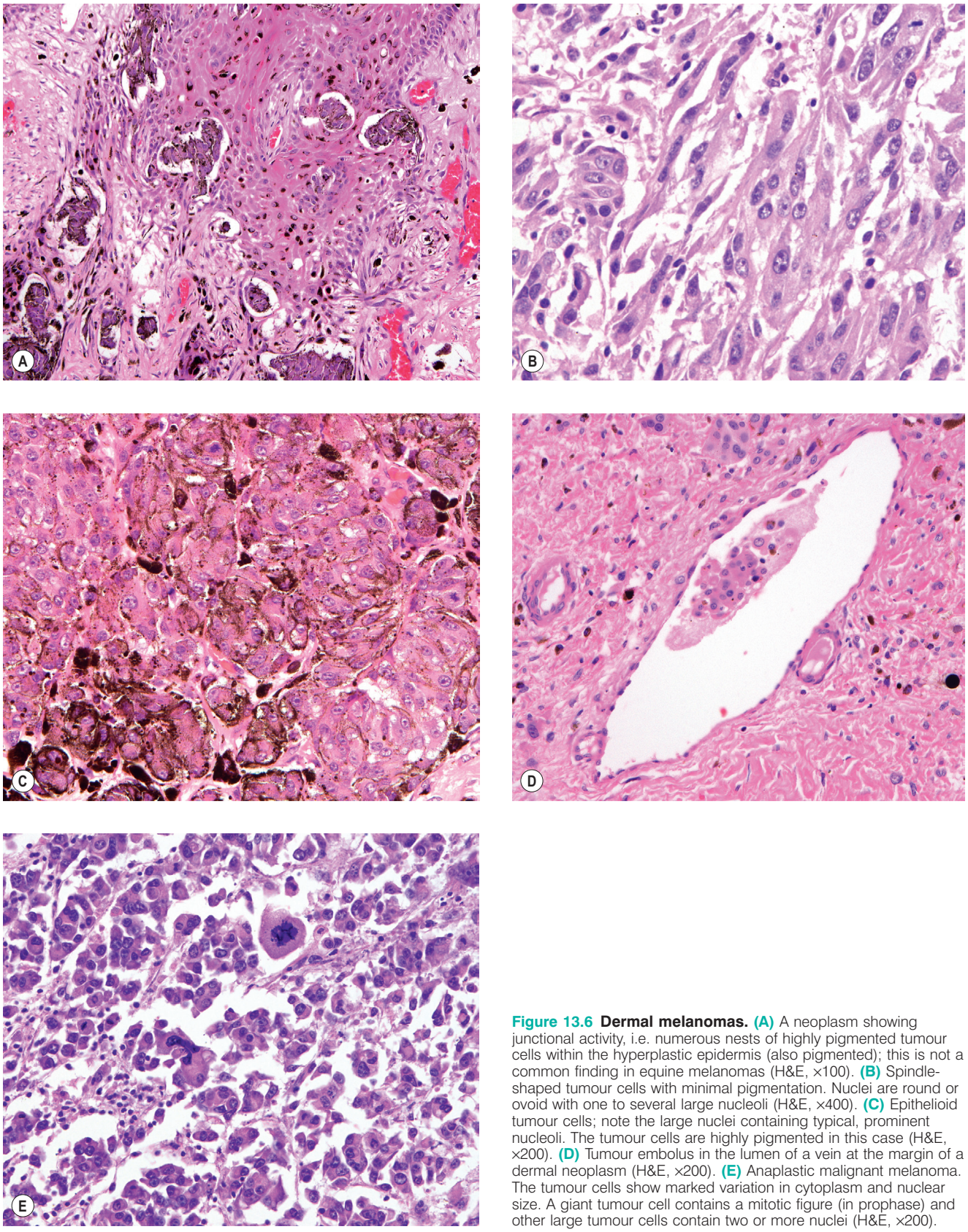


Figure 13.6 Dermal melanomas. (A) A neoplasm showing junctional activity, i.e. numerous nests of highly pigmented tumour cells within the hyperplastic epidermis (also pigmented); this is not a common finding in equine melanomas (H&E, ×100). **(B)** Spindle-shaped tumour cells with minimal pigmentation. Nuclei are round or ovoid with one to several large nucleoli (H&E, ×400). **(C)** Epithelioid tumour cells; note the large nuclei containing typical, prominent nucleoli. The tumour cells are highly pigmented in this case (H&E, ×200). **(D)** Tumour embolus in the lumen of a vein at the margin of a dermal neoplasm (H&E, ×200). **(E)** Anaplastic malignant melanoma. The tumour cells show marked variation in cytoplasm and nuclear size. A giant tumour cell contains a mitotic figure (in prophase) and other large tumour cells contain two or more nuclei (H&E, ×200).

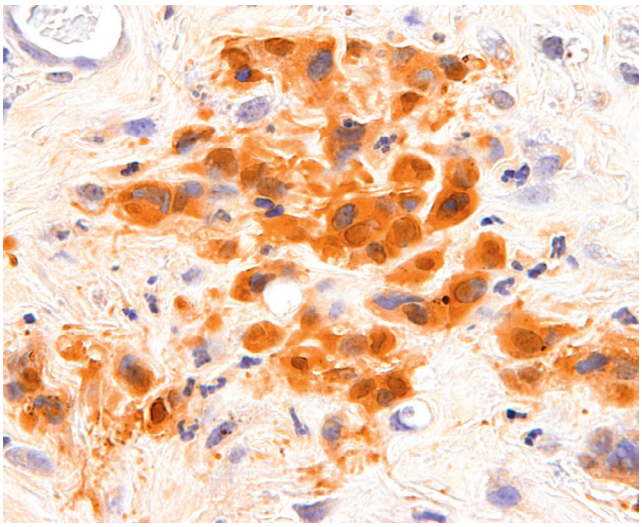


Figure 13.7 Intradermal common melanocytic naevus. Most of the tumour cells show strong positive cytoplasmic and nuclear labelling for S100 (immunohistochemistry, ×400). *(Histological slide courtesy of Professor Brian Summers, Royal Veterinary College, University of London, UK.)*

cytokeratin-negative. Neuron-specific enolase (NSE) is often used but is also not specific, and not all neoplasms will be positive.[14] In a study of equine melanocytic naevi, intradermal common melanocytic naevi were S100 positive (cytoplasmic more than nuclear), cytokeratin-negative and glycoprotein 100-negative, and cellular blue naevi were S100 positive (cytoplasmic more than nuclear) (Fig. 13.7).[2] The HMB45 antibody detects glycoprotein 100, a premelanosomal antigen that is usually expressed in melanomas as opposed to naevi.

Dermal melanomas and anaplastic melanomas have shown positive labelling with HMB45, with higher levels in malignant tumours.[55] In the same study, malignant melanomas showed (elevated) positive labelling for tyrosinase (T-311 antibody), and both benign and malignant tumours were CD44-positive. CD44, i.e. extracellular matrix receptor type III, is thought to play a role in facilitation of melanoma metastasis.[16]

Positive labelling of equine melanocytic tumours for Melan-A has not been reported.[32] In one case where a melanoma was negative for this marker, normal melanocytes in the skin did show positive labelling.[14]

In a study in which benign and malignant equine melanomas were compared, the malignant tumours did not show any difference in proliferation indices, as assessed by positive Ki-67 or PCNA labelling; however, apoptotic cells were only seen in the malignant masses.[22]

Electron microscopy

Melanosomes may be primary or secondary, the latter being lysosomes extruded by melanocytes and taken up by keratinocytes or macrophages. True melanosomes usually have cross-striations, and tumour cells may contain aberrant melanosomes.[16]

Differential diagnoses

These are listed in Box 13.1.

Box 13.1 Differential diagnoses for melanocytic neoplasms

Neoplastic
- Sarcoid
- Papilloma
- Squamous cell carcinoma
- Mast cell tumour
- Fibroma, fibrosarcoma, peripheral nerve sheath tumour
- Lymphosarcoma
- Medulloepithelioma (intraocular)

Non-neoplastic
- Inflammatory lesions, including granulomas
- Ocular: uveal or iris cysts, hyperplasia of the corpora nigra, iris colobomata, iridal trauma, uveitis
- Melanotic hamartoma: a single case report identified large numbers of melanocytes in the meninges and extending within connective tissue into the medulla that was diagnosed in the hindbrain of a 3.5-year-old cob-type gelding[56]

References

1. Valentine BA. Equine melanocytic tumours: a retrospective study of 53 horses (1988 to 1991). J Vet Intern Med 1995; 9:291–297.
2. Schöniger S, Summers BA. Equine skin tumours in 20 horses resembling three variants of human melanocytic naevi. Vet Dermatol 2009; 20:165–173.
3. McFadyean J. Equine melanomatosis. J Comp Pathol Ther 1933; 46: 186–204.
4. Fleury C, Bérard F, Leblond A, et al. The study of cutaneous melanomas in Camargue-type gray-skinned horses (2): epidemiological survey. Pigment Cell Res 2000; 13:47–51.
5. Rodriguez F, Forga J, Herráez P, et al. Metastatic melanoma causing spinal cord compression in a horse. Vet Rec 1998; 142:248–249.
6. Lerner AB, Cage GW. Melanomas in horses. Yale J Biol Med 1973; 46:646–649.
7. Seltenhammer MH, Simhofer H, Scherzer S, et al. Equine melanoma in a population of 296 grey Lipizzaner horses. Equine Vet J 2003; 35:153–157.
8. Caston SS, Fales-Williams A. Primary malignant melanoma in the oesophagus of a foal. Equine Vet Educ 2010; 22:387–390.
9. Hamilton DP, Byerly CS. Congenital malignant melanoma in a foal. J Am Vet Med Assoc 1974; 164:1040–1041.
10. Cox JH, DeBowes RM, Leipold HW. Congenital malignant melanoma in two foals. J Am Vet Med Assoc 1989; 194:945–947.
11. Foley GL, Valentine BA, Kincaid AL. Congenital and acquired melanocytomas (benign melanomas) in eighteen young horses. Vet Pathol 1991; 28:363–369.
12. McMullen RJ, Clode AB, Pandiri AKR, et al. Epibulbar melanoma in a foal. Vet Ophthalmol 2008; 11:44–50.
13. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
14. LeRoy BE, Knight MC, Eggleston R, et al. Tail-base mass from a 'horse of a different colour'. J Am Vet Med Assoc 2005; 34:69–71.
15. Rowe EL, Sullins KE. Excision as treatment of dermal melanomatosis in horses: 11 cases (1994–2000). J Am Vet Med Assoc 2004; 225:94–96.
16. Smith SH, Goldschmidt MH, McManus PM. A comparative review of melanocytic neoplasms. Vet Pathol 2002; 39:651–678.
17. Dugan SJ. Ocular neoplasia. Vet Clin North Am Equine Pract 1992; 8:609–626.
18. Mangrulkar MY. Melanomata in domesticated animals. Indian J Vet Sci 1944; 14:178–185.
19. Levene A. Equine melanotic disease. Tumori 1971; 57:133–168.
20. Pielberg GR, Golovko A, Sundström E, et al. A cis-acting regulatory mutation causes premature hair graying and susceptibility to melanoma in the horse. Nat Genet 2008; 40:1004–1009.
21. Zhang Q, Li J, Deavers M, et al. The subcellular localisation of syntaxin 17 varies among different cell types and is altered in some malignant cells. J Histochem Cytochem 2005; 53:1371–1382.
22. Roels S TK, Van Daele A, Van Marck E, et al. Proliferation, DNA ploidy, p53 overexpression and nuclear DNA fragmentation in six equine melanocytic tumours. J Vet Med A Physiol Pathol Clin Med 2000; 47:439–448.
23. Thamm DH, Ehrhart EJ, Charles JB, et al. Cyclooxygenase-2 expression in equine tumours. Vet Pathol 2008; 45:825–828.
24. Bastianello S. A survey on neoplasia in domestic species over a 40-year period from 1935 to 1974 in the Republic of South Africa. IV. Tumours occurring in Equidae. Onderstepoort J Vet Res 1983; 50:91–96.
25. Priester WA, MacKay FW. The occurrence of tumours in domestic animals. Natl Cancer Inst Monogr 1980; 54:1–210.
26. Kunze DJ, Monticello TM, Jakob TP, et al. Malignant melanoma of the coronary band in a horse. J Am Vet Med Assoc 1986; 188:297–298.
27. Honnas CM, Liskey CC, Meagher DM, et al. Malignant melanoma in the foot of a horse. J Am Vet Med Assoc 1990; 197:756–758.

28. Kirker-Head CA, Loeffler D, Held JP. Pelvic limb lameness due to malignant melanoma in a horse. J Am Vet Med Assoc 1985; 186:1215–1217.
29. Kamposioras K, Pentheroudakis G, Pectasides D, et al. Malignant melanoma of unknown primary site. To make the long story short. A systematic review of the literature. Crit Rev Oncol Hematol 2011; 78:112–126.
30. Baptiste KE, Moll HD, Robertson JL. Three horses with neoplasia including growth in the guttural pouch. Can Vet J 1996; 37:499–501.
31. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 2: A contribution of 28 case reports. Vet J 1999; 157:279–294.
32. Tyler RJ, Fox RI. Nasopharyngeal malignant amelanotic melanoma in a gelding age 9 years. Equine Vet Educ 2003; 15:19–26.
33. Pascoe RR, O'Sullivan BM. Sudden death in a Thoroughbred stallion. Vet Clin North Am Equine Pract 1980; 12:211–212.
34. Murray MJ, Cavey DM, Feldman BF, et al. Signs of sympathetic denervation associated with a thoracic melanoma in a horse. J Vet Intern Med 1997; 11:199–203.
35. Barnett KC, Platt H. Intraocular melanomata in the horse. Equine Vet J Suppl 1990; 10:76–82.
36. Ramadan RO. Primary ocular melanoma in a young horse. Equine Vet J 1975; 7:49–50.
37. Murphy J, Young S. Intraocular melanoma in a horse. Vet Pathol 1979; 16:539–542.
38. Latimer CA, Wyman M. Sector iridectomy in the management of iris melanoma in a horse. Equine Vet J 1983; 2:101–104.
39. Davidson HJ, Blanchard GL, Wheeler CA, et al. Anterior uveal melanoma, with secondary keratitis, cataract, and glaucoma, in a horse. J Am Vet Med Assoc 1991; 199:1049–1050.
40. Moore CP, Collins BK, Linton LL, et al. Conjunctival malignant melanoma in a horse. Vet Ophthalmol 2000; 3:201–206.
41. Cutler TJ. Corneal epithelial disease. Vet Clin North Am Equine Pract 2004; 20:319–343.
42. Scotty NC, Barrie KB, Brooks DE, et al. Surgical management of a progressive iris melanocytoma in a Mustang. Vet Ophthalmol 2008; 11:75–80.
43. Matthews AG, Barry DR. Bilateral melanoma of the iris in a horse. Equine Vet J 1987; 19:358–360.
44. Sweeney CR, Beech J. Retrobulbar melanoma in a horse. Equine Vet J 1983; 15:123–124.
45. Hirst LW, Jabs DA, Stoskopf M, et al. Benign epibulbar melanocytoma in a horse. J Am Vet Med Assoc 1983; 183:333–334.
46. MacGillivray KC, Sweeney RW, Del Piero F. Metastatic melanoma in horses. J Vet Intern Med 2002; 16:452–456.
47. Johnson PJ. Dermatologic tumors (excluding sarcoids). Vet Clin North Am Equine Pract 1998; 14:625–658.
48. Patterson-Kane JC, Sanchez LC, Uhl EW, et al. Disseminated metastatic intramedullary melanoma in an aged grey horse. J Comp Pathol 2001; 125:204–207.
49. Traver DS, Moore JN, Thornburg LP, et al. Epidural melanoma causing posterior paresis in a horse. J Am Vet Med Assoc 1977; 170:1400–1403.
50. Grant B, Lincoln S. Melanosarcoma as a cause of lameness in a horse. Vet Med Small Anim Clin 1972; 67:995–998.
51. Schott HC, Major MD, Grant BD, et al. Melanoma as a cause of spinal cord compression in two horses. J Am Vet Med Assoc 1990; 96:1820–1822.
52. Covington AL, Magdesian KG, Madigan JE, et al. Recurrent oesophageal obstruction and dysphagia due to a brainstem melanoma in a horse. J Vet Intern Med 2004; 18:245–247.
53. Tarrant J, Stokol T, Bartol J, et al. Diagnosis of malignant melanoma in a horse from cytology of body cavity fluid and blood. Equine Vet J 2001; 33: 531–535.
54. Garvican ER, Elce YA, Woolard K, et al. Preputial melanoma with systemic metastasis in a pony gelding and disseminated metastatic melanoma in a Thoroughbred gelding. Equine Vet Educ 2007; 19:312–315.
55. Seltenhammer MH, Heere-Ress E, Brandt S, et al. Comparative histopathology of grey-horse-melanoma and human malignant melanoma. Pigment Cell Res 2004; 17:674–681.
56. Mair TS, Pearson GR. Melanotic hamartoma of the hind brain in a riding horse. J Comp Pathol 1990; 102:239–243.

14

Other epithelial neoplasms: cutaneous, mucocutaneous and ocular adnexal

Skin and ocular adnexa
Viral squamous papilloma 247
Non-viral squamous papilloma and fibropapilloma 249
Basal cell tumour (trichoblastoma) 252
Trichoepithelioma 253
Epitrichial (apocrine) sweat gland adenoma and carcinoma 254
Sebaceous gland adenoma and carcinoma 254
Adenocarcinoma and carcinoma of the nictitating membrane gland 255
Keratoma 256
Sinonasal
Squamous cell carcinoma 257
Adenoma 257
Adenocarcinoma 257
Non-neoplastic nasal masses 258
Salivary glands
Adenoma and adenocarcinoma 260
Mammary glands
Adenocarcinoma, carcinoma and adenoma 260
Thorax
Thymoma 263
Pulmonary adenocarcinoma, carcinoma and adenoma 263
Abdomen (excluding the urogenital tract)
Gastric and oesophageal squamous cell carcinoma 265
Intestinal adenoma 265
Gastric or intestinal adenocarcinoma 265
Exocrine pancreatic adenocarcinoma 267
Hepatocellular carcinoma and adenoma 268
Hepatoblastoma 270
Cholangiocellular carcinoma 270
Biliary adenofibroma (biliary cystadenoma/cholangioma) 271
Urogenital tract
Renal carcinoma and adenoma 271
Urinary bladder transitional carcinoma and adenoma 273
Ovarian cystadenoma (serous cystadenoma) 274
Ovarian cystadenocarcinoma and adenocarcinoma 275
Oviductal adenoma 276
Endometrial adenocarcinoma 276

SKIN AND OCULAR ADNEXA

Viral squamous papilloma

Cellular origin

Stratum basale of the epidermis/epithelium.

Profile

These are benign neoplasms caused by equine papillomaviruses. They are considered to be very common, but as specimens are not commonly submitted for histological diagnosis, the true prevalence has not been confirmed. Forms of this disease include warts ('grass warts', verrucae, cutaneous papilloma), genital papilloma, aural plaques (equine ear papilloma) and congenital papilloma.

Warts typically occur in young horses aged 9 months to 3 years that are out at grass (hence the colloquial name 'grass warts'). More rarely, adult horses can be affected.[1,2]

Genital papilloma are infrequent lesions that tend to occur in older horses (13–28 years)[3]; the mean ages for warts and genital papillomas are 4 and 17 years, respectively.[4]

Aural 'plaques' are common lesions and can occur in any horse over 1 year of age.

Congenital papillomas have been reported on rare occasions in mules and horses, in both aborted fetuses and newborn foals.[5] Of 555 cutaneous tumours received over a 10-year period by a Canadian pathology laboratory, four cases were documented (with one additional case after that period).[6] Five further cases were documented in foals ranging in age from 6 months' gestation to 2 days, in a survey conducted at Cornell University.[5,7]

There are no apparent breed, coat colour or gender predilections for any of these types of papilloma.[3]

Oncogenesis

Warts are associated with equine papillomavirus 1 (EcPV1). Sequenced viruses from penile papillomas and aural plaques, respectively, have been designated EcPV2 and EcPV3.[8] Differences in L1 gene sequences between

EcPV1, EcPV2 and EcPV3 are significant enough to suggest that they belong to different genera, although they are phylogenetically clustered. EcPV1 belongs in the genus *Zetapapillomavirus* and EcPV2 in the genus *Dyoiotapapillomavirus*.[9]

In early experimental studies, papillomas were induced in horses by injection of ground papilloma material and cell-free extracts.[10,11] Papillomaviruses infect the epidermal stratum basale following inoculation, or entry into areas that have lost epidermal integrity as result of trauma or other causes (e.g. dermatitis).[12]

The virus is transmissible between horses either directly or via fomites; this is supported by occurrence in horses sharing housing, feed and/or water containers and by annual recurrence on infected properties (in subsequent offspring). There may also be sexual transmission.

An association between aural plaques and black flies (*Simulium* sp.) has been suggested, as they were frequently observed feeding within ears of affected horses; certainly the flies may serve as a viral vector and are known to irritate the plaques.[13,14] In congenital cases, it has been theorized that there was transplacental papillomavirus infection due to latent infection of the mare. However, in one case series, immunohistochemical labelling for viral antigens was negative.[5] It is therefore possible that at least some congenital papillomas of equines are actually best regarded as hamartomas (benign focal overgrowths of normal tissue); non-viral lesions in children have been suggested to result from either a cutaneous developmental abnormality or from attachment of the amnion to the epidermis during gestation.

There are three phases of papilloma development:

1. Growth
2. Development – certain forms
3. Regression (see Histopathology, below).

Biological behaviour

Warts usually appear suddenly in small numbers, but multiply rapidly, often coalescing over wide areas, within a 39–54-day period.[3,15] They are typically self-limiting within 1–9 months (usually 3–6), in horses that have normal immune function.[2,15] Most immature horses develop complete immunity and there is usually no recurrence. When the condition develops in adult horses, there is far less tendency to spontaneous regression.

Equine genital papillomas rarely undergo spontaneous regression. Occasional progression to squamous cell carcinoma (SCC) occurs and it is therefore advisable to obtain biopsy specimens from such cases for histological examination. In an aged Quarter Horse mare, lesions of SCC in situ (SCCIS; pp. 220–221) were found within vulvar papilloma tissue.[16] A 9-year-old horse was diagnosed with penile viral papillomatosis, with lesions covering more than two-thirds of the free part of the penis distal to the preputial ring, including the glans. This did not resolve over >2 years and was associated with persistent EcPV2 infection, without evidence of progression to SCC.[17] This interesting case suggests that persistent EcPV2 infection alone is not sufficient for progression.

Aural plaques do not spontaneously regress and have not been reported to progress to malignancy.[13,14]

Congenital papillomas do not usually undergo spontaneous regression, and surgical removal is frequently required.

Gross pathology

Warts occur most frequently on the muzzle, nose and commissures of the lips (see Fig. 3.10A). Less common sites (or sites to which lesions extend in more severe cases) include other areas of the face (including eyelids), neck, distal limbs, thorax and male and female genitalia.[2] They have *not* been reported to occur in the oral cavity.[18] Warts are variable in number (<10 to >100), depending on the stage of the disease. They may form coalescing clusters measuring up to 2–10 cm in diameter; in one study, these large clusters were only found on the head.[2] Individual warts start as 1 mm diameter, smooth, grey-white papules and grow to 5–20 mm diameter, at which stage they are hyperkeratotic, may be broad-based or pedunculated and are highly variable in colour (including white, pink, grey or black).[3,19] Solitary papillomas are rare and measure up to 10 mm diameter.[19] During regression, a slight colour change to a 'pinkish hue' has been noted.[2]

Genital papillomas also vary significantly in number, with one report of approximately 100 masses.[9] They may measure up to 2 cm in diameter, may be smooth-surfaced or papillary and often broad-based; some may form keratinized horns. Non-viral papillomas may also occur in these locations (p. 250).

Aural plaques preferentially involve inner surfaces of one or both pinnae.[13] Similar lesions have been reported less frequently on the external genitalia and in perianal locations.[14] The distribution of the lesions corresponds to insect transmission (probably through *Simulium* sp.), that have a preference for feeding from the inner pinnal skin and the skin of the sheath and medial thigh. Aural plaques are solitary or multiple lesions that are bilaterally symmetrical. They begin as 1–2 mm diameter papules that enlarge (to 1–3 cm diameter), coalesce and become hyperkeratotic; they are usually not pigmented and have broad-based attachment and flat surfaces.[3,19]

Congenital papillomas have been identified on the forehead, nostril, lower lip, thorax, rump and hindlimb.[5–7,20–22] They range in size (1 × 1.5 to 5 × 33 cm), are usually pedunculated and intensely pigmented and either papillary or smooth-surfaced.[5,6,20,21]

All papillomas are easily traumatized and may be eroded, ulcerated and/or prone to bleeding.

Histopathology

The histological changes during growth, development and regression of naturally occurring warts have been described in detail.[12,23,24]

Growth phase

There is swelling and hyperplasia of basal epidermal cells and hair follicle external root sheath cells. This is followed by epidermal acanthosis, with orthokeratotic and parakeratotic (i.e. nucleated) hyperkeratosis. Acanthosis is defined as increased thickness of the stratum spinosum due to hyperplasia (and occasionally also hypertrophy) of

those cells and hyperkeratosis as increased thickness of the stratum corneum.[24] Basophilic viral intranuclear inclusion bodies may be seen in cells of the outer stratum spinosum, the stratum granulosum and cornified layers, but not the stratum basale. Small numbers of swollen cells with a pale cytoplasm and irregularly-shaped enlarged nuclei containing multiple nucleoli are scattered in the stratum spinosum. The stratum basale is depleted of melanin pigment, but some may still be present in keratinocytes in suprabasal layers.[25] Mild lymphocytic inflammatory cell infiltrates may be noted in adjacent dermal tissue.

Development phase

Papillated hyperplasia of the epidermis occurs, i.e. thickening with formation of digitated projections from the surface.[24] The basal layer is hyperplastic and folded with formation of numerous long rete pegs (epidermal projections into the underlying connective tissue). There may also be hypertrophy of basal cells and an increase in mitotic figures – this should not be mistaken for malignant transformation.[20] There is ballooning degeneration of cells in the outer stratum spinosum and stratum granulosum; these cells with their eccentric, pyknotic nuclei are known as koilocytes. Koilocytes vary in number and may occur singly or in clusters of 2–4 cells.[5,26] More frequently, superficial keratinocytes may have swollen basophilic to grey cytoplasm and large nuclei with margination of the chromatin.[23] Keratinocytes in spinous and granular layers can contain viral intranuclear inclusion bodies, but they will not necessarily be numerous.[24] There are enlarged, irregularly-shaped eosinophilic keratohyalin granules in the stratum granulosum. There is more pronounced hypopigmentation relative to the growth phase, with no melanin pigment in any epidermal cell layer.[25] Epidermal Langerhans cells (LC) are markedly reduced in number and size; these cells usually function to modulate cutaneous immune responses, including antigen presentation via the Class II major histocompatibility complex (MHC) pathway.[27] In the dermis, there are infiltrates of lymphocytes and macrophages, with oedema, capillary dilation and fibroblastic proliferation.[12] Superficial erosion or ulceration may occur, with associated inflammation and secondary bacterial colonization.

Regression phase

The epidermis regains a relatively normal appearance including pigmentation, sometimes with mild hyperplasia and retention of rete pegs. The LC are markedly increased in number, particularly at the epidermal–dermal junction, with their ultrastructural appearance indicating high activity; this finding in conjunction with infiltrates of T lymphocytes indicates a cell-mediated immune response.[27] In the dermis, lymphohistiocytic infiltrates and fibroblastic proliferation are still noted.[27]

Genital papillomas have been described as well-demarcated areas of epidermal hyperplasia and hyperkeratosis, with scattered koilocytes and some swollen keratinocytes containing giant keratohyalin granules and occasional eosinophilic intranuclear viral inclusion bodies (Fig. 14.1).[17] There is formation of rete pegs and there may be superficial papillary epidermal projections; dermal lymphoid infiltrates are also noted.

Aural plaques are also similar histologically, but the epidermal hyperplasia is not as significantly papillated and hypopigmentation is a striking feature.[3]

Congenital lesions also have a hyperplastic epidermis forming multiple, branching short rete pegs with variably extensive vacuolation of stratum spinosum cells (and in some cases, associated hair follicles and/or sebaceous glands) and mild to marked, orthokeratotic or parakeratotic hyperkeratosis.[6] There is variable melanin pigmentation of the stratum basale, but it can be increased. The supporting fibrovascular stroma does not show evidence of fibroblastic proliferation and inflammatory changes are rare. In the Cornell University study of five congenital papillomas in which viral antigen was *not* identified (p. 248), there were no koilocytes or abnormal keratohyalin granules (as would be expected in a virally-induced lesion).[5]

Immunohistochemical labelling

In 45 papillomas from various anatomical locations (genital, cutaneous, ocular, oral), seven cutaneous masses and five genital lesions were positive for papillomavirus structural antigens, with positive epidermal nuclei including those of cells in the stratum granulosum.[28] Genital papillomas in one case showed positive immunolabelling for papillomavirus antigen in nuclei of swollen keratinocytes in the stratum granulosum (see Fig. 14.1); papillomavirus DNA was identified in the same cells by in situ hybridization.[17] Papillomavirus antigen has also been demonstrated by immunohistochemical labelling of aural plaques, being located in nuclei of koilocytes and cells in the stratum corneum.[26]

Electron microscopy

Viral inclusions have been noted in nuclei of cells in the stratum granulosum of warts, with scattered viral particles in stratum spinosum nuclei and extracellular aggregates in surface keratin debris.[1] Toluidine blue-positive intracytoplasmic inclusions noted histologically in the stratum granulosum and spinosum were electron-dense inclusions not limited by a membrane and were proposed to be an aberrant form of keratohyalin.[1] Melanocytes have been shown to contain degenerate melanogenic organelles, with reductions in number and size of melanosomes and some giant melanosomes; this correlates with the hypopigmentation seen histologically.[25]

Differential diagnoses

These are listed in Box 14.1.

Non-viral squamous papilloma and fibropapilloma

Cellular origin

Epidermis/epithelium. In fibropapillomas, proliferating dermal fibroblasts predominate. Non-viral papillomatous lesions are not necessarily neoplastic.[23]

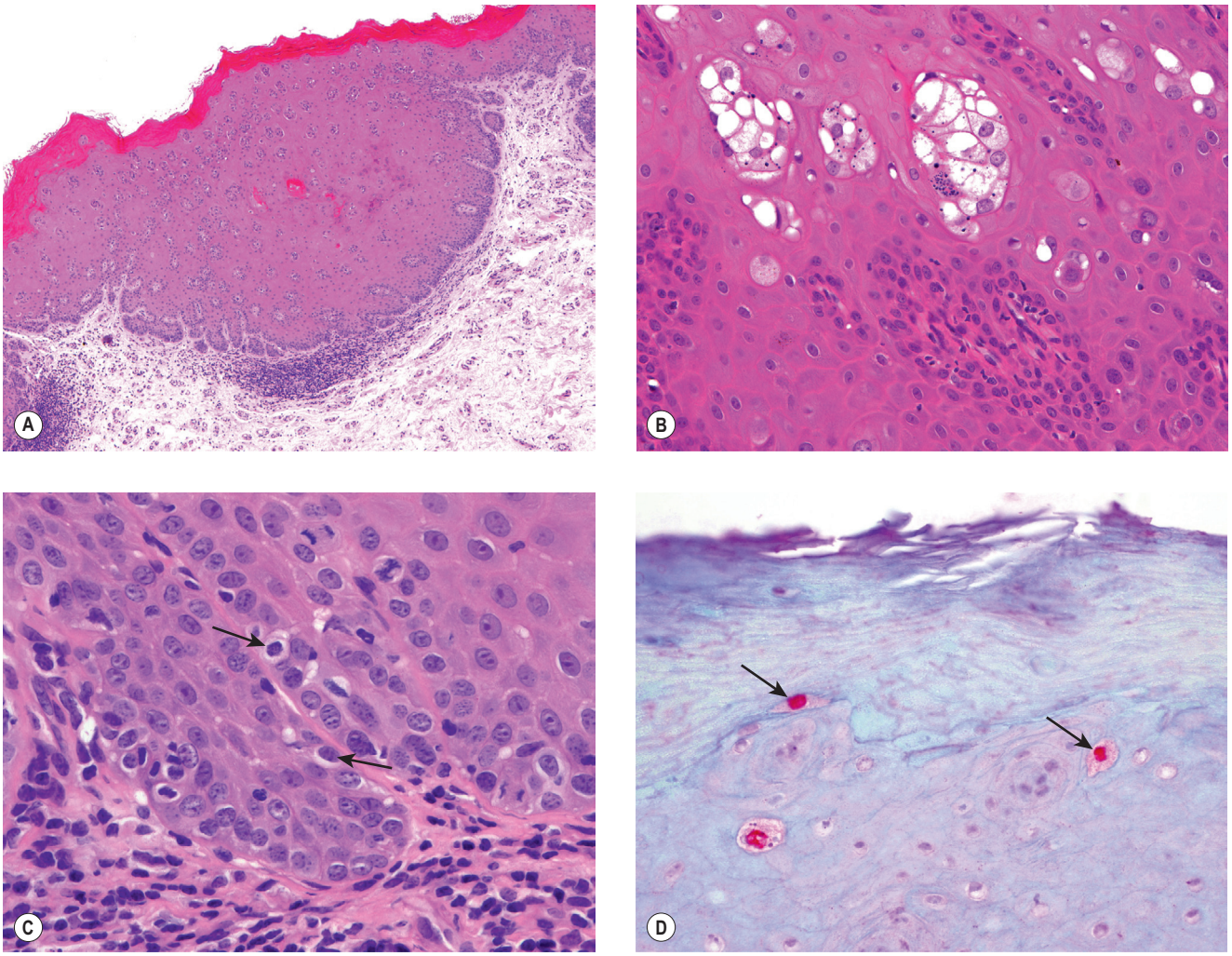


Figure 14.1 Histological appearance of viral genital papillomas. **(A)** Marked epidermal hyperplasia with orthokeratotic hyperkeratosis, formation of broad, often branching rete pegs into the subjacent dermis and prominent subepidermal lymphocytic inflammatory cell infiltrates. The dermis is oedematous (H&E, ×40). **(B)** Swollen epidermal cells in the stratum granulosum containing giant keratohyalin granules (H&E, ×200). **(C)** The dermal–epidermal junction, with hyperplasia of the basal cells (some of which contain mitotic figures) that are forming rete pegs and are not breaching the basement membrane. Some of the basal cells have a pale-staining or clear, slightly swollen cytoplasm (arrows) (H&E, ×400). **(D)** Demonstration of papillomavirus antigen in nuclei of swollen epidermal cells in a penile papilloma, by immunohistochemical labelling (arrows). *(Courtesy of Dr Cameron Knight, Faculty of Veterinary Medicine, University of Calgary and Dr Matti Kiupel, College of Veterinary Medicine, Michigan State University; reprinted from Knight et al. Veterinary Dermatology 2011; 22(6):570–574 (Fig. 2c)).*[17]

Box 14.1 Differential diagnoses for viral squamous papilloma

Neoplastic
- Verrucose sarcoid
- Non-viral papilloma
- Squamous cell carcinoma
- Verrucous haemangioma

Non-neoplastic
- Dermatophytosis
- Dermatophilosis
- Traumatic lesion
- Exuberant granulation tissue

Profile

In a UK survey of neoplasms of the male external genitalia of horses ($n = 48$), 32% were squamous papillomas (the viral status was not investigated).[29] In a small study of genital papillomas of this type ($n = 21$), they were found to be more common in males (mean age 11.6 years) than females (mean age 8.7 years) and papillomavirus antigen was not found in all of them.[28] There has been a report of multiple fibropapillomas of the glans penis in an 18-year-old stallion, that were papillomavirus-negative.[30]

Oncogenesis

Solitary papillomas are more likely to have a non-viral aetiology, as are those in non-genital sites of old horses.[28] Non-infectious irritants are one possible cause.

Biological behaviour

Squamous papillomas are benign lesions; however, they are believed to be capable of malignant transformation to a squamous cell carcinoma (SCC) by some authors and in approximately one-third of cases are found in association

with an SCC.[29] Some horses have had a history of excision or biopsy of a papilloma that occurred some time before diagnosis and excision of an SCC at the same site.[29] Premalignant changes have been identified in 5/23 cases of squamous papilloma of the male genitalia (see below).[29,31] Any conclusions are complicated by whether papillomavirus infection is really involved or not.

Gross pathology

In older horses, squamous papillomas occur almost exclusively on the male or female external genitalia, including the penis, vulva, vestibule and clitoral fossa (see Fig. 3.10C).[31] In one study of 23 cases of squamous papilloma of male genitalia, 61% involved the glans penis, 26% the penile body and 13% the preputial mucosa.[29] They have also been reported on the eyelids and in the oral cavity.[18,32]

Squamous papillomas are papillary or plaque-like masses, measuring a few millimetres to several centimetres in diameter, that have a broadly similar macroscopic appearance to those of viral aetiology (p. 248–249). Multiple fibropapillomas of the glans penis in one stallion were smooth, exophytic nodules circumferentially surrounding the external orifice of the urethra.[30]

Histopathology

There is papillated, mild to severe hyperplasia of the epidermis that in many cases is well-differentiated and with normal organization; there may also be formation of rete ridges (Fig. 14.2). There should be no evidence of viral infection including koilocytes, viral inclusion bodies, blue-grey swollen cytoplasm, or abnormal keratohyalin granules. Compared with virus-induced lesions, the epithelial hyperplasia, hyperkeratosis and inflammatory changes are generally less severe.[23]

Fibropapillomas have more abundant supporting fibrovascular stroma with proliferating fibroblasts; unlike sarcoids, the fibroblastic cells do not palisade at the epithelial interface.[30] Inflammatory cells, including lymphocytes and plasma cells, may be noted in the stromal tissue.

Premalignant changes have been described as loss of polarity and an increased mitotic rate in basal cells of the hyperplastic epithelium, without invasion of the basement membrane (see Fig. 14.2)[29]; these are similar to lesions described as squamous cell carcinoma in situ (SCCIS; pp. 220–221). Due to the potential for malignant transformation, all squamous papillomas must be examined *carefully* by the pathologist for these intraepithelial abnormalities.

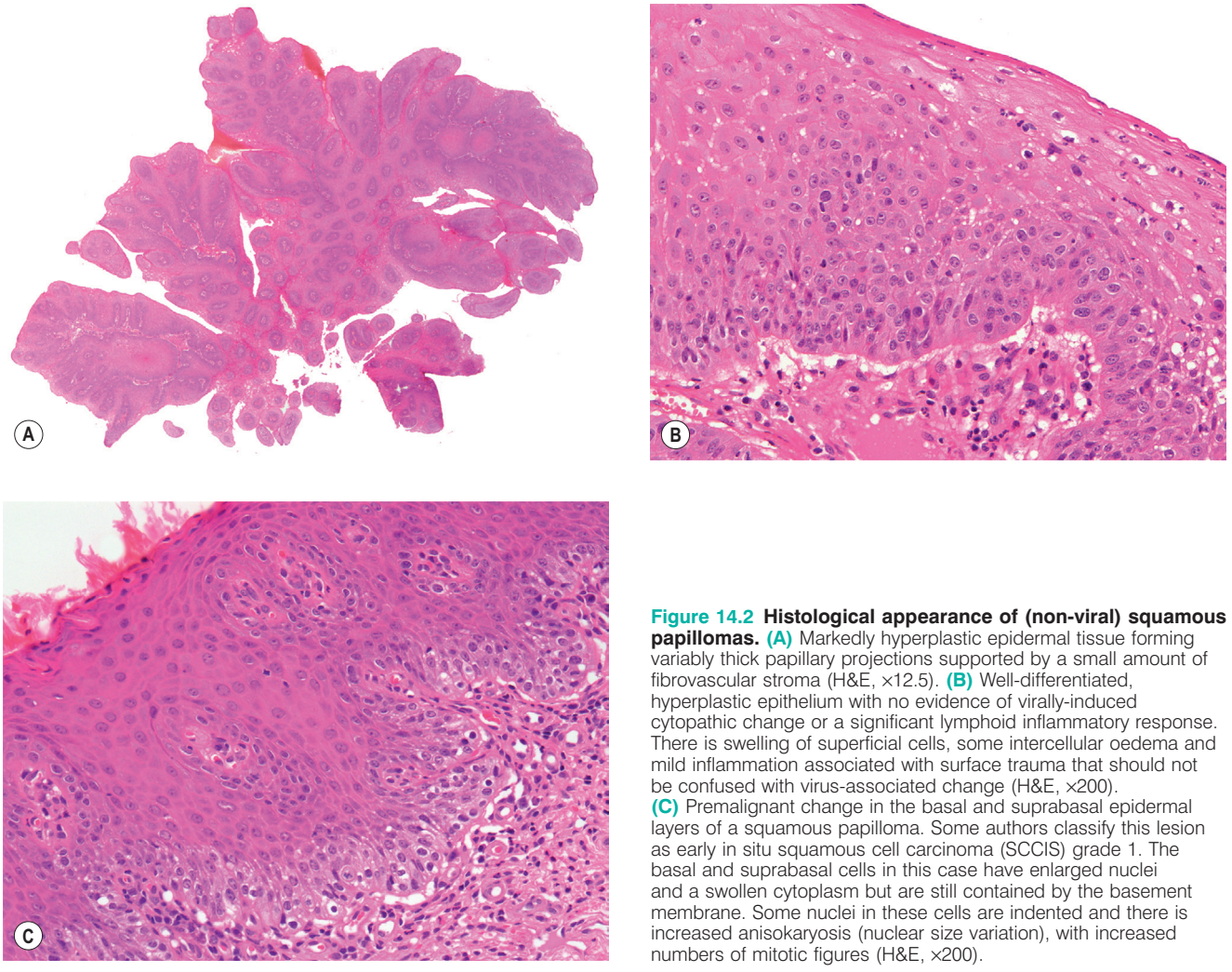


Figure 14.2 Histological appearance of (non-viral) squamous papillomas. **(A)** Markedly hyperplastic epidermal tissue forming variably thick papillary projections supported by a small amount of fibrovascular stroma (H&E, ×12.5). **(B)** Well-differentiated, hyperplastic epithelium with no evidence of virally-induced cytopathic change or a significant lymphoid inflammatory response. There is swelling of superficial cells, some intercellular oedema and mild inflammation associated with surface trauma that should not be confused with virus-associated change (H&E, ×200). **(C)** Premalignant change in the basal and suprabasal epidermal layers of a squamous papilloma. Some authors classify this lesion as early in situ squamous cell carcinoma (SCCIS) grade 1. The basal and suprabasal cells in this case have enlarged nuclei and a swollen cytoplasm but are still contained by the basement membrane. Some nuclei in these cells are indented and there is increased anisokaryosis (nuclear size variation), with increased numbers of mitotic figures (H&E, ×200).

Basal cell tumour (trichoblastoma)

Cellular origin

These tumours are derived from the basal (germinal) layer of the epidermis, hair follicles, or sebaceous glands. They have also been suggested to arise from dormant embryonic nests of cells (naevi) or the hair matrix (i.e. rapidly dividing epithelial cells around the hair follicle papilla). Some authors refer to these neoplasms as 'trichoblastomas'; histologically, many do have a similar appearance to trichoblastomas described in other species, in which the general term 'basal cell tumour' is no longer used.[23]

Profile

Basal cell tumours are rare in animals other than dogs and cats. In one study of equine cutaneous biopsy specimens (n=3,351) conducted in the USA, 1.2% were basal cell tumours.[33] They have been reported in horses 4–26 years of age, although mostly in animals ≥6 years.[34] There does not appear to be a gender predilection. In the previously mentioned survey, Morgans and ponies were more likely than other breeds to be diagnosed with this tumour type.[33]

Basal cell tumours in horses are most common on the distal limbs, trunk, face and neck.[3] There have been specific reports of this neoplasm involving the eyelids, nictitating membrane, commissure of the mouth, neck, trunk, limbs, prepuce, vulva and tail.[31,35–40] In a case series of six horses with basal cell tumours, five involved a distal extremity.[34]

Oncogenesis

There is no indication that ultraviolet radiation is a specific aetiological factor.

Biological behaviour

Basal cell tumours are benign neoplasms that may be present for weeks to months prior to presentation.[34,38] Recurrence has not been reported in horses following complete surgical excision; margins of at least 4–5 mm should be achieved.

A few cases have been described as malignant and are perhaps better diagnosed specifically as basal cell carcinoma[2,41]; a 14-year-old horse had a tumour involving the nictitating membrane, with extension into the retrobulbar tissue.[42]

Gross pathology

Basal cell tumours are usually solitary, freely movable, well-demarcated, raised, nodular or multinodular, firm dermal masses (Figs. 14.3 and 31.21). The overlying epidermis may be ulcerated, alopecic or hyperpigmented.[3] Basal cell tumours usually measure 0.5–5 cm in diameter, but masses up to 12 cm in diameter have been reported. They are firm and pale tan to brown on sectioned surfaces (with colour depending on the degree of melanization).

Histopathology

Basal cell tumours are symmetrical, well-circumscribed and occasionally lobulated. Direct connection with the epidermis may be noted in some masses.[34] Solid, adenoid and medusoid patterns have been described in horses, although this may be an academic exercise only, as these subtypes have not been correlated with biological behaviour in humans or animals.[34,38]

The solid pattern of arrangement is thought to be the most common,[3] in which packets of tumour cells are arranged in sheets that are less dense superficially. In the adenoid pattern, tumour cells are arranged in islands and coalescing bands (3–4 cells thick); the cells palisade around connective tissue strands, blood vessels and spaces containing eosinophilic material that may become large. In the medusoid pattern, tumour cells are arranged in compact central clusters with radiating arms or peripheral small clusters (see Fig. 14.3).[38] These centres can be necrotic with cholesterol clefts.

Tumour cells are predominantly basal in type with scanty cytoplasm that has poorly-defined margins and may, in some cases, contain melanin pigment. Spindle-shaped cells may be noted in the solid subtype; they can form whorls associated with hyalinized connective tissue, which resembles the hair follicle basement membrane. Spindle cells may also been seen in the medusoid subtype. Tumour cells with a clear cytoplasm may be noted; for example, at tips of radiating arms in the medusoid tumours (see Fig. 14.3). Prominent apocrine, sebaceous or squamous differentiation has not been reported in equine basal cell tumours, although in one medusoid tumour, there were structures suggestive of cystic apocrine glands and, in another, occasional sebaceous-type cells were noted.[34,38]

Nuclei are oval or round and pale, with granular chromatin and one to several nucleoli. Mitotic figures are usually abundant.

The surface is often ulcerated, with associated inflammation. The adjacent skin may be hyperkeratotic and form a prominent epidermal collarette.[38] Other associated lesions include lymphocytic infiltrates, either diffuse or multifocal and perivascular. There should only be concern regarding recurrence where an infiltrative margin is noted histologically, irrespective of the pattern of tumour cell arrangement.

Immunohistochemical labelling

The neoplastic cells are cytokeratin-positive.

Differential diagnoses

These are listed in Box 14.2.

Box 14.2 Differential diagnoses for basal cell tumours (trichoblastoma or basal cell carcinoma)

Neoplastic
- Sarcoid
- Squamous cell carcinoma
- Melanoma
- Trichoepithelioma
- Sebaceous or apocrine neoplasms

Non-neoplastic
- Follicular cyst(s)

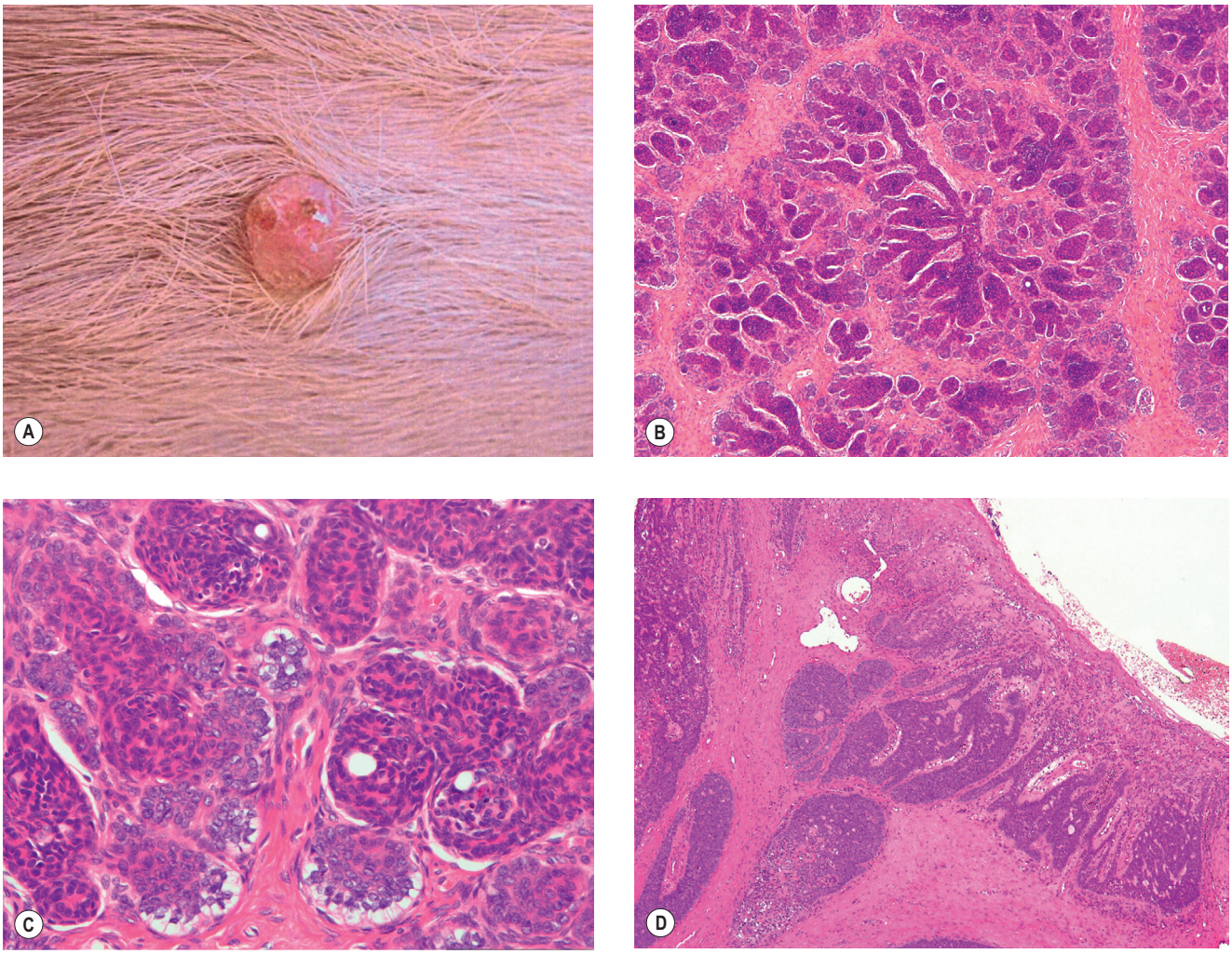


Figure 14.3 Basal cell tumours. **(A)** A small nodular benign mass, with a multifocally ulcerated surface. **(B)** Histological appearance of a benign mass that could also be classified as a trichoblastoma, showing the medusoid pattern, i.e. radiating cords of tumour cells that are forming multiple round or ovoid aggregates (H&E, ×40). **(C)** Higher-power view of the same neoplasm, showing tumour cells with swollen, clear, vacuolated cytoplasm at the tips of the radiating clusters (H&E, ×200). **(D)** Histological appearance of a basal cell carcinoma, showing tumour cells forming cords and trabeculae that are contiguous with the epidermis (on the right) (H&E, ×40).

Trichoepithelioma

Cellular origin

Keratinocytes that differentiate toward all three segments of the hair follicle.[23]

Profile

The only specific report of this type of neoplasm in a horse is in the skin overlying the mandible of a 22-year-old Thoroughbred gelding, but they have been seen at other sites (see Fig. 31.36).[3]

Biological behaviour

Trichoepitheliomas are benign neoplasms.

Gross pathology

Trichoepitheliomas have a nodular or multinodular structure and can measure up to several centimetres in diameter, involving the dermis and/or subcutaneous tissues. Partial or complete alopecia and/or ulceration of the overlying skin can occur.[23]

Histopathology

Trichoepitheliomas are well-circumscribed and unencapsulated and may be focally contiguous with the epidermis or a hair follicle.[23] The neoplasm is composed of islands and variably-sized cystic structures formed by predominantly basaloid epithelial cells resembling follicular bulb matrical cells; there is differentiation toward hair follicle-like structures that may include cells resembling those from inner and outer root sheaths, isthmus or infundibular segments and, in rare cases, formation of

Box 14.3 Differential diagnoses for trichoepithelioma

Neoplastic
- Sarcoid
- Squamous cell carcinoma
- Melanoma
- Basal cell tumour (trichoblastoma)
- Sebaceous or apocrine neoplasms

Non-neoplastic
- Follicular cyst(s)

abortive or rudimentary hairs.[3,23] Cystic structures ('horn cysts') may predominate and their lumens often contain keratinized 'ghost' cells. The epithelial tumour cells are supported by a moderately abundant stroma that may be myxoid (although the latter has not specifically been described in the horse).[23]

Immunohistochemical labelling

The neoplastic cells are cytokeratin-positive.

Differential diagnoses

These are listed in Box 14.3.

Epitrichial (apocrine) sweat gland adenoma and carcinoma

See also page 581.

Cellular origin

Epitrichial (apocrine) sweat gland glandular or ductular epithelium.

Profile

These are very rare neoplasms in equines. A 14-year-old Danish Warmblood gelding had multiple nodular epitrichial sweat gland carcinomas of ductular origin, initially involving the hindlimbs, but that were eventually found metachronously (i.e. arising at different times) on all four limbs over a 2-year period.[43]

Epitrichial glands in horses occur in greatest numbers in submandibular, mucocutaneous, mane and coronary band regions.[44] Neoplasms derived from these glands are most regularly found on the pinna and in genital sites.[3] Adenomas have been reported in the vulva ($n = 2$) and eyelid ($n = 1$).[2,45] Solitary carcinomas were reported in the prepuce of a 17-year-old pony and the vulva of an aged mare, respectively.[46,47] There has been one case of multiple carcinomas of ductular origin involving skin of the distal limbs.[43]

Biological behaviour

Epitrichial sweat gland tumours in horses are most frequently benign (i.e. adenomas) and should be curable by surgical excision.[3] Carcinomas are locally infiltrative and metastasis has not been documented in the horse. In dogs and cats, it has been stated by some authors that highly aggressive sweat gland malignancies appear to be rare; however, metastasis might be expected in some cases, depending on the grade of malignancy and histological subtype.[23]

Gross pathology

Adenomas are solitary, well-circumscribed, firm or cystic, and nodular or multinodular. They measure up to several centimetres in diameter. Surfaces may be normal, irregular or occasionally ulcerated, and alopecia can develop.[3] Carcinomas may also be firm or cystic, but are poorly-circumscribed. The reported preputial apocrine carcinoma measured 2 cm in diameter and was hyperpigmented with a hyperkeratotic surface.[47]

Histopathology

Histologically, epitrichial sweat gland tumours are multilobular with a prominent fibrous stroma and no epidermal contiguity. Tumour cells may resemble secretory or ductal epithelial cells and can have a solid or cystic arrangement.

Secretory-type tumour cells in adenomas are often arranged in single layers in acinar, tubular or papillary patterns; they are cuboidal or columnar, with moderate to large amounts of eosinophilic cytoplasm and may show apical (secretory) blebbing.[23] In secretory carcinoma/adenocarcinoma, the tumour cells are arranged in single to multiple layers and may line papillary projections extending into highly branching acini.[47] Well-differentiated carcinoma cells may still show apical cytoplasmic blebbing. There is variable nuclear pleomorphism, nucleoli may be larger and mitotic rates also vary.

Tumour cells that are ductular in origin are arranged in trabeculae and in double layers lining tubules. In ductular carcinomas in one case, the tumour cells were described as cuboidal with round nuclei containing prominent nucleoli and moderate mitotic activity (1 per ×400 field).[43]

There may be multiple areas of tumour cell necrosis in malignant neoplasms and evidence of invasion of the surrounding stroma may be observed.[47]

Immunohistochemical labelling

The neoplastic cells are cytokeratin-positive.

Sebaceous gland adenoma and carcinoma

See also page 580.

Cellular origin

Sebaceous glandular or ductular epithelium. It should be noted that in the eyelids the specialized tarsal sebaceous glands are termed 'meibomian glands'.

Profile

Neoplasms arising from sebaceous glands are rare in animal species other than dogs. If the classification currently employed for sebaceous gland neoplasms in dogs and cats is used, they may be classified as adenomas (benign), epitheliomas (low malignant potential) or carcinomas

(malignant).[23] A meibomian adenoma of the eyelid was mentioned in a 10-year survey of equine necropsy examinations conducted in the USA.[48] Four sebaceous carcinomas have been reported: one in the abdominal wall and three in the nictitating membrane.[49–52] One nictitating membrane carcinoma was thought to have arisen from the lacrimal caruncle.

Biological behaviour

Sebaceous adenomas are benign and should be cured by complete surgical excision, if necessary. Epitheliomas have not been diagnosed in horses, but in dogs they may be locally aggressive, can recur following surgical excision and only metastasize in rare cases.[23] Sebaceous carcinomas can be locally aggressive; they may recur following excision and metastasize, but the potential for this differs between species.[23] As reports of sebaceous carcinoma in horses are so rare, metastatic rates are not known. The abdominal wall carcinoma was large and infiltrative (see below) with metastasis to the inguinal, internal iliac and caudal lumbar lymph nodes.[49]

Gross pathology

Sebaceous adenomas are generally described as nodular or papillated masses that are yellow, opalescent or pigmented, with alopecic or sometimes ulcerated overlying skin.[23] Carcinomas are usually firm and nodular, with frequent overlying alopecia and ulceration (see Fig. 31.35). The 20 cm-thick sebaceous carcinoma reported in the abdominal wall of one horse extended into and nearly filled the caudo-dorsal abdominal cavity, surrounding the abdominal aorta.[49] The mass was white and fibrous on sectioning and contained multiple white or pale yellow 1–4 mm nodules; some of the larger nodules had necrotic centres.

Histopathology

Sebaceous gland neoplasms are lobulated. Adenomas are well-demarcated and the lobules are composed of well-differentiated sebaceous cells (containing lipid vacuoles) of variable shape and size.[3] Reserve (basal) cells have scanty eosinophilic cytoplasm and may contain small numbers of mitotic figures.[23] There is often cystic degeneration in centres of sebaceous lobules and there may be associated granulomatous inflammation. Sebaceous epitheliomas may be well-demarcated or infiltrative, have a predominant reserve cell component with scattered small foci of sebaceous differentiation, may be melanized and have a moderate to high mitotic index.[23]

Sebaceous carcinomas vary in their degree of differentiation, but most contain at least some cells with intracytoplasmic lipid. Tumour cells comprising the abdominal wall carcinoma described above were well-differentiated: i.e. large and polygonal with a foamy cytoplasm and large nuclei.[49] In invasive areas, the tumour cells resembled basal cells, contained frequent mitotic figures and were arranged in cords.

Immunohistochemical labelling

The neoplastic cells are cytokeratin-positive.

Adenocarcinoma and carcinoma of the nictitating membrane gland

Cellular origin

Epithelium of the large seromucinous lacrimal gland located around the cartilage of the nictitating membrane.

Profile

An adenocarcinoma and a solid carcinoma of the nictitating membrane gland were reported in a 5-year-old Draft horse gelding and a 7-year-old Warmblood mare, respectively.[51,53]

Biological behaviour

These neoplasms grow rapidly, elevate the nictitating membrane, cause pressure on the globe and invade surrounding tissues.[53] Where an adenocarcinoma was present for 4 months prior to surgical excision, there was no evidence of recurrence or metastasis 16 months following removal.[53] In contrast, a solid carcinoma metastasized extensively, to parotid and mandibular salivary glands, the soft palate, oesophagus, mandibular region, and parotid, mandibular and retropharyngeal lymph nodes.[51]

Gross pathology

The reported adenocarcinoma was lobulated, fleshy, pink to red and ulcerated and replaced the entire nictitating membrane.[53] The solid carcinoma, located around the nictitating membrane cartilage, was lobulated, firm and white; the membrane was 1 cm thick.[51] Secondary lesions may include corneal ulceration, conjunctival hyperaemia, mucopurulent discharge and haemorrhage.[53]

Histopathology

The solid carcinoma was poorly-demarcated from normal glandular tissue.[51] Tumour cells in these neoplasms are arranged in packets, disorganized clusters or acini supported by a fine fibrovascular stroma; they may form occasional tubular structures.[51,53] There may be areas of abundant fibrous stroma (scirrhous reaction). The tumour cells are polygonal or cuboidal with pale-staining eosinophilic cytoplasm that, if the cells are well-differentiated, may contain pale basophilic or amphophilic (serous) secretory material.[53] Anisocytosis and anisokaryosis can be marked and nuclei contain large nucleoli. The mitotic rate is variable (e.g. 1–2 per 10 high power (×400) fields), and bizarre mitotic figures may be noted. *Demodex caballi* mites were noted in the eyelid meibomian (sebaceous) glands in one case, but were presumed to be incidental.[53] Other associated lesions may include marked necrosis and intense infiltrates of lymphocytes, plasma cells and neutrophils with smaller numbers of macrophages and eosinophils.[53]

Differential diagnoses

These are listed in Box 14.4.

Box 14.4 Differential diagnoses for adenocarcinoma and carcinoma of the nictitating membrane gland

Neoplastic
- Squamous cell carcinoma
- Papilloma
- Melanoma
- Lymphangioma
- Lymphangiosarcoma
- Lymphosarcoma
- Haemangiosarcoma
- Basal cell tumour

Non-neoplastic
- Conjunctival pseudotumour

Keratoma

See page 582.

Cellular origin

Epidermal/epithelial cells of the coronary band, solar corium, or inner hoof wall (or rarely the sole) (see Fig. 31.37).

It is debatable whether keratoma is a genuinely neoplastic state, with some authors regarding them as non-neoplastic epidermal cysts[31]; this theory is supported by their histological appearance (see below).

Profile

Keratomas are rare, but this is the most frequently diagnosed mass involving the equine hoof. There have been reports in horses 2–20 years of age.[54] The coronary band appears to be the most common site of origin. On rare occasions, these lesions arise in the sole.[54]

Oncogenesis

Keratomas may be produced by germinal epithelial cells in response to chronic irritation of the coronary band, dorsal laminae or solar corium by pressure, injury, abscess formation or chronic pododermatitis.[54–56]

Biological behaviour

Keratomas are slow-growing, benign and usually unilateral; rare bilateral cases have been reported.[57] If large enough, a keratoma that occurs between the distal phalangeal bone (P3) and the hoof wall will create sufficient pressure on sensitive hoof lamellae and bone to result in significant continuous or intermittent lameness. In one case diagnosed in a mule, there was secondary pathological fracture of P3 extending from the solar to articular surface.[58] Additionally, a keratoma can allow access of bacteria, with complication of the lesion by inflammation and potentially abscess formation.

Surgical excision results in a return to normal function for most horses. Recurrence has not been noted 1–11 years following resection with wide margins.[54] Recurrence may follow incomplete excision, this being particularly likely at the coronary band, where there is concern regarding permanent damage of the coronary corium.[56] It has been speculated that there could be progression to squamous cell carcinoma.

Gross pathology

Keratomas are usually solitary, but on occasion, multiple masses have been reported.[59] Typically arising just distal to the coronary band, they appear at that site as a raised lesion on the dorsal or lateral hoof wall, if sufficiently large to cause hoof deformation (see Fig. 31.37).[31] As they grow downwards, keratomas may be found at the time of presentation at any location from the coronary band to the solar surface of the foot; they are most usually found in the toe or quarters of the hoof. In some cases, lameness is not noted until the mass actually reaches the weight-bearing surface of the hoof.[57]

Recently, a keratoma was reported in the corium of the frog.[56] There have also been reports of keratomas proximal to the coronary band, that (unusually) were mineralized and therefore visible radiographically; this finding suggests that these masses are not always caused by hoof irritation or trauma.[60]

Keratomas grow between the inner stratum of the hoof wall and the distal phalanx, in general measuring 1–2.5 cm in diameter. Cylindrical and spherical forms have been described, with the latter found most often near the toe. On sectioned surfaces, they are seen to be discrete and encapsulated. The central material is grey, tan, yellow, white or brown and friable and may have a concentrically laminated ('onion-skin') appearance. In long-standing cases there may be focal thickening or inward deviation of the white line, behind the mass.[61,62] The white line is split as the mass reaches the sole and the overlying epidermis may bulge, with thinning and discoloration. There is often associated purulent exudate and there may be a fistula leading to the keratoma.[55] Pressure on P3 may cause erosion (although this is not invariable) and there can be concurrent solar infection.

Histopathology

The cyst wall is composed of proliferating well-differentiated, stratified squamous epithelium that keratinizes centrally. Peripherally, it may form rete ridges into surrounding tissue. The central cystic space is filled with keratin debris. The epithelial layer may be thin in some cases.[61] In keratomas in the area of the coronary band, partial mineralization of the keratin debris has been reported and this is visible radiographically, as mentioned above.[54,63] There may be associated inflammation and granulation tissue formation.[54,56] Adjacent primary epidermal lamellae of the hoof wall are flattened and distorted, blunted or absent.[54]

Differential diagnoses

These are listed in Box 14.5.

SINONASAL

Neoplasms of the nasal cavities and sinuses are thought to be uncommon, with a reported incidence of 0.25% in one teaching hospital over an 8-year period.[64]

Box 14.5 Differential diagnoses for keratoma

Neoplastic
- Squamous cell carcinoma (the second most common tumour type of the equine hoof)
- Anaplastic malignant melanoma
- Osteosarcoma
- Sarcoid

Non-neoplastic
- Abscess
- Intraosseous epidermoid cyst (of the distal phalanx)
- Exuberant granulation tissue

Squamous cell carcinoma

See pages 232–233.

Adenoma

Cellular origin

Surface or glandular epithelium of the nasal cavity or paranasal sinuses.

Profile

There have been a small number of reports of adenomas arising in the caudal nasal cavity and ethmoturbinate regions of older horses.[65]

Biological behaviour

These benign neoplasms grow progressively and can become very large (e.g. 500 g), with distortion and thinning of surrounding bony structures but no invasion. One ethmoturbinate mass extended through the fronto-maxillary ostium into the maxillary sinus.[65]

Gross pathology

Adenomas are typically soft, smooth-surfaced and well-circumscribed.

Histopathology

Tumour cells line acini, clefts or cysts; they are cuboidal and occasionally ciliated.[65] The overlying mucosa may be intact.

Immunohistochemical labelling

The neoplastic cells are cytokeratin-positive.

Adenocarcinoma

Cellular origin

Surface or glandular epithelium of the nasal cavity or paranasal sinuses. Adenocarcinomas are thought to arise more frequently from the surface epithelium than from nasal or paranasal glandular tissue.

Profile

This is a rare type of neoplasm in the equine sinonasal cavities, comprising less than 0.05% of total neoplasms in these locations based on submissions to referral hospitals.[65,66] Predilection sites include the frontal sinus, nasal and ethmoidal regions rather than the maxillary sinuses (as for squamous cell carcinoma).[65–69] Adenocarcinomas arising from the hard or soft palate have also been reported.[65,70] Horses affected have fallen within the age range of 8–17 years.[66]

Anaplastic carcinomas are particularly unusual; a congenital ethmoid carcinoma was diagnosed in a Belgian filly.[71]

Biological behaviour

Adenocarcinomas are highly aggressive, with bony disruption and lysis including destruction of nasal turbinates (see Figs. 29.3, 29.4). Neoplasms arising in the nasal cavity frequently invade through the cribriform plate into the frontal sinus and may also extend into the oral cavity (including through the hard palate) and nasal septum.

Adenocarcinomas may invade into the cranial cavity with or without compression of the brain, including cerebral olfactory and frontal lobes and the base of the cerebrum (Figs. 5.2, 29.3).[65,71–74] The parenchyma of the brain may be infiltrated.[72] One frontal sinus adenocarcinoma invaded through the cribriform plate into the left orbit (resulting in exophthalmos) and then followed the optic nerve into the cranial cavity, where there was marked compression of the cerebrum.[67] If surgical excision is to be attempted, the cribriform plate should be examined carefully for defects. This is because the size of communication of the main neoplastic mass with the cranial cavity may be small.[69]

Metastasis is rare but has been reported, to sites including the parotid salivary gland, cranial cervical, submandibular and pharyngeal lymph nodes, cervical fascial tissue and lungs.[73]

Gross pathology

Adenocarcinomas/carcinomas are soft, granular or firm in consistency, vary in colour (yellow, grey, pink, white, red) and occasionally contain cystic cavities filled with yellow fluid (Figs. 5.2, 29.3, 29.4).[65–67] They grow to fill the involved nasal cavities and sinuses. There may be bulging of sinuses, deviation of the nasal septum, and marked infiltration and destruction of bone. One such neoplasm invading the cerebrum measured 8 cm in maximal diameter within the cranial cavity.[72] There may be associated purulent nasal discharge or epistaxis and sinuses may be filled with purulent exudate.[67] Exophthalmos is not uncommon and is usually associated with ocular discharge. A concurrent progressive ethmoidal haematoma was reported in one case but any direct relationship between the two conditions was debatable (Fig. 29.3).

Box 14.6 Differential diagnoses for sinonasal adenocarcinoma

Neoplastic
- Lymphosarcoma
- Osteoma, osteosarcoma
- Melanoma
- Olfactory neuroblastoma

Non-neoplastic (see below)
- Progressive ethmoidal haematoma
- Paranasal sinus cyst
- Nasal polyp (inflammatory)
- False nostril epidermal inclusion cyst (atheroma)
- 'Tumour-like' nasal amyloidosis

Histopathology

The overlying sinonasal epithelium may be intact, and thin encapsulation of the neoplastic mass(es) may be noted. Tumour cells are arranged in sheets, nests, cords, trabeculae and/or lining acini and cysts, and may also form papillary structures in one or more layers.[66,71] The tumour cells are usually cuboidal or columnar but may also be round or elongate/spindle-shaped and some mucous or serous-secreting cells may be noted.[72] Serous cells will not stain positively using the periodic acid-Schiff method. Nuclei are round or ovoid, may be vesicular and contain multiple large nucleoli; there are often high mitotic rates, e.g. 10 per high power (×400) fields. Areas of squamous metaplasia may be noted and cysts may form.[66] There may be large areas of necrosis, inflammation and haemorrhage within and surrounding neoplastic tissue.

In anaplastic (undifferentiated) carcinoma, the tumour cells are arranged in solid sheets, cords or islands; they are large and pleomorphic with no squamous or glandular features.[66] In some cases where the tumour cells are spindle-shaped, immunohistochemical labelling may be required for differentiation from sarcoma.

Immunohistochemical labelling

Tumour cells stain positively for cytokeratin.

Differential diagnoses

These are listed in Box 14.6.

Non-neoplastic nasal masses

Progressive ethmoidal haematoma (PEH)

See also page 489.

Profile

This is the most common mass lesion of the equine head, most frequently originating from the ethmoidal labyrinth.[75,76] Haematomas may also arise in the adjacent sphenopalatine sinus, frontal sinus and floor and walls of the maxillary sinuses (see Fig. 29.9).[77]

Biological behaviour

The lesions are diagnosed in middle-aged to older horses (most often 8–12 years). Arabian and Thoroughbred horses are over-represented and the condition may be more common in geldings than stallions or females.[66,78]

A persistent, chronic serosanguineous nasal discharge is a characteristic clinical feature (see Fig. 29.8). This is thought to be due to vascular damage. Underlying haemangiomatous lesions were noted histologically in the sinuses of one affected horse at post-mortem examination, i.e. tissue containing abundant small arteries, venules and capillaries.[75] A primary low-grade vascular neoplastic process has also been proposed.[31]

Progressive ethmoidal haematomas frequently recur following surgical excision. Recurrence rates of approximately 45% have been reported.[75,78] Severe haemorrhage is an expected complication of surgical intervention.

Gross pathology

Progressive ethmoidal haematomas are usually solitary; however, bilateral disease (most common in mares) can result from extension across the ethmoidal septum.[66] Grossly, the masses are smooth-surfaced and dark red, red-purple or yellow-grey/yellow-green, depending on the age of the most recent haemorrhages (see Figs. 29.8, 29.9, 29.11). There may be encapsulation and areas of dense fibrous tissue may be noted on sectioned surfaces, this being evidence of fibrous organization.[75,78] As the mass enlarges, it becomes ulcerated with surface haemorrhage and unilateral epistaxis is the most common clinical sign.[66] In some cases, there is mucopurulent nasal discharge.

The whole nasal cavity may be occupied and there can be extension through the choana into the nasopharynx (see Fig. 29.9), or occasionally dorsal or ventral extension into frontal or sphenopalatine sinuses, respectively.[75,77,78] Further extension may occur from either frontal or sphenopalatine sinuses into caudal and, sometimes, rostral maxillary sinuses. As the haematoma enlarges, it causes soft tissue destruction.[78] There may be pressure necrosis, but there is rarely distortion of the surrounding bone; facial swelling is rare.[66,78]

Histopathology

Histologically, haematomas are typically covered by pseudostratified columnar epithelium containing mucous cells (i.e. the sinonasal epithelium). The epithelium may be ulcerated or have undergone squamous metaplasia. Alternative epithelial linings may include flattened, columnar or cuboidal and ciliated.[76] Centrally beneath a submucosal fibrous pseudocapsule there are multiple changes including: chronic and active haemorrhage; areas of vascular channels that may be thrombosed and are lined by plump endothelial cells with hyperchromatic nuclei; variable degrees of fibrosis; deposition of mineral, globin-derived pigments and haemosiderin on blood vessels and collagen fibres; and infiltration by haemosiderophages, multinucleate histiocytic giant cells, lymphocytes, plasma cells and, less commonly, neutrophils and eosinophils.[66,75,76] Some macrophages in older lesions may contain phagocytosed fragments of encrusted collagen fibres.[75]

Immunohistochemical labelling

The encrusted collagen fibres, which are basophilic, golden brown or brown-yellow in routinely stained sections (HE), stain strongly positive for ferric iron and are weakly von

Kossa-positive (a stain for mineral).[75] Crystalloid concretions may stain strongly positive using von Kossa's method. Unlike sinus cysts (see below), there is rarely thinning and remodelling of adjacent bone to form a 'capsule'.[76] Secondary mycotic infection has been reported in small numbers of cases, complicating the histological diagnosis.[79]

Paranasal sinus cyst

See also page 494.

Profile

Paranasal sinus cysts have been reported to account for up to 24% of total cases of paranasal sinus disease in horses (see Fig. 29.2).[76]

Biological behaviour

Sinus cysts arise in the maxillary sinuses or ventral conchae, with potential extension into the frontal sinus; these cysts tend to involve the more caudal sinus compartments.[77,80,81] Smaller numbers originate in the frontal sinuses or ethmoid labyrinth.[79] In one study, paranasal sinus cysts were reported as tending to occur either in young horses ≤2 years of age (as young as 6 weeks) *or* older horses >9 years; however, this involved only 15 cases.[80] In two further, larger studies also conducted in the UK (total n = 89), no such biphasic age distribution was noted, with median ages of 7 and 11 years, respectively (range 3 months to 23 years).[79,82,83] Congenital cysts have also been reported.[84,85]

The precise aetiology of sinus cysts is not known, but it seems likely they are developmental; some authors believe them to be of dentigerous origin, but they are not always physically associated with teeth.[85] Other authors have suggested that sinus cysts and ethmoid haematoma share a common pathogenesis, originating from haemorrhage into restricted and unrestricted sites, respectively, but this view is not universally accepted.[80]

Sinus cysts are space-occupying, expansile lesions that may become very large (Fig. 29.12). They are usually unilateral, but there have been rare reports of bilateral lesions, including a 17-day-old foal (i.e. congenital) and a 2-year-old filly.[84,86]

Sinus cysts are more frequently associated, along with sinonasal neoplasms, with gross distortion of the nasal cavities and frontal or maxillary bones than are other sinonasal disorders (Fig. 29.12).[81] The overlying facial bones are most often thinned and demineralized; thickening has been reported in some cases, but that would more often indicate chronic sinus infection.[79,80] In one study (n = 52), 83% of affected horses presented with facial swelling extending into the retrobulbar space that and resulting in exophthalmos in a few cases.[82,87] There may be pressure lysis of surrounding bone, resulting in facial distortion, dental displacement, flattening/loss/rotation of tooth roots, nasal septum deviation and/or distortion of ventral conchae.[77,79,80]

Recurrence following complete excision or curettage is considered to be rare. In a study of 28 horses followed for a median time of 31 months following surgical removal, 82% were asymptomatic and a further 11% showed only occasional mucoid nasal discharge.[83,87] In a UK study, 45 of 48 horses showed complete resolution of clinical signs after surgical treatment.[82]

Gross pathology

Sinus cysts have variably thick walls supported by fine bony trabeculae and may be multiloculated or multicystic, containing clear yellow sero-mucoid fluid.[76,88] Many affected horses have mucopurulent nasal discharge from the affected side.[82]

Histopathology

Histologically, the cyst epithelium is pseudostratified (i.e. sinonasal) and can include mucous cells. It should be noted that this type of epithelium may not be identified in small biopsy specimens, as there may be extensive ulceration or, in some cases, squamous metaplasia.[66] The epithelium may be seen on both surfaces, which differentiates these lesions from epidermoid cysts and progressive ethmoidal haematomata (PEH; p. 258); additionally, PEH lesions are solid rather than fluid-filled.[76] There is an underlying, variably thick fibrous tissue layer, within which there may be: chronic inflammation that can include siderophages and giant cells; haemorrhage and, in some cases, areas of haematoma formation (as in progressive ethmoidal haematomas); oedema; cholesterol deposits; and granulation tissue formation.[80,82] Sinus cysts may become secondarily infected and filled with purulent exudate, requiring histological differentiation from an abscess (that would not be lined by epithelium). Within the surrounding bone, there are areas of marked osteoclastic remodelling, with other (variable) changes including oedema, fibrosis, haemorrhage, inflammation, haemosiderophages and necrosis.[66,76,88]

Nasal polyp

See also page 488.

Profile and biological behaviour

Nasal polyps are encountered in adult horses and are generally considered to be an overgrowth response to inflammatory or allergic stimulation, arising from the nasal septum or conchae (usually the caudal aspect). They have been associated with chronic sinusitis and rhinitis.[76,89]

Gross pathology

Nasal polyps may be solitary or multiple. They are by definition pedunculated, have a smooth white surface and may reach a large size, up to 20 cm in length (see Figs. 5.4 and 29.7). On sectioning they have a fibrous consistency and small cystic spaces may be noted.[89] Strictly speaking, progressive ethmoidal haematomas are also polyps.

Histopathology

Histologically, the overlying (nasal) mucosal epithelium is variably cuboidal, columnar, flattened or proliferative. There is a fibrovascular core that is described as granulation tissue in some cases or may be myxomatous. This stroma incorporates normal nasal glandular structures and contains inflammatory cells, including neutrophils and plasma cells.[76] In some cases, rupture of cysts within the mass may contribute to the inflammatory response.[89] Granulomatous inflammatory changes associated with bacteria (staphylococci or streptococci), parasites or mycotic infections may be noted histologically, as potential primary causes of polyp formation.[66]

False nostril epidermal inclusion cyst (atheroma)

See also page 487.

Biological behaviour

False nostril epidermal inclusion cysts arise in the dorsolateral aspect of the nasal diverticulum (false nostril). They are most often diagnosed in 1–3-year-old horses (see pp. 487–488).

Gross pathology

These asymptomatic cystic lesions are usually unilateral, soft and measure up to 2–5 cm in diameter (see Fig. 29.6). On sectioned surfaces, they contain opaque white or grey viscous material.[66,90] They often bulge laterally rather than into the lumen of the diverticulum.

Histopathology

Histologically, the cysts are keratin-filled and lined by stratified squamous epithelium.

'Tumour-like' nasal amyloidosis

Profile

Nasal amyloidosis has only been observed in horses. It is an uncommon and localized condition not associated with other or underlying diseases.[91] The deposits of reactive amyloid usually occur in the nasal atrium, but occasionally also extend into the nasal septum and turbinates, and in extreme cases involve the entire nasal cavity, pharynx, larynx, guttural pouch, upper airways, conjunctiva and regional lymph nodes.[91,92]

Single or coalescing nodules are noted that histologically are submucosal and composed of coalescing deposits of fibrillar/hyaline eosinophilic material surrounded by multinucleate histiocytic giant cells, macrophages and other inflammatory cells (see Fig. 12.7); there may also be associated areas of granulation tissue and haemorrhage.[93] This amyloid material may fill lymphatic vessels and surround or be deposited between submucosal blood vessels and nasal glands.[91] Amyloid is orange-red and shows apple-green birefringence under polarized light, when stained using the Congo red method.

SALIVARY GLANDS

Adenoma and adenocarcinoma

See also page 448.

Cellular origin

Salivary glandular or ductular epithelial cells.

Profile

There is only one specific report of a primary salivary gland tumour in a horse; this was an adenocarcinoma of the mandibular salivary gland in an 18-year-old Morgan mare.[94] The same authors, in a review of previous literature, found mention of two further cases (with no details given) out of a total of 1148 cases of equine neoplasia.[94,95]

One equine salivary carcinoma was noted in a multi-species survey conducted in 1959, using cases from the Armed Forces Institute of Pathology and the University of Minnesota.[96] In a USA National Cancer Institute survey, five tumours of salivary tissue (noted as 'duct') were reported, including adenocarcinoma (two cases), mixed tumour (one case) and two cases of squamous cell carcinoma.[41] A salivary cystadenoma was mentioned in one survey.[95]

Biological behaviour

Adenocarcinomas have been described as locally invasive (see Fig. 28.17), with metastasis to retropharyngeal and cervical lymph nodes, and the thoracic cavity.[94] A parotid gland carcinoma in one pony caused unilateral Horner's syndrome and facial paralysis (see Fig. 28.17).

Gross pathology

Adenocarcinomas are grey-white, lobulated masses. One neoplasm in a mare extended from the mandibular salivary gland tissue to a point dorsal to the larynx and measured 7 × 9 × 23 cm. There was marked subcutaneous oedema extending from the intermandibular space to pectoral and brachial areas.[94]

Histopathology

In one case, the tumour cells were arranged in sheets and were poorly-differentiated; the neoplastic tissue was intermingled with glandular acini and ducts and supported by a scirrhous stroma. The mitotic rate was high.[94]

MAMMARY GLANDS

Mammary neoplasia in the mare is rare, with a reported prevalence of 0.11–1.99% in European abattoir surveys.[41,97,98] In a more recent necropsy survey in France (1986–2003) of 1771 horses, one mammary carcinoma was diagnosed.[99]

Adenocarcinoma, carcinoma and adenoma

See also page 647.

Cellular origin

Mammary glandular or ductular epithelium.

Profile

Although very rare in total, adenocarcinoma/carcinoma is the most common primary mammary tumour type in horses, usually affecting older mares (12–21 years).[100–104] There has been one report of a highly anaplastic mammary carcinoma in a mule.[105] Usually only one mammary gland is involved, but the neoplastic involvement can be bilateral.[101,104] Two mammary adenomas have been observed, one in an 18-year-old mare.[41,106]

Biological behaviour

In a survey of mammary neoplasia in mares conducted at the University of Kentucky ($n = 11$), all were malignant and more than half had gross and/or histological evidence of metastasis.[107,108] Metastasis occurs via lymphatic vessels to regional lymph nodes (inguinal, supramammary and external iliac), with distant spread to multiple sites including lumbar, aortic, renal, bronchial, sternal, mediastinal, bronchial and mesenteric lymph nodes, the abdominal cavity, small intestine, liver, kidneys, adrenal glands, ovaries, spleen, omentum, pleura, pericardium, mediastinum, lungs, diaphragm, cerebrum, bone (femur in one case) and skeletal muscles.[31,98,101,103,104,107,109–112] A French study indicated that lung metastasis is a frequent occurrence.[113] In one report, a mammary carcinoma had metastasized haematogenously to the lungs (without involvement of regional lymph nodes).[98]

If surgical excision of the primary mass is performed, most mares will present with local recurrence and/or metastatic disease within 5 months.[100,102] However, survival for at least 1 year post-surgery was reported in two cases.[110,114]

A reported mammary adenoma was surgically excised (by hemi-mastectomy) with no evidence of recurrence 1 year later.[106]

Gross pathology

Neoplasia should be suspected where the gland is enlarged and aerobic bacterial culture has been negative[115]; there is often an initial misdiagnosis of mastitis. However, there may also be positive bacterial cultures due to secondary infection.[100]

Mammary carcinomas may be located superficially or deeply in right or left glands, and there may be a thick capsule.[103] Masses have measured up to 40 cm in maximal diameter and some extend through the median septum to involve both glands (Figs. 14.4, 35.15).[100–102,112] The gland is enlarged by firm, white, grey-white, cream, orange-yellow, yellow-red or tan tissue, which may form nodules or lobules with intervening fibrous septa (see Figs. 14.4, 35.15). Discoloured or suppurative mammary discharge may be noted.[112] There may be deep ulceration, necrosis and infection of the surfaces, in some cases with serosanguineous fluid exuding from multiple sinuses and ulcerated areas (see Figs. 14.4, 35.15).[108,111,114] On sectioned surfaces, there may be central cavitations containing thick red or brown fluid, or necrotic debris.[102] Similar neoplastic tissue may be seen in draining lymph nodes.

Affected horses often present with oedema of the ventral body wall and/or hindlimbs relating to metastasis along lymphatic vessels. Marked pleural and peritoneal effusion was reported in a horse with carcinomatosis (i.e. widespread dissemination).[111]

One reported mammary adenoma was unilateral, cylindrical and firm, with a large amount of serosanguineous discharge from the associated teat.[106]

Histopathology

Cytological examination of mammary gland fluids may be of value in the diagnosis of neoplasia; however, this can be confounded by large numbers of inflammatory cells.[108,116] When biopsy specimens are taken, areas of ulceration and necrosis should be avoided. It should be noted that as glands containing mammary neoplasms can be infected with bacteria (i.e. develop secondary mastitis), there might be a misdiagnosis of primary infectious/inflammatory disease if sufficient or adequate biopsy specimens are not taken.

Histological types of mammary carcinoma reported in horses include solid carcinoma, tubular adenocarcinoma, papillary ductal adenocarcinoma, invasive micropapillary carcinoma and squamous cell carcinoma.[100,112] The masses may be lobulated, as in other species, with lobules separated by broad fibrous tissue septa. Within lobules, the tumour cells may be arranged in sheets, trabeculae, small nests, packets, cords, lining acini or tubules, or in mixed patterns, with variable amounts of supporting fibrous stroma that is abundant in some cases (i.e. scirrhous).[109] In cases of papillary ductal adenocarcinoma, multiple layers of tumour cells line and form projections into the ductal structures.[114] In micropapillary carcinomas, tight clusters of tumour cells are noted within clear spaces (see Fig. 14.4).[112]

The epithelial tumour cells are cuboidal, columnar and/or polygonal with small to moderate amounts of eosinophilic cytoplasm, which may be vacuolated. One ductal carcinoma was composed of polygonal and fusiform tumour cells with scanty cytoplasm.[104] Nuclei are round to oval, with vesicular, finely stippled or marginated chromatin and one to several prominent nucleoli. Cellular pleomorphism can be marked, including tumour giant cells. Mitotic rates of up to 15 per high power (×400) field have been reported in addition to mitotic figures with a bizarre appearance.[101,103,111] Tubules or acini may contain homogeneous eosinophilic secretory fluid, degenerate neutrophils and mineralized material. Tumour cells may be seen invading the stroma, adjacent mammary gland tissue, lymphatic vessels and/or blood vessels.[101–103] Associated changes may include extensive necrosis and heavy stromal inflammatory cell infiltrates (including multinucleate histiocytic giant cells). Metastatic masses have a similar appearance, although they may be more pleomorphic (see Fig. 14.4)[103]; where possible, wedge biopsy specimens from regional lymph nodes should be submitted for examination for metastatic lesions including micrometastases.

The mammary adenoma was nodular and encapsulated.[106] There were 1–2 layers of cuboidal epithelial cells, with eosinophilic cytoplasm lining irregularly-shaped tubules supported by a fine to moderately abundant fibrous stroma. Tumour cell nuclei were uniform, contained finely stippled chromatin and did not have visible nucleoli. There was multifocal squamous metaplasia of the tumour epithelium and, in the surrounding mammary gland, abnormalities included ductal ectasia, cysts and sclerosing adenosis (fibrosis with proliferation of distorted or elongate glands and ducts).

Immunohistochemical labelling

The neoplastic cells should be cytokeratin-positive. Additional weak positive staining for vimentin was reported in a ductal carcinoma and that has also been seen in mammary neoplasms of this type in human patients.[104] In the case of micro-papillary carcinoma, there was positive epithelial membrane antigen (EMA) labelling of the cytoplasm facing the surrounding stroma; this is referred to

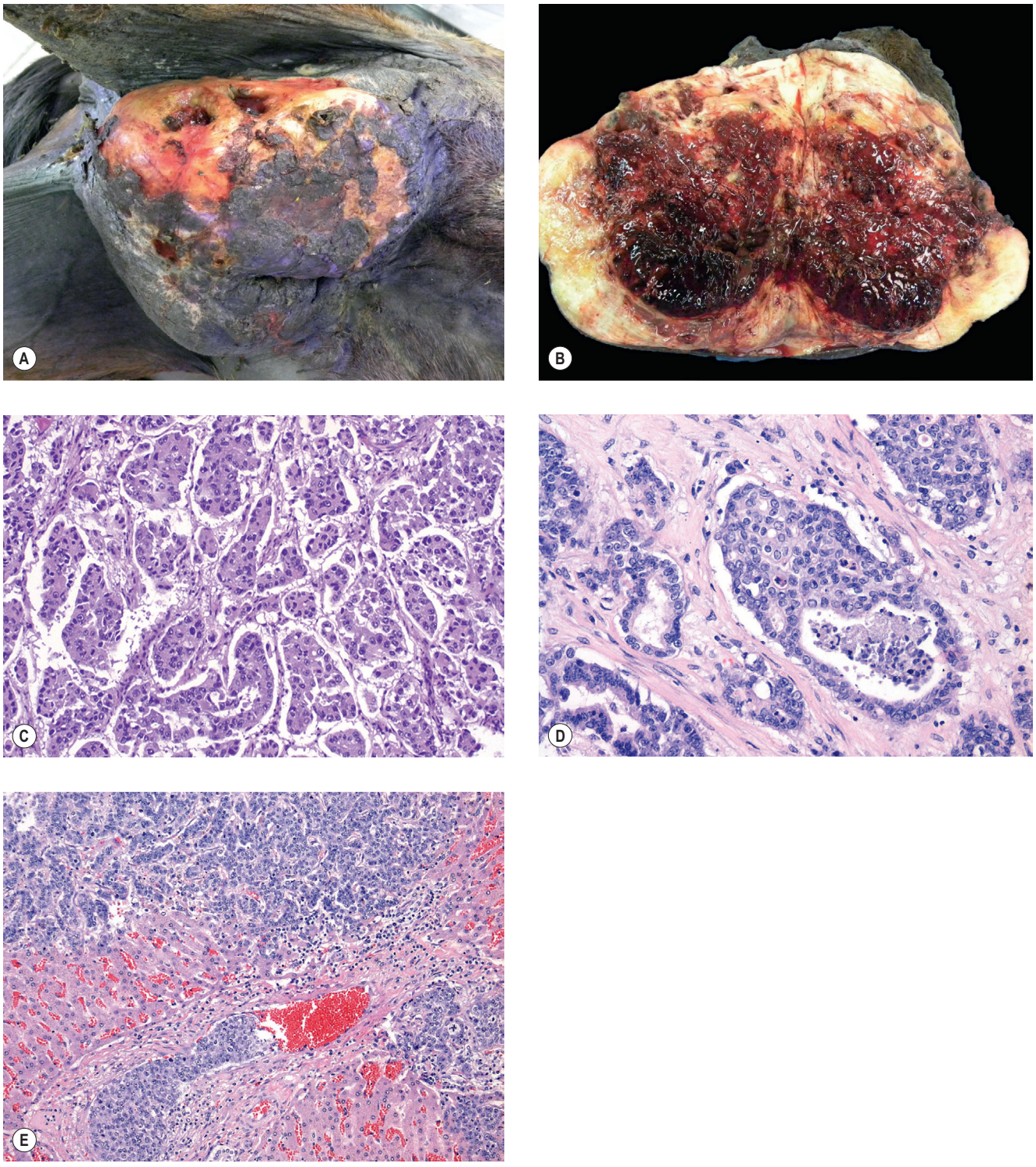


Figure 14.4 Mammary carcinomas in mares. **(A)** Marked enlargement of both mammary glands in a mare of unknown age by a neoplastic mass, with extensive ulceration of the overlying skin and sinus tracts containing haemorrhagic exudate. **(B)** Sectioned surface of the same mass, showing the thick capsule and extensive, friable areas of necrosis and haemorrhage. **(C)** Histological appearance of the same mass (as in A and B). The tumour cells are arranged in packets within small cystic spaces formed by a fine fibrovascular stroma (micro-papillary pattern) (H&E, ×200). **(D)** Histological appearance of a mammary adenocarcinoma diagnosed in a 22-year-old Dutch Warmblood mare, who was pregnant at the time. The cuboidal tumour cells line variably-sized acini within an abundant collagenous stroma (H&E, ×200). **(E)** Metastatic tumour cells within the liver of the same horse (as in D), filling and expanding hepatic sinusoids and a portal vein, with replacement of large numbers of hepatocytes. The tumour cells have a similar appearance to those forming the primary mass (H&E, ×100). *(Figures A, B and C courtesy of Prof. Dr. Roselene Ecco, Escola de Veterinária, Universidade Federal de Minas Gerais, Brazil; reprinted from Gamba CO, et al. Veterinary Quarterly 2011; 31(4):207–210, copyright Taylor & Francis, 2011, by permission of Taylor & Francis[112]; Figures D and E courtesy of Dr Guy Grinwis, Faculty of Veterinary Medicine, Universiteit Utrecht, the Netherlands.)*

Box 14.7 Differential diagnoses for mammary gland adenocarcinoma, carcinoma and adenoma

Neoplastic
- Melanoma
- Lymphosarcoma
- Fibrosarcoma
- Squamous cell carcinoma (this can be of mammary gland origin)

Non-neoplastic
- Severe chronic mastitis with fibrosis

as an 'inside-out' growth pattern in neoplasms of this type in human patients.[112]

Labelling for oestrogen and progesterone receptors in two cases was negative; however, it was not indicated if the antibodies had been validated for use with equine tissue.[114] In a more recent case, there was positive nuclear labelling for progesterone receptor (25% of cells) *and* oestrogen receptor (10% of cells).[112] There was positive labelling of less than 5% of tumour cells in a mammary adenoma for oestrogen receptor antigen.[106]

A case of mammary carcinoma showed positive labelling of tumour cells for alpha lactalbumin (ALA) in both primary and metastatic masses, although fewer positive cells were noted in the latter.[103] This allowed differentiation of mammary carcinoma from hepatic carcinoma in a mare with disseminated neoplastic disease. It should be noted that in human patients some neoplasms that are *not* of mammary origin will label positively for ALA.

Differential diagnoses

These are listed in Box 14.7.

THORAX

Intrathoracic epithelial neoplasia is uncommon in Equidae.

Thymoma

See also page 501.

Cellular origin

Epithelial reticular cells of the thymus, with varying degrees of benign lymphocytic infiltration.[117]

Profile

These tumours are located in the lower cervical region or anterior thoracic cavity and are rare, but have been reported in small numbers of middle-aged to older horses (≥8 years).[118]

Biological behaviour

As in other species, thymomas may be benign or malignant. Malignant tumours are locally infiltrative and can metastasize widely within the thoracic cavity to sites including the lungs, pulmonary artery, mediastinal and bronchial lymph nodes and ribs.[118,119] There may also be more distant metastasis to peripheral lymph nodes and intra-abdominal organs. The thyroid glands and sympathetic nerve trunks may be infiltrated; Horner's syndrome was noted in one horse.[118]

Box 14.8 Differential diagnoses for thymoma

Neoplastic
- Lymphosarcoma
- Metastatic squamous cell carcinoma

Gross pathology

Benign thymomas are singular and encapsulated. In cases of malignant thymoma, single or multiple masses are noted in the thymic region, which can extend to involve the anterior mediastinum, pericardium at the base of the heart and adjacent lung tissue (Fig. 29.17). On sectioned surfaces, thymomas are grey-white or white and firm; there may be multiple cystic areas containing serosanguineous fluid and areas of necrosis.[117,118]

Histopathology

Thymomas are (usually) encapsulated and lobulated and corticomedullary distinction is not noted (as in the normal thymus). Histologically, these neoplasms are classified as predominantly epithelial, predominantly lymphocytic or mixed.[117] However, the epithelial cells are the neoplastic component and are arranged in variable patterns, including solid, trabecular, cribriform, whorled or rosetted.[117] The epithelial tumour cells are spindle-shaped, round, oval or polygonal with an abundant eosinophilic (or sometimes clear) cytoplasm that has poorly-defined margins. In a malignant thymoma, there was multifocal squamous differentiation, i.e. those tumour cells had an eosinophilic granular to fibrillar cytoplasm with prominent intercellular bridges, individual keratinized cells and keratin pearls.[118] Nuclei are round or ovoid and may be vesicular, with 1–2 prominent nucleoli. There may be central keratinization within lobules and Hassall's corpuscle-like structures may be seen.[119] Variable numbers of well-differentiated lymphocytes are scattered between the tumour cells and/or they may form small follicles. There may be variable numbers of other inflammatory cells, including eosinophils, mast cells, neutrophils, plasma cells and macrophages.[117]

Immunohistochemical labelling

The neoplastic cells are cytokeratin-positive; this is the best way of differentiating thymomas from lymphosarcomas.

Differential diagnoses

These are listed in Box 14.8.

Pulmonary adenocarcinoma, carcinoma and adenoma

Cellular origin

Pulmonary epithelial cells.

Profile

In the lungs, primary tumours are far less common than metastatic lesions. Primary pulmonary epithelial neoplasms reported in horses include pulmonary adenocarcinoma/carcinoma (including cystic mucinous and papillary), anaplastic bronchogenic carcinoma or squamous cell carcinoma (SCC), bronchiolar or bronchiolo-alveolar adenocarcinoma and bronchiolar adenoma.[120–125] In a USA survey of 33 horses with primary pulmonary neoplasms, 12 were adenocarcinomas and seven carcinomas (57%).[126,127] These neoplasms occur in older horses and ponies (≥12 years); in the USA survey, the mean age was 16 years.

Biological behaviour

Pulmonary carcinomas are highly invasive and can disseminate throughout the thoracic cavity via lymphatic vessels, blood vessels, airways or transcoelomically, to sites including the lungs, mediastinal lymph nodes, pleura, pericardium, epicardium, myocardium, cardiac chambers and diaphragm.[123,128,129]

More distant metastatic sites have included the kidneys, paravertebral and appendicular skeletal muscles and the peripheral and abdominal lymph nodes.[128] Hypertrophic osteopathy was reported in a case of bronchogenic SCC.[125]

Adenomas are not invasive and it is possible that they are more often clinically silent.[129]

Gross pathology

Intrathoracic primary epithelial neoplasms are solitary or multiple, nodular or sometimes extensive masses that may involve the lungs, pleura, heart and/or mediastinum; the site of origin may sometimes be difficult to determine (Fig. 14.5).[31,124,129] There may be thousands of masses within the lung tissue, and in one case the right lung was almost completely replaced.[122] Large masses may result from coalescence of multiple smaller lesions (see Fig. 14.5).[129] The right lung lobes are more frequently involved, in particular the caudal (diaphragmatic) lobe.[127] Bronchoalveolar neoplasms tend to occur in more peripheral locations in the lungs, while those of large airway origin are presumed to originate at or near the hilus.[129]

The neoplastic masses are soft and friable to firm in consistency, may be subdivided by connective tissue septa and are white, yellow, yellow-grey, tan or brown (see Fig. 14.5). Cystic spaces filled with viscous straw-coloured fluid may be seen on sectioned surfaces. Other masses contain large areas of necrosis and haemorrhage and central necrosis may give some an umbilicated appearance.[129] There may be adhesions between pulmonary neoplastic tissue and the parietal pleura and pericardium.[122] Gross occlusion of pulmonary vessels and bronchi by neoplastic tissue may be noted.[123,128] Other associated lesions can include large amounts of mucoid or mucopurulent material in airways (due to airway obstruction or neoplastic secretion), atelectasis of adjacent lung tissue and pleural effusion (that contains tumour cells).[129] In one case, the neoplastic mass extended out of the thoracic cavity into the axilla, surrounding the brachial plexus.[123]

As intrathoracic neoplasms are more likely to be metastatic, post-mortem examinations in these cases must be complete to rule out other possible primary sites of origin.

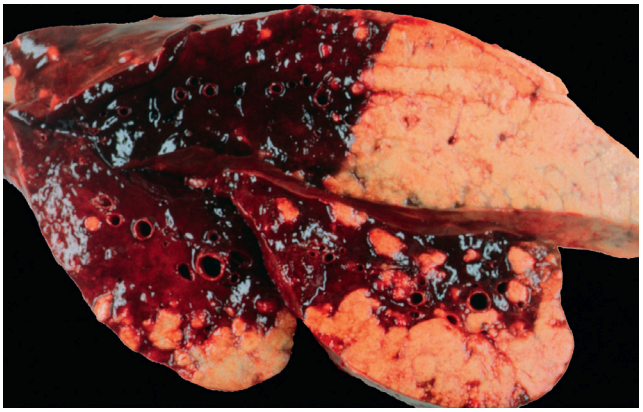


Figure 14.5 Pulmonary carcinoma. Large numbers of firm, nodular, tan-yellow masses are coalescing to replace the normal architecture of extensive regions of the pulmonary parenchyma (including airways).

Histopathology

As in other species, the tumour cells may be arranged in sheets, cords, papillary structures or lining acini, tubules or ductules. They are supported by a fibrous stroma that may be abundant (scirrhous). Tumour cells of a bronchiolo-alveolar carcinoma were described as cuboidal with a vacuolated cytoplasm and multifocal ciliation, while those of a bronchogenic carcinoma were large and frequently ciliated.[123,124] Mucous cells may be noted in large numbers and, in some neoplasms, acini or tubules are cystically dilated by mucinous material.[123] Nuclei may be round, ovoid or C-shaped and vesicular, with one to several prominent nucleoli and (often) numerous mitotic figures that may have a bizarre appearance. Multifocal squamous metaplasia of tumour cells may be noted and the stroma sometimes contains metaplastic osteoid and/or irregularly mineralized bone.[123]

There is often extensive infiltration of the pulmonary parenchyma, and multiple tumour emboli may be observed in both blood and lymphatic vessels. Associated lesions can include necrosis, haemorrhage, lymphoid infiltration and bronchopneumonia.

Immunohistochemical labelling

At least some of the tumour cells will show positive labelling for cytokeratin.

Differential diagnoses

These are listed in Box 14.9.

Equine multinodular pulmonary fibrosis (EMPF) is a progressive fibrotic lung disease that has been associated with equine herpesvirus-5 (EHV-5) infection.[130–132] There may be co-infection with EHV-2 in some horses, this being a closely related gammaherpesvirus.[130,132] This disease occurs in adult horses (age range 4–28 years); affected animals tend to be older, with mean ages of 13 and 14.5 years in two studies.[130,131] There is no apparent breed or gender

Box 14.9 Differential diagnoses for pulmonary adenocarcinoma, carcinoma and adenoma

Neoplastic
- Lymphosarcoma
- Metastatic carcinoma and other types of neoplasm
- Granular cell tumours
- Pulmonary blastoma

Non-neoplastic
- Equine multinodular pulmonary fibrosis (EMPF)
- Multisystemic eosinophilic epitheliotropic disease (MEED)
- Idiopathic granulomatous pneumonia or eosinophilic granulomas
- Pulmonary hamartomas
- Idiopathic chronic interstitial pneumonia with fibrosis

predilection. In most cases, there are numerous coalescing nodules of fibrotic tissue that measure <1–5 cm in diameter, but in some horses, the nodules are larger (up to 10 cm diameter) with grossly normal regions of lung tissue between them; the latter form is particularly difficult to differentiate clinically from a neoplastic process and might progress to diffuse involvement.[130,131] The nodules are pale, tan or tan-white, firm, bulge slightly from surrounding tissue and, on sectioned surfaces, have a homogeneous appearance. Other intrathoracic tissues/organs are not involved and pleural effusion is not common, but the lymph nodes may be grossly enlarged due to reactive lymphoid hyperplasia. Histologically, the well-demarcated nodular lesions are found in the alveolar parenchyma. They are composed of (generally) mature collagenous tissue containing 'alveolar-like' structures lined by cuboidal epithelial cells and containing intraluminal neutrophils and macrophages; mixed inflammatory cell infiltrates are noted within the stroma, that may include multinucleate giant cells.[130,131] Eosinophilic intranuclear viral inclusion bodies have been noted in enlarged macrophages in these lesions.[130–132] Polymerase chain reaction (PCR) can be used to detect EHV-5 DNA in lung tissue, bronchoalveolar lavage fluid, or both, for confirmation of the diagnosis.[130,131] Asinine herpesvirus type 5 (AHV-5) was also detected by PCR in one case. Hypertrophic pulmonary osteopathy was reported in one horse.[133,134]

Horses may present with multiple eosinophilic granulomas in the lungs as part of multisystemic eosinophilic epitheliotropic disease (MEED) or as an idiopathic condition confined to pulmonary tissue.[135]

Pulmonary hamartomas have been diagnosed (congenital polyalveolar lobes) in foals only (n = 3).[136] These tumour-like masses involved the entire right lung. They were spongy, pink to dark red and lobulated, and histologically were composed of normal alveoli, bronchioli and blood vessels.[136]

ABDOMEN (EXCLUDING THE UROGENITAL TRACT)

Gastric and oesophageal squamous cell carcinoma

See page 230.

Intestinal adenoma

Cellular origin

Intestinal epithelium.

Profile

Multiple adenomatous polyps (adenomas) were reported throughout the entire jejunum and ileum in two adult horses; in one of these cases they occurred in conjunction with a small intestinal adenocarcinoma.[137,138] Rarely, adenoma has been reported in other sites including the caecum.[139] Adenomatous polyposis of the intestine in other species including humans may occur as a spontaneous or familial disease.

Biological behaviour

The risk of malignant transformation in horses with multiple intestinal adenomas should be considered, if all of the masses cannot be excised. In one horse with intestinal adenomas that presented with protein-losing enteropathy and was euthanized, no evidence of malignancy was found (Fig. 14.6).[137] A focal distal jejunal adenocarcinoma in a further case indicated that there may have been malignant transformation of an adenoma, this being a well-known occurrence in canine and human patients.[138]

Gross pathology

Large numbers of 0.2–5 cm diameter multinodular polypoid masses, often arranged in botryoid clusters, may be either scattered or almost completely replacing the normal mucosa (see Fig. 14.6).[137,138] The masses are firm to friable and purple or tan with smooth surfaces; haemorrhage may be noted.

Histopathology

The well-demarcated pedunculated masses are composed of papillary and glandular structures lined by pseudostratified, well-differentiated cuboidal to columnar epithelial cells, including mucous cells, that are supported by a thin to moderately abundant fibrous stroma containing lymphoid cells.[137,138] There is minimal anisokaryosis and anisocytosis and mitotic figures are rare.

Immunohistochemical labelling

Immunohistochemical labelling for papillomavirus antigen in one case was negative.[137]

Gastric or intestinal adenocarcinoma

See also page 464.

Cellular origin

Glandular crypt epithelium of the stomach (glandular region), small intestine, caecum or colon.

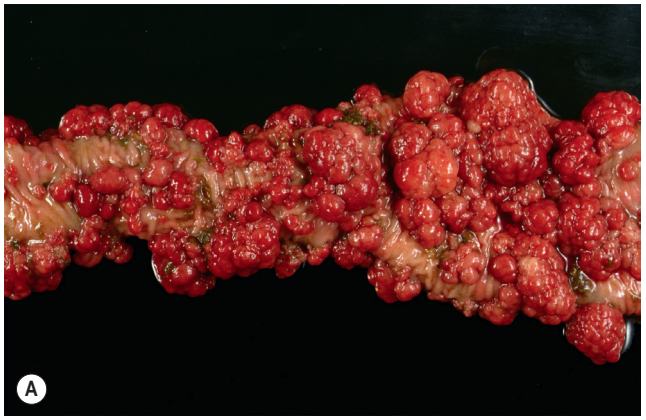




Figure 14.6 Intestinal adenomas. (A) Large numbers of adenomas forming multifocal botryoid clusters (adenomatous polyposis) in the mucosa of the ileum of a 4-year-old Quarter Horse. **(B)** The histological appearance of a polypoid adenoma, lined by well-differentiated epithelial cells and supported by a branching fibrovascular stroma; muscularis mucosae tissue is noted in the pedicle. There is an abrupt transition from the adjacent normal mucosa (H&E, ×20). *(Figure A reprinted from Patterson-Kane JC, Sanchez LC, MacKay RJ, et al. Small intestinal adenomatous polyposis resulting in protein-losing enteropathy in a horse. Veterinary Pathology 2000; 37(1):82–85, copyright 2000 by Sage Publications Ltd., reprinted by permission of Sage Publications Ltd.*[137]*; Figure B courtesy of Dr Juan A. Muñoz Moran, Clinique Vétérinaire du Grand Renaud, France. Reprinted from Muñoz Moran JA, Lemberger K, Cadoré J-L, et al. Small intestine adenocarcinoma in conjunction with multiple adenomas causing acute colic in a horse. Journal of Veterinary Diagnostic Investigation 2008; 20(1):121–124, copyright 2008 by Sage Publications Ltd., reprinted by permission of Sage Publications Ltd.*[138]*)*

Profile

Gastrointestinal adenocarcinoma/carcinomas comprise less than 1% of all neoplasms in horses. Those arising in the glandular region of the stomach are exceedingly rare; in two studies, only 3/21 and 1/20 horses with gastric carcinoma had this diagnosis.[105,140–142] In the intestine, the neoplasms can be located in the jejunum, ileum, caecum, right ventral colon, right dorsal colon or the transverse colon.[143–150] In one study of equine intestinal neoplasia (n = 34), 32% were adenocarcinomas, of which 82% involved the small intestine; 18% the large intestine; 9% the small colon; and 9% the small intestine *and* small colon.[151] However, a predilection for the large intestine has been suggested by other authors.[152]

Gastrointestinal carcinomas tend to arise in middle-aged to older horses.[144] The mean age in horses with intestinal adenocarcinoma in one study (n = 11), was 20 years.[151] They have been seen in younger horses, with one report of a colonic adenocarcinoma in a 5-year-old horse.[149]

There does not appear to be a gender bias. In the intestinal tract, there may be a predilection for the Arabian breed, comprising 9 of 11 horses in one study.[151]

Biological behaviour

Adenocarcinomas are highly invasive and can metastasize. It has been suggested that, in horses, this neoplasm may actually have low metastatic potential. However, in some studies (admittedly involving small numbers of animals), it occurred frequently; intra-abdominal metastasis was evident in 4 of 11 horses with intestinal adenocarcinoma.[138,148,151] Metastasis occurs via lymphatic vessels to regional lymph nodes and other sites, including the liver, omentum, spleen, lungs and thoracic lymph nodes.[142,143,149–150,153–155] Transcoelomic dissemination with implantation on serosal surfaces of the intestine and other abdominal organs may occur.[105,142]

In one horse with a gastric adenocarcinoma, metastasis to the liver and portal vein (with thrombosis) resulted in hepatic encephalopathy.[156] Tertiary metastasis (i.e. metastasis from secondary sites of involvement) was reported in a case of colonic adenocarcinoma, to bones (ribs, sternum, ilium, thoracic vertebrae), skeletal muscle and multiple internal parenchymal organs; most of the osseous metastases were occult.[149] In another case involving the large colon, there was metastasis to the left humerus, resulting in necrosis, osteolysis and pathological fracture.[155]

In a horse with large colon adenocarcinoma, *Clostridium difficile* and *Clostridium perfringens* toxins were isolated incidentally from the faeces and were not then found following successful surgical excision of the mass; clostridial infections have also been reported on rare occasions in human patients.[157] Other associated changes may include hypoalbuminaemia (protein-losing enteropathy) and hyperglobulinaemia, the latter most likely due to chronic inflammation.

Pemphigus foliaceus was seen in one gelding with intestinal adenocarcinoma, that was believed to be paraneoplastic (see Fig. 6.4).

The median survival time for horses with intestinal adenocarcinoma is 1.8 months.[151]

A focal distal jejunal adenocarcinoma in a horse with multiple adenomatous polyps indicated that there may have been malignant transformation of an adenoma, as is well-known in canine and human patients.[138]

Gross pathology

Adenocarcinomas are white, white-yellow, white-grey or tan on outer and sectioned surfaces and are fleshy, gritty or

firm in consistency; they often invade deeply into the gastrointestinal wall from the mucosa and may extend transmurally as well as intraluminally (see Fig. 28.28).[105,144,151] There may be adhesions to adjacent organs.

Where the stomach is involved, the distal oesophagus may be dilated with linear mucosal erosions – pyloric constriction has also been reported.[154]

In the small intestine, these masses are often annular/segmental, measure several cm in thickness and are variable in length and circumferential involvement.[138,157] In one study, three of five intestinal adenocarcinomas formed intraluminal masses.[151] Intraluminal masses have measured up to 30 cm diameter, are papillary, nodular or polypoid and may have extensive central ulceration and necrosis that in some cases results in haematochezia.[105,148,149,155,157] Annular or intraluminal masses may both narrow the intestinal lumen sufficiently to cause partial obstruction and impaction or complete obstruction.[151] There may be hypertrophy or dilation of proximal intestinal segments; proximal segment distension was not seen in horses with intestinal lymphosarcoma.[151]

Large intestinal adenocarcinomas are also variable in appearance and effects, with the least severe manifestation being reported as mild thickening of the wall.[151] There may be severe, craterous ulceration of the luminal surface (see Fig. 28.28).[151] In one horse, detachment of caecal neoplastic tissue into the lumen caused obstruction of the small colon.[148] An adenocarcinoma around the base of the caecum in another animal almost completely occluded the caecocolic orifice and was associated with caecal rupture.[146]

Metastatic masses are white or tan, nodular, firm and vary in size.

There may be large amounts of serosanguineous fluid within the abdominal cavity, in addition to dependent oedema, weight loss and diarrhoea. Neoplastic cells are not usually found in peritoneal fluid.[151]

Histopathology

Adenocarcinomas are often poorly-demarcated, unencapsulated and infiltrative, but may be discrete. Neoplastic infiltration may extend into the muscularis externa or even to the serosal surface.[149] In gastric masses, focal or multifocal contiguity with surrounding glands may be noted.[105]

The tumour cells line acinar structures of varying size and/or form cords, nests or sheets with highly variable amounts of supporting stroma that may be abundant. The tumour cells are round, polygonal, cuboidal or columnar, with an eosinophilic cytoplasm that has poorly-defined margins; goblet cells may be noted and lumens may be filled with mucin[143] (periodic acid-Schiff-positive) in addition to necrotic debris.[146,156,157] Nuclei are large, round to ovoid and often basal (although there may be loss of this polarity) and contain one to several nucleoli, with variable chromatin content, pleomorphism and mitotic rates.[138,148] Multinucleate tumour cells have been noted in some cases.[105] Tumour cell emboli may be noted in lymphatic vessels within and surrounding the mass.

There may be dystrophic mineralization and/or osseous metaplasia within primary and/or metastatic lesions that is a feature of this type of neoplasm in horses; the bone is produced by aberrant stromal cells under the influence of unknown factors produced by the neoplastic epithelium and may form a network of interconnecting trabeculae around tumour cell acini.[147–150,152,153] Other associated lesions can include mucinous degeneration, necrosis, fibrosis, inflammation and extensive surface ulceration with bacterial colonization and granulation tissue formation.

Immunohistochemical labelling

The neoplastic cells are cytokeratin-positive.

Box 14.10 Differential diagnoses for gastric or intestinal adenocarcinoma

Neoplastic
- Intestinal lymphosarcoma
- (Gastric) squamous cell carcinoma
- Gastrointestinal stromal tumour
- Leiomyoma
- Leiomyosarcoma

Non-neoplastic
- Polypoid hamartoma
- Other polyps (see rectal polyp, Fig. 3.9)
- Submucosal haematoma

Differential diagnoses

These are listed in Box 14.10.

Polypoid hamartomas are composed of increased amounts of well-differentiated tissue and require histological differentiation from neoplastic lesions. A mass reported in the pylorus of a 13-year-old horse measured 20 cm in length (including a 10 cm long stalk) and was composed of hyperplastic gastric mucosal tissue with an inflamed stroma.[158] An inflammatory polyp in the small colon of an Arabian yearling filly resulted in ulceration, perforation and peritonitis; it was composed of fibrous tissue, adipose tissue and blood vessels.[159] These may also occur in the rectum (Fig. 3.9). A cystic hamartoma was reported in the rectum of a newborn foal.[160]

Submucosal haematomas of the intestinal tract are uncommon but may also cause a mass-effect and can be differentiated histologically.

Exocrine pancreatic adenocarcinoma

See also page 473.

Cellular origin

Exocrine cells of the pancreas.

Profile

Fewer than 10 equine cases have been documented. All have involved middle-aged to older, male or female animals (≥7 years), with the exception of one report in a 4-year-old Thoroughbred.[161–165] Two of these animals were aged donkeys (≥15 years), one of which had a history of hepatic damage and failure due to chronic pyrrolizidine alkaloid

ingestion.[166,167] The estimated rate per 100 000 patient-years at risk for horses is 1.6.[168]

Biological behaviour

Pancreatic adenocarcinomas are highly infiltrative. By the time of diagnosis, these neoplasms may extend from the pancreas into adjacent organs, including the liver, common bile duct, caecal wall and mesenteric lymph nodes; involvement of the latter suggests that spread may also occur via lymphatic vessels. Occlusion of the common bile duct has been reported in three cases, with associated jaundice in one animal.[161,162,166]

Metastatic nodules and larger masses may be widespread, with extensive transcoelomic implantation within the abdomen and involvement of the thoracic cavity including the pleura and lymph nodes.[162–164,166] One horse with metastatic spread to the mediastinum and pleura presented with respiratory signs.[165]

It is possible that neoplastic tissue might damage or replace endocrine cells in the islets of Langerhans; however, clinical signs indicating that occurrence have not been reported in horses.[165] In some cases, there will be elevations in liver enzyme concentrations.

Gross pathology

Pancreatic adenocarcinomas are variably sized, but there is generally extensive replacement of normal pancreatic tissue and, in some cases, complete replacement has been recorded.[161] There is often firm adhesion to and/or encircling of surrounding organs that can include the stomach, spleen, kidneys, adrenal glands, abdominal aorta, omentum, abdominal lymph nodes, intestines, liver, diaphragm and body wall.[163,164] The pylorus may be completely surrounded by neoplastic tissue.[166] Extension of the neoplasm into the duodenal lumen and obscuring of the minor duodenal papilla has been recorded.[165] In one case, infiltration of the left kidney caused haematuria that was proposed to occur due to disruption of pelvic blood vessels.[163]

The gross appearance of pancreatic adenocarcinomas is typical of that for carcinomas in any site: i.e. they are lobulated, multinodular or nodular, firm, glistening and white or tan-white. There may be large, soft areas of necrosis on sectioned surfaces. Necrosis of surrounding adipose tissue resulting from leakage of pancreatic enzymes may occur. The remainder of the pancreatic parenchyma may be fibrosed.[163]

Metastatic masses have a similar appearance to the primary tumour, are often nodular, cream to grey and vary markedly in size.

Affected horses show marked signs of weight loss. There will often be large amounts of serosanguineous, clear or cloudy fluid in the peritoneal and thoracic cavities and the carcass (at post-mortem examination) may be jaundiced.

Histopathology

As in other species, the epithelial tumour cells can be arranged lining acini or tubules, or in solid cords, islands and/or sheets, frequently supported by large amounts of (scirrhous) stromal tissue. The pattern of arrangement will often vary within the same mass. In tubular forms, one or two layers of cuboidal or columnar, mucus-secreting tumour cells form structures resembling pancreatic ducts.[162,165] In acinar forms, the tumour cells mimic the arrangement of the normal parenchyma. Zymogenic granules may or may not be noted depending on the stage of differentiation or the tumour cell origin; in theory, tubular forms are derived from ductal epithelium and those containing granules are of acinar epithelial origin, although pluripotent stem cells could give rise to both.[164,166,169] Nuclei are large, central, round or ovoid, contain densely packed or more dispersed chromatin and are pleomorphic with one or multiple prominent nucleoli and a variable but potentially high mitotic rate.

In one case, there was metaplasia to squamous cell carcinoma in some metastatic masses.[166] There may be extensive areas of tumour cell necrosis, some surrounded by dense fibrous tissue.[163,167] Associated lesions can include microabscesses or lymphoid aggregates, and peri-pancreatic necrosis.[164,165]

Tumour cells have been identified cytologically in peritoneal and/or pleural fluid samples.[163]

Immunohistochemical labelling

The neoplastic cells are cytokeratin-positive.

Hepatocellular carcinoma and adenoma

(See also p. 467)

Cellular origin

Hepatocytes.

Profile

Less than 1% of primary tumours in horses are thought to involve the liver[153,170] and not all of those will be of hepatocellular origin. Hepatocellular carcinomas can affect young horses (1–3 years) in addition to older animals, of multiple breeds.[171,172] There was one report of a carcinoma with both hepatocellular and cholangiocellular elements in an 18-year-old Thoroughbred mare[173]; the authors have seen a similar case (Fig. 14.7).

Biological behaviour

Hepatocellular carcinomas may reach a large size and cause extensive destruction of the liver parenchyma before metastasizing.[174] Metastasis is often extensive, occurring in remaining liver lobes, hepatic and other abdominal lymph nodes, abdominal organs, including the kidneys, and potentially throughout the abdominal cavity with implantation on serosal surfaces. There may also be widespread metastasis into the thoracic cavity, with lungs and thoracic lymph nodes being involved. Intrathoracic metastasis was seen in both cases of mixed hepatocellular/cholangiocellular carcinoma (see Fig. 14.7).[173]

Absolute secondary erythrocytosis can occur as a paraneoplastic syndrome (pp. 76 and 469), due to production of erythropoietin by neoplastic cells; α-fetoproteinaemia and persistent hypoglycaemia (with normal serum insulin

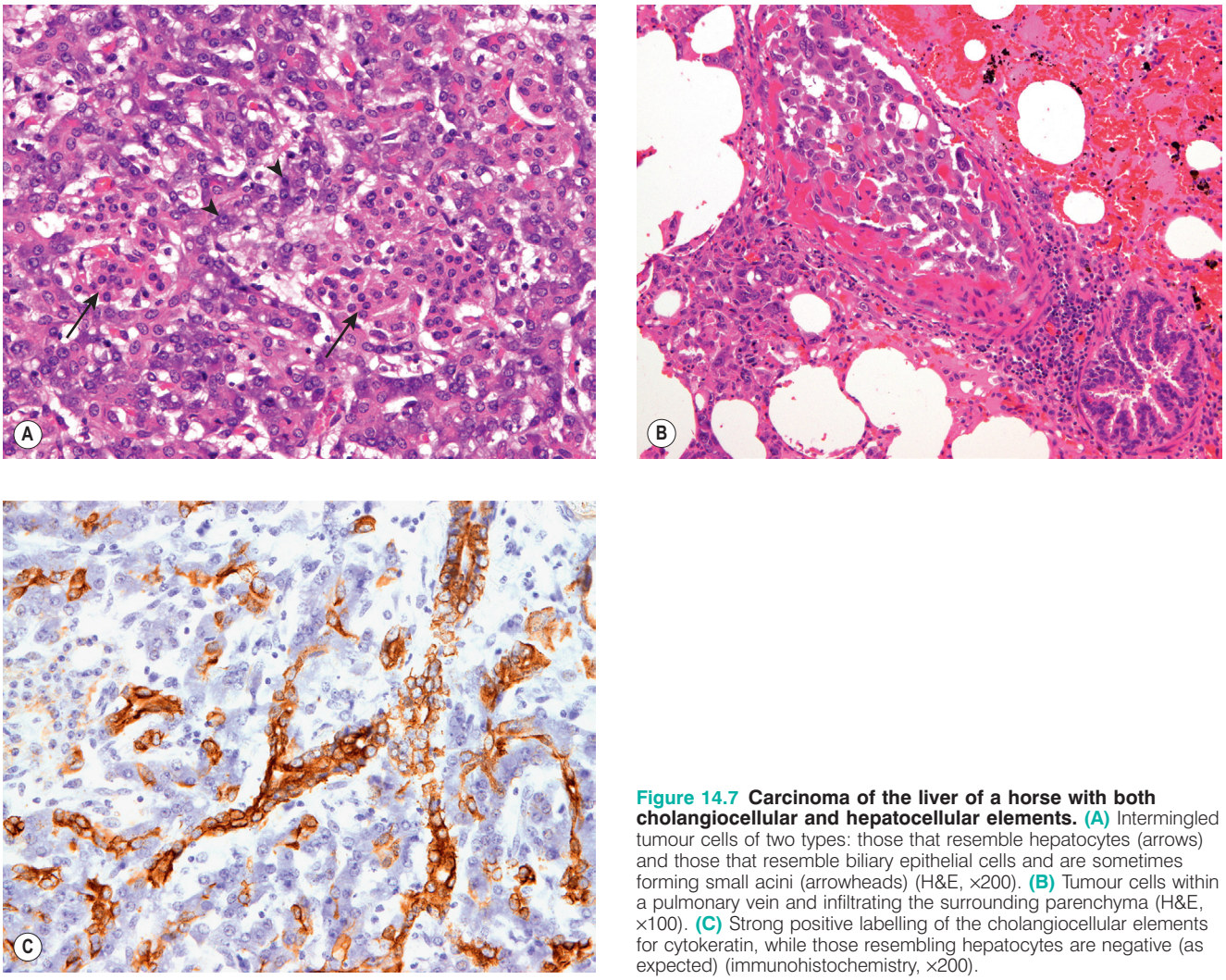


Figure 14.7 Carcinoma of the liver of a horse with both cholangiocellular and hepatocellular elements. **(A)** Intermingled tumour cells of two types: those that resemble hepatocytes (arrows) and those that resemble biliary epithelial cells and are sometimes forming small acini (arrowheads) (H&E, ×200). **(B)** Tumour cells within a pulmonary vein and infiltrating the surrounding parenchyma (H&E, ×100). **(C)** Strong positive labelling of the cholangiocellular elements for cytokeratin, while those resembling hepatocytes are negative (as expected) (immunohistochemistry, ×200).

values) have also been documented.[172] Alpha-fetoprotein is an α_1-globulin usually only synthesized by fetal liver cells; serum levels are used as a diagnostic marker for human patients with hepatocellular carcinoma and this protein has been documented immunohistochemically in equine hepatocellular neoplasms (see below).[175]

Gross pathology

The liver is usually enlarged and the primary mass is of variable size, but may occupy an entire lobe and exceed its original size. Adenomas are usually solitary and well-demarcated (but usually unencapsulated), with compression of surrounding tissue; they are nodular or multilobular and may reach a large size in some cases.[176] Adenomas do not have a consistency firmer than normal liver tissue, as the nature of the stroma is similar.[177] Carcinomas are usually irregular in shape with an uneven or multinodular surface, but will frequently have well-defined margins (Fig. 28.31).[177] Although they may be solitary, more typically there will be numerous further but smaller masses throughout the liver parenchyma.[173] A 'diffuse' carcinoma is defined as small, indistinct masses spread throughout the entire parenchyma.[177] The neoplastic masses are tan, yellow, grey or grey-yellow (Fig. 28.31); when malignant there is often varied colour on sectioned surfaces due to haemorrhage, necrosis (softening) and/or bile pigmentation, but umbilication is not a typical feature.[176] Scirrhous carcinomas are firm and white, but usually the consistency is friable. There may be invasion of the liver capsule or hepatic vein by neoplastic tissue.

Affected horses often show evidence of weight loss. Serous or serosanguineous fluid (5–20 litres) may be noted within the abdominal cavity; haemoperitoneum was seen in one case due to capsular rupture overlying a large mass.[171,172,173]

Histopathology

Adenomas are sharply demarcated from the surrounding parenchyma, which is usually compressed. These benign neoplasms are composed of tumour cells that have a very similar appearance to normal hepatocytes and are arranged in cords or trabeculae of even thickness (usually ≤3 cell layers), without evidence of normal portal tracts or central veins.[176] The arrangement of the hepatocytes tends to intersect adjacent normal lobular tissue at right angles, allowing identification of the margin of the neoplasm.[177] If

Box 14.11 Differential diagnoses for hepatocellular carcinoma and adenoma

Neoplastic
- Cholangiocellular carcinoma
- Lymphosarcoma
- Metastatic neoplasia (e.g. gastrointestinal or pancreatic carcinoma)

Non-neoplastic
- Hamartomas

more than one portal tract is observed, this is usually due to entrapment of normal structures. The tumour cells may contain lipid and/or glycogen.

In carcinomas, the tumour cells are frequently arranged in cords or trabeculae that may be 3 to >20 cells thick,[177] often vary in thickness within the mass and are separated by sinusoids that may be dilated; solid sheets with few vascular channels may also be noted in poorly-differentiated neoplasms. Acini or cystic spaces may be noted within the trabeculae.[174] These tumour cells also resemble hepatocytes (see Fig. 14.7), but with varying degrees of pleomorphism, depending on the (potentially highly variable) degree of differentiation. Relative to hepatocytes the nuclear:cytoplasmic ratio is increased and the cytoplasm is often voluminous and granular but may contain lipid and/or glycogen.[174] Nuclei are round, oval or irregularly-shaped, contain enlarged nucleoli and have a variable mitotic rate (very few in well-differentiated carcinoma); binucleate or multinucleate tumour cells may be noted. There may be biliary canalicular structures within the neoplastic tissue, sometimes containing bile plugs. Necrosis may be noted in the centres of larger trabeculae.[177] Clusters of tumour cells may be seen in hepatic blood vessels or blood vessels in other organs (where metastasis has occurred).

Immunohistochemical labelling

Alpha-fetoprotein expression can be demonstrated in many hepatocellular carcinomas, but they are cytokeratin-negative (see Fig. 14.7).

Differential diagnoses

These are listed in Box 14.11.

There have been rare reports of hamartomas involving the livers of foals, i.e. masses resulting from faulty development and composed of abnormal amounts and mixtures of tissue elements that are normally present. Potentially, such masses could be found clinically or incidentally in older animals. A mixed hamartoma was reported in the liver of a late-term aborted fetus; it measured 1.5 cm in diameter and was comprised histologically of disorganized large hepatocytes intermingled with numerous bile ducts and a few portal tract-like regions.[178] A mesenchymal hamartoma in another late-term equine fetus was composed of abnormal bile ducts supported by abundant myxoid stroma.[179]

Hepatoblastoma

See page 407 (neoplasms arising from precursor cells).

Cholangiocellular carcinoma

Cellular origin

Cholangiocellular carcinomas are malignant neoplasms derived from intrahepatic biliary epithelial cells.

Profile

Cholangiocellular carcinomas are thought to be the most common primary neoplasms of the equine liver, particularly in horses and mules ≥10 years.[31,180–182]

Jeffcott (1969) reviewed 10 cases of primary hepatic tumours in horses (1882–1946), eight of which were cholangiocellular carcinomas.[171] There was one report of a carcinoma with hepatocellular and cholangiocellular elements in an 18-year-old Thoroughbred mare. The author has diagnosed a similar, further case (see Fig. 14.7).

Oncogenesis

A cholangiocellular carcinoma arose in a liver affected by chronic inflammation and fibrosis, raising the question as to whether those lesions (relatively common in horses) predispose to neoplastic transformation.[181]

Biological behaviour

Cholangiocellular carcinomas tend to progress slowly.[183] They are considered to metastasize more frequently than hepatocellular carcinomas. In addition to spreading within the liver (intrahepatic metastasis), they may also extend to and through the hepatic capsule to invade adjacent tissues, including the diaphragm. They may also spread widely within the abdomen. Widespread metastasis may additionally occur via portal lymphatic vessels and veins, although haematogenous metastasis is considered to be the less common route.[174,176,180,184] Intrathoracic metastasis was seen in both cases of mixed hepatocellular/cholangiocellular carcinoma (see Fig. 14.7).[173]

Neoplastic tissue has been seen to invade the caudal vena cava.[184] In another report, there was metastasis to the synovium of the left metacarpophalangeal joint, with invasion and erosion of bone.[181]

Gross pathology

The liver is usually markedly enlarged and contains multiple (potentially hundreds of) coalescing masses that may occupy a large percentage of the parenchyma.[183,184] It is not known if multiple masses of this type of neoplasm are metastatic and/or multicentric in origin.[176] The masses range from a few millimetres to >5 cm in diameter, are unencapsulated but well-demarcated, nodular or irregularly-shaped and sometimes lobular. On outer and sectioned surfaces cholangiocellular carcinomas are white or white-yellow and firm. They are typically umbilicated if at the liver surface (usually due to central necrosis) and there may be partial mineralization.[181]

Affected horses may present with icterus and if there is metastasis throughout the abdomen (carcinomatosis) an

Box 14.12 Differential diagnoses for cholangiocellular carcinoma

Neoplastic
- Hepatocellular adenoma or carcinoma
- Lymphosarcoma or leukaemia
- Metastatic neoplasia (e.g. gastrointestinal or pancreatic carcinoma)

effusion will be seen. Pleural effusion may also be noted if there are intrathoracic masses.[180] There may be involvement of regional lymph nodes.

Histopathology

Cholangiocellular carcinomas show pronounced invasion of surrounding tissue, including hepatic sinusoids.[180] Tumour cells are arranged in lobules, cords or in one to multiple layers that line and sometimes fill ducts or acini; on occasion, there may be papillary formations.[176,181] In less well-differentiated neoplasms, there may be solid cords of tumour cells with rare lumen formation.[174] The tumour cells are supported by a fine to abundant (scirrhous) fibrous stroma, amounts of which may vary within the same liver.

The tumour cells resemble biliary epithelial cells and are cuboidal to columnar with a small to moderate amount of clear or eosinophilic cytoplasm (see Fig. 14.7); there may be mucin production. The basal nuclei are oval or elongate, may be vesicular and in some cases contain one to several prominent nucleoli. The mitotic rate is high (e.g. 5–18 per high power (×400) field), but multinucleate cells and karyomegaly are not typical features.[173,177,181] The high mitotic rate assists in differentiation from hepatocellular carcinoma. Tumour acini may contain bile and in some cases, where mucin production is marked, it may form 'lakes'.[174] There is marked invasion of surrounding tissue, which is often necrotic.[177]

Other associated lesions may include central necrosis and mineralization, mixed inflammatory cell infiltrates and in the surrounding hepatic parenchyma, portal fibrosis, biliary hyperplasia and cholangiohepatitis.[182]

Immunohistochemical labelling

Cholangiocellular carcinoma cells are α-fetoprotein negative, but most should label positively for cytokeratin (see Fig. 14.7).[181] In one case, strong positive nuclear immunolabelling for p53 was demonstrated in neoplastic but not normal bile ducts, i.e. aberrant overexpression that might indicate a p53 mutation.[182]

Differential diagnoses

These are listed in Box 14.12.

Biliary adenofibroma (biliary cystadenoma/cholangioma)

Cellular origin

Biliary epithelium. The biliary adenofibroma is a morphological variant of the biliary cystadenoma.

Box 14.13 Differential diagnoses for biliary adenofibroma

Neoplastic
- Cholangiocarcinoma

Non-neoplastic
- Congenital or acquired bile duct cysts

Profile

There has been one report of this type of neoplasm, as an incidental finding in a 10-year-old horse.[185]

Biological behaviour

These are benign, expansile masses.

Gross pathology

The one reported mass was 16 cm in maximal diameter, well-circumscribed, ovoid and firm, with multiple small cysts on sectioned surfaces (2 mm maximal diameter).[185]

Histopathology

The mass was expansile and unencapsulated. Tubules, acini and cysts were lined by single layers of epithelial cells within an abundant fibrous stroma. The tubules were dilated and branching, with some intraluminal papillary projections.[185] The epithelial cells were columnar to flattened (in cysts) with some apical cytoplasmic blebbing (apocrine-type). The cysts contained proteinaceous fluid and some cellular debris.

Immunohistochemical labelling

Epithelial cells stain positively for cytokeratins 7 and 19, confirming origin from biliary ducts.[185]

Differential diagnoses

These are listed in Box 14.13.

Multiple 4–20 cm diameter congenital bile duct cysts, associated with fibrosis and ascending cholangitis, i.e. congenital polycystic liver disease, were reported in a 3-week-old foal.[186] Polycystic liver disease was also reported in a 13-year-old mare that presented with respiratory signs due to a thoracic granular cell tumour.[187]

UROGENITAL TRACT

Renal carcinoma and adenoma

See also page 652.

Cellular origin

Renal carcinomas/adenocarcinomas and adenomas are malignant and benign tumours respectively, that usually arise from cortical tubular epithelium. The transitional epithelium of the renal pelvis is a rare site of origin.[188] A squamous cell carcinoma of renal pelvic origin has also been reported as an incidental finding.[189]

Profile

Primary renal neoplasia is rare in horses, with a prevalence of 0.1–0.15% in post-mortem surveys, and renal carcinomas are the most commonly reported type (see p. 654).[190,191]

Usually, renal neoplasia is unilateral. In reports of bilateral renal carcinoma, masses in one of the kidneys are generally considered to be metastatic.[192,193] There are conflicting reports as to right versus left predilection of carcinomas; in one report (n = 15), 64% involved the right kidney, in another (n = 23), 65% arose in the left kidney, while in a third, the left and right were affected with approximately equal frequency.[193–195]

Carcinomas have been reported in horses 4–25 years of age.[191,195–202] In one survey of 23 reported cases (1977–2008), the mean age was 13 years.[193] However, in an earlier report of renal carcinomas in 15 horses (1934–1986), seven were 10 years or less.[195]

Renal carcinomas have been reported in various breeds. In the 23 cases previously mentioned, Quarter Horses were under-represented compared with Thoroughbreds and Arabians; however, the small numbers involved make it difficult to draw firm conclusions as to breed susceptibility.[193] There was one report of renal neoplasms having a three-fold higher incidence in horses with a dark coat colour.[190] Carcinomas occur with approximately equal frequency in males and females.

There have been few reports of renal adenomas, as they are usually clinically silent and therefore only diagnosed incidentally at necropsy.[120,203] Renal adenoma has been reported as a cause of haematuria.[204,205] Cystadenomas arising from renal mucous glands were reported in a 35-year-old mare, again as an incidental finding at necropsy; horses are unique in that low numbers of such glands are located in the renal pelvic stroma and proximal ureter.[206]

Biological behaviour

In a case series of 23 horses with renal carcinoma, the median survival time following diagnosis was 11 days (0 days to 1 year).[193] Renal carcinomas are invasive and may disseminate widely by peritoneal seeding.[191,192] There may also be direct invasion of adjacent organs, including the liver.[207] Metastasis is common and occurs via lymphatic and/or blood vessels to multiple internal sites, with the lungs, liver and regional lymph nodes being most frequently involved.[192,193,196,198,200,207–209] In a retrospective series of nine cases, three had lung metastases.[199]

More unusual metastatic sites include the vertebral canal, skeletal muscle and bone. One horse developed marked lameness following metastasis to the distal phalanx of the right forelimb.[210] In another unusual case, a metastatic mass occurred in the gingiva of the incisor area with loosening and displacement of teeth.[211] However, metastasis is not invariable and in young horses with no overt evidence of it, it has been suggested that nephrectomy may be a therapeutic option.[195]

Paraneoplastic hypoglycaemia may occur and has been proposed to be caused by production of an abnormal form of insulin-like growth factor 2; the hypoglycaemia may be clinically insignificant in many cases and may be unrecognized.[201,212] In a horse with a renal carcinoma that occupied almost half of the abdominal cavity, hypercupraemia was diagnosed, the cause of which was uncertain; certain neoplasms in human patients are known to promote reduced catabolism of ceruloplasmin.[195] Generalized paraneoplastic pruritis has also been observed (see Fig. 6.3).

A papillary renal adenoma was cured by nephrectomy.[205]

Gross pathology

Renal carcinomas are solitary masses of variable size; the tumour may occupy one pole of the kidney or may replace the entire organ; masses up to 75 cm in maximal diameter and 48 kg in weight have been reported (see Figs. 36.2, 36.3).[191,194,195,197,199,201,207,209] There may be a thin rim of remnant normal renal tissue (Fig. 36.2). There may also be multiple masses within the affected kidney.[200]

Renal carcinomas are generally well-demarcated, ovoid or spherical; they may be lobulated and some have a thick fibrous capsule.[195,198,201,213] The surface may be smooth and/or irregular and nodular. There may be adhesions to the liver, peritoneum, stomach and/or adjacent intestinal tract, invasion of the ventral lumbar muscles and encirclement of the caudal abdominal aorta and caudal vena cava.[195,199,207] Extension into the caudal vena cava via the renal vein may be observed.[192,199]

Renal carcinomas are soft to firm, depending on the abundance of stromal tissue and some are cystic/fluctuant. These masses are white, grey-white, grey, pale yellow or pale tan, with central and sometimes very extensive areas of necrosis and haemorrhage (Figs. 7.11, 36.2).[191] Metastatic masses are nodular, with a similar gross appearance. A horse that died suddenly was diagnosed with a carcinoma that had a gelatinous consistency; it ruptured and resulted in marked intra-abdominal haemorrhage.[202]

A carcinoma arising from the transitional epithelium of the renal pelvis was described as 34 cm in maximal diameter, oval, encapsulated, grey-white and protruding from the pelvis, with the main structure of the kidney being intact.[188] It was adherent to adjacent tissues and extended around the abdominal aorta and renal vessels.

Haematuria (Fig. 36.1) is a common finding (reported in 50% of 15 horses in one study); there may also be ascites (particularly when there is intra-abdominal metastasis) and/or ventral and hindlimb oedema.[191,195] Haemoperitoneum and haemothorax have been reported, resulting from haemorrhage from the neoplastic masses.[197,199] In two horses with renal carcinoma, there were associated nephroliths.[193] Compensatory hypertrophy of the contralateral kidney is usually not noted.

Renal adenomas are solitary, nodular, well-demarcated, usually unencapsulated and can measure <2 cm in diameter. Since equine renal adenomas may also be large (>6 cm in diameter), the criterion of size cannot be used to differentiate adenoma from carcinoma.[214] If they do not involve the superficial parenchyma, smaller masses may only be noticed on sectioning of the kidney. One mass found in a horse was granular and paler than normal renal parenchyma on sectioning, while another was friable and dark red to yellow.[205] Larger adenomas may contain central regions of necrosis.

Renal cystadenomas arising from mucous glands were multiple, contained translucent yellow fluid and measured 1–4 cm in diameter.[206] Another renal adenoma was polypoid, dilated the right renal pelvis and, similarly, on sectioning,

contained numerous cystic spaces measuring up to 8 mm in diameter.[204] The latter mass was also considered to be of pelvic mucous gland origin, although the histological appearance was not reported.

Histopathology

It should be noted that although it is possible to obtain a diagnosis of neoplasia from biopsy specimens, in a study of the renal biopsy procedure in horses there were complications in three of four neoplasia cases.[215] Neoplastic cells may be found in cytological examinations of peritoneal fluid, but they have not been reported in urine specimens.[192]

Histologically, there may be a wide variation in the arrangement and morphology of carcinoma cells. The tumour cells may be arranged in nests, sheets, tubules, cords, tubulopapillary patterns and/or packets; more than one pattern of arrangement may be seen within the same mass and tumour cells may be arranged in one to multiple layers with supporting stroma that may be abundant.[191,207] The epithelial tumour cells may be round, polygonal, cuboidal or columnar and in some fields they may be elongate and arranged in streams; they resemble sarcoma cells, particularly when there are large amounts of stromal tissue.[201,214] Granular and eosinophilic or basophilic and mucous cells have been noted; clear cells (high lipid and glycogen content) may also occur, even only as small foci, which assist in the diagnosis of renal cell origin.[214] Nuclei are large and round, basal or central, may be vesicular and contain prominent nucleoli.[195,208] The mitotic rate is variable but may be high and multinucleate tumour giant cells or single giant nuclei may be noted.[207,213] There may be extensive necrosis of the neoplastic tissue.[197] Invasion of surrounding tissues by tumour cells has been described as 'pushing … more than by infiltrating'.[214] Tumour cell emboli may be identified within lymphatic vessels and blood vessels.[191,192] In one case, psammoma bodies were noted, i.e. round clusters of calcified material, as have been seen in renal carcinoma in other species.[207] Associated changes in the remaining renal tissue in cases of carcinoma may include fibrosis, tubular dilation with cyst formation, haemorrhage, haemosiderophages and inflammation.[209]

A transitional cell carcinoma involving the renal pelvis was composed of papillary and tubular arrangements of cuboidal or columnar tumour cells, with vesicular nuclei and prominent nucleoli.[188] There were multiple foci of mineralization and osseous metaplasia in the stromal tissue.

Adenomas may be classified histologically as papillary, tubular or solid, depending on the arrangement of the tumour cells; more than one pattern may be noted in the same mass.[213] Tumour cells are supported by a fine stroma, arranged in single layers when lining tubules or papillary projections. They are cuboidal to flattened and have an eosinophilic cytoplasm with well-defined margins. Nuclei are round and central or basal and may be hyperchromatic.[214] There is low cellular pleomorphism with few or no mitotic figures.[203,205] It can be difficult to distinguish small, very well-differentiated renal carcinomas from adenomas. Associated lesions may include stromal oedema, haemorrhage and haemosiderophage infiltration and mineralization.[203]

Renal mucous gland cystadenomas were composed of well-demarcated, encapsulated cysts in the medulla, lined by tall columnar epithelial cells forming occasional papillary projections; the cytoplasm of tumour cells and cyst lumens contained mucinous material (periodic acid-Schiff and mucicarmine positive) and nuclei were basal.[206] These lesions must be differentiated from mucous gland hyperplasia in the equine renal pelvis; in such cases there is no encapsulation, no compression of adjacent tissue and intraluminal papillary projections of epithelium do not occur.[206]

Box 14.14 Differential diagnoses for renal carcinoma and adenoma

Neoplastic
- Metastatic carcinomas

Non-neoplastic
- Polycystic kidney disease
- Renal polyp
- Renal pelvic mucous gland hyperplasia

Immunohistochemical labelling

Renal carcinoma and adenoma cells stain positively for cytokeratin. Positive labelling for vimentin may be seen in neoplastic renal epithelium, but not normal renal tubules.[203]

Differential diagnoses

These are listed in Box 14.14.

In cases of polycystic kidney disease, variably sized cystic structures are lined by single layers of flattened, well-differentiated epithelial cells within dense fibrous tissue.[216] In one foal, fibroepithelial polyps unilaterally obstructed the renal pelvis and ureter and were thought to be the cause of renal dysplastic lesions.[217] The polyps were similar to those reported in other locations, being composed of loose fibrovascular stroma with overlying epithelium.

Urinary bladder transitional carcinoma and adenoma

See also page 658.

Cellular origin

Transitional cell carcinomas and adenomas are derived from the mucosal transitional epithelium.

Profile

Urinary bladder neoplasms are very rare in horses and tend to affect older animals (>10 years), with SCC being the most common type (see p. 233).[218,219]

Transitional cell carcinoma is the most common type of urinary bladder neoplasm in other domestic species, but is rarely reported in horses (see p. 233–234).[218,220–222]

One urinary bladder cystadenoma has been reported.[223]

Oncogenesis

Urinary bladder cancers in horses, as in cattle and sheep, have been linked geographically to the distribution of

bracken fern (*Pteridium aquilinum*), including in regions in North and South America, the UK, Australia and Continental Europe.[224]

However, the exact pathogenesis of urinary bladder carcinoma in horses is not understood. Some authors have suggested that chronic cystitis may be an instigating factor.

Pyelonephritis is noted in many cases, that potentially might have caused chronic urinary bladder irritation with progression to neoplastic transformation; however, alternatively, the pyelonephritis might have resulted from ascending infection from cystitis caused by the presence of a urinary bladder neoplasm.[218,219]

An 8-year-old stallion, with metastatic transitional cell carcinoma of the urinary bladder had a proceeding >2-year history of bladder dysfunction causing urospermia; it was not known how, or if, these two conditions were related.[225]

A urinary bladder cystadenoma diagnosed in a 2.5-year-old Thoroughbred filly is thought to have arisen from a congenital urachal anomaly or remnant.[223]

Biological behaviour

Urinary bladder carcinomas are locally invasive, often extending through the bladder wall to pelvic and abdominal organs and perivesicular tissue; they may also seed within the abdominal cavity, resulting in carcinomatosis.[218]

Metastasis can occur (but not always) via lymphatic vessels to internal iliac and sublumbar lymph nodes; haematogenous metastasis to lungs and other organs can also occur late in the disease course.[218,220] Haematuria is a common clinical sign.

Gross pathology

Transitional cell carcinomas are usually solitary, variably firm and white or tan, often with an irregular surface that projects into the urinary bladder lumen (see Figs. 36.4, 36.5). Grossly, they are not distinguishable from squamous cell carcinomas (p. 234). Mucosal erosion or ulceration is frequent, resulting in or at least contributing to haematuria.[226] Carcinomatosis and more distant metastasis are often diagnosed histologically rather than grossly.[214] Urinary tract obstruction can result in ureteral dilation and hydronephrosis or pyelonephritis.[218,221]

A reported cystadenoma was intraluminal, well-demarcated, measured 10 cm in diameter and was pink-grey with polypoid projections, large areas of haemorrhage, surface ulcerations and multiple 0.3–5 cm diameter cysts on sectioned surfaces.[223]

Histopathology

Histological confirmation is often needed in these cases and diagnosis from biopsy specimens is usually possible.[218] However, multiple specimens of appropriate depth will be necessary to determine the extent of infiltration. Transitional cell carcinomas are typically classified on the pattern of growth, i.e. papillary or non-papillary and infiltrating or non-infiltrating. Papillary and non-infiltrating neoplasms do not show invasion of their own stalk or stroma, or extension beyond the lamina propria; non-papillary and non-infiltrating neoplasms are by definition confined to the mucosal epithelium (i.e. intraepithelial).[214]

Box 14.15 Differential diagnoses for urinary bladder transitional carcinoma and adenoma

Neoplastic
- Squamous cell carcinoma

Non-neoplastic
- Fibromatous or fibroepithelial polyps
- Cystic calculi in the urinary tract (might cause similar clinical signs)

The tumour cells are arranged in lobules, cords, packets or multiple layers lining papillary projections. They are cuboidal or polygonal, with a small amount of eosinophilic cytoplasm that has well-defined margins; there may be small areas of squamous and/or glandular metaplasia.[220] The cytoplasm is likely to be more strongly eosinophilic than that of normal transitional epithelial cells.[214] Nuclei are central and round or ovoid with finely granular, often marginated chromatin and one to several small central nucleoli; they may also be vesicular. Cellular pleomorphism and mitotic rates are variable but may be high, and binucleate and multinucleate tumour cells may be observed. Clusters of tumour cells may be seen within lymphatic vessels.[220]

Other lesions include tumour cell necrosis, neutrophilic or lymphoid inflammation and surface erosion or ulceration.

A cystadenoma is composed of mucous-filled cysts lined by simple columnar or flattened epithelial cells.[223]

Immunohistochemical labelling

Tumour cells should be cytokeratin-positive.

Differential diagnoses

These are listed in Box 14.15.

Fibromatous or fibroepithelial polyps are pedunculated intraluminal masses composed of fibrous tissue covered by transitional epithelium, which may undergo extensive squamous metaplasia.[218,227]

Ovarian cystadenoma (serous cystadenoma)

See also page 643.

Cellular origin

These benign neoplasms have been proposed to be derived from the epoöphoron (cranial mesonephric tubules) and/or rete ovarii.[228] However, their appearance in horses specifically (in the few cases described) is more suggestive of origin from the ovulation fossa epithelium.[229,230] Some authors have suggested that ovarian cystadenomas arise indirectly from germinal inclusion (fossa) cysts (p. 275).

Profile

This is the most common ovarian epithelial neoplasm, but is rarely diagnosed in horses.

Biological behaviour

These neoplasms are benign. Most ovarian cystadenomas are considered to be non-functional, although there are a few reports of elevated plasma testosterone levels in affected mares.[229,231] Therefore, the contralateral ovary should not be affected and mares may continue to cycle and become pregnant.

Gross pathology

Ovarian cystadenomas occur unilaterally in horses. The masses are composed of one or more usually multiple, thin-walled cystic structures that on sectioned surfaces contain clear, translucent yellow or cloudy brown fluid (see Fig. 35.12).[230–232] The ovulation fossa may still be intact, as opposed to the situation with most granulosa cell tumours.

Ovarian cystadenomas may be very large, with destruction of all normal ovarian tissue. One mass was reported to weigh 5 kg (including fluid) and measure 26 cm in maximal diameter.[230]

The contralateral ovary should have a normal appearance.

Histopathology

The cystic spaces comprising the tumour mass are lined by a single layer of cuboidal, low columnar or flattened epithelial cells that may be ciliated.[232] There is a supporting fibrous stroma and in some cases the tumour cells line multiple branching papillary projections into the cystic spaces.[229] Pseudostratified epithelium is sometimes seen. There are thin, poorly-vascularized, mature fibrous septa separating cystic structures, that are not seen in their malignant counterparts (see below).[233] Mitotic figures are rare.

Differential diagnoses

These are listed in Box 14.16.

Germinal inclusion cysts ('fossa cysts') of mares arise from surface epithelial cells in the region of the ovulation fossa, which become pinched off and entrapped in the ovary post-ovulation.[228] They are considered to arise from the paramesonephric (Müllerian) region of the fossa lining.[234] Germinal inclusion cysts are multiple and increase in size and number with age. Usually, they are not sufficiently numerous or large enough to interfere with ovulation and only in rare, very advanced cases do they replace most or all of the ovarian parenchyma.[235] In one study, germinal inclusion cysts were identified in 27 (64%) of 42 randomly chosen ovaries from mares; in 17 of those ovaries, the cysts measured >1–6.5 mm in diameter.[234] Histologically the blind-ending cysts may be simple, branched, tubular or vesicular and frequently contain eosinophilic secretory material. They are lined by epithelium varying from simple squamous or cuboidal, to columnar and pseudostratified with frequent ciliation; there may be occasional epithelial infoldings.[234] In the larger cysts, there is a well-defined supporting layer of connective tissue.

Parovarian cysts are common in horses. They arise from mesonephric tubule/duct remnants, may reach 6–8 cm in diameter, are mobile and are filled with clear fluid.[235,236] Parovarian cysts are located adjacent to the ovary, rather than within it.[237] Histologically, parovarian cysts are lined by a single layer of cuboidal or low columnar epithelial cells that have a clear cytoplasm and a basement membrane, with a thin supporting wall of connective tissue and smooth muscle fibres.[232,235]

Fimbrial cysts (hydatids of Morgagni) are not intra-ovarian, arising from the paramesonephric duct. They are located on the oviductal fimbria (and have a similar lining), reach up to 9 cm in diameter and have been associated with hydrosalpinx.[234,235,237] Larger cysts of this type may cause infertility.[237]

Box 14.16 Differential diagnoses for ovarian cystadenoma

Neoplastic
- Granulosa cell tumour
- Ovarian cystadenocarcinoma

Non-neoplastic
- Germinal inclusion cysts
- Parovarian cysts
- Fimbrial cysts

Ovarian cystadenocarcinoma and adenocarcinoma

Cellular origin

Malignant epithelial neoplasms of the ovary may arise from the germinal surface epithelium, paramesonephric epithelial inclusions, follicular epithelium, medullary or cortical embryonic cords, or rete ovarii. One ovarian adenocarcinoma was associated with teratomatous elements and was proposed to have arisen by malignant transformation of epithelial cells in a pre-existing teratoma.[238]

Profile

Cystadenocarcinomas in the ovaries of mares are rarer than their benign counterparts. They have been reported in a few mares, all 9–11 years of age.[233,238–240]

Biological behaviour

Metastasis usually occurs transcoelomically following cyst rupture, rather than by vascular routes. A papillary adenocarcinoma was reported to metastasize to sublumbar and tracheobronchial lymph nodes, in addition to the mediastinum.[233] In the case of the adenocarcinoma with teratomatous elements, disseminated intra-abdominal metastasis was diagnosed within 2 months, with further masses in the lungs.[238]

Gross pathology

One cystadenocarcinoma measured 10 cm in maximal diameter with a smooth surface; on sectioned surfaces, numerous cysts 5–30 mm in diameter contained serosanguineous fluid.[240] The opposite ovary in that case

was atrophic. A papillary adenocarcinoma measured 15 cm in diameter, was soft, friable and red-brown, and contained numerous 1–3 mm diameter cysts; a large 35 cm diameter metastatic mass in the cranial mediastinum caused marked pleural effusion.[233] The adenocarcinoma with teratomatous elements was 10 cm in diameter and white, with necrotic and haemorrhagic areas on sectioned surfaces and an eccentric cavity containing red fluid, gelatinous material and hair.[238]

There may be ascites, ventral oedema and hindlimb oedema due to peritoneal metastasis and/or obstruction of lymphatic vessels.[233]

Histopathology

In the papillary cystadenocarcinoma, one to multiple layers of disorganized cuboidal or columnar epithelial tumour cells are supported by fibrous stroma lined and formed papillary projections into cystic spaces, some of which are multilocular.[240] The tumour cells in these neoplasms have an eosinophilic cytoplasm with poorly-defined margins and a large apical or central, vesicular, round or ovoid, variably-sized nucleus containing one to several prominent nucleoli. The mitotic rate is variable and multifocal invasion of the surrounding stroma may be noted. In the reported papillary adenocarcinoma, there were narrow lumens between papillae rather than large cystic spaces; additionally, some tumour cells had a foamy cytoplasm and a hyaline eosinophilic matrix was noted that was amyloid-negative.[233] The small cysts noted macroscopically were non-neoplastic inclusion cysts. In the adenocarcinoma with teratomatous elements the epithelial tumour cells were arranged in sheets and multiple layers lining ducts, with infiltration of the tumour capsule.[238] These tumour cells were highly pleomorphic with a high mitotic index. In the same mass there were whorls, bundles and herringbone patterns formed by spindle-shaped cells, this being interpreted as reactive stromal hyperplasia.

Large masses may contain areas of necrosis and haemorrhage, and cystic spaces may contain eosinophilic fluid, detached tumour cells, necrotic debris and neutrophils.[233]

Oviductal adenoma

Cellular origin

Oviductal epithelium.

Profile

There have been rare reports of this neoplasm in horses, involving the oviductal infundibulum.[228,241]

Biological behaviour

Oviductal adenoma is not invasive.

In one case, association of a large mass with infertility was considered to be due to obliteration of the ovarian fossa.[241] Following surgical removal of the adenoma and adjacent ovary, the mare cycled and subsequently foaled normally.

Box 14.17 Differential diagnosis for oviductal adenoma

Non-neoplastic
- Fimbrial cyst

Gross pathology

In one case, a large adenoma had a papillary structure and was attached to the infundibulum.[228] In a further case, there was a large, loose, pedunculated periovarian mass, that was also papillary.[241]

Histopathology

Oviductal adenomas resemble the normal oviductal mucosa; the normal mucosa has ciliated, secretory, basal and (non-ciliated) 'peg' cells.[228] One mass from a mare was described as having a papillary stroma lined by crowded pseudostratified columnar epithelial cells, with basal nuclei and apical cilia.[241]

Differential diagnoses

These are listed in Box 14.17.

Endometrial adenocarcinoma

Cellular origin

Endometrial epithelium

Profile

This neoplasm has been reported rarely, in 11–14-year-old mares.[242,243]

Biological behaviour

In one case, metastasis to internal iliac lymph nodes, a bronchial lymph node and the lungs was reported, with one metastatic mass bulging into a bronchial lumen.[242] In a further case, metastasis to the lungs, liver, spleen and peritoneal surfaces occurred.[243]

Gross pathology

One mare had marked ascites and variable numbers of 3–60 mm diameter, pale tan, firm, serosal nodules (i.e. carcinomatosis) within the abdominal cavity.[241] In this one case, the primary mass was small (0.3 cm diameter) and located in the uterine body but some of the metastatic masses were larger (up to 24 cm in diameter).

In the other case reported in a mare, there was segmental firm thickening of the uterine wall with small serosal cysts and a diffusely thickened, folded, multicystic endometrium.[242] A very large metastatic mass (30 cm in diameter) was present in the lung.

Box 14.18 Differential diagnoses for endometrial adenocarcinoma

Neoplastic
- Fibroma
- Fibrosarcoma
- Leiomyoma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Lymphosarcoma

Non-neoplastic
- Endometrial polyps
- Uterine haematomas
- Uterine abscesses

Histopathology

Tumour cells are arranged in single or multiple layers lining acini, tubules or papillary projections with an abundant supporting stroma. This stroma in the primary neoplasm may not be as prominent as in endometrial adenocarcinoma of cows. However, metastatic masses can contain very large amounts of fibrous tissue.[243] There may be intermingling of normal and neoplastic acini and tubules.[243]

The tumour cells are cuboidal or columnar with deeply eosinophilic cytoplasm; there may be goblet cells and apical blebbing of the cytoplasm has been noted.[242] Nuclei are large and hypochromatic, with distinct nucleoli and a variable mitotic rate. Acini and tubules may contain mucinous material, the abundance of which may vary between primary and metastatic masses. Tumour cells may penetrate into the myometrium and through the uterine serosal surface.[242] Tumour cell emboli may be noted within uterine lymphatic and blood vessels.[228] Associated changes include lymphoplasmacytic inflammation of the stromal tissue.

Differential diagnoses

These are listed in Box 14.18.

Endometrial polyps are rare lesions that may be pedunculated or sessile and small or large, with the largest masses filling the uterine lumen and potentially protruding through the cervix.[244] Histologically, the polyps are composed of loose fibrovascular stroma covered by endometrial epithelium that may contain inflammatory cell infiltrates. Larger masses may become ulcerated and secondarily infected.

Uterine haematomas (of uterine artery origin) have also been reported and usually follow parturition; they have a different ultrasonographic appearance to solid neoplasms, as do uterine abscesses.[245]

References

1. Fulton RE, Doane FW, MacPherson LW. The fine structure of equine papillomas and the equine papilloma virus. J Ultrastruct Res 1970; 30:328–343.
2. Pascoe RR, Summers PM. Clinical survey of tumours and tumour-like lesions in horses in south east Queensland. Equine Vet J 1981; 13:235–239.
3. Scott DW, Miller WH. Neoplasms, cysts, hamartomas and keratoses, 2nd edn. Maryland Heights: WB Saunders Co.; 2011.
4. Valentine BA. Survey of equine cutaneous neoplasia in the Pacific Northwest. J Vet Diagn Invest 2006; 18:123–126.
5. White KS, Fuji RN, Valentine BA, et al. Equine congenital papilloma: pathological findings and results of papillomavirus immunohistochemistry in five cases. Vet Dermatol 2004; 15:240–244.
6. Garma-Aviña A, Valli VE, Lumsden JH. Equine congenital cutaneous papillomatosis: a report of 5 cases. Equine Vet J 1981; 13:59–61.
7. Misdorp W. Congenital tumours and tumour-like lesions in domestic animals. 3. Horses. A review. Vet Q 2003; 25:61–71.
8. Lange CE, Tobler K, Ackermann M, et al. Identification of two novel equine papillomavirus sequences suggests three genera in one cluster. Vet Microbiol 2011; 149:85–90.
9. Knight CG, Munday JS, Peters J, et al. Equine penile squamous cell carcinomas are associated with the presence of equine papillomavirus type 2 DNA sequences. Vet Pathol 2011; 48:1190–1194.
10. Cadeac M. Sur la transmission experimentale des papillomes des diverses especes. Bull Soc Sci Vet Med Comp Lyon 1901; 4:280–286.
11. Cook RH, Olson C. Experimental transmission of cutaneous papilloma of the horse. Am J Pathol 1951; 27:1087–1097.
12. Hamada M, Oyamada T, Yoshikawa H, et al. Histopathological development of equine cutaneous papillomas. J Comp Pathol 1990; 102:393–403.
13. Binninger CE, Piper RC. Hyperplastic dermatitis of the equine ear. J Am Vet Med Assoc 1968; 153:69–75.
14. Fadok VA. Overview of equine papular and nodular dermatoses. Vet Clin North Am Equine Pract 1995; 11:61–74.
15. Pascoe RR. The nature and treatment of skin conditions observed in horses in Queensland. Aust Vet J 1973; 49:35–40.
16. Smith MA, Levine DG, Getman LM, et al. Vulvar squamous cell carcinoma in situ within viral papillomas in an aged Quarter Horse mare. Equine Vet Educ 2009; 21:11–16.
17. Knight CG, Munday JS, Rosa BV, et al. Persistent, widespread papilloma formation on the penis of a horse: a novel presentation of equine papillomavirus type 2 infection. Vet Dermatol 2011; 22:570–574.
18. Head KW. Tumours of the upper alimentary tract. Bull World Health Organ 1976; 53:145–146.
19. Johnson PJ. Dermatologic tumors (excluding sarcoids). Vet Clin North Am Equine Pract 1998; 14:625–658.
20. Njoku CO, Burwash WA. Congenital cutaneous papilloma in a foal. Cornell Vet 1972; 62:54–57.
21. Schueler RL. Congenital equine papillomatosis. J Am Vet Med Assoc 1973; 162:640.
22. Atwell RB, Summers PM. Congenital papilloma in a foal. Aust Vet J 1977; 53:299.
23. Gross TL, Ihrke PJ, Walder EJ, et al. Skin diseases of the dog and cat. Clinical and histopathologic diagnosis. Ames: Blackwell Science; 2005: 567–571, 616–634, 641–694.
24. Ginn PE, Mansell JE, Rakich PM. Skin and appendages. In: Maxie MG, ed. Jubb, Kennedy and Palmer's pathology of domestic animals. Philadelphia: Elsevier Saunders; 2007: 553–781.
25. Hamada M, Itakura C. Ultrastructural morphology of hypomelanosis in equine cutaneous papilloma. J Comp Pathol 1990; 103:119–213.
26. Fairley RA, Haines DM. The electron microscopic and immunohistochemical demonstration of a papillomavirus in equine aural plaques. Vet Pathol 1992; 29:79–81.
27. Hamada M, Takechi M, Itakura C. Langerhans' cells in equine cutaneous papillomas and normal skin. Vet Pathol 1992; 29:152–160.
28. Junge RE, Sundberg JP, Lancaster WD. Papillomas and squamous cell carcinomas of horses. J Am Vet Med Assoc 1984; 185:656–659.
29. Howarth S, Lucke VM, Pearson H. Squamous cell carcinoma of the equine external genitalia: a review and assessment of penile amputation and urethrostomy as a surgical treatment. Equine Vet J 1991; 23:53–58.
30. Gardiner DW, Teifke JP, Podell BK, et al. Fibropapilloma of the glans penis in a horse. J Vet Diagn Invest 2008; 20:816–819.
31. Valentine BA. Neoplasia. In: Bertone JJ, ed. Equine geriatric medicine and surgery. St Louis: Saunders Elsevier; 2006: 147–167.
32. Rebhun WC. Tumours of the eye and ocular adnexal tissues. Vet Clin North Am Equine Pract 1998; 14:579–606.
33. Schaffer PA, Wobeser B, Martin LE, et al. Cutaneous neoplastic lesions of equids in the central United States and Canada: 3,351 biopsy specimens from 3,272 equids (2000–2010). J Am Vet Med Assoc 2013; 242:99–104.
34. Slovis NM, McEntee MC, Fairley RA, et al. Equine basal cell tumours: 6 cases (1985–1999). J Vet Intern Med 2001; 15:43–46.
35. Feldman WH. Neoplasms of domesticated animals. London: WB Saunders Co.; 1932.
36. Blodi FC, Ramsey FK. Ocular tumours in domestic animals. Am J Ophthalmol 1967; 64:627–633.
37. Baril C. Basal cell tumour of third eyelid in a horse. Can Vet J 1973; 14:66–67.
38. Schuh JCL, Valentine BA. Equine basal cell tumours. Vet Pathol 1987; 24:44–49.
39. Dugan SJ. Ocular neoplasia. Vet Clin North Am Equine Pract 1992; 8:609–626.
40. Van den Top JGB, de Heer N, Klein WR, et al. Penile and preputial tumours in the horse: a retrospective study of 114 affected horses. Equine Vet J 2008; 40:528–532.
41. Priester WA, MacKay FW. The occurrence of tumours in domestic animals. Natl Cancer Inst Monogr 1980; 54:1–210.
42. Cilliers I, Williams J, Carstens A, et al. Three cases of osteoma and an osseous fibroma of the paranasal sinuses of horses in South Africa. J S Afr Vet Assoc 2008; 79:185–193.
43. Cihocki LM, Divers TJ, Johnson AL, et al. A case of multiple epitrichial sweat gland ductal carcinomas in a horse. Vet Dermatol 2007; 18:134–137.

44. Scott DW, Miller WH. Chapter 1. Equine dermatology. St Louis: WB Saunders Co.; 2003: 43–45.
45. Damoderan S, Ramachandran PV. A survey of neoplasms of equidae. Indian Vet J 1975; 97:339.
46. Cotchin E. Tumours of farm animals. Vet Rec 1960; 72:816–823.
47. Anderson WI, Scott DW, Crameri FM. Two rare cutaneous neoplasms in horses: apocrine gland adenocarcinoma and carcinosarcoma. Cornell Vet 1990; 80:339–345.
48. Kerr KM, Alden CL. Equine neoplasia, a ten year survey. Proc Annu Mtg Am Assoc Vet Lab Diagn 1974; 17:183.
49. McMartin DN, Gruhn RF. Sebaceous carcinoma in a horse. Vet Pathol 1977; 14:532–534.
50. Kunze DJ, Schmidt GM, Tvedten HW. Sebaceous adenocarcinoma of the third eyelid of a horse. J Equine Med Surg 1979; 3:452–455.
51. van der Linde-Sipman JS, van der Gaag I, van der Velden MA. Solid carcinoma of the glandula superficialis palpebrae tertiae in a horse. J Vet Med A 1986; 33:208–211.
52. Payne RJ, Lean MS, Greet TRC. Third eyelid resection as a treatment for suspected squamous cell carcinoma in 24 horses. Vet Rec 2009; 165: 740–743.
53. Mathes RL, Carmichael KP, Peroni J, et al. Primary lacrimal gland adenocarcinoma of the third eyelid in a horse. Vet Ophthalmol 2011; 14:48–54.
54. Lloyd KC, Peterson PR, Wheat JD, et al. Keratomas in horses: seven cases (1975–1986). J Am Vet Med Assoc 1988; 193:967–970.
55. Wagner PC, Balch-Burnett O, Merritt F. Surgical management of keratomas in the foot of the horse. Equine Pract 1986; 8:11–14.
56. McDiarmid A. Keratoma from the frog corium of a horse. Equine Vet Educ 2007; 19:285–287.
57. Chan C-H, Munroe GA. Treatment of a keratoma in a Clydesdale horse. Vet Rec 1997; 140:453–456.
58. Ali F. An unusual case of keratoma in the os pedis of a mule. J R Army Vet Corps 1944; 15:67–68.
59. Christman C. Multiple keratomas in an equine foot. Can Vet J 2008; 49:904–906.
60. Gasiorowski JC, Getman LM, Richardson DW. Supracoronary approach for keratoma removal in horses: two cases. Equine Vet Educ 2011; 23:489–493.
61. O'Grady SE, Horne PA. Lameness caused by a solar keratoma: a challenging diagnosis. Equine Vet Educ 2001; 13:87–89.
62. Honnas CM. Supracoronary approach for keratoma removal. Equine Vet Educ 2011; 23:494–495.
63. Valentine BA, Scott EA, Watrous BJ, et al. What is your diagnosis? Keratoma in a horse's hoof. J Am Vet Med Assoc 2000; 217:993–994.
64. Boulton CH. Equine nasal cavity and paranasal sinus disease: a review of 85 cases. J Equine Vet Sci 1985; 5:268–275.
65. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 2: A contribution of 28 case reports. Vet J 1999; 157:279–294.
66. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 1: Review of the literature and tumour classification. Vet J 1999; 157: 261–278.
67. Hill FW, Moulton JE, Schiff PH. Exophthalmos in a horse resulting from an adenocarcinoma of the frontal sinus. J S Afr Vet Assoc 1989; 60: 104–105.
68. Hance SR, Bertone AL. Neoplasia. Vet Clin North Am Equine Pract 1993; 9:213–234.
69. Zaruby JF, Livesey MA, Percy DH. Ethmoid adenocarcinoma perforating the cribriform plate in the horse. Cornell Vet 1993; 83:283–289.
70. Baker JR, Leyland A. Histological survey of tumours of the horse with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
71. Acland HM, Orsini JA, Elkins S, et al. Congenital ethmoid carcinoma in a foal. J Am Vet Med Assoc 1984; 184:979–981.
72. Reynolds BL, Stedham MA, Lawrence JM, et al. Adenocarcinoma of the frontal sinus with extension to the brain in a horse. J Am Vet Med Assoc 1979; 174:734–736.
73. Davis JL, Gilger BC, Spaulding K, et al. Nasal adenocarcinoma with diffuse metastases involving the orbit, cerebrum and multiple cranial nerves in a horse. J Am Vet Med Assoc 2002; 221:1460–1463.
74. Hepburn RJ, Furr MO. Sinonasal adenocarcinoma causing central nervous system disease in a horse. J Vet Intern Med 2004; 18:125–131.
75. Platt H. Haemorrhagic nasal polyps of the horse. J Pathol 1975; 115:51–55.
76. Tremaine WH, Clarke CJ, Dixon PM. Histopathological findings in equine sinonasal disorders. Equine Vet J 1999; 31:296–303.
77. Freeman DE. Sinus disease. Vet Clin Equine 2003; 19:209–243.
78. Nickels FA. Diseases of the nasal cavity. Vet Clin North Am Equine Pract 1993; 9:111–121.
79. Tremaine WH, Dixon PM. A long-term study of 277 cases of equine sinonasal disease. Part 1: Details of horses, historical, clinical and ancillary diagnostic findings. Equine Vet J 2001; 33:274–282.
80. Lane JG, Longstaffe JA, Gibbs C. Equine paranasal cysts: a report of 15 cases. Equine Vet J 1987; 19:537–544.
81. Dixon PM, Parkin TD, Collins N, et al. Equine paranasal sinus disease – a long-term study of 200 cases (1997–2009): Ancillary diagnostic findings and involvement of the various sinus compartments. Equine Vet J 2012; 44:267–271.
82. Woodford NS, Lane JG. Long-term retrospective study of 52 horses with sinunasal cysts. Equine Vet J 2006; 38:198–202.
83. Tremaine WH, Dixon PM. A long-term study of 277 cases of equine sinonasal disease. Part 2: Treatments and results of treatments. Equine Vet J 2001; 33:283–289.
84. Sanders-Shamis M, Robertson JT. Congenital sinus cyst in a foal. J Am Vet Med Assoc 1987; 190:1011–1012.
85. Beard WL, Robertson JT, Leeth B. Bilateral congenital cysts in the frontal sinuses of a horse. J Am Vet Med Assoc 1990; 196:453–454.
86. Silva LC, Zoppa AL, Fernandes WR, et al. Bilateral sinus cysts in a filly treated by endoscopic sinus surgery. Can Vet J 2009; 50:417–420.
87. Annear MJ, Gemensky-Metzler AJ, Elce YA, et al. Exophthalmus secondary to a sinonasal cyst in a horse. J Am Vet Med Assoc 2008; 233:285–288.
88. Gilroy BJ, Lofstedt J, Pack L, et al. Paranasal sinus cyst as a cause of stridor in a standardbred colt. Can Vet J 1999; 40:49–51.
89. Watt BC, Beck BE. Removal of a nasal polyp in a standing horse. Can Vet J 1997; 38:108–109.
90. Frankeny RL. Intralesional administration of formalin for the treatment of epidermal inclusion cysts in five horses. J Am Vet Med Assoc 2003; 223:221–222.
91. Shaw DP, Gunson DE, Evans LH. Nasal amyloidosis in four horses. Vet Pathol 1987; 24:183–185.
92. Jakob W. Spontaneous amyloidosis of mammals. Vet Pathol 1971; 8:292–306.
93. Nappert G, Vrins A, Doré M, et al. Nasal amyloidosis in two Quarter Horses. Can Vet J 1988; 29:834–835.
94. Stackhouse LL, Moore JJ, Hylton WE. Salivary gland adenocarcinoma in a mare. J Am Vet Med Assoc 1978; 172:271–273.
95. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
96. Gorlin RJ, Barron CN, Chaudhry AP, et al. The oral and pharyngeal pathology of domestic animals. A study of 487 cases. Am J Vet Res 1959; 20:1032–1061.
97. Feldman WH. Malignant growths in domestic animals. J Am Vet Med Assoc 1929; 75:192–200.
98. Schmahl VW. Solides Karzinom der Mamma bei einem Pferd. Berl Munch Tierarztl Wochenschr 1972; 85:141–142.
99. Laugier C, Tapprest J, Foucher N, et al. Prevalence of equine tumours in 1771 horses examined post-mortem. Prat Vét Equine 2004; 36:21–35.
100. Madewell BR, Theilen GH. Tumours of the mammary gland. In: Theilen GH, Madewell BR, eds. Veterinary cancer medicine, 2nd edn. Philadelphia: Lea & Febiger; 1987: 327–344.
101. Munson L. Carcinoma of the mammary gland in a mare. J Am Vet Med Assoc 1987; 191:71–72.
102. Seahorn TL, Hall G, Brumbaugh GW, et al. Mammary adenocarcinoma in four mares. J Am Vet Med Assoc 1992; 200:1675–1677.
103. Kato M, Higuchi T, Hata H, et al. Lactalbumin-positive mammary carcinoma in a mare. Equine Vet J 1998; 30:358–360.
104. Hirayama K, Honda Y, Sako T, et al. Invasive ductal carcinoma of the mammary gland in a mare. Vet Pathol 2003; 40:86–91.
105. Jackson C. The incidence and pathology of tumours of domesticated animals in South Africa. Onderstepoort J Vet Sci Anim Ind 1936; 6:1–460.
106. Spadari A, Valentini S, Sarli G, et al. Mammary adenoma in a mare: clinical, histopathological and immunohistochemical findings. Equine Vet Educ 2008; 20:4–7.
107. Shank M. Mammary gland tumours in mares. Equine Dis Q 2008; 17:5–6.
108. Shank AM. Mare mammary neoplasia: difficulties in diagnosis and treatment. Equine Vet Educ 2009; 21:475–477.
109. Acland HM, Gillette DM. Mammary carcinoma in a mare. Vet Pathol 1982; 19:93–95.
110. Runnells RA, Benbrook EA. Epithelial tumours of horses. Am J Vet Res 1942; 3:176–179.
111. Foreman JH, Weidner JP, Parry BW, et al. Pleural effusion secondary to thoracic metastatic mammary adenocarcinoma in a mare. J Am Vet Med Assoc 1990; 197:1193–1195.
112. Gamba CO, Araújo MR, Palhares MS, et al. Invasive micropapillary carcinoma of the mammary glands in a mare. Vet Q 2011; 31:207–210.
113. Surmont J. L'epitheliome mammaire de la jument et ses metastases pulmonaires. Bull l'Assoc Franç l'Étude Cancer 1926; 15:98–101.
114. Reppas GP, McClintock SA, Canfield PJ, et al. Papillary ductal adenocarcinoma in the mammary glands of two horses. Vet Rec 1996; 138:518–519.
115. Perkins NR, Threlfall WR. Mastitis in the mare. Equine Vet Educ 2002; 5:99–102.
116. Freeman KP. Cytological evaluation of the equine mammary gland. Equine Vet Educ 1993; 5:212–213.
117. Jacobs RM, Messick JB, Valli VE. Tumours of the haemolymphatic system. In: Meuten DJ, ed. Tumours in domestic animals, 4th edn. Ames: Iowa State Press; 2002: 165–166.
118. Whiteley LO, Leininger JR, Wolf CB, et al. Malignant squamous cell thymoma in a horse. Vet Pathol 1986; 23:627–629.
119. Furuoka H, Taniyama H, Matsui T, et al. Malignant thymoma with multiple metastases in a mare. Jpn J Vet Sci 1987; 49:577–579.
120. Cotchin E, Baker-Smith J. Tumours in horses encountered in an abattoir survey. Vet Rec 1975; 97:399.
121. Anderson JD, Leonard JM, Zeliff JA, et al. Primary pulmonary neoplasm in a horse. J Am Vet Med Assoc 1992; 201:1399–1401.
122. Uphoff CS, Lyncoln JA. A primary pulmonary tumour in a horse. Equine Pract 1987; 9:19–20.
123. Schultze AE, Sonea I, Bell TG. Primary malignant pulmonary neoplasia in two horses. J Am Vet Med Assoc 1988; 193:477–480.
124. Van Rensberg IB, Stadler P, Soley J. Bronchiolo-alveolar adenocarcinoma in a horse. J S Afr Vet Assoc 1989; 60:212–214.
125. Lavoie JP, Carlson GP, George L. Hypertrophic osteopathy in three horses and a pony. J Am Vet Med Assoc 1992; 201:1900–1904.
126. Monlux WS. Primary pulmonary neoplasms in domestic animals. Southwest Vet (suppl) 1952; 6:17–20.
127. Monlux WS. Primary pulmonary neoplasms in domestic animals. Southwest Vet 1953; 6:131–133.

128. Dill SG, Moise NS, Meschter CL. Cardiac failure in a stallion secondary to metastasis of an anaplastic pulmonary carcinoma. Equine Vet J 1986; 18:414–417.
129. Wilson DW, Dungworth DL. Tumours of the respiratory tract. In: Meuten DJ, ed. Tumours in domestic animals, 4th edn. Ames: Iowa State Press; 2002: 365–400.
130. Williams DW, Maes R, Del Piero F, et al. Equine multinodular pulmonary fibrosis: a newly recognized herpesvirus-associated fibrotic lung disease. Vet Pathol 2007; 44:849–862.
131. Wong DM, Belgrave RL, Williams KJ, et al. Multinodular pulmonary fibrosis in five horses. J Am Vet Med Assoc 2008; 232:898–905.
132. Niedermaier G, Poth T, Gehlen H. Clinical aspects of multinodular pulmonary fibrosis in two Warmblood horses. Vet Rec 2010; 166:426–430.
133. Back H, Kendall A, Grandon R, et al. Equine multinodular pulmonary fibrosis in association with asinine herpesvirus type 5 and equine herpesvirus type 5: a case report. Acta Vet Scand 2012; 54:57.
134. Tomlinson JE, Divers TJ, McDonough SP, et al. Hypertrophic osteopathy secondary to nodular pulmonary fibrosis in a horse. J Vet Intern Med 2011; 25:153–157.
135. Uhlhorn M, Hurst M, Demmers S. Disseminated pulmonary granulomas in a pony. Equine Vet Educ 2006; 18:178–181.
136. Hong CB. Congenital polyalveolar lobe in three foals. J Comp Pathol 1996; 115:85–88.
137. Patterson-Kane JC, Sanchez LC, MacKay RJ, et al. Intestinal adenomatous polyposis resulting in protein-losing enteropathy in a horse. Vet Pathol 2000; 37:82–85.
138. Moran JAM, Lemberger K, Cadoré J-L, et al. Small intestine adenocarcinoma in conjunction with multiple adenoma causing acute colic in a horse. J Vet Diagn Invest 2008; 20:121–124.
139. Dart AJ, Hodgson DR, Snyder JR. Caecal disease in equids. Aust Vet J 1997; 75:552–557.
140. Thoonen J, Ide M. Maagkanker bij een Paard. Vlaams Diergen Tijds 1941; 10:94–99.
141. Krahnert R. Zum magenkrebs des pferdes. Monatsh Veterinarmed 1952; 7:399–404.
142. Taylor SD, Haldorson GJ, Vaughan B, et al. Gastric neoplasia in horses. J Vet Intern Med 2009; 23:1097–1102.
143. Fulton IC, Brown CM, Yamini B. Adenocarcinoma of intestinal origin in a horse: diagnosis by abdominocentesis and laparoscopy. Equine Vet J 1990; 22:447–448.
144. Honnas CM, Snyder JR, Olander HJ, et al. Small intestinal adenocarcinoma in a horse. J Am Vet Med Assoc 1987; 191:845–846.
145. Hausken T, Lande K, Nygaard S. Adenocarcinom I tynntarm hos hest. Nor Veterinaertidsskr 1984; 96:542.
146. Wright JA, Edwards GB. Adenocarcinoma of the intestine in a horse: an unusual occurrence. Equine Vet J 1984; 16:136–137.
147. Rottman JB, Roberts MC, Cullen JM. Colonic adenocarcinoma with osseous metaplasia in a horse. J Am Vet Med Assoc 1991; 198:657–659.
148. Kirchhof N, Steinhauer D, Fey K. Equine adenocarcinoma of the large intestine with osseous metaplasia. J Comp Pathol 1996; 114:451–456.
149. East LM, Steyn PF, Dickinson CE, et al. Occult osseous metastasis of a colonic adenocarcinoma visualised with technetium tc 99m hydroxymethylene diphosphate scintigraphy in a horse. J Am Vet Med Assoc 1998; 213:1167–1170, 1132–1133.
150. Harvey-Micay J. Intestinal adenocarcinoma causing recurrent colic in the horse. Can Vet J 1999; 40:729–730.
151. Taylor SD, Pusterla N, Vaughan B, et al. Intestinal neoplasia in horses. J Vet Intern Med 2006; 20:1429–1436.
152. Tamaschke C, Dobberstein J. Die blastome des darmes. In: Dobberstein J, Pallaske G, Stünzi H, eds. Handbook of the special pathology anatomy of domestic animals, 3rd edn. Berlin: Verlag Paul Parry; 1967: 522–525.
153. East LM, Savage CJ. Abdominal neoplasia (excluding urogenital tract). Vet Clin North Am Equine Pract 1998; 14:475–493.
154. Titus RS, Leipold HW, Anderson NV. Gastric carcinoma in a mare. J Am Vet Med Assoc 1972; 161:270–273.
155. Jann HW, Breshears MA, Allison RW, et al. Occult metastatic intestinal adenocarcinoma resulting in pathological fracture of the proximal humerus. Equine Vet J 2009; 41:915–917.
156. Patton KM, Peek SF, Valentine BA. Gastric adenocarcinoma in a horse with portal vein metastasis and thrombosis: a novel cause of hepatic encephalopathy. Vet Pathol 2006; 43:565–569.
157. Roy M-F, Parente EJ, Donaldson MT, et al. Successful treatment of a colonic adenocarcinoma in a horse. Equine Vet J 2002; 34:102–104.
158. Morse CC, Richardson DW. Gastric hyperplastic polyp in a horse. J Comp Pathol 1988; 99:337–342.
159. Saulez MN, Cebra CK, Snyder SP. Small colon polyp with peritonitis in an Arabian yearling filly. Equine Vet Educ 2004; 16:184–187.
160. Dunkel B, Shokek AB, Wilkins PA. Congenital cystic polypoid rectal hamartoma in a newborn foal. Vet Pathol 2004; 41:700–702.
161. Rowlatt U. Spontaneous epithelial tumours of the pancreas. Br J Cancer 1967; 21:82–107.
162. Church S, West HJ, Baker JR. Two cases of pancreatic adenocarcinoma in horses. Equine Vet J 1987; 19:77–79.
163. Carrick JB, Morris DD, Harmon BG, et al. Hematuria and weight loss in a mare with pancreatic adenocarcinoma. Cornell Vet 1992; 82:91–97.
164. Furr MO, Robertson J. Two cases of equine pancreatic disease and a review of the literature. Equine Vet Educ 1992; 4:55–58.
165. Rendle DI, Hewetson M, Barron R, et al. Tachypnoea and pleural effusion in a mare with metastatic pancreatic adenocarcinoma. Vet Rec 2006; 159:356–359.
166. Kerr OM, Pearson GR, Rice DA. Pancreatic adenocarcinoma in a donkey. Equine Vet J 1982; 14:338–339.
167. Spanton JA, Mair TS, Krudewig C. Pancreatic adenocarcinoma in a donkey. Use of laparoscopy to aid the diagnosis. Equine Vet Educ 2009; 21:19–24.
168. Priester WA. Data from eleven United States and Canadian Colleges of Veterinary Medicine on pancreatic carcinoma in domestic animals. Cancer Res 1974; 34:1372–1375.
169. Charles JA. Pancreas. In: Maxie MG, ed. Kennedy and Palmer's pathology of domestic animals, 5th edn. Philadelphia: Elsevier Saunders; 2007: 407–408.
170. Tamaschke C. Beitrage zur vergleichenden onkologie der haussaugtiere. Berlin: Wiss Z Humboldt-University; 1952: 1:37–77.
171. Jeffcott LB. Primary liver-cell carcinoma in a young Thoroughbred horse. J Pathol 1969; 97:394–397.
172. Roby KA, Beech JC, Black M. Hepatocellular carcinoma associated with erythrocytosis and hypoglycaemia in a yearling filly. J Am Vet Med Assoc 1990; 196:465–467.
173. Kato M, Higuchi T, Orita Y, et al. Combined hepatocellular carcinoma and cholangiocarcinoma in a mare. J Comp Path 1997; 116:409–413.
174. Ponomarkov V, Mackey LJ. Tumours of the liver and biliary system. Bull World Health Organ 1976; 53:187–194.
175. Johnson PJ. The role of serum alpha-fetoprotein estimation in the diagnosis and management of hepatocellular carcinoma. Clin Liver Dis 2001; 5:145–159.
176. Stalker MJ, Hayes MA. Liver and biliary system In: Maxie MG, ed. Jubb, Kennedy and Palmer's pathology of domestic animals, 5th edn. Philadelphia: Elsevier Saunders; 2007: 382–386.
177. Cullen JM, Popp JA. Tumours of the liver and gall bladder. In: Meuten DJ, ed. Tumours in domestic animals, 4th edn. Ames: Iowa State Press; 2002: 485–498.
178. Roperto F, Galati P. Mixed hamartoma of the liver in an equine foetus. Equine Vet J 1984; 16:218–220.
179. Brown DL, Anderson M, Cullen JM. Mesenchymal hamartoma of the liver in a late-term equine fetus. Vet Pathol 2007; 44:100–102.
180. Mueller PO, Morris DD, Carmichael KP, et al. Antemortem diagnosis of cholangiocellular carcinoma in a horse. J Am Vet Med Assoc 1992; 201: 899–901.
181. Durando MM, MacKay RJ, Staller GS, et al. Septic cholangiohepatitis and cholangiocarcinoma in a horse. J Am Vet Med Assoc 1995; 206: 1018–1021.
182. Sironi G, Riccaboni P. A case of equine cholangiocarcinoma displaying aberrant expression of p53 protein. Vet Rec 1997; 141:77–78.
183. Conti MB, Marchesi MC, Zapulla F, et al. Clinical findings and diagnosis in a case of cholangiocellular carcinoma in a horse. Vet Res Commun 2008; 32(Suppl 1):S271–S273.
184. Habershon-Butcher JL, Smyth JBA, Hallowell GD. Bile duct carcinoma in a gelding. Vet Rec 2008; 162:281–282.
185. Salvaggio A, Caracappa S, Gurrera A, et al. Hepatic biliary adenofibroma: A hitherto unrecognized tumour in equines. Report of a case. Vet Pathol 2003; 40:114–116.
186. Stocker H, Kaser-Hotz B, Lischer C, et al. Congenital bile duct cysts and liver fibrosis in a foal. Tierarztl Prax 1996; 24:44–47.
187. Godber LM, Brown CM, Mullaney TP. Polycystic hepatic disease, thoracic granular cell tumour and secondary hypertrophic osteopathy in a horse. Cornell Vet 1993; 83:227–235.
188. Servantie J, Magnol JP, Regnier A, et al. Carcinoma of the renal pelvis with bony metaplasia in a horse. Equine Vet J 1986; 18:236–238.
189. Vítovec J. Carcinoma of the renal pelvis in slaughter animals. J Comp Pathol 1977; 87:129–134.
190. Cesari E. Quelques remarques au sujet du cancer chez le cheval. Bull Soci Central Méd Vét 1922; 75:171–176.
191. Haschek WM, King JM, Tennant BC. Primary renal cell carcinoma in two horses. J Am Vet Med Assoc 1981; 179:992–994.
192. West HJ, Kelly DF, Ritchie HE. Renal carcinomatosis in a horse. Equine Vet J 1987; 19:548–551.
193. Wise LN, Bryan JN, Sellon DC, et al. A retrospective analysis of renal carcinoma in the horse. J Vet Intern Med 2009; 23:913–918.
194. Berggren PC. Renal adenocarcinoma in a horse. J Am Vet Med Assoc 1980; 176:1252–1253.
195. Owen RA, Haywood S, Kelly DF. Clinical course of renal adenocarcinoma associated with hypercupraemia in a horse. Vet Rec 1986; 119:291–294.
196. Struck M. A remarkable case of kidney adenoma in the horse. Dtsch Tierarztl Wochenschr 1934; 42:21–22.
197. Pomroy W. Renal adenocarcinoma in a horse. Equine Vet J 1981; 13: 198–200.
198. Van Amstel SR, Huchzermeyer D, Reyers F. Primary renal cell carcinoma in a horse. J S Afr Vet Assoc 1984; 55:35–38.
199. Brown PJ, Holt PE. Primary renal cell carcinoma in four horses. Equine Vet J 1985; 17:473–477.
200. Rumbaugh ML, Latimer FG, Porthouse KP, et al. Renal carcinoma with osseous and pulmonary metastases in an Arabian gelding. Equine Vet J 2003; 35:107–109.
201. Swain JM, Pirie RS, Hudson NPH, et al. Insulin-like growth factors and recurrent hypoglycaemia associated with renal cell carcinoma in a horse. J Vet Intern Med 2005; 19:613–616.
202. Knowles EJ, Withers JM, Day MJ, et al. Renal carcinoma as a cause of sudden death in an aged horse. Equine Vet Educ 2008; 20:452–455.
203. Matsuda K, Kousaka Y, Nagamine N, et al. Renal adenoma of distal nephron differentiation in a horse. J Vet Med Sci 2007; 69:763–765.
204. Penninck DG, Eisenberg HM, Teuscher EE, et al. Equine renal ultrasonography: normal and abnormal. Vet Radiol 1986; 27:81–84.
205. Ferguson N, Couëtil L, Hawkins J, et al. Unilateral nephrectomy in two aged horses. Equine Vet Educ 2007; 19:300–305.

206. Loynachan AT, Bryant UK, Williams NM. Renal mucus gland cystadenoma in a horse. J Vet Diagn Invest 2008; 20:520–522.
207. Van Mol KAC, Fransen JLA. Renal carcinoma in a horse. Vet Rec 1986; 119:238–239.
208. Rhind SM, Hawe C, Dixon PM, et al. Oral metastasis of renal cell carcinoma in a horse. J Comp Pathol 1999; 120:97–103.
209. Hilton HG, Aleman M, Maher O, et al. Hand-assisted laparoscopic nephrectomy in a standing horse for the management of renal cell carcinoma. Equine Vet Educ 2008; 20:239–244.
210. Oosterlinck M, Raes E, Verbraecken S, et al. Severe lameness caused by metastatic renal adenocarcinoma of the third phalanx in a Warmblood mare. Equine Vet Educ 2011; 23:512–516.
211. Dixon PM, Tremaine WH, Pickles K, et al. Equine dental disease. Part 1: a long-term study of 400 cases: disorders of incisor, canine and first premolar teeth. Equine Vet J 1999; 31:369–377.
212. Baker JL, Aleman M, Madigan J. Intermittent hypoglycemia in a horse with anaplastic carcinoma of the kidney. J Am Vet Med Assoc 2001; 218: 235–237.
213. Nielsen SW, Mackey LJ, Misdorp W. Tumors of the kidney. Bull World Health Organ 1976; 53:237–246.
214. Meuten DJ. Tumours of the urinary system. In: Meuten DJ, ed. Tumours in domestic animals, 4th edn. Ames: Iowa State Press; 2002: 509–546.
215. Tyner GA, Nolen-Walston RD, Hall T, et al. A multicentre retrospective study of 151 renal biopsies in horses. J Vet Intern Med 2011; 25:532–539.
216. Rhind SM, Keen JA. Polycystic kidney disease in a mature horse: report and review of previously reported cases. Equine Vet Educ 2004; 16: 178–183.
217. Jones SL, Langer DL, Sterner-Kock A, et al. Renal dysplasia and benign ureteropelvic polyps associated with hydronephrosis in a foal. J Am Vet Med Assoc 1994; 204:1230–1234.
218. Fischer AT, Spier S, Carlson GP, et al. Neoplasia of the equine urinary bladder as a cause of hematuria. J Am Vet Med Assoc 1985; 186: 1294–1296.
219. Traub-Dargatz JL. Urinary tract neoplasia. Vet Clin North Am Equine Pract 1998; 14:495–504.
220. Patterson-Kane JC, Tramontin RR, Giles RC, et al. Transitional cell carcinoma of the urinary bladder in a Thoroughbred, with intra-abdominal dissemination. Vet Pathol 2000; 37:692–695.
221. Cornelisse CJ. Urinary tract neoplasia. In: Robinson WF, ed. Current therapy in equine medicine, 5th edn. Philadelphia: WB Saunders; 2003: 835–837.
222. Gavez E, Duvic A, Sudaric F. Carcinoma vesicae urinariae luminen obturans slucaj kod konja. Vet Sarajevo 1960; 9:603–605.
223. Gibson KT, Cantley CEL, Donald JJ, et al. Urachal cystadenoma in a filly. Aust Vet J 1999; 77:638–640.
224. Hopkins NCG. Arteriology of enzootic hematuria. Vet Rec 1986; 118: 715–717.
225. Turner RM, Love CC, MacDonnell SM, et al. Use of imipramine hydrochloride for treatment of urospermia in a stallion with a dysfunctional bladder. J Am Vet Med Assoc 1995; 207:1602–1606.
226. Barrell E, Hendrickson DA. Tumours of the equine bladder: what makes treating these cases so difficult? Equine Vet Educ 2009; 21:267–268.
227. Ricketts SW, Frauenfelder H, Button CJ, et al. Urinary retention in a pony gelding associated with a fibroepithelial polyp in the bladder. Equine Vet J 1983; 15:170–172.
228. McEntee K. Reproductive pathology of domestic mammals. San Diego: Academic Press Inc.; 1990.
229. Hughes JP, Kennedy PC, Stabenfeldt GH. Pathology of the ovary and ovarian disorders in the mare. Proceedings of the 9th International Conference on Animal Reproduction and Artificial Insemination 1980; 1:203–222.
230. Held JP, Buergelt C, Colahan P. Serous cystadenoma in a mare. J Am Vet Med Assoc 1982; 181:496–498.
231. Hinrichs K, Frazer GS, deGannes RV, et al. Serous cystadenoma in a normally cyclic mare with high plasma testosterone values. J Am Vet Med Assoc 1989; 194:381–382.
232. Buergelt CD. Colour atlas of reproductive biology of domestic animals. St Louis: Mosby; 1997.
233. Morris DD, Acland HM, Hodge TG. Pleural effusion secondary to metastasis of an ovarian adenocarcinoma in a horse. J Am Vet Med Assoc 1985; 187:272–274.
234. O'Shea JD. Cysts in the ovulation fossa region of the equine ovary. J Morphol 1968; 124:313–320.
235. Schlafer DH, Miller RB. Female genital system. In: Maxie MG, ed. Jubb, Kennedy and Palmer's pathology of domestic animals, 5th edn. Philadelphia: Elsevier Saunders; 2007: 429–564.
236. Nielsen SW, Misdorp W, McEntee K. XV. Tumours of the ovary. Bull World Health Organ 1976; 53:203–215.
237. Archbald LF, Mather EC, McClure JR. Fimbrial cysts as a cause of infertility in the mare. Vet Med Sm Anim Clin 1974; 69:1163–1165.
238. Van Camp SD, Mahler J, Roberts MC, et al. Primary ovarian adenocarcinoma associated with teratomatous elements in a mare. J Am Vet Med Assoc 1989; 194:1728–1730.
239. DiMartino M. Ovarian cystadenocarcinoma in a horse. Nuova Vet 1949; 25:289.
240. Son YS, Lee CS, Jeong WI, et al. Cystadenocarcinoma in the ovary of a Thoroughbred mare. Aust Vet J 2005; 83:283–284.
241. Vest DJ. Oviductal adenoma in a mare. J Equine Vet Sci 2008; 28:40–45.
242. Gunson DE, Gillette DM, Beech J, et al. Endometrial adenocarcinoma in a mare. Vet Pathol 1980; 17:776–780.
243. Chaffin MK, Fuentealba IC, Schmitz DG, et al. Endometrial adenocarcinoma in a mare. Cornell Vet 1990; 80:65–73.
244. Yamini B, Borg L. Endometrial polyps and endometritis in a Thoroughbred filly. J Vet Diagn Invest 1994; 6:496–498.
245. Pycock JF. Uterine haematoma in 2 mares. Equine Vet Educ 1994; 6:132–134.

15 Internal surface-based neoplasia: mesothelioma

Cellular origin 281
Profile 281
Oncogenesis 281
Biological behaviour 281
Gross pathology 281
Histopathology 281
Differential diagnoses 283

Cellular origin

See also pages 474 and 503.

Mesothelial cells line the peritoneal, pleural, pericardial and scrotal (tunica vaginalis) cavities. Mesothelial cells are mesodermal in origin.

Profile

Mesotheliomas are rare neoplasms in horses. Authors of a survey looking at literature between 1902 and 1987 only identified 16 cases.[1] Sites have included the peritoneum, pericardium, pleura and tunica vaginalis; the neoplasms tend to involve both visceral and parietal layers and they may be multicentric in origin.[2–20] Pleural mesotheliomas may be primary neoplasms or occur secondary to pericardial or peritoneal origin; however, the exact site of origin is often not clear.[9] In the abdomen, mesotheliomas often arise on the greater omentum.

Mesothelioma is most often diagnosed in middle-aged to older horses (8–27 years), but may occur in young adults (2–6 years of age).[10–12] There is no known breed or gender predilection.

Oncogenesis

There has been no known association with asbestos exposure (as in humans) in the small numbers of documented equine cases.[9]

Biological behaviour

Mesotheliomas are malignant neoplasms that frequently spread by (transcoelomic) implantation within the involved cavity, followed by dissemination throughout most or all body cavities (see Fig. 28.33). Spread between the scrotal cavity and the abdomen has also been reported.[1,6] Less frequently, mesotheliomas invade underlying tissues (e.g. the lung) and metastasize via blood or lymphatic vessels to regional lymph nodes or more distant sites.[12,13] Where there is involvement of regional lymph nodes, this may more frequently be a consequence of invasion from the serosal surfaces rather than true metastasis.[1] There is one report of a large mass on the abdominal diaphragmatic surface, that penetrated directly through the diaphragm and into the thoracic cavity.[14] Extension from the thoracic to the abdominal cavity or vice versa may also occur via lymphatic vessels.[15]

Hypoglycaemia and acute renal failure with severe metabolic derangements (hyperkalaemia, hyperphosphataemia, hypocalcaemia) indicative of tumour lysis syndrome were reported in one horse.[14] Hypoglycaemia associated with mesothelioma (as with other types of neoplasm) is thought to be due to the effects of an abnormal form of insulin-like growth factor-2 that is produced by the tumour cells.[14]

One stallion had a postoperative survival period of at least 1 year following removal of a testis with associated mesothelioma of the tunica vaginalis.[7]

Gross pathology

Affected horses may be emaciated, and there may be ventral oedema and diarrhoea.[12] Large amounts of effusion fluid that fill the cavity of origin are usually stimulated by the neoplastic process; up to 100 litres of serous or serosanguineous fluid may be noted in the pleural and/or peritoneal cavities, and fibrinous or fibrous adhesions have been observed on parietal and visceral surfaces.[14,16,17]

Multiple nodular or villous, grey-white or tan, firm masses of varying size (1 mm to 20 cm in diameter) may be noted (see Fig. 28.33), usually involving both visceral and parietal mesothelial surfaces bilaterally and potentially involving more than one cavity (e.g. pleural and peritoneal); alternatively, there may be diffuse thickening of the pericardium/pleura/peritoneum/tunica vaginalis, with a granular surface.[4,7,11,17–19] It is possible for only part of a cavity to be involved, e.g. the anterior abdomen in one case, where the omentum appeared to be the site of origin.[10]

Histopathology

Although it is possible to diagnose mesothelioma based on examination of cytological smears, it is not possible in all

cases due to failure of some neoplasms to exfoliate significant numbers of cells and/or difficulties in distinguishing neoplastic change from mesothelial reaction or even carcinomatosis.[20] It should be noted, however, that some authors do not consider marked reactive mesothelial changes to be a common feature associated with cavity effusions in horses, as opposed to some other domestic animal species.[9] Histological examination will frequently be required for confirmation; antemortem diagnosis of mesothelioma has been achieved by examination of multiple parietal and visceral pleural biopsy specimens, for horses with thoracic cavity involvement.[9]

Histologically, the normal (or hyperplastic) mesothelium is contiguous with single to multiple layers of tumour cells. These tumour cells frequently line fibrous nodular or papillary projections; the latter often branch or have secondary projections (Fig. 15.1).[2,8] The tumour cells vary in morphology (both between and within individual neoplasms). There may be epithelioid cells, spindle-shaped (sarcomatoid) cells or both (i.e. biphasic).[19] Within the supporting stroma, the infiltrating epithelioid cells may be arranged in ribbons, nests, acini, sheets, tubules, or tubulopapillary structures that can fill with tumour cells as the process advances.[7,12] It is important to note this stromal invasion to confirm the diagnosis of neoplasia.

The epithelioid mesothelioma cells may be cuboidal, columnar, polygonal, ovoid, squamous or flattened, with a moderate to large amount of eosinophilic cytoplasm that in some cases contains variable numbers of variably-sized, clear (lipid) vacuoles (see Fig. 15.1).[8,9,14] In one case of peritoneal mesothelioma in a 9-year-old mare (a lipid-rich variant), the tumour cells contained vacuoles measuring up to 80 µm in diameter, that stained positively with Oil Red O (see Fig. 15.1).[8] Nuclei are large and round or oval with marginated chromatin (or they may be hyperchromatic) and one to multiple central, prominent nucleoli. There can be marked anisocytosis and anisokaryosis with binucleate or multinucleate tumour giant cells in some lesions, and variable numbers of mitotic figures that may have a bizarre appearance.[7,8,10,12] Spindle-shaped ('sarcomatoid') tumour cells may be arranged in random, storiform or whorled patterns and are supported by a dense fibrous or myxoid stroma.[12]

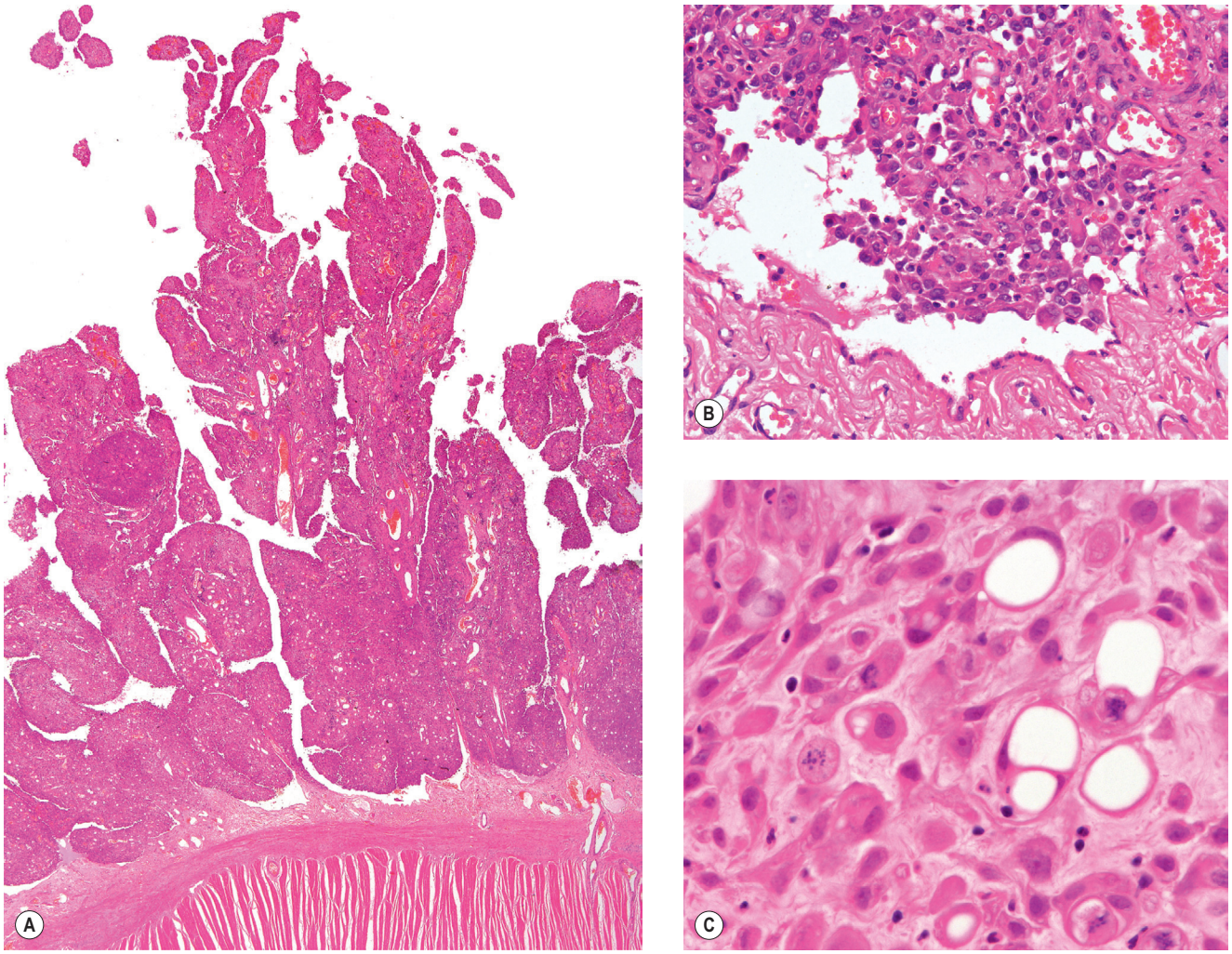


Figure 15.1 Peritoneal mesothelioma. **(A)** Multiple layers of tumour cells lining branching papillary projections on the serosal surface of the intestine. The outer margin of the muscularis externa can be seen at the bottom of the figure (H&E, ×12.5). **(B)** Epithelioid tumour cells with moderate amounts of deeply eosinophilic cytoplasm. The tumour mass is contiguous with the normal mesothelium, i.e. the flattened cells lining stromal tissue in the lower part of the figure (H&E, ×200). **(C)** Tumour cells containing large lipid vacuoles (lipid-rich variant) (H&E, ×400).

It is important to distinguish mesothelioma from carcinoma. Both normal and neoplastic mesothelial cells contain glycogen, which is periodic acid-Schiff (PAS) positive and diastase-sensitive; the neutral mucins found in epithelial cells are diastase-resistant (although not all carcinomas produce them) (Fig. 15.2).[13] Mesotheliomas are neutral mucin-negative. However, this PAS staining may not be seen once specimens have been processed for histology, possibly due to glycogen extraction by alcohol during dehydration for paraffin embedding. Fixed specimens may be snap-frozen and sectioned prior to staining, or cytological specimens examined. Additionally, mesotheliomas characteristically contain intracellular acid mucin, indicated by Alcian blue staining, that can be removed or significantly reduced by hyaluronidase pretreatment.[21]

Local invasion of the serosa may be noted and tumour emboli may be seen within lymphatic or blood vessels.[17]

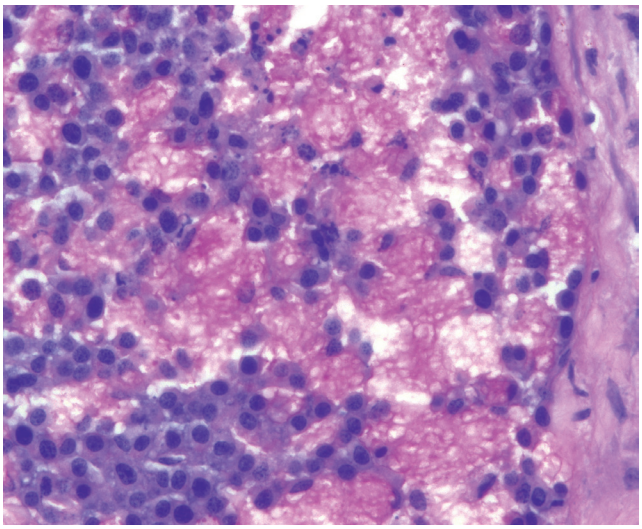


Figure 15.2 Carcinoma that presented as disseminated pleural masses. Intra- and extracellular mucin is periodic acid-Schiff (PAS) positive following diastase treatment; this would not be expected in the case of a mesothelioma (×400).

There may be significant inflammatory cell infiltrates, including large numbers of neutrophils, and areas of necrosis and/or haemorrhage. Other associated changes include adjacent mesothelial hyperplasia, hypertrophic mesothelial cells lining papillary fibrous projections and fibrosis.[2,9]

Immunohistochemical labelling

Epithelioid mesothelioma cells should label positively for cytokeratins. Coexpression of cytokeratin and vimentin confirms the diagnosis, i.e. allows differentiation from carcinoma (Fig. 15.3).[14] Calretinin is a calcium-binding protein used as a marker for normal mesothelial and epithelioid (not sarcomatous) mesothelioma cells that has been used to label equine tumours (and therefore also allow differentiation from carcinomas).[7,12] There is both cytoplasmic and nuclear staining.

Electron microscopy

Ultrastructurally, mesothelioma cells have intercellular tight junctions and a microvillous border; the microvilli have a high length-to-diameter ratio. There may be neolumen formation with lining of these structures by microvilli.[11]

Differential diagnoses

These are listed in Box 15.1.

Box 15.1 Differential diagnoses for mesothelioma

Neoplastic

- Carcinomatosis (i.e. disseminated carcinomas) originating in the ovary, pancreas, lung, gastrointestinal tract or (in females) the secondary Müllerian system

Non-neoplastic

- Granulomatous inflammation involving serosal surfaces

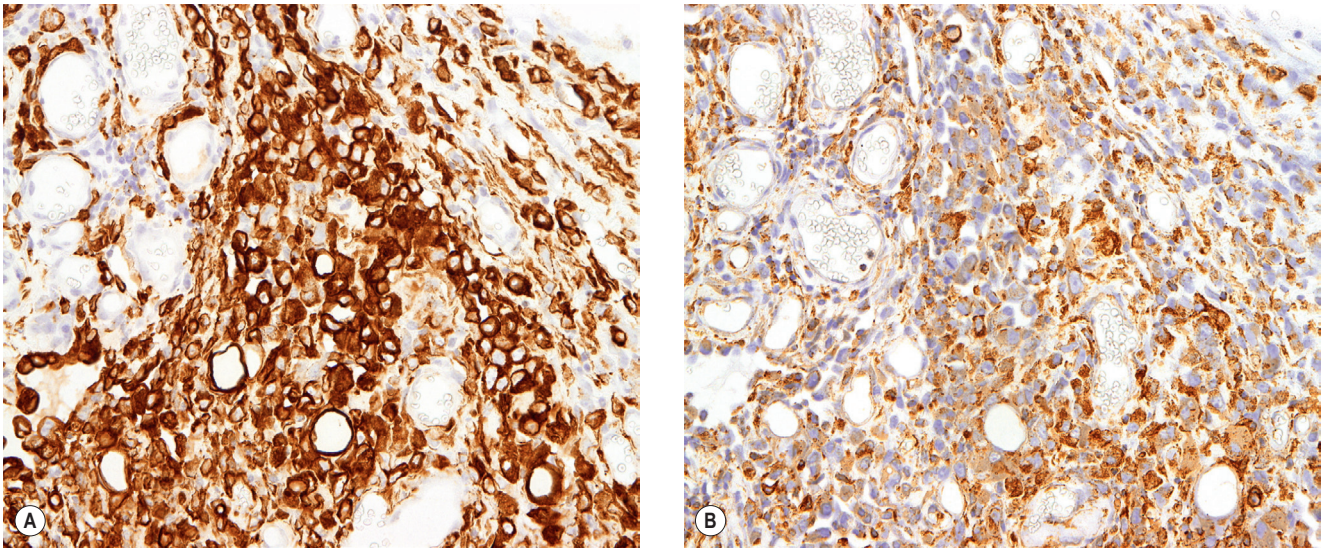


Figure 15.3 Peritoneal mesothelioma. There is strong positive immunolabelling in the same microscopic field for **(A)** cytokeratin and **(B)** vimentin (immunohistochemistry, ×200).

References

1. Wallace SS, Jayo MJ, Maddux JM. Mesothelioma in a horse. Compend Contin Educ Pract Vet 1987; 9:210–216.
2. Jackson C. The incidence and pathology of tumours of domesticated animals in South Africa. Onderstepoort J Vet Sci Anim Ind 1936; 6:3–460.
3. Straub R, von Tscharner C, Pauli B, et al. Pleural mesothelioma in a horse. Schweiz Arch Tierheilkd 1974; 116:207–211.
4. Carnine BL, Schneider G, Cook JE, et al. Pericardial mesothelioma in a horse. Vet Pathol 1977; 14:513–515.
5. Harps O, Brumhard J, Bartmann CP, et al. Ascites as a result of peritoneal mesotheliomas in a horse. Tierarztl Prax 1996; 24:270–274.
6. Edwards JF. Pathologic conditions of the stallion reproductive tract. Anim Reprod Sci 2008; 107:197–207.
7. Johnson AK, Love CC, Casillo AL, et al. Mesothelioma of the tunica vaginalis testes in a stallion. Equine Vet Educ 2008; 20:480–484.
8. Dobromylskyj MJ, Copas V, Durham A, et al. Disseminated lipid-rich peritoneal mesothelioma in a horse. J Vet Diagn Invest 2011; 23:615–618.
9. Fry MM, Magdesian KG, Judy CE, et al. Antemortem diagnosis of equine mesothelioma by pleural biopsy. Equine Vet J 2003; 35:723–727.
10. Ricketts SW, Peace CK. A case of peritoneal mesothelioma in a Thoroughbred mare. Equine Vet J 1976; 8:78–80.
11. Colbourne CM, Bolton JR, Mills JN, et al. Mesothelioma in horses. Aust Vet J 1992; 69:275–278.
12. Stoica G, Cohen N, Mendes O, et al. Use of immunohistochemical marker calretinin in the diagnosis of a diffuse malignant metastatic mesothelioma in an equine. J Vet Diagn Invest 2004; 16:240–243.
13. Kramer JW, Nickels FA, Bell T. Cytology of diffuse mesothelioma in the thorax of a horse. Equine Vet J 1976; 8:81–83.
14. LaCarrubba AM, Johnson PJ, Whitney MS, et al. Hypoglycaemia and tumour lysis syndrome associated with peritoneal mesothelioma in a horse. J Vet Intern Med 2006; 20:1018–1022.
15. Ghergariu S, Rotaru O. Generalized mesothelioma in a horse. Proc 20th World Vet Congr 1976; 2146–2147.
16. Sweeney CR, Gillette DM. Thoracic neoplasia in equids: 35 cases (1967–1987). J Am Vet Med Assoc 1989; 195:374–377.
17. Mair TS, Hillyer MH, Brown PJ. Mesothelioma of the pleural cavity in a horse: diagnostic features. Equine Vet Educ 1992; 4:59–61.
18. Scarratt WK, Crisman MV. Neoplasia of the respiratory tract. Vet Clin North Am Equine Pract 1998; 14:451–473.
19. Ulrich R, Eydner M, Grün A, et al. A biphasic malignant mesothelioma of the peritoneum and pleura in a horse. Dtsch Tierarztl Wochenschr 2009; 116:186–191.
20. Barrelet A. Peritoneal fluid: Part 2 – cytological examination. Equine Vet Educ 1993; 5:126–128.
21. Warnock ML, Stoloff A, Thor A. Differentiation of adenocarcinoma of the lung from mesothelioma. Periodic acid-Schiff, monoclonal antibodies B72.3, and Leu M1. Am J Pathol 1988; 133:30–38.

16 Mesenchymal neoplasms: fibrous and adipose

Fibroblastic tumours
Summary 285
Sarcoids 285
Fibroma 285
Myxoma (myxofibroma) 286
Fibrosarcoma 287
Myxosarcoma 288
Myofibroblastic tumours
Haemangiopericytoma 290
Giant cell tumour of soft parts (malignant fibrous histiocytoma) 290
Anaplastic sarcoma 292
Malignant mesenchymoma 292
Primary retroperitoneal tumour 293
Non-neoplastic mesenchymal masses
Fibrous hamartoma 293
Fibromatosis (intramuscular desmoid 'tumours', musculoaponeurotic fibromatosis) 294
Lipocytic (adipose) tumours
Lipoma 294
Infiltrative lipoma 295
Liposarcoma 296

FIBROBLASTIC TUMOURS

Summary

This group of neoplasms (if sarcoids are excluded) are reported at a low frequency and involve various sites. To some extent, the literature is confusing in terms of their true prevalence, due to some authors reporting sarcoids as fibromas or sarcomas (p. 201). In a 1935–1974 survey of 378 neoplasms of horses conducted in South Africa, 12% were fibromas, fibrosarcomas, myxomas or undifferentiated sarcomas.[1]

Sarcoids

See pages 203 and 545.

Fibroma

See also page 561.

Cellular origin

These benign neoplasms arise from fibroblasts.

Profile

Fibromas are most frequently diagnosed in the dermis or subcutis (although in many reports they actually may be misdiagnosed as sarcoid). In one survey of equine neoplasms, a few cases of fibroma involved the sole of the foot or frog, with no associated lameness although lameness has been seen in some further cases (see Fig. 31.19A).[2]

Fibromas have been stated to be the most common neoplasm arising in the bones of the head; they typically occur in foals/young horses aged 2–14 months, but have also been reported in adults.[3–5] A fibroma in the left retrobulbar space of an 11-year-old Quarter Horse was a cause of exophthalmos.[5] They are rare in other parts of the skeleton; lesions termed 'fibromas' have been reported in limb bones of young horses in association with lameness but are not necessarily classifiable as neoplasms. Bilateral non-ossifying fibromas around cruciate ligament insertions in the proximal tibiae of a yearling were thought to be developmental, i.e. associated with excessive mechanical loading due to an upright hock conformation.[6] A 'fibroma' involving the first phalanx of an 8-year-old colt was classified as a metaphyseal defect, and did contain spicules of osteoid rimmed by osteoblasts (see ossifying fibroma, p. 313).[7] Fibromas have also been reported in rare instances attached to surfaces of tendons, including dorsal hock structures, the extensor carpi radialis and the extensor carpi obliquus.[8]

Other rare sites of fibroma development have included nasal cavities and paranasal sinuses, oral cavity (see Fig. 28.13), stomach, abdominal cavity, ovary and cervix.[9–14]

Biological behaviour

Fibromas grow slowly and are locally expansile. They should not recur when completely excised with wide margins. However, for non-ossifying fibromas of bone, this may not be possible where a mass is located adjacent to an articular surface.[6] Recurrence of one tendon fibroma was reported following incomplete excision; in another case, incomplete resection of an orbital fibroma was not followed by recurrence 14 months' post-surgery.[5,8]

Gross pathology

Fibromas are firm and white to tan on sectioning, and should be well-demarcated but unencapsulated. When they involve bones of the head, they may cause loosening of teeth. In any

Box 16.1 Differential diagnoses for fibromas

Neoplastic
- Sarcoid, fibrosarcoma. Sarcoids may have a very similar appearance histologically in masses where the collagenous stroma is prominent (see Fig. 11.3E)

Non-neoplastic
- Granulation tissue, fibrous hamartoma

osseous site there can be peripheral areas of reactive bone formation and/or remodelling. An intraphalangeal non-ossifying fibroma occupied approximately 80% of the width of the bone and was associated with a pathological cortical fracture.[7] One large (70 cm diameter) intra-abdominal mass was attached to the anterior mesenteric root and caused displacement of the intestinal tract.[11]

Histopathology

The tumour cells form streams or bundles within abundant, variably dense collagenous matrix. These patterns of arrangement tend to be repetitive. In the skin, it is important to distinguish fibromas from sarcoids, the latter being a far more common occurrence. Fibromas will typically be well-demarcated, while sarcoids have infiltrative margins; the margins must be visualized in the biopsy specimen to allow differentiation. Some sarcoids will also have overlying epidermal hyperplasia (p. 213). The tumour cells in fibromas are spindle-shaped with a small amount of cytoplasm that has poorly-defined margins and small oval or elongate nuclei. Non-ossifying fibromas in bone have been described as primarily composed of bundles of fibroblastic cells with some osteoclasts, vascular proliferation, haemorrhage and 'little bone production'; the latter would need to be metaplastic.[6]

Differential diagnoses

These are listed in Box 16.1.

Myxoma (myxofibroma)

See also pages 315 and 485.

Cellular origin

This is a benign neoplasm of fibroblastic origin that produces abundant myxomatous matrix, i.e. a matrix rich in glycosaminoglycans.

Profile

Myxomas are rare neoplasms that have been reported in the gingiva, mandible, maxilla, conjunctiva, sinonasal cavities, bronchus, heart and conjunctiva (see Figs. 29.5, 30.11, 34.10).[9,15–20] They tend to occur in aged horses; however, in one report, myxomas were diagnosed in the right caudal nasal cavities of three Finnish-bred horses 5–9 years of age.[15] A large mass in the guttural pouch of a 13-year-old Quarter Horse mare was diagnosed as a fibroma, but had the histological appearance of a myxoma and was associated with litres of intraluminal mucinous exudate.[21] Myxomas were also reported in the subcutis in a 4-month-old colt and two mules, respectively.[22,23]

Biological behaviour

Myxomas have been described as infiltrative with potential for extension along fascial planes, resulting in a high rate of recurrence following excision; they do not metastasize.[24,25] Sinonasal myxomas of horses that have been incompletely excised have been reported to recur.[18,20]

Gross pathology

Myxomas are solitary, fleshy or gelatinous, smooth-surfaced, and pale tan or yellow. If protruding into a cavity (e.g. oral), the surface may be ulcerated. On sectioned surfaces, they exude clear, viscous fluid and may contain mucus-filled cavities; those arising in the caudal maxilla are surrounded by a thin shell of bone.[15] Nasal myxomas have been associated with purulent and/or haemorrhagic discharge, with destruction of nasal conchae and extension into paranasal sinuses.[15] The reported guttural pouch mass was pedunculated and weighed almost 500 g.[21]

Histopathology

Myxomas are unencapsulated, poorly-circumscribed and sparsely cellular (Fig. 16.1). Fibroblastic cells (spindle-shaped or stellate) with small hyperchromatic nuclei are noted within large amounts of basophilic, fibrillar (myxomatous) matrix that can vary significantly in staining intensity (see Fig. 16.1); the myxomatous matrix stains positively for glycosaminoglycans using the Alcian blue method (at pH 2.5) and can be digested by hyaluronidase.[15] There may be cystic cavities within the mass filled with this substance. Variable amounts of collagenous stroma are also noted (see Fig. 16.1). Mitotic figures are rare. There may be small fibrotic areas, and in nasal masses, remnants of nasal conchal cartilage and epithelium.

As tumour cell morphology and arrangement can be very similar in myxomas and myxosarcomas, the latter diagnosis is ruled out if there is not significant cellular pleomorphism or observation of atypical mitotic figures.[25]

Differential diagnoses

These are listed in Box 16.2.

In the sinonasal cavities, polyps of putative inflammatory origin may also contain significant amounts of myxomatous matrix (pp. 259–260).

Box 16.2 Differential diagnoses for myxoma

Neoplastic
- Myxosarcoma

Non-neoplastic
- Nasal polyps

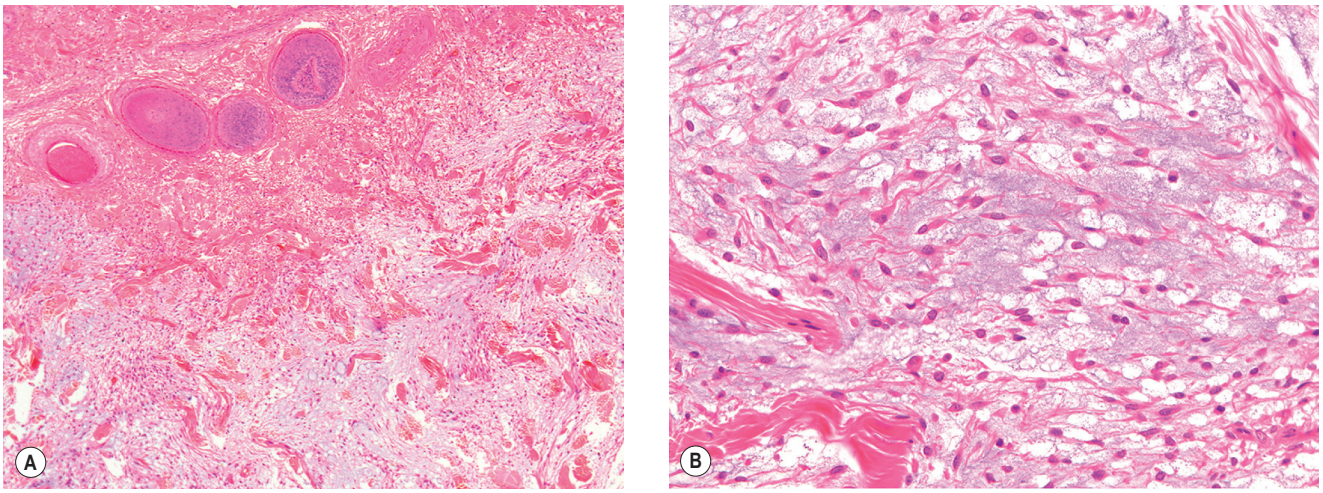


Figure 16.1 Histological appearance of a myxoma involving the deep dermis and subcutis. (A) The mass is poorly-circumscribed in this case, with adnexal structures seen above it in the normal dermis (H&E, ×40). **(B)** Stellate and spindle-shaped tumour cells are loosely arranged within large amounts of basophilic (myxomatous) matrix. Scattered bundles of collagenous stroma are also noted (H&E, ×200).

Fibrosarcoma

See also page 562.

Cellular origin

These malignant neoplasms arise from fibroblasts. There is some overlap between the diagnoses of fibrosarcoma and myofibroblastic tumour (p. 289), as myofibroblasts are present in most fibroblastic neoplasms.

Profile

Fibrosarcomas may occur in horses of any age, including neonates; they have also been reported in mules and donkeys. In a 1964–1977 survey (using data from the US Veterinary Medical Data Program), of the 54 fibrosarcomas reported, 21% involved various soft tissues, 16% were ocular and 12.5% were found in the skin.[10] In one case, a fibrosarcoma developed in non-healing wound tissue in the gluteal region of a 2-year-old Quarter Horse stallion, 13 months after receiving extensive partial thickness burns.[26]

Other sites of primary or secondary involvement have included the external genitalia, nasal cavities and paranasal sinuses, oral cavity, larynx, mediastinum, pericardium, lungs, thoracic wall, abdominal cavity, perirenal connective tissue, omentum, liver and uterus (see Fig. 36.8).[9,10,14,27–35] In some disseminated cases, the site of origin has been uncertain.[32]

In the musculoskeletal system, fibrosarcomas are rare; they can arise from the periosteum, fascial tissue, paratendon (the outer layer of connective tissue surrounding areas of tendons without synovial sheaths) or other soft tissues.[36] One mass reported in a 14-month-old Quarter Horse was attached to the deep digital flexor tendon and tarsal synovial sheath.[37] Nasomaxillary fibrosarcomas have also been diagnosed, almost exclusively in young horses (<20 months of age) and may be congenital; one was reported in a 7-year-old mare.[36,38,39] Occasional mandibular fibrosarcomas have also been reported.[40,41]

Biological behaviour

As in other species, fibrosarcomas in equines are locally invasive and destructive. They often recur locally after surgical excision, meaning that wide margins (of at least 3 cm) are required[29,37]; anaplasia can increase in recurrent masses. Some fibrosarcomas of horses have been successfully excised without recurrence.[37] Nasomaxillary and premaxillary masses in young horses may respond to surgical excision and curettage.[36,39]

Fibrosarcomas are either non-metastatic, or metastatic only late in the disease course. Metastasis when it does occur, is most often to the lungs and/or liver.[35,42] One subcutaneous tumour in a 6-year-old stallion metastasized to internal (thoracic and abdominal) organs, with involvement of the left ventricle of the heart, resulting in widespread tertiary metastasis.[28] In that horse, an extradural mass in the thoracic spine caused progressive posterior paralysis. Another horse with disseminated internal disease (of uncertain origin) presented with pleural effusion and lameness; the latter was associated with invasion of the medullary cavity of the left humerus.[32]

Gross pathology

Fibrosarcomas are poorly-demarcated, may be multinodular, and in the skin and subcutis can reach a large size, with maximal diameters of 30–65 cm reported.[23,28] They are firm on sectioning and variable in colour but often white, yellow, grey or tan (see Fig. 31.19). There is frequently ulceration of the overlying epidermis. Invasion of surrounding tissues is typical; in superficial sites fibrosarcomas tend to invade deeper structures such as tendons, fascia and skeletal muscle (see Fig. 31.19B, C). There may also be invasion of bone, and some reactive osseous tissue may form in response to this.

Fibrosarcomas protruding into cavities (e.g. nasomaxillary sinuses) or lumens may be ulcerated. One mare had multiple exophytic to pedunculated masses at the endometrial surface of the uterus, with marked ulceration and significant

amounts of intraluminal haemorrhagic fluid.[35] Fibrosarcomas involving intra-abdominal organs may also be large in size (e.g. an omental mass measured 60 cm in maximal diameter), with extensive adherence to surrounding organs and structures.[30]

Nasomaxillary fibrosarcomas may originate on outer or inner surfaces of maxillary bones or both, and again may reach a large size, with one external mass measuring 25 cm in maximal diameter.[39] There may be associated nasal septum deviation, adherence to tooth roots, mucoid discharge and filling of sinuses with fluid. Incisor teeth may be disrupted and displaced by fibrosarcomas arising in the premaxilla.[36]

Histopathology

Fibrosarcomas are non-encapsulated or pseudo-encapsulated, poorly-circumscribed, infiltrative masses that, in some cases occur as coalescing nodules.[38] The tumour cells are variably densely packed (including within the same mass) in interlacing bundles, streams and/or whorls supported by varying amounts of collagenous stroma. The presence of collagen cannot be used to differentiate fibrosarcomas from other types of sarcoma, and immunohistochemical labelling may be required.

The tumour cells are polygonal or spindle-shaped with moderate amounts of fibrillar eosinophilic cytoplasm that may have indistinct margins. Nuclei are large and round, ovoid or spindle-shaped, with single or multiple small or prominent nucleoli. Nuclear and cellular pleomorphism and mitotic rates are highly variable, and multinucleate tumour cells may be noted in more anaplastic masses. There are often finger-like projections of the neoplasm into surrounding tissues and along fascial planes, that account for difficulties in identifying margins for complete surgical excision.[25] In some cases, tumour cell emboli may be noted within blood vessels.

Other changes may include large central areas of necrosis and haemorrhage, and mixed inflammatory cell infiltrates; one fibrosarcoma of the frontal and caudal maxillary sinuses contained eosinophilic infiltrates.[14] Where adjacent bone is infiltrated, there may be osteonecrosis with osteoclastic resorption, in addition to reactive bone formation.[38]

Immunohistochemical labelling

Tumour cells should show diffuse vimentin expression.[25,37]

Electron microscopy

Viral particles have not been noted in ultrastructural studies, although a viral aetiology for fibrosarcomas of the nasal cavity, skin and oral cavity has been suspected by some authors.[38]

Differential diagnoses

These are listed in Box 16.3.

The most important differential diagnosis in the skin would be a sarcoid. A sarcoid could have an identical histological appearance and the tumour cells would also be vimentin positive; theoretically, bovine papillomavirus DNA should not be found in a non-sarcoid neoplasm (i.e. polymerase chain reaction (PCR) testing might be of value).

Box 16.3 Differential diagnoses for fibrosarcomas

Neoplastic
- Sarcoid
- Peripheral nerve sheath tumour
- Myofibroblastic tumour
- Spindle cell carcinoma
- Giant cell tumour of soft parts

Non-neoplastic
- Granulation tissue
- Fibromatosis

Myxosarcoma

Cellular origin

This is a malignant neoplasm of fibroblastic origin that produces abundant myxomatous matrix: i.e. a matrix rich in glycosaminoglycans.

Profile

Myxosarcomas (and myxomas) may occur in the gingiva of older horses.[19] There have been three reports of caecal myxosarcoma, one of which appeared to arise in the muscularis externa.[43,44]

Biological behaviour

Myxosarcomas are locally invasive. Metastasis to mesenteric lymph nodes was reported for all of the caecal masses mentioned above.[43,44]

Gross pathology

Myxosarcomas are solitary, fleshy, gelatinous or firm/fibrous, and pale tan, yellow or red-brown. On sectioned surfaces they exude clear, viscous fluid or yellow gelatinous material, and may contain mucus-filled cavities. Surfaces may be irregular and/or ulcerated. One caecal myxosarcoma (26 cm in maximal diameter) had a thick fibrous capsule and was pedunculated, protruding into the lumen of ventral colon through the caecocolic orifice and resulting in obstruction.[44]

Histopathology

Myxosarcoma has a similar histological appearance to myxoma (pp. 286–287).

Fibroblastic cells (spindle-shaped or stellate) are noted within large amounts of basophilic, fibrillar (myxomatous) matrix; the latter stains positively for glycosaminoglycans using the Alcian blue method (at pH 2.5) and can be digested by hyaluronidase.[15] Variable amounts of collagenous stroma are also noted. Nuclear and cytoplasmic pleomorphism and mitotic activity are more apparent than in myxomas, although this is assessed subjectively. The differentiation from myxoma might be dependent on evidence of highly invasive behaviour and/or metastasis, in cases where the tumour cells are particularly well-differentiated.

Box 16.4 Differential diagnoses for myxosarcoma

Neoplastic
- Myxoma
- Fibrosarcoma
- Sarcoid
- Gastrointestinal stromal tumour
- Myofibroblastic tumour

Non-neoplastic
- Inflammatory polyp
- Gingival hyperplasia

Differential diagnoses

These are listed in Box 16.4.

MYOFIBROBLASTIC TUMOURS

Cellular origin

Myofibroblasts are spindle-shaped cells having features of both fibroblasts and smooth muscle cells.[45] There is some overlap between the diagnoses of fibrosarcoma and myofibroblastic tumour, as myofibroblasts are present in most fibroblastic neoplasms (pp. 287–288).

Profile

There have been three reports of intra-abdominal myofibroblastic tumours. Two arose from the intestinal mesentery and were diagnosed in a 2-year-old colt and an 18-year-old Thoroughbred gelding, respectively; the former neoplasm was diagnosed as a myofibroblastoma and the latter as a sarcoma.[46,47] A large mass extending from the abdominal wall into the abdominal cavity of a 22-year-old pony was surgically removed and diagnosed as a myofibroblastic tumour, without publication of a histological description.[48] Additionally, a myofibroblastic sarcoma was reported at the site of equine influenza vaccination, this being noted shortly after the second injection.[49] These cases will be looked at in more depth below.

Biological behaviour

The intestinal mesenteric myofibroblastoma was locally infiltrative.[47] The mesenteric myofibroblastic sarcoma was encapsulated with no evidence of metastasis, despite a prolonged clinical course.[46] The vaccination site myofibroblastic sarcoma grew rapidly over a 6-month period but was not locally invasive, with no evidence of metastasis and no recurrence 4 months post-excision; the association of this neoplasm with vaccination was interesting, given the well-known phenomenon of vaccine-associated sarcomas (including those of myofibroblastic origin) in other domestic species.[49] No other cases of vaccination-associated sarcoma have been reported in equines.

Gross pathology

The mesenteric myofibroblastoma measured 25 cm in diameter and was associated with haemoperitoneum; it was fibrous and fused to the jejunum.[47] The mesenteric myofibroblastic sarcoma weighed 82 kg and was encapsulated, multiloculated and cystic with central necrosis and a thick fibrous capsule. The capsular tissue surrounded associated mesenteric lymph nodes and showed numerous adhesions to serosal surfaces of the small and large intestine.[46] The abdominal wall myofibroblastic tumour reported in a pony was pedunculated, multilobulated and multicystic and was also large, weighing 64.5 kg.[48]

In the case involving a vaccination site, the myofibroblastic sarcoma grew to a diameter of 20 cm on the left side of the neck, with marked elevation of the skin (by approximately 10 cm).[49]

Histopathology

In the mesenteric myofibroblastoma, spindle-shaped to stellate tumour cells were supported by large amounts of fibrous and myxoid stromal tissue. Their nuclei were oval, fusiform or irregularly-shaped, with clumped chromatin and few mitotic figures.

The myofibroblastic sarcomas were composed of spindle-shaped or ovoid tumour cells arranged in interlacing sheets, bundles, fascicles and/or perivascular whorls supported by a sparse fibrovascular stroma; in one case, the cells were large and plump and in the other, they had scanty cytoplasm.[46,49] Nuclei were large and ovoid with finely granular or vesicular chromatin and prominent nucleoli; there was marked anisokaryosis with a high mitotic rate (21 per 10 high power (×400) fields in one case) and occasional binucleate or multinucleate tumour cells were noted. Associated lesions included multifocal necrosis, oedema, haemorrhage, neutrophilic inflammation and multiple foci of metaplastic bone.

Immunohistochemical labelling

The myofibroblastoma tumour cells stained positively for vimentin and smooth muscle actin, with occasional desmin-positive cells and pericellular staining for fibronectin; fibronectin should not be found in neoplasms of smooth muscle origin.[47,50]

Tumour cells in both cases of myofibroblastic sarcoma showed strong positive immunolabelling for vimentin and α-smooth muscle actin; labelling for fibronectin was not performed, which would have been desirable to rule out the diagnosis of leiomyofibrosarcoma.[46,49] In one case, the tumour cells were also desmin-positive.[46] It should be noted that (normal) myofibroblasts found in wound tissue usually do not express desmin, with the exception of some chronic lesions.[46] The tumour cells in both cases were S100 negative.

Electron microscopy

Ultrastructurally, the tumour cells should show features indicating smooth muscle differentiation, including bundles of intracytoplasmic microfilaments.

Differential diagnoses

These are listed in Box 16.5.

Box 16.5 Differential diagnoses for myofibroblastic tumours

Neoplastic
- Gastrointestinal stromal tumour
- Leiomyoma
- Leiomyosarcoma
- Fibroma
- Fibrosarcoma

Non-neoplastic
- Granulation tissue

Box 16.6 Differential diagnoses for haemangiopericytoma

Neoplastic
- Fibroma
- Fibrosarcoma
- Peripheral nerve sheath tumour
- Leiomyoma
- Leiomyosarcoma
- Sarcoid

Non-neoplastic
- Granulation tissue

Haemangiopericytoma

Cellular origin

The histogenesis of haemangiopericytomas is uncertain; however, some immunohistochemical and ultrastructural findings in other species have supported a pericyte origin.[25] Pericytes surround the endothelial cells of capillary blood vessels, where they regulate endothelial cell function, in addition to microvascular perfusion and permeability. Some authors categorize these neoplasms as 'soft tissue sarcomas' or peripheral nerve sheath tumours (p. 299).

Profile

Haemangiopericytomas are most frequently diagnosed in dogs, but are occasionally seen in horses.[25] They are usually dermal or subcutaneous. There has been one specific report of a haemangiopericytoma in the subcutis of the right lower eyelid of a 14-year-old Arabian mare.[51]

Biological behaviour

The behaviour of haemangiopericytomas in horses is uncertain. In other species, they tend to be slow-growing and rarely metastasize, but they often recur locally due to difficulties in identifying margins.[25] Surgical excision of the one reported equine case was curative.[51]

Gross pathology

Haemangiopericytomas are usually well-circumscribed, pale and soft to firm on sectioned surfaces.[25] The reported equine eyelid mass measured 4 cm in maximal diameter, and was encapsulated, soft and mobile. The sectioned surface was lobulated and mottled white and red.[51]

Histopathology

Tumour cells comprising haemangiopericytomas are arranged in interlacing bundles and in characteristic prominent whorls, often centred on blood vessels; they are supported by a delicate fibrovascular stroma. The tumour cells are plump and spindle-shaped with a homogeneous eosinophilic cytoplasm. Nuclei are round or oval with vesicular or finely stippled chromatin, and a single nucleolus; the mitotic rate is usually low and in the reported neoplasm was 2 per high power (×400) field.[51]

Immunohistochemical labelling

Tumour cells should stain positively for vimentin, and frequently express smooth muscle actin. Negative staining for S100 should rule out a peripheral nerve sheath origin, although some S100-positive neoplasms have been diagnosed as haemangiopericytomas in other species.[25] Haemangiopericytomas are desmin-negative.

Differential diagnoses

These are listed in Box 16.6.

Giant cell tumour of soft parts (malignant fibrous histiocytoma)

See also page 566.

Cellular origin

The exact histogenesis of this type of neoplasm is controversial: primordial or mesenchymal stem cell origin has been suggested, and it is possible that the giant cells (see below) are a recruited non-neoplastic population.[52] Some veterinary pathologists do not believe this to be a distinct tumour type, but rather a collection of anaplastic neoplasms of various origins that have a similar histological appearance, i.e. mixtures of fibroblast-like, histiocyte-like and multinucleated giant cells.[25,53]

Profile

In one survey of equine cutaneous neoplasia in the Pacific North-West of the USA, giant cell tumours of soft parts comprised 1.3% of cases.[19] Superficial masses occur in the dermis, subcutis or superficial fascia and have most frequently been reported on the shoulders or legs (see Fig. 31.23), with further reports on the muzzle, neck, trunk and, in one case, in the mammary gland.[19,54–56] Deeper masses tend to involve fascial tissue, skeletal muscle, and tendons of the thigh. In one report, four of six cases involved the hindlimb. There was a mean age of 6.8 years in this study (range 3–12 years).[57] In a further study of a larger number of horses (n=21; 3–23 years), most were over 10 years of age.[52]

No breed predilection has been indicated, but the results of one study suggested a male predisposition.[52] There has been one report of a giant cell tumour of soft parts in a mule.[58] Donkeys may also be affected.

Biological behaviour

Giant cell tumours of soft parts in superficial locations have a moderate growth rate, are locally invasive and can recur locally after incomplete surgical excision (there is one report of a rate of 50%), but very rarely metastasize.[57] Recurrence has been noted in some cases within 1–1.5 months. Deep masses (involving the hindlimbs) tend to be large and may have higher metastatic potential. Due to the potential for local recurrence, clean surgical margins of at least 2–3 cm are advised.

Gross pathology

Giant cell tumours of soft parts tend to be solitary, but multiple masses have been reported.[59] Superficial masses in the skin and subcutis are variable in size (from 1 to 4 cm in diameter), potentially encapsulated, firm, raised, partially or completely lobulated, or sometimes nodular.[55] A few of these neoplasms have been pedunculated, and ulceration may occur (Figs. 4.27A and B, 31.23).[52] Giant cell tumours of soft parts are dark brown or mottled red and white on sectioned surfaces, and firmly attached to subcutaneous tissue.[57] They may *seem* well-demarcated grossly but, histologically, this is not the case (see below). Haemorrhage and necrosis may be noted.[54]

Histopathology

Giant cell tumours are usually poorly-circumscribed and infiltrative, and may be divided by fibrous tissue into incomplete lobules.[54] Spindle-shaped (fibroblastic) tumour cells are arranged in variably dense sheets, interconnecting bundles and/or storiform (radiating or 'cartwheel') patterns with a fine supporting fibrous stroma that is occasionally myxomatous (Fig. 16.2).[57] A second population of polygonal (histiocyte-like) tumour cells are either scattered diffusely throughout the mass or form multiple aggregates.[25] There is an additional population of polygonal multinucleated giant cells (resembling osteoclasts) with abundant eosinophilic cytoplasm and 30–150 oval vesicular nuclei; these giant cells may be numerous (see Fig. 16.2).[55,57] In many cases, tumour cells contain lipid vacuoles of various sizes (liposarcomatous change).[52,54] Anisokaryosis and mitotic rates are variable.

In one giant cell tumour of soft parts diagnosed in a horse, tumour cells were noted within a small vessel[54]; the author has also observed vascular invasion (see Fig. 16.2). If the mass is encapsulated, there may be tumour cell

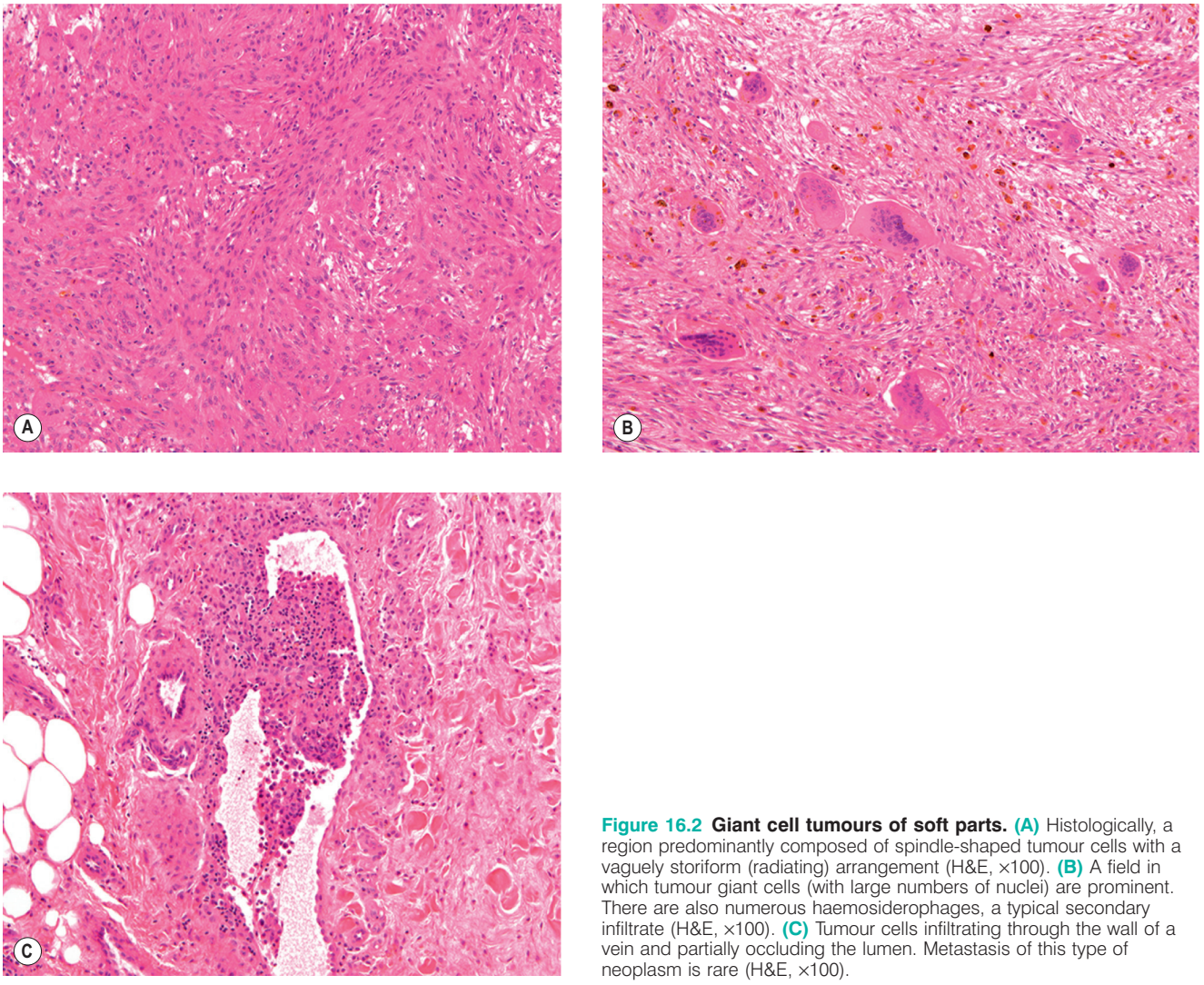


Figure 16.2 Giant cell tumours of soft parts. (A) Histologically, a region predominantly composed of spindle-shaped tumour cells with a vaguely storiform (radiating) arrangement (H&E, ×100). **(B)** A field in which tumour giant cells (with large numbers of nuclei) are prominent. There are also numerous haemosiderophages, a typical secondary infiltrate (H&E, ×100). **(C)** Tumour cells infiltrating through the wall of a vein and partially occluding the lumen. Metastasis of this type of neoplasm is rare (H&E, ×100).

Box 16.7 Differential diagnoses for giant cell tumour of soft parts

Neoplastic
- Fibrosarcoma
- Myxosarcoma
- Osteosarcoma
- Liposarcoma
- Lymphosarcoma
- Rhabdomyosarcoma
- Anaplastic sarcoma

infiltration of the capsular tissue; additionally, small nests of multinucleate giant cells may be seen in surrounding tissues, sometimes widely separated from the main mass.[55,59]

Other changes include necrosis (sometimes with cavitation), haemorrhage and varying numbers of infiltrating haemosiderophages (see Fig. 16.2). There may be marked lymphoid infiltrates, particularly at the periphery.[55,57] There is *no* evidence of osteoid production.

Immunohistochemical labelling

There is no unique immunohistochemical profile for this type of neoplasm.[25] In most giant cell tumours of soft parts, the spindle-shaped cells are vimentin-positive and the giant cells CD18-positive.[52] On the basis of the latter result, it has been suggested but not proven that giant cells are a recruited histiocytic population. The tumour cells are negative for cytokeratin, smooth-muscle actin, CD3, CD79a, CD31 and desmin.

Differential diagnoses

These are listed in Box 16.7.

Anaplastic sarcoma

Cellular origin

Mesenchymal cells.

Profile

Some sarcomas are so poorly-differentiated as to be of uncertain origin (as in other domestic animal species). They have been reported in the caudal thigh and sinonasal cavities of adult horses.[60,61] Extradural undifferentiated sarcomas causing spinal cord compression were reported in two horses, with extensive vertebral bone invasion.[62]

Biological behaviour

As expected, anaplastic sarcomas are highly invasive and there may be widespread metastasis; the caudal thigh mass can metastasize to the lungs and myocardium.[60]

Gross pathology

As with other sarcomas, masses are usually poorly-circumscribed, firm/fibrous and pale in colour. On sectioned surfaces there may be areas of haemorrhage and necrotic cavitation.

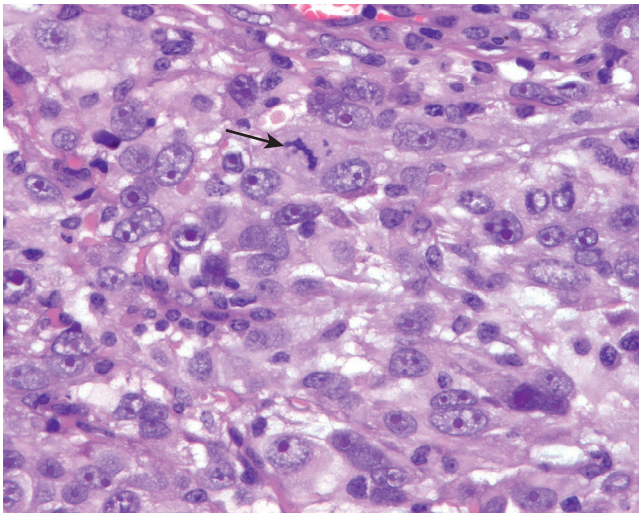


Figure 16.3 Anaplastic sarcoma. The tumour cells are round or polygonal, with large, irregularly-shaped nuclei containing one to several large nucleoli. There is an abnormal mitotic figure in this field (arrow). Immunolabelling would be required to rule out other differential diagnoses, including anaplastic carcinoma and malignant melanoma.

Box 16.8 Differential diagnoses for anaplastic sarcoma

Neoplastic
- Other sarcomas
- Giant cell tumour of soft parts
- Anaplastic carcinoma
- Lymphosarcoma and other round cell tumours
- Amelanotic (or poorly-pigmented) melanoma

Histopathology

The tumour cells are round, polygonal or spindle-shaped. Nuclei may be round, ovoid, elongate and/or irregularly-shaped, and multinucleate tumour cells may be noted. There is marked cellular pleomorphism and a high mitotic rate (Fig. 16.3). Tumour cell emboli may be noted in lymphatic and/or blood vessels.

Differential diagnoses

These are listed in Box 16.8.

Malignant mesenchymoma

Cellular origin

These soft tissue mesenchymal neoplasms contain two or more histological types of sarcoma, other than fibrosarcoma; they are composed of tumour cells differentiating into unrelated malignant forms and may possibly arise from primitive multipotent cells.

Box 16.9 Differential diagnoses for malignant mesenchymoma

Neoplastic
- Anaplastic sarcoma or carcinoma
- Osteosarcoma
- Chondrosarcoma
- Malignant teratoma

Profile

These neoplasms are extremely rare in any species. There was one report in the cranial abdominal cavity of a 2-year-old horse.[63] The details are expanded on below.

Biological behaviour

Malignant mesenchymomas are generally accepted to be high-grade malignancies, i.e. a particularly aggressive form of sarcoma.[64] In the case in the 2-year-old horse, the abdominal mass did not metastasize, but was associated with hypercalcaemia that was not caused by renal disease or bone infiltration.[63]

Gross pathology

The abdominal malignant mesenchymoma of the 2-year-old horse weighed 54 kg and measured 500 cm in diameter. It was attached to the mesentery between the dorsal and ventral large colon and was adhered to the small intestine.[63] The mass was encapsulated with necrotic areas noted on sectioned surfaces.

Histopathology

The abdominal malignant mesenchymoma contained areas with appearances consistent with the diagnoses of haemangiosarcoma, fibrosarcoma and leiomyosarcoma.[63]

It should be noted that malignant mesenchymomas with true differentiation to osteosarcoma and/or chondrosarcoma should be distinguished from those with areas of osseous and/or chondroid metaplasia.

Differential diagnoses

These are listed in Box 16.9.

Primary retroperitoneal tumour

Cellular origin

Primary retroperitoneal tumours may be of mesenchymal, extra-gonadal germ cell or epithelial origin. The one reported case in a horse was largely of mesenchymal origin.

Profile

A primary retroperitoneal tumour was reported in a 10-year-old Thoroughbred gelding that presented with colic and haemoperitoneum.[65]

Box 16.10 Differential diagnoses of primary retroperitoneal tumours

Neoplastic
- Other sarcomas

Biological behaviour

The reported mass was adhered to the left kidney, aorta, caudal vena cava and small intestine but was not invasive. Surgical excision was not possible due to the location.[65]

Gross pathology

The mass, located within the left retroperitoneal space, was spherical, well-circumscribed and firm and measured 30×28×16 cm. Sectioned surfaces were white, firm and multilobulated, with large central haematomas.[65]

Histopathology

Tumour cells were arranged in short streams and bundles, with intervening bands of collagenous stroma. The tumour cells were polygonal or spindle-shaped, with abundant pale-staining eosinophilic cytoplasm. Nuclei were round or ovoid and vesicular, with sparse chromatin and 0–1 mitotic figures per high power (×400) field. The neoplasm was classified as being poorly-differentiated and largely of mesenchymal but not of muscle origin with scant epithelial-like components.[65]

Immunohistochemical labelling

There was strong positive staining of tumour cells for vimentin, with only multifocal labelling for smooth muscle actin, muscle-specific actin and keratin.[65]

Differential diagnoses

These are listed in Box 16.10.

NON-NEOPLASTIC MESENCHYMAL MASSES

Fibrous hamartoma

Summary

Fibrous hamartomas are benign focal overgrowths of normal fibrous tissue, the growth of which is coordinated with that of surrounding tissue; they are not encapsulated or compressive.

Profile

A subcutaneous fibrous hamartoma was diagnosed in the subcutis of a 13-week-old foal.[66] This mass extended from the base of the right ear to the caudal aspect of the third cervical vertebra.

Histopathology

Histologically, it was composed of bundles and whorls of well-differentiated fibroblasts within collagenous tissue.[66]

Fibromatosis (intramuscular desmoid 'tumours', musculoaponeurotic fibromatosis)

Profile

This is a rare progressive, non-neoplastic fibrosing disease of skeletal muscle. These lesions arise from fibroblasts and/or myofibroblasts; they may begin as myofibroblastic lesions with maturation to a fibroblastic phenotype.[67] This condition is most frequently diagnosed in pectoral or cervical muscles of young adult horses (4–5 years of age).[19,67] There is one report of right-sided paranasal sinus fibromatosis in an 11-year-old Thoroughbred gelding.[68] In skeletal muscle, there is progressive infiltration by fibrous tissue that may be markedly invasive when it reaches an advanced stage.[19] There may be recurrence following incomplete surgical excision; curative excision has been reported.[67,68]

Gross pathology

The gross presentation is an often extensive, poorly-defined area of swelling or induration of skeletal muscle; on sectioned surfaces this is seen to be dissecting fibrous tissue that may contain 0.5–3 cm diameter cystic cavities filled with mucoid material.[67] Where these lesions extend to bony surfaces, there may be periosteal thickening.[67] The reported paranasal lesions were smooth, tan, partially ossified masses replacing normal ethmoid turbinate structure and filling the frontonasal and maxillary sinuses, with firm attachment to and invasion of underlying bone.[68]

Histopathology

Histologically, these lesions are composed of streams and fascicular bundles of well-differentiated fibroblasts, fibrous tissue and small to medium-sized blood vessels; in skeletal muscle, this tissue dissects between myofibres.[68,69] The collagenous stroma may be finely fibrillar and myxoid in some fields or may form thick ('keloidal') fibres. There may be osteolysis and reactive bone formation if bony tissue is infiltrated. Other associated lesions include granulation tissue, perivascular lymphocytic and eosinophilic inflammatory cell infiltrates, inflammatory cells within cystic spaces containing proteinaceous fluid, extension of inflammatory changes into adjacent bone, and atrophy and regeneration of entrapped and adjacent remnant skeletal muscle fibres.[67,69] The areas of cystic degeneration and inflammation might indicate initiating trauma, or ischaemic necrosis.

Differential diagnoses

An important differential diagnosis in skeletal muscle is equine fibrotic myopathy, in which there is marked atrophy, hypertrophy and fibrous replacement of myofibres; at least some of those cases may be secondary to denervation rather than traumatic injury.[71]

LIPOCYTIC (ADIPOSE) TUMOURS

Lipoma

See also pages 465 and 567.

Cellular origin

These benign neoplasms arise from lipocytes. Some authors classify lipomas as hamartomatous or hyperplastic, rather than neoplastic.

Profile

Of total neoplasms, most estimates of the prevalence of lipomas have been 2–3%.[1,10,70] However, in one abattoir survey (n=1308), 13% of the reported 151 tumours were mesenteric lipomas; the higher prevalence in this particular survey may have been more accurate because lipomas are frequently an incidental finding.[71] Lipomas are the most common intra-abdominal neoplasm of horses, where they arise in the mesentery or intestinal serosa and most commonly cause clinical signs in older horses (mean age 17–19 years) (see below).[72] In two reports, geldings were considered to be at higher risk than stallions and mares, and ponies at higher risk than horses. Breeds predisposed to the development of pedunculated lipoma are said to include ponies, Saddlebreds, Arabians and Quarter Horses.[73,74]

In one US survey, although 49% of lipomas were intra-abdominal and/or intestinal, 44% involved the skin or other soft tissues.[10] In the skin, lipomas have been reported in young horses (often ≤18 months of age). Sites include the neck, stifle, abdomen, thorax and hindlimb.[2,75–77] Some lesions are congenital and might be more appropriately diagnosed as lipomatous harmatomas.[78] In older horses, multiple lipomas (or these might be more correctly termed 'atypical fat deposits') can occur in the subcutis.[79] Obese animals may be predisposed to lipoma development.

Other, rare sites for lipoma development in horses have included the testis, spermatic cord, penile sheath, nictitating membrane, orbit, pericardium, myocardium, thoracic cavity, meninges and digital extensor tendon sheaths.[70,77,80–85]

Biological behaviour

Lipomas are benign, slow-growing masses. Most of the large number of older horses and ponies that develop intra-abdominal lipomas show no clinical signs; however, they have been estimated to cause up to 17% of all colic cases requiring surgery.[73,74] Simple intestinal strangulation or obstruction may be caused if the mass is pedunculated and becomes torsed around a viscus; strangulation is by far the more frequent occurrence and the risk increases with age.[72,86,87] The small intestine is most frequently involved, most likely due to the greater mobility of those segments (see Figs. 3.7, 28.30). Only 6–7% of intestinal strangulation due to lipomas involves the small colon and this occurs most frequently in animals >15 years of age.[73,86,88,89] In one study of horses with small intestinal strangulation (submitted to a US referral hospital), those caused by a lipoma occurred in

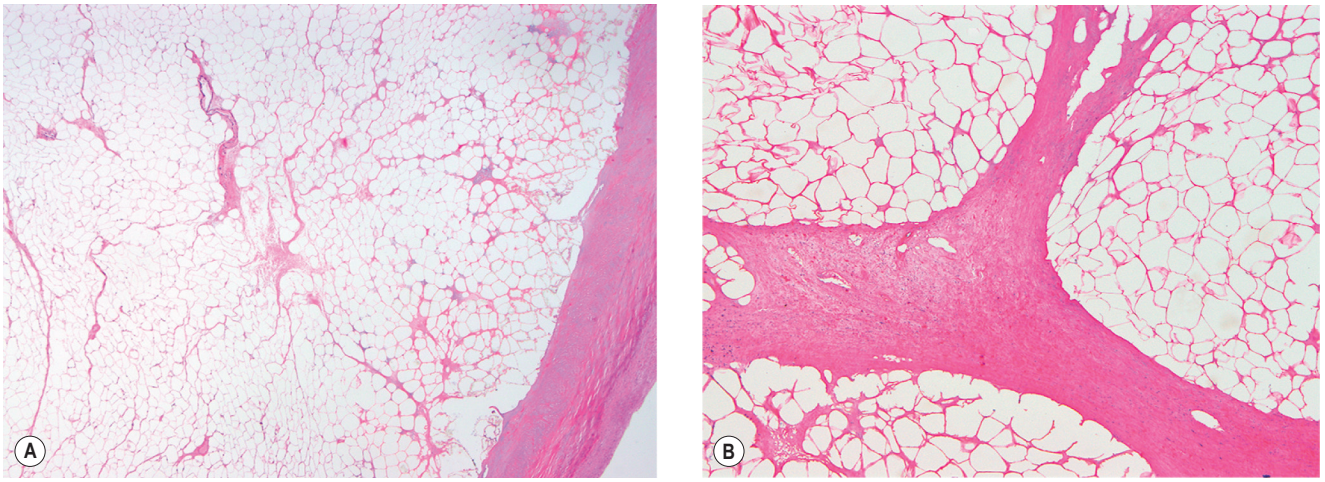


Figure 16.4 Lipomas. (A) Histological appearance of a mesenteric lipoma with a thick fibrous capsule; internally, the mass is composed of lobules of well-differentiated adipocytes supported by fine fibrous tissue septa (H&E, ×12.5). **(B)** Histological appearance of a fibrolipoma that occurred in the skin of the mammary region. Fibrolipomas are a variant, in which the lobules of well-differentiated adipocytes are supported by prominent bands of fibrous tissue rather than the more typical thin septa (H&E, ×40).

significantly older horses (mean age 19.2 years) than those due to other causes including epiploic foramen entrapment (mean age 7.7–9.6 years).[72] There is only one report of rectal strangulation.[82]

Lipomas do not usually recur following surgical excision.

Gross pathology

Grossly, lipomas are well-demarcated, may be encapsulated and are soft and fatty (see Fig. 3.7). Necrosis, haemorrhage and fibrosis may occur in these masses as a result of trauma.[25] Lipomas are usually multiple within the abdomen, but can be solitary; in the mesentery, they are thought to arise as localized fat plaques between the two serosal layers, with the serosa stretching to form a fibrous pedicle (of variable length) as the mass enlarges (Fig. 28.30).[73] Larger masses on long and thin stalks may be necrotic and/or mineralized on sectioned surfaces or contain haemorrhagic cavities, and occasional lipomas become free-floating within the abdominal cavity. In one study, pedunculated lipomas causing intestinal obstruction had a greater median weight (164 g; range 33–688) than those that did not (21 g; range 3–259).[73]

In the subcutis, lipomas may be poorly-delineated and can reach a very large size, weighing up to 8 kg and measuring up to 50 cm in diameter (Fig. 31.24).[75,76] These masses may occur deep to the cutaneous trunci or the fascial tissue of abdominal musculature.[76]

Histopathology

Lipomas are encapsulated or unencapsulated masses composed of lobules of well-differentiated adipocytes that are indistinguishable from normal fat, and are supported by a fine fibrovascular stroma (see Fig. 16.4). There may be a compressed boundary of delicate stroma at margins of lipomas that are not encapsulated.[25] Lipomas that contain significant amounts of fibrous tissue may be diagnosed as fibrolipomas (see Fig. 16.4). Other changes can include necrosis, haemorrhage, areas of fibrosis and macrophage infiltration.

Infiltrative lipoma

Cellular origin

Lipocytes.

Profile

This is a rare form of lipoma in any species. Infiltrative lipomas have been reported in the subcutis of young horses (≤2 years of age), usually involving the neck, trunk or extremities.[19,76,90–92] There is one report of destruction of the longitudinal layer of the muscularis externa of the transverse and small colon in a 7-year-old Quarter Horse gelding, by multiple masses.[93] A similar small colon lesion was diagnosed in a 2-year-old Tennessee Walking horse, that also presented with refractory impaction.[94] A solitary mass was reported in the free wall of the right ventricle of the heart in a 3-year-old Morgan horse.[95]

The occurrence of infiltrative lipomas in younger horses has been suggested to indicate a congenital origin, and some have been diagnosed in neonates/foals.[91,92,96]

Biological behaviour

Infiltrative lipomas have a morphologically benign appearance; however, they grow by infiltration and expansion of adjacent soft tissues, including skeletal muscle. Type-specific muscle atrophy and degeneration associated with atrophy was observed recently in association with infiltrative lipomas, and was proposed to be the driver of the infiltrative behaviour of this tumour type.[97]

Local tissue invasion by these neoplasms can be massive, but metastasis has not been reported. Complete excision is frequently not achieved, with repeated surgical procedures being required.[92,96] Some horses have been euthanized due to extensive involvement of underlying soft tissues by masses arising in the subcutis or due to masses arising in internal organs.

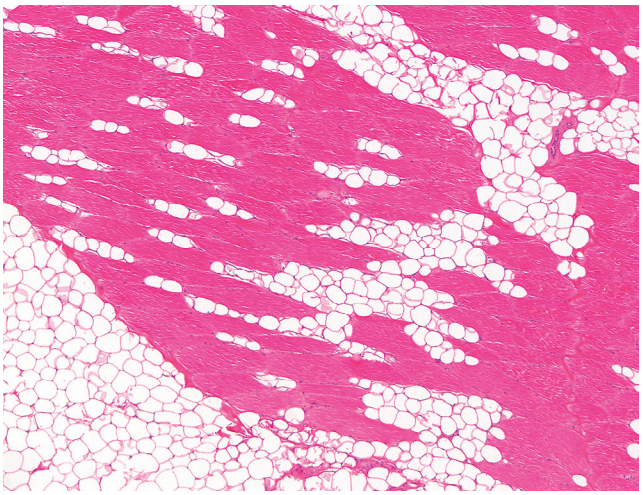


Figure 16.5 Infiltrative lipoma of the subcutis. Rows and irregularly-shaped sheets of well-differentiated adipocytes are infiltrating between and replacing myofibres in adjacent skeletal muscle. This is a diagnostic feature (H&E, ×40).

Gross pathology

Subcutaneous masses are soft or firm, non-painful, unencapsulated, covered by intact skin and non-mobile; they may reach a large size, i.e. 25–36 cm in maximal diameter.[90,92]

In one case of colonic lipomatosis, the fatty masses were located on the anti-mesenteric border, measured 1–30 cm in diameter and were nodular to papillary with central areas of necrosis and haemorrhage.[93] In a second case, the neoplastic tissue covered most of the serosal surface and extended transmurally to the mucosal surface; in both cases there were associated intestinal diverticula.[93,94]

A myocardial infiltrative lipoma was expansile, yellow and soft with dark streaks on sectioned surfaces representing remnant myocardial fibres.[95]

Histopathology

Infiltrative lipomas are composed of well-differentiated adipocytes supported by a fine fibrovascular stroma. The adipocytes infiltrate and replace adjacent tissue, including skeletal muscle; dissection through bundles of skeletal muscle and along fascial planes is characteristic of the subcutaneous neoplasms (Fig. 16.5). In one case, a subcutaneous mass infiltrated the full thickness of the underlying abdominal wall.[90] In both skeletal and cardiac muscle, there may be associated myofibre degeneration. In cases involving the small colon, the lipocytic cells were invading and replacing the muscularis externa, and in one case, extending into the submucosa with elevation and ulceration of the overlying mucosa.[93,94] Secondary changes include necrosis, haemorrhage and inflammation.

Liposarcoma

Cellular origin

Liposarcomas are malignant neoplasms derived from lipocytes.

Box 16.11 Differential diagnoses for liposarcoma

Neoplastic
- Sebaceous carcinoma
- Balloon cell melanoma
- Lipid-rich mesothelioma
- Meningioma (e.g. in periocular locations)

Profile

Liposarcomas are rare neoplasms in horses and other domestic animal species.[1,25] In surveys, they have been reported in the skin, mandible, tongue and pelvic adipose tissue; no macroscopic or histological descriptions were provided.[10] A liposarcoma has been described in the cranial mediastinum of a 23-year-old mare.[98]

Biological behaviour

Liposarcomas are malignant, invasive neoplasms that in other species may recur, but rarely metastasize, when arising in the skin.[25]

Gross pathology

The mediastinal liposarcoma measured 23×20×18 cm, was irregularly-shaped, friable, and tan to red, and was focally adhered to the pericardium.[98] On sectioned surfaces, this mass was pale tan to yellow with observation of cystic cavities containing red fluid. The lungs were displaced caudally and there were 20 L of serosanguineous fluid within the pleural cavity.

Histopathology

In other animal species, tumour cells comprising liposarcomas are arranged in sheets and are usually round, polygonal or spindle-shaped, with variable cytoplasmic vacuolation and infrequent mitotic figures.[25] In the mediastinal liposarcoma, classified as well-differentiated, the tumour cells were spindle-shaped, had indistinct cytoplasmic margins and contained variably-sized, clear, circular vacuoles.[98] Nuclei were round to elongate, and central or eccentric with coarse chromatin and a prominent nucleolus; there was moderate cellular pleomorphism and a low mitotic rate (5 per 10 high power (×400) fields). Frozen sections from formalin-fixed tissue were stained with Oil Red O to confirm the presence of lipid in tumour cell vacuoles.[98]

Differential diagnoses

These are listed in Box 16.11.

References

1. Bastianello S. A survey on neoplasia in domestic species over a 40-year period from 1935 to 1974 in the Republic of South Africa. IV. Tumours occurring in Equidae. Onderstepoort J Vet Res 1983; 50:91–96.
2. Pascoe RR, Summers PM. Clinical survey of tumours and tumour-like lesions in horses in south east Queensland. Equine Vet J 1981; 13:235–239.
3. Pirie RS, Dixon PM. Mandibular tumours in the horse: a review of the literature and 7 case reports. Equine Vet Educ 1993; 5:287–294.

4. Schooley EK, Hendrickson DA. Musculoskeletal system neoplasia. Vet Clin North Am Equine Pract 1998; 14:535–542.
5. Colitz CMH, Gilger BC, Davidson MG. Orbital fibroma in a horse. Vet Ophthalmol 2000; 3:213–216.
6. Kidd JA, Bradshaw J. Bilateral nonossifying fibromas in the proximal tibiae of a yearling Thoroughbred filly. Equine Vet J 2002; 34:317–320.
7. Attenburrow DP, Heyse-Moore GH. Non-ossifying fibroma in phalanx of a Thoroughbred yearling. Equine Vet J 1982; 14:59–61.
8. Adams SB, Fessler JF, Thacker HL. Tendon fibromas in 2 horses. Equine Vet J 1982; 14:95–97.
9. Madewell BR, Priester WA, Gillette EL, et al. Neoplasms of the nasal passages and paranasal sinuses in domesticated animals as reported by 13 veterinary colleges. Am J Vet Res 1976; 37:851–856.
10. Priester WA, MacKay FW. The occurrence of tumours in domestic animals. Natl Cancer Inst Monogr 1980; 54:1–210.
11. Wilson JD, Sykes GP. Fibroma in the abdomen of a horse. Vet Rec 1981; 108:334.
12. Meinecke B. Clinical aspects of ovary tumours in mares. Tierarztl Prax 1986; 14:501–508.
13. Sertich PL. Cervical problems in the mare. In: McKinnon AO, Voss JL, eds. Equine reproduction. Philadelphia: Lea & Febiger; 1993: 404.
14. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 2: A contribution of 28 case reports. Vet J 1999; 157:279–294.
15. Rahko T, Alitalo I, Paatsama S. Myxoma in the nasal cavity of the Finnish-bred horse. A report on three cases recently observed in Finland. Acta Vet Scand 1972; 13:131–133.
16. Murphy JR, Breeze RG, McPherson EA. Myxoma of the equine respiratory tract. Mod Vet Pract 1978; 59:529–532.
17. Boulton CH. Equine nasal cavity and paranasal sinus disease: a review of 85 cases. J Equine Vet Sci 1985; 5:268–275.
18. Barakzai SZ, Dixon PM. Sinonasal myxoma in a four-year-old thoroughbred gelding. Vet Rec 2003; 152:210–211.
19. Valentine BA. Neoplasia. In: Bertone JJ, ed. Equine geriatric medicine and surgery. St Louis: Saunders Elsevier; 2006: 147–167.
20. Dixon PM, Parkin TD, Collins N, et al. Equine paranasal sinus disease: a long-term study of 200 cases (1997–2009): treatments and long-term results of treatments. Equine Vet J 2011; 44:272–276.
21. Merriam JG. Guttural pouch fibroma in a mare. J Am Vet Med Assoc 1972; 161:487–489.
22. Jackson C. The incidence and pathology of tumours of domesticated animals in South Africa. Onderstepoort J Vet Sci Anim Ind 1936; 6:1–460.
23. Runnells RA, Benbrook EA. Connective tissue tumours of horses and mules. Am J Vet Res 1941; 2:427–429.
24. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 1: Review of the literature and tumour classification. Vet J 1999; 157:261–278.
25. Ginn PE, Mansell JEKL, Rakich PM. Skin and appendages. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's pathology of domestic animals, 5th edn, Vol. 1. Philadelphia: Elsevier Saunders; 2007: 553–781.
26. Schumacher J, Watkins JP, Wilson SR, et al. Burn-induced neoplasia in two horses. Equine Vet J 1986; 18:410–412.
27. Gorlin RJ, Barron CN, Chaudhry AP, et al. The oral and pharyngeal pathology of domestic animals. A study of 487 cases. Am J Vet Res 1959; 20:1032–1061.
28. Reinertson EL. Fibrosarcoma in a horse. Cornell Vet 1974; 64:617–621.
29. Riggott JM, Quarmby WB. Treatment of fibrosarcoma in a horse. Equine Vet J 1980; 12:193–196.
30. Harvey KA, Morris DD, Saik JE, et al. Omental fibrosarcoma in a horse. J Am Vet Med Assoc 1987; 191:335–337.
31. Bonfig H, Ingenhorst I. Surgical removal of a pedunculated uterine tumour in a donkey mare. Tierarztl Prax 1992; 20:65–68.
32. Jorgensen JS, Geoly FJ, Berry CR, et al. Lameness and pleural effusion associated with an aggressive fibrosarcoma in a horse. J Am Vet Med Assoc 1997; 210:1328–1331.
33. Roels S, Ducatelle R, van de Vijver B, et al. Successful treatment of an equine preputial fibrosarcoma using 5-fluorouracil/evaluation of the treatment using quantitative PCNA and Ki67 (MIB1) immunostaining. Zentralbl Veterinarmed A 1998; 45:591–598.
34. Van den Top JG, de Heer N, Klein WR, et al. Penile and preputial tumours in the horse: a retrospective study of 114 affected horses. Equine Vet J 2008; 40:528–532.
35. Govaere J, Maes S, Saey V, et al. Uterine fibrosarcoma in a Warmblood mare. Reprod Domest Anim 2011; 46:564–566.
36. Barber SM, Clark EG, Fretz PB. Fibroblastic tumour of the premaxilla in two horses. J Am Vet Med Assoc 1983; 182:700–702.
37. Story MR, Gaughan EM, Andrews GA, et al. Fibrosarcoma over the tarsal groove of a 14-month-old Quarter horse. Vet Comp Orthop Traumatol 2005; 18:115–118.
38. Hultgren BD, Schmotzer WB, Watrous BJ, et al. Nasal-maxillary fibrosarcoma in young horses: a light and electron microscopic study. Vet Pathol 1987; 24:194–196.
39. Schmotzer WB, Hultgren BD, Watrous BJ, et al. Nasomaxillary fibrosarcomas in three young horses. J Am Vet Med Assoc 1987; 191:437–439.
40. Fulton IC, Stickle R. What is your diagnosis? Probable neoplasm of the rostral portion of the mandible. J Am Vet Med Assoc 1989; 195:1772–1773.
41. Misdorp W, van der Heul RO. XXI. Tumours of bones and joints. Bull World Health Organ 1976; 53:265–283.
42. Groom LJ, Gaughan EM, Andrews G. Fibrosarcoma in the epaxial musculature of a horse. Equine Pract 1997; 19:33–36.
43. Feldman WH. Neoplasms of domesticated animals. London: WB Saunders; 1932.
44. Edens LM, Taylor DD, Murray MJ, et al. Intestinal myxosarcoma in a Thoroughbred mare. Cornell Vet 1992; 82:163–167.
45. Biselli R, Boldrini R, Ferlini C, et al. Myofibroblastic tumours: neoplasias with divergent behaviour. Ultrastructural and flow cytometric analysis. Pathol Res Pract 1999; 195:619–632.
46. Newman SJ, Cheramie H, Duniho SM, et al. Abdominal spindle cell sarcoma of probably myofibroblastic origin in a horse. J Vet Diagn Invest 1999; 11:278–282.
47. Hikita M, Ishikawa Y, Shibahara T, et al. Mesenteric myofibroblastoma in a horse. Vet Rec 2004; 154:795–796.
48. Boyle AG, Higgins JC, Durando MM, et al. Management of hemodynamic changes associated with removal of a large abdominal myofibroblastic tumour in a pony. J Am Vet Med Assoc 2004; 225:1079–1083.
49. Kannegieter NJ, Schaaf KL, Lovell DK, et al. Myofibroblastic fibrosarcoma with multifocal osseous metaplasia at the site of equine influenza vaccination. Aust Vet J 2010; 88:132–136.
50. Eyden BP, Christensen L. Leiomyosarcoma versus myofibrosarcoma: observations and terminology. Ultrastruct Pathol 1993; 17:231–239.
51. Serena A, Joiner KS, Schumacher J. Haemangiopericytoma in the eyelid of a horse. Vet Pathol 2006; 43:576–578.
52. Bush JM, Powers BE. Equine giant cell tumour of soft parts: a series of 21 cases (2000–2007). J Vet Diagn Invest 2008; 20:513–516.
53. Del Piero F. Malignant fibrous histiocytoma: a controversial neoplasm. Equine Vet Educ 2009; 21:473–474.
54. Ford GH, Empson RN, Plopper CG, et al. Giant cell tumour of soft parts: a report of an equine and a feline case. Vet Pathol 1975; 12:428–433.
55. Hamir AN. Equine giant cell tumour of soft tissues. Cornell Vet 1989; 79:173–177.
56. Reesink HL, Parente EJ, Sertich PL, et al. Malignant fibrous histiocytoma of the mammary gland in a mare. Equine Vet Educ 2009; 21:467–472.
57. Render JA, Harrington DD, Wells RE, et al. Giant cell tumour of soft parts in six horses. J Am Vet Med Assoc 1983; 183:790–791.
58. Danks AG, Olafson P. Giant-cell sarcoma. Cornell Vet 1939; 29:68–70.
59. Maryatt PA. Malignant giant cell tumour of soft parts in a mare. Can Vet J 2003; 44:743–745.
60. Danton CA, Peacock PJ, May SA, et al. Anaplastic sarcoma in the caudal thigh of a horse. Vet Rec 1992; 131:188–190.
61. Cissell DD, Wisner ER, Textor J, et al. Computed tomographic appearance of equine sinonasal neoplasia. Vet Radiol Ultrasound 2012; 53:245–251.
62. Van Biervliet J, Alcaraz A, Jackson CA, et al. Extradural undifferentiated sarcoma causing spinal cord compression in 2 horses. J Vet Intern Med 2004; 18:248–251.
63. McCoy DJ, Beasley R. Hypercalcemia associated with malignancy in a horse. J Am Vet Med Assoc 1986; 189:87–89.
64. Brady MS, Perino G, Tallini G, et al. Malignant mesenchymoma. Cancer 1996; 77:467–473.
65. McKay JS, Clegg PD, Morthole VI, et al. Primary retroperitoneal tumour in a horse. Equine Vet J 2003; 35:103–106.
66. Collins N, Kelly G, Pollock PJ, et al. Subcutaneous fibrous hamartoma in a foal. Vet Rec 2004; 154:474–476.
67. Valentine BA, Del Piero F, Edwards RB. Intramuscular desmoid tumour (musculoaponeurotic fibromatosis) in two horses. Vet Pathol 1999; 36: 468–470.
68. Ahern BJ, Engiles J, Smith JJ, et al. Paranasal sinus fibromatosis in a horse. Equine Vet Educ 2010; 22:23–28.
69. Cooper BJ, Valentine BA. Tumours of muscle. In: Meuten DJ, ed. Tumours in domestic animals, 4th edn. Ames: Iowa State Press; 2002:359–361.
70. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
71. Cotchin E, Baker-Smith J. Tumours in horses encountered in an abattoir survey. Vet Rec 1975; 97:399.
72. Freeman DE, Schaeffer DJ. Age distributions of horses with strangulation of the small intestine by a lipoma or in the epiploic foramen: 46 cases (1994–2000). J Am Vet Med Assoc 2001; 219:87–89.
73. Edwards GB, Proudman CJ. An analysis of 75 cases of intestinal obstruction caused by pedunculated lipomas. Equine Vet J 1994; 26:18–21.
74. Garcia-Seco E, Wilson DA, Kramer J, et al. Prevalence and risk factors associated with outcome of surgical removal of pedunculated lipomas in horses: 102 cases (1987–2002). J Am Vet Med Assoc 2005; 226: 1529–1537.
75. Blackwell JG. Unusual adipose tissue growth in a colt. J Am Vet Med Assoc 1972; 161:1141–1142.
76. Bristol DG, Fubini SL. External lipomas in three horses. J Am Vet Med Assoc 1984; 185:791–792.
77. Hammer EJ, Chope K, Lemire TD, et al. A lipoma of the extensor tendon sheaths in a horse. Vet Radiol Ultrasound 2002; 43:63–65.
78. Dunkerley SAC, Williams A, Gillis JP. Lipoma in a foal. J Am Vet Med Assoc 1997; 210:332–333.
79. Valentine BA. Survey of equine cutaneous neoplasia in the Pacific Northwest. J Vet Diagn Invest 2006; 18:123–126.
80. Damodaran S, Ramachandran PV. A survey of neoplasms of equidae. Indian Vet J 1975; 52:531–534.
81. Lavach JD, Severin GA. Neoplasia of the equine eye, adnexa and orbit: a review of 68 cases. J Am Vet Med Assoc 1977; 170:202–203.
82. Mason TA. Strangulation of the rectum of a horse by the pedicle of a mesenteric lipoma. Equine Vet J 1978; 10:269.
83. Anderson WI, King JM. Incidental meningeal lipoma in a horse. Vet Pathol 1988; 25:530–531.
84. McEntee K. Reproductive pathology of domestic mammals. San Diego: Academic Press Inc.; 1990.
85. Pérez-Ecija RA, Mendoza FJ, Zafra R, et al. Clinical, pathological and immunohistochemical features of a pulmonary blastoma in a horse. Vet Rec 2009; 164:182–183.

86. Blikslager AT, Bowman KF, Haven ML, et al. Pedunculated lipomas as a cause of intestinal obstruction in horses: 17 cases (1983–1990). J Am Vet Med Assoc 1992; 201:1249–1252.
87. Downes EE, Ragle CA, Hines MT. Pedunculated lipoma associated with recurrent colic in a horse. J Am Vet Med Assoc 1994; 204:1163–1164.
88. Dart AJ, Snyder JR, Pascoe JR, et al. Abnormal conditions of the equine descending (small) colon. J Am Vet Med Assoc 1992; 200:971–978.
89. Dart AJ, Snyder JR, Pascoe JR. Extensive resection and anastomosis of the descending (small) colon in a mare following strangulation by a mesenteric lipoma. Aust Vet J 1991; 68:61–64.
90. Lepage OM, Laverty S, Drolet R, et al. Infiltrative lipoma in a quarter horse. Cornell Vet 1993; 83:57–60.
91. Olle E, Saunders JH, Desmecht D. Infiltrative lipoma in the foreleg of a horse. Vlaams Diergen Tijds 2002; 71:142–144.
92. Erkert RS, Moll HD, MacAllister CG, et al. Infiltrative lipoma in an American Quarter Horse gelding. Equine Vet Educ 2007; 19:380–383.
93. Henry GA, Yamini B. Equine colonic lipomatosis. J Vet Diagn Invest 1995; 7:578–580.
94. Riley E, Martindale A, Maran B, et al. Small colon lipomatosis resulting in refractory small colon impaction in a Tennessee Walking Horse. Equine Vet Educ 2007; 19:484–487.
95. Baker D, Kreeger J. Infiltrative lipoma in the heart of a horse. Cornell Vet 1987; 77:258–262.
96. Rebsamen E, Gygax D, Dennler M, et al. External infiltrating lipoma in a two-week-old foal: computed tomographic evaluation for the assessment of the extension and invasiveness of the tumour. Equine Vet Educ 2010; 22:602–607.
97. Mori K, Chano T, Matsumoto K, et al. Type-selective muscular degeneration promotes infiltrative growth of intramuscular lipoma. BMC Musculoskelet Disord 2004; 5:20.
98. Kondo H, Wickins SC, Conway JA, et al. Cranial mediastinal liposarcoma in a horse. Vet Pathol 2012; 49:1040–1042.

17 Nerve sheath neoplasms

Benign and malignant peripheral nerve sheath tumours
Cellular origin 299
Profile 299
Oncogenesis 299
Biological behaviour 300
Gross pathology 300
Histopathology 300
Differential diagnoses 302

Granular cell tumours (putative Schwann cell tumours)
Cellular origin 302
Profile 302
Biological behaviour 302
Gross pathology 302
Histopathology 302
Differential diagnoses 303

BENIGN AND MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS

See also page 562.

Cellular origin

The generic term 'peripheral nerve sheath tumour' (PNST) is now used to encompass neurofibroma, schwannoma (neurilemmoma), perineurioma (atypical perineurial cell proliferative disorder), nerve sheath myxoma and some other rare neoplasms. PNSTs may be either benign or malignant. It is not known if these neoplasms in animals have the same underlying genetic alterations as those in human patients. There are three main types of benign PNST:

- *Schwannoma*: is only derived from Schwann cells (myelinating cells of the peripheral nervous system).
- *Neurofibroma*: is composed of cells variously derived from Schwann cells, perineurial (fibroblastic) cells and fibroblasts. While these neoplasms therefore contain all of the cellular elements of a peripheral nerve sheath, the Schwann cell is still the likely primary cell.
- *Perineurioma*: is derived only from perineurial fibroblastic cells. There has been some debate as to whether these lesions are neoplastic, but intraneural perineuriomas are now accepted as neoplasms.

Profile

In surveys of equine neoplasms, 3–4% were of nerve sheath derivation.[1,2] In a survey of equine ocular tumours (n=68), three (4.4%) were PNST, two of which were benign.[3]

Many benign PNSTs are found in the dermis or subcutis of adult horses, mainly of the face, eyelids, neck, axillary region and limbs.[4] In one survey in which the neoplasms (n=56) were referred to as 'neuromas', 43% occurred in the skin, 32% involved peripheral nerves and 12.5% were ocular.[2] Neurofibromas of the eyelid (upper and lower) have been reported as a specific entity in horses and mules.[5–8] The lateral and medial canthi may also be sites of origin.[3] Other reported sites have included the tongue, cheek, gastric serosa, colon, mediastinum, nictitating membrane, nasal cavities/paranasal sinuses and meninges.[8–16] The one reported meningeal mass occurred in a 2-year-old Thoroughbred filly and caused compression of the left cerebral hemisphere; this neoplasm did not arise from cranial nerves and was thought to have developed from either aberrant Schwann cells in the meninges or by conversion of pial cells to Schwann cells.[12] Multiple PNSTs (variably diagnosed as neurofibroma and schwannoma), in addition to hyperplastic enteric plexuses, were reported in the distal jejunum and ileum of a 6-year-old horse, these being defined as different neoplastic developmental stages.[17] Benign PNST have been reported in horses 2–24 years of age.

There have been only small numbers of reports of malignant PNSTs in horses. Extensive neoplasms involving the eye (including cornea), eyelids and/or periocular tissues have been diagnosed in adult horses.[3,18–20] Other reported sites have included the cervical intumescence, skin, abdominal cavity, proximal aorta, heart (left auricle, right atrium and both ventricles), penis and prepuce.[14,21,22] Malignant PNST have been reported in horses 2–23 years of age, with one occurring in a 1-month-old foal.[14]

There is a single report of a perineurioma in the tongue of a 5-year-old mare.[23] In the human, this type of neoplasm, which usually arises from peripheral motor nerves, is also exceedingly rare.[24]

Oncogenesis

A point mutation of the *neu* oncogene was identified in each of three malignant PNSTs.[14]

Biological behaviour

Whatever their exact cellular origin, benign PNSTs are slow-growing, with effects generally relating to space occupation and/or interference with nerve conduction. These neoplasms can extend locally and therefore recur following excision (see Fig. 31.20); a 'diffuse' neurofibroma shows infiltrative growth but no other indicators of malignancy.[4,25] In cases involving the eyelids, further lesions may develop adjacent to areas where neoplasms have previously been excised in over 50% of horses.[6,7]

It is not known if benign PNSTs in animals have the potential to undergo malignant transformation. Malignant PNSTs are locally invasive, but successful excision with no evidence of recurrence has been reported.[19]

A mare diagnosed with perineurioma developed more than 50 coalescing masses over a 2-year period.[23]

Gross pathology

A benign PNST is usually solitary, well-demarcated, potentially lobulated, encapsulated and expansile – but infiltrative (diffuse) forms have been reported.[4,13,25] In the eyelids, these nodular, white, firm, sometimes mobile neoplasms may be single or multiple, first being noted at 2–3 mm in diameter and usually expanding up to 2 cm or more (see Fig. 31.20).[5–8] In the case of larger eyelid masses, the overlying epithelium may ulcerate, with reactive granulation tissue formation.[6] In the skin and other sites, they have reached 35 cm in diameter.[13] A 4-year-old pony was presented with a large dermal to subcutaneous PNST in the perianal region that involved the proximal sacral vertebrae.[25] A benign PNST arising in the commissure of the lip in an 11-year-old horse extended to involve the skin and oral cavity.[15] In the intestinal tract, there may be associated signs of colic.[9] A horse with multiple intestinal neoplasms had numerous grey-white, firm, well-circumscribed nodular masses in the subserosa and muscularis externa of a 20 cm length of small intestine, with associated muscular hypertrophy; these lesions resulted in herniation through the epiploic foramen.[17] A mediastinal neoplasm displaced the lungs and was associated with haemorrhage of uncertain origin.[13] PNSTs are variable in consistency; although often firm, they may also be soft and gelatinous and may contain areas of cystic degeneration on sectioned surfaces.[13,16] They are white, yellow or tan.

Malignant PNSTs have been described as unencapsulated, firm, and grey to cream, with irregular margins.[21] One intra-abdominal mass (malignant schwannoma) measured 46 cm in maximal diameter, was multilobulated, and had a necrotic centre.[14] An oral mass in a 17-year-old mare was multinodular and ulcerated, with cranial pedunculations, displacement of teeth and effacement of the hard palate.[18]

A perineurioma reported in the tongue of a mare measured up to 3 cm in diameter, and was smooth-surfaced with elevation and some ulceration of the overlying mucosa; the tumour was firm and white on sectioned surfaces.[23]

Histopathology

In order to differentiate between benign and malignant PNSTs, it is essential to obtain biopsy specimens that include marginal tissue. Benign tumours are usually (but not always) well-demarcated and may be thinly, partially encapsulated and/or rimmed by compressed adjacent tissue.[4]

Schwannomas contain regions of high and low cellular density, often within the same mass. The Antoni A pattern is defined as fusiform neoplastic Schwann cells arranged in small dense palisades that are supported by sparse collagenous tissue (Fig. 17.1). Formation of Verocay bodies, i.e. bundles of palisading tumour cell nuclei alternating with anuclear (eosinophilic) zones containing cell processes, may be noted in these Antoni A regions. The Antoni B pattern is defined as thin tumour cells with a looser arrangement within an abundant myxoid stroma; such areas may contain microcysts, foamy macrophages, cartilage and/or bone. Tumour cells are usually spindle-shaped with small to large amounts of homogeneous or fibrillar eosinophilic cytoplasm that has poorly-defined margins (see Fig. 17.1). There may be foci in which tumour cells have an epithelioid appearance, i.e. they are round.[16] In one case, typical spindle-shaped tumour cells were forming loose whorled arrangements around small foci of epithelioid tumour cells (Fig. 17.2).[25] Nuclei are central and elongate with tapered or round ends, finely granular chromatin and occasional small nucleoli; there should not be mitotic figures, cellular atypia or areas of necrosis. There may be hyalinization of the walls of small blood vessels within these neoplasms.

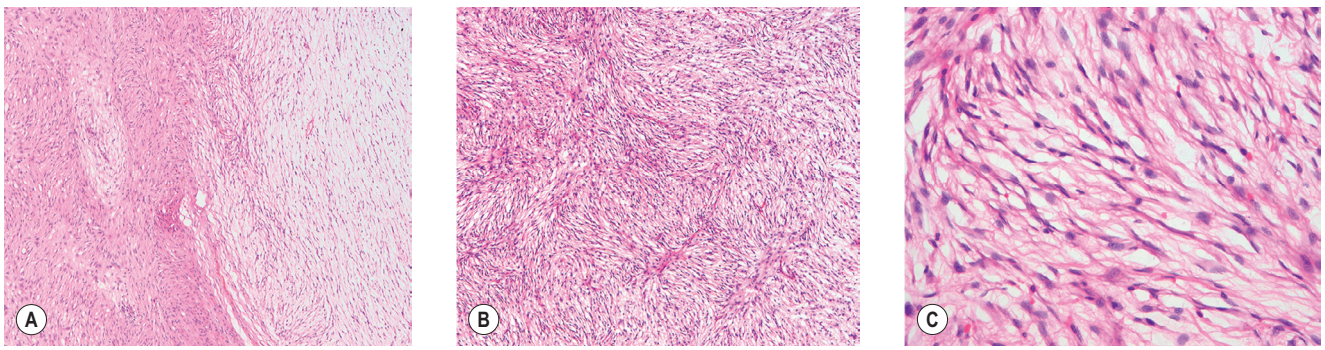


Figure 17.1 Benign peripheral nerve sheath tumour (PNST) of the penile sheath. (A) The tumour cells on the left are densely arranged in palisading bundles, known as the Antoni A pattern. On the right, they are more loosely arranged within an amphophilic (myxomatous) stroma, i.e. in an Antoni B pattern (H&E, ×40). **(B)** Another area of the same neoplasm, showing a more pronounced palisading arrangement of the tumour cells (H&E, ×100). **(C)** The spindle-shaped tumour cells, with finely fibrillar eosinophilic cytoplasm (H&E, ×200).

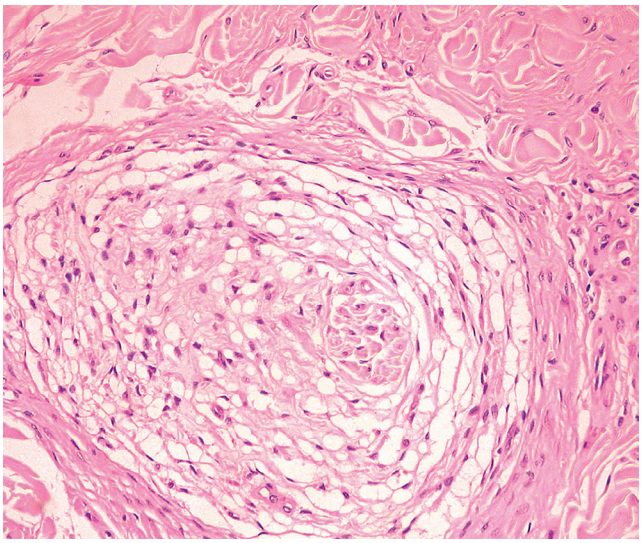


Figure 17.2 Benign peripheral nerve sheath tumour of the perianal region. Spindle-shaped tumour cells are forming a whorled pattern around a central focus of cells with an epithelioid morphology (H&E, ×200). *(Figure courtesy of Dr Elspeth Milne, Royal (Dick) School of Veterinary Studies, University of Edinburgh, Scotland. Reprinted from Sturgeon BP, et al. Journal of Veterinary Diagnostic Investigation 2008; 20(1):93–96, copyright 2008 by Sage Publications Ltd., by permission of Sage Publications Ltd.*[25]*)*

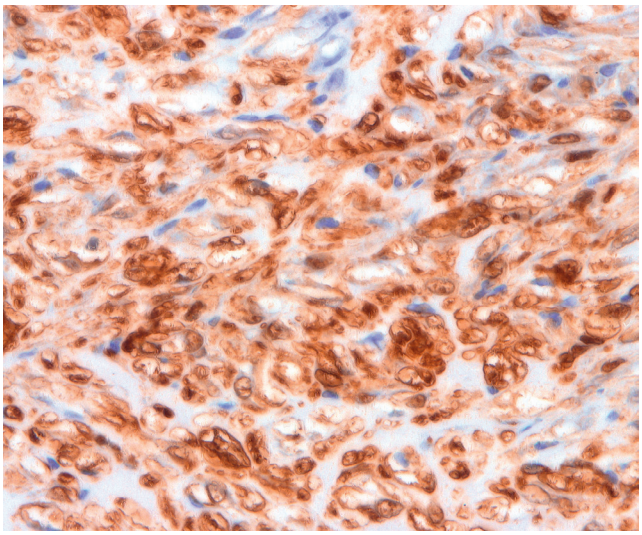


Figure 17.3 Benign peripheral nerve sheath tumour of the penile sheath. The tumour cells show strong cytoplasmic labelling for S100, consistent with a Schwann cell origin. Some nuclear labelling is also noted (immunohistochemistry, ×400).

Neurofibromas grow within and along nerves, expanding them while entrapping the native neural elements. This intraneural growth pattern is a key feature used to differentiate a neurofibroma from a schwannoma.[24] A schwannoma arises in the Schwann cell cylinder surrounding an axon, compressing normal adjacent axons in the nerve as it grows within a capsule that remains peripherally attached. A neurofibroma is diagnosed as 'plexiform' when the neoplasm involves multiple branches of a nerve plexus, or multiple fascicles within a large nerve, becoming anatomically tortuous. It is composed of very thin, elongated cells with buckled and/or wavy nuclei, supported by a fibromyxoid stroma.[4] Histological subtypes have been described in human cases, many of which have also been found in animals: i.e. classic (moderate cellular density and fibromyxoid stroma); cellular (areas of high cellular density without nuclear atypia or elevated mitotic activity); collagenous (abundant thick collagen fibre bundles); myxoid (abundant myxoid matrix); and pigmented (melanin pigment within a proportion of tumour cells). The cellular and collagenous subtypes have been reported in horses,[4] but other authors have not classified equine PNSTs in this way.

It should be noted that benign PNSTs may contain areas of hypercellularity, hyperchromasia and nuclear pleomorphism that are considered to represent degeneration resulting from vascular insufficiency, i.e. 'ancient change'.[16] A diagnosis of malignancy cannot be made purely on cellular pleomorphism and mitotic rate. Additionally, a diagnosis of malignancy cannot be made purely on evidence of infiltration; an infiltrative PNST with no cytological or other evidence of malignancy may actually be a diffuse form of neurofibroma (as above).[4,25]

Malignant PNSTs are unencapsulated and infiltrative; sections of nerves are often found within them or in adjacent tissue.[6] These neoplasms are also composed of fascicular bundles of spindle-shaped tumour cells that may include whorled patterns. Nuclei are round or elongate and may be wavy, fusiform or oval with finely stippled chromatin and one to several prominent central nucleoli.[21] In malignant tumours, there is more marked anisokaryosis and the mitotic rate may be high. Surrounding tissues that may be invaded include bone.[19] Associated histological lesions may include ulceration, oedema, necrosis, haemorrhage, cystic degeneration and inflammation including haemosiderophages. Ossification of one colonic neurofibroma has been described.[10]

Perineuriomas may also contain entrapped axons. In the one reported equine case, neoplastic masses were expanding the submucosa and muscular tissue of the tongue.[23] The tumour cells were arranged in whorls surrounding nerves and replacing the perineurium, with small amounts of collagenous stroma. Whorled patterns of this prominence are not noted in schwannomas or neurofibromas. The tumour cells blended peripherally with surrounding fibrocytes; they were thin and spindle-shaped, with plump, central, oval or elongate nuclei. Associated lesions included mucosal ulceration with chronic glossitis.

Immunohistochemical labelling

There are no specific markers for PNSTs. Tumour cells of Schwann cell origin should label positively for S100 (nuclear and cytoplasmic) (Fig. 17.3), but other peripheral nerve sheath cells are S100-negative. This means that in neurofibromas, S100 labelling is restricted to a proportion of cells, i.e. the neoplastic Schwann cells only. Staining for glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE), neurofilament protein, type IV collagen or laminin is variable (see Fig. 17.3).[16,17,20,21,25] Neurofilament protein labelling has been interpreted as indicating pre-existing entrapped neuronal elements. Positive staining for vimentin may be more consistent but is not specific. Positive labelling for desmin has been demonstrated in both equine and human neurofibromas but was not noted in malignant PNST in horses.[17,21] Labelling for α-smooth muscle actin should be negative.

Box 17.1 Differential diagnoses for nerve sheath neoplasms

Neoplastic
- Other sarcomas
- Sarcoid

Non-neoplastic
- Traumatic neuroma ('pseudoneuroma')

In the one equine case of perineurioma, the tumour cells were negative for S100, neurofilament protein, and smooth muscle actin, but were vimentin-positive.

Antibodies against perineurial markers (i.e. epithelial membrane antigen and claudin-1) have not been used successfully (or validated for use) with equine tissue.

Electron microscopy

Ultrastructurally, a basal lamina should be noted around the tumour cells of Schwann cell derivation and their processes, but this is not always a diffuse feature and may be seen with other types of neoplasm. In one case of perineurioma, the tumour cells had long slender cytoplasmic processes, sometimes prominent pinocytotic vesicles, and associated extracellular collagen fibrils consistent with but not specific for perineurial origin.[23]

Differential diagnoses

These are listed in Box 17.1.

Traumatic neuroma ('pseudoneuroma') is a common complication of neurectomy in equines. In one study involving 63 neurectomy procedures on 46 animals, postoperative neuroma occurred in 50% (31).[26] Neuromas are composed of unregulated proliferating nerve tissue, i.e. Schwann cells, fibroblasts and collagenous tissue with some embedded regenerated axons. In painful neuromas, the nervous tissue predominates, while in non-painful lesions, there is massive proliferation of collagenous tissue around small numbers of degenerate nerve fibres.[26]

GRANULAR CELL TUMOURS (PUTATIVE SCHWANN CELL TUMOURS)

See also page 500.

Cellular origin

Granular cell tumours (GCTs) were originally thought to be derived from skeletal muscle precursor cells, but this has now been disproven. The results of immunohistochemical studies have indicated that they are of neural crest and possible Schwann cell origin; however, there is a lack of complete Schwann cell derivation.[27] Other authors have suggested that GCTs are of varied histogenesis, particularly when compared between species, with potential cells of origin including Schwann cells, perineural fibroblasts, perineural epithelial cells and pluripotent mesenchymal cells.[28]

Profile

Granular cell tumours appear to be the most common primary pulmonary neoplasm of equines, although overall they are very rare, with a reported incidence of 0–0.08% of horses examined at slaughter.[10] In one survey of equine neoplasms submitted to a US State diagnostic laboratory (1988–1992; $n=530$), only 1.1% were GCT.[29]

Horses diagnosed with pulmonary GCT have a mean age of approximately 13 years, and there is a predominance in mares.[30] This type of neoplasm in equines shows considerable similarity to endobronchial GCT in human patients.

Although most GCTs in horses occur in the lung, an optic disc mass has been seen in an aged pony.[31]

Biological behaviour

Pulmonary GCTs are progressive and may be associated with respiratory distress due to airway compression; however, in many cases, they have been incidental findings at post-mortem examination.[28,30] Invasiveness and metastasis have not been reported. In some horses, there is a very chronic course of disease, with survival for several years.[32,33] Some horses with this type of neoplasm develop hypertrophic pulmonary osteopathy (see Fig. 6.7).

Gross pathology

Granular cell tumours in the lungs of horses are usually unilateral and extensive by the time of diagnosis. It has been stated that the right lung is more frequently affected than the left; however, this has not been true for all case series or reports.[29,34,35] Bilateral involvement is rare.[36] Multiple firm, well-circumscribed, expansile, yellow-white, tan, grey-white or white, 1–12 cm diameter, nodular masses with smooth surfaces near the hilus of the involved lung are typically associated with and protrude into the lumens of bronchi as pedunculated or sessile masses (see Figs. 29.15 and 29.16).[27,29,32,34,37] In one report ($n=3$), the lungs contained 50–100 such nodules, and in another case, the right lung was similarly extensively infiltrated and weighed 14.5 kg.[30,34] The lung may be almost completely replaced.[38]

The bronchial lumens may be obstructed, and may contain mucopurulent (white) exudate.[29,32,35] Other associated lesions can include enlarged bronchial lymph nodes and (in small numbers of horses) pneumonia.[32,39]

Histopathology

Pulmonary GCT may be diagnosed by examination of transendoscopic biopsy specimens due to their close location to airways; however, small mucosal pinch biopsies will often not obtain neoplastic tissue.[30,33] An alternative method is to pass uterine biopsy forceps through a small tracheotomy incision at the level of the thoracic inlet.[40]

The nodular masses are composed of tumour cells arranged in multiple lobules or sheets separated by fibromuscular septa that are usually centred on and disrupt bronchi and bronchioles (Fig. 17.4).[27,29] Within sheets, the tumour cells may be grouped in nests or rows. Where there

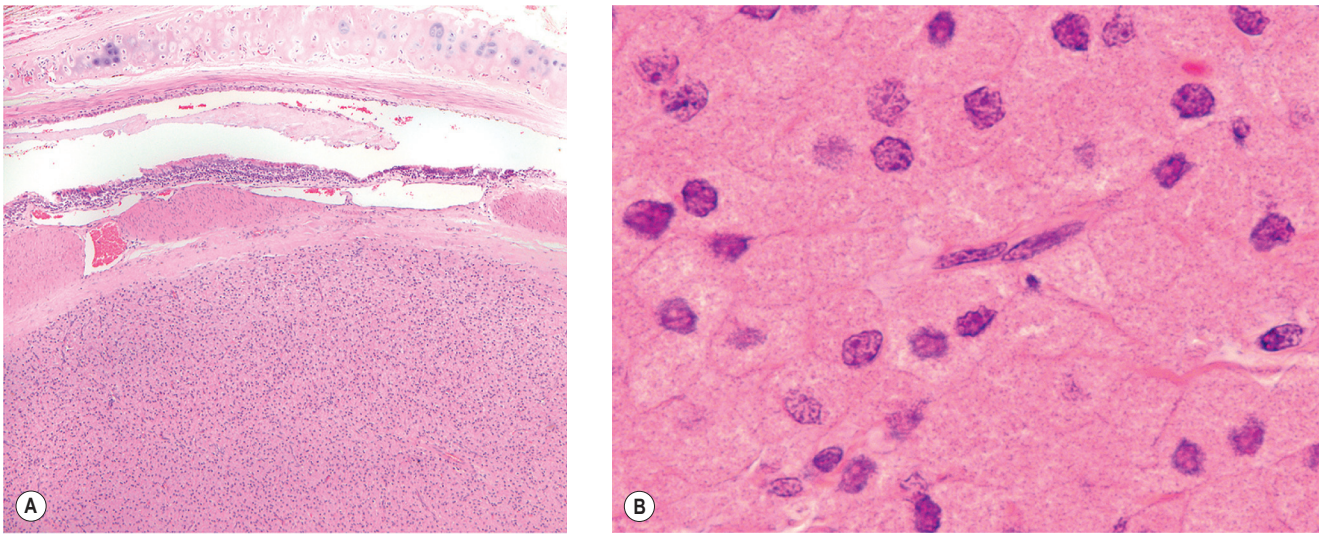


Figure 17.4 The histological appearance of a bronchial granular cell tumour. **(A)** Sheets of tumour cells are forming a mass that is compressing and largely occluding the bronchial lumen, with overlying normal respiratory epithelium. There is a small amount of mucoid material within the lumen (H&E, ×40). **(B)** Large, polygonal tumour cells with a granular eosinophilic cytoplasm (H&E, ×1000). *(Figure B courtesy of Professor Keith Thompson, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, New Zealand.)*

is nodular extension of a neoplasm and the overlying normal to flattened respiratory epithelium into the airway lumen, partial or complete occlusion is noted (see Fig. 17.4).[29] Normal structures around involved airways may be replaced by neoplastic tissue, bronchial cartilage may be fragmented, and the adjacent pulmonary parenchyma compressed.

The tumour cells are large and round or polygonal, with abundant, coarsely granular, eosinophilic cytoplasm that has variably well-defined margins (see Fig. 17.4). The cytoplasmic granules may be periodic acid-Schiff (PAS)-positive and diastase-resistant, although this is variable; only 10–30% of the cells in a tumour mass may stain in this way. They are dark red when stained with Movat pentachrome or Masson's trichrome stains.[39] Positive staining of granules with Luxol fast blue is variable; uniform blue-green staining with a cresyl violet counterstain was reported, demonstrating the presence of choline-based phospholipids (i.e. a myelin-like product).[29] When Luxol fast blue with a PAS-haematoxylin counterstain was used, various ratios of blue-green and pink granules were noted in the tumour cells, indicating the presence of myelin and myelin breakdown products, respectively. Tumour cells are negative when stained using the Grimelius' technique for neuroendocrine granules. In one case, angulate bodies were noted within tumour cells at the periphery of masses that showed high affinity for the PAS stain.[34]

Tumour cell nuclei are small to moderately sized, ovoid or round and paracentral or eccentric, with stippled or finely clumped, marginated chromatin and a central nucleolus.[29,34] Mitotic figures are either not noted, or only seen in small numbers.

Formation of small regions of cartilage in granular cell tumour nodules was reported in one case.[35]

Immunohistochemical labelling

In three cases, the tumour cells were diffusely and strongly positive for vimentin and S100 (the latter cytoplasmic and nuclear), and negative for neuron-specific enolase (NSE).[27] In similar studies (total $n=15$), there was variable positive labelling for all three of those markers, with additional staining of some tumour cells for glial fibrillary acidic protein (GFAP).[28–30,36,41] Variable labelling has been reported for myelin basic protein and Leu 7, an antibody directed against components of Schwann cell myelin.[41] Negative labelling has been variably reported for keratins (AE1/AE3/cytokeratin clone Lu-5), neurofilament protein, desmin, smooth muscle actin, lysozyme, chromogranin A, α_1-antichymotrypsin and myoglobin.

Box 17.2 Differential diagnoses for granular cell tumours

Neoplastic
- Pulmonary carcinoma
- Lymphosarcoma

Non-neoplastic
- Equine multinodular pulmonary fibrosis (p. 264–265)

Electron microscopy

Ultrastructurally, there are small granules associated with an active Golgi apparatus, and large granules that represent multivesicular autophagic vacuoles.[34] Membrane-bound packets of granules have been described, and myelin figures were noted in one case.[39] Angulate bodies noted in peripheral tumour cells in one case were composed of parallel 10 nm diameter filaments.[34] Muscle filaments have not been detected.

Differential diagnoses

These are listed in Box 17.2.

References

1. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
2. Priester WA, MacKay FW. The occurrence of tumours in domestic animals. Natl Cancer Inst Monogr 1980; 54:1–210.
3. Lavach JD, Severin GA. Neoplasia of the equine eye, adnexa and orbit: a review of 68 cases. J Am Vet Med Assoc 1977; 170:202–203.
4. Schöniger S, Valentine BA, Fernandez CJ, et al. Cutaneous schwannomas in 22 horses. Vet Pathol 2011; 48:433–442.
5. Blodi FC, Ramsey FK. Ocular tumours in domestic animals. Am J Ophthalmol 1967; 64:627–633.
6. Pascoe RR, Summers PM. Clinical survey of tumours and tumour-like lesions in horses in south east Queensland. Equine Vet J 1981; 13:235–239.
7. Pascoe RR. Equine nodular and erosive skin conditions: the common and not so common. Equine Vet Educ 1991; 3:153–159.
8. Dugan SJ. Ocular neoplasia. Vet Clin North Am Equine Pract 1992; 8:609–626.
9. Pascoe PJ. Colic in a mare caused by a colonic neurofibroma. Can Vet J 1982; 23:24–27.
10. Cotchin E, Baker-Smith J. Tumours in horses encountered in an abattoir survey. Vet Rec 1975; 97:339.
11. Boulton CH. Equine nasal cavity and paranasal sinus disease: a review of 85 cases. J Equine Vet Sci 1985; 5:268–275.
12. Williamson LH, Farrell RL. Intracranial schwannoma in a horse. Cornell Vet 1990; 80:135–141.
13. Andreasen CB, Hedstrom OR, Allison P. Mediastinal schwannoma in a horse – cytologic, histologic, and immunochemical evaluation. Vet Clin Pathol 1993; 22:54–59.
14. Stoica G, Tasca SI, Kim H-T. Point mutation of the neu oncogene in animal peripheral nerve sheath tumours. Vet Pathol 2001; 38:679–688.
15. Lykkjen S, Strand E, Haga HA, et al. Radical surgical resection of locally invasive oro-cutaneous tumours in the buccal region of 2 horses. Vet Surg 2006; 35:319–323.
16. Schneider A, Tessier C, Gorgas D, et al. Magnetic resonance imaging features of a benign peripheral nerve sheath tumour with 'ancient' changes in the tongue of a horse. Equine Vet Educ 2010; 22:346–351.
17. Kirchhof N, Scheidemann W, Baumgärtner W. Multiple peripheral nerve sheath tumours in the small intestine of a horse. Vet Pathol 1996; 33:727–730.
18. Snook ER, Wakamatsu N. Diagnostic exercise: oral tumour in an aged mare. Vet Pathol 2011; 48:785–787.
19. Strubbe DT. Periocular neurofibrosarcoma in a horse. Vet Ophthalmol 2001; 4:237–241.
20. Kappe EC, Köhler K, Felbert IV, et al. Pleomorphic corneal sarcoma resembling malignant peripheral nerve sheath tumour in a horse. Vet Pathol 2009; 46:444–448.
21. Quinn GC, Fews D, Scase TJ, et al. Malignant peripheral nerve sheath tumour of the heart in a horse. Vet Rec 2005; 157:847–849.
22. Van den Top JGB, de Heer N, Klein WR, et al. Penile and preputial tumours in the horse: a retrospective study of 114 affected horses. Equine Vet J 2008; 40:528–532.
23. Vashisht K, Rock RW, Summers BA. Multiple masses in a horse's tongue resulting from an atypical perineurial cell proliferative disorder. Vet Pathol 2007; 44:398–402.
24. Wippold FJ, Lubner M, Perrin RJ, et al. Neuropathology for the neuroradiologist: Antoni A and Antoni B tissue patterns. AJNR Am J Neuroradiol 2007; 28:1633–1638.
25. Sturgeon BPR, Milne EM, Smith KC. Benign peripheral nerve sheath tumour of the perianal region in a young pony. J Vet Diagn Invest 2008; 20:93–96.
26. Said AH, Khamis Y, Mahfouz MF, et al. Clinicopathological studies on neurectomy in equids. Equine Vet J 1984; 16:442–446.
27. Bouchard PR, Fortna CH, Rowland PH, et al. An immunohistochemical study of three equine pulmonary granular cell tumours. Vet Pathol 1995; 32:730–734.
28. Patnaik AK. Histologic and immunohistochemical studies of granular cell tumours in seven dogs, three cats, one horse, and one bird. Vet Pathol 1993; 30:176–185.
29. Kelley LC, Hill JE, Hafner S, et al. Spontaneous equine pulmonary granular cell tumours: morphologic, histochemical, and immunohistochemical characterisation. Vet Pathol 1995; 32:101–106.
30. Pusterla N, Norris AJ, Stacy BA, et al. Granular cell tumours in the lungs of three horses. Vet Rec 2003; 153:530–532.
31. Riis RC, Rebhun WC. Proliferative optic neuropathy in a horse caused by a granular cell tumour. Equine Vet J Suppl 1990; 10:69–72.
32. Scarratt WK, Crisman MV, Sponenberg DP, et al. Pulmonary granular cell tumour in 2 horses. Equine Vet J 1993; 25:244–247.
33. Mair TS, Rush BR, Tucker RL. Clinical and diagnostic features of thoracic neoplasia in the horse. Equine Vet Educ 2004; 16:30–36.
34. Turk MA, Breeze RG. Histochemical and ultrastructural features of an equine pulmonary granular cell tumour (myoblastoma). J Comp Pathol 1981; 91:471–481.
35. Inoue S, Okada N, Midoro K, et al. An equine case of granular cell tumour with chondroplasia. Nihon Juigaku Zasshi 1987; 49:581–583.
36. Heinola T, Heikkilä M, Ruohoniemi M, et al. Hypertrophic pulmonary osteopathy associated with granular cell tumour in a mare. Vet Rec 2001; 149:307–308.
37. Ohnesorge B, Gehlen H, Wohlsein P. Transendoscopic electrosurgery of an equine pulmonary granular cell tumour. Vet Surg 2002; 31:375–378.
38. Sutton RH, Coleman GT. A pulmonary granular cell tumour with associated hypertrophic osteopathy in a horse. N Z Vet J 1995; 43:123.
39. Parker GA, Novilla MN, Brown AC, et al. Granular cell tumour (myoblastoma) in the lung of a horse. J Comp Pathol 1979; 89:421–430.
40. Facemire PR, Chilcoat CD, Sojka JE, et al. Treatment of a granular cell tumour via complete right lung resection in a horse. J Am Vet Med Assoc 2000; 217:1522–1525.
41. Kagawa Y, Hirayama K, Tagami M, et al. Immunohistochemical analysis of equine pulmonary granular cell tumours. J Comp Pathol 2001; 124: 122–127.

18

Smooth muscle and skeletal muscle neoplasms

Leiomyoma and fibroleiomyoma
Cellular origin 305
Profile 305
Oncogenesis 305
Biological behaviour 305
Gross pathology 306
Histopathology 306
Differential diagnoses 307
Leiomyomatosis
Cellular origin 307
Profile 307
Biological behaviour 307
Gross pathology 307
Histopathology 307
Leiomyosarcoma
Cellular origin 307
Profile 307
Biological behaviour 307
Gross pathology 307
Histopathology 308
Differential diagnoses 308
Rhabdomyoma
Cellular origin 308
Profile 308
Biological behaviour 308
Gross pathology 308
Histopathology 308
Rhabdomyosarcoma
Cellular origin 309
Profile 309
Biological behaviour 309
Gross pathology 309
Histopathology 309
Differential diagnoses 310

LEIOMYOMA AND FIBROLEIOMYOMA

See also page 640.

Cellular origin

Leiomyoma is a benign neoplasm derived from smooth muscle cells. Fibroleiomyoma is a rare variant, in which the tumour cells appear to synthesize a collagenous matrix.

Profile

In horses, leiomyomas most frequently arise in the alimentary tract (including the oesophagus, stomach, jejunum, caecum, large colon, small colon, rectum and omentum) and the reproductive tract.[1–12] In one study of 24 horses with gastric tumours, two were leiomyomas.[13]

Leiomyoma is the most common type of neoplasm arising in the uterus, with an increasing risk in older mares.[14] In a survey of equine uterine neoplasms (n=27), 26% were leiomyomas.[15] There have been rare reports of cervical, vaginal and vulval tumours; they are the most common vaginal neoplasm.[16,17]

Three cases of fibroleiomyoma involving the cervix (os uterus) were found in an Indian survey of 70 equine neoplasms, most of which were multiple and one of which extended into the vagina.[18] An ovarian leiomyoma has also been reported, and a primary ovarian fibroleiomyoma in a 9-year-old pregnant mare.[19,20]

Other rare sites of origin include the tunica albuginea/paratesticular tissue, testicular parenchyma and perineal dermis.[21–24] A stallion with a testicular leiomyoma had a seminoma in the contralateral testicle.[24] In the skin, leiomyomas are rare and may arise from either arrector pili muscles or vascular smooth muscle.

Oncogenesis

Although in women and bitches, there is a link between oestrogen and leiomyoma development in the genital tract, this may not be the case in horses. For example, leiomyomas developed in the cervix of mares that had already undergone ovariohysterectomy for uterine leiomyoma.[15] Familial occurrence of uterine leiomyoma was indicated in this case of two half-sibling Appaloosa fillies (15–16 months of age) sired by the same stallion but not kept on the same property; this was thought to be due to a dominant gene from the stallion.[15]

Biological behaviour

Leiomyomas are slow-growing, expansile masses that do not invade or metastasize. In the stomach, they arise in the *muscularis externa* and may extend into the mucosa; these neoplasms may be associated with signs of recurrent colic. In the small intestine, including the duodenum, a leiomyoma may cause obstruction (potentially with secondary gastric rupture) or may instigate intussusception; an intraluminal, pedunculated leiomyoma in the small colon of a pony resulted in intussusception.[4,5,7,9,25–27] They have also been reported as incidental findings.[1,8]

Uterine leiomyomas are most frequently identified during breeding soundness examinations of subfertile animals. Smaller uterine leiomyomas are usually an incidental finding in both horses and donkeys; however, larger masses may cause clinical problems, including infertility, pain (e.g. due to torsion), protrusion of neoplastic tissue into the vulva, haemorrhage and secondary endometritis or metritis.[28–31] Infertility may be associated with distortion of the uterine lumen.[17,31] It is possible for pregnancy to be carried to term, but one uterine leiomyoma was associated with a fetal death,[32] and in another case the mare delivered normally at term but the foal had (possibly unrelated) limb deformities.[14]

Gross pathology

Leiomyomas are discrete, nodular or oval, sometimes encapsulated or lobulated, firm, solid, smooth-surfaced, and white, pale yellow, tan or pink (see Fig. 35.9). They may protrude into the lumen of tubular organs, are often pedunculated and may be polypoid. There may be superficial and central areas of haemorrhage, and surface ulceration and necrosis.[33]

In the intestinal tract, leiomyomas may cause segmental thickening with narrowing of the lumen, or protrude from luminal or anti-mesenteric surfaces.[7,8] There may be evidence of intestinal obstruction, intussusception and mural devitalization.[11] One omental mass was 70 cm in maximal diameter and weighed 41 kg.[12]

Uterine and cervical leiomyomas may be single or multiple, and are usually pedunculated, although they may in some cases be intramural.[28,34] They generally measure 2–6 cm in diameter (up to 15 cm), and may be well-vascularized.[17,31] There are a number of reports where fertility has been restored following surgical removal of a uterine leiomyoma, although this seems less likely for medium-sized to large neoplasms.[35] Leiomyomas occurring in the vagina are usually small. One reported ovarian fibroleiomyoma was approximately 20 cm in diameter, had obliterated the normal ovarian tissue, and was filled with brown-red fluid (central necrosis).[20]

In the dermis, leiomyomas are discrete, solitary, firm, nodular masses that can elevate the overlying epidermis.[36]

Histopathology

Leiomyomas are well-demarcated, moderately cellular expansile masses, usually located within the muscular layers of the wall in the uterus and intestine. The use of endometrial biopsy forceps or transendoscopic methods to obtain specimens from uterine leiomyomas is difficult and of limited value for moderate to large-sized neoplasms, in terms of obtaining diagnostic material.[35] The tumour cells are arranged in sheets and thick, interweaving bundles that may be fascicular (Fig. 18.1). Amounts of fibrous tissue are variable, with some neoplasms that contain larger amounts being diagnosed as fibroleiomyoma or 'fibroids'.[20] The tumour cells are well-differentiated (i.e. closely resembling surrounding smooth muscle cells) and uniform; they are plump and spindle-shaped, with moderate to large amounts of fibrillar eosinophilic cytoplasm that has variably well-defined margins (see Fig. 18.1). The cytoplasm of some tumour cells may contain small perinuclear vacuoles (see Fig. 18.1). Nuclei are central, elongate or cigar-shaped with rounded ends; they may be vesicular or hypochromic. Mitotic activity is non-existent to low. Masson's trichrome or van Gieson's stains may be used to confirm the smooth muscle origin. In ulcerated masses, there may be associated granulation tissue, fibrosis and inflammation.

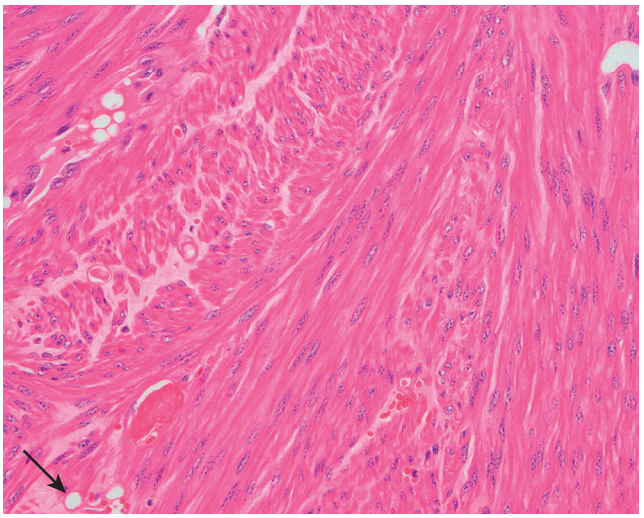


Figure 18.1 Leiomyoma in the muscularis externa of the jejunum. This mass in a 26-year-old horse had resulted in intestinal obstruction. The spindle-shaped tumour cells are arranged in interconnecting fascicular bundles. Some of the tumour cells contain round, clear, intracytoplasmic vacuoles (arrow) (H&E, ×200).

Box 18.1 Differential diagnoses for leiomyoma and fibroleiomyoma

Neoplastic
- Leiomyosarcoma
- Fibroma
- Fibrosarcoma
- Other soft tissue tumours

Non-neoplastic
- Uterine cysts
- Intramural haematomas
- Abscesses

Immunohistochemical labelling

Tumour cells should label positively for desmin (an intermediate filament expressed by smooth, skeletal and cardiac muscle cells), muscle-specific actin (a globular protein expressed by all types of muscle cells) and α-smooth muscle actin (a cytoskeletal protein expressed by smooth muscle and myoepithelial cells).[20,22] There should be negative labelling for myoglobin, which is only expressed by skeletal and cardiac muscle cells. The omental leiomyoma also showed positive labelling for neuron-specific enolase, and mild focal expression of c-kit but was not classified as a gastrointestinal stromal tumour due to desmin positivity and lack of any association with the gastrointestinal tract (pp. 369–370).[12]

Differential diagnoses

These are listed in Box 18.1.

LEIOMYOMATOSIS

Cellular origin

Leiomyomatosis (multiple leiomyoma) is thought to be an abnormal proliferative response of dormant Müllerian epithelial cells to ovarian hormones in predisposed individuals, with these cells following lines of smooth muscle differentiation.

Profile

Leiomyomatosis is a rare, non-malignant proliferation of smooth muscle tissue in the subperitoneal mesenchyme. In women, this condition often develops during pregnancy.[37] Disseminated leiomyomatosis was described in the peritoneal cavity of one 6-year-old Quarter Horse mare; surgical resection was curative.[38] An omental mass in another mare diagnosed as a fibrosarcoma was not immunolabelled, and may also have been a case of leiomyomatosis.[38] The 34 kg mass was loosely attached to the parietal peritoneum and occupied the ventral two-thirds of the abdominal cavity, extending from the urinary bladder to the liver. It was surgically excised, with no recurrence during a 22-month follow-up period; the mare subsequently gave birth to a healthy foal.[38]

Biological behaviour

This is a rare type of neoplasm, and little is known about its behaviour.

Gross pathology

The one mass reported (and confirmed) in a horse was irregularly-shaped, friable, highly vascularized and contained numerous small cystic cavities filled with clear yellow fluid, blood or serosanguineous fluid.[38]

Histopathology

Tumour cells were arranged in sheets and bundles supported by a fine fibrovascular stroma. They were spindle-shaped with fibrillar or vacuolated eosinophilic cytoplasm that had well-defined margins. Nuclei were elongate to cigar-shaped, with rounded ends and indistinct nucleoli. The mitotic rate was low (0–1 per ×400 field). In the abdominal mass, tumour cells were emanating from the tunica media of small blood vessels.

Immunohistochemical labelling

Tumour cells stained positively for smooth muscle actin and vimentin.

LEIOMYOSARCOMA

See also page 640.

Cellular origin

Leiomyosarcoma is a malignant neoplasm derived from smooth muscle cells.

Profile

Leiomyosarcomas are less common than leiomyomas. There have been occasional reports in the muscularis externa of the stomach or intestine of middle-aged to older horses.[7,39,40] In the small intestine, this is the second most common primary neoplasm (the most common being adenocarcinoma), with less frequent occurrence in the large intestine and rectum.[25,39,41] One rectal tumour was diagnosed in a 4-year-old horse.[41]

There have also been reports of uterine leiomyosarcoma, with one large neoplasm involving the urinary bladder and vagina of a filly only 2 years of age.[42–44]

Bilateral testicular leiomyosarcomas, considered to be congenital, were diagnosed in an 11-month-old cryptorchid colt.[45] A post-mortem diagnosis of leiomyosarcoma of the right lung was made in the case of a 13-year-old Thoroughbred stallion that presented with respiratory signs.[46]

In a 2-year-old Thoroughbred, multiple leiomyosarcomas were extensively distributed throughout multiple bones, including the skull, vertebral bodies and long bones.[47]

Biological behaviour

Leiomyosarcomas are locally invasive but are believed to be slow to metastasize in horses and other domestic species. Local invasion may be extensive, with one gastric mass involving the cranial two-thirds of the stomach, the distal oesophagus and the visceral surface of the liver.[40] In the uterus, these neoplasms may interfere with propagation of uterine contractions and/or result in ulceration of the endometrial surface, affecting fertility.[42,43,44] In adult horses, complete surgical excision should in theory be curative, and this has been reported for uterine neoplasms.[42,43]

Metastasis of a large intestinal tumour occurred to the liver and peritoneum in one case.[25] Widespread metastasis of the congenital testicular leiomyosarcoma was documented to sites including the masseter muscle, cervical and popliteal lymph nodes, caudal vena cava and diaphragm.[45]

Gross pathology

Leiomyosarcomas are variable in size and may be solitary or composed of coalescing nodules. They are firm on sectioning and may be tan, white or cream-coloured; some contain haemorrhagic cavities and/or areas of necrosis.[46] Neoplasms involving the wall of the gastrointestinal or urogenital tracts may cause annular segmental thickening with a reduction in luminal diameter, and may or may not protrude into the lumen (some are pedunculated) with resultant ulceration, necrosis, infection and haemorrhage

Box 18.2 Differential diagnoses for leiomyosarcoma

Neoplastic
- Fibrosarcoma
- Rhabdomyosarcoma
- Leiomyoma

(see Fig. 28.29).[39,42–44] One pedunculated rectal tumour protruded through the anal sphincter, where it had an ulcerated surface.[41] There may be extension into adjacent organs.

Histopathology

Some leiomyosarcomas are well-circumscribed but in many the tumour cells are invading the surrounding tissue or the stalk of a pedunculated mass.[7,39,41] In tubular organs, leiomyosarcoma will not necessarily be confined to muscular layers, extending into other layers (e.g. myometrium, endometrium) or through the serosa.[43] A lung mass appeared to arise from the smooth muscle layer of a bronchus.[46]

Tumour cells in these masses, which may be lobulated, are arranged in sheets, haphazardly interlacing fascicles or bundles or whorls. The tumour cells usually show features of smooth muscle differentiation, i.e. they are spindle-shaped with finely fibrillar eosinophilic cytoplasm that has poorly-defined margins. Nuclei are oval or spindle-shaped with prominent nucleoli. The tumour cells are more pleomorphic than those noted in leiomyomas, with nuclear atypia, marked anisokaryosis and a higher mitotic rate. Masson's trichrome or van Gieson's stains may be used to confirm smooth muscle origin.

Metaplastic bone formation has been documented, with multiple variably-sized foci of woven bone between tumour cells.[47] Other associated changes may include fibrosis, haemorrhage and inflammatory cell infiltrates.

Immunohistochemical labelling

Tumour cells should label positively for desmin (an intermediate filament expressed by smooth, skeletal and cardiac muscle cells), muscle-specific actin (a globular protein expressed by all types of muscle cells) and α-smooth muscle actin (a cytoskeletal protein expressed by smooth muscle and myoepithelial cells).[20,22,46] There should be negative labelling for myoglobin, which is only expressed by skeletal and cardiac muscle cells.

Differential diagnoses

These are listed in Box 18.2.

RHABDOMYOMA

See also page 674.

Cellular origin

Rhabdomyomas are benign neoplasms arising from skeletal or cardiac (i.e. striated) muscle fibres. In most cases, these neoplasms are thought to originate from pluripotent mesenchymal stem cells rather than fully differentiated myofibres or satellite cells.[48]

Profile

Rhabdomyoma is a rare neoplasm in horses. There was one report of a rhabdomyoma in the inguinal canal of a horse with a strangulated hernia, but this did not include a histological description.[49] In a 2-year-old Thoroughbred filly, a large mass was found caudal to the heart attached by a stalk to the diaphragm, from which it was suggested to have originated.[50] A (congenital) fetal rhabdomyoma was reported in the cervical subcutis of a newborn Appaloosa foal.[51]

Biological behaviour

Rhabdomyomas are benign, and in sites where it is possible, should be cured by surgical excision.[48]

Gross pathology

Rhabdomyomas are usually well-circumscribed but unencapsulated, smooth-surfaced, pale fleshy masses measuring 1–30 cm in diameter that may be highly vascularized; cystic cavitation may be noted in larger masses on ultrasound and sectioning.[50]

Histopathology

Rhabdomyomas have well-defined margins and may be lobulated. The tumour cells have an abundant eosinophilic cytoplasm that may be granular or vacuolated; intrasarcoplasmic glycogen may be revealed by periodic acid-Schiff staining.[48] Better-differentiated tumour cells may have peripheral nuclei and cytoplasmic cross-striations. Cross-striations may be revealed using a phosphotungstic acid-haematoxylin stain (PTAH).

In human patients, adult, fetal and genital types have been described. In a fetal rhabdomyoma case in a foal, the tumour cells were haphazardly arranged and spindle-shaped or strap-like, with a fibrillar eosinophilic cytoplasm of variable staining intensity; they were located within an abundant myxoid stroma.[51] Nuclei were small, oval or elongate and hyperchromatic with clumped chromatin and a low mitotic rate; some larger nuclei were noted in well-differentiated tumour cells.

Immunohistochemical labelling

Many striated muscle neoplasms express desmin and muscle actin, although this does not allow differentiation of cardiac or skeletal muscle origin; cross-striations may be more readily revealed by desmin labelling than by PTAH staining.[48] They may or may not express myoglobin, as this marker is expressed later in myocyte differentiation. It should be noted that normal adult skeletal muscle cells do not express vimentin and tumour cells may also be negative.[52] Tumour cells in the equine fetal rhabdomyoma labelled

positively for myoglobin, desmin, actin, vimentin and S100. There was negative staining for keratin and glial fibrillary acidic protein.[51]

RHABDOMYOSARCOMA

See also page 674.

Cellular origin

Rhabdomyosarcoma is a malignant neoplasm arising from skeletal or cardiac (striated) muscle fibres. In most cases, these neoplasms are thought to originate from pluripotent mesenchymal stem cells rather than fully differentiated myofibres or satellite cells.[48] It has also been suggested that they may arise from as remnants of embryonic myotomes, or embryonic muscle tissue that is displaced during development. In the urogenital system such neoplasms may arise from progenitor/stem cells around paramesonephric or mesonephric ducts.

Profile

Rhabdomyosarcomas have rarely been diagnosed in horses; less than 20 cases have been reported.[50,52–60] They have been diagnosed in horses ranging in age from newborn to 21 years, with a mean age of 6.4 years. Rhabdomyosarcomas most frequently arise in the skeletal muscles of limbs, the tongue and the abdominal wall, but they have also been reported in the masseter muscle, latissimus dorsi, thoracic wall, left ventricle of the heart, buccal mucosa, abdominal subcutis, uterus, urinary bladder and mediastinum.

Biological behaviour

Rhabdomyosarcomas grow rapidly, are locally invasive, and may metastasize via blood vessels (see Fig. 37.5). Masses are frequently too large to excise, and success is more likely when the diameter is <10 cm. In one report, eight horses with rhabdomyosarcoma did not show metastasis.[54] However, in five previously published cases, metastasis had occurred to sites including the lungs, thoracic inlet, pleura, pericardium, peritoneum, omentum and spleen.[50,57,60]

Gross pathology

Rhabdomyosarcomas in horses have ranged from 1 to 17 cm in diameter; they have a fleshy or firm consistency, and may be lobular and grey or tan in colour.[54] There may be central areas of necrosis and haemorrhage on sectioned surfaces.[48] A pectoral muscle rhabdomyosarcoma contained scattered cysts up to 3 cm in diameter that were filled with gelatinous yellow-tan material.[54]

Some rhabdomyosarcomas are well-demarcated and completely or partially encapsulated, while others are completely or partially poorly demarcated with invasion of surrounding tissues. For example, one mass involving the tongue was soft and red, unencapsulated and infiltrative, whilst another was well-circumscribed and pedunculated and caused dorsal displacement of the soft palate.[54,58]

A botryoid ('grape-like') rhabdomyosarcoma arising in the urinary bladder of a 2-year-old filly was 10 cm in maximal diameter, polypoid, occupied a third of the mucosal surface and protruded through the vulva; it was multilobular, rubbery, and cream on sectioned surfaces.[52] A botryoid rhabdomyosarcoma with a similar gross appearance was reported in the uterus of a yearling Quarter Horse.[56]

Histopathology

Rhabdomyosarcomas are classified histologically into three subtypes:

1. Embryonal
2. Alveolar (juvenile)
3. Pleomorphic (adult).

In eight cases of rhabdomyosarcomas, seven were embryonal and one was pleomorphic.[54]

Embryonal rhabdomyosarcomas may be composed of small round cells (myoblast-like) and spindle cells (myotube-like).[54] There may be strap-shaped or racquet-shaped cells. The cytoplasm is fibrillar and eosinophilic, and cytoplasmic striations may be visible; phosphotungstic acid (PTAH) stain can be used to assist in discerning Z-band and sarcomere arrangements, but they will not be observed in less well-differentiated cases. Where striations are not noted, immunohistochemistry is essential for the diagnosis (see below). Tumour cells may have a vacuolated cytoplasm in some cases ('spider web cells').[48] Some multinucleate tumour cells may contain globular eosinophilic intracytoplasmic inclusions.

In the botryoid type of embryonal rhabdomyosarcoma (reported in the equine urinary bladder and uterus) (see above), there is a similar composition of differentiated myoblasts intermixed with poorly-differentiated cells, and the stroma is often myxoid.[56]

Alveolar rhabdomyosarcomas are composed of undifferentiated round cells arranged in sheets, usually with formation of alveoli due to multifocal loss of tumour cell cohesion.[48] The tumour cells tend to be smaller and more uniform that in other subtypes.

Pleomorphic tumours are composed of highly pleomorphic tumour cells, including multinucleate strap-like cells within an abundant fibrous stroma.[54] Nuclei contain prominent nucleoli, have marginated chromatin and are often arranged in tandem in multinucleate cells. There is moderate to marked anisocytosis and anisokaryosis, with mitotic rates of 0–10 per 10 high power (×400) fields; a higher mitotic rate (4.5–10) has been noted in more infiltrative neoplasms, but cellular pleomorphism has not been found to be of prognostic value to date.[54] Associated histological changes may include inflammatory cell infiltrates (lymphoid cells and macrophages), haemorrhage, necrosis and mineralization.

Immunohistochemical labelling

Variable expression of vimentin, actin, desmin and myoglobin would be expected[54,58]; it should be noted that normal adult skeletal muscle cells do not express vimentin and tumour cells may also be negative.[52] Globular

Box 18.3 Differential diagnoses for rhabdomyosarcoma

Neoplastic
- Rhabdomyoma
- Leiomyoma
- Fibrosarcoma
- Myxosarcoma
- Anaplastic sarcoma
- Anaplastic melanoma
- Anaplastic lymphosarcoma
- Anaplastic carcinoma

intracytoplasmic inclusions in multinucleate tumour cells are sarcomeric actin-positive.[54] Cross-striations may be more readily revealed by desmin labelling than by PTAH staining.[48] Tumour cells may or may not express myoglobin, as this marker is expressed later in myocyte differentiation.

In an alveolar rhabdomyosarcoma involving left hindlimb skeletal muscle tissue, tumour cells stained positively for vimentin and actin but not desmin; however, the latter antibody used had not been validated for use in the horse.[57]

Positive labelling of variable proportions of tumour cells in the embryonal rhabdomyosarcoma of a foal was observed for the myogenic regulatory proteins Myo D1 and Myf-4 but not Myf-3; however, validation of the mouse anti-human antibodies for use in equines was not documented other than the observed positive staining.[55]

In a case of botryoid rhabdomyosarcoma, scattered tumour cells were cytokeratin-positive, the reason for which is uncertain.[52]

Electron microscopy

Ultrastructurally, typical findings in rhabdomyosarcoma cells include thick (15 nm) myosin filaments, Z-band formation, thick filament-ribosomal complexes, thin filaments, numerous mitochondria, abundant smooth and rough endoplasmic reticulum and glycogen granules.[55,57] There may be filament aggregates within the cytoplasm.

Differential diagnoses

These are listed in Box 18.3.

References

1. Cotchin E, Baker-Smith J. Tumours in horses encountered in an abattoir survey. Vet Rec 1975; 97:339.
2. Feldman WH. Neoplasms of domesticated animals. Philadelphia: WB Saunders; 1932.
3. Ramakrishna K, Reddy MV, Mahander M. Leiomyoma in a mare: a note. Indian J Animal Sci 1971; 41:498–499.
4. Collier MA, Trent AM. Jejunal intussusception associated with leiomyoma in an aged horse. J Am Vet Med Assoc 1983; 182:819–821.
5. Hanes GE, Robertson JT. Leiomyoma of the small intestine in a horse. J Am Vet Med Assoc 1983; 182:1398.
6. Ramey DW, Reinertson EL. Strangulating lipoma and small intestinal leiomyoma in a horse. A case report. J Equine Vet Sci 1984; 4:88–89.
7. Livesey MA, Hulland TJ, Yovich JV. Colic in two horses associated with smooth muscle tumours. Equine Vet J 1986; 18:334–337.
8. Haven ML, Rottman JB, Bowman KF. Leiomyoma of the small colon in a horse. Vet Surg 1991; 20:320–322.
9. Mair TS, Davies EV, Lucke VM. Small colon intussusception associated with an intralumenal leiomyoma in a pony. Vet Rec 1992; 130:403–404.
10. Dart AJ, Hodgson DR, Snyder JR. Caecal disease in equids. Aust Vet J 1997; 75:552–557.
11. Watt BC, Trostle SS, Cooley AJ. Intraluminal leiomyoma colon polyp in a mare. Equine Vet J 2001; 33:326–328.
12. Schaudien D, Müller JM, Baumgärtner W. Omental leiomyoma in a male adult horse. Vet Pathol 2007; 44:722–726.
13. Taylor SD, Haldorson GJ, Vaughan B, et al. Gastric neoplasia in horses. J Vet Intern Med 2009; 23:1097–1102.
14. Grant DL. Uterine tumour in a mare – leiomyoma. Vet Rec 1964; 76:474–475.
15. Romagnoli SE, Momont HW, Hilbert BJ, et al. Multiple recurring uterocervical leiomyomas in two half-sibling Appaloosa fillies. J Am Vet Med Assoc 1987; 191:1449–1450.
16. Priester WA, MacKay FW. The occurrence of tumours in domestic animals. Natl Cancer Inst Monogr 1980; 54:1–210.
17. McCue PM. Neoplasia of the female reproductive tract. Vet Clin North Am Equine Pract 1998; 14:505–515.
18. Damodaran S, Ramachandran PV. A survey of neoplasms of equidae. Indian Vet J 1975; 52:531–534.
19. Meinecke B. Clinical aspects of ovary tumours in mares. Tierarztl Prax 1986; 14:501–508.
20. Carstanjen B, Schönert S, Heblinski N, et al. Primary unilateral fibroleiomyoma of the ovary in a pregnant mare: a case report. Reprod Domest Anim 2009; 44:952–957.
21. Klug E, von Lepel JD. Leiomyoma an hodenpaar eines 18 jahrigen Warmbluthengstes. Dtsch Tierarztl Wochenschr 1979; 12:304.
22. Bailey KL, Kinsel MJ, Connell KA. Multiple cutaneous leiomyomas in the perineum of a horse. J Vet Diagn Invest 2003; 15:454–456.
23. Johnson RC, Steinberg H. Leiomyoma of the tunica albuginea in a horse. J Comp Pathol 1989; 100:465–468.
24. Weiermayer P, Richter B. Simultaneous presence of a seminoma and a leiomyoma in the testes of a horse. Equine Vet Educ 2009; 21:172–176.
25. Taylor SD, Pusterla N, Vaughan B, et al. Intestinal neoplasia in horses. J Vet Intern Med 2006; 20:1429–1436.
26. Kasper C, Doran R. Duodenal leiomyoma associated with colic in a 2-year-old horse. J Am Vet Med Assoc 1993; 202:769–770.
27. Wilson T, Modransky P, Savage CJ. Small intestinal intussusception in a mule. Equine Pract 1994; 16:36–38.
28. Broome TA, Allen D, Baxter GM, et al. Septic metritis secondary to torsion of a pedunculated uterine fibroleiomyoma in a filly. J Am Vet Med Assoc 1992; 200:1685–1688.
29. Sokkar SM, Hamouda MA, Abdel-Rahman SM. Histopathological studies on neoplasms in the genital tract of female donkeys in Egypt. Berl Munch Tierarztl Wochenschr 2001; 114:166–168.
30. Muurlink T, Walmsley J, Whitton C. Successful laparoscopic surgery for a uterine leiomyoma in a mare. Equine Vet Educ 2008; 20:508–511.
31. Janicek JC, Rodgerson DH, Boone BL. Use of a hand-assisted laparoscopic technique for removal of a uterine leiomyoma in a standing mare. J Am Vet Med Assoc 2004; 225:911–914.
32. Heijltjes JM, Rijkenhuizen AB, Hendriks WK, et al. Removal by laparoscopic partial ovariohysterectomy of a uterine leiomyoma assumed to have caused fetal death in a mare. Equine Vet Educ 2009; 21:198–203.
33. Berezowski C. Diagnosis of a uterine leiomyoma using hysteroscopy and a partial ovariohysterectomy in a mare. Can Vet J 2002; 43:968–970.
34. Caira M, Rosmini R. Su di un caro caso di fibroleiomioma della carvice osservato in una cavalla trottatrice. Atti Soc Ital Sci Nat 1981; 35:476–477.
35. Quinn GC, Woodford NS. Infertility due to leiomyoma in a Thoroughbred mare: clinical findings, treatment and outcome. Equine Vet Educ 2005; 17:150–155.
36. Ginn PE, Mansell JE, Rakich PM. Skin and appendages. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's pathology of domestic animals. Philadelphia: Elsevier Saunders; 2007: 553–781.
37. Dallenbach C, Miklaw H, Dallenbach FD, et al. Disseminated peritoneal leiomyomatosis. A rare disease picture. Geburtshilfe Frauenheilkd 1989; 49:201–204.
38. Johnson PJ, Wilson DA, Turk JR, et al. Disseminated peritoneal leiomyomatosis in a horse. J Am Vet Med Assoc 1994; 205:725–728.
39. Mair TS, Taylor FGR, Brown PJ. Leiomyosarcoma of the duodenum in two horses. J Comp Pathol 1990; 102:119–123.
40. Boy MG, Palmer JE, Heyer G, et al. Gastric leiomyosarcoma in a horse. J Am Vet Med Assoc 1992; 200:1363–1364.
41. Clem MF, DeBowes RM, Leipold HW. Rectal leiomyosarcoma in a horse. J Am Vet Med Assoc 1987; 191:229–230.
42. Lofstedt RM, Spurlock G, Williams R. Leiomyosarcoma in the uterus of a mare. Comp Cont Ed Pract Vet 1987; 9:93–96.
43. Hinojosa AM, Holyoak GR, Moll D, et al. Theriogenology question of the month. Leiomyosarcoma. J Am Vet Med Assoc 2003; 223:786–788.
44. Hurcombe SDA, Slovis NM, Kohn CW, et al. Poorly differentiated leiomyosarcoma of the urogenital tract in a horse. J Am Vet Med Assoc 2008; 233:1908–1912.
45. Allison N, Moeller RB Jr. Bilateral testicular leiomyosarcoma in a stallion. J Vet Diagn Invest 1999; 11:179–182.
46. Rossdale PD, Greet TRC, McGladdery AJ, et al. Pulmonary leiomyosarcoma in a 13-year-old Thoroughbred stallion presenting as a differential diagnosis to recurrent airway obstruction. Equine Vet Educ 2004; 16:21–28.
47. MacGillivray KC, Graham TD, Parente EJ. Multicentric leiomyosarcoma in a young male horse. J Am Vet Med Assoc 2003; 223:1017–1021.
48. Van Vleet JF, Valentine BA. Muscle and tendon. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's pathology of domestic animals. Philadelphia: Elsevier Saunders; 2007: 185–280.
49. Sohrabi Haghdoost I, Zakarian B. Neoplasms of equidae in Iran. Equine Vet J 1985; 17:237–239.
50. Hamir AN. Striated muscle tumours in horses. Vet Rec 1982; 111:367–368.
51. Meyerholz DK, Caston SS, Haynes JS. Congenital fetal rhabdomyoma in a foal. Vet Pathol 2004; 41:518–520.

52. Turnquist SE, Pace LW, Keegan K, et al. Botryoid rhabdomyosarcoma of the urinary bladder in a filly. J Vet Diagn Invest 1993; 5:451–453.
53. Baker JR, Leyland A. Histological survey of tumours of the horse with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
54. Castleman WL, Toplon DE, Clark CK, et al. Rhabdomyosarcoma in 8 horses. Vet Pathol 2011; 48:1144–1150.
55. Aupperle H, Börgel C, Raila G, et al. Morphological, immunohistochemical, and ultrastructural findings in an embryonal rhabdomyosarcoma of a newborn Thoroughbred foal. J Equine Vet Sci 2004; 24:159–164.
56. Torbeck RL, Kittleson SL, Leathers CW. Botryoid rhabdomyosarcoma of the uterus of a filly. J Am Vet Med Assoc 1980; 176:914–916.
57. Clegg PD, Coumbe A. Alveolar rhabdomyosarcoma: an unusual cause of lameness in a pony. Equine Vet J 1993; 25:547–549.
58. Hanson PD, Frisbie DD, Dubielzig RR, et al. Rhabdomyosarcoma of the tongue in a horse. J Am Vet Med Assoc 1993; 202:1281–1284.
59. Valentine BA. Neoplasia. In: Bertone JJ, ed. Equine geriatric medicine and surgery. St Louis: Saunders Elsevier; 2006: 147–167.
60. Finnochio EJ, Coffman JR, Strafuss AC. Rhabdomyosarcoma in a horse. Vet Med Small Anim Clin 1969; 64:494–496.

19

Bone and dental region neoplasms

Skeletal neoplasms
Non-neoplastic bone masses
Odontogenic neoplasms
Classification of odontogenic neoplasms 323
Neoplasms of odontogenic epithelium without odontogenic mesenchyme 323
Neoplasms of odontogenic epithelium with odontogenic mesenchyme 326
Neoplasms composed primarily of odontogenic ectomesenchyme 327
Neoplasms derived from the tissues of the periodontal ligament 329
Non-neoplastic (cystic) lesions of the jaw 329

SKELETAL NEOPLASMS

Neoplasia of the skeletal system in horses is considered to be rare. In one retrospective South African survey of equine neoplasms, carried out on cases seen between 1935 and 1974 (n=378), they comprised <1.5% of the total.[1] Neoplasms more often involve the axial than the appendicular skeleton.[2] In the limbs, the pedal bone may be the most common site of involvement.[3] Bones are not common metastatic sites in horses.

It should be noted that, where biopsy specimens from suspected neoplasms of bone or in the oral cavity are submitted, the diagnosis by the pathologist is likely to be facilitated and in many cases more precise if there is provision of appropriate images (with interpretations); this includes digital photographs of the lesion(s), and any radiographs, MRI scans or other diagnostic images. It also assists the pathologist if the biopsy site (or preferably sites) are indicated in these images. In bone and dental pathology, perhaps more than any other field, a group effort of the pathologist, clinician/surgeon and imaging specialist may be required for optimal interpretation and to avoid misdiagnosis and inappropriate case management. From the pathologist's point of view, it is better to delay the interpretation and contact the clinician for further information than to make a potential misdiagnosis purely for the purposes of meeting a rapid turnaround time.

It should also be kept in mind by both pathologist and clinician that in most cases there will be associated osseous lesions, including reactive bone and pathological fracture sites (both of which can be extensive). These may be, unintentionally, the only areas sampled during the biopsy procedure; if neoplasia is indicated by the clinical examination and imaging results, the pathologist should be made aware prior to histological examination, such that there is recognition that lesions seen in the necessarily small specimens may only be secondary. Even where the neoplasm is sampled, variation in matrix production and tumour cell arrangement between different areas, even when quite closely adjacent, can also result in misdiagnosis (as detailed below, and including odontogenic neoplasms). Frequently, more definitive diagnoses are only possible when the entire bone or affected segment of that bone is sectioned.

When bony specimens are processed for histological examination, there is a conflict between the speed with which a result is desired, and the time taken to decalcify them. The more rapid decalcification methods using strong acids (e.g. nitric) will reduce detail seen in the stained sections; that reduction may be very significant and can in some circumstances preclude an accurate diagnosis. Wherever possible, slower decalcification using a weak acid (10% formic acid) is preferable; where rapidity is essential, a softer part of the tissue may be more easily decalcified for a preliminary diagnosis. The most optimal decalcification in terms of cellular detail is carried out using a chelating agent, e.g. EDTA; however, this can take weeks to months, depending on the size of the specimen.

Ossifying fibroma

Cellular origin

It has been suggested that ossifying fibromas arise from fibroblastic cells in the periodontium. The osteoblasts seen in these lesions are of stromal fibroblastic derivation (see below). Not all authors agree that these lesions are true neoplasms, with some classifying them as hamartomas or areas of excessive bone resorption with attempted repair.[4] Others have suggested that ossifying fibromas represent an ossified variant of fibrous dysplasia that is confined to the mandible (pp. 321 and 674).

Profile

Ossifying fibromas occur most frequently in juvenile horses (2–15 months of age) and have a predilection for the rostral mandible. It was suggested in one report (n=6) that this be classified as a distinct clinicopathological syndrome termed 'equine juvenile mandibular ossifying fibroma'.[5] Ossifying

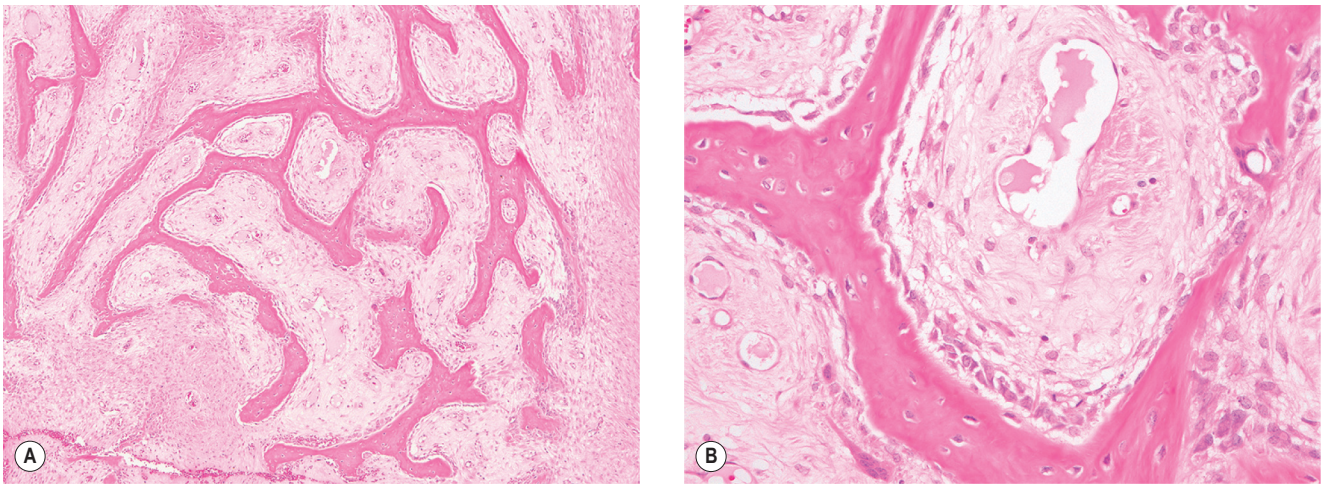


Figure 19.1 Ossifying fibroma. (A) Histological appearance of an ossifying fibroma, with randomly oriented and irregularly-shaped, interconnecting trabeculae of woven bone within a moderately to highly cellular (fibroblastic) stroma (H&E, ×40). **(B)** Plump, well-differentiated osteoblasts lining the bone, with maturation to osteocytes (within the osteoid) (H&E, ×200).

fibromas may, however, occur in any of the membranous bones of the skull, and extend into and fill paranasal sinuses.[6] Similar lesions have also been reported occasionally in adult horses, with reports in the paranasal sinuses of a 7-year-old mare, and in the distal fourth metacarpal bone of a 13-year-old gelding.[7,8] The metacarpal mass was also called a 'fibro-osseous tumour' by the authors, as the histological appearance was consistent with the diagnosis of ossifying fibroma; however, the latter term usually refers to masses involving the head rather than the appendicular skeleton. Rare ossifying fibromas have been diagnosed in tubular bones of human patients. There can be difficulty in differentiating between ossifying fibromas, osteomas (pp. 314–315) and fibrous dysplasia (particularly if examining small biopsy specimens) (p. 321), and this has resulted in some confusion in the literature.

Oncogenesis

The typical occurrence of ossifying fibromas in such young animals suggests a developmental component and/or interference with normal mandibular intramembranous ossification. It is also possible that trauma is an aetiological factor in at least some cases.

Clinical features

Ossifying fibromas are benign, expansile masses that progressively enlarge and destroy pre-existing bone (Fig. 28.14); they may replace alveolar and cortical bone and predispose to pathological fractures.[6] There is usually a clinical history of weeks to months. Ossifying fibromas frequently recur if they are not completely surgically excised.[7,9] Malignant transformation has not been reported.

Gross pathology

In the mandible, ossifying fibromas present as expansile lesions with replacement of normal bone (see Fig. 28.14). They usually measure up to 15 cm in diameter, and may be bilaterally symmetrical (i.e. involve both hemimandibles). Some masses become significantly larger, as they have the propensity for continued growth. Ossifying fibromas are usually sharply-demarcated, although margins abutting soft tissue may be irregular.[10] The degree of mineralization may prevent easy sectioning of the neoplastic tissue and use of a band-saw may be required to obtain specimens for decalcification.

There may be disfigurement of the lip and nearby teeth, disruption of the mandibular cortex, osteolysis of roots of incisor teeth with loosening and loss, and extensive ulceration and/or hyperplasia of the overlying oral mucosa (in the case of larger masses).[5] In paranasal sinuses, there may be extensive destruction of surrounding bone.[6]

Histopathology

Morphologically, ossifying fibromas are fibromas containing metaplastic bone.[11] The highly cellular and moderately vascular fibrous stroma is composed of spindle-shaped and/or stellate cells arranged in interlacing fascicles (see Fig. 19.1). This stroma is more cellular in deeper regions, and superficially may extend to the nasal/oral mucosal basement membrane.[5] It is more cellular than the stroma expected in the marrow spaces of an osteoma.[10] Multifocally, the fibroblastic cells transform into plump osteoblasts lining radiating spicules of largely woven bone (see Fig. 19.1); these increase in thickness more centrally and more deeply in the mass, with patchy deposits of lamellar bone and a less cellular intervening stroma. Typically, lamellar bone occurs peripherally and woven bone more centrally.[11] The bony trabeculae of the ossifying fibroma may merge with pre-existing cortical bone. In normal mandibular cortical intramembranous bone formation, the trabeculae form parallel to the periosteum, while in ossifying fibromas, the arrangement is random (see Fig. 19.1).[5] The osteoblastic cells may contain small numbers of mitotic figures (1–2 per 10 high power (×400) fields), but are not highly pleomorphic. There is no overlying periosteal membrane (unlike an osteoma, p. 314), and no cartilage formation will be seen.[6,10]

Other histological changes may include perivascular hyalinization within the fibroblastic stroma, observation of osteoclasts with associated resorption (these can be numerous in some fields) and lymphoplasmacytic infiltrates. It should be noted that the pre-existing bone is removed by osteoclastic resorption.[6]

Differential diagnoses

As there may be a spectrum of lesions in cases of ossifying fibroma/osteoma, including 'ossifying fibromas' in which bony trabeculae predominate or 'osteomas' with areas of osteoblast-rimmed osteoid within fibrous stroma, it may be difficult to distinguish between them in some cases.[12,13] Some authors have suggested that ossifying fibroma lesions mature into osteomas. However, it may just be the case that in some deeper areas where bone is more densely deposited, there is a histological resemblance.[6] It is therefore important to provide multiple biopsy specimens inclusive of both deep and superficial/peripheral areas to the pathologist. Additionally, a number of masses have been reported in the maxillary sinuses of adult horses and donkeys that have been considered to have histological features of both fibrous dysplasia and ossifying fibroma, i.e. only scattered bone spicules are lined by osteoblasts and osteoclasts.[14] Those masses were diagnosed as 'fibro-osseous tumours' (pp. 321 and 665).

Osteoma

Cellular origin

There is some debate as to whether osteomas are neoplastic or hamartomas. Other authors refer to them as 'fibro-osseous tumours', and define them as a mature form of ossifying fibroma or fibrous dysplasia.[15] Osteomas usually arise from the periosteal surfaces of bones that form by intramembranous ossification.

Profile

Osteomas are thought to be present at birth and they have been diagnosed in young foals; however, years may elapse before they are noticed.[6,16] Osteomas are usually restricted to the skull and mandibular bones, with the most typical presentation being a paranasal sinus mass in a young horse (Fig. 19.2).[14,17–22] In the maxilla they occur around the cheek teeth. There was one report of an osteoma overlying the left tuber calcaneus of a 12-year-old mare; this mass was not attached to the bone, but was adherent to the tarsal flexor sheath.[23] An osteoma was also diagnosed in the proximal tibia of an adult gelding.[24]

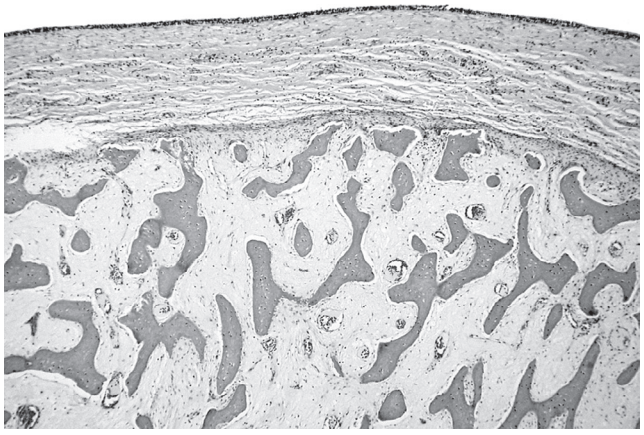


Figure 19.2 Paranasal sinus/orbital osteoma that had caused exophthalmos in an 11-year-old horse. Histological appearance, showing a mass composed of well-differentiated bony trabeculae separated by a loose fibrovascular stroma. The overlying sinus mucosa is intact. *(Figure courtesy of Dr Fred Williams III, University of Missouri College of Veterinary Medicine, and Dr Christine Loiacano, National Animal Health Laboratory Network, Ames, Iowa.)*

Oncogenesis

As above, some authors consider osteomas to be hamartomas. Osteomas in some cases have been proposed to arise secondary to trauma or infection; however, they can be impossible to differentiate from exostoses by histological examination.[2]

Biological behaviour

Osteomas are expansile masses that generally grow slowly and exert pressure on surrounding bone; they may then become quiescent for years. There may be distortion of the bone, including (depending on the location) distortion and/or disruption of nasal conchae, the nasal meatus, the nasal septum and teeth.[19] However, unlike ossifying fibromas, osteomas do not replace underlying normal tissue.[11] One horse, with a large paranasal sinus osteoma that extended into the retrobulbar space, presented with exophthalmos (see Fig. 19.2).[16] Smaller masses may not be clinically apparent, including those in paranasal sinuses. Some authors have stated that there will not be recurrence even if surgical excision is not complete; however, partial regrowth has been reported.[20,21] Osteomas have not been reported to undergo malignant transformation. It is important to differentiate them from ossifying fibromas, as the latter being more aggressive and more likely to recur following incomplete excision (p. 313).

Gross pathology

Osteomas are solitary expansile bony masses that preferentially arise from the periosteal surface, where the base merges with underlying cortical bone. In one case, there was focal fusion with the root surface of a tooth.[25] Osteomas are usually nodular, well-circumscribed and sessile or pedunculated with a smooth contour. They may reach a large size, with one paranasal osteoma reported to measure 26 cm in maximal diameter.[21] The bone that osteomas produce becomes abnormally dense, and intertrabecular spaces may or may not contain bone marrow tissue. This marrow tissue is not contiguous with that of the parent bone (unlike that of an osteochondroma, pp. 315–316).

Paranasal sinus or nasal osteomas may extend intraluminally, have a mucoid surface, and be pedunculated. Other lesions associated with paranasal osteomas include displacement and/or resorption of adjacent teeth, facial deformity, deviation of the nasal septum, turbinate distortion, disruption of septal tissue between sinuses, and unilateral nasal and ocular discharge.[19,22,25] One osteoma arising in the caudal maxillary sinus wall caused a swelling beneath the eye.[14]

Histopathology

Osteomas are typically formed by intramembranous ossification. While they are still growing, they are composed of woven bone spicules within a fibrovascular stroma (see Fig. 19.2), and the overlying periosteum has fibrous and osteogenic layers.[10] At the periphery, the trabeculae are oriented perpendicular to the surface and the periosteal covering may be poorly differentiated.[16] Osteocytes are noted within lacunae in the well-differentiated bone. As the

osteoma matures, the stroma between trabeculae shrinks and may be replaced by adipose or haematopoietic tissue, and the spicules fuse to form compact lamellar bone.[14] Osteomas, when mature, are therefore comprised only of dense, lowly cellular lamellar bone that develops Haversian systems.[19,25] The stroma may contain abundant mucinous material in nasal osteomas.

Less well-structured osteomas have been described in which some or all of the following histological features are noted[10]:

- The periosteum only has a fibrous layer
- Osteoblasts are not noted in the periosteum or in large numbers lining trabeculae
- Trabeculae are formed by periosteal and stromal fibrous metaplasia
- Trabeculae are irregular in size, shape and orientation and are largely or completely composed of woven bone
- The stroma is myxomatous.

Differential diagnoses

As there may be a spectrum of lesions in cases of ossifying fibroma/osteoma, including 'ossifying fibromas' in which bony trabeculae predominate or 'osteomas' with areas of osteoblast-rimmed osteoid within fibrous stroma, it may be difficult to distinguish between them in some cases.[12,13] Some osteomas may have features of ossifying fibroma, classic osteoma and fibrous dysplasia in various areas, implying that this may be the end stage of more than one process. It is therefore important to provide multiple biopsy specimens, inclusive of both deep and superficial/peripheral areas, to the pathologist.

Myxomatous neoplasms of the jaw

Cellular origin

The exact cellular origin of these neoplasms is not known, although they are centred on dental arches of the molar region[10] Some authors have listed them as odontogenic, although without definitive proof. In the World Health Organization (WHO) International Histological Classification of Tumours of Domestic Animals, this type of neoplasm is listed as a bone tumour rather than an odontogenic tumour.[11]

Profile

This rare type of neoplasm has been reported in the jaws of a large animals.[11] They have been cited as involving dental arches of maxillary molar teeth (see Fig. 28.15).[10] However, there has been one specific report of a myxoma in the mandible of a 1.5-year-old cross-bred filly.[26]

Biological behaviour

Benign neoplasms are slow-growing, locally destructive, intraosseous masses. Malignant neoplasms (myxosarcomas) have been reported that are more rapidly invasive.[10,11] Local excision may be difficult, depending on the size and location.

Gross pathology

These neoplasms cause distortion and swelling of the involved bone, and may project into nasal or oral cavities. On sectioned surfaces, the tissue is soft and gelatinous or rubbery, may be lobulated, and there is destruction and replacement of normal bony tissue with a thin shell of periosteal new bone.[10,26] Malignant masses may infiltrate surrounding soft tissues with more marked bony reaction.

Histopathology

There may be incomplete lobulation, and there is usually no capsule.[11] The tumour cells are stellate or spindle-shaped, and randomly arranged within abundant myxoid matrix. The stellate cellular shape is maintained in areas of secondary fibrosis[10] In the mandibular myxoma, the nuclei were ovoid and vesicular, with one or more indistinct nuclei, and the mitotic rate was low.[26] In malignant neoplasms, there is higher cellularity, with larger, more pleomorphic tumour cells.[10] No areas of bone or cartilage formation should be noted.[10,11] Extensive resorption of adjacent bone may be seen, i.e. large numbers of osteoclasts.

Immunohistochemical labelling

In the mandibular myxoma case, tumour cells stained positively for vimentin, S100 and lysozyme and were negative for cytokeratin and actin.[26]

Electron microscopy

Ultrastructurally, the tumour cells show evidence of high secretory activity, i.e. there is dilation of the endoplasmic reticulum cisternae by flocculent secretory material.[26]

Osteochondroma, osteochondromatosis (cartilaginous exostoses; hereditary multiple exostoses)

See also pages 667 and 669.

Cellular origin

An osteochondroma is a benign neoplasm arising from the bone surface, that is formed by endochondral ossification. Some authors believe that such lesions are more appropriately classified as dysplastic. Osteochondromatosis refers to a polyostotic form (see below).

Profile

Solitary osteochondromas (without any apparent hereditary transmission) are rare in horses, and have been reported mainly in 4–8-year-old animals, usually affecting the distal diaphysis or metaphysis of the radius ('supracarpal exostosis').[27–30] Other affected sites have included the distal tibia and nasal bones in horses 18 months to 3 years of age.[31–33] To date, there is only one report of a (congenital) osteochondroma of the tarsus (left calcaneus), in a 10-week-old Clydesdale foal.[34]

Osteochondromatosis is an inherited disorder and therefore diagnosed at or shortly after birth (see below). It is autosomal dominant with complete or nearly complete penetrance; this disease has only been reported in North America, with one report from Australia in a horse of which both sire and dam were imported from the USA.[35,36] Affected horses transmit it to 50% of their progeny, but normal individuals from families with the disease do not transmit the trait even with generation skips. There is no gender predilection. The osteochondromas are largely located in metabolically active areas where high stress is expected (i.e. tendonous insertions of major muscles).

Areas affected include[35,37]:

- The diaphragm
- Costochondral junctions of ribs
- Metaphyseal areas of radioulnar, tibiofibular, metacarpal and metatarsal bones.

Medial and lateral surfaces of the scapulae may be involved. The skull and jaws are *not* affected; however, some (usually small) lesions may be noted on the vertebrae, including dorsal spinous processes, and occasionally occur either adjacent to the intervertebral foramina or within the vertebral foramen.[35,38] Horses are considered to be a model for human osteochondromatosis in terms of motion impairment, hereditary pattern, histological appearance and potential for malignancy.[37]

Oncogenesis

There is some support for the theory that solitary osteochondromas are dysplastic lesions arising from focal herniation or separation of a small area of the physeal growth plate; this remains in a subperiosteal location but grows separately and undergoes endochondral ossification. This might arise from[39]:

- Trauma causing detachment and rotation of a region of the cartilage
- Herniation of cartilage through a perichondrial defect
- Nests of cartilage derived from the periosteum.

These theories are supported by the cessation of growth of osteochondromas at skeletal maturity, histological studies of human specimens, the lack of a genetic predisposition for solitary lesions and experimental creation of osteochondromas by physeal cartilage transplantation.[40,41] Endocrine stimulation has also been suggested to be involved.

Biological behaviour

Solitary osteochondromas may cause lameness, with distal radial masses causing interference with the carpal sheath, and in some cases, deep digital flexor tendonosis (due to impingement), i.e. carpal canal syndrome. An osteochondroma of the caudal aspect of the distal tibia caused tenosynovitis of the tarsal sheath.[32]

In cases of osteochondromatosis, the masses are noted at or shortly following birth and become more prominent during the growth phase, particularly those on the ribs and scapulae. They do not increase in size following maturity (4 years of age), and new lesions do not appear. A few of these osteochondromas have been documented to reduce in size, particularly those on the limbs; limb masses specifically do not enlarge as the animal matures.[35] Impingement on tendons, muscles, blood vessels and nerves by the neoplasms can interfere with normal movement and anatomical positioning.[35] In one 22-month-old colt that showed signs of lameness, weight loss and prolonged recumbency, at least three spinal nerves from the upper thoracic spinal cord were found to be entrapped by large confluent masses involving the articular processes of associated thoracic vertebrae.[36] Progression to malignancy (i.e. sarcomas) does not occur in horses; it was not noted in any case in one 10-year study.[35,37]

Gross pathology

Osteochondromas are sessile exostoses on surfaces of bones beneath the periosteum, with a blue-grey cartilage cap and usually, but not always, well-circumscribed outer margins. A pedunculated radial osteochondroma was reported that was associated with persistent carpal swelling.[27] Radial osteochondromas may rarely be multiple.

Multiple osteochondromas in horses are bilaterally symmetrically distributed but vary in size, shape and texture. In one horse, masses described on the long bones were bilaterally symmetrical in both size and location.[38] Mature affected horses often have extensive rib lesions on both lateral and medial surfaces they are particularly prominent on the latter. The size and severity of osteochondromatosis involving the ribs reduces towards the cranial part of the rib cage; it is most severe in the lower halves of caudal ribs and lower thirds of sternal ribs.[35] The masses may be conical, round, multilobular, pedunculated or spur-like; the latter two shapes are less common in horses than in human patients. Curvature or deformation of affected bones has not been documented in horses, but has occurred in human patients.

Histopathology

The histological appearance of solitary and polyostotic masses is similar. Variably dense, predominantly lamellar trabecular bone merges at the base with underlying cortical bone. The mass is capped by hyaline cartilage, with an overlying perichondrial membrane that is continuous with the periosteum of the parent bone. The cartilage only partially caps the bony tissue in maturing lesions and may be absent once maturity has been reached.[10] Intertrabecular spaces contain bone marrow tissue, and the core of the mass may communicate with the medullary cavity of the parent bone. There is normal endochondral ossification at the bone–cartilage interface (resembling a physeal growth plate). Some areas of the cartilage may be cellularly inactive. Focal cartilaginous metaplasia has been seen in some cases within the inner layer of the overlying periosteum, and there may be foci of retained cartilage cells in the bone underlying the cartilage cap or in deeper trabeculae, i.e. also consistent with endochondral growth.[27,28,35,38] Intertrabecular spaces near the surface may contain fibrous tissue, with active haematopoietic tissue in deeper areas.[38]

Osteosarcoma

See also page 665.

Cellular origin

Osteosarcomas are malignant neoplasms arising from mesenchymal cells that, by definition, include osteoblasts producing osteoid and/or bone.[11]

Profile

Although osteosarcomas are a rare type of neoplasm in the horse, this is the most common malignant neoplasm arising in bone, and possibly the most common bone neoplasm overall.[42] The age range is wide, with reports in 7-week to 6-month-old foals, and in adult horses up to 27 years of age.[2,12,43–46] In one case series (n=8), most were in male horses 7 years or older and, in another, the mean age was 5.6 years (n=10).[12,45]

Most cases of osteosarcoma in the horse have involved the skull, in particular the maxilla and mandible (including

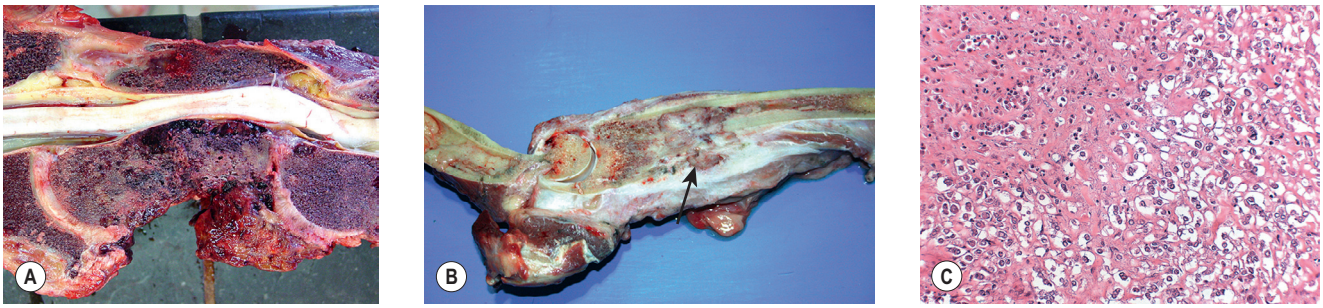


Figure 19.3 Osteosarcoma. (A) A poorly-demarcated, haemorrhagic osteosarcoma mass infiltrating and distorting a cervical vertebral body and resulting in compression of the spinal cord. The mass has destroyed the ventral cortex. **(B)** A white-grey osteosarcoma mass with haemorrhagic margins occupying the medullary cavity of the proximal radius, and infiltrating through the palmar cortex and adjacent ulna into soft tissue (arrow). The cranial radial cortex is eroded and thinned. **(C)** Histological appearance of the radial osteosarcoma. Tumour cells are polygonal or round, and lining or enclosed by lace-like, osteoid matrix (H&E, ×200). *(Figures B and C courtesy of Dr Florent David, School of Veterinary Medicine, University College Dublin. Figure C is reprinted from Kilcoyne I, Wilson M, Terzo E, et al. Osteosarcoma of the proximal radius in a donkey. Equine Veterinary Education 2010; 22:125–129, by permission of John Wiley & Sons Ltd.[52])*

involvement of the cheek teeth and nasal cavity); however, other sites have included the scapula, distal femur, proximal tibia, middle phalanx of the hindlimb, tarsal and metatarsal bones, vertebrae and ribs (Fig. 19.3).[43–52] A proximal radius osteosarcoma was reported in a 10-year-old donkey (see Fig. 19.3).[52] One case of extraosseous osteosarcoma involved soft tissue caudal to the right shoulder in a 20-year-old gelding.[45]

Oncogenesis

Trauma, viral agents, radiation exposure and genetic influences have all been suggested as predisposing factors (as for many types of neoplasm).[44] It is possible that the mandible is a predilection site in herbivorous species (including horses, cattle, and sheep) due to the greater likelihood of trauma associated with (persistent) chewing.

Biological behaviour

Common clinical problems in horses with osteosarcoma, due to the sites involved, are impaired mastication or respiration. Osteosarcomas in horses progress after incomplete surgical excision. Metastasis appears to be rare in contrast to other domestic species, such as the dog; in one cases series (n=8), no metastatic lesions were identified.[45] One horse survived for at least 8.5 years following surgical excision of a tarsal/metatarsal mass.[51] In a 7-week-old foal with osteosarcomas, there were multiple masses involving the left maxilla, bodies of the fourth and seventh lumbar vertebrae, spinous process and neural arch of the eighth thoracic vertebra, and head of the eleventh rib, with associated spinal cord compression and degeneration.[53] This case was interpreted as metastasis to metaphyseal growth centres, as masses were also noted in the lungs. In one case of radial osteosarcoma in a 10-year-old donkey, metastasis occurred to regional lymph nodes and the liver.[52]

Gross pathology

Osteosarcomas typically arise in and expand the medullary cavity (i.e. they are of central origin), often of the metaphyseal region, resulting in destruction and distortion of normal bone (see Fig. 19.3). The balance between bony destruction, production of osteoid by the neoplasm and production of reactive bone by the remaining endosteum and periosteum can be highly variable; as a result osteosarcomas may be classified (particularly in conjunction with their radiographic appearance) as lytic, productive or mixed.[10] The medullary mass will usually be firm and pale (white/grey), but softer than normal bone (containing variable amounts of bony tissue), mineralized or partially mineralized, white, pink or red and homogeneous, and may contain cystic, mucoid, necrotic and/or haemorrhagic areas (see Fig. 19.3). Some masses are soft and fleshy, with only small amounts of gritty material (i.e. less production of osteoid/bone).[44]

Osteosarcomas typically invade extensively, causing thinning and/or destruction of cortical bone that should be identifiable on sectioned surfaces. The neoplastic tissue can penetrate through the entire thickness of the cortex (see Fig. 19.3), invading and forming masses within surrounding soft tissues. Reactive bone formed by the periosteum is seen as a roughened surface, multiple tufts and knobs or (where growth of the neoplasm is slow enough) it can have an appearance similar to a callus; the endosteum may attempt to form abutments at margins of the infiltrating mass.[10] Osteosarcomas rarely infiltrate articular cartilage to affect joint spaces; however, bridging of intertarsal and scapulohumeral joints has been reported, respectively, in equine cases.[44,49] The osteosarcoma mass bridging the scapulohumeral joint originated in the scapula and was thought to be periosteal rather than medullary in origin.[49] Another unusual finding was noted in a donkey with radial osteosarcoma, where the adjacent ulnar cortex was invaded (see Fig. 19.3).[52]

Maxillary masses may protrude into and fill the overlying nasal cavity, and mandibular masses can cause marked malocclusion.[14,53] There may be pathological fracture(s) associated with osteosarcoma masses an, depending of the site of involvement, subchondral bone collapse.[42,44]

Histopathology

By definition, osteoid or woven bone formation by tumour cells must be noted for a definitive diagnosis of osteosarcoma. As the malignant mesenchymal cells have a multipotent nature, there may also be areas of cartilage and collagen; however, even if those matrices predominate, the finding of only one focus of (tumour cell-produced) osteoid or bone is sufficient for the diagnosis. The pathologist must differentiate formation of osteoid/bone by tumour cells from reactive bone, endochondral ossification of tumour cartilage and osseous metaplasia (also from multipotent mesenchymal cells).[10] This can be extremely difficult or even impossible where small and/or solitary biopsy specimens are submitted.

Additionally, on this basis, where reactive bone formation, fibrosarcoma or chondrosarcoma are diagnosed by examination of biopsy specimens, osteosarcoma cannot be completely ruled out. As above, radiographs (and other images if available) should be submitted to the pathologist, with an indication of where the specimens were taken from.

Tumour cells in osteosarcomas may be arranged in sheets, streams or clusters. If the tumour cells also line blood-filled spaces, the diagnosis of telangiectatic osteosarcoma may be made, of which there has been one report in a horse.[51] Tumour cells that more closely resemble osteoblasts are polygonal, oval or round with deeply eosinophilic cytoplasm. Others may be spindle-shaped or stellate, i.e. fibroblastic; in one case series, six of the eight osteosarcomas contained fibroblastic tumour cells.[45] Osteosarcoma cells are often highly pleomorphic with large nuclei (high nuclear:cytoplasmic ratio) that are vesicular or contain clumped chromatin. The mitotic rate is variable but frequently high. The tumour cell-produced osteoid is extremely variable in amount (i.e. in productive versus non-productive osteosarcomas) and in the pattern of arrangement. It may have a 'lace-like' pattern (highly characteristic of osteosarcoma), or be arranged in islands or spicules, and is lined by and partially or completely surrounds the tumour cells (see Fig. 19.3).[10] As osteoid contains collagenous tissue and will not necessarily be mineralized, it can be very difficult to differentiate histologically from a purely collagenous matrix, particularly in areas where the osteoid is sparsely arranged. Noting tumour cells within lacunae assists in this differentiation. The tumour cell-produced osteoid must also be differentiated from reactive woven bone: as a rule, reactive bone is lined by a single layer of osteoblasts that show normal maturation, and the trabeculae interconnect in an orderly manner; tumour bone is not rimmed in this way, the trabeculae are randomly connected if at all, and there is usually filling of intertrabecular spaces by the osteoblastic tumour cells (or multilayering at least).[10] It should be noted that tumour cells do not produce lamellar bone. The most immature, i.e. non-productive, tumour cells tend to be found at the periphery of the neoplastic mass.

Another complicating factor in the histological diagnosis of osteosarcomas is the frequent occurrence of pathological fractures, as well as the need to differentiate neoplasia from a primary fracture. Again, this may be impossible to achieve by examination of biopsy specimens alone. Features of fracture repair include proliferating mesenchymal cells with a primitive appearance that should not show atypia, and evidence of callus maturation with gradual chondro-osseous transition.[10]

Other variable features include osteoclast-like multinucleate giant cells, tumour necrosis and haemorrhage.

There is no widely used histological grading system for osteosarcomas in domestic animal species. Although some pathologists will subclassify osteosarcomas as osteoblastic, chondroblastic, fibroblastic, telangiectatic, giant cell type or poorly-differentiated, there is no prognostic information on these categories for the horse.[10,11]

Differential diagnoses

These are listed in Box 19.1.

A differential diagnosis for telangiectatic osteosarcoma is haemangiosarcoma; the latter diagnosis may be ruled out by negative immunolabelling of tumour cells lining the blood-filled spaces for factor VIII-related antigen.

Box 19.1 Differential diagnoses for osteosarcoma

Neoplastic
- Chondrosarcoma
- Fibrosarcoma
- Haemangiosarcoma (telangiectatic osteosarcoma)
- Osteoblastoma

Non-neoplastic
- Fracture
- Synovial osteochondromatosis

Osteoblastoma

Cellular origin

Osteoblastomas are conventionally thought to be benign neoplasms of osteoblastic origin, with similarity to osteoid osteomas. The diagnosis is a controversial one in human patients, with some authors believing osteoblastomas to be a type of osteoid osteoma, and recent reports of an aggressive type with similar characteristics to osteosarcoma.

Profile

An osteoblastoma was reported in the distal radial metaphysis of a 4.5-year-old pony.[54] This mass was successfully excised.

Biological behaviour

Osteoblastomas tend to grow progressively, but may have an indolent course.

Gross pathology

Osteoblastomas are well-circumscribed, measure up to 10 cm in diameter and are often surrounded by a thin shell of cortical bone or periosteum.[55] The sectioned surface may be friable and deep red, or if more ossified, yellow-brown and gritty.[54]

Histopathology

Irregularly-shaped, sized and oriented trabeculae of osteoid and/or woven bone are noted within an abundant, highly cellular fibrovascular stroma. These trabeculae may be variably mineralized. Osteoblasts or osteo-fibroblastic cells rim the trabeculae, at least focally, and there may be numerous (osteoclastic) giant cells around trabeculae and in the stroma.[54,55]

Differential diagnoses

These are listed in Box 19.2.

The authors of the report of osteoblastoma in a pony described ossifying fibromas as having a similar histological appearance, but occurring only in the jaw.[54]

Box 19.2 Differential diagnoses for osteoblastoma

- Osteoma
- Ossifying fibroma
- Osteosarcoma

Multilobular tumour of bone (chondroma rodens)

Cellular origin

The cellular origin of this type of neoplasm is uncertain. Derivation from cells of aponeuroses (sheet-like tendonous expansions) overlying the bone or altered periosteal elements has been suggested, and disturbance of intramembranous bone formation may be involved.[10,17]

Profile

Multilobular tumours of bone usually occur in the skull, or rarely, involve the ribs.[11] There has been one report in a 12-year-old Thoroughbred mare, presenting with exophthalmos of the left eye.[56]

Biological behaviour

Multilobular tumours of bone can be locally aggressive and have been known to undergo malignant transformation, with pulmonary metastasis reported in dogs.[10,11] The one reported case in a horse arose in a retrobulbar location and did not recur following excision.[56] Masses that project into the cranial cavity cause compression of the brain without invasion.[10]

Gross pathology

These firm, non-mobile, discrete masses project from external or internal surfaces of the skull. The multilobular tumour of bone reported in a horse was thinly encapsulated by fibrous tissue, and on sectioning, was red-grey, friable and gritty.[56]

Histopathology

As indicated by the name, these neoplasms are lobulated, with spindle cells and radially arranged fibrous tissue surrounding round or elongate islands of partly calcified or ossified cartilage and bone[17]; the extent of differentiation of cartilage and bone may vary significantly between lobules.[11] The bone may be rimmed by primitive osteoblasts and osteoclasts. Mitotic figures are usually rare, but when present in significant numbers, indicate malignant transformation.[10] Less well-defined lobulation may also occur in poorly-differentiated neoplasms, with other features of malignancy including necrosis, haemorrhage, overgrowth of one mesenchymal element (e.g. spindle cells) and invasion of adjacent tissue.[11] Blood vessels are noted between lobules, but may extend into those undergoing endochondral ossification at the time of examination.[10]

Differential diagnoses

These are listed in Box 19.3.

Box 19.3 Differential diagnoses for multilobular tumour of bone

- Chondrosarcoma
- Osteosarcoma

Giant cell tumour of bone (osteoclastoma)

See also Giant Cell Tumour of Soft Parts, pp. 290–292.

Cellular origin

Giant cell tumours of bone arise from primitive bone marrow stromal cells, possibly histiocytic, with the tumour cells showing some similarities to osteoclasts.[11]

Profile

There has been one report of giant cell tumour of bone in the proximal tibia of an 8-year-old Arabian cross mare.[57] This type of neoplasm is rare in all domestic animal species.[10]

Biological behaviour

As giant cell tumours of bone are so rare in animals, there is no general information regarding their behaviour. Benign and malignant forms have been reported in non-equine species. The one mass reported in a horse was expansile, and metastatic lesions were not noted.

Gross pathology

Giant cell tumours of bone tend to be lytic and expansile, being surrounded by a thin shell of bone, resulting in a 'soap bubble' appearance radiologically.[10,11] They typically arise near the ends of long bones. The giant cell tumour of bone reported in an equine tibia expanded the proximal condyle, was soft, red and irregularly-shaped, and measured 6 cm in maximal diameter.[57] The overlying cortex was characteristically thin, and there was a pathological fracture extending into the overlying joint space.

Histopathology

These neoplasms are composed of mononuclear cells, and large numbers of multinucleate giant cells with similar nuclei.[10] In the one reported equine case, the tumour cells were arranged in sheets or occasional whorls; mononuclear cells were oval or spindle-shaped with scanty eosinophilic cytoplasm.[57] There were large numbers of giant cells with up to 10 nuclei. Nuclei were vesicular and appeared similar in all tumour cells, with only occasional mitotic figures.

There may be osteoid formation in giant cell tumours of bone, but this is not prominent. In the giant cell type of osteosarcoma, nuclei of the osteoclastic cells and mononuclear tumour cells will not have a similar appearance; additionally, the giant cells are not likely to be as prominent a component.[10,11] Definitive differentiation of giant cell tumour of bone and the giant cell type of osteosarcoma is not possible based on examination of small biopsy specimens alone.

Some giant cell tumours of bone may also contain cavernous spaces and areas of haemorrhage; this will require differentiation from an aneurysmal bone cyst (p. 322).

Differential diagnoses

These are listed in Box 19.4.

Box 19.4 Differential diagnoses for giant cell tumours of bone

Neoplastic
- Giant cell type (or telangiectatic type) of osteosarcoma
- Haemangiosarcoma
- Fibrosarcoma
- Osteoblastoma

Non-neoplastic
- Aneurysmal bone cyst

Fibrosarcoma

See page 287.

Chondroma

See also page 672.

Cellular origin

These benign neoplasms arise from cartilage cells or other transformed mesenchymal cells, and produce cartilaginous matrix.

Profile

Chondromas are rare neoplasms in any domestic animal species, but tend to arise from flat bones and ribs.[11] They have been reported in the skull of horses in paranasal sinuses/nasal cavities.[3,48,58] They may also occur in extraskeletal sites such as the external ear, skin and larynx (see Fig. 29.14B).[48,59,60]

Biological behaviour

Chondromas are usually solitary, and slow-growing but not locally invasive. They may grow to a size that causes clinical problems, depending on the location. Some chondromas may undergo malignant transformation; however, most chondrosarcomas are thought to arise *de novo*.[10]

Gross pathology

In bone, chondromas may be classified as enchondromas (arising in the medullary cavity) and ecchondromas (arising in other skeletal cartilages).[10] Chondromas are smooth, circumscribed, sometimes encapsulated, expansile masses composed of multilobulated, blue-white or white, cartilaginous tissue. In some masses, there may be areas of gelatinous (myxoid) material.[11]

The spherical laryngeal chondroma reported in one horse measured 3 cm in diameter; it was reducing the diameter of the rima glottidis and had a hyperaemic, ulcerated surface.[60]

Histopathology

Chondromas are composed of lobules or nodules of well-differentiated hyaline cartilage. The tumour cells generally occur individually within lacunae, but lack orderly arrangement. These tumour cells are not markedly pleomorphic, binucleate or mitotically active and have small hyperchromatic nuclei.[17] There may be foci of calcification, endochondral ossification, fibrosis and myxoid change.[11,60] It may be difficult to distinguish between chondromas and well-differentiated chondrosarcomas based on histological examination alone.

Differential diagnoses

These are listed in Box 19.5.

Box 19.5 Differential diagnoses for chondroma

- Osteochondroma
- Well-differentiated chondrosarcoma
- Well-differentiated chondroblastic osteosarcoma
- Synovial osteochondromatosis (non-neoplastic)

Chondrosarcoma

Cellular origin

These malignant neoplasms arise from cartilage or other transformed mesenchymal cells, and produce cartilaginous matrix cells.

Profile

Chondrosarcomas are rare in horses. They most commonly arise in the axial skeleton (i.e. skull, vertebrae, ribs and pelvis), in addition to the scapulae, and may originate from the medullary cavity or periosteum in any given location.[2,11,48,61] A synovial or periosteal origin was hypothesized in two cases for chondrosarcomas arising in the radius and the first phalangeal bone (P1), respectively; a pedal chondrosarcoma was diagnosed in an 18-year-old donkey.[62,63] In human patients, chondrosarcomas may arise from sites of chondromatosis or osteochondromatosis in the synovium, and this may have occurred in these equine cases.

Chondrosarcomas may also arise in extraskeletal sites; one such neoplasm was reported in the mid-portion of the tongue (where cartilage is found normally in the horse) in a 4-year-old Arab gelding.[64]

Biological behaviour

Chondrosarcomas are considered to be low-grade malignancies with slow, but locally destructive growth. They usually grow asymmetrically, and will ultimately infiltrate into and through adjacent cortical bone. There may be recurrence following incomplete excision. Haematogenous metastasis is considered to be rare; however, this did occur to the lungs and lymph nodes from rib lesions in one horse.[61]

Gross pathology

Chondrosarcomas are generally well-circumscribed, but margins may be irregular; they are firm, white, white-tan or blue-white and often multinodular or multilobulated, with irregular margins.[62] These neoplasms may have a gelatinous consistency, where there is myxomatous degeneration. Additionally, white chalky areas of calcification may be noted, with bone tending to occur in central and basal areas of some masses.[10] There may be extensive infiltration of surrounding bone that is often asymmetrical for neoplasms involving the flat bones; chondrosarcomas of ribs and pelvic bones frequently extend into body cavities. There may be reactive bone on overlying surfaces that is typically smooth and dense, and is ultimately penetrated multifocally by neoplastic tissue.[10]

Adjacent soft tissues and other bones may be infiltrated: for example, a radial mass infiltrated through the caudal cortex and into the medullary cavity, with caudal projection into the carpal canal and distal infiltration of the radiocarpal joint (including synovium) and carpal bones.[63] Other changes may include pathological fractures, nasal discharge (for nasal chondrosarcomas) and compression of adjacent organs.

Histopathology

The histological appearance of chondrosarcomas is highly variable depending on the degree of differentiation. The tumour cells (the density of which varies) are located within variably-sized, often large lacunae in a chondroid or mucinous matrix that is poorly vascularized; there may be multiple cells within one lacuna. The tumour cells

Box 19.6 Differential diagnoses for chondrosarcoma

- Chondroma
- Chondroblastic osteosarcoma
- Multilobular tumour of bone
- Giant cell tumour of bone
- Synovial osteochondromatosis (non-neoplastic)

are round and pleomorphic. In less well-differentiated chondrosarcomas, the tumour cells may be spindle-shaped (mesenchymal chondrosarcomas) and arranged in streams with small amounts of basophilic matrix and rudimentary lacunae.[64] Nuclei may be round or irregularly-shaped and are often plump; plump nuclei, clumping of chromatin and large cells with one or multiple nuclei are considered to be signs of malignancy.[10,63] There may be marked anisokaryosis and anisocytosis, with a variable mitotic rate that can be very low in well-differentiated neoplasms.[61] It has been suggested that even one mitotic figure in a section is sufficient for a diagnosis of chondrosarcoma rather than chondroma.[65]

The tumour cells in chondrosarcomas do not directly form osteoid or bone, but there can be evidence of endochondral ossification and/or osseous metaplasia. This must be differentiated from direct bone formation by the tumour cells (i.e. osteosarcoma). Alcian blue stains may be used to differentiate the two, with the osteoid in a chondrosarcoma being surrounded by deep blue matrix (i.e. arising in a mucochondroid matrix).[65] There may also be areas of entrapped pre-existing bone or cartilage.

Central necrosis may occur in deeper regions of the masses. Invasion and replacement of bone by tumour cells without marked associated osteoclastic activity or distortion has been noted.[61]

Differential diagnoses

These are listed in Box 19.6.

NON-NEOPLASTIC BONE MASSES

Fibrous dysplasia

See also page 674.

Classification

This is a benign mass of fibro-osseous tissue that is classified by many authors as a developmental lesion and tends to be diagnosed in young animals.[11]

Profile

There have been few reports in horses, with sites including the maxillary sinuses, nasal cavity and accessory carpal bone (Figs. 19.4 and 37.4).[66,67] Fibrous dysplasia masses are mono- or polyostotic and expansile, with local disruption of bone and a surrounding periosteal reaction (Fig. 28.23). Grossly, they are dense and gritty on sectioning, and may contain blood-filled cystic spaces.[20]

Histopathology

Histologically, highly cellular fibrovascular tissue containing well-differentiated fibroblastic cells (with occasional mitotic figures) separates irregularly-shaped, thin, poorly-mineralized spicules of woven osteoid (see Fig. 19.4) or poorly-differentiated bone that do not have any particular orientation and tend to be equidistant.[10] There is no lamellar bone, other than in very mature lesions.[11] There is only occasional lining (rimming) of the spicules by osteoblasts (i.e. the spicules are 'naked'; see Fig. 19.4), and osteoclasts may also be observed; the osteoid is formed directly by the fibroblastic (i.e. by metaplasia) without an intervening osteoblastic stage; any osteoclasts are likely to be vestigial. This differs from ossifying fibromas, in which osteoblastic rimming is prominent (pp. 312–313). There may also be areas of cystic degeneration and haemorrhage with associated giant cells, which do not occur in ossifying fibromas.[66] Osteoclastic resorption of bone surrounding the mass may be observed, and there is no surrounding periosteal membrane. Pathological fracture may occur, which will complicate the histological appearance. Malignant transformation has not been reported in animals.[10]

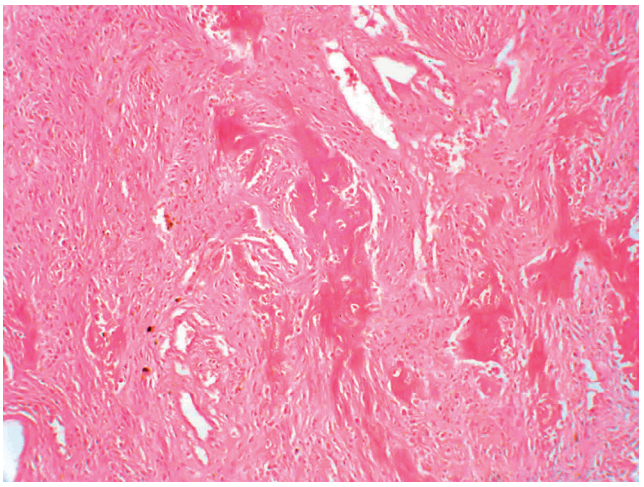


Figure 19.4 Fibrous dysplasia in the accessory carpal bone of a 9-year-old gelding.[67] Irregularly-shaped spicules of woven osteoid are noted within a highly cellular fibrous stroma, but are not 'rimmed' by osteoblasts (only small numbers are noted) (H&E, ×100).

Fibro-osseous tumours

See also page 665.

A number of masses have been reported in the maxillary sinuses of adult horses and donkeys that have histological features of both fibrous dysplasia and ossifying fibroma: i.e. scattered bone spicules are lined by osteoblasts and osteoclasts.[14]

Bone cysts

Intraosseous epidermoid cysts

These rare, cystic (lytic) lesions are lined by stratified squamous epithelium that keratinizes centrally, with an outer layer of fibrous tissue and thickening of surrounding bony trabeculae (Fig. 19.5).[10] Their exact origin is uncertain, but possible sources include traumatically implanted or post-traumatic invasion of epidermal tissue, a metaplastic process or a congenital focus of heterotopic ectodermal tissue.[68] Intraosseous epidermoid cysts have been reported in the mandible of a 21-year-old horse, and the third phalanx in each of two 11-year-old horses (see Fig. 19.5).[68–70] If there is marked hyperplasia of the epithelial lining, squamous cell carcinoma is an important differential diagnosis.

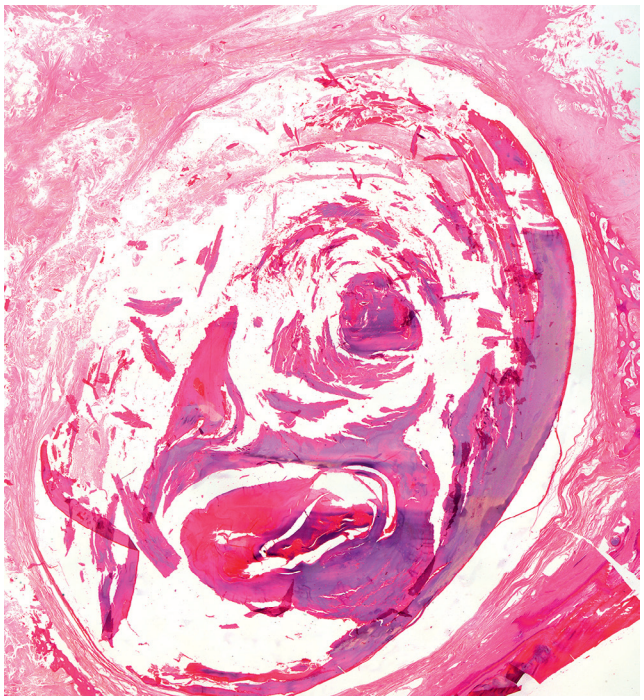


Figure 19.5 Epidermoid cyst. Histological appearance of a cyst that is replacing and expanding distal phalangeal bone. There is a thin stratified squamous epithelial lining, with large amounts of intraluminal keratin material (H&E, ×12.5).

Aneurysmal bone cysts (See also p. 672)

Aneurysmal bone cysts are thought to arise due to a disruption to (but not interruption of) the bone marrow vasculature of bones of the axial or appendicular skeleton. They may be primary lesions caused by congenital or developmental vascular anomalies, or occur secondary to a number of processes including neoplasia, fibrous dysplasia, haematomas, fractures or trauma.[71] Aneurysmal bone cysts usually occur in rapidly growing young animals, but can be reported in adults, including older animals.[72] Reports in horses have been rare, with sites including the mandible, distal radius, third metacarpal bone and distal third metatarsal bone.[71–77] Multiple lesions were reported in a 5-day-old Thoroughbred foal (left third metacarpal and left tibial bones).[76] A similar congenital lesion was reported in the mandible of a foal that had resulted in death associated with dystocia. There have been limited numbers of reports of successful removal of these cysts in horses, and recurrence may follow curettage or excision; the prognosis appears to be better when there is no underlying disease process.[75] Aneurysmal bone cysts are usually, solitary, variably-sized, expansile, thin-walled and often multilocular, contain blood, and lack an epithelial lining; they are not true cysts. There may be progressive swelling of the involved bone, with potential destruction of large areas of cortical bone (Figs. 28.21 and 37.3).[71,77] There may be associated periosteal bony reaction and/or pathological fracture.[71] New, thin cortical bone may be continually formed adjacent to the periosteum and then disrupted as the cyst grows.[72] There is often haemorrhage into surrounding tissues. Histologically, the cavities may or may not be lined by endothelial cells, and are separated (and sometimes subdivided) by well-vascularized fibrous septa that may contain areas of reactive woven and/or lamellar bone. Some cysts have been described as being lined by haemosiderophages, multinucleate giant cells and reactive fibroblasts.[74,75] Associated lesions include mineral-encrusted fibrinous deposits, siderophage infiltration and osteoclastic resorption. In the jaw, differential diagnoses include sinus and dental cysts, mucocoele, nutritional secondary hyperparathyroidism and odontogenic tumours.[77] Other neoplastic differential diagnoses include haemangiosarcoma, osteosarcoma and fibrosarcoma.

Unicameral bone cysts (simple or solitary bone cysts)

These are single-chambered cavities (monostotic or polyostotic) that are expansile, lytic, fluid-filled and lined by reactive fibrous tissue. The exact cause is not known, but theories include developmental vascular anomalies, repeated trauma, growth plate disorders (in relevant sites) or encapsulation of intramedullary haemorrhage. Two such lesions have been reported in the mandible of young horses[78,79]; in one case, there was thinning of the lateral cortex and the lesion was successfully treated by curettage followed by corticocancellous bone grafting. Histologically, the fibrous walls may contain scattered multinucleate giant cells and haemosiderophages.[10]

Subchondral bone cysts (juxtacortical bone cysts)

These lesions occur in young horses as one manifestation of osteochondrosis or as a result of trauma and may be articular or non-articular.[80] The relationship to osteochondrosis is indicated by the high frequency of these lesions in young horses and the fact that they are often bilateral. Trauma may result in similar cysts, due to damage to articular cartilage and subchondral bone that allows entry of joint fluid and bone resorption.[80] Most lesions involve the stifle, fetlock, pastern, coffin and elbow joints, with smaller numbers of cases in other sites, including for example the tarsocrural joint.[81,82] There is an infolding of abnormal cartilage into the bone; the cartilage becomes necrotic and surrounded by fibrovascular tissue (that does not infiltrate).[82]

Acquired bone cysts of the tarsus

These may occur in the distal tibia, distal talus (adjoining the proximal intertarsal joint) or proximal talus, and are of varied aetiology, including bacterial infection and developmental orthopaedic disease (DOD).[80] There may be associated synovial effusion.

Miscellaneous lesions

Osseous hamartoma

An osseous hamartoma (15×10×9 cm) was reported on the medial side of the distal radius of an Arab cross foal that was not attached to the underlying bone. This mass was composed of disorganized juvenile skeletal elements, including nodules of cancellous bone, fibrocartilage, models of hyaline cartilage with foci of endochondral ossification, areas of epiphyseal-like osteogenesis, ligamentous tissue and joint-like structures.[83]

Suture line osteitis ('unicorn syndrome')

This is a proliferative lesion involving suture lines of the skull of adult horses, usually not appearing as a single

elongated mass.[3] After initial growth, there is no worsening or regression.

Synovial osteochondromatosis

This is a metaplastic disease; the cause is proposed to be trauma, in which connective tissue supporting the synovial membrane forms slow-growing, self-limiting cartilaginous nodules that calcify and may undergo endochondral ossification. There may be extrusion of osteocartilaginous bodies into the joint space; this can include intervertebral joints. Synovial osteochondromatosis is a rare disease involving one joint.[84] Histologically, chondrocytes may form chondrones and contain large nuclei, and binucleate or multinucleate cells may be observed; however, these changes are consistent with active proliferation rather than malignancy. The diagnosis is made in conjunction with anatomical location and requires differentiation from chondrosarcoma.

Tumoral calcinosis

This is a disease of undetermined cause, occurring by definition in periarticular tissues of one or more joints, including the subcutis, fascial tissue and joint capsule. In horses, tumoral calcinosis tends to occur unilaterally or bilaterally over tibiofibular joints, with additional lesions in other sites in rare cases (e.g. shoulders, neck, pectoral regions).[85–87] Young adult horses are most frequently affected (18 months to 4 years of age), and male Standardbred horses may be predisposed.[85,86] These multiloculated, encapsulated lesions measure up to 12 cm in diameter, and are firm, dense, mobile and ovoid. On sectioned surfaces, pockets of chalky material are noted. Histologically, they are composed of granular masses of mineralized material with surrounding, palisading macrophages, multinucleate histiocytic giant cells and fibroblasts, and thin subdividing septa of fibrous tissue. Excision is usually not necessary but should be curative.

Actinomycosis

Actinomycosis of the mandible that clinically mimicked neoplasia was reported in a 4-year-old horse.[88] Histologically, there were inflammatory cell infiltrates, including neutrophils and macrophages, associated with typical Gram-positive forms of *Actinomyces* sp. bacteria.

ODONTOGENIC NEOPLASMS

Neoplasms of odontogenic origin (arising in the maxilla or mandible) are the most common type occurring in the equine skull. They are most frequently diagnosed in younger horses but can be noticed at any age. Horses have tall (hypsodont) teeth that are completely covered with coronal cement when they erupt; the teeth grow over a substantial portion of the lifetime of equines (20–25 years) and take a long time to be worn away.[89] The cementum is worn away, followed by the underlying enamel, to then expose the softer dentin, i.e. the true functioning occlusal surface.[89,90] This juxtaposition of cementum and enamel does not occur in simple teeth and results in differences in the odontogenic neoplasms that may develop in horses and some other domestic animal species.[91]

It should be noted that diagnosis of odontogenic tumours by examination of biopsy specimens can be exceedingly difficult and may lead to misdiagnosis. For example, a mass that is largely consistent in appearance with an ameloblastic odontoma could have a small area resembling a more complex tumour.[92] The ultimate diagnosis must be made based on examination of sections from the excised mass. Complete excision is of course more easily achieved with mandibular masses, as a hemi-mandibulectomy may be performed.

Classification of odontogenic neoplasms

The classification of odontogenic neoplasms below follows the system developed for the World Health Organization International Histological Classification of Tumours of Domestic Animals, and includes those arising from the periodontal ligament.[11]

Neoplasms of odontogenic epithelium without odontogenic mesenchyme

Ameloblastoma (adamantinoma)

See also page 432.

Cellular origin

These neoplasms resemble the odontogenic epithelial part of the tooth germ only, and arise from embryonic remnants of the developing root sheath and dental lamina in the mandible and maxilla. They do not produce enamel.

Profile

Ameloblastomas are rare in equines, with few reported cases, but this is the most common type of odontogenic neoplasm.[3] They occur more commonly in the mandible than the maxilla.[93–95] In one survey of horses referred with disease of the primary cheek teeth (n=101), 4% had dental tumours and all of these were ameloblastomas.[96] In a similar survey of horses with diseases of the incisor, canine or first premolar teeth (n=42), only one had an ameloblastoma (in the rostral mandible).[50]

Ameloblastomas have been reported in horses and ponies ranging in age from neonatal to 19 years.[14,50,93–101] The majority of affected horses have been geldings or stallions.[94,98,99]

Biological behaviour

Most ameloblastomas are expansile and locally aggressive but there is no known risk of metastasis.[101] Most are slow-growing, but one ameloblastoma involving the mandibular symphysis completely destroyed the rostral mandible in only 2 weeks (Fig. 28.4).[98] Removal must be performed with tumour-free margins, which can be difficult to achieve due to the large size of some of these masses or difficulties in differentiating neoplastic tissue from surrounding bone at surgery.

There is one report of humoral hypercalcaemia of malignancy associated with an ameloblastoma in a 16-year-old gelding; immunohistochemical labelling and Western

blot analyses demonstrated production of parathyroid hormone-related protein (PTHrP).[100]

Gross pathology

Ameloblastomas may arise deep in the bone of the mandible or maxilla (central) or within the gingival soft tissue (peripheral).[102] There is often clear margination by thick sclerotic bone, with cortical thickening on lingual or buccal surfaces.[92] The masses often protrude from lingual or buccal surfaces (see Figs. 28.3 and 28.4), and those arising in the maxilla may displace the hard palate and extend into the nasal cavity.[103] Ameloblastomas can reach a very large size (e.g. up to 57 cm in diameter).[100,101] On sectioned surfaces, there are alternating regions of soft fleshy, grey-white or pale yellow tissue with mineralized material. There may be multiple cystic spaces, containing mucoid or spongy substance.[93] As a result, the overall consistency is variable, but in general, although firm, it is softer than surrounding bone.

Ameloblastomas cause resorption, expansion, distortion and cortical thinning of the adjacent or surrounding bone that is often marked. There may be destruction of cortical bone and normal periodontal structures, with displacement and/or resorption of teeth or other dental abnormalities.[20,93,94] Tooth roots may be lysed and shortened, with loss of the lamina dura and periodontal membrane. Associated bone may show a periosteal reaction. There may also be atrophy of skeletal muscle tissue, e.g. the masseter muscle.[97] It is possible for masses to extend through the cheek (see Fig. 9.43).

Histopathology

Odontogenic epithelium has the following defining characteristic arrangement and morphology[102]:

- A palisading arrangement at the periphery, with these palisading epithelial cells having apical nuclei and showing basilar cytoplasmic clearing (resembling the inner enamel epithelium)
- Epithelial cells internally that are connected by long intercellular bridges and therefore have the appearance of stellate reticulum: i.e. cells seen at the centre of the enamel organ of a developing tooth.

In neoplasms of odontogenic epithelial derivation, those typical features may be easily identified or present in only a very small area. These and other histological features described here are considered to be characteristic, but it should be noted that not all ameloblastomas in horses (or humans) exhibit all of them.[99] The epithelial tumour cells are arranged in sheets, islands (follicular or spindle cell patterns) or dissecting thin cords (plexiform pattern) that mimic the enamel organ (see Fig. 19.6). They are supported by a moderately to markedly abundant, dense or loose, well-vascularized fibrous stroma that does not resemble any

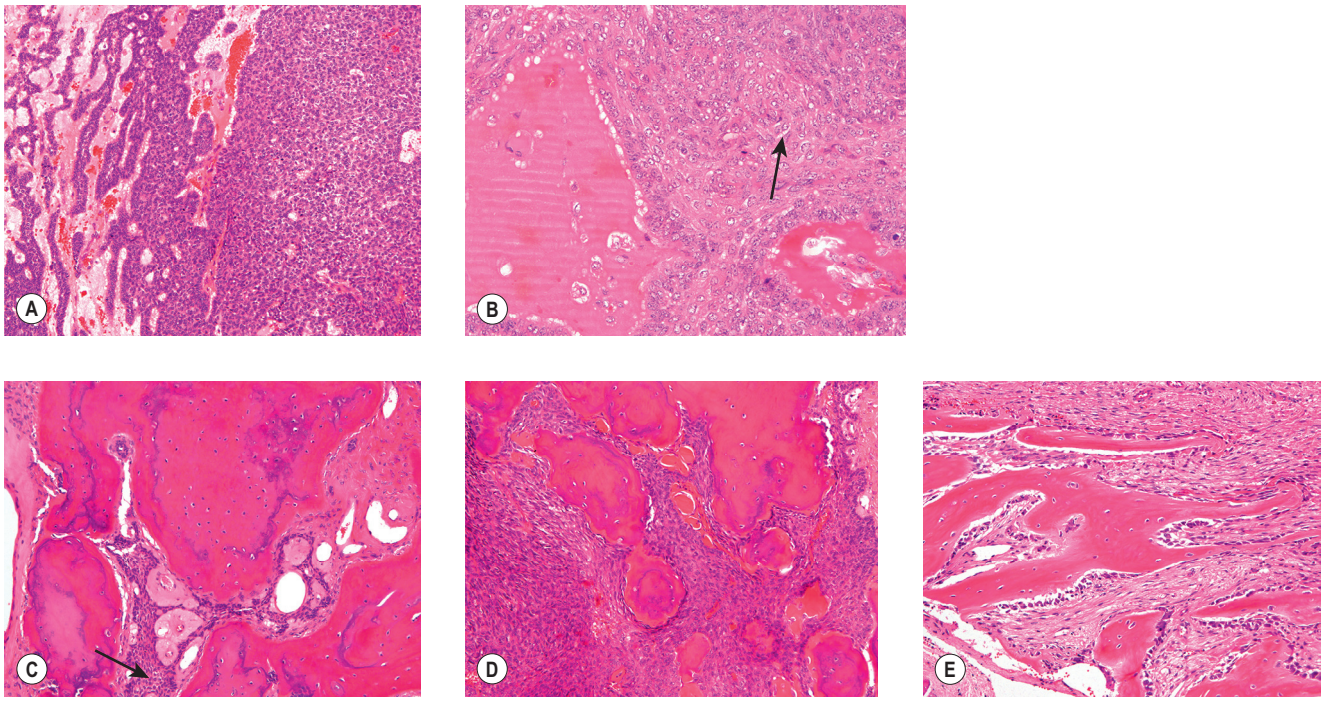


Figure 19.6 Ameloblastoma in the rostral mandible. (A) Histological appearance, with palisading cords and sheets of epithelial tumour cells (H&E, ×100). **(B)** Another area in the same mass. Tumour cells at the periphery are palisading and cuboidal, while those located more centrally in the sheet are polygonal; some have obvious intercellular bridges (arrow). The stroma is filled with proteinaceous (eosinophilic) fluid (H&E, ×200). **(C)** Epithelial tumour cells dissecting between multiple, coalescing regions of cementum matrix. Note the mosaic-like pattern of scalloped basophilic (reversal) lines within that matrix, this being typical for cementum (see p. 328). There is no associated odontoblastic differentiation of tumour cells and the cementum is considered to represent a proliferative response specific to ameloblastomas in horses (or herbivores); some authors consider its presence inconsistent with the diagnosis of ameloblastoma. Epithelial cells towards the deep margin in this field have an appearance resembling stellate reticulum (arrow) (H&E, ×100). **(D)** A further field in which epithelial tumour cells directly abut the cementum; this again contains mosaic-like basophilic reversal lines, and has rounded outlines. There is no intervening odontoblastic population (H&E, ×100). **(E)** Reactive (woven) bone within the same mass, to indicate the different appearance to the cementum. Note the rimming of osteoid forming the interconnecting trabeculae by plump osteoblasts that show orderly maturation into osteocytes (within lacunae). There is intervening fibrous tissue (H&E, ×100).

dental structure. Tumour cells arranged in cords may (or may not) show typical palisading along the basement membrane with apical polarization of nuclei.[97,101] The tumour cells may, in some cases, enclose numerous cystic spaces containing loose matrix and capillary blood vessels or basophilic material.[93,99]

The tumour cells are often polygonal with moderate amounts of pale-staining eosinophilic cytoplasm that has well-defined margins (see Fig. 19.6); stellate, cuboidal and columnar cells have also been reported. Peripheral cells may be tall and columnar, or cuboidal with variable cytoplasmic vacuolation (and as above, may palisade).[93] In ameloblastomas with a follicular pattern, the central cells in islands may be loosely arranged and resemble the stellate reticulum[97,101]; however, that feature is often rare or absent in the horse. The central cells may also be spindle-shaped and closely packed, which is consistent with the spindle cell pattern seen (rarely) in human patients.[99] Nuclei of the basal cells are classically hyperchromatic (but this is not always seen) with apical polarization and a low mitotic rate.[93,99] Other nuclei are round, oval or fusiform with stippled chromatin and 1–3 central nucleoli.[104]

There may be areas of squamous metaplasia with keratin formation that can dominate in some neoplasms; the keratinocytes in these cases, classically, are large, 'glassy' and polygonal.[97,102] Squamous cell carcinoma is an important differential diagnosis for this type of ameloblastoma, with ameloblastoma cells showing more limited nuclear pleomorphism and less aggressive infiltration.[102] Areas of tumour cell necrosis may also be noted.

There is some confusion in the literature regarding neoplasms with features of ameloblastoma that contain hard tissue. By definition, ameloblastomas do not include odontogenic mesenchyme; there should not be production of dentin or cementum. Abnormal dentin was noted in one case that was diagnosed as a 'dentino-ameloblastoma'.[99] In another mass, there was multifocal deposition of matrix described as cementum, amongst dissecting cords and nests of the epithelial tumour cells.[101] Either cemental proliferation is a feature specific to equine ameloblastomas, or it was actually bone; cementum and osteoid can be difficult to differentiate based on their histological appearance; however, this author has also noted cementum (in addition to reactive bone; see Fig. 19.6). Cemental proliferation can be seen in various neoplastic and non-neoplastic conditions of the jaw in herbivores rather than just horses specifically: i.e. the presence of this matrix in such a tumour is not surprising.[101] Various authors have described areas of bone and osteoid formation in the supporting stroma, and some have diagnosed those neoplasms as 'ossifying ameloblastomas'.[93,97] It is possible that tumour cells in ameloblastomas of equines and some other species are able to induce mesenchymal progenitor/stem cells in adjacent tissue to differentiate into odontoblasts or osteoblasts.

Immunohistochemical labelling

The tumour cells are cytokeratin-positive.

Differential diagnoses

These are listed in Box 19.7.

Box 19.7 Differential diagnoses of ameloblastoma

- Squamous cell carcinoma
- Other odontogenic neoplasms
- Osteoma
- Ossifying fibroma
- Osteosarcoma

Osteosarcomas could have a very similar gross appearance, but are rare in the equine jaw.

Ameloblastic carcinoma

Cellular origin

The histogenesis of this (often intraosseous) type of neoplasm is controversial. Some authors have suggested that these carcinomas be subdivided into two forms[105]:

1. Ameloblastic carcinomas arising from ameloblastomas
2. Ameloblastic carcinomas with unknown origin (previously diagnosed as primary intraosseous carcinoma *de novo*).

The latter may arise from odontogenic epithelial remnants within the jaw bones.

Profile

Ameloblastic carcinomas have been reported in the right maxilla of an 8-year-old Hanoverian gelding (diagnosed as primary intraosseous carcinoma), and the left maxilla of a 30-year-old Quarter Horse mare, respectively.[103,106] In human patients, the mandible is the predilection site.

Biological behaviour

Metastasis was not ruled out in either of the reported equine cases, as post-mortem examinations were not performed and/or reported.[103]

Gross pathology

The right maxillary mass measured 12 cm in diameter in the premolar region, and extended into the buccal mucosa and palate, with bulging into the ventral nasal meatus where it was covered by the mucous membrane.[106] The mass was firm and grey-white on sectioned surfaces with areas of necrosis and haemorrhage.

Histopathology

Tumour cells in the right maxillary mass were arranged in cords and islands; peripheral cells were palisading and more central cells were loosely arranged and resembled the stellate reticulum cells of the enamel organ.[106] As there was only mild pleomorphism and the mitotic rate was low, diagnosis as (the equivalent of) an ameloblastic carcinoma rather than a central ameloblastoma is perhaps questionable.

Tumour cells in the left maxillary mass were densely packed in broad sheets and large islands, with slight peripheral palisading in addition to cord formation; these cells were supported by a fine fibrovascular stroma that was more abundant between cords. The pleomorphic tumour cells were round, oval or spindle-shaped with a moderate amount of deeply eosinophilic cytoplasm and large, oval and hyperchromatic nuclei containing indistinct nucleoli;

Box 19.8 Differential diagnoses for ameloblastic carcinoma

- Squamous cell carcinoma
- Other odontogenic neoplasms
- Osteoma
- Ossifying fibroma
- Osteosarcoma

centrally they were vacuolated, and as in the other case, resembled the stellate reticulum. There were up to nine mitotic figures per high power (×400) field.[103]

Immunohistochemical labelling

Ameloblastic carcinoma cells in one case showed positive cytoplasmic staining for vimentin, pancytokeratin (weak; type I and II cytokeratins) and AE1/AE3 (type I cytokeratins). They also stained positively for certain specific cytokeratins previously reported to be expressed by ameloblastomas, i.e. CK5/6 and CK14. There was negative staining for S100, melan-A and CD31.[103]

Differential diagnoses

These are listed in Box 19.8.

Neoplasms of odontogenic epithelium with odontogenic mesenchyme

Classification

Odontomas are defined as odontogenic neoplasms with both epithelial and mesenchymal elements.

Ameloblastic fibro-odontoma

Cellular origin

Ameloblastic fibro-odontomas are the most undifferentiated form of odontoma, containing epithelial tumour cells in addition to poorly-differentiated dentin and/or enamel matrix.[102] These neoplasms may potentially arise from the enamel organ, rests of Malassez, reduced enamel epithelium or the epithelial lining of odontogenic cysts.[107]

Profile

Ameloblastic fibro-odontomas have been reported in the maxilla or mandible of young horses and ponies (up to 1 year), including foals.[108–111] There have been occasional reports in older horses 11–14 years of age.[104] Some authors define them as strictly congenital neoplasms that most likely are only small at birth (2–3 cm diameter) and are not noted until they have grown and caused facial distortion.[111] The caudal maxilla is a common site.

Biological behaviour

Ameloblastic fibro-odontomas are slow-growing; however, the ameloblastic (epithelial) component is aggressive and invades bone. There may be recurrence if surgical excision is not complete; this excision must be performed with wide margins. Metastasis to regional lymph nodes, other tissues of the head and internal organs has not been reported in horses. In one foal, the neoplasm caused significant upper airway obstruction.[110]

Gross pathology

Ameloblastic fibro-odontomas are expansile and osteolytic masses associated with a tooth. One mandibular mass contained a retained molar tooth in the centre.[104] They may reach a very large size (e.g. 15–24 cm in diameter) and maxillary neoplasms may partially obliterate the overlying maxillary sinus; one such mass was associated with a large haematoma.[110] Ameloblastic fibro-odontomas are white, firm and well-circumscribed and obliterate normal bony architecture.[109] On sectioning, they may have the consistency of cancellous bone due to the presence of hard dental tissues and/or mineralization, and may be multinodular with associated cystic spaces (<1 cm) that are sometimes blood-filled.[104] There is frequently a central cystic region.

Associated changes can include tooth displacement, periosteal bone proliferation, ulceration of the overlying oral or sinonasal mucosa, deviation of nasal turbinates and the nasal septum and obstruction and distortion of nasal passages. There may be nasal and ocular discharge, and where maxillary sinuses are involved, they may be filled with fluid.

Although in human patients there can be palatine artery destruction resulting in profuse haemorrhage, this has not yet been seen in the horse.[111]

Histopathology

There is a soft tissue component resembling ameloblastoma (see above) composed of well-differentiated odontogenic epithelial cells that may have follicular and plexiform arrangements. The epithelial component is seen within a background of loose mesenchymal tissue, resembling dental pulp, which contains a loose network of spindle-shaped or stellate cells.[112] In some areas, there is deposition of matrix that may include cementum (see p. 328), and irregular masses of dentin (immature and/or calcified) *formed by odontoblasts* that are sometimes induced by adjacent ameloblastic production of enamel.[109] Dentin is osteoid-like but tends to be cell-poor.[102] Enamel is largely composed of mineral and is almost impossible to preserve through a complete decalcification process that results in the tissue being soft enough for paraffin wax sectioning; it is usually only observed in ground sections from plastic-embedded material.[113] The ameloblastic component is usually found at the periphery of the mass, while the hard tissue component is more central. Associated purulent inflammation may be noted.

Differential diagnoses

These are listed in Box 19.9.

Box 19.9 Differential diagnoses for ameloblastic fibro-odontomas

- Other odontogenic neoplasms
- Osteosarcoma
- Ossifying fibroma

Complex odontoma

See also page 435.

Cellular origin

Dental tissues in these tissues are disorganized and do not form tooth-like structures, but they are well-differentiated compared with those comprising ameloblastic fibro-odontomas (above). Some authors consider these lesions to be hamartomas rather than neoplasms.[91,102]

Profile

Complex odontomas are rare in any species. In horses, they are more frequently diagnosed in young adults (2–4 years of age), and occur more often in the maxilla than the mandible.[91,114,115]

Biological behaviour

Complex odontomas are benign, slow-growing and expansile masses that are locally destructive but do not recur following complete surgical excision.[115] Because these neoplasms grow by expansion rather than infiltration, the prognosis may in theory be better than for ameloblastomas.[92] There is no potential for metastasis.[102]

Gross pathology

Complex odontomas are smooth, expansile, well-demarcated, lobulated and located immediately adjacent to and encircling one or more teeth. Reported masses have measured 5–10 cm in diameter.[91,114,115] The consistency of these masses is similar to that of bone – very firm – although there may be areas of soft tissue.[91] On sectioned surfaces, jumbled, well-differentiated odontogenic matrices are noted, including white enamel, grey dentin and almost transparent enamel.[112] There may be displacement of associated normal teeth, and thinning of cortical bone.

Histopathology

Complex odontomas contain most tooth components, including cementum (eosinophilic material with numerous lacunae containing small oval cells, i.e. cementocytes; see p. 328), predentin (homogeneous and eosinophilic), dentin, enamel, ameloblasts, odontoblasts, stellate reticulum and dental pulp mesenchymal cells. The amounts of odontogenic epithelium in these neoplasms vary.[112] The enamel is often fully mineralized. Cementum formation on enamel matrix may be noted, which has not been reported in complex odontomas of simple-toothed animals due to their differing normal structure.[91] These components do not recapitulate normal tooth structure, although some structures that slightly resemble developing teeth have been reported.[114] Mitotic figures are rare.

Differential diagnoses

These are listed in Box 19.10.

Box 19.10 Differential diagnoses for complex odontoma

- Other odontogenic neoplasms

Compound odontoma

See also page 435.

Cellular origin

Compound odontomas have all of the features of tooth formation in an orderly pattern (as 'denticles'). Some authors consider these lesions to be hamartomas rather than neoplasms.[91,102]

Profile

Compound odontomas described to date have involved premolars and/or molars of the mandible or maxilla, in young horses (9–11 months of age).[116,117]

Biological behaviour

Compound odontomas are benign but locally destructive.[117] Recurrence has not been reported following aggressive and extensive surgical excision, but the latter can be very difficult.[116] There is no metastatic potential.[102]

Gross pathology

These expansile masses are well-demarcated, very firm swellings immediately adjacent to and encircling one or more teeth. The consistency of these masses is similar to that of bone, and they extend into the cortex. On sectioning, compound odontomas contain multiple, abnormally-shaped but tooth-like structures referred to as denticles.[112] Maxillary masses may extend into and occupy maxillary sinuses and nasal turbinates, displace the nasal septum, and displace and destroy developing normal teeth (see Fig. 28.6).[117]

Histopathology

Histologically, these neoplasms contain most normal tooth components. There is a high degree of morpho-differentiation with formation of denticles, resembling small deformed teeth. Usually there are multiple denticles with intervening foci of normal bone. Denticles have a core of primitive mesenchyme resembling dental pulp, surrounded in turn by disorganized odontogenic epithelium, dentin and primitive ameloblasts.[116]

Neoplasms composed primarily of odontogenic ectomesenchyme

Cementoma (true cementoma or benign cementoblastoma)

See also page 433.

Cellular origin

These lesions are of cementoblastic origin.

Profile

These are very rare neoplasms that have only recently been described in horses.[118,119] There are no known age or breed predilections, and the cause is uncertain. In one report of three such lesions, the horses were aged 2, 17 and 18.7 years, respectively.[118]

Oncogenesis

In humans, cementomas are thought to either have a genetic basis or be a response to periodontal ligament damage/inflammation. In some cases in animals, this may also be a reactive hyperplasia (in association with periodontal inflammation, dental displacement or dental loss), but truly neoplastic lesions can also occur.[102]

Biological behaviour

Cementomas are benign and slow-growing. They have been reported as incidental findings in some horses[118]; however, as cementomas have been associated with malocclusion and local pain, at least some incidental lesions might actually represent hypercementosis (see below). Recurrence has not been reported following excision of cementomas involving the sinuses.[120]

Gross pathology

Cementomas are well-circumscribed, firm, rounded, grey-white, mineralized masses surrounding the roots of normal teeth that measure 2–7 cm in diameter (see Fig. 28.5). The demarcation between cementomas and normal tissue can be seen on sectioned surfaces. In one report of three cases, all presented with multiple masses, including involvement of upper and lower jaws; it was also found that the teeth affected included incisors and premolars, with incisors being most commonly involved.[118]

Histopathology

Normal cementum contains vascular channels and lacunae of variable size within which cementoblasts are located. It is difficult to differentiate from osteoid by histological examination; however, typically, there is either a mosaic pattern of reversal (basophilic and scalloped) lines that is either disorganized or lamellar (see Fig. 19.6).[102] It is helpful to examine this matrix under polarized light, as the pattern of collagen fibres differs from that which would be expected in bone; it forms swirling bundles and whorls rather than the hatched pattern of woven bone.

In cementomas, there is deposition of a well-differentiated, irregularly mineralized cementum-like matrix with abundant collagen fibres, which surrounds and fuses with the tooth root. Within this matrix, clusters of neoplastic cementoblasts are noted within abnormal lacunae. The tumour cells have small to moderate amounts of eosinophilic cytoplasm and medium-sized oval nuclei, and do not show significant pleomorphism or mitotic activity. There is local destruction of the lamina dura (the layer of bone immediately lining the tooth socket). There may also be deformation of the surrounding bone.[118] In one case, inflammation at the periphery was noted, including giant cells that may have been histiocytic or cementoclasts.[118]

Differential diagnoses

These are listed in Box 19.11.

Hypercementosis is characterized by accumulation of excessive, newly formed cementum that is regularly mineralized and does not destroy the lamina dura.[118] The excess matrix is contiguous with the normal radicular cementum and is deposited in radial layers. Cemento-osseous dysplasia is a proliferative periapical tooth lesion of unknown aetiology; such lesions are poorly-demarcated and composed of collagenous tissue containing variable amounts of cementum and/or bone. The cementum is arranged in spherules, and the bone (when present) is trabeculae and may be woven and/or lamellar (Fig. 19.7).

Box 19.11 Differential diagnoses for cementomas

Neoplastic
- Ossifying fibroma
- Osteoma
- Other odontogenic neoplasms

Non-neoplastic
- Hypercementosis
- Cemento-osseous dysplasia
- Fibrous dysplasia (p. 321).

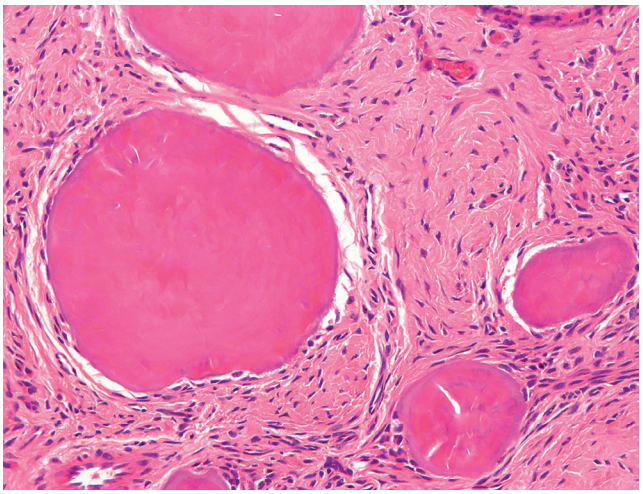


Figure 19.7 Cemento-osseous dysplasia. Spherules of cementum-like material have formed within fibrous tissue (H&E, ×200).

Cementifying fibroma

Cellular origin

Cementifying fibromas arise from mesenchymal cells (unspecified). These neoplasms are analogous to ossifying fibromas (pp. 312–313).

Profile

These are rare neoplasms seen in horses and dogs.[102]

Biological behaviour

Cementifying fibromas are locally aggressive and require wide excision.

Histopathology

The histological appearance is similar to that of ossifying fibroma (p. 313), but the (non-fibrous) matrix component has an appearance more consistent with cementum than osteoid, e.g. a mosaic or lamellar pattern of scalloped (reversal) lines.[102]

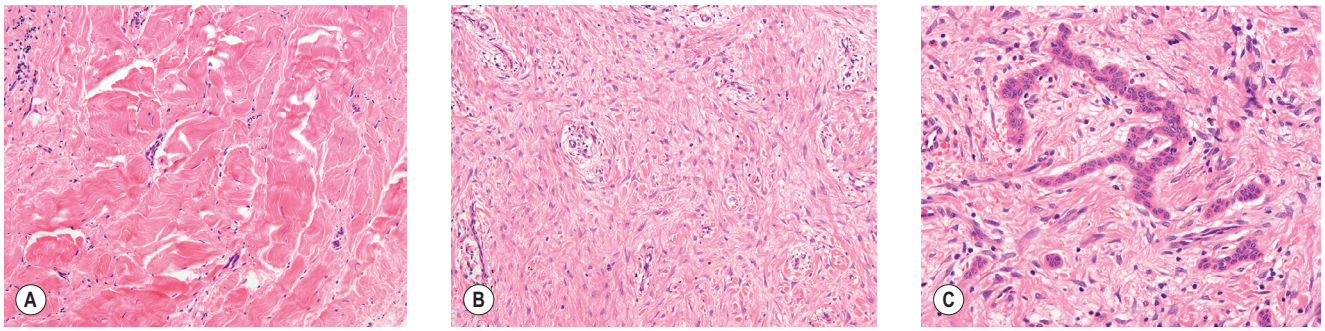


Figure 19.8 Fibromatous epulis of periodontal ligament origin in a 4-year-old gelding. (A) Histological appearance. Bundles of crimped (wavy) ligament-like tissue (H&E, ×100). **(B)** Regularly-spaced, stellate fibroblastic cells within a collagenous matrix (H&E, ×100). **(C)** Ribbon-like cords of odontogenic-type epithelium (H&E, ×200).

Neoplasms derived from the tissues of the periodontal ligament

Fibromatous epulis of periodontal ligament origin

Cellular origin

These lesions appear to arise from the periodontal ligament. Some authors consider fibrous epulides of this type to be hyperplastic rather than neoplastic lesions.[102]

Profile

While common and well-known in dogs, these neoplasms are rare in horses.

Biological behaviour

Fibromatous epulides of periodontal ligament origin are benign and non-invasive, and should be cured by *complete* surgical excision.

Gross pathology

Fibromatous epulides of periodontal ligament origin arise in the gingival soft tissue adjacent to a tooth and are usually covered by epithelium, although this may become ulcerated with secondary inflammation (Fig. 28.20). They may measure up to several centimetres in diameter and, when large, may interfere with mastication.[112]

Histopathology

The fine collagenous stroma is similar to that of the periodontal ligament (not other, coarser gingival connective tissue) and shows a crimped pattern under polarized light; crimp is a planar zig-zag waveform followed by collagen fibrils in connective tissues under tension, including tendons and ligaments (see Fig. 19.8). Under polarized light, the crimp appears as a black-and-white banding pattern. Within this matrix are regularly positioned stellate cells and regularly positioned, dilated blood vessels that often appear to be empty (see Fig. 19.8).[112] Contiguity between the neoplasm and the adjacent periodontal ligament is unlikely to be visualized in biopsy specimens. Sparse cords of odontogenic-type epithelium (thought to arise from rests of Malassez and/or surface epithelium) may be noted (see Fig. 19.8), and deposition of hard matrices. Bone-like tissue in these lesions may contain Sharpey's fibres extending into the surrounding collagenous tissue, this being typical of both normal cementum and alveolar bone.[102]

Box 19.12 Differential diagnoses of fibromatous epulis of periodontal ligament origin

Neoplastic
- Ameloblastoma or other odontogenic neoplasms

Non-neoplastic
- Gingival fibrous hyperplasia

Differential diagnoses

These are listed in Box 19.12.

Non-neoplastic (cystic) lesions of the jaw

Temporal teratoma

See also page 436.

Classification

Temporal teratomas have been classified as congenital malformations and have been variably referred to as dentigerous cysts, heterotopic polyodontia, ear fistulas or temporal cysts.[102,111,121–125]

Biological behaviour

These lesions are usually extracranial and unilateral, occurring next to the right or left ear (with equal frequency).[111] Temporal teratomas may also occur at other sites on or in the head, including the frontal bones, petrous portion of the temporal bone and paranasal sinuses.[111,121,123,125] Although congenital, they have been reported in adult horses up to 10 years of age, as they are not necessarily detected immediately; however, most do enlarge during the first few weeks of life and the majority are diagnosed in horses <2 years of age.[111,125]

Dental elements of temporal teratomas are proposed to arise from tooth germ displaced towards the ear with the first branchial cleft, with cysts developing from ectodermal nests following failure of closure of the first branchial arch.[122] Not all temporal teratomas contain teeth, these being referred to by one author as 'dermoid type' rather than 'dentigerous type'; however, in a review of 20 cases

(1900–1922) all were dentigerous, this being suggested to be associated with draught horse parentage.[125] Complete surgical excision of these lesions should be curative, but removal of attached teeth can be challenging.

Temporal teratomas usually present shortly after birth as soft fluctuant swellings antero-ventral to the external auditory meatus. They are typically firmly attached, either to the temporal bone or the conchal cartilage.[125] Each mass is connected to the skin surface by a fistulous tract that opens on the rostral surface of the adjacent pinna or in skin close to the meatus (Fig. 28.7). Atypical lesions without a draining tract have also been reported. Temporal teratomas may be secondarily infected, with discharge of mucoid or purulent material to the surface; in some cases, matting of the hair in this area by this discharge is the only external sign.[122] It should be noted that not all of these lesions contain teeth; small teeth will not necessarily be seen radiographically. However, many temporal teratomas contain one or more dental elements that vary in extent of development, from fragments of enamel to molar-like structures that may be enclosed in rudimentary alveolar processes.[111]

Histopathology

Histologically, temporal teratomas have been described as cystic structures lined by stratified squamous epithelium with hair follicles and adnexal glands; there may also be associated salivary gland tissue.[111,125] The contents can include calcified granular material, layers of keratin, cell rests of dental laminae, reduced enamel epithelium, malformed enamel organs or Malassez rests; the teeth when present are usually firmly attached to underlying bone, but may also be loosely enclosed.[111]

References

1. Bastianello S. A survey on neoplasia in domestic species over a 40-year period from 1935 to 1974 in the Republic of South Africa. IV. Tumours occurring in Equidae. Onderstepoort J Vet Res 1983; 50:91–96.
2. Schooley EK, Hendrickson DA. Musculoskeletal system neoplasia. Vet Clin North Am Equine Pract 1998; 14:535–542.
3. Valentine BA. Neoplasia. In: Bertone JJ, ed. Equine geriatric medicine and surgery. St Louis: Saunders Elsevier; 2006: 147–167.
4. Campanacci M, ed. Osteofibrous dysplasia of the long bones. In: Bone and soft tissue tumours. Berlin: Springer; 1990: 419–431.
5. Morse CC, Saik JE, Richardson DW, et al. Equine juvenile mandibular ossifying fibroma. Vet Pathol 1988; 25:415–421.
6. Cilliers I, Williams J, Carstens A, et al. Three cases of osteoma and an osseous fibroma of the paranasal sinuses of horses in South Africa. J S Afr Vet Assoc 2008; 79:185–193.
7. Orsini JA, Baird DK, Ruggles AJ. Radiotherapy of a recurrent ossifying fibroma in the paranasal sinuses of a horse. J Am Vet Med Assoc 2004; 224:1483–1486.
8. Pieber K, Kuebber-Heiss A, Kuebber P, et al. Fibro-osseous tumour of the fourth metacarpal bone in a horse: clinical, radiographic and long-term post operative findings. Equine Vet Educ 2010; 22:62–65.
9. Robbins SC, Arighi M, Ottewell G. The use of megavoltage radiation to treat juvenile mandibular ossifying fibroma in a horse. Can Vet J 1996; 37: 683–684.
10. Thompson KG, Pool RR. Tumours of bones. In: Meuten DJ, ed. Tumours in domestic animals, 4th edn. Ames: Iowa State Press; 2002: 245–317.
11. Slayter MV, Boosinger TR, Pool RR, et al. Histological classification of bone and joint tumours of domestic animals. Washington, DC: Armed Forces Institute of Pathology, CL Davis DVM Foundation, and The World Health Organization Collaborating Centre for Comparative Oncology; 1994.
12. Jacobson SA. Comparative pathology of the tumors of bone. Springfield: Thomas; 1971: 164–211.
13. Puff C, Ohnesorge B, Wagels R, et al. An unusual mucinous osteoma with features of an ossifying fibroma in the nasal cavity of a horse. J Comp Pathol 2006; 135:52–55.
14. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 2: A contribution of 28 case reports. Vet J 1999; 157:279–294.
15. Pool RR. Tumours of bone and cartilage. In: Moulton MS, ed. Tumours of domestic animals, 3rd. edn. Berkeley: University of California Press; 1990: 157–230.
16. Scotty NC, Ford M, Williams FR, et al. Exophthalmia associated with paranasal sinus osteoma in a Quarterhorse mare. J Vet Diagn Invest 2004; 16:155–160.
17. Misdorp W, van der Heul RO. XXI. Tumours of bones and joints. Bull World Health Organ 1976; 53:265–282.
18. Boulton CH. Equine nasal cavity and paranasal sinus disease: a review of 85 cases. J Equine Vet Sci 1985; 5:268–275.
19. Schumacher J, Smith BL, Morgan SJ. Osteoma of paranasal sinuses of a horse. J Am Vet Med Assoc 1988; 192:1449–1450.
20. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 1: Review of the literature and tumour classification. Vet J 1999; 157: 261–278.
21. Steinman A, Sutton GA, Lichawski D, et al. Osteoma of paranasal sinuses in a horse with inspiratory dyspnoea. Aust Vet J 2002; 80:140–142.
22. Ragle CA, de Mira MC, Pearson LK, et al. Pneumocephalus secondary to removal of an osteoma from the paranasal sinuses of a horse. J Am Vet Med Assoc 2009; 235:184–188.
23. Rabuffo TS, Richardson DW, Baird DK. What is your diagnosis? An osseous mass associated with the lateral aspect of the tuber calcaneus, with some degree of soft tissue swelling. J Am Vet Med Assoc 2002; 221:635–636.
24. Collins JA. Ossifying fibroma/osteoma in the proximal tibia of a mature gelding. Vet Rec 1998; 143:367–368.
25. Kold SE, Østblom LC. Headshaking caused by a maxillary osteoma in a horse. Equine Vet J 1982; 14:167–169.
26. Chandra AMS, Buergelt CD, Ethell MT. Odontogenic myxoma of the mandible in a filly. J Vet Diagn Invest 1999; 11:274–277.
27. Lee HA, Grant BD, Gallina AM. Solitary osteochondroma in a horse: a case report. J Equine Med Surg 1979; 3:113–114.
28. Held JP, Patton CS, Shires M. Solitary osteochondroma of the radius in three horses. J Am Vet Med Assoc 1988; 193:563–564.
29. Squire KR, Adams SB, Widmer WR, et al. Arthroscopic removal of a palmar radial osteochondroma causing carpal canal syndrome in a horse. J Am Vet Med Assoc 1992; 201:1216–1218.
30. Southwood LL, Stashak TS, Fehr JE, et al. Lateral approach for endoscopic removal of solitary osteochondromas. J Am Vet Med Assoc 1997; 210: 1166–1168.
31. Adair HS, Duncan RB, Toal RL. Solitary osteochondroma of the nasal bone in a horse. Cornell Vet 1994; 84:25–31.
32. Secombe CJ, Anderson BH. Diagnosis and treatment of an osteochondroma of the distal tibia in a 3-year-old horse. Aust Vet J 2000; 78:16–18.
33. Pasolini MP, Greco M, Trapani F, et al. Nasal bone osteochondroma in a horse. Vet Rec 2009; 164:534–535.
34. Chan CC-H, Munroe GA, Callanan JJ. Congenital solitary osteochondroma affecting the tarsus in a filly foal. Equine Vet Educ 1996; 8:153–156.
35. Shupe JL, Leone NC, Olson AE, et al. Hereditary multiple exostoses: clinicopathologic features of a comparative study in horses and man. Am J Vet Res 1979; 40:751–757.
36. Wilson RG, Auer DE, Kelly WR. Multiple cartilaginous exostoses in a horse. Equine Vet J 1985; 17:462–465.
37. Leone NC, Shupe JL, Gardner EJ, et al. Hereditary multiple exostosis. A comparative human-equine-epidemiologic study. J Hered 1987; 78: 171–177.
38. Hanselka DV, Roberts RE, Thompson RB. Equine multiple cartilaginous exostoses. Vet Med Sm Anim Clin 1974; 69:979–986.
39. Laing AJ, Dillon JP, Suiluman B, et al. Osteochondroma development subsequent to traumatic hip dislocation. Orthopaedics 2008; 31:84.
40. D'Ambrosia R, Ferguson AB. The formation of osteochondroma by epiphyseal cartilage transplantation. Clin Orthop Relat Res 1968; 61: 103–115.
41. Milgram JW. The origin of osteochondromas and enchondromas: a histopathologic study. Clin Orthop Relat Res 1983; 174:264–284.
42. Cillan-Garcia E, Kearns LJ, Hetzel U, et al. Osteosarcoma of the middle phalanx in a horse. Equine Vet Educ 2010; 22:535–539.
43. Wan PY, Purcell KL, Blackford JT, et al. Osteogenic sarcoma of the femur in a mare. J Equine Vet Sci 1994; 14:430–432.
44. Jenner F, Solano M, Gliatto J, et al. Osteosarcoma of the tarsus in a horse. Equine Vet J 2003; 35:214–216.
45. Bush JM, Frederickson RL, Ehrhart EJ. Equine osteosarcoma: A series of 8 cases. Vet Pathol 2007; 44:247–249.
46. Springer T, Elce YA, Green E. Treatment of an osteoblastic osteosarcoma in an aged gelding. Equine Vet Educ 2010; 22:159–162.
47. Baker JR, Leyland A. Histological survey of tumours of the horse with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
48. Priester WA, MacKay FW. The occurrence of tumours in domestic animals. Natl Cancer Inst Monogr 1980; 54:1–210.
49. Zaruby JF, Williams JW, Lovering SL. Periosteal osteosarcoma of the scapula in a horse. Can Vet J 1993; 34:742–744.
50. Dixon PM, Tremaine WH, Pickles K, et al. Equine dental disease. Part 3: a long-term study of 400 cases: disorders of wear, traumatic damage and idiopathic fractures, tumours and miscellaneous disorders of the cheek teeth. Equine Vet J 2000; 32:9–18.
51. Gutierrez-Nibeyro SD, Sullins KE, Powers BE. Treatment of appendicular osteosarcoma in a horse. Equine Vet Educ 2010; 22:540–544.
52. Kilcoyne I, Wilson M, Terzo E, et al. Osteosarcoma of the proximal radius in a donkey. Equine Vet Educ 2010; 22:125–129.
53. Livesey MA, Wilkie IW. Focal and multifocal osteosarcoma in two foals. Equine Vet J 1986; 18:407–410.
54. Goedegebuure SA, Firth EC, Dik KJ. Osteoblastoma in the radius of a pony. Vet Pathol 1983; 20:650–652.
55. Fechner RE, Mills SE. Tumors of the bone and joints. Atlas of tumour pathology. Washington, DC: Armed Forces Institute of Pathology; 1992: 33–36.

56. Richardson DW, Acland HM. Multilobular osteoma (chondroma rodens) in a horse. J Am Vet Med Assoc 1983; 182:289–291.
57. May SA, Baker JR. A giant cell tumour (osteoclastoma) of the tibia in a horse. Equine Vet J 1985; 17:477–479.
58. Madewell BR, Priester WA, Gillette EL, et al. Neoplasms of the nasal passages and paranasal sinuses in domesticated animals as reported by 13 veterinary colleges. Am J Vet Res 1976; 37:851–856.
59. Jackson C. The incidence and pathology of tumours of domesticated animals in South Africa. Onderstepoort J Vet Sci Anim Ind 1936; 6:1–460.
60. Trotter GW, Aanes WA, Synder SP. Laryngeal chondroma in a horse. J Am Vet Med Assoc 1981; 178:829–830.
61. Sullivan DJ. Cartilaginous tumours (chondroma and chondrosarcoma) in animals. Am J Vet Res 1960; 21:531–535.
62. Riddle WE, Wheat JD. Chondrosarcoma in a horse. J Am Vet Med Assoc 1971; 158:1674–1677.
63. Bertone AL, Powers BE, Turner AS. Chondrosarcoma in the radius of a horse. J Am Vet Med Assoc 1984; 185:534–537.
64. Wilson GJ, Anthony ND. Chondrosarcoma of the tongue of a horse. Aust Vet J 2007; 85:163–165.
65. Brodey RS, Misdorp W, Riser WH, et al. Canine skeletal chondrosarcoma: a clinicopathologic study of 35 cases. J Am Vet Med Assoc 1974; 165: 68–78.
66. Livesey MA, Keane DP, Sarmiento J. Epistaxis in a Standardbred weanling caused by fibrous dysplasia. Equine Vet J 1984; 16:144–146.
67. Jones NY, Patterson-Kane JC. Fibrous dysplasia in the accessory carpal bone of a horse. Equine Vet J 2004; 36:93–95.
68. Fraser B, Jones E, Else RW. Intraosseous epidermoid cyst of the third phalanx in a thoroughbred gelding. Vet Rec 2006; 159:360–362.
69. Camus AC, Burba DJ, Valdes MA, et al. Intraosseous epidermoid cyst in a horse. J Am Vet Med Assoc 1996; 209:632–633.
70. Headley SA, Kummala E, Saarinen H, et al. Diagnostic exercise: intraosseous epidermoid cysts in the third phalanx of a dressage mare. Vet Pathol 2009; 46:355–357.
71. Ordidge R. Pathological fracture of the radius secondary to an aneurysmal bone cyst in a horse. Equine Vet Educ 2001; 13:239–242.
72. Purdy CM. Mandibular aneurysmal bone cyst in a horse. Equine Pract 1985; 7:22–24.
73. Steiner JV, Rendano VT. Aneurysmal bone cyst in the horse. Cornell Vet 1982; 72:57–63.
74. Momiyama N, Tagami M, Tsunoda N, et al. Aneurysmal bone cyst in a colt. Equine Vet Educ 1999; 11:243–246.
75. Stenberg T, Dowling BA, Dart AJ. Mandibular bone cysts in two horses. Aust Vet J 2004; 82:417–418.
76. Thomas HL, Livesey MA, Caswell JL. Multiple aneurysmal bone cysts in a foal. Can Vet J 1997; 38:570–573.
77. Lamb CR, Schelling SH. Congenital aneurysmal bone cyst in the mandible of a foal. Equine Vet J 1989; 21:130–132.
78. Blackwell JG, Griffith AD, Crosky WJ. Surgical correction of an alveolar mandibular bone cyst. Equine Pract 1985; 7:70–73.
79. Jackman BR, Baxter GM. Treatment of a mandibular bone cyst by use of a corticocancellous bone graft in a horse. J Am Vet Med Assoc 1992; 201:892–894.
80. Baxter GM, Stashak TS. Lameness in the extremities. Adams and Stashak's lameness in horses, 6th edn. Chichester: Wiley-Blackwell; 2011: 475–832.
81. Garcia-López JM, Kirker-Head CA. Occult subchondral osseous cyst-like lesions of the equine tarsocrural joint. Vet Surg 2004; 33:557–564.
82. McIlwraith CW. Principles of musculoskeletal disease. Adams and Stashak's lameness in horses, 6th edn. Chichester: Wiley-Blackwell; 2011: 871–955.
83. Rothwell TL, Wood AK, Rayson CH, et al. An unusual congenital osseous tumour in a foal. Aust Vet J 1987; 64:322–323.
84. Kirk MD. Radiographic and histologic appearance of synovial osteochondromatosis of the femorotibial bursae in a horse: a case history report. Vet Radiol 1982; 23:167–170.
85. Dodd DC, Raker CW. Tumoral calcinosis (calcinosis circumscripta) in the horse. J Am Vet Med Assoc 1970; 157:968–972.
86. Hutchins DR. Tumoral calcinosis in the horse. Aust Vet J 1972; 48:200–202.
87. Goulden BE, O'Callaghan MW. Tumoral calcinosis in the horse. N Z Vet J 1980; 28:217–219.
88. Vos NJ. Actinomycosis of the mandible, mimicking a malignancy in a horse. Can Vet J 2007; 48:1261–1263.
89. Boyde A. Equine dental tissues: a trilogy of enamel, dentine and cementum. Equine Vet J 1997; 29:171–172.
90. Kilic S, Dixon PM, Kempson SA. A light microscopic and ultrastructural examination of calcified dental tissues of horses: 1. The occlusal surface and enamel thickness. Equine Vet J 1997; 29:190–197.
91. Dubielzig RR, Beck KA, Levine S, et al. Complex odontoma in a stallion. Vet Pathol 1986; 23:633–635.
92. Hance SR, Bertone AL. Neoplasia. Vet Clin North Am Equine Pract 1993; 9:213–234.
93. Hanselka DV, Roberts RE, Thompson RB. Adamantinoma of the equine mandible. Vet Med Small Anim Clin 1974; 69:157–160.
94. Vaughan JT, Bartels JE. Equine mandibular adamantinoma. J Am Vet Med Assoc 1968; 153:454–457.
95. Hackett ES, Baxter GM. Odontogenic tumours in the horse. Equine Vet Educ 2008; 20:652–654.
96. Dixon PM, Tremaine WH, Pickles K, et al. Equine dental disease part 1: a long-term study of 400 cases: disorders of incisor, canine and first premolar teeth. Equine Vet J 2000; 31:369–377.
97. Summers PM, Wells KE, Adkins KF. Ossifying ameloblastoma in a horse. Aust Vet J 1979; 55:498–500.
98. Pirie RS, Dixon PM. Mandibular tumours in the horse: a review of the literature and 7 case reports. Equine Vet Educ 1993; 5:287–294.
99. Gardner DG. Ameloblastomas in the horse: a critical review and report of an additional example. J Oral Pathol Med 1994; 23:41–44.
100. Rosol TJ, Nagode LA, Robertson JT, et al. Humoral hypercalcaemia of malignancy associated with ameloblastoma in a horse. J Am Vet Med Assoc 1994; 204:1930–1933.
101. Kutzler MA, Feleciano J, Valentine BA. Mandibular ameloblastoma in a mare. Equine Vet Educ 2007; 19:471–475.
102. Head KW, Cullen JM, Dubielzig RR, et al. Histological classification of the tumours of the alimentary system of domestic animals. Washington, DC: Armed Forces Institute of Pathology, CL Davis DVM Foundation, and The World Health Organization Collaborating Centre for Comparative Oncology; 2003.
103. De Cock HEV, Labelle P, Magdesian KG. Ameloblastic carcinoma in a horse. J Comp Pathol 2003; 128:210–215.
104. Knowles S, Blas-Machado U, Butler AM, et al. Ameloblastic fibro-odontoma associated with a retained molar in an Oldenberg mare. J Vet Diagn Invest 2010; 22:987–990.
105. Kruse ALD, Zwahlen RA, Grätz KW. New classification of maxillary ameloblastic carcinoma based on an evidence-based literature review over the last 60 years. Head Neck Oncol 2009; 1:31.
106. Weber A, Ligthelm AJ, Verstraete FJM. Primary intra-osseous carcinoma of the maxilla in a horse. J Comp Pathol 1991; 104:443–448.
107. Regazi JA, Sciubba JJ, Jordan RCK. Odontogenic tumours. Oral pathology: clinical pathologic correlations, 4th edn. Philadelphia: WB Saunders; 2003: 286–288.
108. Peter CP, Myers VS, Ramsey FK. Ameloblastic odontoma in a pony. Am J Vet Res 1968; 29:1495–1498.
109. Lingard DR, Crawford TB. Congenital ameloblastic odontoma in a foal. Am J Vet Res 1970; 31:801–804.
110. Roberts MC, Groenendyk S, Kelly WR. Ameloblastic odontoma in a foal. Equine Vet J 1978; 10:91–93.
111. Gaughan EM, DeBowes RM. Congenital diseases of the equine head. Vet Clin North Am Equine Pract 1993; 9:93–110.
112. Head KW, Else RW, Dubielzig RR. Tumours of the alimentary tract. In: Meuten DJ, ed. Tumours in domestic animals, 4th ed. Ames: Iowa State Press; 2002: 401–481.
113. Bancroft JD, Gamble M. Theory and practice of histological techniques, 6th edn. Philadelphia: Churchill Livingstone, Elsevier; 2007: 359.
114. Dillehay DL, Schoeb TR. Complex odontoma in a horse. Vet Pathol 1986; 23:341–342.
115. Snyder C, Dubielzig RR, Gengler W, et al. Surgical treatment of a rostral mandibular complex odontoma in a 3-year-old horse. Equine Vet Educ 2008; 20:647–651.
116. Brounts SH, Hawkins JF, Lescun TB, et al. Surgical management of compound odontoma in two horses. J Am Vet Med Assoc 2004; 225: 1423–1427.
117. Rubio-Martinez LM, Nykamp S, Trout D. What is your diagnosis? A large heterogeneous mass containing small enamel density circular opacities with central radiolucencies is evident within the right maxillary sinus. J Am Vet Med Assoc 2011; 238:695–696.
118. Kreutzer R, Wohlsein P, Staszyk C, et al. Dental benign cementomas in three horses. Vet Pathol 2007; 44:533–536.
119. Levine DG, Orsini JA, Foster DL, et al. What is your diagnosis? Benign true cementoma (benign cementoblastoma). J Am Vet Med Assoc 2008; 223:1063–1064.
120. Dixon PM, Parkin TD, Collins N, et al. Equine paranasal sinus disease: a long-term study of 200 cases (1997–2009): treatments and long-term results of treatments. Equine Vet J 2012; 44:272–276.
121. Lindsay WA, Beck KD. Temporal teratoma in a horse. Comp Cont Ed Pract Vet 1986; 8:S168–S171.
122. Fessler JF. Heterotopic polyodontia in horses: nine cases (1969–1986). J Am Vet Med Assoc 1988; 192:535–538.
123. Gardner DG. Dentigerous cysts in animals. Oral Surg Oral Med Oral Pathol 1993; 75:348–352.
124. Marien T, Peremans K, Adriaenssen F. Temporal teratomas in two horses. Vlaams Diergen Tijds 1998; 67:181–182.
125. Mason BJE. Temporal teratomata in the horse. Vet Rec 1974; 95:226–228.

20 Vascular neoplasms

Neoplastic vascular masses
Haemangioma (vascular hamartoma, vascular naevus) 332
Haemangiosarcoma 334
Lymphangioma 337
Lymphangiosarcoma 338
Angiosarcoma 339

Non-neoplastic vascular masses
Vascular hamartoma 340
Haemangiomatosis 340
Intravascular papillary endothelial hyperplasia 340

NEOPLASTIC VASCULAR MASSES

Neoplasms derived from the vascular endothelium in human patients are divided into three groups, although it is considered likely that they form a spectrum, with some lesions that are not easily placed into a certain category[1]:

- *Haemangioma* – benign
- *Haemangioendothelioma* – intermediate in appearance and biological behaviour, with local recurrence and some metastatic potential
- *Angiosarcoma* – highly malignant.

Classification of equine vascular neoplasms has been confusing, with variation between authors in the diagnostic terminology used. This classification is likely to develop further in complexity with recent descriptions of histological variants including epithelioid neoplasms; however, it cannot be presumed that ultimately there will be exact matching to the above system. In the descriptions below, the term 'haemangioendothelioma' is not used, as vascular neoplasms with intermediate features in animals have not been found to show all of the diagnostic features of this category in human patients. It has been suggested that intermediate-type neoplasms of blood vessel endothelial origin in domestic animals be diagnosed as 'low-grade haemangiosarcoma'.[1]

Neoplasms of vascular origin are rare in horses and mules. They are most frequently diagnosed in the skin, where their prevalence has been estimated at approximately 0.25%.[2–5]

Haemangioma (vascular hamartoma, vascular naevus)

See also page 512.

Cellular origin

Haemangiomas have been variably defined as either hamartomas or benign neoplasms derived from blood vessel endothelial cells.[6] By definition, a hamartoma is a mass of disordered mature tissues indigenous to that site, that is typically present at birth and grows at a rate coordinated with that of the surrounding tissue.

Profile

Vascular neoplasms in younger horses are usually benign. In a study of 21 cutaneous vascular tumours, 18 were benign; 12 were diagnosed in horses ≤1 year of age and six of those were congenital (see Fig. 30.2).[5,7] One congenital lesion was documented to grow proportionately with body growth for 3.5 months, i.e. it could have been diagnosed as a hamartoma.[5] However, many such lesions do show autonomous growth typical of a neoplastic process. Other names applied to these tumours in young horses include lobular capillary haemangioma and vascular naevus.[8]

In young horses (≤18 months of age), most cutaneous haemangiomas occur on the extremities.[6,8–10] Less common sites of origin of haemangioma (or vascular hamartoma) have included the subcutis, eye (eyelid, conjunctiva, limbus, cornea, canthus), pleura, peritoneum and ovary, guttural pouch, colon, rectum, male external genitalia, and synovium of the deep digital flexor tendon sheath.[11–19] There have been a small number of reports of hamartomas on the limbs of young horses (1–5 years), involving subcutaneous and deeper tissues of the dorsal carpus or dorsal metatarsus.[20,21]

Oncogenesis

In the skin and eye, exposure to ultraviolet radiation may play a role in horses, as suggested for other domestic animal species.[17,22]

Biological behaviour

Haemangiomas are often small and may gradually enlarge. Multiple haemangiomas may occur in a small number of cases.[5] These benign neoplasms should not recur following complete surgical excision, where that is possible.[4] Very large lesions in young horses may not be operable, necessitating euthanasia (see Fig. 30.2).[22] A haemangioma

reported in a 1-year-old horse recurred twice following excision and cryotherapy.[5]

Gross pathology

Haemangiomas are, classically, well-circumscribed, expansile, nodular, fluctuant or firm, blue to red-black masses that vary in size but are often small[22]; one conjunctivals mass was pedunculated.[13] In young horses, haemangiomas in the dermis and subcutis are variably-sized, tan to pink fleshy nodules or papillary masses separated by normal tissue; from the surface the epidermis has a finely nodular texture or wart-like appearance, and it may be thickened, alopecic and/or ulcerated (Fig. 20.1; see also Fig. 30.1).[8,9] Blood may ooze from sectioned surfaces when pressure is applied.[6] Haemangioma on the limbs may extend between muscle heads and around lymph nodes, nerves and blood vessels.[8]



Figure 20.1 Haemangioma/hamartoma on the distal limb of a young horse. A small mass in the pastern region, with a nodular surface. *(Figure courtesy of Dr Gil Riley, Pool House Equine Clinic, Lichfield, Staffordshire.)*

Histopathology

Classical haemangiomas are unencapsulated and composed of well-differentiated endothelial cells that line closed, sometimes tortuous vascular channels of varying sizes. The vascular channels contain erythrocytes, and often also thrombi; they may be defined as capillary or cavernous based on their sizes. Dermal neoplasms may incorporate adnexal structures.[22] There may be necrotic areas, and the connective tissue septa between vascular channels may contain inflammatory cells, including mast cells, haemosiderophages and lymphocytes.

Haemangiomas in young horses tend to have a different appearance and are thought to be analogous to human infantile haemangiomas: nodular aggregates of vascular channels that vary in size occupy the dermis and extend into the superficial papillary dermis and deeper subcutis (Fig. 20.2).[6,8] These vascular nodules separate pre-existing adnexal structures and stroma, which may be oedematous.[6] The vascular component is often comprised of arrays of arteries, veins and capillaries of varying compactness, with substantial numbers of supporting pericytes and reticulin fibres.[9] There may be thin-walled, slit-like spaces towards margins of some nodules.[9] In one report, the neoplasms had a similar histological appearance, but they did not contain mixtures of arterial, venous and capillary blood vessels. Based on morphology of the vascular spaces, they were classified as capillary, cavernous or mixed (see Fig. 20.2).[5] Larger vessels with muscular walls are noted both between nodules and in peripheral locations within them. In all cases, there may be papillary hyperplasia of the overlying epidermis and secondary ulceration is frequent.[5,16]

Subcutaneous 'hamartoma' of the limbs has been described as being composed of large amounts of myxomatous or fibrous connective tissue containing cavernous vascular spaces, some of which have muscular walls.[20,21]

The epithelioid variant (dermal) of haemangioma has also been described, on the neck and lateral metatarsus of a 13-year-old Morgan gelding and a 4-year-old Thoroughbred gelding, respectively.[1] This diagnosis is challenging, as the vascular channels are not as obvious and the tumour cells have an epithelioid morphology suggestive of other types of neoplasm. Epithelioid haemangioma variants are multilobular to coalescing, with small vascular channels that

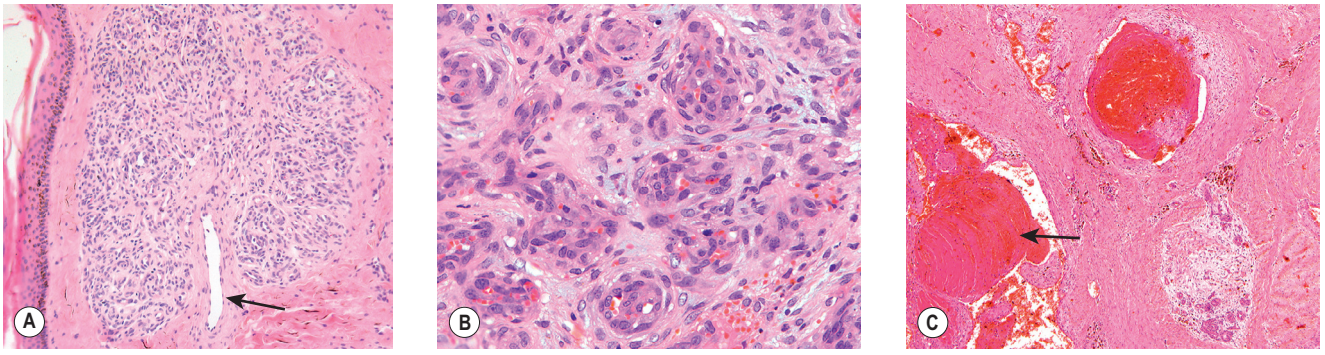


Figure 20.2 Haemangiomas in the dermis of young horses. (A) A nodular aggregate of vascular channels of various types, that was located beside a hair follicle. There is a larger muscular artery within the deeper aspect of this mass (arrow) (H&E, ×100). **(B)** The vascular structures in this superficial dermal mass are capillary-type, with plump tumour cells lining the small vascular spaces. There is a supporting myxomatous stroma (H&E, ×400). **(C)** Another mass in which some nodules contain small vessels supported by myxomatous stroma, and others are composed of cavernous spaces. The space on the left contains a large fibrin thrombus (arrow) (H&E, ×40).

Box 20.1 Differential diagnoses for haemangioma

Neoplastic
- Lymphangioma
- Haemangiosarcoma
- Carcinoma (for the epithelioid variant)

Non-neoplastic
- Vascular hamartoma
- Intravascular papillary endothelial hyperplasia

may be lined by several concentric layers of tumour cells. There may be tumour cell arrangements reminiscent of epithelial neoplasia, including simple and branching tubules.[1] Luminal tumour cells are plump with abundant eosinophilic cytoplasm that may be vacuolated, and often obscures the vascular lumen. One feature considered to be diagnostic is the formation of occasional large clear intracytoplasmic vacuoles with displacement of the nucleus ('signet ring' appearance).[1] The cytoplasmic vacuoles appear to represent attempts to form primitive blood vessels, and can contain a single erythrocyte. There may be lymphocytic infiltrates that are often confined to the periphery of the neoplasm.

Immunohistochemical labelling

Tumour cells label positively for vimentin, factor VIII-related antigen (von Willebrand factor) and CD31 (platelet-endothelial cell adhesion molecule; PECAM)[23]; CD31 is a component of intercellular junctions of endothelial cells and should show linear membranous labelling, while the other markers are cytoplasmic. Expression of factor VIII-related antigen is more consistent and intense in cells of vascular endothelial origin as opposed to those derived from lymphatic vessels. There may be smooth muscle cells supporting the vascular channels; these will stain positively for smooth muscle actin.[24] Lymphatic vessels do not contain smooth muscle. The tumour cells stain negatively for cytokeratin, melan-A and S100. Epithelioid haemangioma stains negatively for cytokeratin, ruling out the differential diagnosis of carcinoma. Basal lamina may be revealed by histochemical staining for reticulin. There should be continuous positive labelling for the basement membrane proteins laminin and type IV collagen.

Differential diagnoses

These are listed in Box 20.1.

Haemangiosarcoma

See also pages 487 and 607.

Cellular origin

This is a malignant neoplasm derived from blood vessel endothelial cells.

Profile

Haemangiosarcoma is rare in horses, only appearing in small numbers in surveys of equine neoplasms (where they are noted at all).[25–28] In the USA, the prevalence of cutaneous haemangiosarcoma has been estimated at 0.02%.[5] There are significant numbers of case reports describing equine haemangiosarcomas in various locations; they may occur in cutaneous, locally invasive and disseminated forms.

Haemangiosarcomas affect middle-aged to older horses, but they have also been reported in younger adult animals and as congenital lesions.[5,29–35] In foals and young adult horses, haemangiosarcomas are often cutaneous or subcutaneous; congenital lesions may be multiple, extensive and involve cutaneous, mucocutaneous and deeper tissues (e.g. tendons).[6,35] The musculoskeletal system is also a common primary site in younger animals, in which limb and bone origin may be more common.[34] Skeletal muscles involved have included intercostal, paravertebral, abdominal wall and thigh muscles.[31,36,37] Skeletal muscles may also be involved secondarily by local infiltration from adjacent tissues or metastasis.[38] Bone is a less likely site of origin, although there is a report of a haemangiosarcoma originating in the medullary cavity of the proximal humerus of an 11-year-old horse.[23] Bone is more usually involved due to local invasion, including neoplasms of skeletal muscle origin. A 2-year-old horse presented with a multifocal haemangiosarcoma of the tarsal synovial sheath that did not extend into adjacent bone.[39]

Other potential sites of origin include the eye, nasal cavities or paranasal sinuses.[40–48] In the eye, primary sites include the eyelids, nictitating membrane, conjunctiva, limbus, sclera and/or orbit; haemangiosarcoma most frequently arise in the non-pigmented limbal conjunctiva, with involvement of the nictitating membrane.[17,24,40,46–48]

In older horses, vascular tumours are almost always malignant and usually disseminated.[7] Disseminated haemangiosarcoma is most common in the lungs and pleura, followed by the skeletal muscle, spleen, heart (pericardium and/or myocardium) and kidneys (Figs. 20.3 and 30.4C).[33,49] Myocardial metastasis of haemangiosarcoma has been associated with ventricular arrhythmia.[50] Further reported sites of involvement in horses (primary or secondary) include the liver, mediastinum, diaphragm, peritoneum, intestinal serosa and mesentery, caecum, ovary, adrenal gland, guttural pouch, colonic pelvic flexure, mesenteric vessels, endometrium and the central nervous system (see Figs. 20.3, 30.4C).[29,30,33,44,49,51–54] Frequently, the site of origin cannot be determined; in one pony, the site of origin was thought to be the spleen (as is often the case in dogs), with metastasis to the lung, liver, kidney and omentum.[55] The brain is an uncommon metastatic site but such lesions have been diagnosed in horses with or without neurological signs (see Fig. 33.5).[29,56] Neurological signs may also result from spinal cord compression by metastatic epidural or vertebral masses, or locally invasive primary paravertebral muscle neoplasms.[37,57–59]

There is no apparent breed or gender predilection.[33]

Oncogenesis

In the skin and eye, exposure to ultraviolet radiation may play a role in horses, as suggested for other domestic animal species.[17,22] A vulvar epithelioid haemangiosarcoma in a mare was seen in association with solar elastosis (p. 223).[60] Haemangiosarcomas have also occurred in wounds, where they could be primary or secondary (Fig. 27.8B).

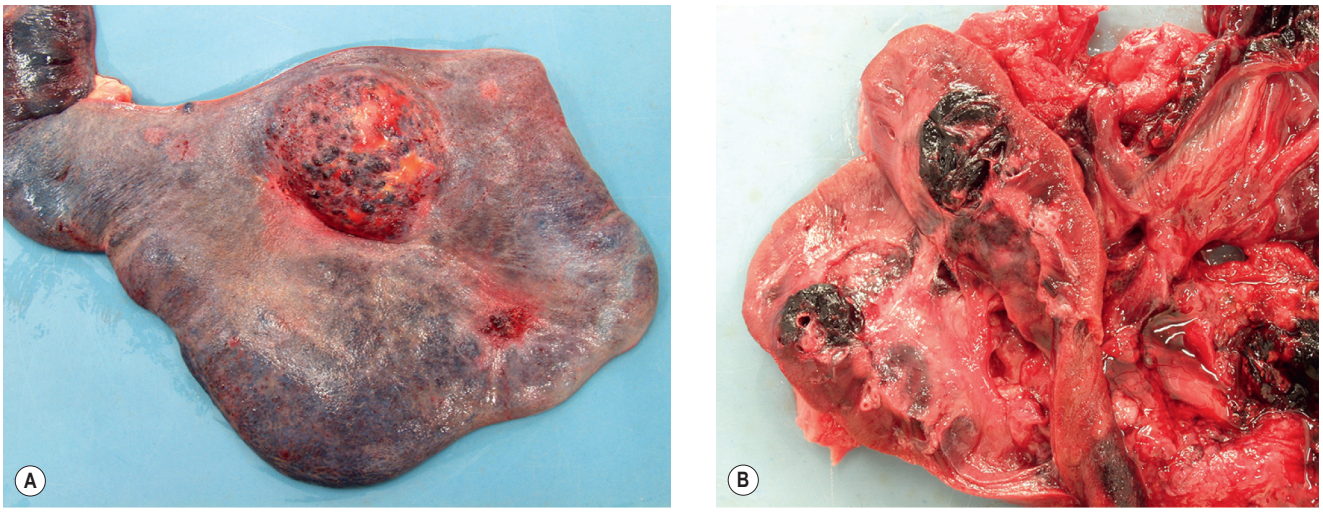


Figure 20.3 Disseminated haemangiosarcoma involving the abdominal organs of a horse. **(A)** A large nodular mass in the spleen that is mottled red, black and yellow and has an irregular surface. Other smaller masses can also be seen on this surface. **(B)** Multiple large perivascular masses in the kidney. Some of these masses have the appearance of clotted blood. *(Figures courtesy of Richard Irvine, School of Veterinary Medicine, University of Glasgow, Scotland.)*

Biological behaviour

Haemangiosarcoma is highly invasive and recurrent locally (including involvement of adjacent bone); it frequently metastasizes widely to regional lymph nodes and internal organs, including the lungs and liver.[17,36] Within body cavities there may be widespread dissemination.

Cutaneous haemangiosarcomas in domestic animals have been suggested to be less aggressive than those of visceral origin, with a longer clinical course and survival time, and potential cure of dermal lesions by excision alone.[22] As this is not frequently diagnosed in horses, the prognosis is difficult to estimate. Cutaneous neoplasms have been successfully excised without recurrence during follow-up periods of up to 8 years, but some have been found to have metastasized to the lungs.[5,61]

Ocular haemangiosarcomas invade the globe, orbit, frontal sinuses, local lymph nodes and facial muscles.[48] In the cornea, haemangiosarcomas may expand substantially into the fornices before they are detected on the outer surface.[47] Lymphatic metastasis is frequent, to sites including the submandibular, retropharyngeal and cervical lymph nodes. Surgical removal, even when an affected nictitating membrane is completely excised, is usually followed by local recurrence and/or discovery of metastatic lesions.[24,34,47] There may, however, be a more positive prognosis for corneolimbal haemangiosarcoma: one horse with a limbic mass that showed significant corneal invasion survived for at least 21 months post-keratectomy.[24,62] Results of a very limited study of ocular haemangiosarcoma treatments (n=4), in which an average survival time of 18 months was achieved, suggested that surgical treatment should be radical, i.e. involve orbital exenteration (removal of globe, adnexa and apart of the bony orbit).[47]

In young horses (<3 years of age), haemangiosarcomas grow more slowly and some animals have survived long term even when excision was not performed; dissemination is also somewhat less likely.[34,39] This particular cohort of cases requires more detailed investigation to establish more evidence on the biological behaviour.

The most common laboratory abnormalities in horses with disseminated haemangiosarcoma include anaemia (due to haemorrhage within neoplasms and/or into body cavities), neutrophilic leukocytosis and thrombocytopaenia.

Paraneoplastic bullous stomatitis was seen in a horse with a haemangiosarcoma of the cervical skeletal muscles; the stomatitis regressed following surgical excision and there was no recurrence of the neoplasm at 14 months.[63]

Gross pathology

Haemangiosarcomas vary in size, and may be solitary but are often multiple. They are soft (or fluctuant) and red to black or mottled red-yellow, i.e. haemorrhagic (see Figs. 20.3, 29.20, 30.3, 30.4, and 33.5); some masses resemble blood clots. Haemangiosarcomas may be lobulated, and some are encapsulated and subdivided by thick fibrous septa.[38] Haemorrhage is common, as the delicate vascular channels forming these neoplasms are prone to rupture.

Cutaneous and subcutaneous masses in young horses often first present as leg swelling or joint effusion; they have also been associated with pressure lysis of adjacent or underlying bone.[34] They may occasionally develop in wound sites (Fig. 30.4B). Congenital masses may be multiple over anatomically widespread areas.[34]

In skeletal muscle, the gross appearance may mimic that of a haematoma and be associated with oedema, or there can be large areas of diffuse haemorrhage.[7,29] An intramuscular mass in the thigh was associated with 15–20 L of clotted blood within encapsulated areas and between muscles that extended into the subcutis, with 15 further litres of blood in the abdominal cavity.[36]

Ocular haemangiosarcomas are red, pink or orange and haemorrhagic or fleshy, or may present simply as a thickened and congested eyelid or nictitating membrane (see Figs. 30.5, 34.6).[24,47,48] Corneolimbal haemangiosarcomas may resemble dense superficial vascularization, granulation tissue or haemorrhage.[62] There is often a serous to serosanguineous discharge that appears at the eye and nostril.[17,64] In the nasal cavity, the overlying mucosa may be largely intact,

with some areas of ulceration and secondary infection; most sinonasal masses have a typical haemorrhagic appearance.

As in other species, haemangiosarcoma involving internal organs (primary or metastatic) may be associated with haemoabdomen, haemothorax and/or haematomas (see Fig. 29.20).[30] There may be very large volumes of blood involved. At post-mortem examination, there may be pallor due to anaemia.

Histopathology

When biopsy specimens are taken from a suspected haemangiosarcoma, care must be taken to sample a number of areas, as there can be marked variation in histological appearance within these masses. Additionally, these neoplasms may contain large areas of haemorrhage and/or haematoma formation. Diagnostic specimens have successfully been taken from thoracic masses by pleuroscopy.[49] Tumour cells may be detected in fluid samples from internal cavities, but in one study cytological examination was negative for two of three horses with intrathoracic neoplasms.[65] Cytological samples often only contain blood.

Haemangiosarcomas are unencapsulated, infiltrative masses with potentially extremely variable degrees of differentiation. Classically, single to multiple layers of tumour cells line variably-sized and shaped, often poorly-formed, anastomosing, blood-filled vascular spaces that can range from capillary-like structures to large cysts and are supported by a delicate to abundant fibrovascular stroma; collagenous trabeculae lined by tumour cells may protrude blindly into them.[22] Tumour cells may also fill the vascular lumens and can form sheets and bundles that predominate in or comprise the entirety of some neoplasms.[47] Those patterns of arrangement create difficulties in making a diagnosis without supportive immunohistochemical labelling, particularly from a small biopsy specimen (see below). Tumour cells in the more solid arrangements may form rudimentary vascular channels, seen as clefts.[47] Vascular spaces can be filled with fibrin, which may be arranged in thrombi, and there may also be fibrin deposits within the supporting stroma.

The tumour cells are flat, or plump and spindle-shaped, with small to large amounts of pale-staining eosinophilic or amphophilic cytoplasm that has poorly-defined margins. Variably-sized nuclei may be flattened or are plump and ovoid, characteristically bulging into the vascular spaces. The nuclei contain coarsely granular or vesicular chromatin and one to several nucleoli. There is usually marked anisokaryosis and a variable but often high mitotic rate. On occasion, multinucleate tumour cells may be noted.[5,6]

In many cases of haemangiosarcoma there is marked invasion of surrounding tissue that can include adjacent bone, and large areas of necrosis and haemorrhage may develop; in one report of an intraosseous tumour, bony sequestra were noted.[23] Other associated lesions may include haemosiderophage infiltration, granulation tissue, and low-grade lymphoplasmacytic inflammation.[38,39] In ocular lesions, the overlying corneal epithelium may be hyperplastic (including rete ridges) with extensive ulceration.[24]

The epithelioid variant of haemangiosarcoma has been described in a small number of older horses (≥12 years) (for epithelioid variant of haemangioma see pp. 333–334), with reported sites including the eye (bulbar conjunctiva and/or third eyelid), nasal and intermandibular tissues, dorsal vulvar commissure and deep dermis of the ventral neck.[1,60,64,66] This diagnosis is challenging, as the vascular channels are not as obvious and the tumour cells have an epithelioid morphology suggestive of other types of neoplasm. Epithelioid haemangiosarcoma variants may be multilobular to coalescing and infiltrative, or alternatively expansile and well-demarcated.[1] Patterns of arrangement of the tumour cells can vary significantly; they are often arranged in sheets, streams or cords but may also form rudimentary capillary or cavernous vascular channels that blend with areas of tubule formation (Fig. 20.4).[1,64] The tumour cells forming vascular structures are spindle-shaped, while those in 'epithelioid' regions are polygonal, cuboidal or columnar, sometimes with intracytoplasmic vacuoles or eosinophilic globules. The cytoplasmic vacuoles appear to represent attempts to form primitive blood vessels, and may

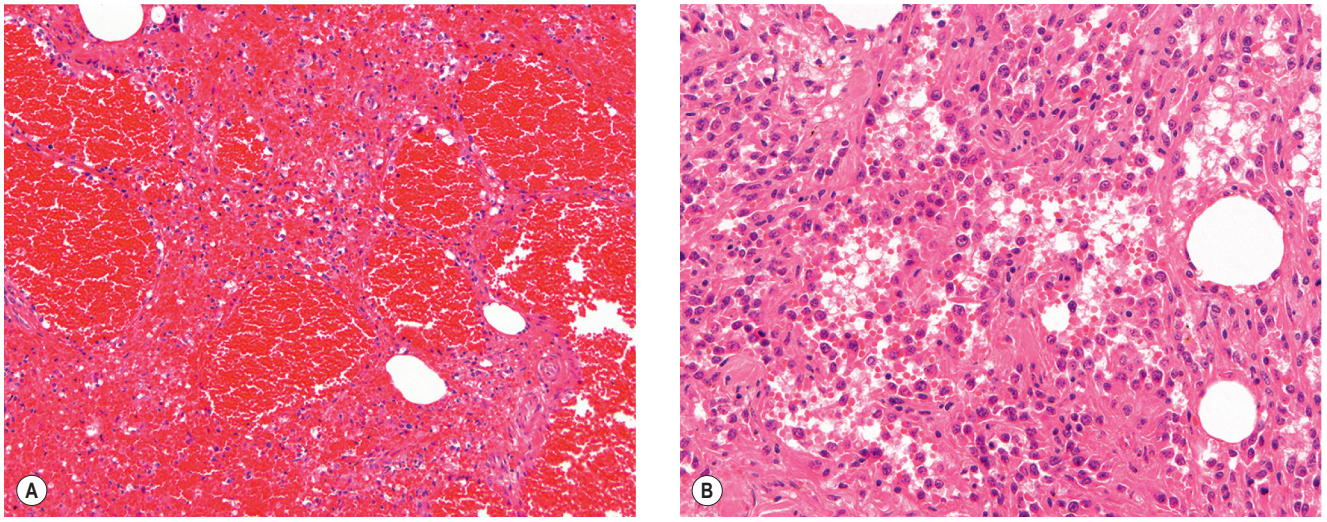


Figure 20.4 Epithelioid variant of haemangiosarcoma in a horse. **(A)** A region of one tumour mass in which there are multiple, blood-filled cavernous spaces lined by spindle-shaped cells (H&E, ×100). **(B)** A further area in which the tumour cells are plump and polygonal, although the tubule-like spaces are still blood-filled (H&E, ×200).

Box 20.2 Differential diagnoses for haemangiosarcoma

Neoplastic
- Lymphangioma or lymphangiosarcoma
- Haemangioma
- Carcinoma (for the epithelioid variant)

Non-neoplastic
- Vascular hamartoma
- Haemangiomatosis

contain a single erythrocyte. Nuclei are round or ovoid with coarsely stippled chromatin and one to several large nucleoli.[1] Degrees of cellular pleomorphism and mitotic rates are highly variable. There may be infiltration by small numbers of eosinophils.

Immunohistochemical labelling

Tumour cells label positively for vimentin, factor VIII-related antigen (von Willebrand factor) and CD31 (platelet-endothelial cell adhesion molecule; PECAM)[23]; CD31 is a component of intercellular junctions of endothelial cells and should show linear membranous labelling; the other markers are cytoplasmic. Expression of factor VIII-related antigen is more consistent and intense in cells of vascular endothelial origin as opposed to those derived from lymphatic vessels. There may be smooth muscle cells supporting the vascular channels (in the subendothelium), i.e. these will stain positively for smooth muscle actin.[24] Lymphatic vessels do not contain smooth muscle. The tumour cells stain negatively for cytokeratin, melan-A and S100. As features of malignancy increase, these markers are likely to be expressed more weakly and by a smaller percentage of the tumour cells.[1] Epithelioid haemangiosarcoma will stain negatively for cytokeratin, ruling out the differential diagnosis of carcinoma. Basal lamina may be revealed by histochemical staining for reticulin. There should be continuous positive labelling for the basement membrane proteins laminin and type IV collagen.

Differential diagnoses

These are listed in Box 20.2.

Lymphangioma

See also page 521.

Cellular origin

Lymphangioma is a benign neoplasm derived from endothelial cells of lymphatic vessels. As for haemangiomas, some authors believe these lesions to be hamartomas rather than a true neoplastic condition. By definition, a hamartoma is a mass of disordered mature tissues indigenous to that site that is typically present at birth and grows at a rate coordinated with that of the surrounding tissue.

Profile

This is a rare type of neoplasm, but there are reports of lymphangioma in horses and mules of various ages. Reported sites of origin have included the skin, subcutis, pleural cavity, hindlimb, caudal abdominal cavity, and retroperitoneum and intestinal tract.[11,16,67–72] The inguinal and axillary regions of skin have been cited as predilection sites in horses.[73] Lymphangiomas arise at locations where the lymphatic system develops from primitive sacs, and occur in young animals – this supports the theory that they are actually developmental defects or hamartomas, or at least begin as such. In other species, suggested initiating causes include chronic lymphoedema, trauma, chronic inflammation and lymphatic obstruction.[72]

Biological behaviour

Lymphangiomas are benign, but they can have significant effects due to progressive enlargement and/or local extension. Larger masses exert considerable pressure on surrounding tissues. A multinodular lymphangioma arising in the abdomen and retroperitoneum extended through the left inguinal and femoral canals to involve deep intermuscular fascial tissue of the hindlimb.[70] Dissection of tumour cells along fascial planes can simulate aggressive growth, but malignant transformation is considered to be rare.[70]

Lymphangiomas may be surgically excised, but this can be limited by their site of origin and size. Masses with poorly-defined margins and local infiltration have a high risk of recurrence.[71]

Gross pathology

Although benign, lymphangiomas are not necessarily encapsulated or well-circumscribed. They may be multinodular, and in some cases they are multiple.[70] Subcutaneous and internal neoplasms measuring up to 30 cm in maximal diameter have been reported (see Fig. 30.8).[70,71] Lymphangiomas are often soft and fluctuant, i.e. fluid-filled, but they may also be firm and solid.[70] The size may vary over time.[73] Significant amounts of clear, yellow or cloudy fluid may exude from sectioned surfaces, on which numerous small cavernous or cystic spaces may be noted. Some of these spaces contain inspissated, gelatinous or purulent material.[70] In cases of cutaneous or subcutaneous lymphangioma, changes including ulceration and necrosis of the overlying skin, and oedema of surrounding tissues and the regional lymph nodes are frequent.[72]

Histopathology

Some lymphangiomas have a thin capsule, but most have poorly-defined margins. The tumour cells are arranged in single layers lining small thin-walled vessels (capillary type), larger cavernous channels (cavernous type) or very large cystic/cavernous spaces (cystic type) (Fig. 20.5). They are supported by a moderately abundant fibrous stroma. There may be mixed capillary and cavernous arrangements.[11] The cystic spaces have thicker walls composed of collagen and variable amounts of entrapped remnant tissues, including fat, lymphoid tissue and skeletal muscle.[70]

The tumour cells are well-differentiated, i.e. flat or oval to elongate, with central, oval, hyperchromatic nuclei. There

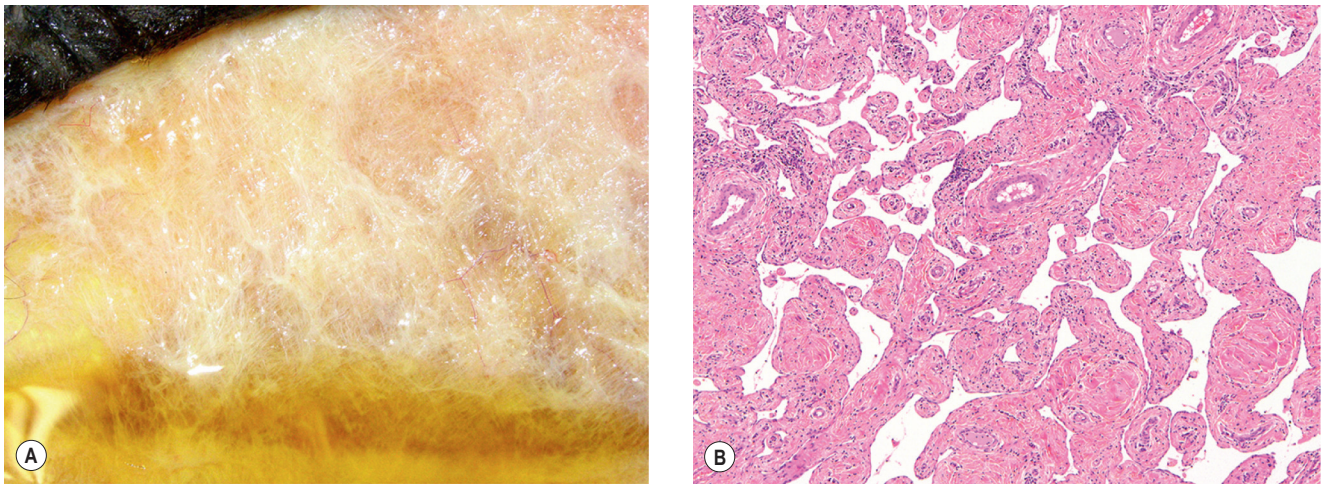


Figure 20.5 Cutaneous neoplasms of lymphatic origin. (A) Macroscopic appearance of a lymphangiosarcoma in the skin of a horse (skin incised). The mass is composed of fine, spongy white tissue that is exuding large amounts of translucent, yellow fluid from the sectioned surface. **(B)** Lymphangioma in the skin of a donkey. Flat, elongate tumour cells are lining multiple, highly irregularly-shaped spaces that do not contain erythrocytes. There is a moderate amount of supporting collagenous stroma containing multifocal infiltrates of lymphocytes and plasma cells (H&E, ×40). *(Figure A courtesy of Dr Siobhan McAuliffe, Kawell Equine Hospital, Buenos Aires, Argentina. Case for Figure B courtesy of Drs. Patrick Pollock and Sam Sharpe of the School of Veterinary Medicine, University of Glasgow.)*

is mild anisokaryosis and no mitotic figures are noted. The basement membrane structure is discontinuous or not obvious in sections stained using the periodic acid-Schiff (PAS) method.[71] Usually, the vascular spaces are empty but they may contain a few erythrocytes and small amounts of eosinophilic material (lymph fluid) (see Fig. 20.5). Lymphangiomas in the skin may extend into the underlying subcutaneous and skeletal muscle tissue.[72]

Associated lesions include oedema and lymphoplasmacytic infiltration of the stroma (see Fig. 20.5), and inflammation, necrosis and ulceration of the overlying skin with granulation tissue formation.[22,72]

Immunohistochemical labelling

Tumour cells stain positively for factor VIII-related antigen (von Willebrand factor) and vimentin; this does not differentiate them from those of blood vessel endothelial origin. Expression of factor VIII-related antigen is more consistent and intense in cells of vascular endothelial origin as opposed to those derived from lymphatic vessels. Staining of lymphatic endothelial cells with factor VIII-related antigen is more reliably detected in cryosections.[74] Antibodies for vascular endothelial growth factor receptor-3 and PROX-1 are useful for more specific labelling of lymphatic endothelium; however, these will not be readily available in veterinary diagnostic laboratories.[72,75] PROX-1 is a highly conserved transcription factor that is expressed by lymphatic endothelial cells at all stages of development. Lymphatic vessels do not contain smooth muscle, i.e. labelling for smooth muscle actin should be negative. There may be discontinuous or absent positive labelling for laminin and type IV collagen (basement membrane proteins), in contrast to the complete basement membranes of blood vessels.

Electron microscopy

Ultrastructurally, lymphatic vessels should not be surrounded by a continuous basement membrane or have associated pericytes; they are attached to underlying connective tissue.[71]

Box 20.3 Differential diagnoses for lymphangioma

Neoplastic
- Lymphangiosarcoma
- Haemangioma
- Haemangiosarcoma

Non-neoplastic
- Oedema associated with other types of neoplasm

Differential diagnoses

These are listed in Box 20.3.

Lymphangiosarcoma

Cellular origin

Lymphangiosarcoma is a malignant neoplasm derived from endothelial cells of lymphatic vessels.

Profile

Lymphangiosarcomas have rarely been diagnosed in horses. Reported sites have included the visceral lymphatic trunk, mediastinum and visceral lymphatic trunk (retroperitoneum), nictitating membrane and conjunctiva, and mesenteric and mediastinal lymph nodes.[47,76–78]

Biological behaviour

Lymphangiosarcomas show marked invasion of surrounding tissues.[76] Metastasis to the spleen, kidneys and lungs from

primary masses in the mesenteric and mediastinal lymph nodes has been reported.[77]

Gross pathology

Lymphangiosarcomas are poorly-circumscribed, oedematous masses composed of spongy and sometimes slightly haemorrhagic tissue. Clear, yellow or cloudy fluid may exude from sectioned surfaces. Associated subcutaneous tissue, fascial tissue and lymph nodes may be oedematous and there may be lymphangiectasia. There may be lymph fluid in associated body cavities, which is *not* white as for chylous fluid seen in cats or dogs.

Histopathology

Lymphangiosarcomas are poorly-defined, infiltrative and unencapsulated. The tumour cells line empty clefts, variably-sized channels or disorganized vascular spaces that are not blood-filled. These channels or spaces may contain a few erythrocytes and small amounts of eosinophilic material (lymph fluid). Tumour cells may line papillary projections of stroma into the vascular spaces.

The tumour cells are flattened or polygonal and pleomorphic, with eosinophilic cytoplasm that may contain a pale perinuclear zone/vacuole and has poorly-defined margins. In one case, some tumour cells contained a large cytoplasmic vacuole that occupied that entire cytoplasm and displaced the nucleus.[77] Nuclei are round or oval with finely stippled chromatin, 1–2 nucleoli and 1–6 mitotic figures per high power (×400) field. There is either no obvious basement membrane structure in sections stained using the periodic acid-Schiff (PAS) method, or it is discontinuous.[71,78] Associated lesions may include stromal oedema, peripheral infiltrates of lymphocytes and macrophages, and oedema and lymphangiectasia in surrounding tissues.

Immunohistochemical labelling

Tumour cells stain positively for factor VIII-related antigen (von Willebrand factor) and vimentin, which does not differentiate them from those of blood vessel endothelial origin. The paranuclear zone is rich in intermediate filaments that label positively for vimentin.[77,78] Expression of factor VIII-related antigen is more consistent and intense in cells of vascular endothelial origin as opposed to those derived from lymphatic vessels. Staining of lymphatic endothelial cells with factor VIII-related antigen is more reliably detected in cryosections.[74] Antibodies for vascular endothelial growth factor receptor-3 and PROX-1 are useful for more specific labelling of lymphatic endothelium, however these will not be readily available in veterinary diagnostic laboratories.[72,75] PROX-1 is a highly conserved transcription factor that is expressed by lymphatic endothelial cells at all stages of development. Lymphatic vessels do not contain smooth muscle, i.e. labelling for smooth muscle actin should be negative. There may be discontinuous or absent positive labelling for laminin and type IV collagen (basement membrane proteins), in contrast to the complete basement membranes of blood vessels. In one equine lymphangiosarcoma case, the tumour cells also showed positively staining for keratin, and this has also been seen in human patients.[77]

Electron microscopy

Ultrastructurally, the tumour cells have a poorly-developed and discontinuous basement membrane or lack it altogether, as opposed to those with a blood vascular origin.[71,76] They lack pericytes and have few micropinocytotic vesicles or intercellular junctions.[79]

Angiosarcoma

See also page 519.

Cellular origin

This diagnosis is used by some authors or pathologists for malignant neoplasms derived from endothelium where it is not certain if the vascular origin is blood or lymphatic.

Profile

Aged horses tend to be affected. Many reports of equine angiosarcoma have involved the eye; in four cases (horses aged 9–17 years) all involved the conjunctiva, and were considered most likely to be of blood vessel origin.[74] A conjunctival angiosarcoma that was reported in a 25-year-old pony extended into the retrobulbar area and caused exophthalmos.[80] Other reported sites include paranasal sinuses and the paravertebral vasculature.[37,81]

Biological behaviour

In both haemangiosarcoma and lymphangiosarcoma, there may be extensive local infiltration and metastasis (pp. 334–335 and 338). From ocular locations, angiosarcoma may invade the globe, orbit and nasal sinuses; conjunctival masses often invade the cornea.[74,80] In one study of four conjunctival angiosarcomas, the mean survival time following diagnosis was 12 months.[74]

Gross pathology, histopathology, immunohistochemical labelling

See haemangiosarcoma and lymphangiosarcoma (pp. 335–337 and above; also Fig. 30.6).

Differential diagnoses

These are listed in Box 20.4.

Box 20.4 Differential diagnoses for angiosarcoma

Neoplastic
- Haemangiosarcoma
- Lymphangiosarcoma
- Spindle cell variant of squamous cell carcinoma

Non-neoplastic
- Vascular hamartoma
- Haemangiomatosis

NON-NEOPLASTIC VASCULAR MASSES

Vascular hamartoma

See also page 512.

Profile

Vascular hamartoma is a benign mass composed of disorganized and excessive proliferations of well-differentiated vascular tissue that, by definition, grow at a rate coordinated with the surrounding tissue. Typically diagnosed in young animals, vascular hamartomas are considered to be developmental in origin. Vascular hamartomas have also been reported or noted in the lung, tongue, ovary, colon and skin).[20,82,83] In three young Thoroughbreds (1–3 years of age), vascular hamartomas were diagnosed in the subcutis of the dorsal carpal region.[20] However, in the histological pictures provided from one of those cases, the appearance is more consistent with a diagnosis of vascular neoplasia. As noted for haemangiomas, there is some debate as to whether (at least in all cases) those lesions are true neoplasms or hamartomas (p. 332).

Haemangiomatosis

Profile

Extensive haemangiomatosis involving leptomeningeal tissue and the underlying parenchyma of one cerebral hemisphere, with smaller multifocal areas in other regions of the leptomeninges of the brain, the choroid plexus, spinal cord and eye, was reported in a 3-year-old horse presenting with intermittent seizures.[84] Histologically, this was composed of proliferative arterioles (large and small), venules and meningothelial hyperplasia with associated neuronal loss, ectopia and disorganization. There were also changes in the left trigeminal nerve and ganglion resembling a hyperplastic or neoplastic proliferation of Schwann cells.[84]

Intravascular papillary endothelial hyperplasia

Profile

This is a rare benign condition that can have a similar gross appearance to a vascular neoplasm, and has been reported in the equine conjunctiva.

Histopathology

Histologically, confluent vascular spaces are lined and filled by fibrous papillary structures covered by a single layer of well-differentiated endothelial cells.[85] These lesions could also potentially occur in the dermis.

References

1. Warren AL, Summers BA. Epithelioid variant of haemangioma and haemangiosarcoma in the dog, horse, and cow. Vet Pathol 2007; 44:15–24.
2. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
3. Baker JR, Leyland A. Histological survey of tumours of the horse with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
4. Cannon SRL, Loh H. Treatment of a cavernous haemangioma-like lesion in a polo pony. Equine Vet J 1982; 14:254–255.
5. Hargis AM, McElwain TF. Vascular neoplasia in the skin of horses. J Am Vet Med Assoc 1984; 184:1121–1124.
6. Johnstone AC. Congenital vascular tumours in the skin of horses. J Comp Pathol 1987; 97:365–368.
7. Valentine BA. Neoplasia. In: Bertone JJ, ed. Equine geriatric medicine and surgery. St Louis: Saunders Elsevier; 2006: 147–167.
8. Vos JH, van der Gaag I, van Dijk JE, et al. Lobular capillary haemangioma in young horses. J Comp Pathol 1986; 96:637–644.
9. Johnson GC, Miller MA, Floss JL, et al. Histologic and immunohistochemical characterization of haemangioma in the skin of seven young horses. Vet Pathol 1996; 33:142–149.
10. Sartin EA, Hodge TG. Congenital dermal haemangioendothelioma in two foals. Vet Pathol 1982; 19:569–571.
11. Jackson C. The incidence and pathology of tumours of domesticated animals in South Africa. Onderstepoort J Vet Sci Anim Ind 1936; 6:3–460.
12. Rhyan JC, D'Andrea GH, Smith LS. Congenital ovarian vascular hamartoma in a horse. Vet Pathol 1981; 18:131.
13. Vestre WA, Turner TA, Carlton WW. Conjunctival haemangioma in a horse. J Am Vet Med Assoc 1982; 180:1481–1482.
14. Greene HJ, O'Connor JP. Haemangioma of the guttural pouch of a 16-year-old thoroughbred mare: clinical and pathological findings. Vet Rec 1986; 118:445–446.
15. Crawley GR, Bryan GM, Gogolewski RP. Ocular haemangioma in a horse. Equine Pract 1987; 9:11–14.
16. Platt H. Vascular malformations and angiomatous lesions in horses: a review of 10 cases. Equine Vet J 1987; 19:500–504.
17. Bolton JR, Lees MJ, Robinson WF, et al. Ocular neoplasms of vascular origin in the horse. Equine Vet J Suppl 1990; 10:73–75.
18. Rebhun WC. Tumours of the eye and ocular adnexal tissues. Vet Clin North Am Equine Pract 1998; 14:579–606.
19. Holzhausen L, Nowak M, Junginger J, et al. Synovial haemangioma in an adult horse. J Vet Diagn Invest 2012; 24:427–430.
20. Colbourne CM, Yovich JV, Richards RB, et al. Vascular hamartoma of the dorsal carpal region in three young Thoroughbred horses. Aust Vet J 1997; 75:20–23.
21. Saifzadeh S, Derakhshanfar A, Shokouhi F, et al. Vascular hamartoma as the cause of hind limb lameness in a horse. J Vet Med A Physiol Pathol Clin Med 2006; 53:202–204.
22. Ginn PE, Mansell JEKL, Rakich PM. Skin and appendages. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's pathology of domestic animals. Philadelphia: Elsevier Saunders; 2007: 553–781.
23. Cottle HJ, Hughes KJ, Philbey AW, et al. Primary haemangiosarcoma in the proximal humerus of a Clydesdale gelding. Equine Vet Educ 2008; 20:575–579.
24. Pinn TL, Cushing T, Valentino LM, et al. Corneal invasion by haemangiosarcoma in a horse. Vet Ophthalmol 2011; 14:200–204.
25. Cotchin E, Baker-Smith J. Tumours in horses encountered in an abattoir survey. Vet Rec 1975; 97:399.
26. Kerr KM, Alden CL. Equine neoplasia, a ten year survey. Proc Ann Mtg Am Assoc Vet Lab Diagnost 1974; 17:183.
27. Bastianello S. A survey on neoplasia in domestic species over a 40-year period from 1935 to 1974 in the Republic of South Africa. IV. Tumours occurring in Equidae. Onderstepoort J Vet Res 1983; 50:91–96.
28. East LM, Savage CJ. Abdominal neoplasia (excluding urogenital tract). Vet Clin North Am Equine Pract 1998; 14:475–493.
29. Waugh SL, Long GG, Uriah L, et al. Metastatic haemangiosarcoma in the equine: report of 2 cases. J Equine Med Surg 1977; 1:311–315.
30. Freestone JF, Williams MM, Norwood G. Thoracic haemangiosarcoma in a 3-year-old horse. Aust Vet J 1990; 67:269–270.
31. Collins MB, Hodgson DR, Hutchins DR, et al. Haemangiosarcoma in the horse: three cases. Aust Vet J 1994; 71:296–298.
32. Schott HC, Southwood LL. Disseminated haemangiosarcoma in horses. Proceedings of the 14th Annual Meeting of the American College of Internal Medicine 1996: 568.
33. Southwood LL, Schott HC, Henry CJ, et al. Disseminated haemangiosarcoma in the horse: 35 cases. J Vet Intern Med 2000; 14:105–109.
34. Johns I, Stephen JO, Del Piero F, et al. Haemangiosarcoma in 11 young horses. J Vet Intern Med 2005; 19:564–570.
35. Dunkel BM, Del Piero F, Kraus BM, et al. Congenital cutaneous, oral, and periarticular haemangiosarcoma in a 9-day-old Rocky Mountain horse. J Vet Intern Med 2004; 18:252–255.
36. Valentine BA, Ross CE, Bump JL, et al. Intramuscular haemangiosarcoma with pulmonary metastasis in a horse. J Am Vet Med Assoc 1986; 188: 628–629.
37. Kennedy FA, Brown CM. Vertebral angiosarcoma in a horse. J Vet Diagn Invest 1993; 5:125–127.
38. Kiupel M, Frank N, Stevenson GW, et al. Intrapelvic haemangiosarcoma in a horse. J Vet Diagn Invest 2000; 12:91–95.
39. Van Pelt RW, Langham RF, Gill HE. Multiple haemangiosarcoma in the tarsal synovial sheath of a horse. J Am Vet Med Assoc 1972; 161: 49–52.
40. Morgan G. Ocular tumours in animals. J Small Anim Pract 1969; 10:563–570.
41. Stencel E, Grotelueschen D. Haemangiosarcoma involving the frontal sinus of a horse. Equine Pract 1989; 11:14–16.
42. Ruggles AJ, Ross MW, Freeman DE. Endoscopic examination and treatment of paranasal sinus disease in 16 horses. Vet Surg 1993; 22:508–514.
43. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 2: A contribution of 28 case reports. Vet J 1999; 157:279–294.

44. Burks BS, Leonard JM, Orsini JA, et al. Interstitial brachytherapy in the management of haemangiosarcoma of the rostrum of the horse: case report and review of the literature. Equine Vet Educ 2009; 21:487–493.
45. Madewell BR, Priester WA, Gillette EL, et al. Neoplasms of the nasal passages and paranasal sinuses in domesticated animals as reported by 13 veterinary colleges. Am J Vet Res 1976; 37:851–856.
46. Lavach JD, Severin GA. Neoplasia of the equine eye, adnexa and orbit: a review of 68 cases. J Am Vet Med Assoc 1977; 170:202–203.
47. Hacker DV, Moore PF, Buyukmihci NC. Ocular angiosarcoma in four horses. J Am Vet Med Assoc 1986; 189:200–203.
48. Sansom J, Donaldson D, Smith K, et al. Haemangiosarcoma involving the third eyelid in the horse: a case series. Equine Vet J 2006; 38:277–282.
49. Rossier Y, Sweeney CR, Heyer G, et al. Pleuroscopic diagnosis of disseminated haemangiosarcoma in a horse. J Am Vet Med Assoc 1990; 196:1639–1640.
50. Delesalle C, van Loon G, Nollet H, et al. Tumour-induced ventricular arrhythmia in a horse. J Vet Intern Med 2002; 16:612–617.
51. Dugan SJ. Ocular neoplasia. Vet Clin North Am Equine Pract 1992; 8:609–626.
52. Dart AJ, Hodgson DR, Snyder JR. Caecal disease in equids. Aust Vet J 1997; 75:552–557.
53. Birks EK, Hultgren BD. Pericardial haemangiosarcoma in a horse. J Comp Pathol 1988; 99:105–107.
54. Baptiste KE, Moll HD, Robertson JL. Three horses with neoplasia including growth in the guttural pouch. Can Vet J 1996; 37:499–501.
55. Geelen SN, Sloet van Oldruitenborgh-Oosterbaan MM. A pony with metastasized haemangiosarcoma. Tijdschr Diergeneeskd 1996; 121:544–546.
56. Ladd SM, Crisman MV, Duncan R, et al. Central nervous system haemangiosarcoma in a horse. J Vet Intern Med 2005; 19:914–916.
57. Newton-Clarke MJ, Guffoy MR, Dykes NL, et al. Ataxia due to vertebral haemangiosarcoma in a horse. Vet Rec 1994; 135:182–184.
58. Berry S-L. Spinal cord compression secondary to haemangiosarcoma in a Saddlebred stallion. Can Vet J 1999; 40:886–887.
59. Hirsh JE, Grant BD, Linovitz R, et al. Diagnosis and surgical treatment of epidural neoplasms in two ataxic horses. Equine Vet Educ 2009; 21: 564–568.
60. Gumber S, Baia P, Wakamatsu N. Vulvar epithelioid haemangiosarcoma with solar elastosis in a mare. J Vet Diagn Invest 2011; 23:1033–1036.
61. Jean D, Lavoie JP, Nunez L, et al. Cutaneous haemangiosarcoma with pulmonary metastasis in a horse. J Am Vet Med Assoc 1994; 204:776–778.
62. Cutler TJ. Corneal epithelial disease. Vet Clin North Am Equine Pract 2004; 20:319–343.
63. Williams MA, Dowling PM, Angarano DW, et al. Paraneoplastic bullous stomatitis in a horse. J Am Vet Med Assoc 1995; 207:331–334.
64. Arenas-Gamboa AM, Mansell J. Epithelioid haemangiosarcoma in the ocular tissue of horses. J Comp Pathol 2011; 144:328–333.
65. Sweeney CR, Gillette DM. Thoracic neoplasia in equids: 35 cases (1967–1987). J Am Vet Med Assoc 1989; 195:374–377.
66. Dawson DR, Scrivani PV, Schaefer DMW, et al. Epithelioid variant of haemangiosarcoma in a gelding. Equine Vet Educ 2009; 21:519–524.
67. Pascoe RR, Summers PM. Clinical survey of tumours and tumour-like lesions in horses in south east Queensland. Equine Vet J 1981; 13:235–239.
68. Markus H. Multiples lymphangiom des Brustfells beim Pferde. Monatshefte für Praktische Tierheilkunde 1903; 15:185–192.
69. Saloman S. Beitrag zur pathologie des darmes. Beri und Münh Wchschrift 1933; 49:505–507.
70. Turk JR, Gallina AM, Liu IM, et al. Cystic lymphangioma in a colt. J Am Vet Med Assoc 1979; 174:1228–1230.
71. Gehlen H, Wohlsein P. Cutaneous lymphangioma in a young Standardbred mare. Equine Vet J 2000; 32:86–88.
72. Junginger J, Rötting A, Stasyk C, et al. Identification of cutaneous lymphangioma by application of a lymphatic endothelial cell marker. J Comp Pathol 2010; 143:57–60.
73. Scott DW, Miller WH. Neoplasms, cysts, hamartomas, and keratoses. In: Equine Dermatology, 2nd edn. Maryland Heights: WB Saunders; 2011: 468–513.
74. Moore PF, Hacker DV, Buyukmihci NC. Angiosarcoma in the horse: morphological and immunohistochemical studies. Vet Pathol 1986; 23: 240–244.
75. De Cock HEV, Baeten S, Affolter VK. Immunohistochemical characterization and description of the lymphatic system in horse skin. Vet Dermatol 2008; 19:82.
76. Ijzer J, van den Ingh TS. Lymphangiosarcoma in a horse. J Comp Pathol 2000; 122:312–316.
77. Sanchez B, Nieto A, Ruiz de Leon MA, et al. Metastatic lymphangiosarcoma in a horse. Vet Pathol 2002; 39:266–268.
78. Puff C, Herder V, Philipp A, et al. Lymphangiosarcoma in the nictitating membrane of a horse. J Vet Diagn Invest 2008; 20:108–110.
79. Maxie MG, Robinson WF. Cardiovascular system. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's pathology of domestic animals. Philadelphia: Elsevier Saunders; 2007: 1–105.
80. Bischofberger AS, Konar M, Posthaus H, et al. Ocular angiosarcoma in a pony – MRI and histopathological appearance. Equine Vet Educ 2008; 20:340–347.
81. Chan CW, Collins EA. Case of angiosarcoma of the nasal passage of the horse – ultrastructure and differential diagnosis from progressive haematoma. Equine Vet J 1985; 17:214–218.
82. Jabara AG, Hazard GH, O'Shea JD. A congenital vascular naevus in a foal. Aust Vet J 1984; 61:286–288.
83. Brunson BL, Taintor J, Newton J, et al. Vascular hamartoma in the tongue of a horse. J Equine Vet Sci 2006; 26:275–277.
84. McEntee M, Summers BA, de Lahunta A, et al. Meningocerebral haemangiomatosis resembling Sturge-Weber disease in a horse. Acta Neuropathol (Berl) 1987; 74:405–410.
85. Herrera HD, Duchene AG, Croxatto JO, et al. H. Intravascular papillary endothelial hyperplasia of the conjunctiva in a horse. Vet Ophthalmol 2003; 6:269–272.

21 Haematopoietic (round cell) neoplasms

Lymphosarcoma (lymphoma)
General pathology of equine lymphosarcoma 342
Multicentric (generalized) lymphosarcoma 346
Alimentary lymphosarcoma 346
Mediastinal, thymic and thoracic lymphosarcoma 348
Subcutaneous and cutaneous lymphosarcoma 349
Hepatosplenic and splenic lymphosarcoma 350
Nasal, paranasal and nasopharyngeal lymphosarcoma 351
Nervous system lymphosarcoma 352
Ocular lymphosarcoma 352

Leukaemia
Myeloid leukaemias 352
Lymphoid leukaemias 353
The importance of myelophthisis 353
Gross pathology 353
Histopathology 354
Immunohistochemical labelling (and histochemical stains) 354
Differential diagnoses 355

Plasma cell neoplasms
Plasmacytoma 355
Multiple myeloma 356

Other 'round cell' neoplasms
Mast cell tumour (mastocytosis, mastocytoma) 357
Histiocytic sarcoma 359

LYMPHOSARCOMA (LYMPHOMA)

See also page 524.

General pathology of equine lymphosarcoma

Cellular origin

Lymphosarcoma arises from lymphocytes of various types. Lymphosarcoma is distinguished from leukaemia (see p. 352) in being peripheral in origin, rather than arising in the bone marrow; lymphosarcoma and leukaemia of the same cell type are often regarded (but not in all classification systems) as different manifestations of the same disease process.[1]

Profile

The prevalence of lymphosarcoma in horses is lower than in other domestic species, including dogs, cats and cattle. It is, however, the most common equine haematopoietic neoplasm, estimated to account for 0.002–5% of total neoplasms in horses.[2–4]

Lymphosarcoma has been diagnosed in horses of all ages, including foals and fetal stages in rare instances.[5–10] In a Canadian study of 37 horses diagnosed with lymphosarcoma, the age range was 0.3–20.5 years, with a mean of 7.5 years.[10] There is no apparent gender or breed predilection.

Oncogenesis

Viral infection (e.g. retroviral) has been proposed as a cause of equine lymphosarcoma pathogenesis, but this has not been proven by transmission experiments. In one case involving abdominal lymph nodes in a neonate, virus-like particles with features suggestive of a type C retrovirus were identified using electron microscopy; these were not identified in lymphocytes cultured from the mare.[11]

Biological behaviour

Lymphosarcoma is a malignant neoplasm, and there are always tumour cells in the circulation, even in cases where they cannot be readily recognized in peripheral blood smears.[1] At the time of diagnosis, the bone marrow is usually relatively uninvolved; however it may become so in very advanced cases. The rate of progression is highly variable with clinical courses ranging from weeks to years, depending on the site(s) involved and the lymphoid cell type from which the neoplasm arises.

There are a number of common laboratory findings that include:

- *Cytopaenia of one or several haematopoietic lineages*: in particular, anaemia occurs in 30–50% of cases. Anaemia may be due to immune-mediated haemolysis, myelophthisis, blood loss or chronic inflammation.[12]
- *Neutrophilia* (the usual cause of leucocytosis): this may relate to inflammation secondary to tumour necrosis.
- *Erythrocytosis*: in one case, erythropoietin gene expression was identified in the neoplasms but the hormone was not detected in serum. This was thought to be due to intermittent production.[13]
- *Hypoalbuminaemia*: this may be caused by protein-losing enteropathy (intestinal infiltration), reduced hepatic production (liver infiltration) or may arise as a

compensatory response to increased serum globulins.[4,10,14–16]

- *Hyperglobulinaemia with monoclonal gammopathy*: this is encountered in a few cases; one horse showed monoclonal aggregating immunoglobulin cryoglobulinaemia (i.e. a paraprotein that precipitates at cold temperatures) and the cryoprecipitation caused sloughing of the ear tips.[17]
- *Hypogammaglobulinaemia, with reduced or virtually absent serum IgM concentrations*: this is associated with equine lymphosarcoma and is suggested to occur where the neoplasms are of T-suppressor cell origin.[18–20] This may result in susceptibility to secondary infections, including pneumonia. In a small study (n=18), serum IgM concentrations were not found to be diagnostic for lymphosarcoma.[21]
- *Hypercalcaemia*: Although this is often quoted as being pathognomonic for bone infiltration, it has been documented in the absence of it.[6,10,22] Hypercalcaemia may result in renal disease due to mineral deposition.[22] Conversely, bone infiltration has been reported in the absence of hypercalcaemia, with local osteolysis in one case most likely caused by local osteoclast-inducing factors (usually produced by tumour-regulated osteoblasts), rather than systemic hormonal action.[20] Many horses with lymphosarcoma are actually hypocalcaemic as a result of hypoalbuminaemia.
- Other clinical chemistry abnormalities: including hyperfibrinogenaemia.[10]

Other paraneoplastic states have included pruritus, alopecia, mucosal ulceration and coronitis (see Fig. 6.6).[23]

General and site-specific pathology

Clinically and morphologically, equine lymphosarcoma tends to be subdivided on a topographical basis, i.e. by the major sites or organ systems involved.[1] The general aspects of lymphosarcoma pathology will be described here prior to more specific consideration of those topographical forms that have been documented in Equidae. It should be noted that it is often difficult to determine the primary location of disease at the time of examination, since metastasis often occurs rapidly and because horses are frequently presented at an advanced stage.

Gross pathology

Lymphosarcoma masses are soft, grey-yellow or tan, and homogeneous on sectioned surfaces. Where lymph nodes are involved, they are usually enlarged, and the normal cortico-medullary distinction is lost due to replacement by neoplastic tissue. In rare cases of lymphosarcoma where hypercalcaemia is sufficiently severe, there may be widespread calcification of walls of the aorta and other major arteries, in addition to the endocardium, heart valves and renal tissues.[22]

Histopathology

Sheets of round tumour cells obliterate or partially obliterate the normal architecture of involved organs/tissues. Where lymph nodes are involved, there is often complete replacement of normal architecture, and tumour cells may infiltrate through the capsule into perinodal adipose tissue. Lymphatic vessels in sections may contain large numbers of proliferating lymphoid cells.

Classification systems for lymphoid neoplasms (and haematopoietic neoplasms in general) as devised for human patients are not easily applied to animals. Both the Revised European–American Lymphoma (REAL) and World Health Organization (WHO) systems have been used,[1] but are not necessarily specific for equine lymphosarcoma. Both systems divide lymphosarcoma into those derived from B and T cells (and for the WHO system, natural killer (NK) cells), due to the fact that B- and T-cell neoplasms with a similar morphology may have very different biological behaviour.[24]

In horses, three immunophenotypes have been identified: these are B-cell, T-cell and T-cell-rich B-cell.[25] There may also be rare neoplasms of NK origin (see p. 345). Diffuse neoplasms, i.e. those that do not contain follicular structures, comprise the majority of equine cases; tumour cell follicles, if found, must be differentiated from remnant (pre-existing) follicles.[10] Lymphosarcoma cells in horses have been classified based on nuclear size, i.e. small (1.5× erythrocyte diameter) or large (×2 or greater).[25] The neoplasm may be classified as predominantly small-cell or large-cell type, respectively, if tumour cells of that size comprise 60% or more of the neoplastic cell population; if proportions are approximately equal, it is a mixed-cell type.[25]

Classifications

The WHO system of classification has been used wherever possible.

Diffuse small cell lymphosarcoma (B- or T-cell origin)

The tumour cells have sparse/inapparent cytoplasm and mature, small nuclei; they are round and regular in outline, their diameter is slightly larger than that of a red blood cell, they are hyperchromatic and lack nucleoli (Fig. 21.1).[24] Some of those neoplasms contain a smaller population of small lymphocytic cells, with irregular or folded nuclei, said to resemble small follicular centre cells.[25]

Diffuse large cell lymphosarcoma of B-cell origin (large B-cell lymphosarcoma)

This is the most common form of equine lymphosarcoma.[24] Lymphosarcomas with diffuse architecture that are composed of large B cells are subclassified using the WHO system and those reported in horses are as follows:

- *T-cell-rich B-cell lymphosarcoma (TCRBL)*. Most TCRBLs have been diagnosed in the subcutis or in abdominal or thoracic organs and associated lymph nodes; extranodal tumours of this type are rare in the horse.[10,25–27] Most cells in these TCRBLs are small, mature, reactive T lymphocytes that are not mitotically active (Figs. 21.1 and 21.2). The smaller numbers of large tumour cells (these may only comprise 5–10% of the total population) are of B-cell origin.[24] These tumour cells have moderate to large amounts of eosinophilic cytoplasm. Their nuclei are ovoid, folded or cleaved and may be multiple, with stippled or vesicular chromatin and multiple, prominent nucleoli.[25] As there is a fine diffuse reticulin framework, artefactual fissures in the tissue do not develop during histological processing, unlike other B-cell lymphosarcomas in this general (diffuse) category.[24]

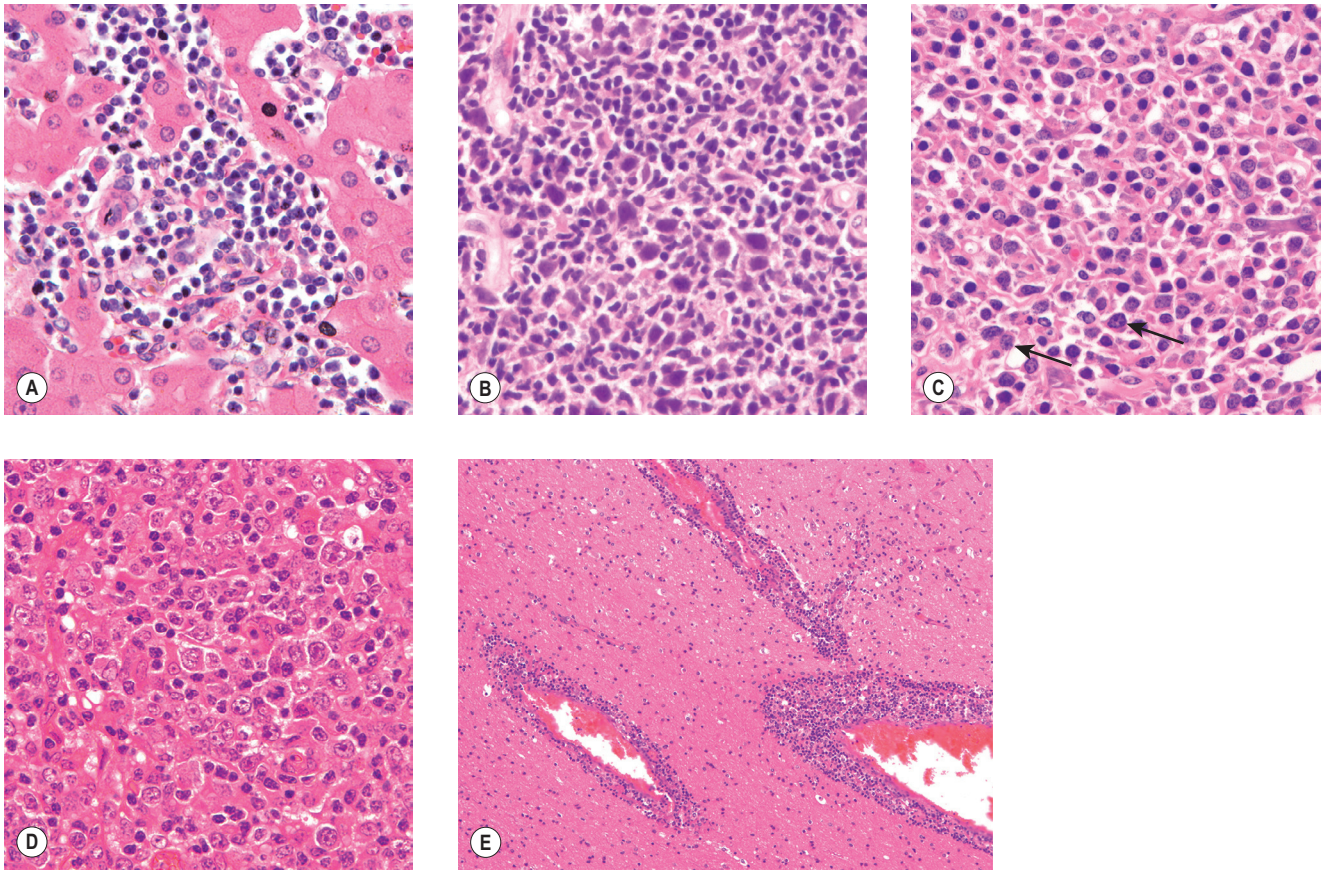


Figure 21.1 Diffuse large B-cell lymphosarcoma classification. **(A)** Diffuse small cell lymphosarcoma in the liver. Small, well-differentiated tumour cells with hyperchromatic nuclei are expanding hepatic sinusoids (H&E, ×400). **(B)** T-cell-rich B-cell lymphosarcoma in the conjunctiva of a 3-year-old horse. Small, well-differentiated lymphocytes predominate with smaller numbers of large tumour cells that have moderate amounts of deeply eosinophilic cytoplasm (H&E, ×400). **(C)** Mixed-cell lymphosarcoma in the small intestine of a 17-year-old pony. Small tumour cells with round or irregularly-shaped, hyperchromatic nuclei are admixed with larger tumour cells, with greater amounts of cytoplasm and larger nuclei containing 1–2 central nucleoli (arrows) (H&E, ×400). **(D)** Large-cell immunoblastic lymphosarcoma in a peripheral lymph node of a 17-year-old horse. Large tumour cells predominate, with moderate amounts of eosinophilic cytoplasm and large nuclei containing large, central nucleoli (H&E, ×400). **(E)** Lymphomatoid granulomatosis in the brain of a horse. Tumour cells are surrounding, infiltrating and expanding the walls of medium-sized blood vessels in the brainstem; the larger tumour cells are intermingled with smaller numbers of small, well-differentiated lymphocytes (H&E, ×100).

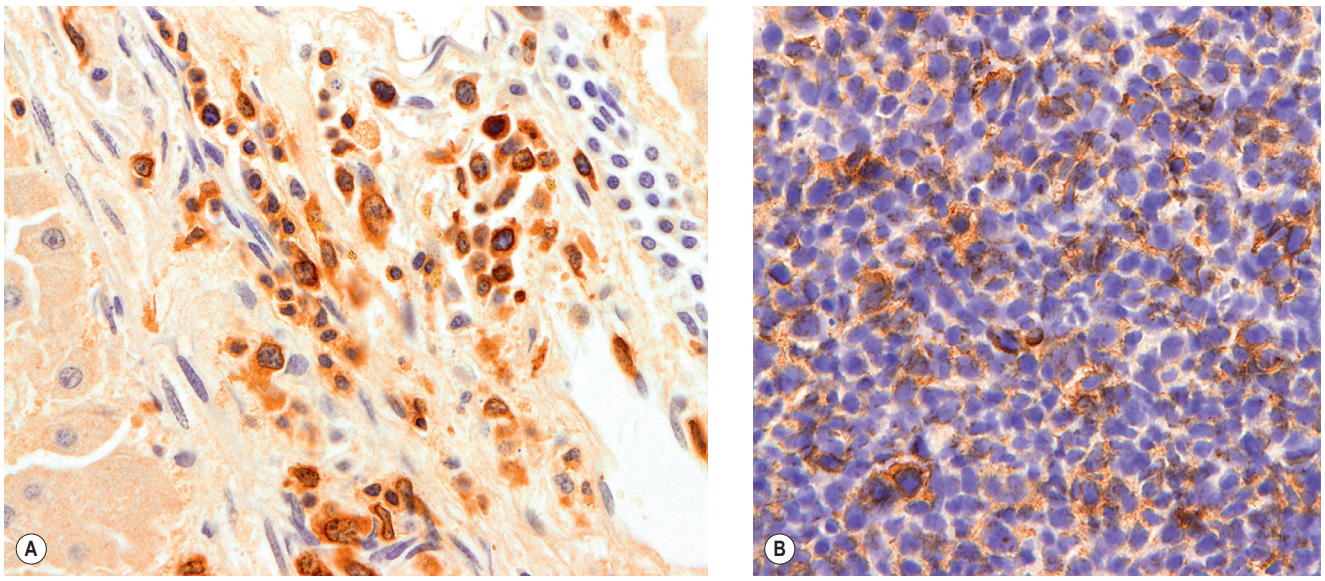


Figure 21.2 Immunolabelling of equine lymphosarcoma cells. **(A)** T-cell lymphosarcoma of the liver, with strongly CD3-positive tumour cells infiltrating a portal tract (immunohistochemistry, ×400). **(B)** BLA-36 staining of cytoplasmic membranes of lymphosarcoma cells of B-cell origin in a conjunctival mass (immunohistochemistry, ×400). The surrounding smaller cells are well-differentiated T-cells (see page 343).

- *Mixed-cell lymphosarcoma*. These neoplasms are composed of large and small (centroblastic and centrocytic) B cells, i.e. related to follicular centre cells.[24,25] Although mixed, they are included in the category of diffuse large B-cell lymphosarcomas if large cells predominate, even focally.[24] The small tumour cells may have mature nuclei or irregularly-shaped or folded nuclei (see Fig. 21.1). The nuclei of the large tumour cells are usually regular and round or angular; however, irregularly-shaped or hyperlobated nuclei with eccentric nucleoli may also be noted.
- *Large-cell immunoblastic lymphosarcoma*. These are diffuse B-cell neoplasms in which immunoblastic cells predominate, i.e. cells with a (variable) moderate to large amount of amphophilic or eosinophilic cytoplasm and a large, regularly-shaped (or cleaved) nucleus with thick nuclear membranes, branched chromatin with parachromatin clearing and a single, prominent and central nucleolus (see Fig. 21.1).[24] The fibrous stroma may divide the tumour cells into packets or nests.
- *Diffuse large B-cell lymphosarcoma (non-cleaved or cleaved)*. The tumour cells usually have scanty cytoplasm and nuclei are immature, with stippled or branched chromatin and prominent multiple (2–7) nucleoli that typically impinge on the nuclear membranes.[24] These neoplasms in horses have been described as having a mixture of regularly-shaped nuclei and cleaved/folded/giant convoluted nuclei that range in size from 12 to 30 µm.[25] However, other authors have stated that, in the horse, most are non-cleaved (i.e. they do *not* have sharp and deep infoldings of nuclear membranes), with the cleaved type comprising only 2% of cases.[24]
- *Lymphomatoid granulomatosis*. This is a progressive disease now classified as a variant of diffuse large B-cell lymphosarcoma that is most common in human patients (compared with TCRBL) and dogs, but has been reported in a horse and a donkey.[28–30] Classically, lesions occur predominantly in the lungs and potentially other sites, including the skin, kidneys, liver, and brain (and spinal cord).[28] Solitary or multiple, often large nodular masses may be noted in lung lobes, and in those cases, there may also be involvement of mediastinal, bronchial and submandibular lymph nodes.[28,30] The affected horse has ulcers in the oral cavity associated with neoplastic infiltration.[28] Histologically, these lesions begin as multifocal, nodular infiltrates centred on and within vascular walls, with transmural destruction of both arteries and veins (see Fig. 21.1), and associated ischaemic necrosis, oedema and haemorrhage.[1] Histological lesions in the lung may also be focussed on airways.[30] The tumour cells in equines with this disease have been moderately sized to large, with oval, indented or irregularly-shaped nuclei and multiple prominent nucleoli. These tumour cells were (as expected) admixed with reactive T cells and B cells and other inflammatory cell types, including macrophages, plasma cells, eosinophils and neutrophils. Phenotypically, lymphomatoid granulomatosis in animals does not necessarily fit with the classification as a form of T-cell-rich B-cell lymphosarcoma (see p. 343). Tumour cells in the horse were CD3-positive, i.e. of T-cell origin.[28] Atypical cells in the case reported in a donkey, including T and B cells, have also been reported in some cases in dogs.[1,30] Multinucleate giant cells in the donkey were of B-cell origin, rather than being histiocytic, as would normally be expected.[1] It has been suggested that as this disease in horses (and other animals) resembles lymphomatoid granulomatosis in human patients in tissue distribution and vascular tropism but not tumour cell origin, it would be more appropriate to diagnose it as 'resembling lymphomatoid granulomatosis'. In humans, the disease has been associated with Epstein–Barr virus (EBV); lesions in the donkey were not positive for EBV latent membrane protein or equine gammaherpesvirus DNA.[30]

Diffuse large cell lymphosarcoma of T-cell origin (Fig. 21.2A)

The tumour cells have a small to moderate amount of amphophilic cytoplasm, but the nuclei are usually regular in outline, with finely stippled chromatin and no prominent nucleoli. There is no associated fibrotic change in this type.

Intravascular (endotheliotropic) lymphosarcoma

There was one report of an intravascular lymphosarcoma in a 12-year-old Thoroughbred mare; tumour cells were proliferating within the lumens of blood vessels in multiple sites, with those cells homing to the endothelial lining.[31] Lymphosarcomas of this type are usually of B-cell origin and classified as a form of large B-cell lymphosarcoma,[1,24] but this was a T-cell neoplasm (as has occasionally been reported in other species).

Large granular lymphosarcoma

Large granular lymphocytes (LGLs) may be of T-cell (CD3+) *or* natural killer (NK) origin.[32] Rare lymphosarcomas derived from these cells have been described in horses ($n=4$) and one mule, mostly as disseminated forms, but in one case, as a focal small intestinal mass.[32–36] The LGL tumour cells have an abundant clear to pale-staining eosinophilic or basophilic cytoplasm with indistinct margins and often contain small eosinophilic granules (≤1 µm) – either forming a perinuclear cluster or more diffusely scattered. The granules stain blue to black with phosphotungstic acid haematoxylin (PTAH), may be periodic acid-Schiff-positive (PAS) and diastase-resistant and are Giemsa- and toluidine blue-negative.[32,33] Ultrastructurally, the granules are oval, electron-dense and limited by a single unit membrane. Nuclei are large, round to oval and central or eccentric with finely stippled or coarsely clumped chromatin and 1–2 nucleoli; some binucleate or multinucleate cells may be seen.[34,36] The nuclei may be deeply clefted.[24] In two equine cases, the tumour cells were demonstrated to be of T-cell origin by immunolabelling; if they are CD3-negative, they may be presumed to be of NK cell origin (see Immunohistochemical labelling, below).[24,36]

Associated lesions

Fibrous thickening of vessel walls and dissecting strands of connective tissue have been noted in equine diffuse small-cell tumours (a feature considered to be typical of follicular centre cell tumours).[25] Lesions in TCRBL may include infiltrates of epithelioid macrophages and multinucleate histiocytic giant cells, eosinophilic crystalline structures within the cytoplasm of giant cells, and amyloid deposition.

Histiocytic giant cells of the Langhans-type (i.e. with peripheral nuclei) have been described in other histological types of lymphosarcoma in horses, and proposed to be induced by tumour cell interferon-γ production.[10] It should be noted that some T-cell lymphosarcomas in horses may contain large areas of histiocytic and giant cell infiltration, and they should not be misdiagnosed as inflammatory lesions or neoplasms of histiocytic origin. There may be significant variation in the presence of necrosis, fibrosis or inflammation between different infiltrated tissues/organs, even in the same animal.[10]

Prevalence of different types

In one study (n=31) that included multicentric, thoracic, subcutaneous, hepatic, splenic and nasal equine lymphosarcomas, all had a diffuse histological pattern; most were large-cell (80%) neoplasms with smaller numbers of mixed-cell (10%) and small-cell (10%) neoplasms.[25] Percentages of B-cell, T-cell and TCRBL types have varied significantly between different studies.[10,25] The TCRBL type have been stated to comprise approximately 35% of lymphosarcomas in horses.[24] It is not known if lymphosarcoma types in horses vary geographically, as occurs in human patients; other potential sources of variation in these different equine populations include breed and age compositions, topographical forms of the disease analysed, referral status of the cases and relatively small numbers of cases (<40 per study).

Immunohistochemical labelling

T-cell lymphosarcoma cells stain positively for CD3 (see Fig. 21.2), while those of B-cell origin may stain positively for CD20, CD21, kappa light chains or lambda light chains.[37,38] Positive labelling of B cells using the anti-BLA-36 antibody has, as would be expected, been described as localized to their cytoplasmic membranes (see Fig. 21.2); however, the specificity is questionable due to additional staining of other lymphoid cells, reticulohistiocytic cells and endothelial cells in control lymph node tissue.[10,38] Other B-cell antibodies reported to stain equine lymphoid tumour cells and normal lymphocytes include those to CD79α and CD79β.[25,30] A small number of neoplasms have been reported (as in other species) in which tumour cells do not label with B- or T-cell markers or they express both.[10] Lack of staining can relate to: technical aspects, e.g. prolonged formalin exposure (ideally it should not be more than 48 h); failure to validate the antibody for use on equine tissue (see p. 202); or the neoplasm being of NK cell or null-cell origin.

Multicentric (generalized) lymphosarcoma

This is believed to be the most common form of lymphosarcoma in horses.

Biological behaviour

As in other species, this form of lymphosarcoma most likely commences in peripheral and/or internal lymph nodes and then invades other tissues (see Fig. 30.12). There is usually a short clinical course of weeks to months.[10] Lymphosarcoma in horses rarely becomes 'leukaemic', i.e. with significant spread of tumour cells to the blood and bone marrow; however, it is most likely with this form of the disease.[4] Cases of congenital lymphosarcoma tend to be disseminated, and this may include involvement of the subcutis and placenta.[8]

Gross pathology

Large numbers of organs and tissues may be involved, including liver, spleen, myocardium, intestine, skin, kidneys, lungs and bone marrow. Rare sites of involvement have included the uterus, vagina, urinary bladder and epididymis (bilaterally in one case).[39,40] Masses in the myocardium (Fig. 30.9) have been associated with left ventricular hypertrophy.[41] In one horse with multicentric lesions, infiltration of the heart was limited to valvular leaflets, the heart base and the pericardium, without myocardial involvement; that pattern is more typical in bovines than horses.[42] In another case, bone marrow infiltration resulted in myelophthisis and bone marrow necrosis, as previously reported in humans and dogs with lymphosarcoma.[43]

Although ocular involvement (see Fig. 34.5) is usually secondary rather than primary, 27% of horses with lymphosarcoma (n=79) had ocular neoplasms, including infiltration of the palpebral conjunctiva and eyelids, uvea, cornea/sclera, nictitating membrane and retrobulbar tissue; it has been suggested that early recognition of ocular lesions prior to obvious lymph node or visceral involvement may allow more rapid diagnosis in horses.[44] Conjunctival pseudotumours, i.e. putative immune-mediate inflammatory lesions and bilateral nodular lymphocytic conjunctivitis are important differential diagnoses for ocular lymphosarcoma.[45]

Alimentary lymphosarcoma

See also page 529.

Profile

Approximately 19% of horses with lymphosarcoma have the alimentary form, which in more advanced stages is difficult to differentiate from the multicentric form.[16] Lymphosarcoma is the most common primary intestinal neoplasm, comprising 56% of cases in one study of equine intestinal neoplasia (n=34).[16] It is a relatively frequent cause of chronic intestinal disease and/or diarrhoea, comprising 10–45% of referred cases (see Fig. 30.14).[46,47] The small intestine is more frequently affected than the large intestine; in one study (n=19), 74% of intestinal lymphosarcoma cases involved the small intestine; 53% the large intestine; and 32% the small colon, with 47% having multisegmental disease.[16] The stomach and rectum may also be involved in some cases.[48] The intestinal tract may be involved secondarily in other topographical forms of lymphosarcoma. The sudden appearance of subcutaneous neoplasms in horses with alimentary lymphosarcoma has been reported, and should be differentiated from the primary subcutaneous form (see below).[49]

In the intestinal tract, lymphosarcoma is thought to arise from local mucosal lymphoid tissue.

Some authors have suggested that most affected horses are young adults (2–7 years of age), while others have

presented it as a disease of older horses (mean age of 16 years in one study).[49,50] Younger horses (<10 years) are more likely to present with multisegment involvement, and older horses with focal lesions.[16,51]

It is not known if previous inflammatory disease predisposes to development of intestinal lymphosarcoma in horses, but some authors have hypothesized there is a progression from inflammation to (well-differentiated) neoplasia.[1] Inflammatory disease may also be secondary; one report of an intestinal lymphosarcoma that had spread to the pancreas and lungs was associated with multisystemic eosinophilic epitheliotropic disease, i.e. eosinophilic and lymphoplasmacytic infiltrates in multiple tissues, with formation of eosinophilic granulomas. This was suggested to be due to interleukin-5 (IL-5) production by the neoplastic T cells, as has been described in some human patients.[37]

Biological behaviour

Focal large colon tumours have been successfully surgically excised; survival can be prolonged by ≥1 year if there is no evidence of multicentric disease or metastasis to regional lymph nodes (see Fig. 28.27).[52] In one study of horses with alimentary lymphosarcoma (n=19), 65% showed involvement of regional lymph nodes and 76% had evidence of more distant metastasis, with pulmonary lesions in 9%.[16]

Particularly in cases where the small intestine is diffusely involved, horses may present with malabsorption, protein-losing enteropathy and weight loss, and in some cases, chronic profuse diarrhoea.[48,53]

Severe haemolytic anaemia has been reported in some cases, and this can be mistaken for equine infectious anaemia.[10,50,54] Hypereosinophilia was reported in one horse with small and large intestinal involvement.[55] In one case with pituitary gland metastasis, the horse presented with clinical signs suggestive of pituitary pars intermedia dysfunction (PPID/equine Cushing's disease), i.e. hirsutism and abnormal fat distribution. Since there was also diffuse pars intermedia hyperplasia, the relationship between the two was uncertain.[56] In another case, extensive effacement of hepatic architecture by tumour cells that had metastasized from a colonic mass resulted in clinical signs of hepatic encephalopathy.[57] In a horse with diffuse gastrointestinal lymphosarcoma (small and large intestine), ulcerative coronitis was documented as a paraneoplastic state.[58]

Gross pathology

Horses with alimentary lymphosarcoma may show ventral pitting oedema, weight loss, diarrhoea and thoracic and abdominal effusions.[54,59] The neoplasms may be solitary, segmental (usually annular) (see Figs. 21.3, 28.26, 28.27, 28.28, 30.16) or diffuse within the tract, and mucosal to transmural, involving the small and/or large intestine.[52,57] The proximal small intestine is most frequently involved.[1] In some cases, the neoplastic process diffusely involves the mucosa and submucosa of the small intestine and may also extend into the caecum and/or colon.[60] Infiltrated areas of the intestinal wall are thickened, with a corrugated or 'cobblestone' appearance to the mucosa. In some cases, solitary or multifocal and coalescing masses that are nodular (or resemble markedly enlarged Peyer's patches) bulge from serosal surfaces, sometimes with adhesion of the omentum.[50] The mucosa overlying masses that protrude into the intestinal lumen, and that of more diffusely thickened segments, may be ulcerated and necrotic.[32,37,41,49,54]

Severe annular thickening may result in intestinal hypomotility (distension and impaction) and there may secondary scarring and stenosis (see Fig. 21.3).[16,48] In three horses with diffuse small intestinal (T-cell) lymphosarcoma, there were multiple associated pseudo-diverticula (1–10 cm diameter), with deep mucosal ulceration and peritonitis in two cases.[61] The anti-mesenteric location of these pseudo-diverticula was postulated to relate to the location of Peyer's patches, from which the neoplasms may have arisen. Masses involving the large colon may protrude into the lumen and result in pelvic flexure impaction.[52] One large transmural mass arising in the ventral wall of the right dorsal colon

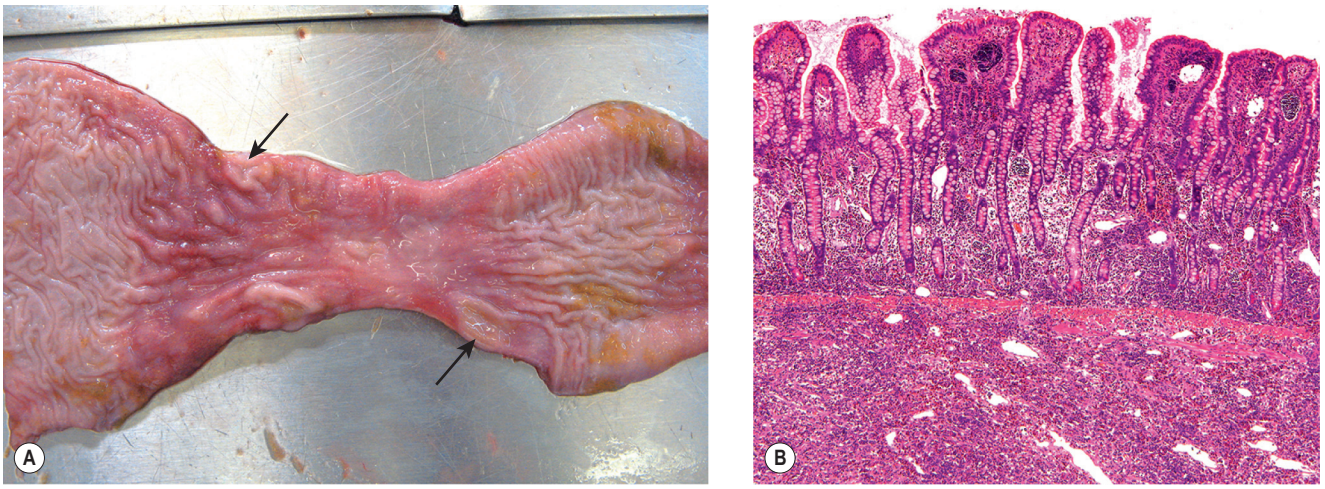


Figure 21.3 Small intestinal lymphosarcoma in horses. (A) Annular thickening of the small intestinal wall that has resulted in narrowing of the lumen (stenosis). The intestinal segment is opened to show the thickened mucosa (and submucosa), with particular prominence of mucosa-associated lymphoid tissue (arrows). **(B)** Histological appearance in a further case, with tumour cells diffusely infiltrating the lamina propria and submucosa, filling and distending some lacteals, and partially disrupting the muscularis mucosae. Villi are short, blunt and thickened, with fusion of some adjacent villi (H&E, ×40).

extended through the mesocolon to the mucosal surface of the right ventral colon, i.e. it created a fistula.[57]

Associated lymph nodes, including mesenteric, hepatic, splenic, inguinal and iliac, may be markedly enlarged and oedematous, and are often infiltrated by neoplastic tissue, as is the pancreas (see Fig. 30.15).[1,50] One study of primary small intestinal lymphoma ($n=6$) found no involvement of parenchymatous organs of the abdomen.[50]

Histopathology

In affected areas, there is diffuse tumour cell infiltration of the lamina propria and/or submucosa (see Figs. 21.3 and 30.14). In the small intestine, there will be marked atrophy and blunting of villi or in some cases a flat mucosal surface.[50] The tumour cells may obliterate normal crypt architecture in some fields; in epitheliotropic tumours, significant numbers infiltrate between the epithelial cells of both crypts and villi. There is variable infiltration of the muscularis externa and serosa; often the muscularis externa is spared and the neoplastic process is centred on the muscularis mucosae and submucosa.[1] Tumour cells may extend between bundles of smooth muscle cells and obliterate some myenteric ganglia.[49] The normal architecture of associated lymph nodes is often largely effaced by similar tumour cells, with extensive infiltration into and through their capsules.

Specific lymphocyte types from which alimentary lymphosarcomas may arise include B cells, epitheliotropic T cells (usually found in the intestinal epithelium) and large granular lymphocytes.[33,59] In the alimentary form, T-cell lymphosarcomas are considered to be more common than those of B-cell origin.[16] In cases where tumour cells have a plasmacytoid appearance, it is important to differentiate lymphosarcoma from a plasma cell-dominated inflammatory process.[1]

Associated lesions in the intestinal tract include inflammation (e.g. plasma cell and macrophage infiltration), crypt abscesses (crypts filled with neutrophils and other leukocytes), thinning of the mucosal epithelium, and ulceration with associated granulation tissue formation and inflammation.[59] Granulomas have been noted in infiltrated lymph nodes that were not associated with histologically identifiable bacteria; this change can be florid and dominate the histological picture.[50]

It may be possible to diagnose alimentary lymphosarcoma in some cases by observation of tumour cells in rectal biopsy specimens, but only if that segment of the intestinal tract is involved, i.e. a negative result does not rule out this diagnosis.[16] An associated lesion seen in 2 rectal biopsy specimens from 7 alimentary lymphosarcoma cases was a depletion in acid mucins (bright blue with Alcian blue-periodic acid-Schiff pH 3.0) and increase in neutral mucins, without depletion or hyperplasia of the goblet cells themselves.[62] There may often be nonspecific proctitis that is not related to neoplasia.

Mediastinal, thymic and thoracic lymphosarcoma

See also pages 503 and 531.

Profile

Lymphosarcoma is also the most common thoracic neoplasm in horses, comprising 54–74% of cases.[63,64] The mediastinal form comprises approximately 18–29% of total equine lymphosarcoma cases.[65] The neoplastic process may arise from and/or involve the mediastinal lymph nodes, mediastinum, thymus (Fig. 21.4), cranial thorax or lung. The thoracic forms do overlap with the multicentric form as a large proportion of horses with thoracic lymphosarcoma also have abdominal tumours.[66] Some authors do not classify equine thoracic or thymic lymphosarcoma as a separate form from the multicentric form.[1]

The mean age is around 10–12 years, but younger animals may also be affected.[67] It has been suggested that this form of equine lymphosarcoma is more common in males (both geldings and stallions).[6]

Biological behaviour

Thoracic lymphosarcomas in horses generally have a very rapid course, with a mean duration of clinical signs prior to

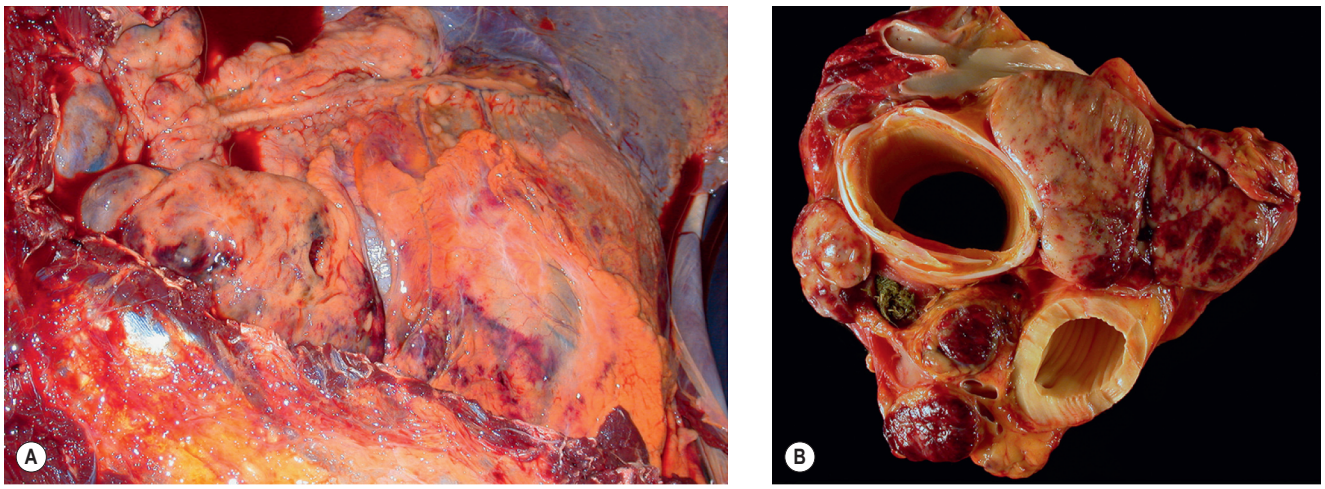


Figure 21.4 Thymic lymphosarcoma. (A) A large multinodular tumour mass seen cranial to the heart on opening the thoracic cavity. **(B)** Sectioned surface of the same mass showing nodules of neoplastic tissue surrounding the trachea (on the left) and oesophagus (on the right). *(Figures courtesy of Professor Keith Thompson, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, New Zealand.)*

euthanasia of approximately 4 weeks.[60] In one study, the predominant clinical signs related to the size of thoracic masses (15–36 cm in diameter) and the associated large volumes of pleural and pericardial effusion.[10] In a study of 38 cases of pleural effusion, four were due to lymphosarcoma and two of those horses presented acutely.[68] Mediastinal masses may compress a number of structures, including the cranial vena cava, left laryngeal nerve (associated with laryngeal hemiplegia), vagus nerve, brachiocephalic trunk, thoracic duct, right lymphatic duct, oesophagus and trachea.[66,69,70]

In one case, a complete atrioventricular block resulted in chronic right-sided heart failure, which was thought to have been due to vagus nerve compression.[70] Involvement of cervical sympathetic nerves by a mediastinal mass can result in Horner's syndrome.

One horse with a large mediastinal mass and involvement of the spleen showed tumour-associated bone resorption resulting in a pathological fracture of the left third metacarpal bone; in dogs with this type of lymphosarcoma-associated bone resorption, 88% had mediastinal involvement.[20]

Gross pathology

In 63–64% of horses with thoracic lymphosarcoma, there are large volumes (5–20 L) of modified transudate or serosanguineous fluid in the pleural cavity (containing neoplastic lymphocytes), resulting in dorsal displacement and compression atelectasis of the lungs (see Fig. 30.17).[64,66] This degree of fluid accumulation usually relates to neoplastic infiltration of mediastinal lymph nodes that reduces pleural lymphatic drainage.[71] Ventral thoracic and pectoral oedema are other common observations.[49,69,71]

Intrathoracic masses may be very large (up to 36 cm in diameter). In most cases where there is mediastinal involvement, the masses are nodular and appear to be coalescing enlarged lymph nodes rather than thymic neoplasms; in some cases, one or more masses protrude though the thoracic inlet and are observed at the base of the jugular groove.[66] There may be nodular masses over pleural surfaces.[72] The heart may be pushed caudally, and neoplastic infiltration of the myocardium has been noted. There may be involvement of thoracic, cervical, abdominal and peripheral lymph nodes, including prescapular and submandibular.[60] Death of one horse with thoracic lymphosarcoma was associated with exercise-induced pulmonary haemorrhage in addition to cardiopulmonary compromise.[73]

Histopathology

Lymphosarcoma cells may or may not be identifiable in aspirates of thoracic fluid (see Figs. 29.18 and 29.19). In one study, cytological examination of pleural fluid samples was useful in 10/12 horses with mediastinal lymphosarcoma that had thoracocentesis.[74] Types described include large cell and mixed-cell B-cell lymphosarcoma and large cell T-cell lymphosarcoma; in one study most mediastinal lymphosarcomas were of the latter type.[25,67] In another study, lymphosarcomas ascertained to be of T-cell origin ($n=26$) most often affected animals <5 years of age that had large mediastinal masses (although this was multicentric disease).[10]

Subcutaneous and cutaneous lymphosarcoma

See also page 533.

Profile

This is a rare form of lymphosarcoma in horses. Although involvement of the skin and subcutis occurs more frequently as part of multicentric disease, these are also sites of origin with exclusive involvement.[1,75] Epitheliotropic lymphosarcoma (mycosis fungoides) is an extremely rare cutaneous subtype in horses.[24,76,77] Subcutaneous and cutaneous nodules particularly affect the shoulders, pectoral area, thorax, flanks, thighs, inguinal regions, hip area, head, neck and perineum.[60,75,78] The lesions often cluster on the lower half of the body.[1] However, any part of the skin may be involved, with rare periarticular involvement.[79] There have been cases in horses with no grossly apparent skin lesions.[24] Epitheliotropic lymphosarcoma tends to present as a multifocal to generalized 'dermatitis'; one case involved mucous membranes of the mouth, nose and vulva and another originated as a vulvar mass with eventual extension into the retroperitoneum.[76,77]

Most horses with this form are 4–10 years of age; however, younger or older horses may be affected (neonatal to >30 years).[38,77,80–82] Purely subcutaneous (nodular) lymphosarcoma occurs predominantly in females.[1,38]

Biological behaviour

The subcutaneous nodular form is considered to be relatively non-aggressive, with some survival times between 5 months and 11 years.[10] Regression of cutaneous and subcutaneous nodules has been reported in some cases in association with pregnancy, administration of progestins and removal of an ovarian granulosa-theca cell tumour.[26] In one study, 6 of 9 equine subcutaneous lymphosarcoma cases expressed progesterone receptors (PR); however, these were also identified in some intrathoracic and intra-abdominal neoplasms.[83] The expression of PR was more frequent in B-cell lymphosarcomas versus those of T-cell origin. The subcutaneous lymphosarcoma that regressed following removal of an ovarian granulosa-theca cell tumour was a T-cell-rich B-cell lymphosarcoma (see p. 343). It was also noted that small numbers of PR-positive lymphocytes were present in normal lymph nodes, i.e. there may be constitutive expression.[83]

Gross pathology

This form of lymphosarcoma manifests as solitary or more usually multiple, well-demarcated but unencapsulated dermal and/or subcutaneous plaques or nodules (see Fig. 30.18). Lesions measure a few millimetres in diameter in their early stages (in some cases resembling urticarial plaques) and may grow to approximately 10 cm in diameter, sometimes with coalescence in advanced disease.[80] As above, neoplasms that are not epitheliotropic often present as multiple subcutaneous nodular masses that are not firmly attached to the overlying dermis. Usually, the overlying skin

is intact and not alopecic, but in some cases there is thickening, ulceration and hair loss. Many subcutaneous masses infiltrate into underlying skeletal muscle tissue.[78,81] In the rare cases when they are located over joints, there is frequently involvement of tendons and ligaments.[25,60] Approximately half of horses with this form of lymphosarcoma have enlarged peripheral lymph nodes.

Horses with epitheliotropic lymphosarcoma have diffusely or multifocally thickened and hardened skin (lichenification) with alopecia, reddening, crusting and scaling and potential ulceration.[77,82] This may progress to relatively large masses (see Figs. 27.15 and 30.19).

Histopathology

True subcutaneous lymphosarcoma tends not to involve the overlying deep dermis. It may track along lymphatic vessels, and tends to be subdivided by bands of collagenous tissue.[1] These neoplasms are nodular, and most are TCRBL.[1,79,81,82] However, tumours of T-cell origin have also been reported; in one report, five cases of the subcutaneous form were all T-cell lymphosarcoma.[38] Ultimately, the regional lymph nodes are also infiltrated by tumour cells.

Where the dermis is involved, the tumour cells surround and/or replace adnexal structures. One form of dermal lymphosarcoma that occurs as a recurrent, ulcerated periorbital mass is also a manifestation of TCRBL.[1]

Epitheliotropic lymphosarcoma has three stages:

1. Patch stage – the tumour cells are largely located within the epidermis and hair follicle epithelium (Fig. 21.5). The epidermis tends to be thickened and contains pathognomonic clusters of tumour cells, termed 'Pautrier's microabscesses'
2. Plaque stage – there is additional involvement of the superficial dermis
3. Tumour stage – nodules form in the dermis and subcutis and there may be progression to involve internal viscera.

The tumour cells are small, with scanty to abundant, eosinophilic or clear cytoplasm and large, hyperchromatic nuclei; they are of T-cell origin (see Fig. 21.5).[76,77] In horses, the nuclei have been shown to have multiple, deep indentations.[24] There may be associated ulceration of the epidermis. In one equine case, there were also circulating malignant T cells, this being a leukaemic form termed 'Sézary syndrome' that develops if the animal survives the chronic epitheliotropic skin disease.[24,42] Sézary cells have a characteristic cerebriform or convoluted nucleus.[1] One horse with an epitheliotropic lymphosarcoma had Sézary-like cells in tissues, but the primary epitheliotropic cells were found in mucosal epithelia (oral, gastric, vaginal, conjunctival) rather than the skin.[84]

Cutaneous lymphosarcoma can be mimicked by chronic insect bite reactions involving dense lymphocytic infiltrates.

Hepatosplenic and splenic lymphosarcoma

See also pages 470 and 535.

Profile

There have been small numbers of reports of lymphosarcoma restricted to or largely involving the spleen and liver, or spleen only.[2,15,85–87] Lymphosarcoma is the most common neoplasm of the equine liver.[88] Splenic and liver involvement are also a frequent component of the multicentric form.[87]

Biological behaviour

Many horses with this form of lymphosarcoma have presented with paraneoplastic syndromes, including hypercalcaemia, haemolytic anaemia, thrombocytopaenia, pseudohyperparathyroidism, and bullous pemphigoid (see Fig. 30.20).[15,22,86,89–93] The anaemia may result from trapping of erythrocytes in normal splenic tissue (i.e. hypersplenism), but potentially could also be immune-mediated.[1]

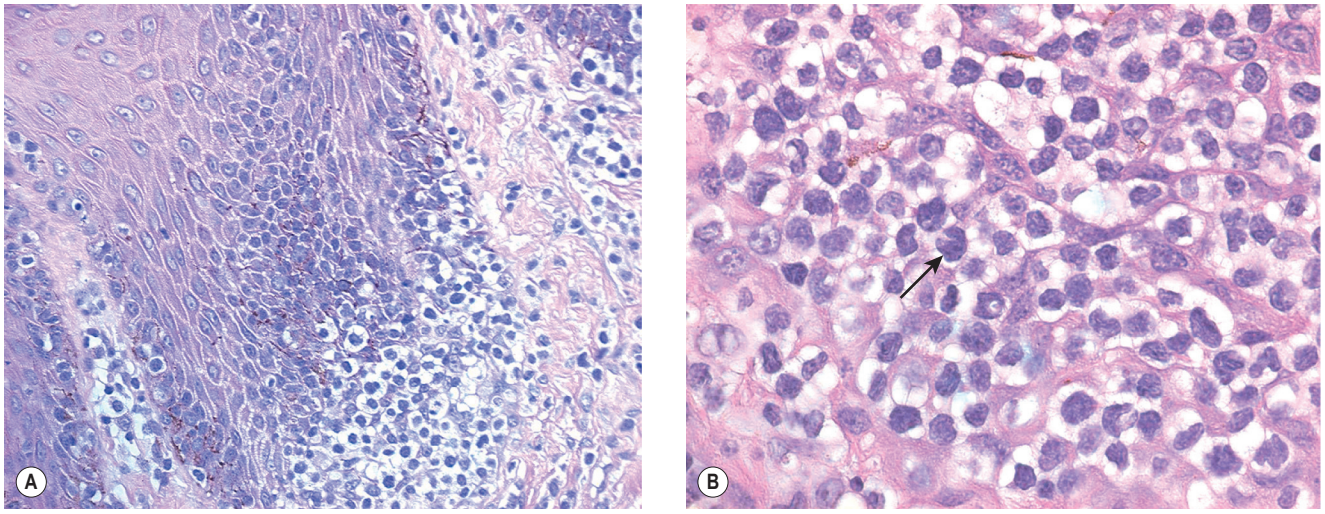


Figure 21.5 Epitheliotropic lymphosarcoma. (A) The tumour cells are infiltrating basal regions of the epidermis, which is hyperplastic (H&E, ×100). **(B)** Tumour cells, with abundant clear cytoplasm and large nuclei, some of which are deeply indented (arrow) (H&E, ×400). *(Figures courtesy of Dr Kathleen Potter, Washington Animal Disease Diagnostic Laboratory, Washington State University.)*

This form of the disease in horses is similar to human hepatosplenic lymphosarcoma; in human patients, thrombocytopaenia is usually the most striking haematological abnormality and is of uncertain aetiology.

Gross pathology

There may be large amounts of intra-abdominal serosanguineous fluid.[15] The spleen is usually enormously enlarged, with reported weights of 25–40 kg.[93,94] The spleen may be diffusely infiltrated (in ¼–⅓ of cases) with rounded margins and a 'cobblestone' appearance of the surface; in other cases, there is a defined, nodular pale tan or white mass expanding the pulp (see Figs. 28.32 and 30.20).[86,89,93,95] On sectioned surfaces of diffusely infiltrated spleens, the parenchyma is bright red and semi-firm, without significant oozing of blood. Focal masses may contain central areas of necrosis and mineralization. Larger masses might be palpated per rectum (see Fig. 30.20).

In cases of hepatosplenic lymphosarcoma, where there is diffuse infiltration, the liver is also enormously enlarged with a homogeneous consistency on sectioning and dilation of blood vessels including sinusoids.[15] The diffuse nature of infiltration of the spleen and liver is in contrast to involvement of these organs in the multicentric form, where nodular masses are usually observed. However, there may be nodular masses in rare cases restricted to *both* the spleen and liver.[87]

Hilar splenic lymph nodes may be enlarged with obliteration of normal architecture noted on sectioned surfaces, but they are not involved in all cases.[15]

Histopathology

In the diffuse form, tumour cells in the spleen are scattered throughout the red pulp and there is lack of distinct periarteriolar lymphoid tissue, i.e. the tumour cells are not confined to white pulp areas.[15,94] Infiltration of splenic trabecular tissue by tumour cells assists in making the diagnosis of neoplasia. Similar tumour cells efface normal regional lymph node architecture and, in the liver, form aggregates in the hepatic sinusoids and around central and portal veins (Fig. 21.6).[94] There may be multifocal trans-sinusoidal invasion of the hepatic parenchyma.[15] There are frequently large areas of necrosis, oedema and congestion. Lymphosarcoma types described include small, mixed- or large cell type B-cell or T-cell tumours and TCRBL.[15,25,94,95]

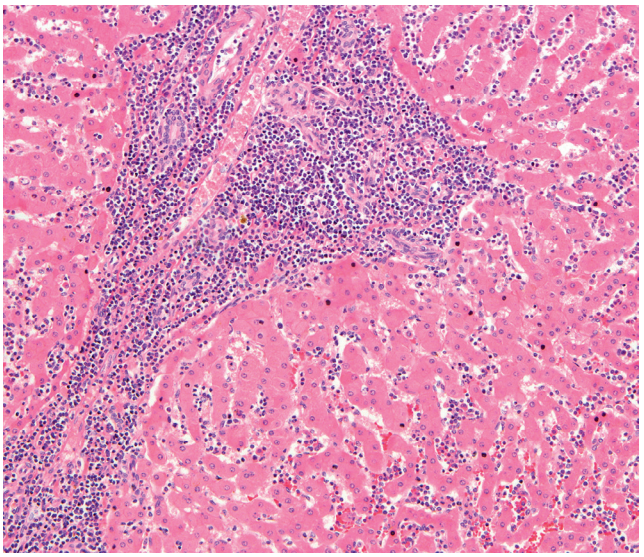


Figure 21.6 Diffuse lymphosarcoma involving the liver. The small tumour cells are infiltrating and expanding a portal tract, and are scattered in moderate numbers within hepatic sinusoids (H&E, ×100).

Nasal, paranasal and nasopharyngeal lymphosarcoma

Profile

Primary lymphosarcoma in these sites is extremely unusual, but can occur in horses or ponies of any age (18 months to 27 years) with specific sites including the nasal cavities, maxillary sinuses, ethmoid regions, soft palate and pharynx.[2,25,96–100] The nasopharynx is a more common site of origin than sinonasal areas, which may relate to higher amounts of lymphoid tissue in that region. Lymphosarcoma masses may also arise in the soft palate and pharynx.[27] There is local and often extensive invasion of both soft tissues and bone. Metastasis may involve regional lymph nodes, visceral lymph nodes and internal organs, including the spleen.[97]

Gross pathology

In these sites, neoplasms may be seen as nodular or multilobed fleshy masses protruding into the lumen (and potentially causing airway obstruction) or diffusely thickened areas.[27,82,99]

Associated lesions may include invasion through the cribriform plate into the calvarium with brain compression and meningeal infiltration, facial distortion, lysis and periosteal reaction of sinonasal bones, nasal septum deviation, permanent soft palate displacement, oronasal fistulation, sinus empyema, haemorrhage/epistaxis, and overlying epithelial ulceration.[27,96,97,99] Ulcerative lesions of the dorsal surface of the soft palate associated with neoplastic infiltration have also been reported in horses with multicentric or cutaneous forms of lymphosarcoma.[101]

Histopathology

An extensive sinonasal mass of B-cell origin was confirmed by positive labelling of tumour cells for BLA-36 and negative labelling for CD3.[96] A pharyngeal mass was diagnosed as a TCRBL.[27]

Differential diagnoses

Non-neoplastic

Lymphosarcoma involving the nasopharynx must be differentiated from pharyngeal lymphoid hyperplasia of young horses.

Nervous system lymphosarcoma

See also page 677, Fig. 37.6.

Profile

In 25 central nervous system neoplasms of horses, nine were of lymphoid origin but only one case was primary.[102] Most lymphosarcoma cases involving the central nervous system arise as part of multicentric disease or by local invasion from an adjacent site. For example, a cutaneous lymphosarcoma that infiltrated the cerebrum and cerebellum was reported in a 6-year-old horse.[103] The spinal cord is more frequently involved than the brain, although both sites may be affected in multicentric disease.[104] Primary meningeal lymphosarcoma has been reported to involve the spinal cord as a diffuse process, and as a lymphomatoid granulomatosis involving the meninges and parenchyma of the brain.[105] There have been small numbers of reports of spinal cord compression and ataxia caused by epidural, dural or vertebral lymphosarcoma masses, generally as part of multicentric disease (see Figs. 33.2 and 37.6).[6,106–109] Lymphosarcoma masses can also involve single or multiple peripheral nerves, particularly the cranial nerves. Polyneuritis equi is a differential diagnosis.

Ocular lymphosarcoma

See also page 620.

Profile

Ocular structures are rarely the primary or exclusive site of lymphosarcoma. More often, ocular lymphosarcoma is the first indication of multicentric or more disseminated peripheral disease (see Fig. 3.2C).[5,44] For example, in one case, diagnosis of bilateral eyelid swelling caused by lymphosarcoma infiltration preceded development of multiple subcutaneous masses.[110]

Ocular lymphosarcoma usually involves the adnexa, but may also occur in the conjunctiva (see p. 346), uvea, cornea/sclera or as a retrobulbar mass (Fig. 34.5).[5,6] There have been a few cases of lymphosarcoma of the nictitating membrane that were diagnosed as primary, including (metachronous) bilateral involvement.[111–113] In one such case, the neoplastic tissue was successfully excised.[112] As stated above (p. 346), conjunctival pseudotumours are a differential diagnosis.

Unusual sites

These have included the parotid salivary gland, mandibular gingiva (with osteolysis), mandible, prepuce, pelvic canal and ovaries.[2,6,114–118]

LEUKAEMIA

See also page 539.

Cellular origin

Primary leukaemia arises from lymphoid, myeloid, monocytic or erythroid cells in the bone marrow and/or peripheral blood and describes the presence of these neoplastic cells in the circulation. Secondary leukaemia occurs when the bone marrow involvement is due to metastasis from another site: i.e. in advanced cases of multicentric lymphosarcoma.[119]

Classification and profile

The current classification standard of veterinary leukaemia is the World Health Organization (WHO) system, which is modified from human systems, including the French–American–British (FAB) and the Revised European–American Lymphoma (REAL) classification system of lymphoid neoplasms.

Myeloid leukaemias

See also page 539.

Myeloid leukaemia is classified according to the stage of differentiation (acute vs chronic) and the cell type of origin.

Acute myeloid leukaemias

Acute (precursor) myeloid leukaemias (AMLs) are poorly-differentiated, rapidly progressive forms arising from myeloid progenitor cells in the bone marrow.[1] The number of blast cells in the bone marrow or blood required to diagnose AML have been set at 20% (rather than 30%). The reason for the reduction of the required blast cell percentage is that, in studies of myelodysplastic syndrome (MDS) in which the blast cells were in the range 20–29%, the majority of cases had an aggressive course similar to that of AML with multilineage dysplasia. In other words, MDS with excess blasts in transformation and acute myeloid leukaemia are likely to be the same disease process.[120] These precursor myeloid leukaemia cases are classified as follows (WHO system), and the forms reported in horses to date are indicated and described:

- **AML M0** *Acute myeloid leukaemia/undifferentiated leukaemia*
- **AML M1** *Acute myeloid leukaemia without maturation*
- **AML M2** *Acute myeloid leukaemia with maturation:*
  There has been one report of this form in a horse.[121] It is similar to M1, except that maturation proceeds to or past the promyelocyte stage in at least 10% of tumour cells.[1] There are poorly-differentiated blasts, promyelocytes and myelocytes with phthisis of normal cells[24]
- **AML M3** *Acute promyelocytic leukaemia*
- **AML M4** *Acute myelomonocytic leukaemia:*
  This is believed to be the most common form of myeloid leukaemia in horses, with a number of reports.[120,122–126] In this form, there is concurrent proliferation of neutrophil and monocytic cell lines; at least 20% of the cells must be of monocyte lineage to distinguish this form from M2[1,24]
- **AML M5A** *Acute monoblastic leukaemia*
- **AML M5B** *Acute monocytic leukaemia:*
  There have been a few reports of this form in adult horses.[127,128] Compared with acute monoblastic leukaemia, there is greater cellular maturity with promonocytes predominating; in both M5A and M5B

at least 80% of bone marrow cells are blastic or promonocytic forms[24]

- **AML M6A** *Erythroleukaemia*
- **AML M6B** *Erythemic myelosis (pure acute erythroid leukaemia):*

  This form was recently reported in a 10-week-old Thoroughbred foal that did not have circulating neoplastic cells.[129] There is proliferation of erythroid cells with extreme anaemia and high numbers of peripheral blood rubricytes[24]
- **AML M7** *Acute megakaryoblastic leukaemia.*

Chronic myeloid leukaemias

Chronic myeloid leukaemias (CML) arise from more mature (i.e. late) precursor cells with release of mature or well-differentiated cells into the circulation.

Chronic leukaemia typically occurs in aged animals. It may progress to a more acute form in some cases, termed 'blast cell crisis'. Additionally, there may be some cases that share features of both acute and chronic forms.[51] They are classified as follows (WHO system), and the forms reported currently in horses are indicated and described:

- **CML** *Neutrophilic or eosinophilic*:

  Most granulocytic leukaemia cases in horses are in young or mature animals and are thought to be neutrophilic in origin.[4,51,130,131] In neutrophilic and eosinophilic forms, there are very high peripheral white blood cell counts with marked myeloid predominance in the bone marrow. There is one report of eosinophilic myeloproliferative disease in a 10-month-old colt that was considered to be neoplastic[132]
- **CML** *Monocytic*
- *Polycythaemia vera*:

  This condition has been reported in one 13-year-old Thoroughbred horse.[133] This is characterized by overproduction of mature red blood cells but without concurrent cytopaenia.[24]
- *Megakaryocytic myelosis/essential thrombocythaemia*.

Lymphoid leukaemias

See also page 540.

Leukaemias derived from lymphoid cells are rare in the horse. The distinction between leukaemia and lymphosarcoma can be difficult (e.g. if large numbers of tumour cells of bone marrow origin infiltrate peripheral tissues), and is usually based on the tissue area containing the largest mass of tumour cells (peripheral vs bone marrow).[1] Lymphosarcoma and leukaemia of the same cell type are often regarded (but not in all classification systems) as different manifestations of the same disease process.[1] These diseases have been reported in a small number of young adult and (predominantly) older horses, of T-cell or B-cell origin and with a possible predisposition for males.[134–138] Older reports do not include immunolabelling for T- or B-cell markers, but in investigated cases in horses, T-cell origin seems to predominate.[137] Large granular lymphocyte leukaemia has also been reported.[139]

Chronic lymphocytic leukaemia is slowly progressive with accumulation (rather than proliferation) of small lymphocytes in the bone marrow and peripheral tissues, as opposed to lymphoblastic leukaemia, which is rapidly progressive with moderately sized (immature) tumour cells.[24] Neoplastic cells may be functionally deficient (e.g. fail to proliferate in response to mitogens), even if there are no signs of immunodeficiency in the affected horses.[137]

The importance of myelophthisis

Replacement of normal haematopoietic tissue in the bone marrow by tumour cells, i.e. myelophthisis, has significant clinical implications, i.e. some degree of bone marrow failure characterized by anaemia, thrombocytopaenia, lymphopenia and/or neutropenia when 50% or more of the bone marrow is involved (see Fig. 30.13).[1] These changes occur before the onset of overt leukaemia and may indicate a dysplastic, i.e. preleukaemic syndrome, as occurs in human patients, during which there is not sufficient arrest in cellular maturation to support a morphological diagnosis of neoplasia.[123] There may be a resultant increased susceptibility to secondary infections, with pulmonary aspergillosis reported in one case.[124] In the same case, there was an increased serum iron concentration, low total iron-binding capacity and high percentage saturation of iron-binding protein, this being a pattern that has been seen in many human leukaemia patients.

Gross pathology

Affected horses are often underweight and peripheral lymph nodes may be enlarged (depending on the type of leukaemia). Ventral and hindlimb oedema may be noted, and in some cases, evidence of haemorrhagic diathesis, i.e. petechial and ecchymotic haemorrhages in the subcutis, internal serosal surfaces, laryngeal and tracheal mucosa, epicardium and endocardium.[125] It has been suggested that ventral oedema may be caused by either obstruction of lymphatic drainage, or vascular damage caused by the circulating tumour cells.[137] There may be mucous membrane and tissue pallor due to anaemia, and oral ulcers can occur. Involvement of the skin is not common, but has been reported in the horse, and skin ulcers may be noted.[128]

The bone marrow in sectioned bones may be white, grey-yellow or deeply red, glistening, fleshy, and uniformly vascular rather than hard and white (due to the normal presence of adipose tissue). There may be foci of remnant fatty tissue in horses.[1] Pale tan/grey masses (>5 mm in diameter) may be seen in many organs (depending on the type of leukaemia), including the spleen, kidneys, lymph nodes (including peripheral nodes) and lungs; lymph nodes show loss of the normal follicular structures on sectioned surfaces. Masses in internal organs may have an obvious perivascular orientation (or peribronchial in the lungs).[124] There can be marked enlargement of the liver and spleen due to diffuse tumour cell infiltration; the liver may show a pronounced lobular pattern, and the spleen will be dry and fleshy on sectioned surfaces.[1] Involvement of the heart, when it occurs, is usually diffuse rather than involving nodular masses.[140] The gastric and intestinal mucosa and submucosa may be thickened, in some cases with ulceration.[124,125,127,136] There may be areas of haemorrhagic

infarction of multiple organs if there has been severe thrombocytopaenia.[1] Other lesions relating to bone marrow failure can include secondary infections, i.e. pneumonia or cellulitis.

Histopathology

The bone marrow tissue is markedly hypercellular and likely to be almost entirely composed of tumour cells.[125,134,141] There may also be myelofibrosis, and areas of tumour cell necrosis. Sheets of lymphoid or myeloid tumour cells may be found infiltrating both the bone marrow and multiple tissues and organs *from* the blood vessels. In the bone marrow, colonization by (acute) lymphoid tumour cells is random, as opposed to those of acute myeloid leukaemias that occupy subendosteal sites (to compete with benign stem cells).[1] The tumour cells within, infiltrating from and surrounding blood vessels (and pulmonary airways), may be associated with thrombosis and infarction. Intravascular leukostasis has been reported in horses with myelomonocytic leukaemia and associated with significant tissue damage.[122,126] In humans (and in horses according to previous reports), leukostasis occurs most commonly in the blast crisis phase of monocytic or myelomonocytic leukaemias, when there is a sudden and rapid rise of circulating leukaemic blast cells to >100 000/μL, which usually signifies complete bone marrow replacement by tumour cells.[122]

Infiltrated tissues may include peripheral and visceral lymph nodes, skin and subcutis, mammary glands, mediastinum, spleen, liver, kidneys, testes, gastrointestinal tract, pancreas, lungs, heart and brain (including meninges). In infiltrated lymph nodes, there is loss of architectural detail, and remnant fading follicles may be noted; extensive involvement of lymph nodes and marked disruption of architecture is more likely in cases of lymphosarcoma than lymphoid (or myeloid) leukaemias. In the liver, tumour cells typically infiltrate portal areas and around central veins, and are noted within sinusoids; there may be periacinar ischaemia.[134] There is minimal or absent periportal infiltration. In the spleen, the tumour cells tend to infiltrate red pulp filtration beds (the equine spleen is non-sinusal), and they may be seen infiltrating walls of larger blood vessels (with a subendothelial location), the fibromuscular trabeculae and the splenic capsule.[1] The splenic lymphoid tissue is typically atrophic (some lymphoid leukaemias will expand the white pulp) and haematopoietic activity is minimal.

The histological morphology of the tumour cells will vary according to the cell type (and stage) of origin and, where possible, should be correlated with cytological findings (see Figs. 7.7 and 30.13). Initially, it is important to determine if the leukaemia is of lymphoid or myeloid lineage, which requires histochemical and/or immunohistochemical labelling (see below). Myeloid blast cells (in cases of AML M2) have a moderate amount of amphophilic or eosinophilic cytoplasm that may be slightly granular and/or vacuolated, and a round nucleus containing multiple eosinophilic nucleoli and marginated chromatin; the mitotic rate is high.[1,24,123] Cases of acute myelomonocytic leukaemia (AML M4) are not distinguishable histologically from AML M2.[1] In acute monocytic leukaemia (AML M5B), the tumour cells are similar to cleaved lymphocytes, with deeply amphophilic cytoplasm, and again this would require confirmation by cytological examination. In erythemic myelosis (AML M6B), the erythroid cells have a moderate amount of deeply stained cytoplasm, and a large primitive nucleus that is round or slightly irregular in shape, with a thickened nuclear membrane, a single and prominent central nucleolus and finely stippled chromatin.[1] In chronic myeloid leukaemias (CML, neutrophilic or eosinophilic), there are mixtures of primitive and mature tumour cells; primitive cells have abundant amphophilic cytoplasm and round or oval nuclei containing coarsely granular chromatin and a prominent central nucleolus.[1]

Lymphocytic tumour cells may be small or medium-sized with oval, indented or convoluted nuclei that have clumped chromatin and indistinct or absent nucleoli. Lymphoblastic cells are medium-sized (with some larger and smaller cells) with high nuclear:cytoplasmic ratios, round nuclei with finely or coarsely granular chromatin and multiple prominent nucleoli. In a case of large granular lymphocyte leukaemia, the tumour cells had an abundant basophilic cytoplasm, and granules were only observed by staining with phosphotungstic acid-haematoxylin and Giemsa.[139]

Associated lesions may include eosinophilic granulomas in T-cell leukaemias, which may relate to production of eosinophilopoietic factors, including interleukin-5 by tumour cells of a T-helper lineage.[136] Septic lesions (noted in myeloid or lymphoid cases) may only contain small numbers of neutrophils due to bone marrow depletion.[1] Lymph nodes may be enlarged due to draining of secondary inflammatory/infectious disease rather than, or in addition to, neoplastic infiltration. Extramedullary haematopoiesis may be noted in various organs, including lymph nodes and adrenal glands.[1]

Immunohistochemical labelling (and histochemical stains)

Lymphoid and myeloid tumour cells may be differentiated by immunolabelling for T- and B-cell markers and use of the Sudan Black B stain or myeloperoxidase reaction.[1] T-cell tumour cells stain positively for CD3, while those of B-cell origin may stain positively for CD20, CD21, kappa light chains or lambda light chains.[37,38] Positive labelling of B cells using the anti-BLA-36 antibody has been described as localized to their cytoplasmic membranes, as expected; however, the specificity is questionable due to additional staining of other lymphoid cells, reticulohistiocytic cells and endothelial cells in control lymph node tissue.[10,38] Other B-cell antibodies reported to stain equine lymphoid tumour cells and normal lymphocytes include those to CD79α and CD79β.[25,30] If snap-frozen tissue is collected, further antibodies may be used to characterize lymphoid tumour cells, including CD2 (T cells); CD4 (T-helper cells); CD5 (T cells and IgM-secreting B cells); CD8 (cytotoxic T cells and natural killer cells); WC1 (T cells and neutrophil subsets); WC2 (T cells and neutrophils); and CD13 (myeloid cells).[136] In one study of six horses with lymphoid leukaemia of T-cell origin, the cells expressed predominantly CD3 in tissue and CD4 in peripheral blood.

Once a myeloid origin has been confirmed, the chloroacetate esterase stain and the nonspecific esterase

stains (α-naphthyl acetate substrate or α-naphthyl butyrate) may be used to identify granulocytic and/or monocytic origin, respectively (i.e. histochemical methods).[1]

Differential diagnoses

Secondary leukaemia results from an advanced stage of lymphosarcoma, where neoplastic cells arising in peripheral tissues invade the bone marrow; horses in the late course of lymphosarcoma disease appear to develop this.[138] As opposed to primary leukaemia, there will be more extensive involvement of peripheral tissues including lymph nodes; however, in contrast to primary leukaemia, the liver and spleen will be less frequently involved. The latter is not always the case; an exception is the hepatosplenic form of lymphosarcoma. Histologically, primary leukaemia in the bone marrow is usually diffuse, while secondary leukaemia involves focal aggregates of tumour cells around blood sinuses.[138]

PLASMA CELL NEOPLASMS

Plasma cell neoplasms are of mature B-cell origin.[24] They originate in soft tissues or bone, with multiple myeloma arising in the bone marrow.

Plasmacytoma

Cellular origin

The condition arises from plasma cells other than those of the bone marrow. These neoplasms are classified as either indolent or anaplastic.[24]

Profile

Plasmacytoma is rare in domestic animal species other than the dog. One report of a disseminated tumour in a 10-year-old Clydesdale mare involved the pericardium, mediastinum, adrenal glands, meninges, atrioventricular valves, aorta, internal fat and nerves, including the trigeminal nerve.[142] A 17-year-old horse had multiple cutaneous and subcutaneous plasmacytomas (over the entire body) in addition to involvement of the lymph nodes, joint capsules, muscles, right eye and nasal mucosa.[143] In another case, a mass involving the third thoracic vertebra extended into the spinal canal and caused spinal cord compression; this appeared to be a solitary mass (i.e. solitary osseous plasmacytoma), although it could not be certain if there was more widespread involvement of bony tissue.[144]

Biological behaviour

Indolent (well-differentiated) plasmacytoma is benign and should be cured by surgical excision. Anaplastic plasmacytomas progress slowly and only metastasize in rare cases.[24] In other species, plasmacytomas of the skin and oral cavity tend to be benign, and those of the oesophagus and gastrointestinal tract, malignant.[1] In the skin of horses, they may be associated with cutaneous amyloidosis, i.e. light-chain amyloid (p. 230).[145] In one horse with extramedullary plasmacytoma that presented with dysphagia and ptyalism, tumour cells infiltrated the trigeminal nerve.[142]

Anaplastic extramedullary plasmacytomas can arise in indolent neoplasms.[24] A localized plasmacytoma in the bone (solitary osseous plasmacytoma) has the potential to progress to multiple myeloma (see below).[1]

Gross pathology

In the skin, plasmacytoma presents as nodular masses that vary in size.

Histopathology

The tumour cells are arranged in sheets, packets and/or cords. In indolent plasmacytomas, the cells are monomorphic, with a moderate amount of deeply eosinophilic cytoplasm that may show perinuclear clearing (Golgi zone).[24] The cytoplasm is intensely pyroninophilic using the methyl-green-pyronin method, although this is not a specific stain. Nuclei are eccentric, round to oval or sometimes compressed, with coarsely clumped chromatin (they are usually <1.5 red blood cells in diameter). Occasional binucleate tumour cells are observed, and the mitotic rate is low. In anaplastic plasmacytomas, the amount of cytoplasm is variable (it may be more abundant for cells with larger nuclei), and there is more marked anisokaryosis with more frequent binucleation/multinucleation/multilobation, hyperchromatic nuclei, multiple nucleoli within larger nuclei (up to 4–5 times red blood cell diameter) and a higher mitotic rate.[1,24] There may be associated areas of non-neoplastic lymphoid proliferation. Amyloid deposition may also be noted (p. 230).

Immunohistochemical labelling

Tumour cells may stain positively for IgA, IgG or IgM. They have been reported to stain negatively for CD79α and BLA-36 (B-cell markers) and CD3 (T-cell marker) but should be vimentin-positive.

Differential diagnoses

These are listed in Box 21.1.

Pseudolymphomas have occasionally been diagnosed in horses, forming multiple nodular masses largely over the head and trunk. They are composed of dense dermal or subcutaneous infiltrates of lymphocytes, macrophages, plasma cells and eosinophils; some may be caused by insect bites.[145]

Box 21.1 Differential diagnoses for plasmacytoma

Neoplastic
- Lymphosarcoma
- Mast cell tumour

Non-neoplastic
- Pseudolymphoma

Multiple myeloma

See also page 536.

Cellular origin

This is a highly malignant neoplasm derived from plasma cells or plasmacytoid lymphocytes (large B lymphocytes with some characteristics of plasma cells) that arises in the bone marrow. Malignant myelomas are characterized by production of monoclonal immunoglobulin, osteolysis, myelophthisis, clinical hyperviscosity and bone pain.[24]

Profile

Few reports of this tumour type have been made. Horses between 3 months and 22 years (and with an approximate median age of 11 years) are affected.[146–155] Quarter Horses may be over-represented, but this is not certain due to the small number of cases.[146,150,154] There does not appear to be any gender predilection.

Biological behaviour

The neoplastic plasma cells usually overproduce a monoclonal immunoglobulin product, i.e. a paraprotein that is not immunologically active (see Figs. 7.6 and 30.21). This may represent complete or partial immunoglobulins, free light chains, light-chain fragments or light-chain polymers. In most equine cases, the paraprotein has been IgG, with reports of IgA in only three cases.[148,152,155] There has been one report of a non-secretory multiple myeloma, in a 20-year-old Thoroughbred gelding, which occurs due to an inability of the tumour cells to either produce or secrete the globulin proteins.[153] There may be detection of Bence Jones proteins in the urine; however this is very uncommon in equine cases.[147,149] Bence Jones proteins are the light-chain component of the myeloma globulin; these proteins have a low enough molecular weight to pass through normal glomerular filtration mechanisms into the urine.

Hypercalcaemia may occur as a result of osteolysis or neoplastic production of prostaglandin E_1 but, in general, does not appear to be as common in horses as it is in human patients.[149,153] Horses may show signs of bone lysis without hypercalcaemia.[149] The tumour cells may secrete osteoclast-activating factor, which increases osteoclast activity and inhibits osteoblasts. In one case, expression of parathyroid hormone-related protein (PTHrP) was associated with hypercalcaemia.[152] Anaemia, thrombocytopaenia and leukopaenia may be present.

Amyloidosis occurring as a primary process, i.e. accompanying monoclonal plasma cell proliferation, is a risk.[1] This may be a cause of renal failure in these cases, and may also often affect the liver and heart. Severe (light-chain) amyloidosis of the intestine, stomach, spleen and bone marrow was reported with a case of multiple myeloma where the horse showed signs of malabsorption.[154]

There may be increased susceptibility to bacterial infections (for multiple reasons, including deficiencies in normal immunoglobulins and impaired neutrophil function), and horses may develop bronchopneumonia and/or lung abscesses.[146,147,151,155]

Most horses die or are euthanized within 3–4 months of presentation, but some have survived for up to 2 years.[146]

Gross pathology

Affected horses are often underweight, and ventral oedema and peripheral lymph node enlargement may be noted. In one survey (n=10), many affected horses had limb oedema.[146] There may be blood within the nasal cavities and urinary bladder, and serosanguineous exudates in body cavities (as a result of coagulation abnormalities including thrombocytopaenia).[151,153]

There is observation of white nodular masses in the bone marrow in some cases and homogeneous tan (neoplastic) marrow tissue in others.[149,152] Bone involvement may vary from small areas of lysis to diffuse osteoporosis; radiographically, there may be well-circumscribed 'punched out' foci or regions of diffuse decalcification. Focal punctate bone lysis is the most frequently reported lesion in horses (see Fig. 7.19), and this may include subperiosteal cortical erosions.[146,149] There may also be adjacent periosteal reaction and sclerosis. In some horses, this disease may result in pathological fractures.

Nodular masses may also be noted in multiple internal and peripheral sites, including kidneys, liver, spleen, lung, brain, pituitary gland, orbit, adrenal glands, mediastinum, tongue, ligamentum nuchae, skeletal muscle, skin and lymph nodes.[146,148,149,152] The frequent involvement of lymph nodes (including peripheral) indicates that they can be sampled for cytological and/or histological diagnosis.

Organs affected by amyloid deposition will be pale and enlarged; the amyloid is grey and waxy. There may be other lesions associated with bacterial infection, including bronchopneumonia and pulmonary abscesses.[146,147,151,155]

Histopathology

The tumour cells in the bone marrow are arranged in sheets that replace (up to 99% of) normal haematopoietic tissue and are often associated with evidence of lysis of bone. They are monomorphic with small nuclei (1.5–2 red blood cells in diameter; this is dissimilar to anaplastic plasmacytomas).[1] The tumour cell cytoplasm is abundant, homogeneous and deeply eosinophilic.[149,154] Intercellular and intracellular crystalline deposits have been noted in some horses, i.e. a structurally aberrant, crystallizable paraprotein. Nuclei are round to oval, may be eccentric, and contain large clumps of chromatin, with parachromatin clearing and 1–3 nucleoli (indolent plasmacytoma cells do not have obvious nucleoli).[1] The mitotic rate (e.g. 0–3 per 10 high power (×400) fields) to 1–2 per field) is not as high as that of normal bone marrow tissue. Involved extramedullary sites may be multiple and diverse.[146]

Bone lesions can include areas of new bone formation, bone lysis and osteonecrosis. In one case where marked bone lysis was noted, tumour cells were infiltrating perivascularly in the periosteum with marked periosteal fibrosis, including down to the cortical bone where osteoclastic activity was marked.[149] It should be noted that osteolysis does not occur in all cases, and that where there is periosteal osteolysis, there may not also be (medullary) trabecular osteolysis.[153]

Associated renal lesions (in addition to tumour cell infiltration) may include glomerulopathy (due to

immunoglobulin deposition), calcification, pyelonephritis (due to infection susceptibility), amyloidosis, and tubular degeneration and atrophy associated with precipitation of Bence Jones proteins.[149] If amyloid is present, it is noted as deposits of amorphous eosinophilic material around the cells that is sometimes surrounded by macrophages.[154]

Immunohistochemical labelling

Tumour cells may stain positively for IgA, IgG or IgM; most equine multiple myelomas express IgG with membranous and cytoplasmic expression.[142] They should stain positively for CD79α.[1] In one report, scattered tumour cells were positive for PTHrP.[152]

Electron microscopy

Ultrastructurally, the cytoplasm of the tumour cells is filled with dilated rough endoplasmic reticulum.[154]

OTHER 'ROUND CELL' NEOPLASMS

Mast cell tumour (mastocytosis, mastocytoma)

See also page 623.

Cellular origin

These tumours originate from mast cells or their progenitors. Mast cell tumour in horses has also been designated as mastocytosis and mastocytoma, suggesting that it may not be a truly neoplastic process.[156] The lesions have been proposed to represent a hypersensitivity response to *Onchocerca* spp. migration or a response to other inflammatory or autoimmune reactions; however, there is no direct evidence for these theories.[80]

Profile

Mast cell tumour is considered to be rare but there have been frequent case reports in the literature. In USA studies, they have comprised 3–7% of total submitted equine cutaneous neoplasms.[82]

Three forms have been reported:

1. Cutaneous nodular mastocytosis/mast cell tumour
2. Malignant mast cell tumours
3. Congenital mast cell tumours.

Cutaneous nodular mastocytosis/mast cell tumour (See also p. 564 and p. 622)

Profile

These tumours are benign, usually solitary masses in the dermis, subcutis or superficial musculature (see Fig. 31.22). Many occur on the head (particularly the ears), neck and trunk, but they can involve the limbs in smaller numbers of cases; in the limbs they are often adjacent to or arising from synovium, in particular that of the carpal region.[80,157,158] A neoplasm involving the common carpal sheath of the digital flexor tendons of the right forelimb was described.[159] An articular mast cell tumour was reported arising from the tarsocrural synovium (of a 14-year-old mare).[160] Rarely, reported sites of origin include ocular structures (e.g. nictitating membrane, eyelids), nasal cavities, the oral cavity (including the tongue), nasopharynx, larynx, trachea and testis (see Figs. 31.22 and 34.7).[111,158,161–171] There was one report of an intraosseous tumour that involved the third phalanx of the left hindlimb resulted in a pathological fracture.[172] In some cases, there are multiple masses, either at widely separated sites or in a single cluster.[173]

Cutaneous mast cell tumours affect horses with a mean age of 7–9.5 years (range 1–25 years) and possibly occur more frequently in males than females.[162,174] The Arabian breed is thought to be predisposed. In one study, no mast cell tumours were diagnosed in Thoroughbreds.[143]

Biological behaviour

Cutaneous mast cell tumours usually expand slowly or are static. They are often of several months' duration by the time they are reported.[162] Rarely, sudden rapid growth of a chronic lesion may occur.

Spontaneous resolution of mast cell tumours is a rare event.[162] In one study (n=25) there was no recurrence at or <6 years following surgical excision in 88%.[162] In two horses, recurrence was noted at 1 year post-surgery. Some horses may develop further masses at other sites. In one case, a 9-year-old Arabian gelding developed numerous mast cell tumours at various sites over a 5-year period, with some becoming ulcerated, discharging caseous material and undergoing spontaneous resolution.[161]

Clinical signs caused by mechanical manipulation of these neoplasms (i.e. vasoactive amine release resulting in erythema and wheal formation) have not been reported in horses.[161] Metastasis has not been reported. Paraneoplastic syndromes, as occur in some dogs, including gastrointestinal ulceration and haemorrhage, have also not been reported in horses.

Malignant mast cell tumours

Profile

These are rare neoplasms that, to date, have mostly arisen around tarsal or carpal joints of horses in Australia.[158,175,176] A 9-year-old Paint horse gelding had multiple cutaneous tumours on the head, neck, thorax, abdomen and upper limbs, with metastatic masses in thoracic and abdominal sites.[177] Associated changes included eosinophilia, neutrophilia and hyperfibrinogenaemia.[176] One horse with a carpal lesion that was strongly suspected to be malignant showed generalized pruritus, the exact cause of which was uncertain; possible factors could have included release of histamine, documented peripheral eosinophilia and inflammatory mediators released from the neoplasm.[158]

Biological behaviour

Malignant mast cell tumours are locally invasive and metastasize to regional lymph nodes.

Congenital mast cell tumours

Profile

This form has not been reported recently. Multiple, enlarging dermal or subcutaneous nodules in the skin of affected

foals are particularly numerous along the trunk and lateral aspects of the hindlimbs. This condition has been suggested to be similar to urticaria pigmentosa in humans.[178]

Biological behaviour

Congenital mast cell tumours progressively enlarge, ulcerate, regress and heal to become fibrous masses over an approximately 30-day period, with continued development of new lesions.[178]

Gross pathology

Cutaneous mast cell tumours are usually solitary, but may occasionally arise as multiple lesions, either at widely separated sites or as a small cluster.[156,179] Usually only the dermis and subcutis are involved, without infiltration of underlying muscle or bone.[179] Mast cell tumours are discrete, sometimes partially encapsulated, firm or fluctuant and measure 0.5–20 cm in diameter.[156] Tumours involving the limbs may be firm and immobile, freely moveable or partially adherent to underlying tendons, and they are often mineralized and therefore visible radiographically; they are often found in proximity to joints (including carpal, metacarpal, metatarsal and pastern joints), although they are usually extracapsular.[157,158,174] In some cases, there is a synovial origin.[160] On external or sectioned surfaces, these masses are homogeneous, white or tan and well-demarcated, some with white caseous foci or darker necrotic areas (see Fig. 34.7).[162] Some masses are fluctuant and sporadically discharge caseous material.[145]

Alopecia, hyperpigmentation and/or ulceration of the overlying skin or mucosa may occur (see Fig. 31.22).[80,156] There may be an associated slight periosteal response of underlying or adjacent bone, but this is not noted in most horses and is considered to be atypical.[157,174] In one case involving multiple mast cell tumours, there was distal limb oedema with draining tracts.[173]

Congenital lesions are nodules ranging in size from several millimetres to 3 cm in diameter; larger masses are often ulcerated and may have soft, necrotic centres.[178]

Histopathology

There is no grading system for mast cell tumours that is currently in use for horses. Mast cell tumours are often, but not always, completely or partially well-delineated by fibrous tissue.[156,162] There may be either compression or infiltration of surrounding tissues, including skeletal muscle (the latter indicating malignancy). The mast cells are arranged in coalescing nodules, nests or sheets supported by a scant fibrovascular stroma; occasionally, the mast cells palisade along this stroma.[162] Tumour cells are usually well-differentiated in the nodular and congenital conditions; they are round, polyhedral or oval, with a moderate to large amount of eosinophilic cytoplasm containing numerous fine, grey-blue intracytoplasmic granules and well-defined cytoplasmic margins (Fig. 21.7). A mast cell origin can be confirmed by positive labelling of the granules with metachromatic stains, including toluidine blue (see Fig. 21.7). Nuclei are central and round or ovoid (or occasionally indented), with finely or coarsely clumped chromatin, and occasionally one to several small nucleoli.[156,162] Mitotic figures are variable in number in the benign form, ranging from 1 to 10 per 10 high power (×400) fields.

Numbers of eosinophils infiltrating equine mast cell tumours are variable. Some lesions contain large numbers of eosinophils, with eosinophilic granulomas and/or eosinophilic collagenolytic granulomas, areas of necrosis and mineralization, haemorrhage and infiltrates of haemosiderophages, degeneration of collagen fibres (fraying, fragmentation and loss of the normal wavy pattern), granulation tissue and/or reactive fibrosis; these lesions can form the majority of the mass and, at this level of severity, are specific for this type of neoplasm in equines

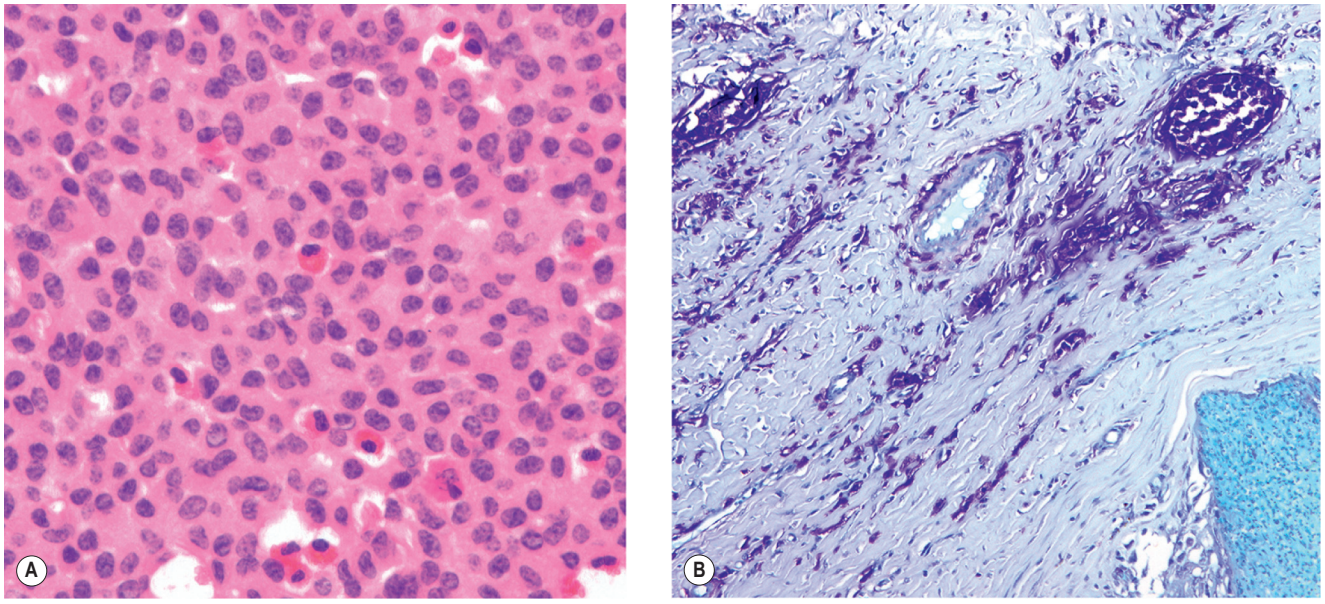


Figure 21.7 Mast cell tumours. (A) Well-differentiated tumour cells, with small numbers of eosinophils scattered between them (H&E, ×400). **(B)** Tumour cells containing large numbers of toluidine blue-positive intracytoplasmic granules, within stromal tissue adjacent to an eosinophilic granuloma (lower right corner). Mast cells would not be noted in these numbers in a purely inflammatory lesion (toluidine blue, ×100).

(see Fig. 21.7).[157,165,179] The latter can result in misdiagnosis as an inflammatory lesion (see p. 38; Fig. 4.17). It has been suggested that masses containing these prominent secondary changes are more advanced, with mild eosinophilic infiltration, necrosis and collagen degeneration sequentially preceding granulomatous inflammation and fibrosis, respectively.[162] There are larger numbers of mast cells (including small residual nodules) than would be expected in a purely inflammatory lesion and metachromatic stains may assist in determining this (Fig. 21.7). In a small number of cases from the USA and Australia, *Onchocerca* sp. microfilariae were noted in the overlying, superficial dermis, but spatially were not directly associated with the neoplastic masses.[156] Eosinophilic synovitis was noted in one horse with a carpal mass.[158]

In appendicular mast cell tumours, areas of mineralization of necrotic tissue (as documented radiographically) may be seen histologically.[82,174,179] Vascular lesions have also been noted, including mononuclear inflammatory cell infiltration of small blood vessels and lymphatics, and adventitial or occasionally intimal fibrosis of arterioles and arteries.[156]

Indications of malignancy include considerable variation in cytoplasmic granulation, large nuclei with a coarse chromatin pattern and prominent nucleoli, and marked anisocytosis and anisokaryosis; the mitotic rate is variable but can be high.[158,175,176] However, in the one reported case of widespread internal metastasis, the tumour cells were relatively well-differentiated; tumour cells were observed within lumens of both blood and lymphatic vessels in multiple sites.[177] In regional lymph nodes, metastatic tumour cells (some of which contain mitotic figures) are noted in cortical and medullary sinuses and may infiltrate surrounding lymphoid tissue.

In congenital lesions, as they regress, there are increasing numbers of fibroblasts and decreasing numbers of mast cells. In one congenital case that was necropsied following euthanasia at 1 year of age, there were increased numbers of mast cells in lymph nodes and the spleen, with aggregates also noted in the bone marrow.[178]

Immunohistochemical labelling

As in other species, the tumour cells may show positive cytoplasmic labelling for CD117 (KIT). CD117 is the transmembrane receptor tyrosine kinase for the stem cell factor encoded by the proto-oncogene c-kit; it is normally expressed by mast cells, melanocytes and haematopoietic cells. In non-neoplastic mast cells, CD117 labelling involves the cytoplasmic membrane only, but in tumour cells it can be cytoplasmic. In three cases (one in the tongue) focal perinuclear clustering of CD117 label was noted, i.e. probable accumulation within the Golgi complex.[170,173] Various abnormal patterns of CD117 labelling of neoplastic mast cells are used prognostically in the dog (in which mast cell tumours have a different biological behaviour), but no such information is available for the horse.[180] Horses showing abnormal CD117 labelling did not have a poor prognosis.

Differential diagnoses

These are listed in Box 21.2.

Box 21.2 Differential diagnoses for mast cell tumours

Neoplastic
- Lymphosarcoma
- Plasmacytoma
- Melanoma (add this to the Neoplastic list)

Non-neoplastic
- Collagenolytic granuloma
- Calcinosis circumscripta
- Nodular necrobiosis
- Cutaneous onchocerciasis or habronemiasis

Calcified mast cell tumours may be misdiagnosed as calcinosis circumscripta (tumoral calcinosis), the latter being composed of mineral deposits surrounded by granulomatous inflammation and fibrosis. These lesions are usually diagnosed on the lateral stifle but do occur in other sites, including the carpus, where they may involve the joint.[181,182]

Histiocytic sarcoma

Cellular origin

These neoplasms are derived from histiocytes: specifically, most histiocytic sarcomas are thought to arise from antigen-presenting dendritic cells.

Profile

This is a rare type of neoplasm in the horse. There is one report in a 16-year-old pony gelding that developed multiple subcutaneous tumours.[183]

Biological behaviour

Histiocytic sarcoma is a solitary or multiple malignant neoplasm that metastasizes rapidly and widely and caries a poor prognosis.[24] It usually affects the skin, subcutis, lymph nodes, liver, spleen and/or bone marrow. In the one reported case, the subcutaneous tumours were assumed to be primary, with evidence of metastasis to the skeletal muscles, mediastinal lymph nodes, pericardium, urinary bladder and soft tissues dorsal and ventral to the spinal column.[183]

Gross pathology

Histiocytic sarcomas are soft, nodular, grey-white or pink masses that may show infiltration of surrounding tissues.

Histopathology

The tumour cells are markedly pleomorphic and include large mononuclear and multinucleate round or polygonal cells in addition to spindle-cell forms.[24] Their nuclei are large (up to 10 red blood cells in diameter) with variable density of chromatin, large or giant nucleoli and variation in nuclear size within single (multinucleate) cells.[24]

Immunohistochemical labelling

In the one equine case, the tumour cells stained positively for lysozyme and MHC class II antigens.

References

1. Valli VEO. Haematopoietic system. In: Maxie M, ed. Jubb, Kennedy, and Palmer's pathology of domestic animals. Philadelphia, PA: Elsevier Saunders; 2007: 107–324.
2. Baker JR, Leyland A. Histological survey of tumours of the horse with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
3. Pascoe RR, Summers PM. Clinical survey of tumours and tumour-like lesions in horses in south east Queensland. Equine Vet J 1981; 13:235–239.
4. Savage CJ. Lymphoproliferative and myeloproliferative disorders. Vet Clin North Am Equine Pract 1998; 14:563–578.
5. Germann SE, Richter M, Schwarzwald CC, et al. Ocular and multicentric lymphoma in a young racehorse. Vet Ophthalmol 2008; 11:51–56.
6. Neufeld JL. Lymphosarcoma in the horse: a review. Can Vet J 1973; 14:129–135.
7. Dewes HF, Blakeley JA. Lymphosarcoma in a thoroughbred filly. N Z Vet J 1980; 28:82.
8. Haley PJ, Spraker T. Lymphosarcoma in an aborted equine fetus. Vet Pathol 1983; 20:647–649.
9. Seahorn TL, Carter GK, Morris EL, et al. Lymphosarcoma in a foal: a case report. J Equine Vet Sci 1988; 8:317–319.
10. Meyer J, DeLay J, Bienzle D. Clinical, laboratory and histopathological features of equine lymphoma. Vet Pathol 2006; 43:914–924.
11. Tomlinson MJ, Doster AR, Wright ER. Lymphosarcoma with virus-like particles in a neonatal foal. Vet Pathol 1979; 16:629–631.
12. Reef VB, Dyson SS, Beech J. Lymphosarcoma and associated immune-mediated haemolytic anaemia and thrombocytopaenia in horses. J Am Vet Med Assoc 1984; 184:313–317.
13. Koch TG, Wen X, Bienzle D. Lymphoma, erythrocytosis, and tumour erythropoietin gene expression in a horse. J Vet Intern Med 2006; 20:1251–1255.
14. Mair TS, Hillyer MH. Chronic colic in the mature horse: a retrospective view of 106 cases. Equine Vet J 1997; 29:415–420.
15. Roccabianca P, Paltrinieri S, Gallo E, et al. Hepatosplenic T-cell lymphoma in a mare. Vet Pathol 2002; 39:508–511.
16. Taylor SD, Pusterla N, Vaughan B, et al. Intestinal neoplasia in horses. J Vet Intern Med 2006; 20:1429–1436.
17. Traub-Dargatz J, Bertone A, Bennett D, et al. Monoclonal aggregating immunoglobulin cryoglobulinaemia in a horse with malignant lymphoma. Equine Vet J 1985; 17:470–473.
18. Dopson LC, Reed SM, Roth JA, et al. Immunosuppression associated with lymphosarcoma in two horses. J Am Vet Med Assoc 1983; 182:1239–1241.
19. Perryman LE, Wyatt CR, Magnuson NS. Biochemical and functional characterization of lymphocytes from a horse with lymphosarcoma and IgM deficiency. Comp Immunol Microbiol Infect Dis 1984; 7:53–62.
20. Moore BR, Weisbrode SE, Biller DS, et al. Metacarpal fracture associated with lymphosarcoma-induced osteolysis in a horse. J Am Vet Med Assoc 1995; 207:208–210.
21. Perkins GA, Nydam DV, Flaminio MJBF, et al. Serum IgM concentrations in normal, fit horses and horses with lymphoma or other medical conditions. J Vet Intern Med 2003; 17:337–342.
22. Mair TS, Yeo SP, Lucke VM. Hypercalcaemia and soft tissue mineralization associated with lymphosarcoma in two horses. Vet Rec 1990; 126:99–101.
23. Finley MR, Rebhun WC, Dee A, et al. Paraneoplastic pruritis and alopecia in a horse with diffuse lymphoma. J Am Vet Med Assoc 1998; 213: 102–104.
24. Valli VE, Jacobs RM, Parodi AL, et al. Histological classification of haematopoeitic tumours of domestic animals. In: Armed Forces Institute of Pathology ARoP, and The World Health Organization Collaborating Centre for Worldwide Reference on Comparative Oncology, Washington, DC, eds. Second Series; 2002.
25. Kelley LC, Mahaffey EA. Equine malignant lymphomas: morphologic and immunohistochemical classification. Vet Pathol 1998; 35:241–252.
26. Henson KL, Alleman AR, Cutler TJ, et al. Regression of subcutaneous lymphoma following removal of an ovarian granulosa-theca cell tumour in a horse. J Am Vet Med Assoc 1998; 212:1419–1422.
27. Jakesova V, Konar M, Gerber V, et al. Magnetic resonance imaging features of an extranodal T cell rich B cell lymphoma in the pharyngeal mucosa in a horse. Equine Vet Educ 2008; 20:289–293.
28. Keen JA, Swain JM, Rhind SM, et al. Lymphoproliferative disease resembling lymphomatoid granulomatosis in a Thoroughbred mare. J Vet Intern Med 2004; 18:904–906.
29. Katzenstein AL, Doxtader E, Narendra S. Lymphomatoid granulomatosis: insights gained over 4 decades. Am J Surg Pathol 2010; 34:e35–e48.
30. Du Toit N, Genovese LM, Dalziel RG, et al. Pulmonary angiocentric lymphoma (lymphomatoid granulomatosis) in a donkey. J Comp Pathol 2012; 146:24–29.
31. Raidal SL, Clark P, Raidal SR. Angiotrophic T-cell lymphoma as a cause of regenerative anaemia in a horse. J Vet Intern Med 2006; 20:1009–1013.
32. Herraez P, Berridge B, Marsh P, et al. Small intestine large granular lymphoma in a horse. Vet Pathol 2001; 38:223–226.
33. Grindem CB, Roberts MC, McEntee MF, et al. Large granular lymphocyte tumour in a horse. Vet Pathol 1989; 26:86–88.
34. Quist CF, Harmon BG, Mahaffey EA, et al. Large granular lymphocyte neoplasia in an aged mare. J Vet Diagn Invest 1994; 6:111–113.
35. Zimmerman B, Jones S, Rotstein DS. Large granular lymphoma in a mule. Vet Rec 2004; 155:462–463.
36. Sheats MK, van Wetter AJNJ, Snyder LA, et al. Disseminated large granular lymphoma in a horse. Equine Vet Educ 2008; 20:459–463.
37. La Perle KMD, Piercy RJ, Long JF, et al. Multisystemic, eosinophilic, epitheliotropic disease with intestinal lymphosarcoma in a horse. Vet Pathol 1998; 35:144–146.
38. De Bruijn C, Veenman JN, Rutten VP, et al. Clinical, histopathological and immunophenotypical findings in five horses with cutaneous malignant lymphoma. Res Vet Sci 2007; 83:63–72.
39. Sweeney RW, Hamir AN, Fisher RR. Lymphosarcoma with urinary bladder infiltration in a horse. J Am Vet Med Assoc 1991; 199:1177–1178.
40. Held JP, McCracken MD, Toal R, et al. Epididymal swelling attributable to generalised lymphosarcoma in a stallion. J Am Vet Med Assoc 1992; 201:1913–1915.
41. Conboy HS, Powers RD. Equine malignant lymphoma. J Am Vet Med Assoc 1971; 159:53–54.
42. Polkes AC, Alleman AR, Lester GD, et al. B-cell lymphoma in a horse with associated Sézary-like cells in the peripheral blood. J Vet Intern Med 1999; 13:620–624.
43. Kelton DR, Holbrook TC, Gilliam LL, et al. Bone marrow necrosis and myelophthisis: manifestations of T-cell lymphoma in a horse. Vet Clin Pathol 2008; 37:403–408.
44. Rebhun WC, Del Piero F. Ocular lesions in horses with lymphosarcoma: 21 cases (1977–1997). J Am Vet Med Assoc 1998; 212:852–854.
45. Gilger BC, Stoppini R. Diseases of the eyelids, conjunctiva, and nasolacrimal system. In: Gilger B, ed. Equine ophthalmology. St Louis: Elsevier Saunders; 2005: 107–156.
46. Platt H. Chronic inflammatory and lymphoproliferative lesions of the equine small intestine. J Comp Pathol 1986; 96:671–684.
47. Love S, Mair TS, Hillyer MH. Chronic diarrhoea in adult horses: a review of 51 referred cases. Vet Rec 1992; 130:217–219.
48. Wiseman A, Petrie L, Murray MJ. Diarrhoea in the horse as a result of alimentary lymphosarcoma. Vet Rec 1974; 95:454–457.
49. Humphrey M, Watson DA, Edwards HG, et al. Lymphosarcoma in a horse. Equine Vet J 1984; 16:547–548.
50. Platt H. Alimentary lymphomas in the horse. J Comp Pathol 1987; 97: 1–10.
51. Muñoz A, Riber C, Trigo P, et al. Haematopoietic neoplasms in horses: myeloproliferative and lymphoproliferative disorders. J Equine Sci 2009; 20:59–72.
52. Dabarainer RM, Sullins KE, Goodrich LR. Large colon resection for treatment of lymphosarcoma in two horses. J Am Vet Med Assoc 1996; 208:895–897.
53. Roberts MC, Pinsent PJN. Malabsorption in the horse associated with alimentary lymphosarcoma. Equine Vet J 1975; 7:166–172.
54. McConnell S, Katada M, Fiske RA, et al. Equine lymphosarcoma diagnosed as equine infectious anaemia in a young horse. Equine Vet J 1982; 14: 160–162.
55. Duckett WM, Matthews HK. Hypereosinophilia in a horse with intestinal lymphosarcoma. Can Vet J 1997; 38:719–720.
56. Mitsui I, Jackson LP, Couëtil LL, et al. Hypertrichosis in a horse with alimentary T-cell lymphoma and pituitary involvement. J Vet Diagn Invest 2007; 19:128–132.
57. Schnabel LV, Njaa BL, Gold JR, et al. Primary alimentary lymphoma with metastasis to the liver causing encephalopathy in a horse. J Vet Intern Med 2006; 20:204–206.
58. Wilson RG, Sutton RH, Groenendyk S, et al. Alimentary lymphosarcoma in a horse with cutaneous manifestations. Equine Vet J 1985; 17:148–150.
59. Pinkerton ME, Bailey KL, Thomas KK, et al. Primary epitheliotropic intestinal T-cell lymphoma in a horse. J Vet Diagn Invest 2002; 14: 150–152.
60. Mair TS, Hillyer MH. Clinical features of lymphosarcoma in the horse: 77 cases. Equine Vet Educ 1991; 4:108–113.
61. Mair TS, Pearson GR, Scase TJ. Multiple small intestinal pseudodiverticula associated with lymphoma in three horses. Equine Vet J 2011; 43:128–132.
62. Lindberg R, Nygren A, Persson SG. Rectal biopsy diagnosis in horses with clinical signs of intestinal disorders: a retrospective study of 116 cases. Equine Vet J 1996; 28:275–284.
63. Mair TS, Brown PJ. Clinical and pathologic features of thoracic neoplasia in the horse. Equine Vet J 1993; 25:220–223.
64. Sweeney CR, Gillette DM. Thoracic neoplasia in equids: 35 cases (1967–1987). J Am Vet Med Assoc 1989; 195:374–377.
65. Scarratt WK, Crisman MV. Neoplasia of the respiratory tract. Vet Clin North Am Equine Pract 1998; 14:451–473.
66. Mair TS, Lane JG, Lucke VM. Clinicopathological features of lymphosarcoma involving the thoracic cavity in the horse. Equine Vet J 1985; 17:428–433.
67. Fukunaga K, Ninomiya M, Oohara Y, et al. Lymphoplasmacytic lymphoma in a stallion. J Vet Med Sci 1993; 55:465–467.
68. Smith BP. Pleuritis and pleural effusion in the horse: a study of 37 cases. J Am Vet Med Assoc 1977; 170:208–211.
69. De Clercq D, van Loon G, Lefère L, et al. Ultrasound-guided biopsy as a diagnostic aid in three horses with cranial mediastinal lymphosarcoma. Vet Rec 2004; 154:722–726.
70. Sugiyama A, Takeuchi T, Morita T, et al. Mediastinal lymphoma with complete atrioventricular block in a horse. J Vet Med Sci 2008; 70: 1101–1105.
71. Sweeney CR. Causes of pleural effusion in the horse. Equine Vet Educ 1992; 4:75–77.

72. Pollock PJ, Russell T. Standing thoracoscopy in the diagnosis of lymphosarcoma in a horse. Vet Rec 2006; 159:354–356.
73. Lawn K. Sudden death due to thoracic lymphoma in a standardbred racing horse. Can Vet J 2005; 46:528–529.
74. Garber JL, Reef VB, Reimer JM. Sonographic findings in horses with mediastinal lymphosarcoma: 13 cases (1985–1992). J Am Vet Med Assoc 1994; 205:1432–1436.
75. Gupta BN, Keahey KK, Ellis DJ. Cutaneous involvement of malignant lymphoma in a horse. Cornell Vet 1972; 62:205–215.
76. Hilbe M, Meier D, Feige K. A case of cutaneous epitheliotropic malignant lymphoma (mycosis fungoides) in a horse. Berl Munch Tierarztl Wochenschr 1997; 110:86–89.
77. Potter K, Anez D. Mycosis fungoides in a horse. J Am Vet Med Assoc 1998; 212:550–552.
78. Sheahan BJ, Atkins GJ, Russell RJ, et al. Histiolymphocytic lymphosarcoma in the subcutis of two horses. Vet Pathol 1980; 17:123–133.
79. Gerard MP, Healy LN, Bowman KF, et al. Cutaneous lymphoma with extensive periarticular involvement in a horse. J Am Vet Med Assoc 1998; 213:391–393.
80. Johnson PJ. Dermatologic tumors (excluding sarcoids). Vet Clin North Am Equine Pract 1998; 14:625–658.
81. Kofler J, Kübber-Heiss A, Schilcher F. Cutaneous, multilocular T-cell lymphosarcoma in a horse. Zentralbl Veterinarmed A 1998; 45:189–190.
82. Valentine BA. Neoplasia. In: Bertone JJ, ed. Equine geriatric medicine and surgery. St Louis: Saunders Elsevier; 2006: 147–167.
83. Henson KL, Alleman AR, Kelley LC, et al. Immunohistochemical characterization of estrogen and progesterone receptors in lymphoma of horses. Vet Clin Pathol 2000; 29:40–46.
84. Staempfli HR, McAndrew KH, Valli VEO, et al. An unusual case of lymphoma in a mare. Equine Vet J 1988; 20:141–143.
85. Damodaran S, Ramachandran PV. A survey of neoplasms of equidae. Indian Vet J 1975; 52:531–534.
86. Nyack B, Padmore CL, Dunn D, et al. Splenic lymphosarcoma in a horse. Mod Vet Pract 1984; 65:269–270.
87. Chaffin MK, Schmitz DG, Brumbaugh GW, et al. Ultrasonographic characteristics of splenic and hepatic lymphosarcoma in three horses. J Am Vet Med Assoc 1992; 201:743–747.
88. East LM, Savage CJ. Abdominal neoplasia (excluding urogenital tract). Vet Clin North Am Equine Pract 1998; 14:475–493.
89. Kirk MD. Lymphosarcoma in a horse. Vet Med Small Anim Clin 1971; 66:448–452.
90. Jubb KVF, Kennedy PC, Palmer N. The urinary system. In: Grant Maxie M, ed. Pathology of domestic animals, 3rd edn. New York: Academic Press; 1985: 383.
91. Jubb KVF, Kennedy PC, Palmer N. The hematopoietic system. In: Grant Maxie M, ed. Pathology of domestic animals, 3rd edn. New York: Academic Press; 1985: 192.
92. Browning AP. Splenic lymphosarcoma in a stallion associated with an acute abdominal crisis. Vet Rec 1986; 119:178–179.
93. Marr CM, Love S, Pirie HM. Clinical, ultrasonographic and pathological findings in a horse with splenic lymphosarcoma and pseudohyperparathyroidism. Equine Vet J 1989; 21:221–226.
94. Buergelt CD, Brown CA, Ginn PE, et al. Severe splenomegaly associated with lymphoproliferative disease in a horse. Eur J Vet Pathol 1998; 4:29–31.
95. Tanimoto T, Yamasaki S, Ohtsuki Y. Primary splenic lymphosarcoma in a horse. J Vet Med Sci 1994; 56:767–769.
96. Gerard M, Pruitt A, Thrall DE. Radiation therapy communication: nasal passage and paranasal sinus lymphoma in a pony. Vet Radiol Ultrasound 2010; 51:97–101.
97. Meschter CL, Allen D. Lymphosarcoma within the nasal cavities of an 18-month-old filly. Equine Vet J 1984; 16:475–476.
98. Lane JG. Palatine lymphosarcoma in two horses. Equine Vet J 1985; 17:465–467.
99. Weaver MP, Dobson JM, Lane JG. Treatment of intranasal lymphoma in a horse by radiotherapy. Equine Vet J 1996; 280:245–248.
100. Dixon PM, Parkin TD, Collins N, et al. Equine paranasal sinus disease: a long-term study of 200 cases (1997–2009): treatments and long-term results of treatments. Equine Vet J 2012; 44:272–276.
101. Adams R, Calderwood-Mays MB, Peyton LC. Malignant lymphoma in three horses with ulcerative pharyngitis. J Am Vet Med Assoc 1988; 193: 674–676.
102. Paradis MR. Tumors of the central nervous system. Vet Clin North Am Equine Pract 1998; 14:543–561.
103. Williams MA, Welles EG, Gallor RJ, et al. Lymphosarcoma associated with neurological signs and abnormal cerebrospinal fluid in two horses. Progr Vet Neurol 1992; 3:51–56.
104. Bentz BG, Van Winkle TJ, Bernard WV. Lymphosarcoma involving the brainstem and spinal cord in a horse. Equine Vet Educ 1995; 7:124–126.
105. Lester GD, MacKay RJ, Smith-Meyer B. Primary meningeal lymphoma in a horse. J Am Vet Med Assoc 1992; 201:1219–1221.
106. Shamis LD, Everitt JI, Baker GJ. Lymphosarcoma as the cause of ataxia in a horse. J Am Vet Med Assoc 1984; 184:1517–1518.
107. Kannegieter NJ, Alley MR. Ataxia due to lymphosarcoma in a young horse. Aust Vet J 1987; 4:377–379.
108. Hartmann E, Baumgärtner W, Hungerland C. Spinal lymphosarcoma in a foal. Tierarztl Prax 1988; 16:175–178.
109. Hirsh JE, Grant BD, Linovitz R, et al. Diagnosis and surgical treatment of epidural neoplasms in two ataxic horses. Equine Vet Educ 2009; 21:564–568.
110. Murphy CJ, Lavoie JP, Groff J, et al. Bilateral eyelid swelling attributable to lymphosarcoma in a horse. J Am Vet Med Assoc 1989; 194:939–942.
111. Rebhun WC. Tumours of the eye and ocular adnexal tissues. Vet Clin North Am Equine Pract 1998; 14:579–606.
112. Glaze MB, Gossett KA, McCoy DJ, et al. A case of equine adnexal lymphosarcoma. Equine Vet J Suppl 1990; 10:83–84.
113. D'Agostino JJ, Brightman AH. Bilateral lymphosarcoma of the nictitating membrane in a Quarter Horse. J Equine Vet Sci 2004; 24:489–491.
114. Lock TF, Macy DW. Equine ovarian lymphosarcoma. J Am Vet Med Assoc 1979; 175:72–73.
115. Coumbe KM. Primary parotid lymphoma in a 10 year old Hanoverian gelding. Equine Vet Educ 1994; 6:91–94.
116. Edwards JF. Pathologic conditions of the stallion reproductive tract. Anim Reprod Sci 2008; 107:197–207.
117. Montgomery JB, Duckett WM, Bourque AC. Pelvic lymphoma as a cause of urethral compression in a mare. Can Vet J 2009; 50:751–754.
118. Greet TRC, Boys Smith SJ, Foote AK, et al. Mandibular lymphoma in a three-year-old thoroughbred filly. Vet Rec 2011; 168:80.
119. Allen BV, Wannop CC, Wright IM. Multicentric lymphosarcoma with lymphoblastic leukaemia in a young horse. Vet Rec 1984; 115:130–131.
120. Snyder LA. Acute myeloid leukaemia. In: Weiss DJ, Wardrop KJ, eds. Schalm's veterinary hematology, 6th edn. Ames: Wiley-Blackwell; 2010: 475–482.
121. Clark P, Cornelisse CJ, Schott HC, et al. Myeloblastic leukaemia in a Morgan horse mare. Equine Vet J 1999; 31:446–448.
122. Boudreaux MK, Blue JT, Durham SK, et al. Intravascular leukostasis in a horse with myelomonocytic leukemia. Vet Pathol 1984; 21:544–546.
123. Spier SJ, Madewell BR, Zinkl JG, et al. Acute myelomonocytic leukemia in a horse. J Am Vet Med Assoc 1986; 188:861–863.
124. Blue J, Perdrizet J, Brown E. Pulmonary aspergillosis in a horse with myelomonocytic leukemia. J Am Vet Med Assoc 1987; 190:1562–1564.
125. Mori T, Ishida T, Washizu T, et al. Acute myelomonocytic leukemia in a horse. Vet Pathol 1991; 28:344–346.
126. Buechner-Maxwell V, Zhang C, Robertson J, et al. Intravascular leukostasis and systemic aspergillosis in a horse with subleukemic acute myelomonocytic leukemia. J Vet Intern Med 1994; 8:258–263.
127. Burkhardt E, Saldern FV, Huskamp B. Monocytic leukemia in a horse. Vet Pathol 1984; 21:394–398.
128. Monteith CN, Cole D. Monocytic leukemia in a horse. Can Vet J 1995; 36:765–766.
129. Forbes G, Feary DJ, Savage CJ, et al. Acute myeloid leukaemia (M6B: pure acute erythroid leukaemia) in a Thoroughbred foal. Aust Vet J 2011; 89:269–272.
130. Searcy GP, Orr JP. Chronic granulocytic leukemia in a horse. Can Vet J 1988; 22:148–151.
131. Johansson AM, Skidell J, Lilliehöök I, et al. Chronic granulocytic leukemia in a horse. J Vet Intern Med 2007; 21:1126–1129.
132. Morris DD, Bloom JC, Roby KA, et al. Eosinophilic myeloproliferative disorder in a horse. J Am Vet Med Assoc 1984; 185:993–996.
133. Steiger R, Feige K. Case report: polycythaemia in a horse. Schweiz Arch Tierheilkd 1995; 137:306–311.
134. Roberts MC. A case of primary lymphoid leukaemia in a horse. Equine Vet J 1977; 9:216–219.
135. Dascanio JJ, Zhang CH, Antczak DF, et al. Differentiation of chronic lymphocytic leukemia in the horse. A report of two cases. J Vet Intern Med 1992; 6:225–229.
136. McClure JT, Young KM, Fiste M, et al. Immunophenotype classification of leukemia in 3 horses. J Vet Intern Med 2001; 15:144–152.
137. Rendle DI, Durham AE, Thompson JC, et al. Clinical, immunophenotypic and functional characterization of T-cell leukaemia in six horses. Equine Vet J 2007; 39:522–528.
138. Lester GD, Alleman AR, Raskin RE, et al. Pancytopenia secondary to lymphoid leukemia in three horses. J Vet Intern Med 1983; 7:360–363.
139. Kramer J, Tornquist S, Erfle J, et al. Large granular lymphocyte leukemia in a horse. Vet Clin Pathol 1993; 22:126–128.
140. Green PD, Donovan LA. Lymphosarcoma in a horse. Can Vet J 1977; 18:257–258.
141. Bruere AN, Sutton RJ, Davis GB. Observations on a case of equine lymphosarcoma. N Z Vet J 1970; 18:244–252.
142. McConkey S, López A, Pringle J. Extramedullary plasmacytoma in a horse with ptyalism and dysphagia. J Vet Diagn Invest 2000; 12:282–284.
143. Scott DW, Miller WH. Equine dermatology. St Louis: WB Saunders; 2003.
144. Drew RA, Greatorex JC. Vertebral plasma cell myeloma causing posterior paralysis in a horse. Equine Vet J 1974; 6:131–134.
145. Scott DW, Miller WH. Neoplasms, cysts, hamartomas, and keratoses, 2nd edn. Maryland Heights: WB Saunders; 2011.
146. Edwards DF, Parker JW, Wilkinson JE, et al. Plasma cell myeloma in the horse. A case report and literature review. J Vet Intern Med 1993; 7:169–176.
147. Cornelius CE, Goodbary RF, Kennedy PC. Plasma cell myelomatosis in a horse. Cornell Vet 1959; 49:478–493.
148. Markel MD, Dorr TE. Multiple myeloma in a horse. J Am Vet Med Assoc 1986; 188:621–623.
149. MacAllister C, Qualls C, Tyler R, et al. Multiple myeloma in a horse. J Am Vet Med Assoc 1987; 191:337–339.
150. Seide RK, Jacobs RM, Dobblestein TN, et al. Characterization of a homogeneous paraprotein from a horse with spontaneous multiple myeloma syndrome. Vet Immunol Immunopathol 1987; 17:69–77.
151. Henry M, Prasse K, White S. Haemorrhagic diathesis caused by multiple myeloma in a three-month-old foal. J Am Vet Med Assoc 1989; 194: 392–394.
152. Barton MH, Sharma P, LeRoy BE, et al. Hypercalcemia and high serum parathyroid hormone-related protein concentration in a horse with multiple myeloma. J Am Vet Med Assoc 2004; 225:409–413.

153. Morton AJ, Davis JL, Redding WR, et al. Nonsecretory multiple myeloma in a horse. Equine Vet Educ 2007; 19:564–568.
154. Kim DY, Taylor HW, Eades SC, et al. Systemic AL amyloidosis associated with multiple myeloma in a horse. Vet Pathol 2005; 42:81–84.
155. Pusterla N, Stacy BA, Vernau W, et al. Immunoglobulin A monoclonal gammopathy in two horses with multiple myeloma. Vet Rec 2004; 155: 19–23.
156. Altera K, Clark L. Equine cutaneous mastocytosis. Path Vet 1970; 7:43–55.
157. Doran RE, Collins LG. Mastocytoma in a horse. Equine Vet J 1986; 18:500–502.
158. Malikides N, Reppas G, Hodgson JL, et al. Mast cell tumours in the horse: four case reports. Equine Pract 1996; 18:12–17.
159. Leadbeater JC, Gutierrez-Nibeyro SD, Brown JA. Mastocytoma in the common carpal sheath of the digital flexor tendons of a horse. Aust Vet J 2010; 88:20–24.
160. Taylor S, Martinelli MJ, Trostle SS, et al. Articular mastocytosis in the tarsocrural joint of a horse. Equine Vet Educ 2005; 17:207–211.
161. Mair TS, Krudewig C. Mast cell tumours (mastocytosis) in the horse: a review of the literature and report of 11 cases. Equine Vet Educ 2008; 20:177–182.
162. McEntee MF. Equine cutaneous mastocytoma: morphology, biological behaviour and evolution of the lesion. J Comp Pathol 1991; 104:171–178.
163. Blodi FC, Ramsey FK. Ocular tumours in domestic animals. Am J Ophthalmol 1967; 64:627–633.
164. Boulton CH. Equine nasal cavity and paranasal sinus disease: a review of 85 cases. J Equine Vet Sci 1985; 5:268–275.
165. Hum S, Bowers JR. Ocular mastocytosis in a horse. Aust Vet J 1989; 66:32.
166. Ward DA, Lakritz J, Bauer RW. Scleral mastocytosis in a horse. Equine Vet J 1993; 25:79–80.
167. Richardson JD, Lane JG, Nicholls PK. Nasopharyngeal mast cell tumour in a horse. Vet Rec 1994; 134:238–240.
168. Lykkjen S, Strand E, Haga HA, et al. Radical surgical resection of locally invasive oro-cutaneous tumours in the buccal region of 2 horses. Vet Surg 2006; 35:319–323.
169. Grint NJ. Anaesthesia for laryngeal mass removal in three ponies. Equine Vet Educ 2007; 19:192–196.
170. Seeliger F, Hess O, Pröpsting MJ, et al. Confocal laser scanning analysis of an equine oral mast cell tumour with atypical expression of tyrosine kinase receptor C-KIT. Vet Pathol 2007; 44:225–228.
171. Brown JA, O'Brien MA, Hodder ADJ, et al. Unilateral testicular mastocytoma in a Peruvian Paso stallion. Equine Vet Educ 2008; 20:172–175.
172. Ritmeester AM, Denicola DB, Blevins WE, et al. Primary intraosseous mast cell tumour of the third phalanx in a Quarter Horse. Equine Vet J 1997; 29:151–152.
173. Millward LM, Hamberg A, Mathews J, et al. Multicentric mast cell tumours in a horse. Vet Clin Pathol 2010; 39:365–370.
174. Samii VF, O'Brien TR, Stannard AA. Radiographic features of mastocytosis in the equine limb. Equine Vet J 1997; 29:63–66.
175. Riley CB, Yovich JV, Howell JM. Malignant mast cell tumours in horses. Aust Vet J 1991; 68:346–347.
176. Reppas GP, Canfield PJ. Malignant mast cell neoplasia with local metastasis in a horse. N Z Vet J 1996; 44:22–25.
177. Tan RHH, Crisman MV, Clark SP, et al. Multicentric mastocytoma in a horse. J Vet Intern Med 2007; 21:340–343.
178. Prasse KW, Lundvall RL, Cheville NF. Generalised mastocytosis in a foal, resembling urticaria pigmentosa of man. J Am Vet Med Assoc 1975; 166:68–70.
179. Cole R, Chesen AB, Pool R, et al. Imaging diagnosis – mast cell tumour. Vet Radiol Ultrasound 2007; 48:32–34.
180. Thompson JJ, Yager JA, Best SJ, et al. Canine subcutaneous mast cell tumours: cellular proliferation and KIT expression as prognostic indices. Vet Pathol 2011; 48:169–181.
181. Fadok VA. Overview of equine papular and nodular dermatoses. Vet Clin North Am Equine Pract 1995; 11:61–74.
182. Tóth F, Schumacher J, Newman S. Calcinosis circumscripta in the antebrachiocarpal joint of a horse. Equine Vet Educ 2009; 21:584–588.
183. Beusker N, Muller JMV, Seehusen F, et al. Histiocytic sarcoma in a 16-year-old pony gelding. Pferdeheilkunde 2010; 26:680–684.

22

Central and peripheral nervous system neoplasms

Introduction 363
Neoplasms of the neuroepithelial tissue (central nervous system)
Astrocytoma 363
Oligodendroglioma 364
Ependymoma 365
Choroid plexus tumour (papilloma or carcinoma) 366
Neuronal and mixed neuronal tumours
Gangliocytoma 366
Olfactory neuroblastoma 367
Embryonal tumours 367
Meningeal neoplasms
Meningioma 367
Haematopoietic neoplasms
Lymphosarcoma 368
Pineal neoplasms
Pineoblastoma 368
Neoplasms of the peripheral nervous system
Ganglioneuroma and peripheral ganglioneuroblastoma 369
Peripheral nerve sheath tumours 369
Gastrointestinal stromal tumours (GISTs) 369
Non-neoplastic mass lesions
Arachnoid diverticulum 370
Epidermoid cysts 370
Cholesterol granulomas 370

Introduction

Neoplasia affecting the central nervous system (CNS) of horses is rare. In one literature review (1970–1997) there were only 25 case reports of central nervous system neoplasms that did not originate from the pituitary gland; only four of those were of primary nervous system origin.[1] Excluding peripheral nerve sheath tumours (p. 299), neoplasms arising in the peripheral nervous system are also infrequent.

NEOPLASMS OF THE NEUROEPITHELIAL TISSUE (CENTRAL NERVOUS SYSTEM)

Astrocytoma

See also pages 602 and 625.

Cellular origin

Astrocytes.

Profile

Astrocytomas may arise in various locations; in equines they have been diagnosed in the optic disc and cerebrum, including a glioblastoma (a high-grade astrocytoma) in the left ventral cerebral hemisphere of a 4-year-old horse.[2–4]

Biological behaviour

Astrocytomas are locally infiltrative, and do not metastasize. Optic nerve astrocytomas in human patients are usually slow-growing and do not invade or metastasize.[2]

Gross pathology

Astrocytomas are solid, white, grey-white or pale yellow, and variably well-demarcated from the surrounding parenchyma (Fig. 22.1); there may be significant effacement of normal tissue. Sometimes these neoplasms are difficult to visualize, with their presence only being indicated by some deviation of normal architecture.[5] Astrocytomas may also appear as a diffuse swelling of a localized area with 'blurring' of normal structures.[6] Centrally, there may be dark yellow-brown, friable tissue, i.e. necrosis, particularly in larger masses. Surrounding tissue may be oedematous.[5]

There may be extension through the meninges, flattening of overlying brain tissue, compression of ventricles, and compression and remodelling of adjacent calvarial bone.[4] The mass reported to involve an optic disc was oval and white-grey with a smooth surface, and protruded from the margin of the disc into the vitreous humour.[2]

Histopathology

Histologically, astrocytomas are infiltrative with poorly-defined margins; however, the invasion of surrounding tissue may be subtle. The optic disc astrocytoma was actually adjacent to the disc, projecting from the retinal nerve fibre layer.[2]

Astrocytomas are classified as low-grade (well-differentiated), medium-grade (anaplastic) or high-grade (glioblastoma) types.[5] In low-grade astrocytomas the tumour cells are generally loosely arranged, often along blood vessels. Medium-grade astrocytomas have a denser cellular arrangement. The tumour cells are variable in terms of size

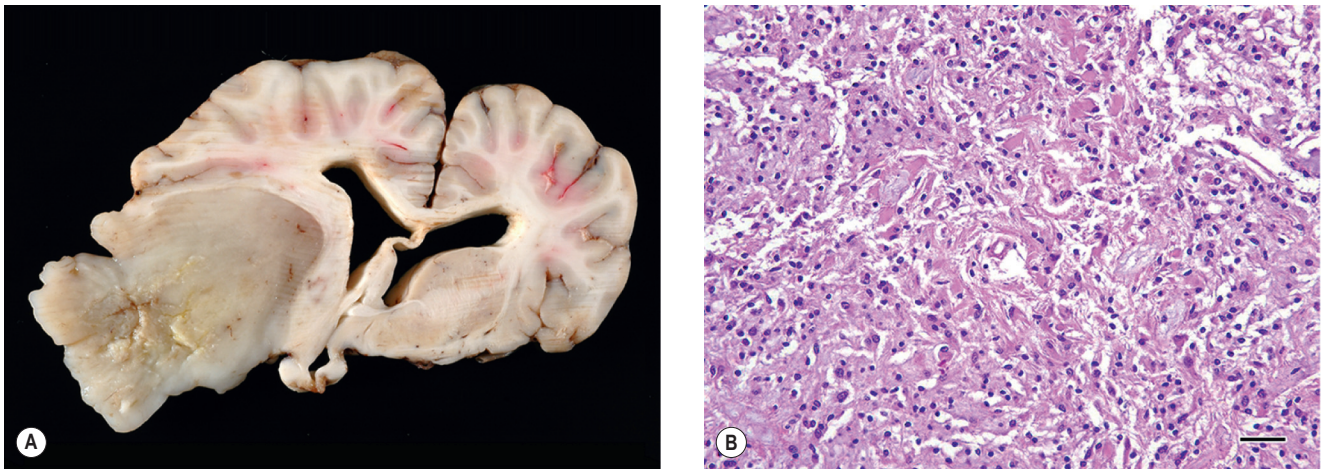


Figure 22.1 Glioblastoma (high-grade astrocytoma) in a 4-year-old horse. (A) A transverse section of the brain showing the well-demarcated, grey to yellow neoplastic mass largely effacing the caudate nucleus and more lateral cerebral tissue, with marked compression of the immediately surrounding white matter. **(B)** Pleomorphic tumour cells, that are either round with small hyperchromatic nuclei, gemistocytic (with voluminous, homogeneous eosinophilic cytoplasm) or spindle-shaped (H&E; bar = 37 mm). *(Figures courtesy of Dr Barbara Gericota and Dr Patricia Pasavento, School of Veterinary Medicine, University of California Davis; reprinted from Gericota B, et al. Journal of Comparative Pathology 2010; 142:332–335.[4])*

Box 22.1 Differential diagnoses for astrocytoma

Neoplastic
- Oligodendroglioma
- Metastatic neoplasms

and shape, particularly in glioblastomas (in which they are difficult to recognize as astrocytes), but they may have ramifying processes.[6] Nuclei contain larger amounts of chromatin than those of normal astrocytes and may be markedly atypical and pleomorphic in glioblastomas, with a high mitotic rate (and bizarre mitotic figures). There may be mono- or multinucleate tumour giant cells in glioblastomas; in these neoplasms, there are typically large areas of necrosis and haemorrhage, around which the tumour cells tend to pseudopalisade.[5] Additionally, endothelial cells of the blood vessels in glioblastomas often proliferate and hypertrophy to form (glomeruloid) structures resembling renal glomeruli (p. 365) (see Fig. 22.1).[6] Other associated changes in astrocytomas can include remnants of normal parenchymal tissue, mucinous degeneration, cystic degeneration and fatty degeneration.[6]

In the single case of glioblastoma, the neoplasm contained peripheral sheets of oligodendrocytic-like cells within mucinous matrix (p. 602); such neoplasms are diagnosed as oligoastrocytomas.[4,5]

Immunohistochemical labelling

Astrocytoma cells should show sparse to strong positive cytoplasmic immunolabelling for glial fibrillary acidic protein (GFAP), in addition to S100 and vimentin.[5] Labelling for factor VIII-related antigen may assist in identifying vascular proliferations.[4]

Differential diagnoses

These are listed in Box 22.1.

Oligodendroglioma

Cellular origin

Oligodendrocytes.

Profile

Oligodendrogliomas usually arise in the white matter of the cerebral hemispheres. An oligodendroglioma reported in a 10-year-old Thoroughbred mare involved approximately one-third of the white matter of the left cerebral hemisphere and caused sudden death.[7]

Biological behaviour

Oligodendrogliomas are always regarded as malignant, are invariably infiltrative and may extend into the overlying meninges. They do not usually metastasize within the cerebrospinal fluid.

Gross pathology

Grossly, oligodendrogliomas often appear to be well-circumscribed.[5] They may extend through overlying or adjacent ventricular or meningeal surfaces. Oligodendrogliomas are soft (with some more solid regions), often large, and red, pink or grey, frequently with extensive gelatinous areas and central necrosis. In the one report of an oligodendroglioma in a horse, the mass was largely well-circumscribed, and compressed the adjacent cerebrum and lateral ventricle, with subfalcine herniation (displacement of the brain beneath the free edge of the falx cerebri).[7]

Histopathology

The neoplasm may be variably well-demarcated, but is usually infiltrative microscopically. The tumour cells are densely packed and arranged in sheets or rows, with almost

Box 22.2 Differential diagnoses for oligodendroglioma

Neoplastic
- Astrocytoma
- Metastatic neoplasms

no stromal tissue. The tumour cells are small and round with a clear cytoplasm but a visible cytoplasmic membrane, giving the mass a classic 'honeycomb' appearance; the latter, characteristic feature is an artefact of fixation. Nuclei are round or occasionally oval or elongate, hyperchromatic and uniform in size (similar to those of normal oligodendroglia), with a low mitotic rate.[6] In some foci, tumour cells may take on the appearance of cells of astrocytic or ependymal origin. There is pronounced proliferation of small blood vessels, especially capillaries, with endothelial hypertrophy and hyperplasia, and formation of glomeruloid structures, i.e. they resemble renal glomeruli. Haemorrhage, mucinous degeneration, cyst formation and mineralization may be noted. Where there are areas of necrosis, there may be pseudo palisading of tumour cells around the margins (p. 364).

Immunohistochemical labelling

Oligodendroglioma cells do not stain positively for glial fibrillary acidic protein (GFAP).[5]

Differential diagnoses

These are listed in Box 22.2.

Ependymoma

See also page 602.

Cellular origin

Epithelial lining cells (ependymal cells) of ventricles of the brain or the central canal of the spinal cord. Recently, it has been proposed that ependymomas and choroid plexus tumours arise from radial glial cells, i.e. multipotent progenitor cells derived from the neuroepithelium of the primitive neural tube.[8]

Profile

This is a rare type of neoplasm in any species. In the horse, ependymomas involve the third and fourth ventricles.[9–11] They are usually diagnosed in aged animals, although there has been one report involving a 2-year-old horse.[9]

Biological behaviour

Ependymomas are expansile, with effects often occurring due to displacement and compression of surrounding structures that can include the hypothalamus, thalamus, optic chiasm and pituitary gland (pars intermedia and pars distalis).[9] In one report, an ependymoma effaced the neurohypophysis by compression, most likely disrupting transport of the vasopressin preprohormone from the hypothalamus to the neurohypophysis; this horse presented with adipsia and resultant hypernatraemia.[9] Ependymomas may invade the ventricular system and meninges by metastasizing within the cerebrospinal fluid.[6]

Gross pathology

Ependymomas are usually large, with poorly-defined margins. They are soft, bulging and grey-white, red or mottled grey/red/yellow. There may be associated haemorrhage into the ventricular lumen and/or ventricular dilation.[9]

In one case, an ependymoma involving the fourth ventricle of a 19-year-old horse was noted at the left side of the cerebellomedullary angle in an extramedullary location; this mass was associated with 'marginal siderosis', i.e. diffuse accumulation of haemosiderin at the surface of the brain and spinal cord due to chronic subarachnoid haemorrhage, giving it an orange-yellow colour.[11]

Histopathology

Ependymomas are densely cellular and highly vascular, arising from the ventricular ependymal surfaces. Columnar tumour cells may line haphazardly arranged acinar, papillary and duct-like structures; they may be arranged in single layers, pseudostratified or stratified.[9] There is a papillary variant (reported in one 17-year-old gelding), in which single layers of tumour cells line multiple branching, papillary stromal projections.[10] The tumour cells may also form pseudorosettes (radial arrangements around blood vessels) or true rosettes (i.e. lining tubular cavities).[5] The cytoplasm may form long processes (in pseudorosettes), form an apical thin limiting membrane, contain globular eosinophilic bodies, and be vacuolated or scanty.[6,9–11] Tumour cell nuclei are luminal or basilar, ovoid or elongate and indented, with finely stippled or coarsely granular, sometimes marginated chromatin. Anisokaryosis and mitotic rates are variable; small numbers of binucleate or multinucleate tumour cells may be noted.

There may be mucinous and cystic degeneration within the neoplasm. Adjacent parenchymal tissue may contain haemorrhage, oedema, increased numbers of glial cells, gitter cells and areas of necrosis; macrophages may contain lipofuscin and/or haemosiderin. In the horse with marginal siderosis caused by a fourth ventricle mass, there was extensive degenerative change in the spinal cord, considered to have resulted from the excessive iron trafficking.[11]

Immunohistochemical labelling

Ependymoma cells, both neoplastic and normal, may show positive immunolabelling for glial fibrillary acidic protein (GFAP), vimentin and cytokeratin. It has been stated that canine ependymomas are usually GFAP-negative. They may stain positively for epithelial membrane antigen (EMA) (this is typical for ependymomas of human patients), but one equine papillary ependymoma was negative.[10]

Electron microscopy

Ultrastructurally, there are complex cytoplasmic interdigitations and connection by prominent adherens junctions, and foot processes rest on a prominent basal lamina at the vascular pole (in pseudorosettes).[10]

Box 22.3 Differential diagnoses for ependymoma

Neoplastic
- Choroid plexus tumour

Differential diagnoses

These are listed in Box 22.3.

Choroid plexus tumour (papilloma or carcinoma)

See also page 603.

Cellular origin

Choroid plexus epithelial cells.

Profile

This is a rare type of neoplasm in horses.[12] Choroid plexus tumours may arise in the third, fourth or lateral ventricles of the brain, where papillomas have been reported in horses 4–11 years of age.[12–14]

Biological behaviour

Choroid plexus papillomas are usually expansile rather than invasive.

Gross pathology

Grossly, choroid plexus papillomas are granular to papillary, grey-white to red, friable and well-circumscribed. Masses reported in horses have measured 5–10 cm in diameter.[12–14] A choroid plexus papilloma (5 cm in maximal diameter) reported in a 5-year-old mare extended from the pons to the level of the lateral ventricles, replaced much of the thalamus and hypothalamus, and caudally was centred on the third ventricle with extension to involve the mesencephalic aqueduct.[13] There was subtentorial herniation of the occipital lobes.

Histopathology

Tumour cells line a branching fibrovascular stroma in single or sometimes multiple layers, forming a papillary pattern that resembles the choroid plexus.[6] There may be pseudorosette formation (i.e. around blood vessels). The tumour cells resemble normal choroid plexus epithelial cells; they are cuboidal or columnar, with an eosinophilic cytoplasm and a small round hyperchromatic nucleus containing coarsely clumped chromatin and distinct nucleoli.[14] Diagnosis as a carcinoma, rather than a papilloma, is based on tumour cell atypia and invasiveness.[5] Associated changes may include necrosis, haemorrhage and mineralization.

Immunohistochemical labelling

Choroid plexus tumour cells are usually positive for cytokeratins and epithelial membrane antigen and negative for glial markers, e.g. glial fibrillary acidic protein (GFAP).[10] In one case, the tumour cells were weakly GFAP-positive; this might indicate a neuroepithelial histogenesis with ependymal differentiation of the tumour cells.[14]

Box 22.4 Differential diagnoses for choroid plexus tumours

Neoplastic
- Ependymoma

Differential diagnoses

These are listed in Box 22.4.

NEURONAL AND MIXED NEURONAL TUMOURS

Cellular origin

These neoplasms are composed of neuronal cells and/or neurons mixed with glial cells.[5] They are classified as:

- *Gangliocytoma* – large ganglion cells
- *Ganglioglioma* – neuronal cells and astrocytic cells
- *Olfactory neuroblastoma* (esthesioneuroblastoma) – neurosensory cells and sustentacular cells, derived from basal cells of the olfactory epithelium.

Gangliocytoma

Profile

A cerebellar mass reported in one horse and diagnosed as a dysplastic lesion has been indicated by other authors to be similar; however, it was not predominantly composed of ganglion/pyramidal cells.[15,16] Gangliocytomas are intracranial and appear to have a predilection for the cerebellum.[5]

Biological behaviour

Gangliocytomas are benign, tend to grow slowly and have not been reported to undergo malignant transformation.

Gross pathology

Gangliocytoma is soft and grey, and replaces a region of the cerebellum, potentially with compression of adjacent structures.[16]

Histopathology

Gangliocytomas are composed of mature neuronal cells resembling pyramidal cells; smaller numbers of immature (neuroblastic) cells may also be noted. The large cells have cytoplasmic processes that may be visualized using silver

stains.[16] There may be binucleate or multinucleate tumour cells.

Immunohistochemical labelling

Gangliocytomas may stain positively for neuronal markers, including neuron-specific enolase (NSE) and synaptophysin, but will be negative for glial cell markers.[5]

Olfactory neuroblastoma

See also page 604.

Profile

There have been several reports of olfactory neuroblastomas in horses.[17–19]

Biological behaviour

Olfactory neuroblastomas are malignant, invasive neoplasms that may penetrate the cribriform plate.[5] In one equine case, tumour emboli were reported in the choroid of the adjacent eye, with subretinal metastatic masses and associated retinal detachment.[18]

Gross pathology

Olfactory neuroblastoma arises in the ethmoturbinate region of the nasal cavity. These tumours are soft, red, grey or yellow, and well vascularized; they may contain areas of haemorrhage and necrosis. Olfactory neuroblastomas are irregularly-shaped with potentially extensive infiltration and destruction of nasal turbinates, frontal sinuses, the cribriform plate and, in some cases, the adjacent orbit (see Fig. 33.1).[19] The nasal cavity may be filled, and the nasal septum displaced. One horse showed severe proptosis of the left eye.[18]

Histopathology

Olfactory neuroblastomas may be difficult to differentiate from round cell tumours of the nasal cavity (e.g. lymphosarcoma). The tumour cells may be arranged in sheets, lobules and nests supported by a fine fibrovascular stroma. There may be formation of Homer Wright rosettes (with a lumen filled with fibrillar neuropil material containing neurites) and/or pseudorosettes (forming around blood vessels); however, although this is a useful diagnostic feature, it is variable and not pathognomonic.[19,20] Tumour cells have a small amount of pale-staining eosinophilic cytoplasm with indistinct margins. Nuclei are round with finely stippled chromatin and indistinct nucleoli. There may be moderate pleomorphism and the mitotic rate is variable but can be high. Tumour giant cells, tumour cells lining microcysts and haemorrhage have been noted.[18,19]

Immunohistochemical labelling

Olfactory neuroblastoma may show (variable) positive cytoplasmic labelling for neuron-specific enolase (NSE), neurofilament protein, S100 and/or synaptophysin, all indicating neural differentiation.[19] The labelling patterns are highly variable between different neoplasms due to varying differentiation stages of the tumour cells. Tumour cells may also stain positively for microtubule-associated protein, glial fibrillary acidic protein (GFAP; indicating differentiation towards glial cells) and vimentin. Positive labelling for cytokeratin, chromogranin A, smooth muscle actin and desmin has not been reported, and there should be negative labelling for melan-A to rule out melanoma. It should be noted that positive cytokeratin labelling could occur, as neurons developing into olfactory neurons express cytokeratin transiently during their development.[21]

Box 22.5 Differential diagnoses of olfactory neuroblastoma

Neoplastic
- Neuroendocrine carcinoma
- Nasal adenocarcinoma or squamous cell carcinoma
- Lymphosarcoma
- Melanoma

Electron microscopy

Electron microscopy is considered necessary to make a definitive diagnosis of olfactory neuroblastoma, i.e. evidence of neuronal processes containing microtubules and neurosecretory granules with electron-dense centres.

Differential diagnoses

These are listed in Box 22.5.

Neuroendocrine carcinoma is the main differential diagnosis for both gangliocytoma and olfactory neuroblastoma (if there is histological similarity); the differentiation may be problematic in this site. Usually, expression of epithelial markers would indicate a diagnosis of neuroendocrine carcinoma rather than neuroblastoma; however, as stated above, neurons arising from the anlage of olfactory nerve express cytokeratin during the embryonic stage.[21] Some authors believe these two types of neoplasm to be different manifestations of the same entity.

Embryonal tumours

See pages 410–411.

MENINGEAL NEOPLASMS

Meningioma

See also page 605.

Cellular origin

In human patients, meningiomas are thought to be derived from the arachnoid granulations or islands of arachnoid cells on the inner surface of the dura mater.[5] Rare meningiomas found in the paranasal sinuses are thought to arise from arachnoid cells entrapped within or outside bone during development of the skull and facial bones.[22]

Profile

There been few reports of meningioma in horses, with one presenting as a retrobulbar mass involving the optic nerve and another case arising in the paranasal sinuses (occupying maxillary, frontal and sphenopalatine sinuses).[22–25]

Biological behaviour

Meningiomas are slow-growing, expansile masses that typically arise under the dura mater and usually exert their effects by compression of the brain or spinal cord. Infiltration of the brain can occasionally occur; infiltration of the underlying brainstem was reported in a pony.[24] Most intracranial meningiomas are considered to be benign, but the paranasal variant is typically locally aggressive.[5]

Gross pathology

Meningiomas are globular, ovoid, tuberous or plaque-like, solid to firm, sometimes lobulated, homogeneous, yellow-white, grey-white or red expansile masses.[5] They are usually found on the surface of the brain or spinal cord and adherent to the dura mater and/or pia mater. Meningiomas are generally well-circumscribed, with smooth or encapsulated surfaces. Areas of necrosis and haemorrhage may be noted. The paranasal meningioma was large and associated with nasal septum deviation and extensive osteolysis, without invasion of the calvarium.[22]

Histopathology

The tumour cells forming meningiomas (as described in other species) can vary widely in patterns of arrangement and morphology, with histological types including meningotheliomatous (epithelioid), psammomatous, fibroblastic, transitional (mixed), angioblastic, papillary and myxoid.[5] The histological type does not have any prognostic value in horses or other domestic species. Tumour cells often form whorls (from a few to several hundred cells), with central disintegration and mineralization, sheets, and/or interwoven streaming bundles, and are supported by a fine fibrovascular stroma. The tumour cells are polygonal to spindle-shaped, with variable but often abundant amounts of eosinophilic cytoplasm with indistinct margins.[24,25] Nuclei are large and round or ovoid, with finely clumped or vesicular chromatin, small but prominent nucleoli, moderate anisokaryosis and a variable mitotic rate (often no mitotic figures are noted). Associated changes may include cysts filled with eosinophilic fluid, connective tissue degeneration, lipopigment or cholesterol deposition, inflammation, haemorrhage and cavernous vascular formations.[6]

Immunohistochemical labelling

Meningioma cells usually label positively for vimentin and epithelial membrane antigen, and they may also be cytokeratin-positive (particularly if cryosections are used). Meningiomas in some studies meningiomas have been reported to be positive for cytokeratin, S100 and/or neuron-specific enolase (NSE).

HAEMATOPOIETIC NEOPLASMS

Lymphosarcoma

See pages 342, 351 and 605.

PINEAL NEOPLASMS

Pineoblastoma

See also page 605.

Cellular origin

Primitive neuroectodermal cells in the pineal gland, pineoblastomas are classified as a supratentorial form of primitive neuroectodermal tumour (PNET) of the central nervous system (pineocytoma is the malignant equivalent, not reported in horses).

Profile

There is one report of a pineoblastoma in an adult Quarter Horse stallion that showed signs of weakness and incoordination.[26]

Biological behaviour

Pineoblastomas are locally invasive, and may spread through the cerebrospinal fluid or within the meninges. There may be extension into the thalamus and midbrain.[5,6]

Gross pathology

Pineoblastomas are diagnosed based on the site. They vary in size, and may completely replace the pineal body. In the one reported equine case, the neoplasm measured 6 cm in maximal diameter, was soft, friable to gelatinous and grey-yellow, and enveloped the brainstem from a point cranial to the cerebellum, to the pituitary fossa.[26] The mass was adherent to ventromedial aspects of the cerebral occipital lobes.

Histopathology

Histologically, there is similarity to medulloblastoma, i.e. small tumour cells with scanty cytoplasm and round to oval, hyperchromatic nuclei; there is potential formation of rosettes. In the one reported case, the tumour cells were arranged in sheets and were invading the third ventricle of the brain and extending into the lateral ventricles, with invasion of periventricular neuropil.[26]

Differential diagnosis

Neoplastic

These tumours are difficult to differentiate from medulloblastomas (an infratentorial form of PNET not reported in horses); this is done on the basis of location.

Pineoblastomas occur in the midline and do not involve the cerebellum.

NEOPLASMS OF THE PERIPHERAL NERVOUS SYSTEM

Ganglioneuroma and peripheral ganglioneuroblastoma

Cellular origin

These neoplasms arise in cranial or spinal ganglia, or sympathetic ganglia of the autonomic nervous system.[5] Ganglioneuromas are composed of ganglion cells and glial cells, and are the peripheral nervous system counterpart of the gangliocytoma (p. 366). Ganglioneuroblastomas contain ganglion cells (of variable degrees of differentiation that may include neuroblasts), Schwann cells and nerve fibres.

Profile

The neoplasms of this type, reported to date in horses have arisen from enteric ganglia. A solitary ganglioneuroma was reported in the jejunum of a 7-year-old stallion associated with obstruction.[27] Multiple ganglioneuromas (ganglioneuromatosis) were reported in an 8-year-old horse, involving a 25 cm long segment of the small colon.[28] This condition, which is typically segmental, may actually be a hyperplastic response.

Biological behaviour

Ganglioneuromas are benign. When locally invasive, complete surgical resection should be curative. Ganglioneuroblastomas are intermediate in behaviour.

Gross pathology

The jejunal ganglioneuroma measured 6 cm in maximal diameter and was intramural, i.e. located between the two layers of the muscularis externa; it was causing significant reduction in the luminal diameter.[27] In the horse with ganglioneuromatosis, there were numerous sessile to pedunculated, firm, nodular, white or red, 3–15 mm diameter masses protruding from the serosal surface of the antimesenteric wall of the small colon.[28] Those masses were located within the muscularis externa and were multifocally adherent to the colonic mesentery.

Histopathology

Histologically, the jejunal ganglioneuroma was incompletely encapsulated, with displacement and infiltration of the outer layer of the muscularis externa, and extension to the serosal surface.[27] The mass was composed of interlacing fascicles of unmyelinated neurofibrils encircled by spindle-shaped (Schwann) cells and thin perineural sheaths and separated by collagenous tissue. Scattered ganglion-type cells were mainly noted adjacent to the inner margin, with larger well-differentiated cells and smaller, bipolar, pyramidal or ovoid cells. In the horse with ganglioneuromatosis, the masses were poorly-demarcated and arose in the myenteric plexus tissue, extending through the outer layer of the muscularis externa. Smaller nodules of neoplastic tissue were noted in the inner muscularis externa and submucosa. These masses were comprised largely of fascicular bundles of Schwann cells, with occasional clusters of well-differentiated neurons (that incorporated small numbers of supporting enteroglial cells).[26]

Immunohistochemical labelling

Schwann cells, neurons and glial cells stain positively for S100. Some Schwann cells and all other glial cells stain positively for glial fibrillary acidic protein (GFAP). Neurons are also neuron-specific enolase (NSE) positive.

Electron microscopy

Ultrastructurally, unmyelinated nerve fibres can be identified, containing intermediate filaments and synaptic vesicles (membrane-bound structures).[28]

Peripheral nerve sheath tumours

See pages 299, 562 and 610.

Gastrointestinal stromal tumours (GISTs)

Cellular origin

Some GISTs are exclusively of neural origin, while others are mixtures of neural, smooth muscle and fibroblastic cells. An origin from pluripotent neural crest or mesenchymal cells within the gastrointestinal wall has been proposed. These tumours might also originate from interstitial cells of Cajal, these being cells normally located between inner and outer layers of the muscularis externa and intimately associated with autonomic nerve plexuses in that location. The interstitial cells of Cajal are thought to serve as pacemakers to create a basal electrical rhythm leading to smooth muscle contraction, and express the tyrosine kinase receptor c-kit (see below).

Profile

Gastrointestinal stromal tumours were first recognized in human patients, with relatively recent descriptions in horses.[29] Spindle cell neoplasms of the equine gastrointestinal tract in the past were usually thought to be of smooth muscle cell origin, i.e. earlier reports may include misdiagnoses. Gastrointestinal stromal tumours specifically with neural differentiation appear to be particularly common in horses. They may occur in the stomach, small intestine, caecum and colon, and are one of the most commonly reported caecal neoplasms.[30,31] In one study (n=10), affected horses ranged in age from 13 to >20 years, with seven being mares and four geldings, i.e. females may be predisposed.[29]

Biological behaviour

Gastrointestinal stromal tumours are most often incidental findings, but they can be associated with colic due

to intestinal impaction or strangulation. A pony had hypoglycaemia that was associated with a particularly large (50 cm diameter) gastric mass; this is also the only report of GIST metastasis in an equine, to the interventricular septum of the heart.[32]

Gross pathology

Gastrointestinal stromal tumours are usually subserosal, although intramuscular and extramural, pedunculated masses have been reported. These solitary or sometimes multiple masses are well-circumscribed, range in size from a few millimetres up to 50 cm in diameter, may be lobulated or multinodular, are soft or friable (occasionally firm) and are round, ovoid, cylindrical or pyriform.[29] On sectioned surfaces, they have a tan, purple, red or grey-white mottled (haemorrhagic) appearance and may ooze viscous fluid.[30] Occasionally, neoplasms contain yellow areas of necrosis.

Histopathology

Most GISTs are encapsulated and expansile (with frequent compression of adjacent serosal and muscular tissues) and are subdivided by coarse fibrovascular septa that may be partially mineralized.[30] The tumour cells are arranged in variable patterns, including interconnecting fascicular bundles, streams, branching trabeculae, whorls (less common) and storiform or cribriform patterns, with occasional palisading.[29,31] The amount of supporting stroma is also variable, and is often myxoid.[30]

The tumour cells are spindle-shaped with abundant eosinophilic fibrillar cytoplasm (that forms elongate cytoplasmic processes), have indistinct margins, and may be vacuolated. Nuclei are relatively uniform, central and ovoid or elongated with blunt or slightly tapered ends, finely or coarsely granular chromatin and 0–3 small nucleoli. There is variable anisokaryosis and rare mitotic figures may be noted. In one unusual case, variable numbers of polygonal multinucleate giant cells with up to 15 nuclei were noted between the tumour cells; the origin of these cells was not certain but they were suspected to be non-neoplastic.[31]

Associated lesions include peripheral infiltrates of haemosiderophages and mixed infiltrates of mononuclear inflammatory cells, and individual cell necrosis/apoptosis.[29] Mucosal ulceration has not been noted.

Immunohistochemical labelling

Gastrointestinal stromal tumour cells stain positively for vimentin. In one study, all of the neoplasms (n=11) were negative for neuron-specific enolase (NSE), but in another study (n=7), all were diffusely and strongly positive.[29,30] Tumour cells may show diffuse cytoplasmic granular labelling for c-kit (CD117).[30,32] Positive labelling for S100 and smooth muscle actin is variable (all GISTs were negative for S100 in one study), and no staining has been reported for factor VIII-related antigen, chromogranin, glial fibrillary acidic protein or desmin in most cases.[29,30] In one unusual case, the tumour cells showed positive labelling for desmin.[31]

Electron microscopy

Ultrastructurally, the cells comprising GIST vary, including undifferentiated mesenchymal, myogenic and neural spindle cells.

NON-NEOPLASTIC MASS LESIONS

Arachnoid diverticulum

A lesion of this type was diagnosed in the dorsal arachnoid membrane of the spinal cord of an 11-month-old Thoroughbred colt at the level of 6–11th cervical vertebrae (C6–C11).[33] This had resulted in marked spinal cord compression and was suspected to be of congenital origin. Diverticula are not true cysts, as they are not epithelium-lined.

Epidermoid cysts

Meningeal epidermoid cysts have been reported to cause brain compression in adult horses, but they can also be incidental findings. Intracranial epidermoid cysts arise during embryonic development, as a result of ectopic inclusion of non-neural ectoderm during closure of the neural tube. As epidermoid cysts grow slowly, they may reach a considerable size before neurological signs develop. Sites involved have included the cerebral hemispheres, or the region between the cerebrum and cerebellum (tentorium cerebelli).[23,34,35] These predilection sites differ from those for dogs or humans. Grossly, the cysts contain brown to grey, friable keratin material. The overlying calvarium may be reduced in thickness. As in other sites (pp. 321–322), histologically, the cystic space is filled with concentric, laminated keratin and lined by centrally keratinizing stratified squamous epithelium. In one case focal malignant transformation was suspected, as epithelial cells were seen invading the fibrous capsule.[35] Transition of epidermoid cysts to squamous cell carcinoma has also been reported in rare occasions in human patients.

Cholesterol granulomas

See also page 609.

These are lesions usually arising within the choroid plexuses of the lateral ventricles, and occurring in up to 20% of aged horses. Most such lesions are found incidentally at post-mortem examination, but a few will grow large enough to cause compression of brain tissue (see Fig. 33.6). The cause is thought to be repeated haemorrhage. Grossly, the masses are granular and dark tan to brown. Histologically, there is haemorrhage. with cholesterol crystals and associated granulomatous inflammation.

References

1. Paradis MR. Tumors of the central nervous system. Vet Clin North Am Equine Pract 1998; 14:543–561.
2. Gelatt KN, Leipold HW, Finocchio EJ, et al. Optic disc astrocytoma in a horse. Can Vet J 1971; 12:53–55.
3. Tyler CM, Davis RE, Begg AP, et al. A survey of neurological diseases in horses. Aust Vet J 1993; 70:445–449.
4. Gericota B, Aleman M, Kozikowski TA, et al. A grade IV glioblastoma with an oligodendroglial component (GBM-O) in a horse. J Comp Pathol 2010; 142:332–335.
5. Maxie MG, Youssef S. Nervous system. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's pathology of domestic animals. Philadelphia: Elsevier Saunders; 2007: 281–457.
6. Fankhauser R, Luginbühl H, McGrath JT. Tumours of the nervous system. Bull World Health Organ 1974; 50:53–69.

7. Reppas GP, Harper CG. Sudden unexpected death in a horse due to a cerebral oligodendroglioma. Equine Vet J 1996; 28:163–165.
8. Poppleton H, Gilbertson R. Stem cells of ependymoma. Br J Cancer 2007; 96:6–10.
9. Heath SE, Peter AT, Janovitz EB, et al. Ependymoma of the neurohypophysis and hypernatraemia. J Am Vet Med Assoc 1995; 207:738–741.
10. Carrigan MJ, Higgins RJ, Carlson GP, et al. Equine papillary ependymoma. Vet Pathol 1996; 33:77–80.
11. Huxtable CR, de Lahunat A, Summers BA, et al. Marginal siderosis and degenerative myelopathy: a manifestation of chronic subarachnoid haemorrhage in a horse with a myxopapillary ependymoma. Vet Pathol 2000; 37:483–485.
12. Sohrabi Haghdoost I, Zakarian B. Neoplasms of equidae in Iran. Equine Vet J 1985; 17:237–239.
13. Pirie RS, Mayhew IG, Clarke CJ, et al. Ultrasonographic confirmation of a space-occupying lesion in the brain of a horse: choroid plexus papilloma. Equine Vet J 1998; 30:445–448.
14. Sardon D, Vazquez F, Cabrera P, et al. Choroid plexus papilloma of the fourth ventricle of the plexus in a horse. J Equine Vet Sci 2008; 28:545–548.
15. Poss M, Young S. Dysplastic disease of the cerebellum of an adult horse. Acta Neuropathol 1987; 75:209–211.
16. Koestner A, Higgins RJ. Tumours of the nervous system. In: Meuten DJ, ed. Tumours of domestic animals, 4th edn. Ames: Iowa State Press; 2002: 697–738.
17. Loupal G, Mikula M. Olfaktorius neuroblastom bei einem Pferd. Pferdeheilkunde 1985; 1:65–69.
18. Döpke C, Gröne A, von Borstel M, et al. Metastatic esthesioneuroblastoma in a horse. J Comp Pathol 2005; 132:218–222.
19. Yamate J, Izawa T, Ogata K, et al. Olfactory neuroblastoma in a horse. J Vet Med Sci 2006; 68:495–498.
20. Wippold FJ, Perry A. Neuropathology for the neuroradiologist: rosettes and pseudorosettes. Am J Neuroradiol 2006; 27:488–492.
21. Okabe H, Okubo T, Adachi H, et al. Problems of the immunohistochemical diagnosis of neuroendocrine carcinoma and neuroblastomas. Rinsho Byori 1997; 45:850–855.
22. Kreeger JM, Templer A, Turnquist SE, et al. Paranasal meningioma in a horse. J Vet Diagn Invest 2002; 14:322–325.
23. Lüginbühl H, Fankhauser R, McGrath JT. Spontaneous neoplasms of the nervous system in animals. Prog Neurol Surg 1968; 2:85–164.
24. Dyson PK, Dunn KA, Whitwell K, et al. Ataxia and cranial nerve signs in a pony suffering a brainstem meningioma: clinical, MRI, gross and histopathological findings. Equine Vet Educ 2007; 19:173–178.
25. Naylor RJ, Dunkel B, Dyson S, et al. A retrobulbar meningioma as a cause of unilateral exophthalmos and blindness in a horse. Equine Vet Educ 2010; 22:503–510.
26. Holshuh HJ, Howard EB. Pineoblastoma, a primitive neuroectodermal tumour in the brain of a horse. Vet Pathol 1982; 19:567–569.
27. Allen D, Swayne D, Belknap J. Ganglioneuroma as a cause of small intestinal obstruction in the horse: a case report. Cornell Vet 1989; 79:133–141.
28. Porter BF, Storts RW, Payne HR, et al. Colonic ganglioneuromatosis in a horse. Vet Pathol 2007; 44:207–210.
29. Del Piero F, Summers BA, Cummings JF, et al. Gastrointestinal stromal tumours in equids. Vet Pathol 2001; 38:689–697.
30. Hafner S, Harmon BG, King T. Gastrointestinal stromal tumours of the equine caecum. Vet Pathol 2001; 38:242–246.
31. Muravnick KB, Parente EJ, Del Piero F. An atypical equine gastrointestinal stromal tumour. J Vet Diagn Invest 2009; 21:387–390.
32. Haga HA, Ytrehus B, Rudshaug IJ, et al. Gastrointestinal stromal tumour and hypoglycaemia in a Fjord pony: case report. Acta Vet Scand 2008; 50:9.
33. Allison N, Moeller RB. Spinal ataxia in a horse caused by an arachnoid diverticulum (cyst). J Vet Diagn Invest 2000; 12:279–281.
34. Kelly DF, Watson WJ. Epidermoid cyst of the brain in a horse. Equine Vet J 1976; 8:110–112.
35. Peters M, Brandt K, Wohlsein P. Intracranial epidermoid cyst in a horse. J Comp Pathol 2003; 129:89–92.

23 Internal ocular neoplasms

Neoplastic masses
Melanoma 372
Lymphosarcoma 372
Iridociliary epithelial tumour (iridociliary adenoma) 372
Medulloepithelioma 372
Retinoblastoma 374
Optic disc astrocytoma 374
Non-neoplastic masses
Proliferative optic neuropathy 374
Other conditions affecting the eye and orbit

NEOPLASTIC MASSES

This section includes neoplasms arising in the uvea, retina or optic nerve.

Melanoma

See pages 237 and 239.

Lymphosarcoma

See pages 342 and 352.

Iridociliary epithelial tumour (iridociliary adenoma)

Cellular origin

Most of these neoplasms arise from the pars plicata (the folded, most anterior region of the ciliary body), but some may originate from the posterior iridal epithelium.[1]

Profile

There has been only one report of this tumor type, in an adult horse.[2]

Biological behaviour

In the one reported case, there was occlusion of both pupils. Even small masses may cause glaucoma and neovascularization.[1]

Gross pathology

Multiple, mottled brown and white neoplastic masses were noted bilaterally in the affected horse.[2]

Histopathology

The tumour cells have a papillary or tubular arrangement, usually resemble mature ciliary epithelium and make abundant basal lamina material oriented towards the interior of the globe (that is periodic acid-Schiff (PAS)-positive).[1] In the one equine report, the neoplastic masses contacted the posterior aspect of the cornea, resulting in displacement of corneal endothelial cells onto their surfaces with production of Descemet-like material.[2]

Immunohistochemical labelling

Iridociliary epithelial tumour cells should show positive labelling for vimentin, S100 and neuron-specific enolase (NSE).[1]

Medulloepithelioma

See also page 623.

Cellular origin

Medulloepithelioma is a congenital (or early-onset) neoplasm derived from primitive neuroectoderm, i.e. it is a form of primitive neuroepithelial neoplasm. Medulloepitheliomas are thought to arise from the embryonic medullary epithelium of the forebrain and optic vesicle or optic cup; during embryonic development this epithelium undergoes regional differentiation into non-pigmented ciliary epithelium, iris pigment epithelium, retinal pigment epithelium, neural elements and the vitreous.[3] These neoplasms arise from cells that fail to differentiate, and retain pluripotentiality.[4] Neoplasms arising from the mature, differentiated ciliary epithelium do not have pluripotency and are diagnosed as ciliary adenoma or carcinoma.

Profile

Medulloepithelioma is rare in horses, with few case reports.[3–7] However, it is considered to be the most common

primary equine intraocular neoplasm.[1] Medulloepitheliomas usually arise from the ciliary body, where the medullary epithelium remains undifferentiated for longer; that may also explain why this type of neoplasm can be diagnosed in adults.[8,9] However, they have also been reported in the retina, optic disc and optic nerve; during development the embryonic medullary epithelium lining the optic vesicle is continuous with epithelium lining the cavities of the optic nerve.[4,7,10] When medulloepitheliomas arise in the retina they must be differentiated histologically from retinoblastoma. Medulloepitheliomas are predominantly diagnosed in younger animals as expected, but may also occur in adults.

Biological behaviour

As so few cases of medulloepithelioma have been documented in horses, no assumptions can be made regarding biological behaviour. Medulloepitheliomas may be benign or malignant (based on histological criteria). They are slow-growing tumours, and this can allow them to escape clinical detection until the eye is overtly enlarged and blindness has developed.[3] Local growth and extension may cause significant problems, including severe exophthalmos and cranial invasion.[4,10,11]

Metastasis is rare and occurs late in the course of disease; this usually follows orbital invasion. Metastatic masses may be found within the calvarium following enucleation, where they may cause brainstem compression and necessitate euthanasia.[10] In a case reported in 1919, metastasis to cervical and retropharyngeal lymph nodes was documented.[3] Therefore, if there is no evidence of extraocular invasion or metastasis, enucleation is the treatment of choice.[3] In one case where enucleation was performed, there was recurrence below the surgical site 13 months later.[9]

Gross pathology

Medulloepitheliomas may fill anterior and posterior segments of the eye, with extension into the vitreous cavity and destruction of normal intraocular architecture that can include the ciliary body and processes, iris and the anterior drainage angle.[3,5,9] Where the optic nerve is involved, there may be massive expansion, and episcleral nodules may develop adjacent to the nerve.[4] Two medulloepithelioma cases arising from the optic disc and optic nerve extended into the retrobulbar area, with only a small part protruding into the vitreous body and invading the adjacent sclera.[7,10]

Medulloepitheliomas are solid or spongy, pink, pink-white, grey-white or yellow-white, well-vascularized masses that are encapsulated, multilobular and can measure several centimetres in diameter (Figs. 8.5, 34.8). The surfaces may be irregular, with small cystic areas.[12] Some posteriorly located masses may resemble detached retinal tissue.[6] Haemorrhage on outer and sectioned surfaces may be seen.

There has been a case where a mass extended around the lens; other masses may displace the lens, resulting in cataract formation.[3,6] Additional associated lesions (typically seen with larger neoplasms) include corneal vascularization and oedema, corneal fibrosis, anterior uveitis, glaucoma, buphthalmos and subretinal haemorrhage.[9,13]

Histopathology

Medulloepitheliomas may only contain neuroepithelial structures, but can also contain more solid areas (retinoblastoma-like). Tumour cells are arranged in sheets and/or tubules and cords, and commonly form clefts or true rosettes, i.e. tumour cells radiating around an empty lumen (Flexner–Wintersteiner rosettes) or a space filled with cytoplasmic processes (Homer Wright rosettes).[14] Tumour cells may also form pseudorosettes, i.e. align around blood vessels.[7] Microcysts filled with eosinophilic homogeneous material have also been noted, with cords of tumour cells extending into the cystic spaces.[7] In one case, this fluid was periodic acid-Schiff (PAS)-positive and Alcian blue-positive, i.e. it contained glycosaminoglycans.[5] The fluid-filled spaces are formed by folding of the tumour cell cords.[12] Basilar regions of tumour cell cords and rosettes face a myxoid matrix analogous to the vitreous.[1]

The tumour cells are stratified and columnar or fusiform/elongate, with small to moderate amounts of homogeneous eosinophilic cytoplasm. The cells show features of the embryonic sensory retina; early in retinal development, medullary epithelial cells acquire polarity with formation of a basement membrane on one side (becomes the retinal internal limiting membrane) and terminal bars on the other (become the outer limiting membrane).[12] Cords of tumour cells have a basement membrane that is the internal limiting membrane analogue, and external limiting membrane equivalents may be seen lining the lumens of clefts and rosettes. In one case, blepharoplasts were demonstrated in tumour cells forming rosettes in some areas, using a phosphotungstic acid-haematoxylin (PTAH) stain; these are basal bodies of cilia, i.e. this indicated a component of ependymal differentiation.[10]

Nuclei are large, elongate and vesicular or hyperchromatic, with up to several large nucleoli; they are pleomorphic and have a variable mitotic rate (that is higher in malignant tumours). Malignant medulloepitheliomas invade adjacent structures, including the ciliary vascular spaces, scleral meshwork and limbus.[3,6]

Non-teratoid medulloepitheliomas are composed only of neuroepithelial cells. Teratoid medulloepitheliomas show neuroglial, neuronal, melanocytic, rhabdomyoblastic, chondroid or spongioblastic differentiation, i.e. this includes structures not normally found in the eye.[3]

There may be necrosis and mineralization of tumour cells. Other lesions associated with medulloepithelioma include vacuolar degeneration and atrophy of the ciliary body epithelium, retinal atrophy, retinal detachment, retinal pigment epithelium hypertrophy, subretinal fluid exudation, optic nerve atrophy (where there is direct tumour compression), cavitations of the optic papilla, and conjunctival inflammation.[7,9]

Immunohistochemical labelling

Tumour cells stain positively for glial fibrillary acidic protein (GFAP), neurofilament protein, synaptophysin, retinal S-protein, S100 and vimentin.[9] They are cytokeratin-negative.

Box 23.1 Differential diagnoses for medulloepithelioma and retinoblastoma

Neoplastic
- Retinoblastoma and medulloepithelioma (for each other)
- Melanoma
- Lymphosarcoma
- Iridociliary adenoma

Non-neoplastic
- Iridal or ciliary body cysts

Electron microscopy

Ultrastructurally, the tumour cells are linked by adherens junctions, and cilia and/or their basal bodies may be identified.[6]

Differential diagnoses

These are listed in Box 23.1.

If a medulloepithelioma spreads to or arises in the retina, histological differentiation from a retinoblastoma is required.

Retinoblastoma

See also pages 115 and 624.

Cellular origin

Retinoblastoma is also a neoplasm arising from primitive neuroepithelium.

Profile

Retinoblastoma is the second most common neoplasm diagnosed in children, but is exceedingly rare in domestic animals; it has been stated that 'a critical review of the literature reveals only a single acceptable diagnosis of this tumour' [in a dog].[1]

Biological behaviour

Retinoblastoma is an aggressive, malignant neoplasm that, in human patients, may have growth patterns that are endophytic, exophytic, a mixture of endophytic and exophytic, diffuse (infiltrating) or spontaneously regressing.[12]

Gross pathology

Histologically, there are sheets of poorly cohesive tumour cells that may show rosette formation; the tumour cells have a scanty cytoplasm, round hyperchromatic nuclei and may show focal differentiation into photoreceptor elements.[12] There are numerous mitotic figures, with large areas of necrosis and mineralization.

Differential diagnoses

These are listed in Box 23.1.

Optic disc astrocytoma

See page 363–364.

NON-NEOPLASTIC MASSES

Proliferative optic neuropathy

This is a benign and usually unilateral non-neoplastic mass; it is most often an incidental finding in aged horses (≥15 years) but has been documented in horses as young as 6 years.[15,16] In surveys of ophthalmic lesions in 83 and 100 geriatric horses, respectively, this was noted in only two animals in each.[15,17] The rate of growth has not been defined, but there is usually some enlargement over months or years, and masses large enough to affect vision have been observed in older horses (>20 years).[18] The well-circumscribed, smooth or papillary, white-grey, yellow-white or pink mass is characteristically observed projecting into the vitreous and retina; it may cover a proportion of the optic disc (see Fig. 34.9). Some larger lesions can be pedunculated.[16] In one case, there was also infiltration of nerve fibre and ganglion cell layers of the adjacent retina, with secondary destruction of inner nuclear and inner plexiform layers.[19]

The masses are thinly encapsulated and composed of proliferating, plump, lipid-laden (vacuolated) glial cells with round to ovoid, often peripheral nuclei. The cytoplasm is partly periodic acid-Schiff-positive and stains with Oil Red O.[15] These cells may be noted within the optic nerve, with adjacent gliosis and demyelination. The surrounding retinal vasculature is tortuous, with thickening and hyaline degeneration of their walls; there may also be proliferation of retinal pigment epithelium.[15]

In one case, the cells contained PAS-positive granules and were S100-positive; this mass was diagnosed as a granular cell tumour of Schwann cell derivation.[20]

Exudative optic neuropathy (again mostly affecting older horses) appears bilaterally as white to grey material obscuring part of the optic nerve, with associated oedema and in some cases haemorrhage.[21]

OTHER CONDITIONS AFFECTING THE EYE AND ORBIT

- Orbital cellulitis
- Retrobulbar abscess or haematoma
- Orbital fracture
- Retrobulbar dermoid cyst
- Hydatid cyst.

References

1. Wilcock BP. Eye and ear. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's pathology of domestic animals. Philadelphia: Elsevier Saunders; 2007: 459–552.
2. Daicker B, Gywat L, Keller M, et al. Adenoma of the pigmented epithelium of the iris with endothelialization and descemetization in the horse. Zentralbl Veterinarmed A 1991; 38:652–659.
3. Szymanski CM. Malignant teratoid medulloepithelioma in a horse. J Am Vet Med Assoc 1987; 190:301–302.

4. Eagle RC, Font KL, Swerczek TW. Malignant medulloepithelioma of the optic nerve in a horse. Vet Pathol 1978; 15:488–494.
5. Bistner SI. Medullo-epithelioma of the iris and ciliary body in a horse. Cornell Vet 1974; 64:588–595.
6. Riis RC, Scherlie PH, Rebhun WC. Intraocular medulloepithelioma in a horse. Equine Vet J Suppl 1990; 10:66–68.
7. Ueda Y, Senba H, Nishimura T, et al. Ocular medulloepithelioma in a Thoroughbred. Equine Vet J 1993; 25:558–561.
8. Blodi FC, Ramsey FK. Ocular tumors in domestic animals. Am J Ophthalmol 1967; 64:627–633.
9. Knottenbelt DC, Hetzel U, Roberts V. Primary intraocular primitive neuroectodermal tumour causing unilateral blindness in a gelding. Vet Ophthalmol 2007; 10:348–356.
10. Bistner S, Campbell RJ, Shaw D, et al. Neuroepithelial tumour of the optic nerve in a horse. Cornell Vet 1983; 73:30–40.
11. Cutler TJ, Brooks DE, Andrew SE, et al. Disease of the equine posterior segment. Vet Ophthalmol 2000; 3:73–82.
12. Chung EM, Specht CS, Schroeder JW. From the archives of the AFIP: Pediatric orbit tumors and tumorlike lesions: neuroepithelial lesions of the ocular globe and optic nerve. Radiographics 2007; 27:1159–1186.
13. Hollingsworth SR. Diseases of the anterior uvea. In: Gilger BC, ed. Equine ophthalmology. St Louis: Elsevier Saunders; 2005: 253–268.
14. Wippold FJ, Perry A. Neuropathology for the neuroradiologist: rosettes and pseudorosettes. Am J Neuroradiol 2006; 27:488–492.
15. Saunders LZ, Bistner SI, Rubin LF. Proliferative optic neuropathy in horses. Vet Pathol 1972; 9:368–378.
16. Rebhun WC. Tumors of the eye and ocular adnexal tissues. Vet Clin North Am Equine Pract 1998; 14:579–606.
17. Chandler KJ, Billson FM, Mellor DJ. Ophthalmic lesions in 83 geriatric horses and ponies. Vet Rec 2003; 153:319–322.
18. Rebhun WC. Retinal and optic nerve diseases. Vet Clin North Am Equine Pract 1992; 8:587–608.
19. Vestre WA, Turner TA, Carlton WW. Proliferative optic neuropathy in a horse. J Am Vet Med Assoc 1982; 181:490–491.
20. Riis RC, Rebhun WC. Proliferative optic neuropathy in a horse caused by a granular cell tumour. Equine Vet J Suppl 1990; 10:69–72.
21. Wilkie DA. Diseases of the ocular posterior segment. In: Gilger BC, ed. Equine ophthalmology. St Louis, MO: Elsevier Saunders; 2005: 341–369.

24

Endocrine and neuroendocrine neoplasms

Endocrine neoplasms
Pituitary adenoma (and hyperplasia) 376
Thyroid adenoma and carcinoma 380
Thyroid C-(parafollicular)cell adenoma and carcinoma 382
Thyroid ultimobranchial remnant (mixed) neoplasms 383
Parathyroid (chief cell) adenoma and carcinoma 384
Adrenal cortical adenoma and carcinoma 384
Metastatic neoplasms 385
Non-neoplastic adrenal cortical lesions 386
Pancreatic islet cell neoplasms 386
Multiple endocrine neoplasia-like syndrome 386
Neuroendocrine neoplasms
Phaeochromocytoma (intra-adrenal sympathetic paraganglioma) 387
Extra-adrenal paragangliomas (sympathetic and parasympathetic) 389
Neoplasms of the dispersed neuroendocrine system 390

Cellular origin

Endocrine-origin neoplasms (most of which are benign) occur predominantly in older horses, and most frequently involve the pituitary, adrenal and/or thyroid glands. Neuroendocrine tissues are less well-understood; their phenotype has neural features but the extent of this differs with location, with those in the larynx, lung, thymus and thyroid (C cells) being most 'neural-like' and the more specialized cells in the gastrointestinal tract and pancreas being the most 'epithelial-like'.[1]

ENDOCRINE NEOPLASMS

Pituitary adenoma (and hyperplasia)

See also page 587.

Cellular origin

The anterior lobe of the pituitary gland (adenohypophysis) is composed of the pars distalis, pars intermedia and pars tuberalis. Most pituitary adenomas of equines arise in the pars intermedia (PI) of the pituitary gland, where the melanotroph is the major cell type; they are presumed to be of melanotroph origin. Rare (corticotroph-origin) neoplasms have been found in the pars distalis.[2] There has been some debate as to whether these lesions are benign neoplasms or actually represent adenomatous hyperplasia secondary to loss of dopaminergic inhibition of the PI.[3] Recently, however, a range of lesions have been described, from focal hypertrophy or hyperplasia, through diffuse adenomatous hyperplasia and microadenomas to adenoma. Strictly speaking, this is more likely to be a neurodegenerative disease as opposed to a primary neoplastic process, based on the suspected pathogenesis (see below).[4]

Profile

It was estimated, based on a study of 4000 horses, that pituitary-dependent disease (now termed 'pituitary pars intermedia dysfunction', PPID) occurs at a frequency of 0.075–0.15%.[5] However, this may be a significant underestimate, with more recent studies of aged equines (>15–20 years) involving owner assessment of hair coat abnormalities (see p. 377) and measurement of relevant plasma hormone levels (see p. 377) indicating prevalences of 10–39%.[6–8] Pituitary adenomas are typically diagnosed in older horses, with approximately 85% being >15 years of age; mean ages of 19–27 years have been documented in various studies.[9–12] The prevalence has been shown to increase with each year of age.[7] However, younger adults can be affected (7–12 years of age).[9] The condition was said to be most common in (aged) females in older literature, but this has not been supported by more recent surveys.[10,13,14] A predisposition for pony breeds has been documented, but has been suggested by some authors to relate more to the fact that those animals are more likely to be kept into old age or, alternatively, to hirsutism being more obviously expressed (see pp. 377 and 587).[7,8,12,15] It is also possible that differences between pony breeds in their risk of developing pituitary disease is confusing the literature.[14] The geographical distribution of pituitary disease in horses and ponies has not been investigated.

Biological behaviour

Melanotrophs of the PI, and corticotrophs of the pars distalis, produce pro-opiomelanocortin (POMC). Pro-opiomelanocortin undergoes extensive post-translational processing that differs between the PI and the pars distalis, due to differential enzyme expression.[14] In both regions, POMC is converted to pro-ACTH and β-lipotropin by prohormone convertase 1 (PC1); PI melanotrophs further

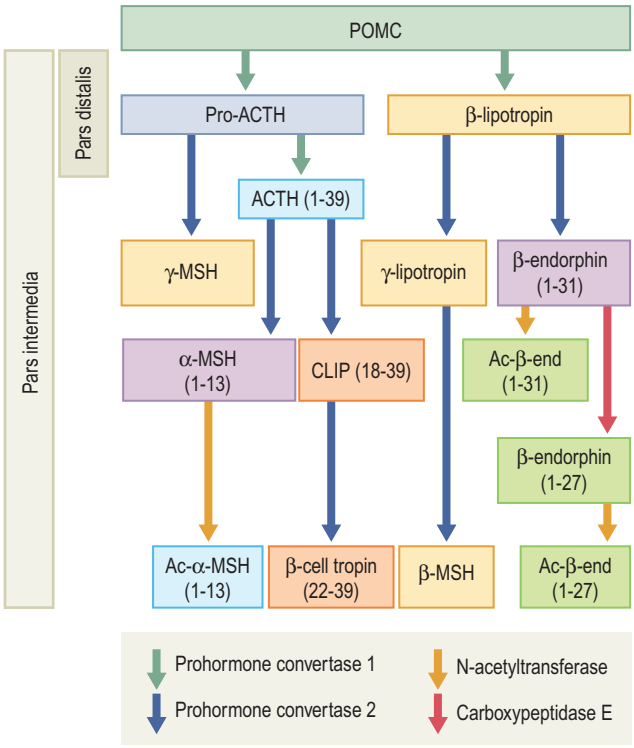


Figure 24.1 Pro-opiomelanocortin (POMC) processing pathway. POMC is processed differently in the corticotrophs of the pars distalis than in the melanotrophs of the pars intermedia because of differential expression of the enzymes involved in the post-translational processing steps. Ac-α-MSH, acetyl-α-MSH; Ac-β-end, acetyl-β-end. *(Figure reprinted from McFarlane D, Equine pituitary pars intermedia dysfunction. Veterinary Clinics of North America Equine Practice 2011; 27:93–113; Fig. 1.)*

process these hormones into products including melanocyte-stimulating hormones (β-MSH, β-MSH, γ_3-MSH), β-endorphin, corticotropin-like intermediate lobe peptide (CLIP), and γ-lipotropin due to expression of prohormone convertase 2 (PC2) (Fig. 24.1).[14,16]

The major product of POMC cleavage in the PI of horses is α-MSH.[14] However, although ACTH functions largely as a precursor for α-MSH and CLIP, some may still be found in the PI region.

Activity of the PI in horses can be inhibited by dopamine and stimulated by thyrotropin-releasing hormone (TRH). Dopamine, released by hypothalamic periventricular neurons that directly innervate the melanotrophs, is known to cause a reduction in POMC transcription and translation.[14,17] It has been proposed that age-related oxidative stress in, and degeneration of, these dopaminergic neurons in horses with PPID allows melanotroph proliferation, with resultant excessive synthesis and processing of PMOC.[4,14] The dopaminergic neurodegeneration hypothesis has been supported by: measurements of significant reductions in levels of dopamine and dopamine metabolites in the PI; alleviation of clinical signs (with decreased concentrations of POMC-derived peptides, including ACTH) in horses treated with dopamine or dopamine agonists (e.g. pergolide); reductions in dopaminergic nerve terminals (in the PI) and neuronal bodies, the latter by 50%, in horses with PPID; and increased levels of an oxidative stress marker (3-nitrotyrosine) in the nerve terminals of those neurons.[13,16,18–20] In one study, there was colocalization of 3-nitrotyrosine with overexpressed α-synuclein in the PI of diseased horses (α-synuclein being a target for nitration, that promotes its aggregation), suggesting some similarity to Parkinson's disease.[14,20] The end result of this putative reduction in dopaminergic control is release of excess PI-derived peptides (MSH, β-endorphins, CLIP) that are increased by 40 times or more, and lesser but still elevated amounts of ACTH; this ACTH is now released from the PI as well as the pars distalis.[3,4,14,21] Increases in plasma and cerebrospinal fluid β-endorphin levels of 60- and 120-fold, respectively, have been measured, with evidence of significantly reduced post-translational processing of this hormone within the neoplastic tissue.[18] Although there are only relatively small increases in ACTH, its steroidogenic properties are significantly potentiated (approximately six-fold) by MSH and β-endorphin.[22] The disease may be diagnosed by measurement of basal ACTH and α-MSH plasma concentrations (with seasonal correction); however, the latter test is not available commercially.[7,14] Resting ACTH concentration is more likely to be elevated (but not invariably) in horses with PI neoplasms than in those with hyperplastic lesions.[10,13]

It should be noted that clinical signs of pituitary pars intermedia dysfunction may be seen in horses with diffuse PI hyperplasia as well as in those with neoplastic changes; conversely, horses not showing clinical signs of PPID have been found to have hypertrophic, hyperplastic or neoplastic lesions.[13] Horses with focal or multifocal rather than diffuse hyperplasia and hypertrophy do not usually show signs.[2]

Metastasis has never been reported. Hypertrophic osteopathy was reported in one pony.[23]

Gross pathology

Hair coat abnormality (Fig. 32.1B,C) is not seen in all cases of equine PI neoplasia.[7,13] However, if post-mortem examination is used as the gold standard, hirsutism can have a positive predictive value of 90%.[24] There is no other known clinical condition that causes hirsutism in horses, including adrenal neoplasia.[10] This should not be confused with normal long winter hair coats that can be retained with certain chronic illnesses or nutritional deficiencies.[25] Hirsutism may involve the whole body, or only a few guard hairs on the face and jugular furrow.[3] It is often most noticeable on the limbs, but the mane and tail are typically not affected.[25] The hair is long (up to 9–10 cm), dense, often curled or wavy and matted, and there will be a history of it either not being shed seasonally, significantly reduced shedding in total, or incomplete shedding.[12,21,25] Early in the disease course, hirsutism often begins on the limbs, ventrum and under the chin.[25] In rare cases, the coat colour changes. The underlying skin may be scaly or greasy in some horses, and bacterial infections may be diagnosed (that may relate to hyperhidrosis).[12,25,14]

Skeletal muscle atrophy may be noted, particularly of epaxial, lumbar and abdominal muscles.[25] Abnormal fat distribution affects approximately 15–30% of cases. This includes bilateral bulging of supraorbital fossa fat, large deposits in tailhead, lumbar, neck and scapular regions and contribution to the typical 'pot belly' (Fig. 32.1A).[12,25]

The PI of the equine pituitary gland normally surrounds the neurohypophysis. The pituitary gland of affected horses/ponies is variably enlarged, but often 2–5 times normal size (Fig. 32.2).

Microadenomas are defined as being <0.5 cm in diameter; adenomas usually measure 1–3 cm.[2,13,14,26] Some microadenomas may only be identifiable microscopically.[9,13] On sectioned surfaces, adenomas are grey, grey-brown or yellow-white, (sometimes) lobulated, expansile and sharply delineated but unencapsulated. They are confluent with the PI and often seen to compress the neurohypophysis and pars distalis; in some cases, the remnant normal pituitary tissue forms a thin rim. Infiltration of the neurohypophysis has been reported.[9,27] Sufficiently large masses may compress the overlying hypothalamus, creating a surface depression that is noted when the brain is removed at post-mortem examination.[26,28] In some cases, the optic nerves may be compressed cranially and laterally. On sectioned surfaces of the masses, areas of necrosis and haemorrhage may be noted.[14]

The adrenal cortices may be bilaterally thickened (hyperplastic) in some, but not all, horses (i.e. pituitary ACTH-dependent hyperadrenocorticism).[28] Lesions consistent with laminitis (of varying severity) have been found in 60 to >80% of cases. In one Finnish study of laminitis (n=36), one-third of the 89% of cases showing evidence of endocrinopathy had a diagnosis of PPID.[15] Other chronic hoof abnormalities may also occur, including white line separation. Increased susceptibility to infectious disease occurs in approximately 35% of cases; secondary lesions noted may include dermatophilosis, sinusitis, pneumonia, abscesses (teeth, skin, feet, pharynx, mandible, lung), endoparasitism, joint or tendon sheath infections, staphylococcal hair folliculitis, and non-healing oral ulcers (Fig. 32.1D).

Histopathology

It is useful when assessing histopathology of the pituitary gland to keep a section of the normal equine pituitary to hand for comparison. For appropriate diagnosis, median sagittal sections should be taken.[13]

The spectrum of histological changes in the PI of horses has been graded (Fig. 24.2)[13]:

- *Grade 1* – Within normal limits
- *Grade 2* – Focal or multifocal hyperplasia or hypertrophy, with focal obscuring of the PI/pars nervosa interface in most horses
- *Grade 3* – Diffuse adenomatous hyperplasia, with irregular thickening of the PI by slightly enlarged but well-differentiated cells and no formation of discrete nodules ≥1 mm in diameter
- *Grade 4* – Diffuse adenomatous hyperplasia with microadenomas measuring 1–5 mm in diameter; some authors include lesions up to 1 cm in diameter[14]
- *Grade 5* – Adenoma. In two studies, 66–68% of horses with PPID (total n=51) had an adenoma (>1 cm); however, it was suggested that this was biased towards finding neoplasia by the selection of end-stage cases.[9,29]

This grading system resulted in high concordance between pathologists, while in a previous study without such a system, the agreement was only fair.[30] The mean age of horses affected strongly and was positively correlated with grade, i.e. horses with microadenomas and adenomas (mean age 23–24 years) were older than those with hyperplastic lesions (mean age 14–20 years) and normal horses (mean age 7 years).[13] Where there is difficulty in establishing a diagnosis, the mean PI area in median sagittal sections may be used to assist, with areas in one study for grades 1–5 being 0.18, 0.29, 0.48, 0.88 and 2.3 cm^2, respectively.[13]

Typically, microadenomas or adenomas occur within a background of hyperplastic change.[14] The tumour cells are arranged in trabeculae, cords, nests, and/or pseudoacini with palisading along blood vessels or follicles. They are supported by a delicate fibrous stroma (Fig. 24.3). Macroadenomas are often subdivided by fine fibrous septa into multiple nodules or follicular structures.[2,9] Cysts or follicles lined by tumour cells contain periodic acid-Schiff (PAS)-positive material (colloid).[31]

In general, the tumour cells resemble non-neoplastic melanotrophs, but are usually larger.[2] Tumour cells forming microadenomas are pyriform, with abundant eosinophilic or amphophilic cytoplasm that has well-defined margins, and enlarged nuclei.[13] Two types of tumour cell have been described in adenomas:

1. Large columnar or spindle-shaped cells with abundant eosinophilic cytoplasm (that may palisade around blood vessels), periodic acid-Schiff (PAS)-positive cytoplasmic granules and large round/ovoid nuclei with a single nucleolus.
2. Cells with cytoplasmic digitations that stain positively with PAS and toluidine blue and have small, hyperchromatic, irregularly-shaped nuclei.[26,32]

Mitotic figures are usually rare and anisokaryosis mild.[9,10] In occasional cases, large bizarre nuclei and greater numbers of mitotic figures have been noted, but there was no evidence of vascular invasion or metastasis.[10]

There may be atrophy and necrosis of cells in the compressed pars distalis; focal hyperplasia is common, and follicles and cysts have been observed. Infiltration of the periphery of the pars nervosa by small numbers of tumour cells has been observed histologically, where there may be gliosis and infiltrating siderophages.[26,27,32] Other associated lesions in the pars nervosa are highly variable and may include axonal spheroids, haemorrhage, haematoidin pigment and necrosis.[10,13] Increased amounts of lipofuscin have been noted in the pars nervosa and in connective tissue septa separating clusters of melanotrophs.[29] These changes may also occur in cases of marked adenomatous hyperplasia. Where there is significant compression of the hypothalamus, histological changes may include satellitosis of neurons, neuronal necrosis and loss, gliosis and perivascular haemorrhage. Vascular mineralization has also been reported; however, this is a common finding in brains of ageing horses.

A number of associated, extra-pituitary lesions have been noted in horses with PPID. Diffuse adrenocortical hyperplasia has been documented in 20–44% of cases, largely due to increased thickness of the zona fasciculata and proposed to be caused by increased ACTH activity.[9,13,26,28,29,32] In one study, 71% of horses with adrenocortical hyperplasia (n=14) also had diffusely swollen and vacuolated hepatocytes,

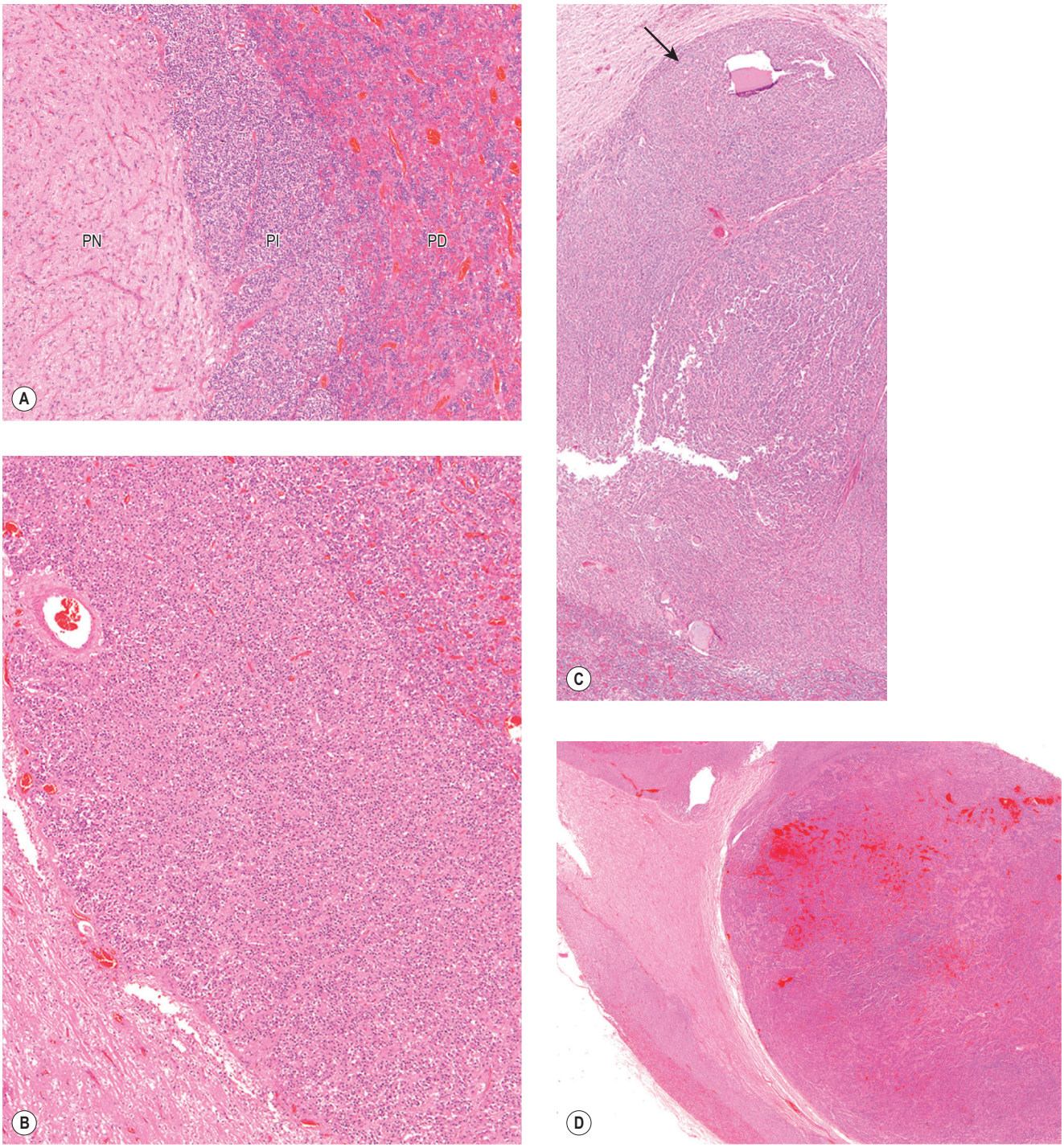


Figure 24.2 Spectrum of hyperplastic and neoplastic lesions in the equine pars intermedia (PI). **(A)** The normal PI, forming a thin, regular band of tissue between the pars distalis (PD) and pars nervosa (PN) (H&E, ×40). **(B)** Diffuse adenomatous hyperplasia expanding the PI (H&E, ×40). **(C)** Severe adenomatous hyperplasia with formation of nodules (microadenoma, arrow) (H&E, ×40). **(D)** Macroadenoma, with compression of the more peripheral normal tissue (H&E, ×12.5).

consistent with steroid-induced hepatopathy (to which the horse is considered to be relatively resistant).[29] Bronchiolitis and bronchointerstitial inflammation are frequent, with lesions including increased bronchiolar mucus (with or without cellular debris), epithelial hyperplasia, peribronchiolar inflammatory cell infiltrates (neutrophils and mononuclear cells) and fibrosis. Mild proliferative glomerulonephritis, myocardial fibrosis and myocardial lipofuscinosis have also been documented at increased levels in PPID cases.[29] In the skeletal muscles, there is atrophy of type 2A and B myofibres, with loss of type B fibres (identification of myofibre types requires histochemical staining of frozen sections for myofibrillar ATPase and oxidative enzymes); other, nonspecific myopathic lesions include increased myofibre size variation, increased numbers of internal nuclei, increased sizes of intrasarcoplasmic lipid droplets and additional fat accumulation in the perimysium and endomysium (demonstrated using Oil Red O staining).[33]

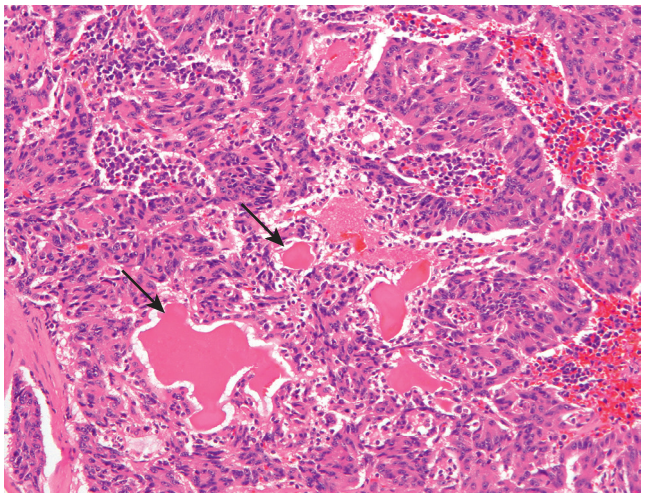


Figure 24.3 Adenoma of the pars intermedia. Tumour cells are arranged in trabeculae, within which they are palisading. Some line irregularly-shaped colloid-filled spaces (arrows) (H&E, ×100).

This type of selective atrophy of type 2 fibres is typically seen in conditions of glucocorticoid excess in equines and other species. For pathologists inexperienced in the examination of equine muscle biopsy specimens, it is helpful to make comparisons with appropriate age- and breed-matched controls.

In specimens from the skin, hair follicles are uniformly in the anagen phase and have a normal morphology, as do all other epidermal and dermal structures; cutaneous endocrinopathic lesions typically associated with pituitary neoplasms in other species, e.g. dogs, are not seen in horses. Nodular and/or diffuse xanthogranulomas of skin over the thorax have been described in some cases; these lesions are composed of large multinucleate histiocytic giant cells with foamy cytoplasm.[25,34]

Immunohistochemical labelling

Tumour cells have stained positively for ACTH, POMC, β-endorphin, β-lipotropin, α-MSH, β-MSH and γ_3-MSH, CLIP, prolactin and follicle-stimulating hormone.[31,32,35,36] Labelling for ACTH is patchy and weaker than that for POMC, α-MSH and β-endorphin, and it does not necessarily represent bioactive hormone.[2,21] Positive labelling with both α- and β-S100 antibodies has also been noted.[35] Immunohistochemical staining patterns have been found to be similar between normal PI tissue and adenomas.[9]

In a study reported in 1997, some cells in the border region of the PI (that is contiguous with the pars distalis) showed strong immunohistochemical labelling for ACTH in normal horses; in PI adenomas, ACTH-positive cells of this border region were increased in size and number.[37] Corticotrophs in the normal pars distalis show strong immunoreactivity for ACTH, with only a few cells staining for α-MSH.[21]

Electron microscopy

Ultrastructurally, PI adenoma cells have well-developed rough endoplasmic reticulum, Golgi apparatus, and membrane-limited secretory granules (300 nm diameter) consistent with high synthetic and secretory activity.[21]

Thyroid adenoma and carcinoma

See also page 590.

Cellular origin

Iodothyronine-producing follicular epithelial cells of the thyroid gland.[2]

Profile

In two surveys of equine neoplasms (UK and India), thyroid-origin neoplasms were the most common type, comprising 47% and 30% of the totals, respectively.[38,39] All thyroid neoplasms in the UK study were adenomas, although it was not determined if they were follicular or parafollicular. In the Indian survey, all affected horses were 16 years of age or older and 76% of the tumours were unilateral.[38] Similarly, in a study of the thyroid glands of 29 horses aged 12–32 years submitted to a New Zealand abattoir, 10 (34%) animals had one or multiple thyroid adenomas; no neoplasms were documented in horses <18 years of age.[40]

Thyroid carcinomas are rare in horses, but have been reported in small numbers of animals 12–24 years of age.[40–46] Concurrent thyroid adenomas and carcinomas have been described.[45]

Biological behaviour

Thyroid adenomas are slow-growing and non-functional, and are usually incidental findings.[47] It is not certain if adenomas progress to carcinomas. Thyroid carcinomas are locally aggressive and may extend around the trachea and oesophagus.[41] They can metastasize, but this is uncommon in horses; metastasis has been reported to regional (cervical) lymph nodes in addition to the pericardium, mediastinum, omentum, adrenal cortex and splenic capsule.[44] Carcinomas are also usually non-functional; however, an elevated free thyroxine level was reported in one horse with a thyroid carcinoma, and this resolved following surgery.[46] In another case of thyroid carcinoma, a competitive trial horse with a 3-month history of work intolerance had low baseline levels of triiodothyronine (T_3) and thyroxine (T_4), that returned to normal post-surgery; that horse was subsequently able to compete successfully.[43]

Gross pathology

Thyroid adenomas are usually not detectable from the exterior surface of the gland; however, there may be enlargement of the gland as a whole. On sectioned surfaces, well-demarcated tan, cream or white nodular masses are noted (Figs. 24.4 and 32.3) that may contain cystic spaces filled with dark orange fluid, i.e. fluid containing haemorrhage and cellular debris.[40] Small masses of neoplastic tissue may project into the cyst lumens.[2]

Carcinomas are firm and white or light tan on sectioned surfaces, and there can be areas of metaplastic cartilage and bone formation. Encapsulation and fibrous tissue septa have also been described.[41] A large thyroid carcinoma reported in one horse measured up to 19 cm in diameter and involved the trachea, oesophagus and carotid arteries.[44]

Histopathology

Adenomas are surrounded by a complete fibrovascular capsule. The tumour cells are arranged in sheets and/or lining irregular cystic spaces and follicles, supported by a fibrous stroma that may be more prominent in the centre of the mass (Fig. 24.5).[2] The follicular pattern is most common in animals (as opposed to papillary), and the follicles may contain pale-staining eosinophilic colloid and/or be partially collapsed. The terms 'microfollicular' and 'macrofollicular' may be used to refer to miniature and large follicles, respectively (relative to those in the normal thyroid gland). Cases of trabecular or solid adenoma are rare in animals, i.e. in which there is little or no evidence of follicle formation.[2] The tumour cells are polygonal, cuboidal or columnar, with round to oval nuclei. Tumour cells lining larger follicles may be flattened. There may be slight variation in cell and nuclear size and shape, but mitotic figures are rare. Compression of the surrounding thyroid parenchyma results in atrophy. Other associated changes may include haemorrhage, oedema, hyalinization, mineralization and (rarely) metaplastic bone formation.[2]

In some horses, there may be adjacent foci of nodular or multinodular hyperplasia; these areas are sharply demarcated, but by definition are not encapsulated and do not compress surrounding tissue or only compress it minimally.[40] In horses, these changes may cause enlargement of the gland and, unlike most neoplasms, the hyperplasia may be bilateral. The cuboidal epithelial cells comprising these nodules line follicles with a variable appearance (within the nodule). Some line small follicles containing little or no colloid, others form one to several layers lining and forming papillary projections into larger follicles, and some follicles are involuted (distended by colloid).[21] This is in contrast to the relatively homogeneous appearance of adenoma tissue.

Carcinomas are multinodular and poorly-encapsulated. In well-differentiated neoplasms, the tumour cells may be arranged in sheets and/or macro- and microfollicles that vary in size and may contain colloid (see Fig. 24.5). The tumour cells lining follicles may form several layers or papillary projections. In poorly-differentiated carcinomas the tumour cells are usually arranged in nests. Undifferentiated carcinomas do not frequently form follicles, and may be composed of spindle cells, small cells or giant cells, arranged largely in a solid growth pattern. Both poorly-differentiated and undifferentiated thyroid carcinomas will usually require immunohistochemical labelling for diagnosis (see below). The pattern of tumour cell arrangement may vary within a mass, and when it does, malignancy should be suspected.[2] The tumour cells are columnar with round or oval basal nuclei containing stippled chromatin and 1–2 prominent nucleoli. Compared with adenomas, thyroid carcinomas may be more cellular and with a greater degree of pleomorphism; binucleate cells and small numbers of mitotic figures may be noted. However, the distinction is more difficult when the tumour cells are well-differentiated (see Fig. 24.5). A definitive diagnosis of

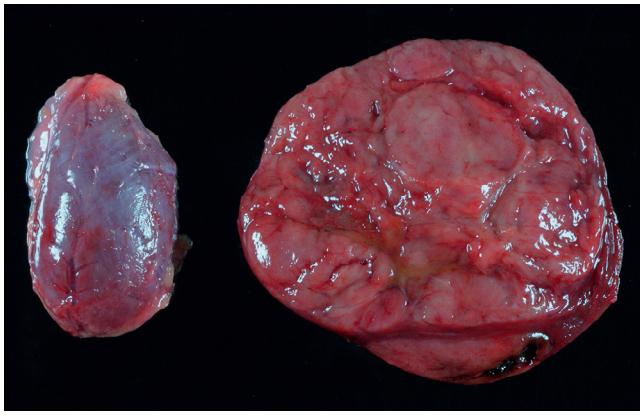


Figure 24.4 Thyroid adenoma. A large adenoma that is seen on the sectioned surface to have largely effaced the normal thyroid parenchyma, and is causing significant enlargement relative to the opposite, normal gland (on the left). *(Figure courtesy of Professor Keith Thompson, Institute of Veterinary, Animal and Biomedical Sciences, Massey University, New Zealand.)*

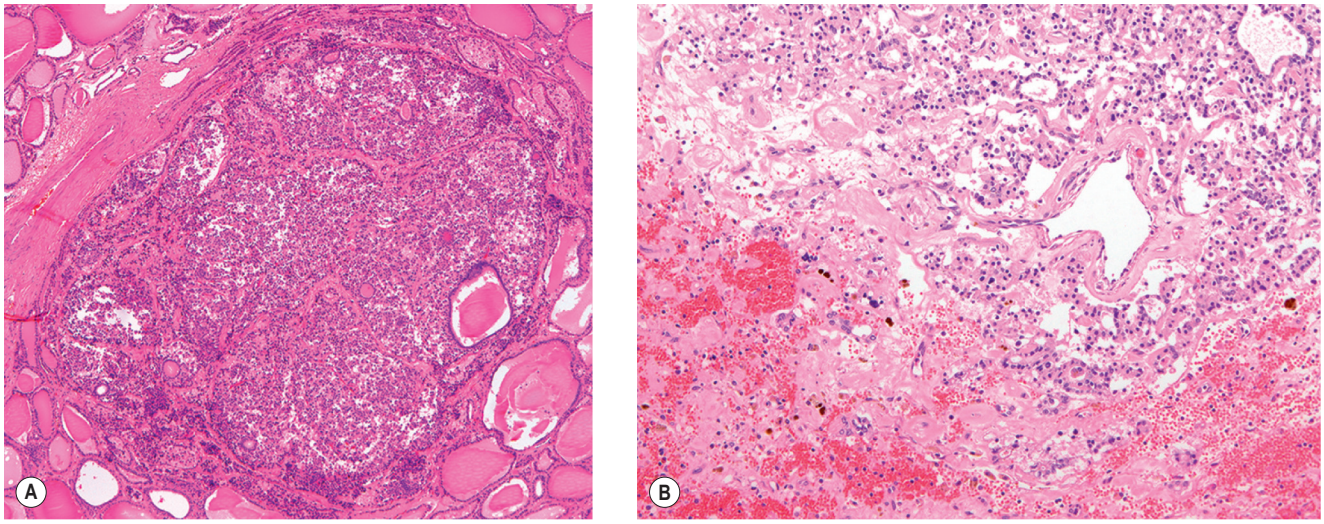


Figure 24.5 Thyroid neoplasms in horses. (A) A thyroid adenoma that is expansile and causing compression of the surrounding parenchyma, particularly at the upper margin. The mass is lobulated, and within lobules, well-differentiated tumour cells are arranged in packets and trabeculae with scattered, variably-sized follicles. This mass was an incidental finding at post-mortem examination (H&E, ×40). **(B)** A well-differentiated thyroid carcinoma, with single layers of tumour cells lining numerous variably sized follicles. There is a large region of haemorrhage and necrosis on the left (H&E, ×100).

malignancy can only be made when tumour cells are seen to penetrate the entire thickness of the capsule (this may require examination of serial sections) and/or there is invasion of one or more blood vessels in the capsule or surrounding parenchyma (not within the neoplasm).[2] The significance of bulging of tumour cells into a vascular lumen without disruption of the overlying endothelial cell layer is not certain.[2] Tumour cells may also multifocally invade the surrounding parenchyma and adjacent adipose tissue, and there may be compressive effects. There are often large areas of tumour necrosis and haemorrhage. Associated inflammatory granulation tissue was noted in one case.[43] Metastatic lesions can have a similar appearance, with microfollicles containing colloid.[41]

Immunohistochemical labelling

Normal thyroid follicular epithelial cells and adenoma cells show positive nuclear staining for thyroid transcription factor 1 (TTF-1) and cytoplasmic labelling for thyroglobulin; there is stronger staining for thyroglobulin in the follicular colloid.[2] It should be noted that TTF-1 can also be expressed by C cells and pulmonary carcinomas.[2] In well-differentiated and poorly-differentiated thyroid carcinomas, there should be positive labelling for thyroglobulin (cytoplasmic and/or colloid); however, this would not be expected in undifferentiated neoplasms.

Thyroid C-(parafollicular)cell adenoma and carcinoma

See also page 591.

Cellular origin

Calcitonin-producing C-(parafollicular)cells found along the basement membrane of the thyroid follicular epithelium.

Profile

In a Japanese survey of 38 horses aged 10–29 years, C-cell adenomas were found in 32% of horses >10 years and 75% of horses >20 years of age.[48] These findings were not in agreement with a similar post-mortem study conducted in New Zealand, in which the significant numbers of thyroid neoplasms found incidentally were diagnosed as being of follicular origin; however, immunohistochemical labelling was not used to confirm those diagnoses.[40] It is also possible that there is geographical variation in the incidence of follicular and C-cell thyroid adenomas, respectively. In one survey of 72 horses diagnosed with endocrine neoplasia at necropsy, four had a C-cell tumour only, and six horses had both a C-cell tumour and a phaeochromocytoma (see Multiple endocrine neoplasia-like syndrome, below).[49] There have been a few reports of other cases, in animals as young as 8 years.[50,51] A C-cell carcinoma was reported in a 12-year-old Warmblood mare.[52]

There is no known gender or breed predisposition.[48,49]

Biological behaviour

Focal and/or diffuse C-cell hyperplasia is often thought to precede development of neoplasia. This hyperplasia may occur as a compensatory process if the other thyroid gland loses C-cell mass (e.g. due to follicular cell hyperplasia or neoplasia) or as a true pre-neoplastic lesion.[2] Hyperplastic cells have a normal appearance.

Adenomas are expansile masses, excision of which should be curative. C-cell carcinomas are invasive and vascular metastasis is possible.[50] Symptoms consistent with calcitonin hypersecretion have not been reported, i.e. neoplasms of C-cell origin in horses are not considered to be functional.[48] The reported C-cell carcinoma was surgically excised and did not recur.[52] C-cell carcinomas can potentially metastasize to cervical lymph nodes and, less frequently, the lungs.[2]

Gross pathology

C-cell adenomas may be either unilateral or bilateral and often occur near the thyroid hilus.[2,48] They are single or multiple, well-circumscribed, nodular, smooth-surfaced, soft, homogeneous, tan, white, yellow-grey or grey-tan and measure 1–15 cm in diameter with compression of the remaining thyroid gland tissue.[49] They may contain areas of haemorrhage, necrosis or cystic degeneration.[50] When found incidentally, they are only noted on sectioning of the thyroid gland, and measure 0.1–2 cm in diameter.[48]

C-cell carcinomas may be also be unilateral or bilateral, and often result in extensive multinodular enlargement of the involved thyroid glands; the entire gland may be replaced by neoplastic tissue.[2] The reported C-cell carcinoma measured 15 cm in diameter.[52]

Histopathology

Adenomas have a thin, partial to complete fibrous capsule, with compression but not invasion of the surrounding parenchyma. By definition, the neoplastic mass should be larger than five normal colloid-filled follicles (guidelines for rat thyroid glands).[2,21] There is often subdivision of sheets of tumour cells into packets by fine fibrovascular septa.[2,51] The tumour cells are well-differentiated, and are polygonal with abundant pale-staining granular eosinophilic or clear cytoplasm. The cytoplasm contains argyrophilic cytoplasmic granules.[51] Nuclei are uniform and round, and contain one or more nucleoli and evenly distributed chromatin.[2] Mitotic figures are rare.[48,49] Some entrapped, colloid-filled thyroid follicles may be noted.[48]

In comparison with adenomas, C-cell carcinomas are more highly cellular and show a greater degree of cellular pleomorphism; there may be similar subdivision of the mass by fibrovascular septa. The tumour cells are polygonal to spindle-shaped, with pale-staining, granular eosinophilic cytoplasm that has poorly defined margins (Fig. 24.6).[21,50] Nuclei are oval to elongate and vesicular.[2] The tumour cells may be seen invading the thyroid parenchyma and surrounding tissues (Fig. 24.6). In the one reported equine case of C-cell carcinoma the tumour cells were arranged in lobules or sheets with some pseudotubule formation and entrapment of thyroid follicles; these tumour cells were not highly pleomorphic, but there was necrosis and infiltration into blood vessels.[52]

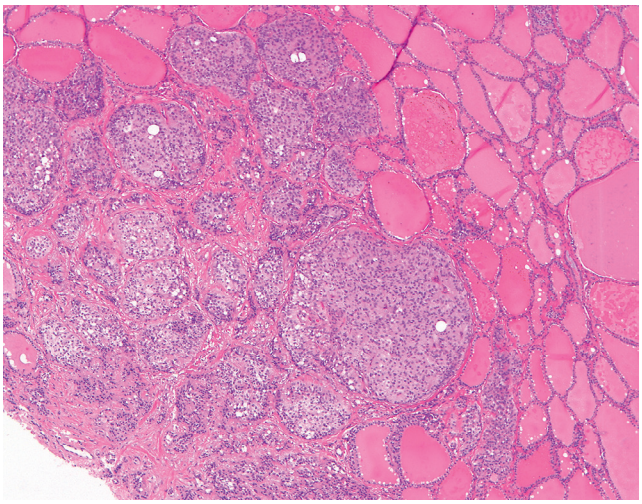


Figure 24.6 Thyroid C-cell carcinoma. The tumour cells are arranged in multiple nodular aggregates and packets, with a moderately abundant collagenous stroma. The mass is not encapsulated and has an irregular margin, with tumour cells infiltrating between and replacing adjacent thyroid follicles. Some remnant follicles remain within the mass. The tumour cells themselves are polygonal, with abundant, pale-staining, granular (and sometimes vacuolated) eosinophilic cytoplasm. This mass was an incidental finding at post-mortem examination (H&E, ×40).

Box 24.1 Differential diagnosis for thyroid C-(parafollicular)cell adenoma and carcinoma

- Thyroid adenoma or carcinoma
- Carotid body neoplasm

Amyloid has not been noted in these tumours in horses, but it is a frequent finding in C-cell neoplasms in human patients and cattle.[51]

Immunohistochemical labelling

Tumour cells should show strong positive cytoplasmic labelling for calcitonin, and neuroendocrine markers including neuron-specific enolase (NSE), chromogranin A and B and synaptophysin.[48,52] Focal positive labelling for somatostatin and bombesin may also be noted.[2] In the Japanese study, negative immunolabelling for calcitonin-gene-related peptide was reported, but it was not indicated if the antibody used had been validated for use with equine tissue. The tumour cells should stain negatively for thyroglobulin.[48]

Electron microscopy

Ultrastructurally, there are membrane-bound, electron-dense, intracytoplasmic secretory granules.[51] Secretory granules were reported as sparse in adenomas in the Japanese study, with this being hypothesized to indicate low secretory activity.[48,50]

Differential diagnosis

These are listed in Box 24.1.

Thyroid ultimobranchial remnant (mixed) neoplasms

See also page 592.

Cellular origin

These neoplasms are composed of mixtures of undifferentiated cells, with two types of differentiated cell i.e. the follicular epithelial cells and C cells (parafollicular). In humans, it has been suggested that these neoplasms are of ultimobranchial body remnant origin, and there is evidence for the presence of stem cells in 'solid cell nests' thought to represent the original remnant tissue.[53] In the World Health Organization classification system for endocrine neoplasms of domestic animal species, they are listed as C-cell neoplasms 'derived from less differentiated ultimobranchial remnants', and it is also proposed that small immature cells noted histologically are stem cells.[2] These neoplasms in animals are considered by some authors to be equivalent to a variant of thyroid carcinoma in human patients termed the 'intermediate type of differentiated thyroid carcinoma'.[21]

Profile

One group (sourcing tissue in England) reported neoplasms of putative ultimobranchial remnant origin as incidental findings in the thyroid glands of 5/96 horses of unknown age, with hyperplastic lesions in a further 13 animals (3–19 years of age; from Japan and England).[54] There is one report of a mixed neoplasm (composed of follicular and C cells only) causing enlargement of the right thyroid gland in a 13-year-old Andalusian horse.[55] It is possible that similar neoplasms may have been misdiagnosed in other surveys of equine thyroid lesions, as being solely of follicular epithelial or C-cell origin. Carcinomas of this type have not been reported in horses.

Biological behaviour

These neoplasms are benign, and are usually incidental findings (as above).

Gross pathology

Adenomas of ultimobranchial remnant origin are well-circumscribed, encapsulated, white, yellow-white or dark tan masses measuring 0.3–5 cm in diameter.[54,55] Masses found incidentally are seen on sectioned surfaces only and measure <1 cm in diameter.[54] There may be compression of surrounding glandular tissue.

Histopathology

These neoplasms are well-demarcated and encapsulated, with compression of surrounding thyroid follicles, and some degenerate follicles in the capsular tissue. Similar, non-encapsulated lesions have been diagnosed as ultimobranchial hyperplasia. Sheets of undifferentiated cells are intermingled with follicular cells and C cells; it is presumed that

undifferentiated cells have differentiated into both cell types.[54] Proportions of the three cell types may differ significantly, with some neoplasms being largely composed of solid sheets of the undifferentiated cells. Undifferentiated tumour cells have large nuclei with prominent chromatin, and can be distinguished from the other cell types by immunolabelling (see below). In one case, only C cells (clear cells with eosinophilic granules) and follicular epithelial cells were noted; those epithelial cells were arranged lining follicles and forming contiguous trabeculae.[55]

Immunohistochemical labelling

The undifferentiated cells are negative for calcitonin (C cells) and thyroglobulin (follicular cells).[54]

Parathyroid (chief cell) adenoma and carcinoma

See also page 592.

Cellular origin

These neoplasms arise from parathyroid chief cells, i.e. the cells responsible for production of parathyroid hormone.

Profile

Neoplasms of parathyroid gland origin are rare in equines. Parathyroid adenomas have been diagnosed in a small number of older ponies and horses.[56,57] In some cases, the presence of a primary parathyroid neoplasm was suspected, based on clinical signs, but no mass was located (see below).[58,59]

Biological behaviour

Parathyroid gland neoplasms do not appear to occur following chronic secondary hyperparathyroidism (renal or nutritional).[2] They may be functional, i.e. result in primary hyperparathyroidism. With increased levels of parathyroid hormone (PTH), there is a rise in serum calcium levels by enhancement intestinal absorption, renal and bone reabsorption; renal reabsorption of phosphate is decreased. The result is persistent hypercalcaemia, hypophosphataemia and hyperphosphaturia, with osteodystrophia fibrosa of the facial bones.[57,58] Regression of bony lesions has been reported following successful surgical excision of an adenoma.[57]

Carcinomas may invade adjacent tissues, and can potentially metastasize to regional lymph nodes and (rarely) the lungs.[2]

Gross pathology

Horses have two pairs of parathyroid glands, with the cranial pair being located adjacent to the cranial poles of the thyroid glands. However, the caudal pair are variably located along the neck, from the level of bifurcation of the carotid trunk at the thoracic inlet, to somewhere along the cranial third of the trachea. Because of this variable location, a gland containing a neoplasm may be impossible to find, either surgically or at post-mortem examination.

Box 24.2 Differential diagnoses for parathyroid (chief cell) adenoma and carcinoma

Non-neoplastic

- Primary or secondary parathyroid hyperplasia
- For bone lesions:
  - Nutritional secondary hyperparathyroidism (hypocalcaemia or normocalcaemia with hyperphosphataemia)
  - Renal secondary hyperparathyroidism
  - Ingestion of oxalate-containing forages
  - Vitamin D toxicosis

Adenomas are usually unilateral, well-encapsulated and light brown to red; carcinomas tend to be larger, completely replace the normal gland and are less mobile.[2] Affected horses show weight loss. In cases of osteodystrophia fibrosa, the mandible, maxilla, nasal and facial bones are thickened; there may be nasal passage stenosis and loosening of teeth (the latter due to resorption of the lamina dura).

Histopathology

Chief cell adenomas are partially or completely encapsulated and composed of packets of cuboidal or polygonal cells with a pale-staining eosinophilic cytoplasm.[2] There may be a rim of compressed atrophic parathyroid tissue, and additional compression of the immediately surrounding thyroid parenchyma. Carcinomas invade the parathyroid gland capsule and may extend into surrounding tissues, and occasionally into blood or lymphatic vessels. The tumour cells have a similar appearance to those of adenomas but are often more pleomorphic and there may be greater numbers of mitotic figures.

In lesions of osteodystrophia fibrosa, there is evidence of increased osteoclastic and osteocytic bone resorption with replacement by fibrous tissue.

Immunohistochemistry

Tumour cells should label positively for PTH, cytokeratins and neuroendocrine markers, including chromogranins, synaptophysins and neurofilaments.[2]

Differential diagnoses

These are listed in Box 24.2.

Adrenal cortical adenoma and carcinoma

See also page 592.

Cellular origin

These originate in the cortical cells of the adrenal gland.

Profile

Primary neoplasia of the adrenal cortex is considered to be rare in equines, with many nodular masses most likely representing hyperplastic lesions.[60] Adenomas have been reported in a few adult horses, frequently as incidental findings.[61,62] Carcinomas have mostly been reported in older animals.[62–65]

Biological behaviour

As in other species, adrenal cortical carcinomas often invade both into the adrenal medulla, and out through the capsule of the gland into the caudal vena cava and aorta; in one case, there was invasion of lymphatic vessels of the tunica adventitia of the caudal vena cava.[62,63] One carcinoma metastasized widely to the liver, spleen, lung, mesenteric, mediastinal and tracheobronchial lymph nodes and was also associated with hypercalcaemia.[64] Other cases have metastasized to internal lymph nodes (including mesenteric and iliac) and the lungs, and there may also be implantation metastasis within the peritoneal cavity.[62,63]

There was one report of a functional adrenal cortical adenoma producing signs of pituitary-independent Cushing's disease.[66] Basal plasma cortisol in a mare with a carcinoma was within reference levels.[65]

Gross pathology

Adenomas are usually single and located in the cortex, but may also arise from islands of cortical tissue in the medulla.[67] They vary in size from small lesions only noted on sectioning of the gland, to large masses bulging from the cortical surface; one such mass measured 30 cm in diameter, with marked central necrosis and haemorrhage.[61]

Horses with carcinomas may present with hindlimb oedema caused by compression of the caudal vena cava, and there may be serosanguineous fluid in the abdomen.[63,65] Carcinomas are usually unilateral and single and may also reach a large size, i.e. up to 40 cm in diameter.[64] They are unencapsulated, white/yellow/tan/grey/brown or mottled, may be multilobular, and haemorrhages or central necrosis and cavitation may be noted on sectioned surfaces.[63,64] The entire adrenal gland may be replaced, with invasion of adrenal vessels and extension around adjacent organs and structures including the kidney.[64,65] One large carcinoma surrounded the cranial mesenteric arteries, with adherence to and infiltration of the dorsal wall of the right dorsal colon, resulting in mucosal ulceration; involvement of the mesenteric arteries was considered to be the cause of jejunal infarction in this case.[63]

If an adrenal cortical neoplasm is functional, there will be severe atrophy of the cortex of the contralateral gland.

Histopathology

Adenomas are expansile (with compression of surrounding tissue) and frequently partially or completely thinly encapsulated, sometimes with subdivision by fibrous trabeculae that may be mineralized. The tumour cells are well-differentiated, and may resemble cortical cells in one or two particular zones (i.e. zona glomerulosa, fasciculata or reticularis). The tumour cells are arranged in trabeculae, cords or nests (or a mixture of these patterns) and are polygonal, cuboidal or columnar.[2,61] The cytoplasm is abundant, pale-staining, eosinophilic and often vacuolated (this may include lipid), and nuclei are round or oval with small nucleoli.[2] The mitotic rate is low. Associated changes include central necrosis, haemorrhage and mineralization.[66]

Box 24.3 Differential diagnoses for adrenal cortical adenoma and carcinoma

Neoplastic
- Phaeochromocytoma
- Metastatic neoplasms e.g. haemangiosarcoma, melanoma, lymphosarcoma

Non-neoplastic
- Cortical folds
- Nodular hyperplasia

Carcinoma cells vary in their degree of differentiation and may also resemble cortical cells of a particular adrenal zone, either in some fields or diffusely.[65] The tumour cells are arranged in sheets, trabeculae, nests or cords (generally with a more heterogeneous pattern than seen in adenomas) with variably abundant supporting stroma.[2] The tumour cells may be round, oval, polygonal, elongate or spindle-shaped with a finely granular or vacuolated eosinophilic cytoplasm; compared with adenoma tumour cells, they are usually larger and more pleomorphic. Positive labelling of vacuolated tumour cells for lipid (using Oil Red O stains) has been reported.[63,64] One carcinoma stained positively using the Lewis and Lobban method for androgenic sterols, which was thought to indicate derivation from the zona reticularis.[64] Nuclei are round or ovoid and vesicular with prominent nucleoli, marked anisokaryosis, and a low or high mitotic rate (usually mitotic figures are common and may be bizarre); multinucleate cells may be noted.[2,62–64] Poorly-differentiated carcinomas may resemble phaeochromocytomas in routinely stained sections. There is often extensive infiltration of the adrenal gland capsule and surrounding structures. In one equine case, tumour emboli were diagnosed microscopically in pulmonary blood vessels.[63] Areas of necrosis, mucinous degeneration, haemorrhage, cystic change, calcification, cholesterol deposition and inflammation may be observed.

It may be difficult to distinguish between adenomas and well-differentiated carcinomas in some cases. Malignancy should be diagnosed where there is evidence of invasive behaviour, however well-differentiated the cells are.

Immunohistochemical labelling

The tumour cells should be cytokeratin-negative, but may express melan-A, vimentin, neuron-specific enolase (NSE) and α-inhibin.[2]

Electron microscopy

Ultrastructurally, the tumour cells are connected by junctional complexes, and lack the electron-dense, membrane-limited secretory granules that would expected in phaeochromocytoma cells.

Differential diagnoses

These are listed in Box 24.3.

Metastatic neoplasms

In one study of disseminated neoplasia in horses ($n=67$), 27% had metastatic lesions in the adrenal gland(s).[68] The

most common types were haemangiosarcoma, melanoma and lymphosarcoma, with smaller numbers of cases of squamous cell carcinoma, renal carcinoma, colonic carcinoma, anaplastic carcinoma and neuroendocrine tumour. In 72% of these cases, the metastatic masses were noted grossly.[68] Histologically, they were bilateral in 39% of cases, limited to the cortex in 71%, limited to the medulla in 14% and involved severe infiltration of the gland in 72%.[68]

Non-neoplastic adrenal cortical lesions

See page 593.

These largely need to be differentiated from adrenal cortical adenoma, and include:

- *Cortical folds*: these are prominent in horses and appear as foci of fibrous tissue surrounded by glomerulosa cells in the cortex[67]
- *Nodular hyperplasia*: this is usually a multifocal change with less pronounced demarcation from the surrounding cortex. The nodules can occupy most of the cortex, occur within or outside the adrenal gland capsule, or affect the medulla. The cells may resemble those of the zona reticularis or fasciculata, and may be lipid-rich (i.e. highly vacuolated).

Pancreatic islet cell neoplasms

Cellular origin

These neoplasms originate from endocrine cells of the islets of Langerhans in the pancreas. Islet cells are of four types, each producing a different hormone:

1. Alpha (α) cells (glucagon)
2. Beta (β) cells (insulin)
3. Delta (δ) cells (somatostatin)
4. PP (or F) cells (pancreatic polypeptide).

In horses, β cells comprise the majority of this endocrine cell population; they form an almost continuous mantle around each islet, with a central mass of α cells and scattered peripheral δ and PP cells.[69] The composition and size of islets does vary between regions of the pancreas, as in other species.

Profile

The only reported pancreatic islet cell neoplasm in an equine (a Shetland pony) was an adenoma hypothesized to be of α-cell origin.[70]

Biological behaviour

Islet cell neoplasms are frequently functional, and are classified according to their hormone production.[2] They may be benign or malignant. The adenoma was reported in a pony with hyperinsulinism and hypoglycaemia in addition to β-cell hyperplasia in other islets.[70] Hyperinsulinaemic hypoglycaemia has been reported in human patients with islet cell hyperplasia, with the proposed cause being increased endocrine cell neogenesis from exocrine ductal epithelium (i.e. this is a differential diagnosis).[71]

Box 24.4 Differential diagnoses for pancreatic islet cell neoplasms

Neoplastic
- Pancreatic adenocarcinoma
- Metastatic neoplasms

Non-neoplastic
- Pancreatic islet cell hyperplasia
- Nesidioblastosis

Gross pathology

Islet cell adenomas are well-circumscribed and encapsulated. The adenoma reported in a pony measured only 2 mm in diameter and was white and firm; other islets were enlarged and pale pink.[70]

Histopathology

Tumour cells may be arranged in lobules, cords, packets and pseudorosettes (around capillary blood vessels) that are supported by a fine fibrovascular stroma. The tumour cells have abundant eosinophilic granular cytoplasm with poorly-defined margins, and small, uniform, round or oval nuclei, each containing a prominent nucleolus. Mitotic figures are rare. There may be proliferation of duct-like structures within the neoplasm.[2]

Differential diagnoses

These are listed in Box 24.4.

Pancreatic islet cell hyperplasia is rarely reported in animals, and when diffuse is usually due to β-cell hypertrophy or hyperplasia; there may be compression of surrounding exocrine glandular tissue.[2]

Nesidioblastosis refers to β-cell hypertrophy and ductular proliferation, and has been described in ageing horses.[72] These changes may be focal or multifocal, and involve (apparent) budding of new islet cells from proliferating ductular epithelium.[2]

Multiple endocrine neoplasia-like syndrome

See also page 593.

Cellular origin

This refers to several neoplasms being diagnosed simultaneously in different endocrine glands of one animal.

Profile

Multiple endocrine neoplasia (MEN) is defined as the appearance of benign and/or malignant neoplasms within two or more different endocrine glands (or paraganglia). In humans, this usually occurs as genetically determined (autosomal dominant) syndromes with various specific combinations of endocrine/neuroendocrine neoplasms in each. Those syndromes are not directly applicable to

domestic animals. There have been small numbers of single reports of older horses (15–18 years of age) with multiple hyperplastic and neoplastic endocrine lesions, including: thyroid carcinoma and an adenoma of the pars intermedia of the pituitary gland; phaeochromocytoma and pituitary adenoma; and malignant phaeochromocytoma, adrenal medullary hyperplasia, thyroid C-cell adenoma, and multiple, bilateral cystic papillary thyroid adenomas.[9,36,44,49] In one survey of 72 horses with endocrine tumours that had undergone necropsy, all but six horses (8%) had only solitary thyroid or adrenal tumours; those six horses had both a thyroid C-cell tumour and a phaeochromocytoma and represented 26% of horses with endocrine neoplasia other than those of thyroid follicular origin.[49]

Biological behaviour, gross pathology, histopathology, immunohistochemical labelling

For individual neoplasms seen in this syndrome, these features are described under the relevant headings.

NEUROENDOCRINE NEOPLASMS

Cellular origin

Paraganglia are neural crest-derived neuroendocrine cells closely associated with the autonomic nervous system, and divided into adrenal (i.e. the adrenal medulla) and extra-adrenal categories.[73] Extra-adrenal paraganglia occur as microscopic aggregates throughout the sympathetic nervous system and along some branches of the (parasympathetic) vagus and glossopharyngeal nerves. They are classified into four subgroups[2]:

1. *Chemoreceptor paraganglia*: including aortic and carotid bodies, that assist in regulating respiration and circulation by detecting changes in blood pH, oxygen and carbon dioxide levels
2. *Intravagal paraganglia* (function not understood): within or adjacent to the vagal trunk, or within or in close proximity to the inferior (nodose) or superior (jugular) ganglia
3. *Sympathetic paraganglia*: along the sympathetic chain and including the superior cervical ganglion. The adrenal medulla is the prototype of a sympathetic paraganglion
4. *Visceral-autonomic* (function not understood): in organs, including the urinary bladder and peripheral blood vessels.

Neoplasms of the adrenal medulla are termed 'phaeochromocytomas' rather than paragangliomas. Neoplasms arising from chemoreceptor paraganglia have also been referred to as chemodectomas. Those derived from parasympathetic ganglia have also been called 'glomus tumours'.[2]

Phaeochromocytoma (intra-adrenal sympathetic paraganglioma)

See also page 593.

Cellular origin

Neuroendocrine (chromaffin) cells of the adrenal medulla. These cells are innervated by the splanchnic nerve, and secrete adrenaline (epinephrine), noradrenaline (norepinephrine), enkephalin and enkephalin-containing peptides (found in their chromaffin granules) into the blood.

Profile

In one UK abattoir survey, 16% of all neoplasms (n=151) involved the adrenal gland, and most of those were phaeochromocytomas.[39] Adrenal medullary neoplasms are thought to be more common in horses than those of cortical origin.[67] Phaeochromocytomas are usually diagnosed in older horses (≥12 years), with mean ages of 17–17.5 years in two surveys; however, there was one report in a 6-month-old foal.[74–82] There is no known breed or gender predisposition.

Biological behaviour

Usually, phaeochromocytomas are benign. A few cases have been malignant, and like adrenocortical carcinomas (see pp. 384–385), these neoplasms may invade into the caudal vena cava and/or the aorta.[78] There was one report of extra-dural spinal metastasis with compression of the spinal cord in a 6-month-old foal, with additional widespread metastasis to internal organs; neoplasms in that case were noted in both adrenal glands.[77]

Phaeochromocytomas may be functional, producing excessive amounts of adrenaline, noradrenaline or both (i.e. catecholamines). The size of the phaeochromocytoma mass has not been associated with functionality.[78] Other normal products of chromaffin cells of the medulla include somatostatin, leu-enkephalin, vasoactive intestinal polypeptide, corticotrophin-like substance and neuron-specific enolase; these products have not been studied in detail in equine phaeochromocytomas (see pp. 388 and 593).

Non-functional phaeochromocytomas appear to be more common, and are usually incidental findings at post-mortem examination.[39] Interestingly, in human patients, physical stimulation including motion, postural changes and constipation can activate such neoplasms; it is thought that pressure might cause expulsion of catecholamine-enriched blood from the mass.[78] Provocative stimuli have not been identified for horses, but might include late pregnancy and colic.[79]

Gross pathology

Phaeochromocytomas are usually unilateral and single, but they may on occasion be multiple and/or bilateral.[77,79] The affected gland will be variably enlarged, sometimes containing small cysts (see Fig. 32.5). The neoplasm may only be visible on sectioned surfaces. Phaeochromocytomas are spherical, soft/friable, red, red-grey or red-tan, often haemorrhagic and/or necrotic, and bulge from the cut surface; they may measure up to 12 cm in maximal diameter.[78] There is often marked compression of surrounding medullary or cortical tissue, and most of the normal medullary tissue or the entire adrenal gland may be

replaced.[2,75] Malignant phaeochromocytoma tends to be larger, with evidence of invasion of the capsule, extension outside of the adrenal gland, and compression and invasion of the caudal vena cava.[2] The diagnosis of phaeochromocytoma may be supported by the gross 'chromaffin reaction'; when the neoplasm is placed in 5% potassium dichromate fixative (pH 5.5) for several minutes, the tissue turns brown as the catecholamines are oxidized.[76,80]

Phaeochromocytomas may rupture, with severe haemorrhage into the abdomen. This is postulated to be due to typically poor vascular integrity within this type of neoplasm and/or high intracapsular pressure developing due to rapid growth.[36,79,80] Horses with ruptured phaeochromocytomas may present with colic.[81] If the bleeding is low grade and continual, it may be contained by the adrenal capsule.

Myocardial degeneration or infarction may also be noted at post-mortem examination in horses with functional phaeochromocytomas, and is thought be caused by catecholamine-induced hypertension.[78,80,81]

Histopathology

When submitted to the laboratory, the formalin fixative is often an orange-brown colour.[75] Phaeochromocytomas are expansile, densely cellular, non- or partially-encapsulated, may be lobulated and may contain fibrous trabeculae (Fig. 24.7).[2,74,79] The tumour cells are variably well-differentiated. They may retain the normal arrangement of adrenal medullary cells or are arranged in irregular trabeculae, cords, sheets or alveoli, supported by a fine fibrovascular stroma and in some cases separated by blood-filled cysts.[49,67] The tumour cells are usually round, polyhedral or elongate with a finely granular basophilic or eosinophilic cytoplasm (chromaffin cells) (see Fig. 24.7); spindle cells may be prominent in rare cases. Granules will be argentaffin when stained by the Grimelius method, i.e. they reduce silver ions and stain black. Nuclei are round or ovoid, central or eccentric within the cell, and hyperchromatic.[80] Mitotic figures may be noted (and may be numerous) but are usually infrequent. Associated changes may include central cystic degeneration, haemorrhage and necrosis, particularly in larger neoplasms; there may also be nodular hyperplasia of remaining medullary tissue.[2]

Gelberg et al. (1979)[76] described two morphological cell types in the normal equine adrenal medulla that both stained olive green using the Giemsa method after dichromate fixation:

1. *Peripheral (juxtacortical), tall columnar cells* arranged perpendicularly to blood vessels and with apical nuclei
2. *Central, smaller, round to polyhedral cells* with less densely stained cytoplasm arranged in packets, with a single cytoplasmic vacuole and central nuclei.

The same authors described a phaeochromocytoma in which the tumour cells showed similar zonal differences in morphology; however, the central cells were basophilic rather than olive-green when stained with the Giemsa method following dichromate fixation.[76]

Malignant phaeochromocytomas have been described as often being composed of a mixture of small well-differentiated chromaffin cells and other, larger and more pleomorphic tumour cells.[2] In a malignant neoplasm described in a foal, the tumour cells had large nuclei, were noted within blood vessels, and there were large areas of necrosis (these often coalesce in malignant neoplasms), haemorrhage and metaplastic bone formation.[77] Invasive behaviour and/or metastasis must be established for a definitive diagnosis of malignancy.

Immunohistochemical labelling

Phaeochromocytomas may stain (variably) positively for leu- and met-enkephalin, phenylethanolamine N-methyltransferase (PNMT), endorphin, protein gene product 9.5 (PGP9.5), chromogranin A+B, synaptophysin, vimentin and S100 protein.[2] Many veterinary diagnostic laboratories are only likely to have the latter 3–4 antibodies available. A phaeochromocytoma from a pony showed positive staining for leu-enkephalin (but not somatostatin), although it is not certain if the antibodies were validated for use on equine tissue.[82]

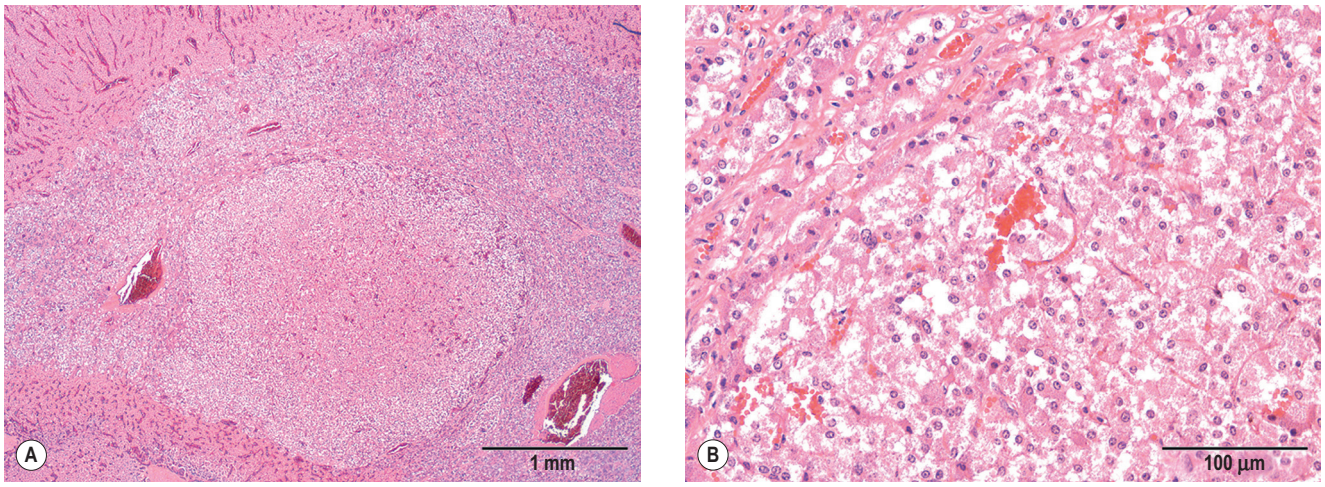


Figure 24.7 Phaeochromocytoma in a 25-year-old pony mare. (A) A small, well-demarcated mass expanding the adrenal medulla. Cortical regions are noted around the edges of the image. **(B)** Polygonal tumour cells with abundant, finely granular, eosinophilic cytoplasm. *(Figures courtesy of Dr Guy Grinwis, Faculty of Veterinary Medicine, Universiteit Utrecht, The Netherlands.)*

Electron microscopy

Normal and neoplastic adrenal medullary cells contain variable numbers of membrane-limited electron-dense, round to elongate intracytoplasmic granules.[76,77,82]

Extra-adrenal paragangliomas (sympathetic and parasympathetic)

See also page 595.

Not all types of extra-adrenal paraganglioma have been reported in horses.

Equine orbital paraganglioma

Cellular origin

These neoplasms originate in non-chromaffin paraganglia that occur near the ciliary ganglion of horses. Orbital paragangliomas (chemodectomas) in humans are thought to arise from chemoreceptor cells and behave more aggressively than those arising in other head or neck sites.

Profile

Equine orbital paragangliomas have been reported in <15 cases in horses ranging in age from 14 to 29 years (mean 16.8).[83–87] There is a predilection for the right eye; the reason for this is not known.

Biological behaviour

All horses with orbital paragangliomas have presented with non-painful exophthalmos (Figs. 7.18, 32.6). These neoplasms are slow-growing but require exenteration for removal when visual disturbances develop. In two horses, hypotension was reported during surgical removal; this may also occur in human patients.[84] In one study 5/6 showed extension through the orbital foramen, and in an earlier report one paraganglioma not only extended into the cranial vault but also was found to have metastasized to the lungs at post-mortem examination.[84,87] Following surgery, 6/7 horses showed no recurrence over 6–48 months.[87]

Gross pathology

Orbital paragangliomas may be encapsulated and lobulated. They are dark red-brown or red-grey and soft, usually measuring 5–6 cm in diameter and with intimate association with the optic nerve, which may be atrophied.[84,87] In many cases, there is periosteal proliferation on surrounding orbital bones, and there may also be thinning and medial deviation of the frontal bone.[87] There is often marked infiltration and destruction of surrounding bony tissue with extension into paranasal sinuses.[86] In one case, there was destruction of the right maxillary bone (forming the medial aspect of the right orbit), with extension into the right conchal sinus and right calvarium. In another horse, the mass extended through the optic canal and into the cranial vault (with lysis of the floor of the cranium) and rostrally to the caudal aspect of the right nasal turbinates; in the same case, encapsulated, nodular metastatic masses measuring 0.5–1 cm in diameter were noted in the lungs.[84]

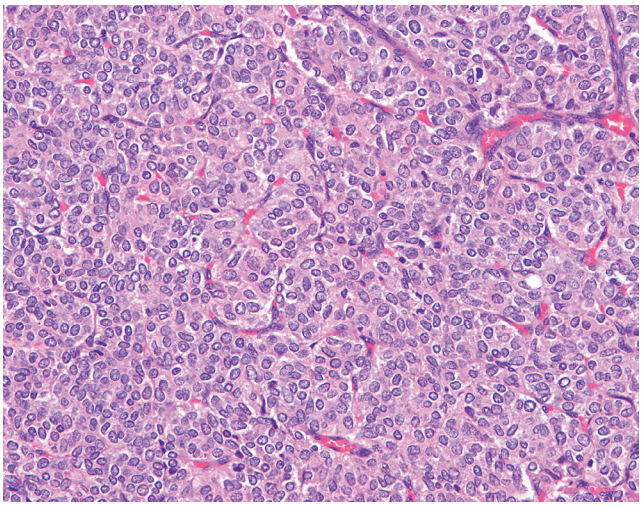


Figure 24.8 Orbital paraganglioma. Polygonal tumour cells with finely granular eosinophilic cytoplasm, arranged in clearly defined packets supported by a delicate fibrovascular stroma (H&E, ×200).

Histopathology

Orbital paragangliomas are composed of nests, packets or ribbon-like cords of polygonal or round, uniform cells supported by a fine fibrovascular stroma (see Fig. 24.8).[84] The tumour cells have abundant finely granular, pale-staining eosinophilic cytoplasm, with variably distinct margins. Nuclei are round or oval and vesicular or hyperchromatic, with 1–3 small nucleoli. The mitotic rate is low. Paragangliomas also contain sustentacular (type 2) cells (equivalent to satellite cells) that are found in reduced numbers in neoplastic versus normal tissue.[2] These cells can usually only be detected by immunohistochemical labelling (see below). Other changes may include central necrosis and haemorrhage.[83]

Immunohistochemical labelling and histochemistry

Equine orbital paragangliomas have stained (variably) positively for chromogranin A, neuron-specific enolase (NSE) and synaptophysin.[83,87] As for other paragangliomas, labelling for catecholamines and protein gene product 9.5 (PGP9.5) may also be of use.[2] The sustentacular cells can be detected by labelling for glial fibrillary acidic protein (GFAP) or S100, and this may assist in making a diagnosis.

The older literature often refers to results of silver staining: argentaffin silver stains (e.g. modified Fontana–Masson) and argyrophilic silver stains (e.g. modified Grimelius) may be used to detect neuroendocrine granules and neurosecretory granule amines/peptides, respectively.[2] Most paragangliomas are argyrophilic, but rarely argentaffinic.[2,83] Immunohistochemical labelling is now the more frequently used technique for establishing a diagnosis.

Chemodectomas

See also page 598.

Cellular origin

Chemoreceptor cells of aortic or carotid bodies: locations for these are the heart base and cranial mediastinum, respectively.

Profile

An aortic body adenoma was reported in a 5-year-old mare, as an incidental finding following slaughter.[88] A chemodectoma involving the base of the heart and the mediastinum (i.e. most likely a large aortic body neoplasm) was diagnosed in a 13-year-old gelding.[89]

Biological behaviour

Chemodectomas are space-occupying masses that displace and compress adjacent structures, are non-functional and usually benign.[2] Malignant forms are possible, which will invade locally and may metastasize. The horse with a chemodectoma presented with exercise intolerance and pleural effusion and was euthanized; although the mass displaced the heart and lungs, invasion or metastasis were not noted.[89]

Gross pathology

As the tumour cells comprising chemodectomas undergo autolysis very rapidly, specimens for histological examination should be fixed as soon as possible. Typically, aortic body adenomas are variable in size, nodular and may contain areas of haemorrhage and necrosis.[2] The aortic body adenoma reported in a mare was round, measured 8 cm in diameter, and was located between the ascending aorta and pulmonary artery at the base of the heart.[88] The sectioned surface was white-red and mottled. The chemodectoma reported in a 13-year-old gelding measured 25 cm in maximal diameter, extended around the base of the heart and into the caudal mediastinum, displaced the heart and lungs caudally and dorsally, and was adhered to the pericardium and pleura.[89] That mass was multilobular, white and contained areas of haemorrhage and necrosis on sectioning.

Histopathology

Aortic body adenomas are completely or partially encapsulated, lobulated and highly cellular. The tumour cells are arranged in nests supported by a fine fibrovascular stroma. They are polygonal with a pale-staining eosinophilic, finely granular (and often vacuolated) cytoplasm that has well-defined margins. Nuclei are large, round and central with one to several nucleoli and rare mitotic figures. There may be areas of necrosis and haemorrhage. Chemodectomas also contain sustentacular (type 2) cells (equivalent to satellite cells) that are found in reduced numbers in neoplastic versus normal tissue.[2] These cells can usually only be detected by immunohistochemical labelling (see below).

Immunohistochemical labelling

Tumour cells may stain positively for neuron-specific enolase (NSE), synaptophysin, catecholamines and protein gene product 9.5 (PGP9.5).[2,89] The sustentacular cells can be detected by labelling for glial fibrillary acidic protein (GFAP) or S100, and this may assist in making a diagnosis.

Aortico-sympathetic paraganglioma

See also page 598.

Cellular origin

Sympathetic paraganglia (chromaffin cells).

Profile

A sublumbar sympathetic paraganglioma arising from superior para-aortic paraganglion tissue was reported in a 20-year-old Warmblood gelding that died after showing signs of colic.[73] A similar (retroperitoneal) mass was reported in a 10-year-old Quarter Horse mare.[90]

Biological behaviour

The sublumbar paraganglioma in one case had metastasized to the spleen and one thyroid gland; in the other case, this occurred to the lung, kidneys, spleen and brain.[73,90] Retroperitoneal paragangliomas are usually non-functional, but they may be the source of massive intra-abdominal haemorrhage.

Gross pathology

The sympathetic paraganglioma in one case was spherical and encapsulated, and measured 22 cm in diameter; it was located cranial to the left kidney and on sectioned surfaces was solid and red-brown.[73] There were adhesions to the large colon with adjacent rupture and haematoma formation, and associated haemoperitoneum. In the second case, the neoplasm measured 10 cm in maximal diameter and was also encapsulated, with lobulation.[90] This mass was tan-grey and on sectioning contained multifocal areas of necrosis and haemorrhage.

Histopathology

Tumour cells are arranged in packets, nests or cords and may show peripheral palisading. The tumour cells may be round, polygonal or spindle-shaped, with a moderate to large amount of granular, deeply eosinophilic cytoplasm that has well-defined margins. Nuclei are round or oval and eccentric with marginated chromatin and single central nucleolus.[90] There is minimal pleomorphism and a low mitotic rate (e.g. 0–2 mitotic figures per high power (×400) field).[73] Other changes may include haemorrhage, necrosis, infiltration by haemosiderophages and vascular invasion by tumour cells.

Immunohistochemical labelling

Tumour cells of one sympathetic paraganglioma stained positively for chromogranin A, synaptophysin and neuron-specific enolase (NSE) but were negative for cytokeratin.[73] In another case, there was positive staining for NSE.[90] As for other paragangliomas, tumour cells may stain positively for neuron-specific enolase (NSE), synaptophysin, catecholamines and protein gene product 9.5 (PGP9.5).[2]

Neoplasms of the dispersed neuroendocrine system

See also page 598.

Cellular origin

These cells of the dispersed neuroendocrine system secrete amines and peptides to assist in physiological control of the metabolism of carbohydrates, proteins and fats; in the intestine, they are found in the crypts and lamina propria.[2]

These cells, and therefore neoplasms arising from them, may be found in almost any site. These neoplasms have also been referred to as 'carcinoids'. The classification systems used for neoplasms of the dispersed neuroendocrine system in human patients are not considered to be applicable to animal species at this stage.[2]

Profile

This type of neoplasm is rare in any domestic animal species. There was one report of a proximal jejunal neuroendocrine neoplasm (carcinoid) in an 18-year-old Thoroughbred mare.[91]

Biological behaviour

In the intestinal tract, these neoplasms may cause obstruction, ulceration and diarrhoea, and predispose to volvulus.[2] Volvulus had occurred in the horse, in which the intestinal neoplasm was reported.[91] It has been stated that all intestinal neuroendocrine neoplasms in domestic animals are considered to be malignant, with typically extensive local infiltration that may extend from mucosa to mesentery.[2] There may be metastasis to regional lymph nodes and more distant organs. In human patients, neoplasms of this type may cause 'carcinoid syndrome' by releasing catecholamines including serotonin, into the circulation; carcinoid syndrome has not been confirmed in horses. They may produce one or more peptides in animals, including serotonin, somatostatin, gastrin, glucagon, vasoactive intestinal peptide and calcitonin.[2]

Gross pathology

The intestinal mass measured 6 cm in diameter and was firm and yellow-white, involving both the intestinal wall (including infiltration of the muscularis externa) and the contiguous mesentery.[91] Intestinal neuroendocrine neoplasms are usually small and annular, and they may project into the lumen.[2]

Histopathology

The tumour cells are arranged in nests, islands, acini or trabeculae supported by a fine fibrovascular stroma (a typical 'endocrine' appearance); wide fibrous bands dissecting the tumour mass were reported in the intestinal case.[91] The tumour cells are round or polygonal, with small to large amounts of pale, eosinophilic, finely granular cytoplasm that has indistinct margins. Nuclei are small, central and hyperchromatic or vesicular, with small nucleoli or no visible nucleoli; mitotic rates are usually low. Other changes may include necrosis, mineralization and vascular invasion.[2]

Immunohistochemical labelling

The tumour cells may stain positively for neuron-specific enolase (NSE), synaptophysin, chromogranin A+B and protein gene product 9.5 (PGP9.5).[2] Labels for other hormonal products, e.g. serotonin, might also be applied.

References

1. Rosai J. The origin of neuroendocrine tumours and the neural crest saga. Mod Pathol 2011; 24:S53–S57.
2. Kiupel M, Capen C, Miller M, et al. Histological classification of tumours of the endocrine system of domestic animals. Vol XII. Washington, DC: Armed Forces Institute of Pathology, C.L. Davis DVM Foundation and The World Health Organization Collaborating Centre for Comparative Oncology; 2008.
3. Paradis MR. Tumors of the central nervous system. Vet Clin North Am Equine Pract 1998; 14:543–561.
4. McFarlane D. Advantages and limitations of the equine disease, pituitary pars intermedia dysfunction as a model of spontaneous dopaminergic neurodegenerative disease. Ageing Res Rev 2007; 6:54–63.
5. Evans DR. The recognition and diagnosis of a pituitary tumour in the horse. Paper presented at the Proceedings of the 18th Convention of the American Association of Equine Practitioners; 1972.
6. Brosnahan MM, Paradis MR. Assessment of clinical characteristics, management practices, and activities of geriatric horses. J Am Vet Med Assoc 2003; 223:99–103.
7. McGowan TW, Pinchbeck GP, McGowan CM. Prevalence, risk factors and clinical signs predictive for equine pituitary pars intermedia dysfunction in aged horses. Equine Vet J. 2012.
8. McGowan TW, Pinchbeck G, Phillips CJ, et al. A survey of aged horses in Queensland, Australia. Part 2: Clinical signs and owners' perceptions of health and welfare. Aust Vet J 2010; 88:465–471.
9. Heinrichs M, Baumgärtner W, Capen CC. Immunocytochemical demonstration of proopiomelanocortin-derived peptides in pituitary adenomas of the pars intermedia in horses. Vet Pathol 1990; 27:419–425.
10. van der Kolk JH, Kalsbeek HC, van Garderen E, et al. Equine pituitary neoplasia: a clinical report of 21 cases (1990–1992). Vet Rec 1993; 133: 594–597.
11. Brosnahan MM, Paradis MR. Demographic and clinical characteristics of geriatric horses: 467 cases (1989–1999). J Am Vet Med Assoc 2003; 223: 93–98.
12. Pilsworth RC, Knottenbelt DC. Hirsutism. Equine Vet Educ 2006; 18: 120–121.
13. Miller MA, Pardo ID, Jackson LP, et al. Correlation of pituitary histomorphometry with adrenocorticotrophic hormone response to domperidone administration in the diagnosis of equine pituitary pars intermedia dysfunction. Vet Pathol 2008; 45:26–38.
14. McFarlane D. Equine pituitary pars intermedia dysfunction. Vet Clin North Am Equine Pract 2011; 27:93–113.
15. Karikoski NP, Horn I, McGowan TW, et al. The prevalence of endocrinopathic laminitis among horses presented for laminitis at a first-opinion/referral equine hospital. Domest Anim Endocrinol 2011; 41:111–117.
16. Orth DN, Nicholson WE. Bioactive and immunoreactive adrenocorticotropin in normal equine pituitary and in pituitary tumours of horses with Cushing's disease. Endocrinology 1982; 111:559–563.
17. Saland LC. The mammalian pituitary intermediate lobe: an update on innervation and regulation. Brain Res Bull 2001; 54:587–593.
18. Millington WR, Dybdal NO, Dawson R, et al. Equine Cushing's disease: differential regulation of beta-endorphin processing in tumours of the intermediate pituitary. Endocrinology 1988; 123:1598–1604.
19. Donaldson MT, LaMonte BH, Morresey P, et al. Treatment with pergolide or cyproheptadine of pituitary pars intermedia dysfunction (equine Cushing's disease). J Vet Intern Med 2002; 16:742–746.
20. McFarlane D, Dybdal N, Donaldson MT, et al. Nitration and increased alpha-synuclein expression associated with dopaminergic neurodegeneration in equine pituitary pars intermedia dysfunction. J Neuroendocrinol 2005; 17:73–80.
21. Capen CC. Endocrine glands. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's pathology of domestic animals, 5th edn, Vol. 3. Philadelphia: Elsevier Saunders; 2007: 325–428.
22. Dybdal NO, Hargreaves KM, Madigan JE, et al. Diagnostic testing for pituitary pars intermedia dysfunction in horses. J Am Vet Med Assoc 1994; 204:627–632.
23. Sweeney CR, Stebbins KE, Schelling CG, et al. Hypertrophic osteopathy in a pony with a pituitary adenoma. J Am Vet Med Assoc 1989; 195: 103–105.
24. Frank N, Andrews FM, Sommardahl CS, et al. Evaluation of the combined dexamethasone suppression/thyrotropin-releasing hormone stimulation test for detection of pars intermedia pituitary adenomas in horses. J Vet Intern Med 2006; 20:987–993.
25. Scott DW, Miller WH. Endocrine, nutritional and miscellaneous hair coat disorders. Equine dermatology, 2nd edn. Maryland Heights: Elsevier Saunders; 2011: 360–377.
26. Loeb WF, Capen CC, Johnson LE. Adenomas of the pars intermedia associated with hyperglycemia and glycosuria in two horses. Cornell Vet 1966; 56:623–639.
27. Tasker JB, Whiteman CE, Martin BR. Diabetes mellitus in the horse. J Am Vet Med Assoc 1966; 149:393–399.
28. Moore JN, Steiss J, Nicholson WE, et al. A case of pituitary adrenocorticotropin-dependent Cushing's syndrome in the horse. Endocrinology 1979; 104: 576–582.
29. Glover CM, Miller LM, Dybdal NO, et al. Extrapituitary and pituitary pathological findings in horses with pituitary pars intermedia dysfunction: a retrospective study. J Equine Vet Sci 2009; 29:146–153.
30. McFarlane D, Miller LM, Craig LE, et al. Agreement in histologic assessments of the pituitary pars intermedia in aged horses. Am J Vet Res 2005; 66:2055–2059.

31. Horvath CJ, Ames TR, Metz AL, et al. Adrenocorticotrophin-containing neoplastic cells in a pars intermedia adenoma in a horse. J Am Vet Med Assoc 1988; 192:367–371.
32. Boujon CE, Bestetti GE, Meier HP, et al. Equine pituitary adenoma: a functional and morphological study. J Comp Pathol 1993; 109:163–178.
33. Aleman M, Watson JL, Williams DC, et al. Myopathy in horses with pituitary pars intermedia dysfunction (Cushing's disease). Neuromuscul Disord 2006; 16:737–744.
34. Scott DW, Miller WH. Equine dermatology. St Louis: WB Saunders; 2003: 360–366.
35. Méndez A, de las Mulas JM, Bautista MJ, et al. Comparative immunohistochemical study of stellate cells in normal canine and equine adenohypophyses and in pituitary tumours. J Comp Pathol 1998; 118:29–40.
36. Germann SE, Rütten M, Derungs SB, et al. Multiple endocrine neoplasia-like syndrome in a horse. Vet Rec 2006; 159:530–532.
37. Okada T, Shimomuro T, Oikawa M, et al. Immunocytochemical localization of adrenocorticotropic hormone-immunoreactive cells of the pars intermedia in thoroughbreds. Am J Vet Res 1997; 58:920–924.
38. Damodaran S, Ramachandran PV. A survey of neoplasms of equidae. Indian Vet J 1975; 52:531–534.
39. Cotchin E, Baker-Smith J. Tumours in horses encountered in an abattoir survey. Vet Rec 1975; 97:399.
40. Dalefield RR, Palmer DN. The frequent occurrence of thyroid tumours in aged horses. J Comp Pathol 1994; 110:57–64.
41. Joyce JR, Thompson RB, Kyzar JR, et al. Thyroid carcinoma in a horse. J Am Vet Med Assoc 1976; 168:610–612.
42. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
43. Held JP, Patton CS, Toal RL, et al. Work intolerance in a horse with thyroid carcinoma. J Am Vet Med Assoc 1985; 187:1044–1045.
44. Chiba S, Okada K, Numakunai S, et al. A case of equine thyroid follicular carcinoma accompanied with adenohypophysial adenoma. Jpn J Vet Sci 1987; 49:551–554.
45. Hovda LR, Shaftoe S, Rose ML, et al. Mediastinal squamous cell carcinoma and thyroid carcinoma in an aged horse. J Am Vet Med Assoc 1990; 197:1187–1189.
46. Ramirez S, McClure JJ, Moore RM, et al. Hyperthyroidism associated with a thyroid adenocarcinoma in a 21-year-old gelding. J Vet Intern Med 1998; 12:475–477.
47. Misdorp W. Tumours in large domestic animals in The Netherlands. J Comp Pathol 1967; 77:211–216.
48. Ueki H, Kowatari Y, Oyamada T, et al. Non-functional C-cell adenoma in aged horses. J Comp Pathol 2004; 131(2–3):157–165.
49. De Cock HE, MacLachlan NJ. Simultaneous occurrence of multiple neoplasms and hyperplasias in the adrenal and thyroid gland of the horse resembling multiple endocrine neoplasia syndrome: case report and retrospective identification of additional cases. Vet Pathol 1999; 36: 633–636.
50. Lucke VM, Lane JG. C-cell tumours of the thyroid in the horse. Equine Vet J 1984; 16:28–30.
51. Turk JR, Nakata YJ, Leathers CW, et al. Ultimobranchial adenoma of the thyroid gland in a horse. Vet Pathol 1983; 20:114–117.
52. van der Velden MA, Meulenaar H. Medullary thyroid carcinoma in a horse. Vet Pathol 1986; 23:622–624.
53. Moreno MJR, Galera-Ruiz H, De Miguel M, et al. Immunohistochemical profile of solid cell nest of thyroid gland. Endocr Pathol 2011; 22:35–39.
54. Tateyama S, Tanimura N, Moritomo Y, et al. The ultimobranchial remnant and its hyperplasia or adenoma in equine thyroid gland. Nihon Juigaku Zasshi 1988; 50:714–722.
55. Kuwamura M, Shirota A, Yamate J, et al. C-cell adenoma containing variously sized thyroid follicles in a horse. J Vet Med Sci 1998; 60:387–389.
56. Peauroi JR, Fisher DJ, Mohr FC, et al. Primary hyperparathyroidism caused by a functional parathyroid adenoma in a horse. J Am Vet Med Assoc 1998; 212:1915–1918.
57. Bienfet V, Dewaele A, van Essche R, et al. A primary parathyroid disorder. Osteofibrosis caused by parathyroid adenoma in a Shetland pony. Recovery after surgical removal. Annls Med Vet 1964; 108:252–256.
58. Frank N, Hawkins JF, Couëtil LL, et al. Primary hyperparathyroidism with osteodystrophia fibrosa of the facial bones in a pony. J Am Vet Med Assoc 1998; 212:84–86.
59. Roussel AJ, Thatcher CD. Primary hyperparathyroidism in a pony mare. Comp Cont Ed Pract Vet 1987; 9:781–783.
60. Valentine BA. Neoplasia. In: Bertone JJ, ed. Equine geriatric medicine and surgery. St Louis: Saunders Elsevier; 2006: 147–167.
61. Evans LH, Siegel ET, Hubben K. Clinico-pathologic conference. J Am Vet Med Assoc 1968; 152:1778–1786.
62. Jackson C. The incidence and pathology of tumours of domesticated animals in South Africa. Onderstepoort J Vet Sci Anim Ind 1936; 6:1–460.
63. Raker CW, Fegley H. Clinico-pathologic conference. J Am Vet Med Assoc 1965; 147:848–860.
64. Fix AS, Miller LD. Equine adrenocortical carcinoma with hypercalcemia. Vet Pathol 1987; 24:190–192.
65. van der Kolk JH, Mars MH, van der Gaag I. Adrenocortical carcinoma in a 12-year-old mare. Vet Rec 1994; 134:113–115.
66. van der Kolk JH, Ijzer J, Overgaauw PAM, et al. Pituitary-independent Cushing's syndrome in a horse. Equine Vet J 2001; 33:110–112.
67. Appleby EC. Tumours of the adrenal gland and paraganglia. Bull WHO 1976; 53:227–235.
68. Labelle P, De Cock HEV. Metastatic tumours to the adrenal glands in domestic animals. Vet Path 2005; 42:52–58.
69. Steiner DJ, Kim A, Miller K, et al. Pancreatic islet plasticity: interspecies comparison of islet architecture and composition. Islets 2010; 2:135–145.
70. Ross MW, Lowe JE, Cooper BJ, et al. Hypoglycemic seizures in a Shetland pony. Cornell Vet 1983; 73:151–169.
71. Ouyang D, Dhall D, Yu R. Pathologic pancreatic endocrine cell hyperplasia. World J Gastroenterol 2011; 17:137–143.
72. Furuoka H, Shirakawa T, Taniyama H, et al. Histogenesis of neoformation in the endocrine pancreas of aging horses. Vet Pathol 1989; 26:40–46.
73. Herbach N, Breuer W, Hermanns W. Metastatic extra-adrenal sympathetic paraganglioma in a horse. J Comp Pathol 2010; 143(2–3):199–202.
74. Buckingham JD. Case report. Pheochromocytoma in a mare. Can Vet J 1970; 11:205–208.
75. Evans LH, Stewart J, Dodd DC. Clinico-pathologic conference. J Am Vet Med Assoc 1971; 159:209–219.
76. Gelberg H, Cockerell GL, Minor RR. A light and electron microscopic study of a normal adrenal medulla and a pheochromocytoma from a horse. Vet Pathol 1979; 16:395–404.
77. Froscher BG, Power HT. Malignant pheochromocytoma in a foal. J Am Vet Med Assoc 1982; 181:494–496.
78. Yovich JV, Horney FD, Hardee GE. Pheochromocytoma in the horse and measurement of norepinephrine levels in horses. Can Vet J 1984; 25:21–25.
79. Johnson PJ, Goetz TE, Foreman JH, et al. Pheochromocytoma in two horses. J Am Vet Med Assoc 1995; 206:837–841.
80. Duckett WM, Snyder JR, Harkema JR, et al. Functional pheochromocytoma in a horse. Comp Cont Ed Pract Vet 1987; 9:1118–1121.
81. Yovich JV, Ducharme NG. Ruptured pheochromocytoma in a mare with colic. J Am Vet Med Assoc 1983; 183:462–464.
82. Wilson RB, Holscher MA, Kasselberg AG, et al. Leu-enkephalin and somatostatin immunoreactivities in canine and equine phaeochromocytomas. Vet Pathol 1986; 23:96–98.
83. van Maanen C, Klein WR, Dik KJ, et al. Three cases of carcinoid in the equine nasal cavity and maxillary sinuses: histologic and immunohistochemical features. Vet Pathol 1996; 33:92–95.
84. Basher AW, Severin GA, Chavkin MJ, et al. Orbital neuroendocrine tumors in three horses. J Am Vet Med Assoc 1997; 210:668–671.
85. Goodhead AD, Venter IJ, Nesbit JW. Retrobulbar extra-adrenal paraganglioma in a horse and its surgical removal by orbitotomy. Vet Comp Ophthalmol 1997; 7:96–100.
86. Matiasek K, Cronau M, Schmahl W, et al. Imaging features and decision making in retrobulbar neuroendocrine tumours in horses – case report and review of literature. J Vet Med A Physiol Pathol Clin Med 2007; 54: 302–306.
87. Miesner T, Wilkie D, Gemensky-Metzler A, et al. Extra-adrenal paraganglioma of the equine orbit: six cases. Vet Ophthalmol 2009; 12:263–268.
88. de Barros CS, dos Santos MN. Aortic body adenoma in a horse. Aust Vet J 1983; 60:61.
89. Levy M, Stegelmeier BL, Hudson LM, et al. Chemodectoma in a horse. Can Vet J 1990; 31:776–777.
90. Kim D-Y, Hodgin EC, Lopez MK, et al. Malignant retroperitoneal paraganglioma in a horse. J Comp Pathol 1994; 110:407–411.
91. Orsini JA, Orsini PG, Sepesy L, et al. Intestinal carcinoid in a mare: an aetiologic consideration for chronic colic in horses. J Am Vet Med Assoc 1988; 193:87–88.

25 Gonadal neoplasms

Sex cord–stromal neoplasms
Granulosa cell tumour (granulosa–theca cell tumour) 393
Interstitial (Leydig) cell tumour 396
Sertoli cell tumour 397
Sertoli–Leydig cell tumour of the ovary (arrhenoblastoma) 398
Adenoma and adenocarcinoma of the rete testis 398

Germ cell tumours
Seminoma 399
Dysgerminoma 400
Teratoma (ovarian or testicular) 401
Teratocarcinoma 402
Embryonal carcinoma 403

Total numbers of testicular neoplasms reported are low; however, this is thought to be due to castration of most male horses at an early age. For examination of testicular neoplasms, it is important to submit the entire testis and attached spermatic cord, so that associated blood and lymphatic vessels may be searched for neoplastic infiltration and/or tumour emboli. If the testis and associated structures are being submitted in formalin fixative, the testis should at least be bisected sagittally using a sharp knife, to allow appropriate fixation of those sectioned surfaces. Ovaries should be similarly sectioned, particularly if they contain large neoplasms.

SEX CORD–STROMAL NEOPLASMS

The sex cords are structures that develop from the gonadal ridge during embryonic development, potentially forming from primordial peritoneum and growing into the mesenchyme. Cells of sex cord origin include Sertoli cells in the testis (and those occurring in rare ovarian neoplasms) and ovarian granulosa (follicular) cells.[1] The cords themselves persist in the testis but regress as recognizable structures in the ovary.[2] Stromal cells include ovarian thecal cells (and their luteinized derivatives), fibroblasts and testicular interstitial (Leydig) cells.[3] Most neoplasms in this category have the potential to secrete steroid hormones.

Granulosa cell tumour (granulosa–theca cell tumour)

See also page 641.

Cellular origin

Granulosa cell tumours (GCTs) may be derived primarily from granulosa cells, or from both granulosa and theca cells of the ovary.

Profile

In one survey, GCTs comprised 2.5% of equine neoplasms presented to a US diagnostic laboratory (n=236).[4] They are the most common type of ovarian neoplasm in mares and comprise more than 85% of total equine female reproductive system neoplasms.[5,6] Granulosa cell tumours are usually unilateral, with an approximately equal distribution between right and left ovaries.[7] The few bilateral neoplasms reported were either concurrent or developed a number of years apart.[8–10]

Granulosa cell tumours have been reported in female horses of all ages, including neonatal and prepubertal foals and maiden, barren, pregnant and foaling mares.[11–15] In one study (n=78), the mean age of affected horses was 10.6 years (range 2–20) and in a further study (n=34), the mean age was 8.1 years, with 20 of these cases involving maiden mares.[16,17] The risk of development of GCT has not been shown to increase with age.[18] There is no breed predilection.

Teratoma (see pp. 401–402 and p. 406) and GCT may occur in the same or opposite ovaries.[19]

Biological behaviour

In most cases, GCTs are slow-growing and benign. It is not known if a mare that has had one GCT is at increased risk of developing one in the contralateral ovary, but metachronous bilateral cases appear to be rare.

A small number of malignant GCTs have been reported. Metastasis is usually confined to the abdominal cavity and sites involved have included omentum, mesentery, liver, spleen, kidneys, sublumbar lymph nodes, abdominal lymph nodes, adrenal glands, ileum, rectum, parietal peritoneum and serosal surfaces of the viscera.[17,20,21] Occasionally, malignant GCTs have also metastasized to thoracic sites, including lymph nodes, lungs and/or pulmonary vasculature.[20,21]

Granulosa cell tumours are often functional and produce different combinations of testosterone, inhibin and oestrogen, with cessation of normal cycling and resulting behavioural changes that include prolonged anoestrus, continuous or intermittent oestrus (nymphomania) or aggressive stallion-like behaviour. Virilistic signs are more common than anoestrus; however, it is possible that those mares are more likely to be presented by owners for investigation.[5,13,22] In one study (n=63), 32% showed anoestrus, 22% continuous oestrus and 46% stallion-like behaviour.[16] In a few cases, mares have been reported to continue to cycle, this being hypothesized to be represent an early stage of tumour development, in which there has not been sufficient time to inhibit contralateral ovarian activity.[13,23] In one such case, the contralateral ovary contained a corpus luteum and serum progesterone levels were as expected; however, no follicles were observed grossly and it was suggested that there may be have been some disturbance in cyclicity, even though the ovary was still active.[24] A 3-month-old foal with a (juvenile) GCT did not show any behavioural changes, i.e. the neoplasm appeared to be non-functional.[12] Although endocrine assays are often valuable in diagnosis, it should be remembered that different diagnostic laboratories frequently use different assays and techniques. As a consequence, the normal ranges may vary and therefore prevent direct comparison. The currently recommended (optimal) diagnostic panel is a combination of inhibin, testosterone and progesterone measurements:[13]

- *Inhibin* is a glycoprotein produced by ovarian granulosa cells in response to follicle-stimulating hormone (FSH) that regulates follicular development. It, in turn, suppresses secretion of FSH by the anterior pituitary gland. During the normal oestrous cycle, inhibin concentrations are positively correlated with levels of oestradiol and both are inversely correlated with FSH levels. Inhibin concentrations vary with stage of the oestrous cycle and the laboratory used, but levels >0.7 ng/mL are generally considered to be elevated and suggestive of the presence of a GCT.[13] Following surgical removal of the GCT, inhibin concentrations rapidly decline (returning to normal within 24 h), with the contralateral ovary returning to normal functional activity on average by 8.5 months.[25,26] In one study plasma inhibin returned to non-detectable levels within 90 min of removal of the GCT.[27] However, low values of inhibin do not exclude the diagnosis.[17] The dimeric protein is the biologically active form and is composed of an α subunit and one of 2 β subunits (βa or βb), to form inhibin A (α-β_A) or inhibin B (α-β_B).[28] In one study, four of six mares had elevated levels of both inhibin A and testosterone; levels of inhibin A in neoplastic fluid may be similar.[28] The free α subunit is not capable of reducing FSH secretion and is also produced by adrenocortical cells.[29] Measurement of α-inhibin using a radioimmunoassay technique has been suggested to be more useful for detection of GCT than measuring (dimeric) $\alpha\beta_A$-inhibin using a two-site immunoradiometric assay.[30] Serum α-inhibin levels have been associated with GCT size. There is a circulating precursor form of the inhibin α subunit (measured as the isoform containing pro- and αC immunoreactivity) that is the predominant form of inhibin secreted by equine granulosa cells.[31] Measurements of these precursor forms may be even more discriminatory in terms of GCT diagnosis.[28,30] Most affected mares have reduced FSH levels and suppression of gonadotrophin-releasing hormone (GnRH)-stimulated release of FSH has also been documented.[13,30,32] This reduction in FSH is hypothesized to be involved in the follicular suppression that occurs in the contralateral ovary. However, not all mares show this reduction in basal and GnRH-stimulated FSH release; it has been suggested that atrophy of the contralateral ovary may actually be due to inhibition of binding of FSH (to its receptors) by the pro- and αC inhibin isoforms.[27] Additionally, anti-Müllerian hormone (AMH) activity may be increased in mares with GCT and AMH is known to have inhibitory effects on FSH response in small follicles.[33] Concentrations of FSH in mares with GCT are not inversely correlated with testosterone levels.[13]
- *Testosterone* levels have been reported to be elevated in 40–67% of mares with GCT, to decline rapidly following surgical removal and, in a number of studies to be associated with stallion-like behaviour.[6,13,15,17,25] It should be noted that some normal pregnant mares also show stallion-like behaviour due to increased testosterone concentrations by 60–90 days, that peak in the 7th month of gestation.[34] Similar behaviour may also occur during the vernal transition into the breeding season.[35] Elevated testosterone levels may also occur with some ovarian cystadenomas, although this is a significantly less common type of neoplasm in horses (see pp. 274–275).[36] McCue (1998) reported that the range for normally cycling mares is 20–45 pg/mL (this has been accepted as the norm).[37] In a later study by the same group, levels in mares with GCT (n=21) ranged from 24.9 to 420 pg/mL.[13] In another study, one mare with bilateral GCT (that developed consecutively) had serum and neoplastic fluid testosterone levels 3× and 10× higher, respectively, than any previously reported.[8] Mares with persistent oestrus or anoestrus behaviour usually have normal testosterone concentrations.[16,25] However, in one study plasma androgen levels (for example, androstenedione and/or dehydroepiandrosterone and/or testosterone) were elevated in mares with GCT showing anoestrus behaviour.[6] Not all mares showing aggressive behaviour have concentrations >100 pg/mL, which has been suggested to be due to fluctuating blood levels relative to the time of sampling.[25,30] Nests of Leydig-like cells that develop from some thecal cells (see p. 396) (Fig. 25.1) have been reported to be most abundant in mares with high serum (and neoplastic fluid) testosterone concentrations and/or stallion-like behaviour and absent in mares with normal levels.[17,25,30,38] These cells have also been shown to be immunopositive for inhibin α and β_A subunits (see above).[38] In a study of nine mares, those with high circulating testosterone showed marked positive immunolabelling of tumour cells for the steroidogenic enzyme $P450_{C17}$, responsible for converting progesterone to androgen.[22] There is no convincing link between elevated testosterone levels in mares with GCT and atrophy of the contralateral ovary.[17] Elevated

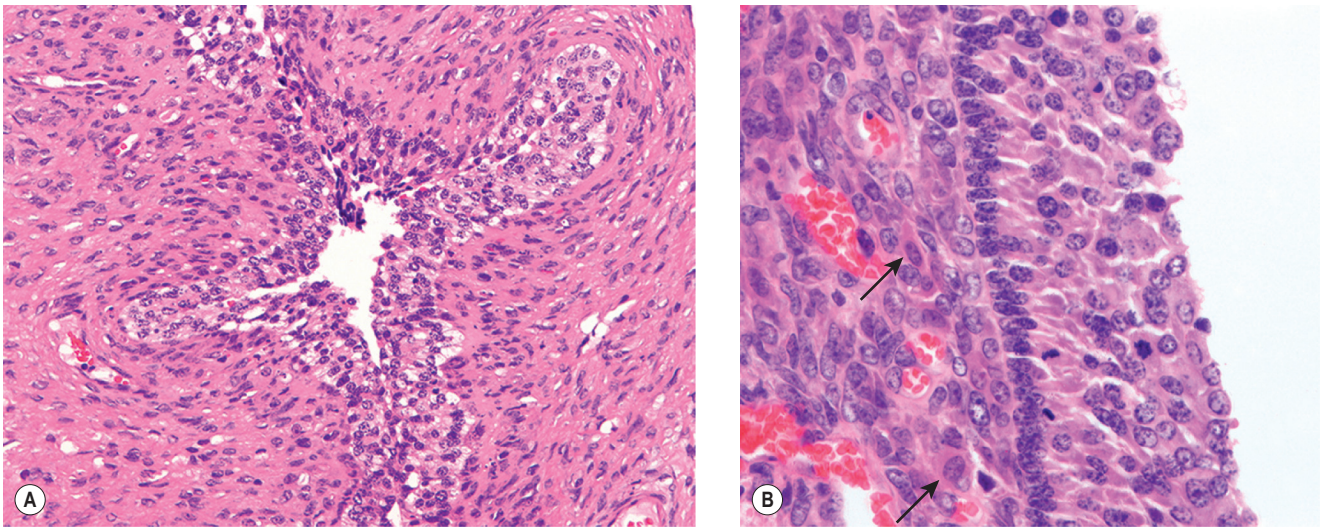


Figure 25.1 Granulosa cell tumours of the ovary. (A) A small, irregularly-shaped follicular space lined by granulosa tumour cells with supporting (spindle-shaped) thecal cells and more peripheral stromal tissue (H&E, ×200). **(B)** Macrofollicular pattern, with several layers of neoplastic granulosa cells lining the cavity (on the right), supported by thecal cells and, in this case, some intermingled Leydig-like cells (arrows). Mitotic figures are present in some of the granulosa tumour cells (H&E, ×400).

concentrations of luteinizing hormone (LH) have been positively associated with testosterone concentrations and it has been suggested that this is due to decreased negative feedback by progesterone.[30]

- *Progesterone* levels are almost invariably low (<1 ng/mL), due to failure of normal follicular development, ovulation and corpus luteum formation.[30] In rare cases, ovulation and active luteal tissue have been detected in mares with GCT, i.e. this diagnosis cannot be ruled out based on progesterone levels alone.[13]
- *Oestrogens* are not as useful clinically. Blood concentrations of oestradiol are variable and have been related to expression of the enzyme aromatase (oestrogen synthetase) by tumour cells. In the normal ovary this enzyme is only expressed by granulosa cells in pre-ovulatory follicles and is responsible in particular for aromatization of androgens to oestrogens. Mares with GCT that have high testosterone concentrations do not also have high oestradiol levels and the GCT cells show minimal or no immunolabelling for aromatase.[22,39] The relationship between plasma oestradiol and oestrone sulphate (conjugated oestrogen) levels and signs of persistent or irregular oestrus in mares with GCT is not consistent.[6,13,15] Significant declines in oestradiol levels have not been documented following surgical removal of GCT.

Occasionally, mares with GCT may present with colic, lameness or weight loss. Complications have included torsion of the affected ovary, small colon obstruction or compression with secondary rupture, adhesions to adjacent abdominal structures, and haemoperitoneum due to rupture of the neoplasm.[10,40–44] Haemoperitoneum is a particular feature of juvenile GCTs, and may be due to susceptibility of the pedicle to forces experienced during parturition.[11,35]

One mare with bilateral GCT had associated diabetes mellitus due to insulin resistance.[13] Hypertrophic osteopathy has also been reported.[45]

Gross pathology

Mares with androgen-producing tumours may develop a crested neck, increased muscle mass (particularly in the forelegs and chest) and an enlarged clitoris. Moderate mammary development may be noted.[5] The affected ovary is enlarged by a spherical, sometimes lobulated or multinodular, usually multicystic ('honeycombed') but sometimes more solid mass that may have a thin to thick capsule or tunica albuginea (see Fig. 35.10); occasionally there is a single, large central cyst or a large cavity in combination with multiple small cysts.[15,37,46] Cyst size can vary markedly and there is no correlation between this and hormone secretion.[22]

Usually, normal ovarian architecture is completely destroyed and the ovarian fossa invaded and effaced at an early stage; however, it may still be identified in some cases (early or well-developed).[5,10,35] The mean neoplasm diameter in one study (n=34) was 11.2 cm and these masses generally range from 10 to 20 cm in diameter; malignant neoplasms may be larger and masses up to 65 cm in diameter have been reported.[10,12,15,17,35] In one remarkable case, a 350 kg mass was removed from a 9-year-old Quarter Horse mare.[47]

On sectioned surfaces, GCTs are grey-yellow and the cysts contain clear, yellow or serosanguineous fluid.[5] There may also be foci of haemorrhage and necrosis that are more extensive in cases of ovarian torsion.[42] If there is a large central cavity filled with clotted blood, this must be differentiated from a haemorrhagic cyst.[48] Small spicules of mineralization were reported in one malignant GCT.[21] The contralateral ovary is usually inactive and small (atrophic).[10]

Histopathology

There may be subdivision into lobules by thin fibrous septa.[15] In one study, the most common patterns of tumour cell arrangement were macro- and microfollicular, tubular and trabecular.[17] In follicular patterns, multiple layers of

granulosa tumour cells line cystic spaces (sometimes forming deep folds) and overlie a supporting stroma that may contain spindle-shaped thecal cells (i.e. this appears to be a disorganized attempt at follicle formation) (see Fig. 25.1).[13] In some cases, there is a gradual change from thecal to granulosa cell morphology in a 'junctional area'.[46] Granulosa and thecal cells may also be mixed in a disorderly fashion. Tubular areas have a Sertoli cell-like appearance, i.e. layers of columnar cells palisading with respect to the basement membranes. These Sertoli-like neoplasms have sometimes been termed 'androblastoma'.[48]

The granulosa tumour cells have an abundant, pale-staining eosinophilic, granular or sometimes vacuolated cytoplasm with well-defined margins. They are cuboidal where they line macro- and microfollicles. Nuclei are basally oriented or central and round, with finely granular chromatin and variably distinct nucleoli. There may be mild anisokaryosis and small numbers of mitotic figures may be noted. Call-Exner bodies may be observed, these being neoplastic cells arranged around secreted product (i.e. resembling a primordial follicle) that stains positively using the periodic acid-Schiff method.[48] Thecal cells are elongate with fibrillar or vacuolated (sometimes almost clear) cytoplasm (see Fig. 25.1). In some mares, nests of large polyhedral cells resembling Leydig cells have been noted among or adjacent to the thecal cells (see Fig. 25.1).[26]

In one report of a malignant GCT, the tumour cells were arranged in rosettes, macrofollicular, tubular and trabecular patterns and in another they were arranged in nests.[17,21] Tumour cells in malignant GCTs show variable degrees of anisocytosis and anisokaryosis, potentially with multiple nucleoli, karyomegaly and 1 to >5 mitotic figures per high power (×400) field.[20,21] In both primary and metastatic masses, there may be intravascular tumour emboli.[20]

Other associated lesions may include extensive haemorrhage and necrosis with mineralization and stromal osseous metaplasia.[21,46]

Immunohistochemical labelling

Granulosa cells in GCTs and those in normal antral follicles express anti-Müllerian hormone (AMH).[33] In the normal ovary, this expression is strongest in small antral follicles and appears to reduce in the larger ones, being lost with follicular atresia. Granulosa cells in GCTs (including Sertoli cell-like areas) and in tertiary and Graafian follicles of the normal ovary stain positively for cytokeratin, vimentin, c-erbB-2 oncoprotein (cerb; cytoplasmic and membranous) and α-inhibin.[17] The granulosa tumour cells also stain strongly for glutathione S-transferase α (GSTα; cytoplasmic and intranuclear), as do granulosa cells of the normal cyclical ovary after ovulation. GSTα plays a role in progestagen and androgen synthesis in the ovary and is localized in the steroid-producing cells.

Thecal cells stain positively for α-actin and desmin and Leydig-like cells strongly express GSTα and weakly express cerb and vimentin.

In one malignant GCT, <10% of granulosa cells stained positively for vimentin, cerb and, in GSTα and metastatic lesions, only GSTα labelling was noted.[17] In another malignant mass, the tumour cells stained positively for vimentin and inhibin and negatively for epithelial membrane antigen and placental alkaline phosphatase.[21]

Box 25.1 Differential diagnoses for granulosa cell tumour

Neoplastic
- Ovarian cystadenoma
- Dysgerminoma
- Teratoma

Non-neoplastic
- Ovarian haematoma or haemorrhagic cyst
- Ovarian hamartoma (e.g. interstitial cell, vascular)
- Ectopic adrenal tissue
- Ovarian abscess
- Haemorrhagic anovulatory follicle
- Germinal inclusion cysts
- Pregnancy-associated ovarian enlargement
- Persistent anovulatory follicle
- Paraovarian cysts
- Polycystic ovary

Differential diagnoses

These are listed in Box 25.1.

Ovarian haematomas are often smaller than GCTs, regress over one to several months, usually occur within the breeding season, do not efface the ovulation fossa and do not interrupt normal cycling.[22] Very large haematomas have been reported, but even these will resolve if there is no secondary infection. Interstitial cell hamartomas of the ovary have been reported in a few cases as incidental congenital lesions; their development is thought to relate to the fact that equine fetal gonads enlarge significantly during the first 9 months of gestation due to interstitial cell hypertrophy and hyperplasia.[49–51]

Interstitial (Leydig) cell tumour

Cellular origin

Interstitial cell tumours arise from androgen-producing interstitial cells of the testis; these are sex cord stromal cells that migrate in from the surface of the gonadal ridge. In stallions, the spaces between seminiferous tubules are largely filled with this cell type. There is a significant increase in interstitial cell populations with age, with these cells replacing non-cellular components of the interstitium and accumulating greater amounts of lipofuscin.[52]

Profile

Interstitial cell tumours are rare in horses. They are, however, the most common non-germ cell testicular neoplasms, with most occurring in cryptorchid testes retained in the abdominal cavity.[53–57] In a survey of 48 published equine testicular tumours, interstitial cell tumours and teratomas each comprised 25% of the total, with only seminomas being more common.[57] In one study, five of nine cases of interstitial cell tumours were bilateral and all but one of those horses was bilaterally cryptorchid.[53] Bilateral involvement of descended testes is rare.[58]

Interstitial cell tumours have been reported in adult horses (3–20 years of age) of various breeds.

There have been reports of a mixed sex cord–stromal cell tumours (features of Sertoli cell tumour in addition to interstitial cell tumour) and two mixed germ cell–sex cord–stromal cell tumours.[59–61]

Oncogenesis

In cryptorchid testes, heat damage to seminiferous tubules is associated with interstitial cell hyperplasia, which may then lead to neoplastic transformation.

Biological behaviour

Interstitial cell tumours are benign and slow-growing. It is possible that they are under-diagnosed due to the small size of many neoplasms.[7] Malignant neoplasms of this type do not appear to have been reported in horses.[56]

Most interstitial cell tumours in horses do not result in elevated systemic levels of androgenic hormones. Interstitial cells in stallions also produce oestrogens and there are reports of aggressive behaviour that might be associated with androgen and/or oestrogen production.[7,53,55,62,63]

Gross pathology

Many testicular neoplasms can be diagnosed based on their gross appearance, although histological confirmation is desirable. Interstitial cell tumours may be single or multiple, vary in size (1 mm to 2 cm in diameter), are well-demarcated, nodular or multinodular, soft, grey, tan or yellow-brown and tend to bulge on sectioning.[56] Haemorrhage frequently occurs within these neoplasms due to a rich vascular supply, with little supporting stroma.[48] The colour and soft consistency of interstitial cell tumours assists in their macroscopic differentiation from other testicular neoplasms.[48] Interstitial cell tumours may also contain cystic areas filled with yellow fluid, seen on sectioned surfaces.[58]

Histopathology

Interstitial cell tumours are usually expansile, thinly encapsulated masses subdivided by connective tissue septa. They are not as sharply demarcated from the surrounding parenchyma in the horse as they are in other domestic species.[7] Tumour cells are arranged in cords or nests with occasional rosette formation, are supported by a fine fibrovascular stroma and may line cysts.[48] The tumour cells are large and round, polygonal or cuboidal, with eosinophilic cytoplasm that is granular, often vacuolated and has well-defined margins. They may be intermingled with well-differentiated interstitial cells containing brown cytoplasmic granules.[7] Nuclei are small, oval or indented and hypochromatic, and mitoses are rare. Binucleate and multinucleate tumour cells may be noted in some neoplasms.

Tumour cells in cryptorchid testes may be spindle-shaped, either as a pure population or admixed with larger interstitial tumour cells; these cells are arranged in packets or interweaving fascicles and have a pale-staining vacuolated or granular, amphophilic or eosinophilic cytoplasm with round or elongate, vesicular or hyperchromatic nuclei.[53,54,56]

Invasion of blood vessels or the tunica albuginea has not been reported. There are often areas of interstitial cell hyperplasia blending with tumour tissue.[53] There has been some debate as to the differentiation between hyperplasia and neoplasia; some authors have classified grossly visible proliferations as neoplastic.[7] Histologically, a neoplastic process is indicated by destruction or displacement of seminiferous tubules by a nodular mass. Remaining seminiferous tubules in the affected testis are degenerate and may only be lined by Sertoli cells. Seminiferous tubules (also degenerate) may be entrapped within the periphery of neoplasms. There may be central necrosis and inflammation and perivascular infiltrates of lymphocytes within the neoplasm and in the surrounding parenchyma.[7,58]

In mixed sex cord–stromal cell and mixed germ cell–sex cord–stromal cell tumours, the different cellular components are intermingled and may require differentiation by immunohistochemical labelling.

Immunohistochemical labelling

Suggested markers for interstitial cells include vimentin, cytokeratin, calretinin, α-inhibin, neuron-specific enolase, CD99 and melan-A.

Sertoli cell tumour

See also page 638.

Cellular origin

Non-spermatogenic (supporting) cells of seminiferous tubules of the testis.

Profile

Sertoli cell tumours are considered to be rare in the stallion, but have been reported in a few horses, in cryptorchid, partially or fully descended testes.[64–68] In one survey of 48 published testicular neoplasms, 12.5% were Sertoli/mixed germ cell/sex cord tumours, occurring in adult horses with a mean age of 17 years (range 10–30 years).[57] Sertoli cell tumours may occur bilaterally and (rarely) in addition to other primary testicular tumours, e.g. interstitial cell tumours.[68]

There has been a report of a mixed sex cord–stromal cell tumour, with features of a Sertoli cell tumour in addition to interstitial cell tumour.[60]

Biological behaviour

The biological behaviour of Sertoli cell tumours in horses is difficult to predict in individual cases due to the small number of previous reports; they may be benign or malignant. Malignant tumours have been reported in both cryptorchid and descended testes.[69] The tumour cells may infiltrate into the capsule of the neoplasm and also into the testicular vein and lymphatic vessels to cause hydrocoele, but metastasis is considered to be uncommon. In two cases (one involving a descended testis and one a cryptorchid), widespread metastasis did occur, with sites including the liver, kidney, sublumbar lymph nodes, spleen, heart, diaphragm and lungs, and haematogenous spread being assumed.[67,69]

Although Sertoli cell tumours are a well-known cause of feminization syndrome in dogs, this has not been reported

in horses other than anecdotally.[62] One author reported ventral alopecia in an affected stallion.[65] High plasma levels of oestrogen are a peculiarity of the stallion under normal circumstances; in the equine testis, Leydig cells play a greater role than Sertoli cells in the production of oestrogens from androgens by the action of testicular (cytochrome p450) aromatase.[70]

Gross pathology

The affected testis is likely to be enlarged and the parenchyma may be completely effaced. Thickening of the tunica albuginea has been noted and this may merge with a neoplastic capsule.[65,67] Sertoli cell tumours are nodular, homogeneous or multi-cystic, white, grey or tan and lobulated and bulge on sectioning of the testis; they may also bulge from the surface.[48,65] Unlike seminomas, they have a very firm consistency. There may be invaginations of neoplastic tissue into the adjacent parenchyma.[7] Contralateral testicular atrophy can occur.[67,68] Metastatic masses are also nodular and fibrous and like the primary mass (Fig. 25.2), may contain central areas of necrosis.[69]

Histopathology

Tumour cell lobules are separated by coarse fibrous tissue bands and myxomatous stromal tissue may also be noted.[65] The tumour cells line and sometimes fill structures mimicking seminiferous tubules supported by collagenous trabeculae, or they may form sheets. They often palisade with respect to tubular basement membranes and range in shape from round or polyhedral to cuboidal or columnar with finely fibrillar, variably vacuolated eosinophilic or amphophilic cytoplasm that has poorly-defined margins; less-differentiated cells may be polygonal, fill tubules, fail to form tubules or form nests.[7,69] Nuclei are large, round, ovoid or spindle-shaped and hypochromatic and mitotic activity is usually low but can be high in some regions.[56] Metastatic masses have a similar appearance and may be noted within blood vessels in those distant sites.[67] There may be areas of haemorrhage, necrosis and mixed inflammation (including eosinophils); necrosis may be noted in centres of tubules.

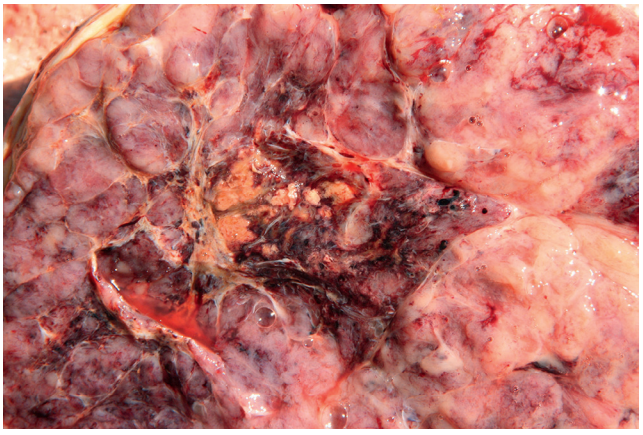


Figure 25.2 Sertoli cell tumour in a stallion. The sectioned surface, showing effacement of the parenchyma by the white, firm, lobulated neoplasm (with central necrosis).

In mixed sex cord–stromal cell and mixed germ cell–sex cord–stromal cell tumours, the different cellular components are intermingled and may require differentiation by immunohistochemical labelling.

Immunohistochemical labelling

Tumour cells should stain positively for anti-Müllerian hormone, vimentin, cytokeratin (some authors noted that these tumours are cytokeratin-negative, but this may depend on the degree of de-differentiation), inhibin, neuron-specific enolase and GATA4 (a differentiation marker for this cell type).[56] Labelling for α-1-antitrypsin and CD99 (that is expressed by Sertoli cells and granulosa cells) has also been reported in a mixed tumour.[60] Low-grade expression of Müllerian inhibiting substance (MIS) was found in well-differentiated regions of one malignant Sertoli cell tumour, this being a Sertoli cell-specific hormone.[69]

Sertoli–Leydig cell tumour of the ovary (arrhenoblastoma)

See also page 638.

Cellular origin

These testicular cell types (i.e. admixtures of Sertoli and Leydig cells) have been proposed to originate from medullary remnants of primary sex cords (medullary cords) in the ovary.

Profile

This is a rare type of ovarian neoplasm in any species. There was one report of surgical excision of an affected ovary from a 14-year-old Appaloosa mare with a 2-year history of aggressive behaviour.[71] Although this was diagnosed as an arrhenoblastoma, this particular neoplasm may have been a form of granulosa cell tumour with hypertrophy of thecal elements.[7]

Biological behaviour

These tumours are not known in horses. In human patients, most of them are benign.[2]

Histopathology

These tumours are solid, or solid with cystic areas, and are composed of a mixture of cells showing Sertoli cell and Leydig cell differentiation. In human patients there is significant variation, with well-differentiated neoplasms comprised largely of Leydig cells, and Sertoli cells predominating in those of intermediate differentiation.[72]

Adenoma and adenocarcinoma of the rete testis

Cellular origin

Rete testis cells. The rete testis is a network of tubules in the mediastinum testis that carry sperm from the seminiferous tubules to the efferent ducts.

Profile

A rete testis adenoma was diagnosed incidentally in a 6-year-old Quarter Horse and an adenocarcinoma was reported in a 5-year-old Quarter Horse cross.[7] Both neoplasms occurred in cryptorchid testes.

Biological behaviour

Metastasis of the adenocarcinoma was not reported.

Gross pathology

Rete testis adenomas may or may not be detected macroscopically. Adenocarcinomas may cause testicular enlargement (up to 30 cm in maximal diameter), with tumour tissue replacing most of the testicular parenchyma; they may contain cavities filled with brown fluid.

Histopathology

In the adenoma, rete tubules were filled by papillary masses of polygonal to cuboidal tumour cells with scanty cytoplasm and uniform round nuclei. The cuboidal to columnar tumour cells comprising the adenocarcinoma were arranged in sheets and lining tubules, and contained numerous mitotic figures. Large areas of necrosis, haemorrhage and mineralization may be present.

GERM CELL TUMOURS

Profile

Germ cells give rise to gametes and in the adult should only be located in the ovaries or testicles. They are initially found in the yolk sac, migrating to the gonadal ridge early in differentiation.[3] Germ cells occurring outside of the gonads imply an error during embryonic development. In both gonadal and extragonadal sites, these cells may on rare occasions give rise to neoplasms. Germ cell neoplasms are further subdivided into non-differentiating (seminoma and dysgerminoma) and those arising from pluripotent cells. If neoplastic pluripotent cells differentiate along embryonic pathways, they result in teratomas or teratocarcinomas; if they differentiate along placental pathways, neoplasms arising include choriocarcinomas and yolk sac tumours.

Seminoma

See also page 635.

Cellular origin

Embryonic germ cells in the seminiferous epithelium (probably basal spermatogonia). Unlike teratoma, somatic differentiation does not occur. This is the male counterpart of the ovarian dysgerminoma (see pp. 400–401 and 645).[7]

Profile

In one survey of equine neoplasms (n=1763), only 0.3% were seminomas.[73] Some authors believe seminomas to be the most common primary neoplasms of the equine testis, with an estimated (maximal) incidence of 0.5% in intact males.[56,74] In one summary of 48 published equine testicular neoplasms, seminoma was the most common, comprising 33% of the total.[57] However, other reports list teratomas as the most common primary testicular neoplasms of horses.[53,66] A malignant (metastatic) seminoma has also been reported in a Zebra-mare cross.[75]

Cryptorchid testes appear to be predisposed to seminoma development as in other species, but they also occur in descended testes.[56,76–79] McEntee (1990) stated that, in horses, 'seminomas usually occur in inguinal or normally descended testes' and that, as a result, they are more likely to be diagnosed than the interstitial cell tumours which usually occur in retained testes.[7] Seminoma are usually unilateral, although bilateral cases have been documented.[80]

Most horses diagnosed with seminoma are over 10 years of age (typical age range 8–22 years), but younger horses may also be affected.[57,63,73,76–79,81]

Rare mixed germ cell and sex-cord stromal tumours have been reported.[59,61]

Biological behaviour

Seminomas in horses are thought to behave more aggressively than those in other domestic animal species, with a similar tendency to metastasize as those in human patients. In one survey, 38% of seminomas (n=16) were considered to be malignant.[57] All cases should be regarded as potentially malignant and capable of widespread metastasis, particularly where there are large masses.[56,77] Metastasis usually occurs within 2 years, initially to the sublumbar lymph nodes and skeletal muscle, retroperitoneum and abdominal cavity, with sites including the peritoneum, liver, omentum, mesenteric tissue, abdominal lymph nodes, abdominal periaortic tissue and perirenal tissue; neoplastic tissue has been found in remnant spermatic cords, suggesting local invasion prior to castration.[63,73,77,78] The pelvic canal may also be involved, in addition to more distant spread into the thoracic cavity, including thoracic lymph nodes, cranial mediastinum, heart and lungs.[75,77,78,81–85] Penetration into the abdominal aortic lumen was reported in one case, with formation of small nodular masses on the intimal surfaces.[77] Metastasis to lymphatic vessels or other sites around the kidneys (or direct invasion of a ureter) has resulted in hydroureter, hydronephrosis and other renal complications.[73,80,84]

Metastasis does not always occur and some horses have been found to be clear at the time of diagnosis.[86] In one stallion, in which the neoplasm had invaded testicular vessels, recurrence was not noted 1 year after surgery and in another with large bilateral seminoma, the horse was still healthy 12 months post-surgery (24 months following the onset of clinical signs).[80] However, in most stallions diagnosed with metastatic (or likely metastatic) seminoma the expected survival time is 10–24 months.[79,80]

There have been reports of torsion of the spermatic cords of cryptorchid testes containing seminoma masses, resulting in colic.[87]

Seminomas in horses do not appear to be functional.

Gross pathology

Many testicular neoplasms can be diagnosed based on their gross appearance, although histological confirmation is desirable. There may be irregularity of the testicular surface, but in many cases the normal contour is preserved.[62,76] Seminoma are often multifocal, i.e. they usually have multiple foci of origin within the affected testis (see Fig. 35.7), but these frequently coalesce into one large mass, and by the time of diagnosis there may be complete effacement of normal architecture with a narrow rim of remaining, atrophic tissue; these neoplasms may measure up to 25 cm in diameter.[63,73,79,80,88,89]

Seminomas are lobulated (when larger), soft to slightly firm (with a 'fish-flesh' consistency), glistening, white to grey or tan and bulging on sectioned surfaces (see Fig. 35.7). On sectioned surfaces, there may be areas of haemorrhage, necrosis or cystic spaces.[7,78] There can be infiltration of the epididymis and vas deferens.[88] Tumour emboli or direct extension of the neoplastic tissue may be noted grossly within vessels of the pampiniform plexus and associated lymphatics.[78] Where metastasis has occurred, neoplastic foci may be noted on the tunica vaginalis and along the spermatic duct and there should be concern if the spermatic cord is thickened on external palpation.[62,75]

Histopathology

Seminomas are often pseudoencapsulated and lobulated.[79] The tumour cells are arranged in sheets and/or packets supported by a fine fibrovascular stroma, but may still be noted within and destroying the walls of seminiferous tubules (where they originate) in some microscopic fields. In testes that contain large masses, there may be separate microscopic masses including small foci of early intratubular development.[77]

The tumour cells are round, ovoid or polygonal, with a small to large amount of granular eosinophilic or amphophilic cytoplasm that has variably well-defined margins (Fig. 25.3).

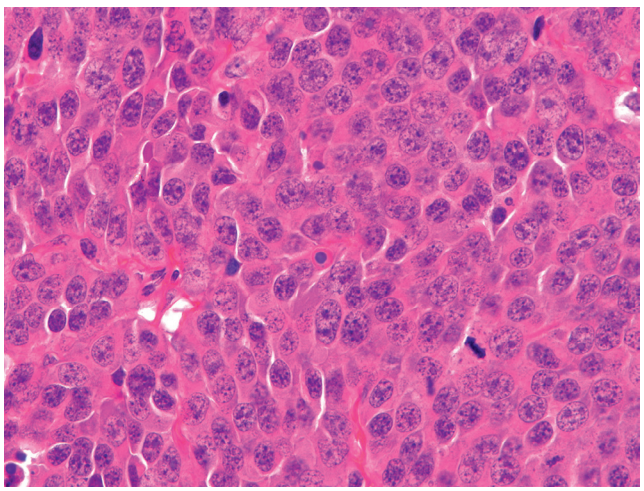


Figure 25.3 A seminoma in a stallion. Histological appearance of a seminoma diagnosed in a 21-year-old stallion with a 1-year history of unilateral testicular enlargement. Large polygonal tumour cells with large nuclei containing multiple, prominent nucleoli (H&E, ×400) (H&E, ×40).

Nuclei are large, round or ovoid and hypo- or hyperchromatic (sometimes vesicular) with one or more prominent nucleoli. Anisokaryosis and mitotic rates are high in malignant tumours but can vary significantly between microscopic fields; mitotic figures with a bizarre appearance may be noted. There may be karyomegaly and small to large numbers of binucleate and multinucleate tumour giant cells. Low mitotic rates, e.g. 1–2 per high power (×400) field, have been reported in some neoplasms that did not show evidence of metastasis.[89] In malignant seminomas, the tumour cells may be identified within lumens of testicular lymphatic and blood vessels and there may be invasion of adjacent structures including the subcapsular and interstitial connective tissue of the testis and the spermatic cord interstitium.[79,80]

Associated lesions may include infiltration of lymphocytes and macrophages and areas of tumour cell necrosis and haemorrhage.[56,73,77,80] The small clusters of lymphocytes are considered to be characteristic.[48] If any seminiferous tubules remain, they are frequently compressed and atrophic i.e. lined by only small numbers of spermatogenic cells, which may be degenerate.

In human patients, carcinoma in situ is a precursor lesion, composed of large intratubular gonocyte-like cells with large nuclei and abundant glycogen.[90] Similar cells were noted in the basal areas of seminiferous tubules in one cryptorchid stallion, adjacent to and within intratubular seminoma lesions.[91] It is possible that these early lesions are not usually diagnosed in horses because the neoplasms are usually advanced by the time of detection and histological examination.

There have been rare reports of mixed germ cell–sex cord stromal cell tumours; i.e. intermixed features of seminoma, Sertoli cell tumour and/or interstitial cell tumour.[59,61]

Immunohistochemical labelling

Seminoma cells may label positively for vimentin, neuron-specific enolase (NSE; some authors mention NSE-negativity), calretinin and various markers for undifferentiated cells, including OCT3/4 and NANOG (the latter label 'germ cell neoplasms').[92]

Dysgerminoma

See also page 645.

Cellular origin

Dysgerminomas are thought to arise from follicular oocytes, primordial or immature germ cells, or testicular rudiments or their homologues within the ovary. Unlike teratomas, somatic differentiation does not occur. This tumour type is considered to be the ovarian (female) counterpart of the testicular seminoma.[7]

Profile

This is an extremely rare malignant tumour in the horse. It occurs most frequently in adults (1–18 years).[93–96]

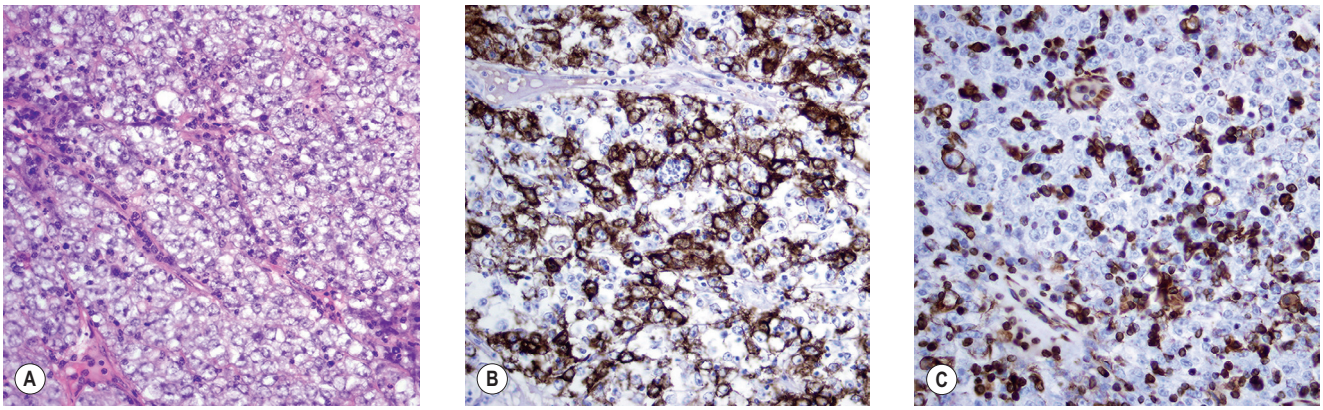


Figure 25.4 Dysgerminoma. (A) Packets of tumour cells with vacuolated, amphophilic cytoplasm and large, vesicular nuclei (H&E, ×400). **(B)** Strong cytoplasmic labelling for cytokeratin in many of the tumour cells (immunohistochemistry, ×400). **(C)** Cytoplasmic labelling for vimentin (immunohistochemistry, ×400). *(Figures courtesy of Dr Neil Horadagoda, Faculty of Veterinary Science, University of Sydney, Australia.)*

Biological behaviour

There can be widespread intra-abdominal metastasis, often with involvement of the kidneys, renal lymph nodes, ureters, adrenal glands and/or perirenal tissue.[95,97] There may be invasion of the caudal vena cava. One case was described as non-metastatic, but there were disseminated abdominal metastases described as from a 'mucinous adenocarcinoma of undetermined origin'; given that some tubular elements and vacuolated tumour cells were noted in the primary mass, the diagnosis of dysgerminoma may not have been correct.[94] In one case, a dysgerminoma was successfully removed and the mare was in foal 7 months following surgery.[96]

Dysgerminomas may be involved in hormone production in some animals.[7] Persistent oestrus has been described in two equine cases; one of these mares had high oestradiol levels (approximately double the level expected at oestrus).[5,94] Hypertrophic osteopathy has also been described in mares in association with dysgerminoma.[93,94]

Gross pathology

The unilateral masses can occur in the left or right ovary and vary in size but may be large (10–45 cm in diameter).[93,94,96,97]

Normal ovarian architecture is obliterated and there may be adherence to the adjacent abdominal wall. Dysgerminomas are soft or firm, round and lobulated and vary in colour from cream to grey-white to tan to black (or they are mottled). Sectioned surfaces may be mottled tan or red and cysts and/or areas of haemorrhage, necrosis and mineralization may be noted (see p. 646 and Fig. 35.14).[5,95–97] The cystic spaces in one case measured up to 6 cm in diameter and contained dark brown to black fluid or gelatinous material.[94]

Histopathology

The tumour cells are arranged in sheets, cords, trabeculae or packets supported by a fine fibrovascular stroma. Lobules are separated by thick bands of connective tissue. The tumour cells are large, uniform and polygonal with eosinophilic or amphophilic cytoplasm that has poorly-defined margins (see Fig. 25.4). In one report, the cytoplasm of tumour cells stained positively using the periodic acid-Schiff method, but in another, they were negative; there should be positive staining with alkaline phosphatase (Gömöri's method).[94,96] Nuclei are large, central and round to ovoid, with varying amounts of chromatin (that may be vesiculated), one or multiple prominent nucleoli, moderate to marked anisokaryosis and a variable but potentially high mitotic rate (see Fig. 25.4); giant tumour cells with multiple nuclei may be observed.[97] Tumour cells may be noted within lymphatic vessels. Other changes may include cystic spaces filled with proteinaceous fluid and cellular debris, haemorrhage, lymphoid or lymphohistiocytic inflammatory cell infiltrates (like the testicular counterpart, seminoma), oedema, necrosis and vascular thrombosis.[94] Histologically in one case, tumour emboli were noted within pulmonary vessels.[93]

Immunohistochemical labelling

In women, dysgerminoma stain positively for vimentin and may also be cytokeratin-positive; one mass in a mare was vimentin-positive only and another showed staining for both types of intermediate filament (see Fig. 25.4).[94,96]

Teratoma (ovarian or testicular)

See also pages 635 and 644.

Cellular origin

These benign neoplasms arise from gonadal or extragonadal germ cells, i.e. pluripotent stem cells. They may contain structures from all three germinal layers (i.e. endoderm, mesoderm, ectoderm), but usually only have derivatives from two. Monodermal or specialized teratoma is mainly composed of a single tissue.

Profile

Teratomas are rare and in the horse have been reported in the ovary and testis.[5,6,98–102] They are thought to be the second most common ovarian tumour in horses after granulosa cell tumours (GCTs); in one survey a ratio of 18:1 between GCTs and teratomas was reported.[100,101] There have also

been a few cases of mares with ovarian teratoma and concurrent GCT, either in the same or opposite ovaries.[19] Bilateral ovarian teratomas were diagnosed in one 8-year-old mare.[103] Ovarian teratomas have been reported in mares 3–18 years of age but are most common in those <5 years and are usually an incidental finding. They have been found in mares during gestation and after parturition, but they are not hormonally active and are not thought to affect fertility.

Although rare in total, teratomas are the most common neoplasms of young entire male horses (usually 1–5 years of age) and they are one of the most commonly reported neoplasms overall in 1–2-year-old horses; some authors believe them to be more common primary testicular neoplasms than seminomas.[7,53,56,66,99] In a recent survey of 48 published equine testicular tumours, interstitial cell tumours and teratomas each comprised 25% of the total, with seminomas being more common.[57] Teratomas occur in both descended and cryptorchid testes of young horses and may actually prevent testicular descent, but there is disagreement as to whether they are more common in cryptorchids.[7,56,99,104–106] One stallion with a teratoma involving a cryptorchid testis was judged to be truly monorchid.[99] Rarely, multiple teratomas occur in both testicles or unilaterally, i.e. multicentric development.[104] There have also been rare reports of testicular teratomas in foals, including neonates, which supports the theory that these may be congenital lesions.[107] There is no particular breed predisposition.[7]

Biological behaviour

Ovarian or testicular teratomas are benign and slow-growing. Mares may continue to cycle, since a teratoma will not be hormonally active and therefore will not affect the contralateral ovary.[13]

Epithelial elements in ovarian teratoma have given rise to an adenocarcinoma with widespread intra-abdominal metastasis and to a teratocarcinoma, respectively, i.e. malignant transformation can occur.[81]

Testicular teratomas may be found incidentally at the time of castration or during fertility examinations.[108] They are not usually linked with behavioural changes.[88] One teratoma involving a cryptorchid testis caused entrapment of the small colon.[109]

Oncogenesis

Ovarian teratoma is thought to develop from a germ cell that has completed the first meiotic division; the karyotype is normal XX, but the cells are homozygous at loci for which the host is heterozygous.

Gross pathology

Teratomas are usually multicystic, lobulated and encapsulated and in the testis will be attached to a normal spermatic cord.[88] They may be small and nondescript, but can reach a very large size, with reports of testicular tumours 3–24 cm in diameter.[99,102,108] Testicular teratomas have an irregular surface that may be covered by the tunica albuginea and are yellow, white or grey in colour (see Fig. 35.5).[5,106] In the testis, teratomas are often multicentric.[108]

Box 25.2 Differential diagnoses for teratoma

Neoplastic
- Teratocarcinoma (testis and ovary)
- Granulosa–theca cell tumour, dysgerminoma, cystadenoma, cystadenocarcinoma (ovary)
- Embryonal carcinoma (testis)

In general, the appearance and consistency of teratoma masses are dependent on the quantity and nature of the constituent tissues. They can have a remarkable appearance, including cysts (that may be hair-filled), keratinized debris, bone, teeth, cartilage and nervous tissue (see Fig. 35.13).[100] There may be some remnant of normal ovarian or testicular tissue; in some cases multiple islands of neoplastic tissue separated by normal parenchyma are seen on sectioned surfaces.[62] The (often multiple) fluctuant cysts may have a pigmented lining on sectioning and/or contain viscous yellow fluid.[99,110] The consistency on sectioning is spongy to firm, but there may be gritty foci and the presence of bone in the head of the epididymis is common.[62,111] Adhesion to surrounding organs may occur, e.g. ovarian tumours to the ovarian bursa.[101]

In the ovary (see Fig. 35.13), teratomas have been reported in association with other types of neoplasm, including cystadenomas and granulosa cell tumours.

Histopathology

Teratomas contain only mature germ cell tissue. This may include: islands of bone (including active bone marrow tissue) being formed by endochondral ossification; cartilage and/or fibrocartilage; teeth; smooth muscle; nerve-like structures; ganglion cells; glial tissue with ependymal surfaces, ependymal-lined cavities and/or choroid plexus tissue; adipose tissue; islands of endocrine-like cells; haired skin with sebaceous and sweat glands; tracheal and lung tissue; and various other epithelial structures, i.e. cysts or tubules lined by transitional, simple or ciliated pseudostratified columnar epithelium (that may include goblet cells), thyroid glandular tissue, salivary glands and keratin and/or hair-filled cysts. The various structures may be supported by a dense collagenous stroma.

Differential diagnoses

These are listed in Box 25.2.

Teratocarcinoma

See also page 635.

Cellular origin

These malignant neoplasms arise from gonadal or extragonadal germ cells, i.e. pluripotent stem cells, and contain both mature and embryonal elements. They may contain structures from all three germinal layers (i.e. endoderm, mesoderm, ectoderm).

Profile

Teratocarcinomas are rare in any species, but testicular and ovarian neoplasms have been documented in horses 1.5–7 years of age; testicular neoplasms may occur more frequently in cryptorchid testicles.[57,112,113]

Biological behaviour

Teratocarcinomas are highly malignant due to continued proliferation of undifferentiated cell populations. Testicular teratocarcinomas may metastasize widely to lymph nodes, liver and lungs, in addition to peritoneal implantation.[56,112] An ovarian teratocarcinoma in a 5-year-old mare metastasized to the pleura, diaphragm, bronchial lymph nodes, liver, kidneys, ovaries and peritoneal surfaces.[113]

Gross pathology

There may be abdominal and thoracic serosanguineous fluid.[113] Teratocarcinomas are unilateral or bilateral, single or multiple and frequently cystic; they may be encapsulated or unencapsulated (see Fig. 35.6). Areas of hair, bone, cartilage, fat and multiple other tissue types may be noted, as in teratomas (see p. 402). One mass reported in the retained right testicle of a 1.5-year-old horse, measured 90 cm in diameter and weighed 123 kg.[112] That mass was firm, round, lobulated and was adherent to a large area of the ventral abdominal wall, with displacement of abdominal organs.

Histopathology

Teratocarcinomas are composed of both primitive and mature germ cell tissue, i.e. undifferentiated germ cells (embryonic carcinoma), together with differentiated tissues. This may include stratified squamous epithelium, epithelium containing goblet cells, epithelial-lined cystic spaces, ductular structures, fibrous tissue, hyaline cartilage, woven bone, melanocytic cells and stellate cells.[112] Tumour cells may be seen infiltrating capsular or adjacent tissue and there may be areas of necrosis.

Embryonal carcinoma

Cellular origin

Embryonal carcinomas arise from gonadal or extragonadal germ cells, i.e. pluripotent stem cells. Some authors consider these neoplasms to be a transitional step in teratoma development.

Profile

This is an extremely rare type of neoplasm in any species but has been reported in older horses. An embryonal carcinoma arising in a descended testis was reported in a 7-year-old Standardbred stallion.[114]

Biological behaviour

Embryonal carcinomas are highly malignant due to continued proliferation of undifferentiated cell populations. The reported testicular neoplasm metastasized to sublumbar and periaortic lymph nodes, the parietal pleura, mediastinum, lung and heart.[114]

Gross pathology

The testicular neoplasm was multilobular with a nodular surface and on sectioned surfaces was firm and white with central necrosis and haemorrhage.[57]

Histopathology

Embryonal carcinomas are composed entirely of poorly-differentiated germ cells arranged in sheets, cords, nests and poorly-differentiated acinar and tubular structures within an abundant loose, primitive mesenchyme. Acini and tubules may be lined by one to several layers of cells.[114] Morphologically, the tumour cells are indistinguishable from embryonic cells of the inner cell mass of a blastocyst. The tumour cells in the testicular mass of the 7-year-old stallion were described as having a finely vacuolated, pale-staining basophilic cytoplasm with poorly-defined margins and large oval, hypochromatic nuclei containing one to multiple nucleoli; there was a high mitotic rate.[114] Small areas of woven bone were noted in necrotic areas and tumour emboli were occupying lymphatic vessels in the testis and blood vessels in the lung. McEntee (1990) considered this neoplasm to have some of the features of a carcinoma of the rete testis.[7]

Immunohistochemical labelling

Embryonal carcinoma cells may stain positively for α-fetoprotein; this labelling may involve focal areas or single cells. In the case of the testicular neoplasm, there was positive labelling in the primary mass but not in a pulmonary metastatic lesion.[114]

Electron microscopy

Ultrastructurally, demonstration of intercellular desmosomes between tumour cells can assist in establishing the diagnosis.[56]

Differential diagnoses

These are listed in Box 25.3.

Box 25.3 Differential diagnoses for embryonal carcinoma

Neoplastic
- Anaplastic seminoma
- Adenocarcinoma of the rete testis
- Teratoma (embryonal carcinomas do not contain differentiated elements)

References

1. Sawyer HR, Smith P, Heath DA, et al. Formation of ovarian follicles during fetal development in sheep. Biol Reprod 2002; 66:1134–1150.
2. Outwater EK, Wagner BJ, Mannion C, et al. Sex cord-stromal and steroid cell tumours of the ovary. Radiographics 1998; 18:1523–1546.
3. MacLachlan NJ. Ovarian disorders in domestic animals. Environ Health Perspect 1987; 73:27–33.
4. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
5. Bosu WTK, Van Camp SC, Miller RB, et al. Ovarian disorders: clinical and morphological observations in 30 mares. Can Vet J 1982; 23:6–14.
6. Meinecke B, Gips H. Steroid hormone secretory patterns in mares with granulosa cell tumours. Zentralbl Veterinarmed A 1987; 34:545–560.
7. McEntee K. Reproductive pathology of domestic mammals. San Diego: Academic Press Inc; 1990.
8. Turner TA, Manno M. Bilateral granulosa cell tumour in a mare. J Am Vet Med Assoc 1983; 182:713–714.
9. McCoy DJ. Diabetes mellitus associated with bilateral granulosa cell tumours in a mare. J Am Vet Med Assoc 1986; 188:733–735.
10. Frederico LM, Gerard MP, Pinto CRF, et al. Bilateral occurrence of granulosa-theca cell tumours in an Arabian mare. Can Vet J 2007; 48: 502–505.
11. Green SL, Specht TE, Dowling SC, et al. Haemoperitoneum caused by rupture of a juvenile granulosa cell tumour in an equine neonate. J Am Vet Med Assoc 1988; 193:1417–1419.
12. Hultgren BD, Zack PM, Pearson EG, et al. Juvenile granulosa cell tumour in an equine weanling. J Comp Pathol 1987; 97:137–142.
13. McCue PM, Roser JF, Munro CJ, et al. Granulosa cell tumours of the equine ovary. Vet Clin North Am Equine Pract 2006; 22:799–817.
14. Charman RE, McKinnon AO. A granulosa-theca cell tumour in a 15-month-old Thoroughbred filly. Aust Vet J 2007; 85:124–125.
15. Crabtree J. Review of seven cases of granulosa cell tumour of the equine ovary. Vet Rec 2011; 169:251.
16. Meagher DM, Wheat JD, Hughes JP, et al. Granulosa cell tumours in mares: a review of 78 cases. Proceedings of the 23rd Annual Convention of the American Association of Equine Practitioners 1977; 23:133–143.
17. Ellenberger C, Bartmann CP, Hoppen H-O, et al. Histomorphological and immunohistochemical characterization of equine granulosa cell tumours. J Comp Pathol 2007; 136:167–176.
18. Priester WA, MacKay FW. The occurrence of tumours in domestic animals. Natl Cancer Inst Monogr 1980; 54:1–210.
19. Panciera RJ, Slusher SA, Hayes KE. Ovarian teratoma and granulosa cell tumour in two mares. Cornell Vet 1991; 81:43–50.
20. Gift LJ, Gaughan EM, Schoning P. Metastatic granulosa cell tumour in a mare. J Am Vet Med Assoc 1992; 200:1525–1526.
21. Patrick DJ, Kiupel M, Gerber V, et al. Malignant granulosa-theca cell tumour in a two-year-old Miniature horse. J Vet Diagn Invest 2003; 15:60–63.
22. Watson ED. Granulosa cell tumours in the mare: – a review of 9 cases. Equine Vet Educ 1999; 11:136–142.
23. Nie GJ, Momont H. Ovarian mass in three mares with regular oestrous cycles. J Am Vet Med Assoc 1992; 201:1043–1044.
24. Hinrichs K, Watson ED, Kenney RM. Granulosa cell tumour in a mare with a functional contralateral ovary. J Am Vet Med Assoc 1990; 197: 1037–1038.
25. Stabenfeldt GH, Hughes JP, Kennedy PC, et al. Clinical findings, pathological changes and endocrinological secretory patterns in mares with ovarian tumours. J Reprod Fertil Suppl 1979; 27:277–285.
26. Hoque S, Senba H, Tsunoda N, et al. Endocrinological changes before and after removal of the granulosa theca cell tumour (GTCT) affected ovary in 6 mares. J Vet Med Sci 2003; 65:887–891.
27. Zelli R, Sylla L, Monaci M, et al. Gonadotropin secretion and pituitary responsiveness to GnRH in mares with granulosa-theca cell tumour. Theriogenology 2006; 66:1210–1218.
28. Watson ED, Heald M, Leask R, et al. Detection of high circulating concentrations of inhibin pro- and -alphaC immunoreactivity in mares with granulosa-theca cell tumours. Equine Vet J 2002; 34:203–206.
29. Christman SA, Bailey MT, Wheaton JE, et al. Dimerin inhibin concentrations in mares with granulosa-theca cell tumours. Am J Vet Res 1999; 60: 1407–1410.
30. Bailey MT, Troedsson MHT, Wheaton JE. Inhibin concentrations in mares with granulosa cell tumours. Theriogenology 2002; 57:1885–1895.
31. Tanaka Y, Nagamine N, Nagata S, et al. Ovarian secretion of inhibin in mares. J Reprod Fertil Suppl 2000; 56:239–245.
32. McCue PM. Equine granulosa cell tumours. Proceedings of the American Association of Equine Practitioners 1992; 38:587–593.
33. Ball BA, Conley AJ, MacLaughlin DT, et al. Expression of anti-Müllerian hormone (AMH) in equine granulosa-cell tumours and in normal equine ovaries. Theriogenology 2008; 70:968–977.
34. Silberzahn P, Zwain I, Martin B. Concentration increase of unbound testosterone in plasma of the mare throughout pregnancy. Endocrinology 1984; 115:416–419.
35. McKinnon AO, Barker KJ. Granulosa theca cell tumours. Equine Vet Educ 2010; 22:121–124.
36. Hinrichs K, Frazer GS, deGannes RV, et al. Serous cystadenoma in a normally cyclic mare with high plasma testosterone values. J Am Vet Med Assoc 1989; 194:381–382.
37. McCue PM. Neoplasia of the female reproductive tract. Vet Clin North Am Equine Pract 1998; 14:505–515.
38. Bailey MT, Christman SA, Wheaton JE, et al. Inhibin localization in equine granulosa-theca cell tumours and inhibin forms in tumour fluid. J Reprod Fertil Suppl 2000; 56:247–255.
39. Hoque S, Derar RI, Senba H, et al. Localization of inhibin alpha-, betaA- and betaB-subunits and aromatase in ovarian follicles with granulosa theca cell tumour (GTCT) in 6 mares. J Vet Med Sci 2003; 65:713–717.
40. Wilson DA, Foreman JH, Boero MJ, et al. Small-colon rupture attributable to granulosa cell tumour in a mare. J Am Vet Med Assoc 1989; 194: 681–682.
41. Gatewood DM, Douglass JP, Cox JH, et al. Intra-abdominal haemorrhage associated with a granulosa-thecal cell neoplasm in a mare. J Am Vet Med Assoc 1990; 196:1827–1828.
42. Sedrish SA, McClure JR, Pinto C, et al. Ovarian torsion associated with granulosa-theca cell tumour in a mare. J Am Vet Med Assoc 1997; 211: 1152–1154.
43. Rambags BPB, Stout TAE, Rijkenhuizen ABM. Ovarian granulosa cell tumours adherent to other abdominal organs; surgical removal from 2 Warmblood mares. Equine Vet J 2003; 35:627–632.
44. Alexander GR, Tweedie MA, Lescun TB, et al. Haemoperitoneum secondary to granulosa cell tumour in two mares. Aust Vet J 2004; 82:481–484.
45. Lavoie JP, Carlson GP, L. G. Hypertrophic osteopathy in three horses and a pony. J Am Vet Med Assoc 1992; 201:1900–1904.
46. Cordes DO. Equine granulosa cell tumours. Vet Rec 1969; 85:186–188.
47. Nyack B, Johnson AD. A mammoth granulosa cell tumour in a mare. Vet Med Small Anim Clin 1983; 78: 218–223.
48. Buergelt CD. Colour atlas of reproductive biology of domestic animals. St Louis: Mosby, 1997.
49. Foley GL, Johnson R. A congenital interstitial hamartoma of the equine ovary. Vet Pathol 1990; 27:364–366.
50. Machida N, Tanaka Y, Taya K, et al. An ovarian interstitial cell hamartoma in a newborn foal. J Comp Pathol 2001; 125:322–325.
51. Misdorp W. Congenital tumours and tumour-like lesions in domestic animals. 3. Horses. A review. Vet Q 2003; 25:61–71.
52. Johnson L, Neaves WB. Age-related changes in the Leydig cell population, seminiferous tubules and sperm production in stallions. Biol Reprod 1981; 24:703–712.
53. Gelberg HB, McEntee K. Equine testicular interstitial cell tumours. Vet Pathol 1987; 24:231–234.
54. Hay WP, Baskett A, Gregory CR. Testicular interstitial cell tumour and aplasia of the head of the epididymis in a cryptorchid stallion. Equine Vet Educ 1997; 9:240–241.
55. Tnibar A, Tibary A, Boulouha L, et al. Ultrasonographic and histopathological features of atypical interstitial (Leydig) cell tumours in two cryptorchid horses. J Equine Vet Science 2006; 26:370–375.
56. Edwards JF. Pathologic conditions of the stallion reproductive tract. Anim Reprod Sci 2008; 107:197–207.
57. Valentine BA. Equine testicular tumours. Equine Vet Educ 2009; 21: 177–178.
58. Melo CM, Papa FO, Prestes NC, et al. Bilateral Leydig cell tumour in a stallion. J Equine Vet Science 2007; 27:450–453.
59. Cullen JM, Whiteside J, Umstead JA, et al. A mixed germ cell-sex cord stromal neoplasm of the testis in a stallion. Vet Pathol 1987; 24: 575–577.
60. Zanghi A CG, Marino G, De Vico G, et al. Malignant mixed sex cord-stromal tumour in a stallion. Reprod Domest Anim 2004; 39:376–379.
61. Kollmann M, Frederike A, Hewicker-Trautwein M. Malignant germ cell and gonadostromal tumour with metastasis in a stallion. Pferdeheilkunde 2006; 22:177–180.
62. Caron JP, Barber SM, Bailey JV. Equine testicular neoplasia. Comp Cont Ed Pract Vet 1985; 7:S53–S59.
63. Brinsko SP. Neoplasia of the male reproductive tract. Vet Clin North Am Equine Pract 1998; 14:517–533.
64. Stickle RL, Fessler JF. Retrospective study of 350 cases of equine cryptorchidism. J Am Vet Med Assoc 1978; 172:343–346.
65. Rahaley RS, Gordon BJ, Leipold HW, et al. Sertoli cell tumour in a horse. Equine Vet J 1983; 15:68–70.
66. Hayes HM. Epidemiological features of 5009 cases of equine cryptorchidism. Equine Vet J 1986; 18:467–471.
67. Duncan RB. Malignant Sertoli cell tumour in a horse. Equine Vet J 1998; 30:355–357.
68. Threlfall WR, Robertson JT, Munsterman AS, et al. Theriogenology question of the month. Seminoma, spermatocoele, sustentacular cell tumour. J Am Vet Med Assoc 2005; 226:1649–1650.
69. Pratt SM, Stacy BA, Whitcomb MB, et al. Malignant Sertoli cell tumour in the retained abdominal testis of a unilaterally cryptorchid horse. J Am Vet Med Assoc 2003; 222:486–490.
70. Sipahutar H, Sourdaine P, Moslemi S, et al. Immunolocalization of aromatase in stallion Leydig cells and seminiferous tubules. J Histochem Cytochem 2003; 51:311–318.
71. Mills JH, Fretz PB, Clark EG, et al. Arrhenoblastoma in a mare. J Am Vet Med Assoc 1979; 171:754–757.
72. Young RH. Sex cord-stromal tumours of the ovary and testis: their similarities and differences with consideration of selected problems. Mod Pathol 2005; 18:S81–S98.
73. Trigo FJ, Miller RA, Torbeck RL. Metastatic equine seminoma: report of two cases. Vet Pathol 1984; 21:259–260.
74. Neely DP. Physical examination and genital diseases of the stallion. In: Morrow DA, ed. Current therapy in theriogenology: diagnosis, treatment and prevention of reproductive disease in animals. Philadelphia: Saunders; 1980: 694–706.
75. Pandolfi F, Roperto F. Seminoma with multiple metastases in a zebra (Equus zebra) X mare (Equus caballus). Equine Vet J 1983; 15:70–72.

76. Knudsen O, Schantz B. Seminoma in the stallion. A clinical, cytological and pathologicoanatomical investigation. Cornell Vet 1963; 53:395–403.
77. Vaillancourt D, Fretz P, Orr JP. Seminoma in the horse: report of two cases. J Equine Med Surg 1979; 3:213–218.
78. Sherman K, Turner TA, Calderwood-Mays MB, et al. Malignant seminoma in a horse. J Equine Vet Science 1990; 10:272–274.
79. Beck C, Charles JA, Maclean AA. Ultrasound appearance of an equine testicular seminoma. Vet Radiol Ultrasound 2001; 42:355–357.
80. Christensen BW, Ernst NS, Powe JR, et al. Theriogenology question of the month. Bilateral testicular neoplasia. J Am Vet Med Assoc 2007; 231:531–534.
81. Valentine BA. Neoplasia In: Bertone JJ, ed. Equine geriatric medicine and surgery. St. Louis: Saunders Elsevier; 2006: 147–167.
82. Mathias D. Seminom bei einem Pferde. Beri und Münh Wchschrift 1941; 20:242–243.
83. Innes JRM. Neoplastic diseases of the testis in animals. J Pathol Bacteriol 1942; 54:485–497.
84. Becht JL, Thacker HL, Page EH. Malignant seminoma in a stallion. J Am Vet Med Assoc 1979; 175:292–293.
85. Smith BL, Morton LD, Watkins JP, et al. Malignant seminoma in a cryptorchid stallion. J Am Vet Med Assoc 1989; 195:775–776.
86. Weiermayer P, Richter B. Simultaneous presence of a seminoma and a leiomyoma in the testes of a horse. Equine Vet Educ 2009; 21:172–176.
87. Hunt RJ, Hay W, Collatos C, et al. Testicular seminoma associated with torsion of the spermatic cord in two cryptorchid stallions. J Am Vet Med Assoc 1990; 197:1484–1486.
88. Peterson DE. Equine testicular tumours. J Equine Vet Sci 1984; 4:25–27.
89. Govaere J, Ducatelle R, Hoogewijs M, et al. Case of bilateral seminoma in a trotter stallion. Reprod Domest Anim 2010; 45:537–539.
90. Dieckmann KP, Skakkebaek NE. Carcinoma in situ of the testis: review of biological and clinical features. Int J Cancer 1999; 83:815–822.
91. Veeramachaneni DN, Sawyer HR. Carcinoma in situ and seminoma in equine testis. APMIS 1998; 106:183–185.
92. Emerson RE, Ulbright TM. Intratubular germ cell neoplasia of the testis and its associated cancers: the use of novel biomarkers. Pathology 2010; 42: 344–355.
93. McLennan MW, Kelly WR. Hypertrophic osteopathy and dysgerminoma in a mare. Aust Vet J 1977; 53:144–146.
94. Meuten DJ, Rendano V. Hypertrophic osteopathy in a mare with a dysgerminoma. J Equine Med Surg 1978; 2:445–450.
95. Chandra AMS, Woodard JC, Merritt AM. Dysgerminoma in an Arabian filly. Vet Pathol 1998; 35:308–311.
96. Harland S, Smith CS, Mogg TD, et al. Surgical resection of a dysgerminoma in a mare. Aust Vet J 2009; 87:110–112.
97. Gehlen H, Haist V, Baumgärtner W, et al. Malignant dysgerminoma in an 18-year-old Warmblood mare. J Equine Vet Sci 2006; 26:23–26.
98. Willis RA. A teratoma of a horse's testis. J Pathol Bacteriol 1938; 46: 198–200.
99. Rebar A, Fessler JF, Erb R. Testicular teratoma in a horse: a case report and endocrinologic study. J Equine Med Surg 1979; 3:361–366.
100. Catone G, Marino G, Mancuso R, et al. Clinicopathological features of an equine ovarian teratoma. Reprod Domest Anim 2004; 39:65–69.
101. Lefebvre R, Theoret C, Doré M, et al. Ovarian teratoma and endometritis in a mare. Can Vet J 2005; 46:1029–1033.
102. Cribb NC, Bouré LP. Laparoscopic removal of a large abdominal testicular teratoma in a standing horse. Vet Surg 2010; 39:131–135.
103. Damodaran S, Ramachandran PV. A survey of neoplasms of Equidae. Indian Vet J 1975; 52:531–534.
104. Willis RA, Rudduck HB. Testicular teratomas in horses. J Pathol Bacteriol 1943; 55:165–171.
105. Cotchin E. Equine testicular teratoma. Proceedings of the 6th Perugia Quadrennial Conference on Cancer, Perugia, Italy; 1977: 699–722.
106. Smyth GB. Testicular teratoma in an equine cryptorchid. Equine Vet J 1979; 11:21–23.
107. Pollock PJ, Prendergast M, Callanan JJ, et al. Testicular teratoma in a three-day-old thoroughbred foal. Vet Rec 2002; 150:348–350.
108. Jasko DJ, Powers BE, Trotter GW, et al. Testicular teratoma in a stallion. J Equine Vet Sci 1991; 11:108–110.
109. Parks AH, Wyn-Jones G, Cox JE, et al. Partial obstruction of the small colon associated with an abdominal testicular teratoma in a foal. Equine Vet J 1986; 18:342–343.
110. Conway DA, McCann PG. A teratoma of the undescended testicle in a horse. Irish Vet J 1966; 20:226–228.
111. Stick JA. Teratoma and cyst formation of the equine cryptorchid testicle. J Am Vet Med Assoc 1980; 176:211–214.
112. Shaw DP, Roth JE. Testicular teratocarcinoma in a horse. Vet Pathol 1986; 23:327–328.
113. Fraser GS, Robertson JT. Teratocarcinoma of the ovary in a mare. J Am Vet Med Assoc 1988; 193:953–955.
114. Valentine BA, Weinstock D. Metastatic testicular embryonal carcinoma in a horse. Vet Pathol 1986; 23:92–96.

26 Stem or progenitor cell neoplasms

Overview 406
Teratoma and teratocarcinoma (placental) 406
Hepatoblastoma 407
Pulmonary blastoma (biphasic) and pleuropulmonary blastoma 408
Nephroblastoma (embryonal nephroma) 409
Malignant rhabdoid tumour 410
Primitive neuroectodermal tumour 410
Pineoblastoma 411
Medulloepithelioma 411
Olfactory neuroblastoma 411

Overview

By definition, stem cells can divide and differentiate into one or more specialized cell types. A stem cell undergoes asymmetric replication to generate a copy of the original stem cell as well as another daughter cell capable of undergoing differentiation. Embryonic stem cells are present in the inner cell mass of blastocysts (early-stage embryos) or earlier morula-stage embryos. Those in the blastocyst are pluripotent (i.e. can differentiate into any endodermal, mesodermal or ectodermal, fetal or adult cell type) and those in the morula are totipotent (i.e. can also give rise to extra-embryonic (placental) tissues).

In juvenile and adult animals, multipotent adult stem cells with more limited lineage restriction (e.g. the ability to only differentiate into mesenchymal cells) are found in many tissues. A progenitor cell, like an adult stem cell, may also differentiate into specific cell types, but these are defined as being more restricted; these cells are unipotent or oligopotent and they cannot replicate indefinitely.

There is still significant controversy as to the exact terminology and definitions that should be used, and it is likely that these populations are both complex and overlapping. It has now been suggested that 'cancer stem cells' (CSCs) are common components of many or most neoplasms (although this has not received significant attention in neoplasms of animals). However, it is not likely that the CSCs actually originate from normal tissue stem (or progenitor) cells in all of them, rather than, for example, arising from a de-differentiation process.[1] The types of neoplasm described below are those considered, at present, to originate from undifferentiated cells.

Teratoma and teratocarcinoma (placental)

For Gonadal, see pages 401–402.

Cellular origin

These neoplasms arise from gonadal or extragonadal germ cells, i.e. pluripotent stem cells. They may contain structures from all three germinal layers (i.e. endoderm, mesoderm and ectoderm), but usually only have derivatives from two. Monodermal or 'specialized teratomas' only contain a single tissue.

Profile

There has been one report of a placental teratoma.[2] An amniotic teratocarcinoma was found following successful delivery of a full-term foal.[3]

Oncogenesis

It is not known how placental teratomas/teratocarcinomas arise, but it is thought that the origin may be from germ cells that have migrated aberrantly from the yolk sac and through the umbilical cord to the placental tissue; this may be promoted by the close approximation of evaginated primitive gut with the umbilical cord and placenta during early gestation.[2]

Biological behaviour

The placental teratoma was considered to result in abortion, as a result of the neoplastic masses occupying 50% of the tissue.[2] The mare bred successfully the following year. An amniotic teratocarcinoma resulted in death of the foal at 2.5 months of age from multiple metastatic masses in the liver, omentum, splenic ligament and splenic and sublumbar lymph nodes.[3]

Gross pathology

The placental teratoma presented as multiple (0.5–4 cm diameter) white or grey, smooth nodules throughout the

Box 26.1 Differential diagnoses for teratoma and teratocarcinoma

Neoplastic
- Choriocarcinoma
- Dermoid cysts
- Dysgerminoma
- Metastatic neoplasms

Non-neoplastic
- Hydatiform moles
- Granulomas
- Fetus acardius amorphous (blighted twin fetus)
- Cystic adenomatous hyperplasia of the allantoic epithelium[4]

fetal surfaces of the chorioallantois, blood vessels and umbilical cord; the nodules had red, soft or 'gritty' centres.[2]

The amniotic teratocarcinoma was dark red-brown and measured 3 cm in diameter.[3] On post-mortem examination of the 2.5 month-old foal, red fluid was found in the peritoneal cavity, with disseminated multilobulated, white masses (up to 5 cm in diameter) in the liver, omentum, splenic ligament and splenic and sublumbar lymph nodes.[3]

Histopathology

The teratoma nodules varied in composition. Some were composed of packets of poorly-differentiated polygonal cells (i.e. undifferentiated germ cells) with hyperchromatic nuclei that contained 1–2 large nucleoli, and a low mitotic rate.[2] Other nodules contained disorganized mixtures of mesenchymal stroma, cartilage, keratinizing squamous epithelium, ducts and acini lined by various epithelial cells. There were areas of necrosis, inflammation, haemorrhage and mineralization.

The amniotic teratocarcinoma had a more prominent component of undifferentiated polygonal tumour cells that contained up to six nucleoli, with large numbers of mitotic figures, and tumour cell aggregates within blood vessels.[3] The polygonal cells were arranged in nests or islands supported by a fibrovascular stroma. A smaller portion of the mass was composed of poorly organized bone, cartilage and epithelial tissues, with rare nerve-like structures. There are large areas of necrosis associated with thrombosed blood vessels.[3] Neoplasms in the liver of the foal were composed of polygonal cells that were smaller than those in the placenta, but were also arranged in islands.

Differential diagnoses

These are listed in Box 26.1.

Cystic adenomatous hyperplasia of the allantoic epithelium[4] is nearly always associated with placentitis and is unique to horses.

Hepatoblastoma

Cellular origin

The cellular origin of hepatoblastoma is uncertain, but is presumed to be pluripotent stem cells or early progenitor cells of the different epithelial components of the liver.[5]

Profile

Hepatoblastomas are extremely rare in horses. Most cases (as would be expected) have been reported in fetuses or foals, but some have occurred in adults up to 3 years of age.[6–13] In human patients, hepatoblastoma is the most common liver neoplasm of early childhood.[5]

Biological behaviour

Hepatoblastomas are malignant, highly invasive neoplasms. Direct invasion and occlusion of the caudal vena cava has been reported.[7] Extensive metastasis can occur within the liver and to the lungs, with other reported metastatic sites including the omentum, skin, brain, meninges, stylohyoid and other bones, frontal sinuses, nasal septum and tracheobronchial lymph node.[7,8,10–12]

Secondary inappropriate erythrocytosis (i.e. that occurring in the absence of tissue hypoxia) in association with increased erythropoietin (or other hormones) has been reported as a paraneoplastic syndrome.[10,11] Such cases have been reported to occur in human patients as a result of abnormal production of:

1. Androgenic hormones
2. Prostaglandin, resulting in enhancement of the effect of erythropoietin
3. A protein with erythropoietin-like action.[8]

Gross pathology

The liver is markedly enlarged and there may be displacement of adjacent organs, including the stomach, and adhesion to the diaphragm.[6] The neoplastic masses are well-demarcated, can bulge from the capsular surface and may measure up to 45 cm in diameter with extensive obliteration of normal liver architecture; there may be numerous coalescing nodules.[6–8] Hepatoblastoma masses are solid (slightly softer in consistency than normal liver), pale tan, cream, grey or red-tan and may be lobulated (particularly larger masses). On sectioned surfaces, they contain areas of central necrosis (softening) with or without cavitation in addition to haemorrhage and calcification.[12] Metastatic nodules have a broadly similar appearance.

Histopathology

Hepatoblastomas are expansile, well-demarcated and may be partially or completely encapsulated; the capsular tissue contains bile ducts, and blood and lymphatic vessels.[10–12] There may be areas of infiltration of the adjacent hepatic parenchyma. In one report, the tumour cells were not invasive, but the adjacent hepatocellular tissue was congested and atrophic.[9]

Hepatoblastomas may have a variety of histological patterns. The types reported in horses are pure epithelial, and mixed epithelial–mesenchymal (spindle cell).[6,7,9,10,12] In the few equine cases, mixed epithelial–mesenchymal

neoplasms have been more common than pure epithelial tumours.

Possible epithelial cell subtypes in hepatoblastoma (in any species) include fetal, embryonal and fetal, macrotrabecular and anaplastic small cell.[7,12]

- Fetal-type tumour cells are arranged in sheets, nests and cords that may contain canaliculi and sinusoid-like (slit-like) spaces. They are small, pleomorphic and resemble hepatocytes, with moderate amounts of vacuolated amphophilic or eosinophilic cytoplasm that may contain glycogen and fat, with well-defined margins.[7,8,12] Their nuclei may be small or similar in size to normal hepatocytes, are round to ovoid, contain finely stippled chromatin (or are vesicular), contain multiple nucleoli and have a highly variable mitotic rate.[10,12]
- Embryonal-type tumour cells are less well-differentiated and may form clusters, acini, tubules or rosettes lined by cuboidal to columnar cells; mucous cells have been noted as has squamous differentiation.[7,8] These tumour cells are small and polygonal or spindle-shaped, with scanty cytoplasm that has variably well-defined margins and hyperchromatic nuclei larger in size than those of normal hepatocytes.[7,12] The arrangement pattern is referred to as macrotrabecular if they are more than 10 cells thick.

Fetal and embryonal tumour cell types may be closely associated and intermingled.[7] In one case of mixed embryonal and fetal cell types, only embryonal cells were noted in the metastatic lesions.[7]

Mesenchymal areas can be composed of osteoid, chondroid and or myxomatous matrix with rare bone spicules.[6,9,12] Strictly speaking, a classification as teratoid should only be made when additional tissue types are noted, including skeletal muscle, and neural or neural crest elements (such as ganglion cells or melanocytes).[13] Haematopoietic tissue may be seen in epithelial or mesenchymal areas and does not prove that the neoplasm is teratoid.

Other changes can include haemorrhage, inflammation, tumour cell and hepatocellular necrosis, mineralization, portal and centrilobular fibrosis, bile duct cholestasis, biliary hyperplasia and tumour emboli within adjacent veins.

Immunohistochemical labelling

Positive labelling of hepatoblastoma cells with α-fetoprotein has been reported in equine cases ($n=9$); this is an α_1-globulin synthesized largely by embryonic liver cells, and it may only be expressed in a small proportion of the tumour cells.[10–12] In one report, the fetal-type tumour cells stained strongly, but the embryonal cells did not.[8] However, hepatocellular carcinoma cells (pp. 269–270 and 468) may also label positively. Epithelial tumour cells in one report were additionally immunoreactive for cytokeratin AE1 and carcinoembryonic antigen, but negative for cytokeratin 19 and epithelial membrane antigen (EMA); negative results for the latter two antibodies may have been due to lack of validation for use in the horse.[9] In another report, the tumour cells were negative for cytokeratin AE1/AE3.[11] Adjacent hepatocytes were not labelled with these markers, but bile duct epithelial cells were strongly cytokeratin AE1-positive. Mesenchymal cells are vimentin-positive and fetal-type epithelial cells may also show variable staining.[12] Negative labelling for neuron-specific enolase (NSE), chromogranin A, S100 and synaptophysin should rule out tumours of neuroendocrine origin (pp. 388, 390 and 391).

Differential diagnoses

Neoplastic

Hepatocellular carcinoma can have a very similar appearance to the epithelial type of hepatoblastoma. Hepatoblastoma cells are normally smaller in size than non-neoplastic hepatocytes.[8] In contrast, hepatocellular carcinoma cells are usually larger than non-neoplastic hepatocytes, show more marked cellular pleomorphism, may contain intranuclear inclusion bodies or cytoplasmic hyaline globules, and multinucleate tumour giant cells are more common. It is possible that some previously reported cases of hepatocellular carcinoma in juvenile horses have actually been hepatoblastomas.

Pulmonary blastoma (biphasic) and pleuropulmonary blastoma

Cellular origin

The cellular origins of pulmonary blastoma are controversial, with some suggesting a stem cell origin and others classifying these neoplasms as carcinosarcomas (true malignant mixed neoplasms). Based on the most recent World Health Organization classification, only those neoplasms that are biphasic, i.e. composed of both epithelial and mesenchymal elements, are classified as pulmonary blastomas.

Pleuropulmonary blastomas are different clinically, histologically and prognostically from (adult-type) pulmonary blastomas, based primarily on the absence of a malignant epithelial component.[14] Pleural location and the age of development are additional diagnostic features.[15]

Profile

There has been one report of a pulmonary blastoma in a 5-year-old crossbred stallion.[16] Even in human patients, these neoplasms are exceedingly rare, but they do most frequently occur in adults. This late development of pulmonary blastoma is considered to occur in humans because pulmonary tissue continues to develop for at least 10 years postnatally. Pleuropulmonary blastomas are also rare in human patients and considered to be virtually restricted to the paediatric age group; they often occur in association with other (familial) diseases, including other neoplasms.[14]

There has been one report of a pleuropulmonary blastoma, in an equine fetus aborted at approximately 240 days' gestation following a 3-week period of illness of the mare (that was subsequently euthanized due to peritonitis).[15]

Biological behaviour

Pulmonary blastomas are malignant neoplasms that behave aggressively with (in human patients) high rates of local recurrence and frequent metastasis.[14] Metastasis to

extra-pulmonary sites did not occur in the one reported case in a horse.[16]

Pleuropulmonary blastomas also tend to be aggressive with the potential for local recurrence and metastasis.[14]

Gross pathology

Pulmonary blastomas have been described in human patients as well-circumscribed, typically solitary and located in peripheral lung tissue (sometimes with smaller satellite lesions), fleshy, white-to-tan on sectioned surfaces, and often centrally necrotic and cystic.[14] In the one reported equine case, both caudal lung lobes contained multiple, poorly-defined, soft nodular masses measuring 1–10 cm in diameter, that protruded from surfaces.[16]

Pleuropulmonary blastomas in children are often large (potentially >20 cm in diameter), surface-based, and vary from solid and rubbery to cystic, with frequent areas of necrosis, haemorrhage and mucoid change.[14] In the one affected equine fetus, there was a well-circumscribed, broad-based, ovoid, soft, pale pink mass measuring 6 cm in maximal diameter that was contiguous with the (visceral) pleura of the right caudal lung lobe.[15] On sectioned surfaces, the mass contained multiple cysts (up to 1.5 cm in diameter).

Histopathology

Pulmonary blastomas (biphasic) have a glandular component and a malignant stroma with a blastematous appearance (a loose matrix containing spindle-shaped, stellate, and/or angular cells with vesicular or hyperchromatic nuclei) that may show condensation around the epithelial structures and show significant mitotic activity and pleomorphism.[14] The epithelial cells may form branching tubules, solid or cribriform areas, cords, ribbons or rosettes and nests of squamous cells ('morules').[14] In the equine case, the neoplastic masses were non-encapsulated and infiltrated alveolar septa.[16] The epithelial cells were arranged in nests, cords and irregular tubules, and were cuboidal, columnar or pleomorphic and non-ciliated (no high-power magnification images were provided).[16] The stromal cells were also pleomorphic (and often blast-like) with myxomatous and mineralized areas.

In children, pleuropulmonary blastomas are subtyped as predominantly cystic (type I), solid-cystic (type II) or predominantly solid (type III). The cysts are lined by benign cuboidal or respiratory-type epithelium, with the intervening loose stroma composed of oval to spindle-shaped cells (undifferentiated blastemal cells); this stromal component may also contain cells showing rhabdomyoblastic or chondroid differentiation, in addition to anaplastic and tumour giant cells.[14] An equine fetal mass contained solid and cystic areas (i.e. type II), with the epithelial component being cuboidal or attenuated, non-ciliated cells showing minimal pleormorphism.[15] Other associated changes may include necrosis and cavitation.

Immunohistochemical labelling

In the equine pulmonary blastoma, epithelial cells were cytokeratin-positive and the mesenchymal cells were vimentin-positive; approximately 10% of the stromal cells were also weakly positive for α-smooth muscle actin.[16] The lack of co-expression of keratins and vimentin in tumour cells did not support a diagnosis of carcinosarcoma in this case.[16]

In the equine (fetal) pleuropulmonary blastoma, the epithelial cells were cytokeratin-positive, and the mesenchymal elements vimentin-positive (as expected).[15] If rhabdomyoblastic differentiation had occurred, markers including desmin, myoglobin and muscle specific actin might be used. S100 is a nonspecific marker for chondroid cells. In human patients, positive labelling of the blastematous component for histiocytic markers has been reported, including α-1-antitrypsin, α-1-chymotrypsin and CD68.[14]

Box 26.2 Differential diagnoses for pulmonary blastoma (biphasic) and pleuropulmonary blastoma

Neoplastic
- Teratoma
- Mesothelioma
- Mixed tumour (carcinosarcoma)

Non-neoplastic
- Pulmonary hamartoma (p. 265)

Differential diagnoses

These are listed in Box 26.2.

Nephroblastoma (embryonal nephroma)

Cellular origin

Nephroblastoma, also known as Wilms' tumour in human patients, is a congenital neoplasm composed of a mixture of embryonal renal tissue types that is thought to arise from the embryonal metanephric blastema (and in foci of renal dysplasia).

Profile

There have been a small number of reports of nephroblastoma in young adult horses, some without gross and/or histological description.[17–23]

Biological behaviour

Metastasis has not been reported in horses. In dogs, the liver and lungs are common metastatic sites.[24] In children, there is usually a good prognosis following surgical removal, and successful laparoscopic removal has been reported in a horse.[23] Tubular and glomerular differentiations are thought to indicate a good prognosis.

Gross pathology

Nephroblastomas can reach a large size (e.g. ≥40 cm in diameter). They are usually unilateral but may be multiple in the affected kidney, and may largely or completely obliterate the normal renal parenchyma.[24] One mass was located in the cranial pole of the right kidney, and extended into the pelvis.[23]

Nephroblastomas are well-circumscribed spherical, white-yellow, grey or tan masses. On sectioned surfaces there may be large cystic areas and regions of necrosis.[22] There may be associated bleeding into the urinary tract.

Histopathology

In triphasic nephroblastomas there are blastemal, epithelial and mesenchymal elements, with evidence of progressive development of the blastema into elementary and then well-differentiated tubules, similar to the process of renal embryogenesis.[22] The epithelial elements form tubular structures; the cells are cuboidal or columnar with pale-staining eosinophilic or clear, vacuolated cytoplasm that has well-defined margins and may show apical blebbing. Epithelial cells may show areas of squamous or oncocytoid differentiation (oncocytoid cells are large and polygonal with a granular cytoplasm). Blastemal cells are arranged in small clusters and packets, and may form glomeruloid structures that protrude into the tubules.[22] These blastemal cells are small and round or oval, with scanty eosinophilic cytoplasm and hyperchromatic nuclei that have a high mitotic rate. Transition between blastemal cells and tubular structures may be noted. Mesenchymal elements between the epithelial and blastemal tissues are fibroblastic cells with intervening myxoid or collagenous stroma. Chondroid, lipoid, myoid and osteoid tissues may also occur, and mesenchymal tissue can comprise the majority of the tumour mass.[25] A compressed remnant of the normal renal parenchyma may be noted.

Immunohistochemical labelling

Epithelial elements stain positively for cytokeratin. All elements are neuron-specific enolase (NSE)-positive; vimentin staining is noted in the stroma, some foci of tubular epithelium and in blastemal cells undergoing tubular differentiation.[22] Stromal cells may stain positively for smooth muscle actin and desmin.

Differential diagnoses

Neoplastic

Teratoma is a differential diagnosis for a triphasic embryonal nephroma. Tubular and glomerular development is typical of nephroma rather than teratoma, and in the latter there should be germ cells, extra-embryonic cell types and non-renal elements.

Malignant rhabdoid tumour

Cellular origin

The cellular origin of malignant rhabdoid tumours (MRTs) is not known, but they are not myogenic and most likely arise from a pluripotent cell type. They were first reported as renal neoplasms of children.

Profile

There has been one report of an MRT in the orbit of a 2-year-old filly.[26]

Biological behaviour

Malignant rhabdoid tumours are highly locally aggressive. The orbital neoplasm completely disrupted and largely destroyed the eye, and metastasized to lymph nodes of the head and neck, guttural pouch, salivary glands, and periocular subcutaneous tissue.[26]

Gross pathology

The masses were poorly-defined, soft, and varied in colour in different sites: i.e. white, pale pink, tan and dark brown. The largest mass, in superficial cervical lymph node tissue, measured 20 cm in maximal diameter.[26]

Histopathology

Tumour cells were arranged in sheets and loose cords; they were polygonal, with abundant eosinophilic cytoplasm, and many had a paranuclear globular inclusion body. Tumour cell nuclei were round, oval, C-shaped or irregularly-shaped, with 1–2 prominent nucleoli. Some binucleate cells were noted and there was a high mitotic rate.[26]

Immunohistochemical labelling

Tumour cells should express both vimentin and cytokeratin, but stain negatively for desmin and smooth muscle actin. The paranuclear inclusion bodies were composed of whorls of vimentin filaments.

Primitive neuroectodermal tumour

Cellular origin

Primitive neuroectodermal tumours (PNETs) originate from the neural crest. Neural crest cells are multipotent, transient and migratory; the cells that reach various axial positions develop into different tissues during embryonic development, including cartilage and bone of the facial skeleton, smooth muscle, glial cells and neurons (peripheral and enteric). There is considerable controversy regarding the precise histogenesis and the relationships between the various embryonal neoplasms; some could arise from cells already committed to differentiation. Some authors, for example, have suggested that the term 'PNET' be applied to a variety of central nervous system neoplasms including medulloblastoma (not reported in the horse), neuroblastoma (p. 367) and pineoblastoma (p. 368).[27]

Profile

In human patients, PNETs are classified as peripheral (part of the Ewing sarcoma family of neoplasms) or central nervous system neoplasms. A peripheral PNET has been reported in multiple organs and tissues of a 2-year-old Paint horse.[28] Medulloepithelioma has been reported in the equine eye (pp. 372–374 and 368).

Biological behaviour

Peripheral PNETs are invariably highly malignant, and rapidly metastasize to lungs and bone. A reported equine

case had large masses present in multiple sites, including both kidneys, and it was proposed that the neoplastic process was of renal origin.[28]

Gross pathology

The one affected horse had serosanguineous fluid in thoracic and abdominal cavities. The neoplastic masses were large, lobulated and white to tan, and occupied both scrotal cavities (extending through the inguinal canals). Both kidneys, the liver, spleen, mesenteric lymph nodes, mesentery, abdominal surfaces of the diaphragm and tracheobronchial lymph nodes were also involved.[28]

Histopathology

Peripheral PNETs are composed of sheets of small round tumour cells that may form Homer Wright rosettes (p. 367). In the equine case, the tumour cells were arranged in sheets, streams and rosettes. They were round or spindle-shaped, with a small amount of eosinophilic cytoplasm that had poorly-defined margins.[28] Nuclei were oval or elongated, with 1–2 distinct nucleoli, rare multinucleate cells and two mitotic figures per high power (×400) field.

Immunohistochemical labelling

The tumour cells are often positive for various neural markers that may include neuron-specific enolase (NSE), S100, neuron filament protein, synaptophysin, and occasionally, glial fibrillary acidic protein (GFAP). The marker CD99 has been used for these neoplasms in human patients; however, antibodies have not been validated for use in horses.

Pineoblastoma

See page 368.

Medulloepithelioma

See pages 372–374.

Olfactory neuroblastoma

See page 367.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144:646–674.
2. Gurfield N, Benirschke K. Equine placental teratoma. Vet Pathol 2003; 40:586–588.
3. Allison N, Moeller RB Jr, Duncan R. Placental teratocarcinoma in a mare with possible metastasis to the foal. J Vet Diagn Invest 2004; 16:160–163.
4. Hong CB, Donahue JM, Giles RC, et al. Adenomatous hyperplasia of equine allantoic epithelium. Vet Pathol 1993; 30:171–175.
5. Von Schweinitz D. Hepatoblastoma: recent developments in research and treatment. Semin Pediatr Surg 2012; 21:21–30.
6. Prater PE, Patton CS, Held JP. Pleural effusion resulting from malignant hepatoblastoma in a horse. J Am Vet Med Assoc 1989; 194:383–385.
7. Neu SM. Hepatoblastoma in an equine fetus. J Vet Diagn Invest 1993; 5:634–637.
8. Lennox TJ, Wilson JH, Hayden DW, et al. Hepatoblastoma with erythrocytosis in a young female horse. J Am Vet Med Assoc 2000; 216:718–721.
9. Cantile C, Arispici M, Abramo F, et al. Hepatoblastoma in a foal. Equine Vet J 2001; 33:214–216.
10. Axon JE, Russell CM, Begg AP, et al. Erythrocytosis and pleural effusion associated with a hepatoblastoma in a Thoroughbred yearling. Aust Vet J 2008; 86:329–333.
11. Gold JR, Warren AL, French TW, et al. What is your diagnosis? Biopsy impression smear of a hepatic mass in a yearling Thoroughbred filly. Vet Clin Pathol 2008; 37:339–343.
12. Loynachan AT, Bolin DC, Hong CB, et al. Three equine cases of mixed hepatoblastoma with teratoid features. Vet Pathol 2007; 44:211–214.
13. Wright JR, Pinto-Rojas A, Trevenen CL, et al. Teratoid features in mixed hepatoblastoma (Letter). Vet Pathol 2010; 47:1003–1004.
14. Weissferdt A, Moran CA. Malignant biphasic tumours of the lungs. Adv Anat Pathol 2011; 18:179–189.
15. Woolford L, Staniek G, Blunden AS. Pleuropulmonary blastoma in an equine fetus. Vet Pathol 2010; 47:1086–1089.
16. Pérez-Ecija RA, Mendoza FJ, Zafra R, et al. Clinical, pathological and immunohistochemical features of a pulmonary blastoma in a horse. Vet Rec 2009; 164:182–183.
17. Nyka W. Sur une tumeur renal de cheval issue du blastème métanéphrique. Bull Canc 1928; 17:241–247.
18. Lombard C. La prédisposition aux tumours renales spontanées dan la monde animal. Bull Canc 1959; 46:460–464.
19. Jackson C. The incidence and pathology of tumours of domesticated animals in South Africa. Onderstepoort J Vet Sci Anim Ind 1936; 6:1–460.
20. Cotchin E, Baker-Smith J. Tumours in horses encountered in an abattoir survey. Vet Rec 1975; 97:399.
21. Priester WA, MacKay FW. The occurrence of tumours in domestic animals. Natl Cancer Inst Monogr 1980; 54:1–210.
22. Jardine JE, Nesbit JW. Triphasic nephroblastoma in a horse. J Comp Pathol 1996; 114:193–198.
23. Romero A, Rodgerson DH, Fontaine GL. Hand-assisted laparoscopic removal of a nephroblastoma in a horse. Can Vet J 2010; 51:637–639.
24. Maxie MG, Newman SJ. Urinary system. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's pathology of domestic animals, 5th edn. Philadelphia: Elsevier Saunders; 2007: 425–522.
25. Nielsen SW, Mackey LJ, Misdorp W. XVIII. Tumours of the kidney. Bull World Health Organ 1976; 53:237–246.
26. Hong CB, Van Meter PW, Latimer CL. Malignant rhabdoid tumour in the orbit of a horse. J Comp Pathol 1999; 121:197–201.
27. Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumours. Brain Pathol 1993; 3:255–268.
28. Facemire PR, Facemire LM, Honnold SP. Peripheral primitive neuroectodermal tumour in a two-year-old paint horse. J Vet Diagn Invest 2012; 24:794–796.

27

Approach to the suspected or confirmed cancer case

Introduction	415	History/anamnesis	419
Epidemiology of tumours in horses	416	Clinical examination	424
Clinical reporting/follow-up/trials design/publication/screening	418	Factors that influence prognosis	426
Client counselling	418	Client management (expectations/complications)	428
Clinical investigation of the suspected cancer case	418	The future of cancer medicine in equine practice	428

Introduction

The variability of the disease conditions between individuals with the same broad tumour type means that 'the only predictable thing about equine oncological disease is that it is unpredictable'. Most cancer patients present with symptoms that may resolve (albeit temporarily) and fluctuate or progress (slowly or more rapidly), depending on the nature of the underlying type and location of the cancer disease present. Often, the signs are overlooked by the owner or attributed by the owner to other 'more recognizable' disorders. For example, a horse that is losing weight over a period of months might be thought by an owner to have parasites or dental disease. Attempts to manage these supposed conditions may or may not bring about some kind of improvement, and in many cases owners do not even consider that a horse might be seriously ill when the symptoms are apparently mild. The weight-loss example here might lead to improved nutrition being offered and to a less demanding workload. Eliminating any concurrent parasites will add to the wellbeing of the case and improve its nutritional status.

Attending veterinarians need to be sensitive to the fact that an owner may have delayed a request for a clinical investigation and, without this, it may be very difficult to obtain a full and complete history. In cancer medicine, the history is at least as important as almost any other aspect of the investigation.

There are several important objectives that a clinician needs to consider when a diagnosis of cancer is suspected (Fig. 27.1). The ultimate objective is to make a definitive diagnosis and then to institute curative treatment. Ancillary issues relate to the extent to which the horse will tolerate the diagnostic and treatment processes and the compliance of the owner in financial and logistical terms. There is a clear responsibility to ensure that the animal's welfare is considered. It is easy to assume that no animal should 'suffer', but there are no treatments for cancer that are without systemic or local implication. It is sensible therefore, perhaps, to accept a degree of suffering, provided that there is a prospect of improvement or preferably 'cure'. There is little point in subjecting an incurable case to intolerable suffering to no end – the concept of palliative care applies to horses just as it does to any other species. Many cases can survive with a perfectly acceptable quality of life for extended periods of time, and if minor measures can be applied to improve the quality of life, then that is a perfectly acceptable approach. Set against that, an owner may have a much harsher attitude to the horse's survival and due regard must be paid to that sentiment. Forcing an owner to 'treat' a cancer horse is counterproductive, no matter how mild or benign the condition. Over-aggressive treatment in animals with incurable states simply results in increased and needless morbidity and increased financial input from owners.

There are several circumstances in which the veterinarian will have to consider neoplastic disease as part of the differential diagnoses:

1. The owner reports the horse to have an obvious mass:
   This is by far the commonest reason for seeking veterinary advice, but obviously relates to tumours that are easily seen. The large majority of these will be cutaneous tumours and it is perhaps fortunate that, in respect of tumours, the skin is by far the commonest organ affected by tumours in the horse.[1] In some circumstances, the visible external feature may be a secondary result of the tumour; a good example of that is the presence of a melanoma in the guttural pouch, which cases pharyngeal/parotid swelling.
   - Ossifying fibroma
   - Fibrosarcoma
   - Perianal melanoma
   - Sarcoid
   - Mast cell tumour
   - Thyroid adenoma.

   There are some states that may be strongly suggestive of neoplastic disease, but are in fact either inflammatory or developmental. These can be mistaken easily by owners of horses who may have an almost irrational fear of cancer diseases.

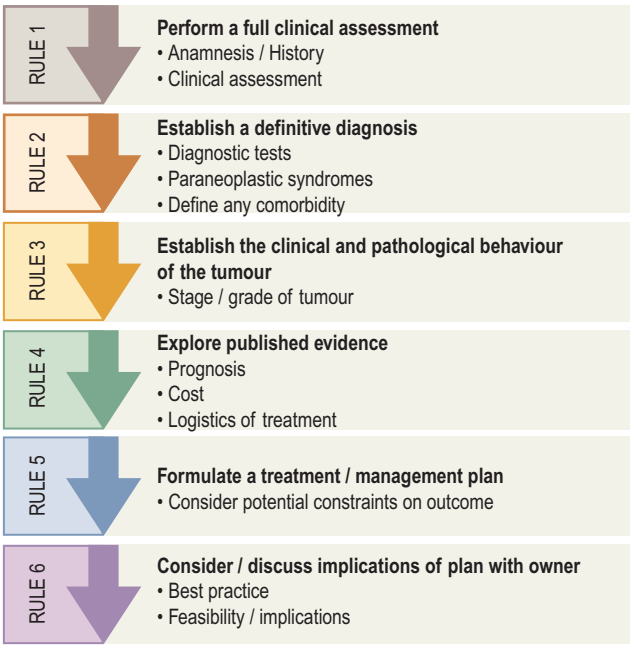


Figure 27.1 Fundamental rules for clinical responsibility to the client and patient. Each of these rules has defined clinical responsibilities that relate to the achievement of a satisfactory outcome that takes account of the welfare of the horse and the sentiments and concerns of its owner. There are aspects of this process that are easily overlooked, but short-cuts will seldom pay in the end and the veterinarian has an absolute duty both to the patient and its owner to provide the best possible clinical process. In this way, the client has confidence in the veterinarian and, even then, if things do not go according to plan, the client is engaged as part of the team and disappointments and recriminations can be minimized.

In some cases these can be mistakenly thought of as tumours, so the diagnostic process has to consider the basic question:

Note

Is neoplasia responsible for this change?

2. There is an overt clinical abnormality that is not directly attributable to the tumour – for example, haemoptyalism from a carcinoma in the mouth or other signs that may be unrelated. Many of the most prominent signs that cancer cases have are paraneoplastic syndromes such as weight loss, anaemia, etc. (p. 70). These signs are often either subtle or are easily mistaken for other disorders; for example, weight loss could be attributed to dental problems, and anaemia could be due to a chronic infection or even gastric ulceration. Of course comorbidity is always an issue and the relevance of any findings has to be considered carefully – *that is the reason that gathering all the information together first, i.e. making a problem list, is so important in all clinical investigation*.
3. The owner reports signs that are vague and less easily attributed to the presence of a tumour: signs that, for example, relate to functional effects of a tumour. A good example is a synovial sarcoma, where the horse may be presented for lameness, or a cerebral or spinal melanoma, where the horse is presented with ataxia or other neurological problems.

Epidemiology of tumours in horses

Evidence-based medicine

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. It is based upon properly conducted studies that compare medical methodology between different groups with the same condition; what works and what does not, when compared with the current gold standard.

The fundamental aspects of evidence-based medicine originate in the mid-nineteenth century and earlier; it is not a new concept at all but it has come to the fore of late, and it remains a contentious and stimulating subject for clinicians, public health practitioners, purchasers, planners and the public. Criticism has ranged from evidence-based medicine being an anachronism to it being 'a dangerous innovation, perpetrated by the arrogant to serve cost cutters and suppress clinical freedom'.[2] As evidence-based medicine continues to evolve and adapt, it has become better accepted and is now the basis of many clinical decisions; it is used to provide proof of efficacy for medical and surgical procedures and it has become the fundamental driver of all good clinical decisions. It is therefore the basis of advice given to owners of animals to allow them to make informed decisions on whether procedures should be carried out and whether the success rates are acceptable to them. Without proper evidence, much of the advice that an owner receives is heavily tainted by the maxim:

> *If you always do what you've always done, you will always get what you always got.*
> *(Antony Robbins, USA)*

An owner of a horse has the right to expect that his/her veterinarian is up to date, well-informed and able to correctly interpret the scientific literature to the benefit of the patient. Evidence-based medicine has become the standard by which clinical practice is governed and audited. It provides the basis for informing the client about the various options that are available for diagnosis and treatment. The principles apply as much to cancer medicine as to other systematic clinical medicine and as much to the horse as to other species.

Evidence-based medicine is the process of systematically finding, appraising and interpreting contemporaneous research findings as the basis for clinical decisions. It is a means of identifying gaps between research evidence and clinical practice that should be interpreted with care and, if possible, should be supported by focussed research effort. The application of evidence-based medicine means that expensive/ineffective/*harmful* decision-making can be avoided. It encourages and supports the practice of quality controlled medicine that uses the information derived from properly conducted scientific trials, published in peer-reviewed journals. It can be applied in any situation where there is good documented data on clinical diagnosis, prognosis and treatment.

Furthermore, evidence-based medicine enables the practice of proven results on new techniques, drugs or procedures derived from combined results from the open sharing of information. The frank exchange of information

on both successes and failures is, however, an ideal that is very difficult to deliver. No clinician really wants to openly admit to repeated failure and may wish to 'protect' his/her successes, especially when this relates to the development of a new drug that may have cost an enormous amount to develop. The whole concept relies on high-quality audited responses and self-critical analysis, free of bias that provides the client with confidence that the best thing is in fact being done for their horse.

The problem with this approach is the generally poor quality of the research, the lack of properly conducted scientific studies and the enormous amount of anecdotal and ill-informed 'information' that is easily available now. Where the published evidence for treatment in particular is poor or non-existent, treatments are often based on a 'hit-and-miss' approach – if a treatment works it must confirm the 'diagnosis'! Whilst the response to well-directed specific treatment may indeed help to establish a diagnosis, this is not a reliable method; it can be counterproductive and misleading.

Where treatments consistently fail, either the diagnosis is wrong, or the treatment choice is wrong or there is no established effective treatment or the way in which the treatment is applied is wrong. There are plenty of options for the failure of treatment.

The steps involved in evidence-based medicine are shown in Figure 27.2.

Frustrated clients often turn in desperation to completely irrational approaches such as homeopathy that are touted as solutions to all problems. As an example, homeopathic treatment has no scientific backing or justification – no clinical benefit beyond the placebo effect has been shown to accrue in any species, in any disease condition and under any circumstances. Diluted water has not been critically compared with the current gold standards for any known cancer treatment and is not an accepted or tested medical principle. Similarly, overdoses of vitamins and some minerals, and even especially restrictive diets, are often employed without any rational reason. Although these alternative approaches probably cannot do anything harmful, neither can they do anything helpful. The reality is that the willing acceptance of a useless 'therapy' is not a choice that the animal can take for itself; it requires a properly trained thinking scientific and caring veterinarian – even the owner is not able to assume clinical responsibility for the animal but can of course do so for him/herself.

Failure to provide proper evidence-based treatment is in itself often indirectly harmful – the disease may progress to the point of being untreatable by any conventional means or at least results in continuation of the suffering. Therefore, using evidence-based medicine, this approach cannot be justified under any conditions, i.e. it does harm by omission rather than commission. The fact that the homeopathic philosophy has an explanation for every possible outcome is something that inherently generates deep scepticism – such a 'treatment' cannot then be assessed using any recognized clinical testing method and so comes to rely on the perception of the owner alone; the animal has no ability to 'report'. If the gathered evidence is distorted by 'rules' that have no scientific logic, it is no evidence at all. Treatments that by the rules of the process have a 100% chance of success are either miraculous or an untruth! The author believes that the only way to counter the 'irrational' approaches of homeopathy, 'faith healers' and other charlatans is to provide the best possible evidence-based medicine and the only way we can do that is by open scientific discussion and by properly conducted studies. Similarly, the way the alternative 'professions' can gain credibility is to allow themselves to be subjected to proper clinical audit.

Evidence-based medicine creates confidence in the veterinary profession in general, and the individual practitioner, who can support his/her clinical approaches on the basis of the results of large numbers of audited cases involving the correct selection of treatment/procedure. It

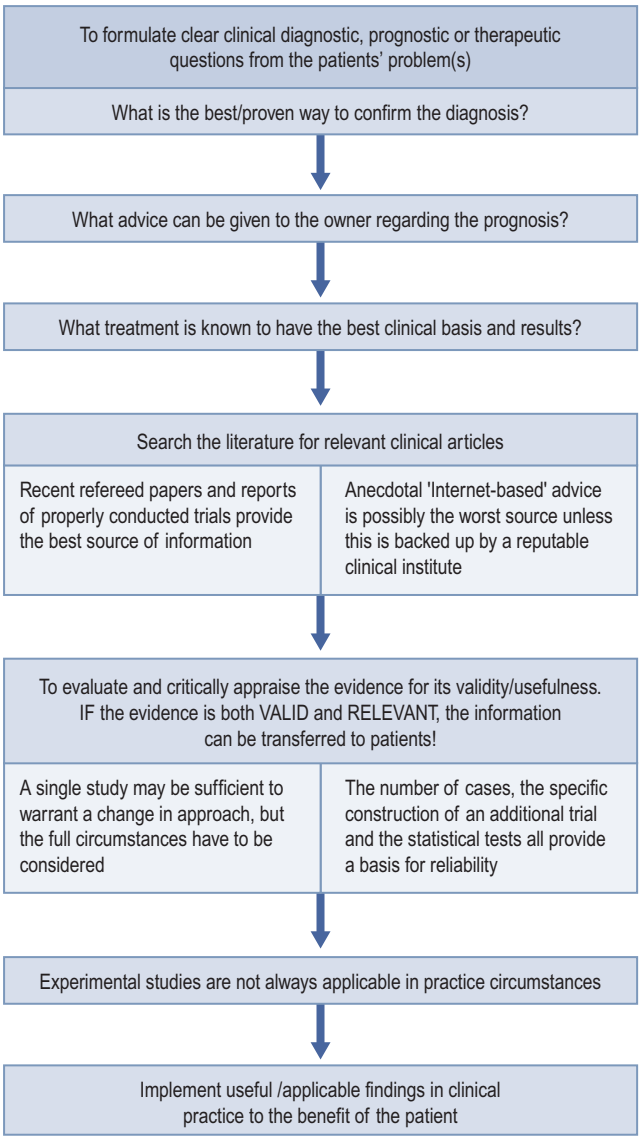


Figure 27.2 Evidence-based medicine has become the single focus of clinical investigation and therapy. In the case of equine medicine, there is a singular lack of properly conducted studies relating to the management of many of the cancer conditions. Enormous numbers of anecdotal reports and single case studies are required before any meaningful results can be achieved in the absence of properly conducted clinical trials. All clinical trials, whether they have positive or negative outcomes, should be published and widely disseminated, so that there is no waste of resources. The veterinarian providing advice to a client needs to be fully aware of what evidence there is and the client needs to be confident that the veterinarian is up to date and is providing the best possible advice.

also provides a solid legal defence for any clinical approaches that have been taken. It does not limit an individual's right to perform any particular treatment or to attempt to expand our knowledge through scientific study – it simply forces 'unusual or new' procedures to be explored and tested against the standard methods in a proper scientific way that imparts clinical confidence.

Clinical reporting/follow-up/trials design/publication/screening

One of the major constraints upon the progress in equine cancer therapy is the relative lack of reported cases and an even more disappointing paucity of large case series. Apart from a few very prevalent and well-recognized conditions, such as sarcoid and melanoma, there is a singular lack of clinical material in the literature. Of course there are the usual individual case reports that are often published by clinicians who encounter an unusual tumour type, but there are certainly few definitive clinical evidence-based publications on prognosis, therapy and even the clinical features of most of the neoplastic diseases of the horse.

An additional and significant factor is the general lack of follow-up information. Often, cases are seen, diagnosed and advice is given to owners about what is possible and what is not. In some cases, treatment may be offered or cases may be referred to specialist centres. Having returned home, the cases are frequently either not followed up or are lost to follow-up. The literature is littered with reported cases and case series where follow-up is inadequate for one reason or another. This is a very unsatisfactory state, since evidence on survival, prognosis and efficacy of treatment can only be sound if the follow-up is consistently good. Dealing with cancer is bound to be a difficult process. Owners may be badly upset when their horse is diagnosed with cancer and may therefore be reluctant to reopen the 'psychological wounds' or may take their own measures to manage or even euthanize the horse. It has become increasingly difficult in many parts of the world to get permission for post-mortem examination of equine cancer cases. In some places, the retention of tissues (even in histological slide form) is no longer possible without the express permission of the owners. All these aspects means that a significant number of cases are never followed through to conclusion.

The deficits in sound evidence-based knowledge can only be addressed by proper data collection and proper clinical trials. The difficulty is that no individual veterinarian is likely to encounter large numbers of most of the tumours that are reported. This means that multicentre studies are required and, unless and until these are instigated in an open and constructive manner, equine oncology will lag behind the other species. A prospective 'survival 'study for the major cancer conditions of horses would be a really significant benefit to the species itself.

Client counselling

Historically, it has been possible to recognize two types of veterinarians who treat 'cancer in horses' very differently.

The first group has been the largest and most dominant; these are the people who immediately condemn a horse when it is diagnosed with a cancerous condition. The reasons for this are understandable; the long-term prognosis is usually poor and they also fear the concept that the horse will suffer unnecessarily when the condition advances. Second, there is a sentiment that the costs of management and ongoing care will be significant and often 'enough to buy another horse'. This approach results in a rather negative sentiment in owners: 'If you call the vet, he/she will simply destroy the horse'. Of course, this is a rather polarized view of the problems of counselling owners but it is an approach that results in a very counterproductive outcome. No attempt is made to treat the horse and so no progress can be made in developing the treatment. This means in turn that there is no 'treatment' apart from euthanasia.

The second group of veterinarians are those who want to try to save the horse at almost any cost – in many cases, there is no long-term prospect of a cure but at least it does begin to develop evidence on what works and what does not. The starting position in most of the neoplastic diseases is derived by extrapolation from other species and the chemotherapeutic approaches are simply converted weight for weight to the horse. The few attempts that have been made to treat serious neoplasia by use of chemotherapy in particular have resulted in poor clinical outcomes with obvious welfare concerns during the treatment and so these have biased the approaches towards the euthanasia group.

Where a patient is diagnosed with a form of cancer, the clinician has a duty to provide all the available evidence for and against treatment, so that the client can make an informed decision on the next step. In many cases, the diagnosis can be confirmed and a reasonable prognosis can be given when this is known for a particular condition. There are the inevitable variations in the expected outcome but a client who has been counselled carefully and fully will quickly accept that there is an inevitable consequence from a diagnosis of cancer. The prognosis will depend on the tumour type and the evidence-based information regarding that tumour type. The treatment options, similarly, will have limitations and restrictions. Once an owner is aware of the situation the horse is in, there is generally no difficulty with the case management in respect of client expectation. Owners are inevitably disappointed, concerned and commonly seek to blame circumstances or individuals.

Clinical investigation of the suspected cancer case

Regardless of the extent to which a disease condition is 'obvious' on cursory examination, a detailed history and a thorough clinical examination are obligatory. Every case will be unique – that is the nature of cancer. A proper logical and thorough clinical assessment will have a profound implication on the outcome of the case. It may be that, for example, a horse with a small mass in its eyelid is diagnosed with lymphoma; this may not be the only tumour on the horse and indeed there may be other tumour types as well. If the horse were found to be anaemic, or had palpable masses per rectum, the prognosis would be considerably worse. The more effort that is put into the clinical assessment, the more sensible the advice is likely to be. Whilst some cases can be intuitively diagnosed, there is still no excuse to

bypass a clinical examination. Low blood proteins and/or concurrent hepatic or renal disease may preclude the use of certain drugs and medication. A horse with serious cardiorespiratory compromise might present significant anaesthetic risks.

The process of clinical diagnosis is the most fundamental basis of the treatment and prognosis options. Throughout the process of clinical investigation, the clinician needs to refine the diagnosis through careful clinical examinations and through the selection and use of appropriate diagnostic tests (Fig. 27.3).

It is easy to assume that a diagnosis is correct either because the visible evidence is '*obvious*' or because of intuitive supposition ('*I have seen this before*') – but there are significant dangers in such an approach. This might foreshorten the clinical investigation and so it might be easy to miss significant concurrent problems or secondary changes or nuances of the condition that may have an influence on treatment and prognosis.

History/anamnesis

It has been said that over 50% of the useful clinical information can be gleaned from a careful history. This certainly emphasizes the importance of both the long-term and adjunctive history in the investigation. Again, it is easy to be diverted into the short-term or specific history of the presenting signs, especially when some of these are obvious and when an owner is particularly keen to provide only information regarding the specific complaint. There is relevance in almost all the information obtained and so there is no such thing as an 'excessive history'. Many serious cancer cases have subtle clinical signs that are not immediately obvious to owners, although with careful questioning, they can provide the diagnostic keys. For example, a horse with a serious multiple myeloma may have been presented for lameness examination but a careful history will possibly identify that it is also lethargic and is drinking excessively. A horse with gastric carcinoma may 'eructate' and may have a variable appetite – preferring to eat grass rather than hay or hard feeds.

The signalment of the horse is usually easily established and it is important to identify the horse definitively, since there might be issues relating to insurance claims or even, in some cases, aspects of litigation in the event, for example, that the horse was purchased with the condition present. Furthermore, the signalment matters because there are defined conditions that might be more or less 'possible' in horses of a particular breed, sex, age or colour.

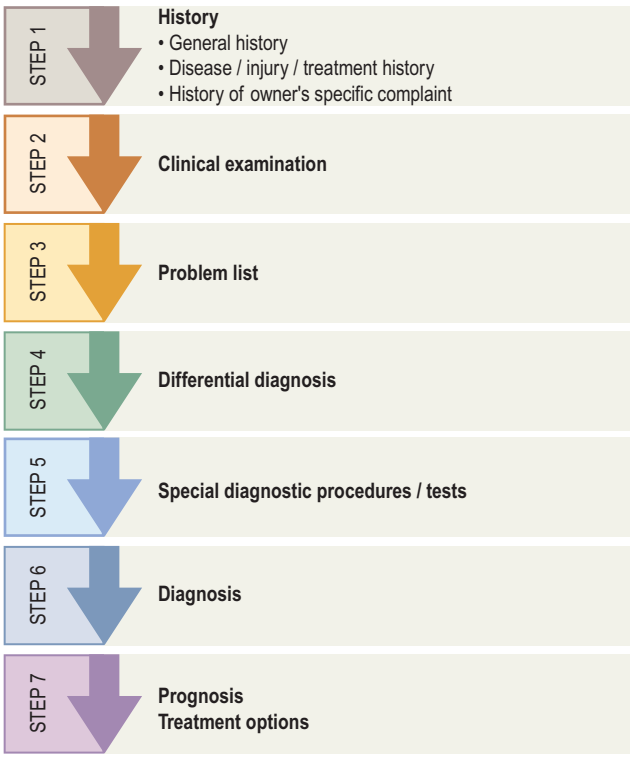


Figure 27.3 Achieving a diagnosis and the selection of appropriate treatment for any disease condition rely upon a totally logical clinical process. The degree of care and precision that is applied to the clinical process is fundamental to the outcome of cancer medicine. There is no stone that should be left unturned up to the point of selection of special diagnostic procedures and the latter should be selected with great care so that resources are not wasted and that every measure taken should lead to some defined objective. Once a diagnosis has been achieved, the prognosis and treatment options become clear, and where this is associated with sound evidence-based studies the owner can be assured that the process is both meaningful and objective.

Why does the breed *matter?*

In terms of tumour development, less is known about the role of breed susceptibility to specific tumour types in the horse than in other domestic species or races in the human. However, there have been some surveys that have identified breed susceptibility or non-susceptibility to tumour development in certain tumour types. For example, the Lipizzaner horse is thought to be more or less resistant to sarcoid. Although other breeds are suggested to be particularly susceptible to sarcoid, there are a number of reports of variable prevalence within certain breeds. There are suggestions that the American Quarter Horse is at greater risk than Standardbred horses. Greys are commonly associated with melanoma, but in spite of the relatively common grey colour (and black skin) among the Eriskay pony breed, melanoma seems to be far less common in them than in grey horses of other breeds.

Breeds that have little periocular or conjunctival pigmentation (including Paint, Pinto and Appaloosa horses) do seem to be more prone to ocular forms of carcinoma. Shire and Clydesdale horses are more susceptible to ocular (nictitans and conjunctival-limbal) carcinoma, in spite of having pigmented eyelids and eyelashes.

Why does the sex *of the patient matter?*

The specific sex of the horse matters also, since the various options of sex organ-related conditions will obviously exist. In terms of the sex, the male/neutered male (gelding) and the female/neutered female need to be taken into account. As examples of the relevance of the sex of the animal, squamous cell carcinoma is a relatively common finding in middle-aged/older geldings: it is very rarely found on the penis of entire stallions but *does* occur from time to time (Fig. 27.4). There are identifiable or at least conjectural carcinogens that are said to be responsible – smegma is usually quoted as being the major carcinogen in the

transformation of cells to carcinoma on the penile and preputial skin. However, it is also true to add that the colour of the skin is also an important aspect – penile carcinoma is much more common on non-pigmented skin but it does occasionally affect pigmented skin (see Fig. 35.1).

Stallions and mares appear to be less susceptible to ocular carcinomas than geldings; the latter are usually over-represented in prevalence studies of ocular carcinoma; the reasons for this are far from clear.

The specific state of the individual animal might also have an influence. For example, it is suggested that mares with a granulosa cell tumour have exacerbated signs of cutaneous lymphoma; this might vary with the breeding cycle or more commonly would not be associated with breeding cyclicity. Nevertheless, there are endocrinological implications for some types of tumour in many species, although the relationships are not very well established in horses.

Cryptorchid testicles have a recognized tendency towards neoplastic disease in many species, but again, this is not well established in horses. It is certainly true, however, that teratoma is more often found in retained testicles than in those that are normally descended.

Why does the age *of the patient matter?*

It is well established that cavernous haemangioma is far more common in very young horses, whilst melanoma, thyroid adenoma and pituitary tumours are far more prevalent in older horses. There are significant differences in clinical behaviour also in respect of age: penile carcinoma tends to be much more aggressive and have a higher malignancy in younger horses than it does in older ones, notwithstanding the fact that the overall incidence of the disease is higher in older animals; when penile carcinoma develops in young horses, the clinician needs to be aware of the extra implication for the prognosis and should be able to adopt a more proactive stance on treatment.

Why does the colour *of the patient matter?*

There are definite colour-related neoplastic conditions in the horse. Squamous cell carcinoma is a disease that predominately affects non-pigmented skin (Fig. 27.5).



Figure 27.4 A Thoroughbred breeding stallion with a highly malignant penile carcinoma. (A) This 17-year-old Thoroughbred breeding stallion developed a highly malignant penile carcinoma with concurrent (possibly seeded) lesions on the preputial pigmented skin. **(B)** The tumour was highly malignant and the inguinal and sub-iliac lymph nodes were grossly enlarged. Secondary tumour involvement of the lymph nodes and lungs were confirmed at necropsy.

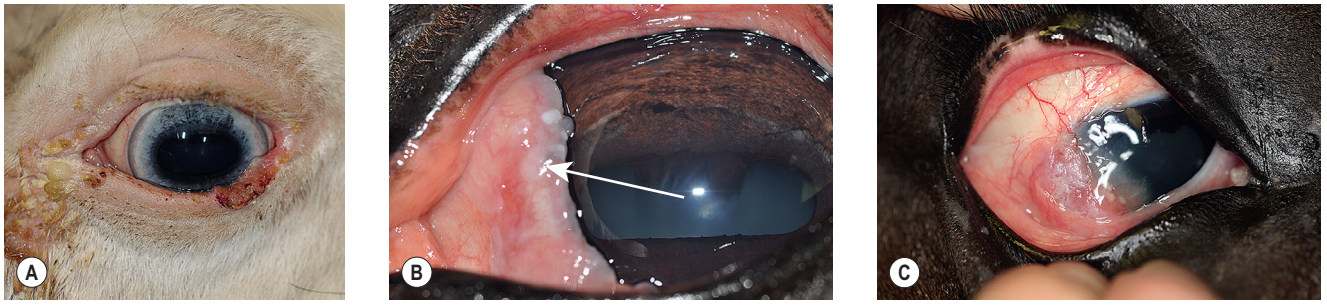


Figure 27.5 The relationship between non-pigmented skin exposed to high levels of sunlight and the subsequent development of squamous cell carcinoma is well recognized. (A) This 120 cm Welsh Mountain pony had a widespread lack of facial pigment and developed a destructive carcinoma of one part of the left lower eyelid with its characteristic purulent discharge. **(B)** Early dysplastic changes consistent with pre-carcinomatous changes developed in the non-pigmented nictitans of this 7-year-old Arab cross mare. The changes are recognized by being paler than the surrounding mucous membrane and by being somewhat thicker than normal conjunctiva (arrow). Several such areas are visible – there were no abnormal changes in the inner conjunctiva of the nictitans. **(C)** The absence of pigment in the lateral limbal bulbar conjunctiva is also a recognized predisposing factor to carcinoma at this site. From this, it may extend into the cornea, as in this 5-year-old Thoroughbred mare.

Probably the most obvious colour-related neoplasm is the equine melanoma (pp. 238 and 568). However, the chestnut flea-bitten grey is much less liable to the condition than the black-skinned true grey.

The colour of the specific skin site can have a major link to neoplastic change. For example, a non-pigmented eyelid or a membrane nictitans or lateral limbal conjunctiva is recognized as having a far greater predisposition to carcinoma development than when those areas are pigmented. Non-pigmented facial skin is far more often affected by cutaneous squamous cell carcinoma than is pigmented skin. It has been suggested that long-term exposure to ultraviolet radiation is a major aetiological aspect, i.e. UV radiation is a potent carcinogen.

Why does the duration of ownership *matter?*

When horses have been owned for several years, or longer, it is usually possible to obtain an effective and full history – provided that the owner is prepared to be honest about this. Horses that have been recently purchased will clearly have much less reliable historical information. Where a full pre-purchase examination has been carried out the attending veterinarian can safely assume that at least, at this one point in time, a complete physical examination had been carried out. It is, however, pertinent to point out that even a pre-purchase examination often does not include some important aspects of cancer medicine. For example, it is not regarded in most countries as necessary to examine the penis of geldings during a pre-purchase examination. The serendipitous finding of early (or even late) carcinoma or pre-carcinomatous dysplasia (leukoplakia) by the new owner within days of purchase may put the examining veterinarian in some professional discomfort (Fig. 27.6).

It is always worth asking how long the horse has been owned and whether it was subjected to a full pre-purchase examination at the time. The significance of the duration of ownership is mostly related to the provision of an indication of the rate of progression of either a tumour or the consequences of the tumour or to the effectiveness or otherwise of previous treatment attempts. An owner who has known a horse for a long time can usually provide more information, but this is also sometimes a bit of a two-edged sword, since the detail might cloud the more general indicators of disease or comorbidity.

Since weight loss is a cardinal and common feature of serious internal neoplasia, a regular accurate bodyweight can be a useful index. However, it is equally important to realize that there are myriad other states that produce weight-loss signs. The feature of cancer-related cachexia is that it features whole body mass loss rather than just fat loss.

Why does the use/management *matter?*

Circumstances that expose a horse to potential environmental carcinogens might be expected to induce a higher number of tumour cases (see Fig. 27.7). Exposure to high levels of ultraviolet light is suspected as being a significant carcinogen in the process of development in ocular, conjunctival and palpebral forms of squamous cell carcinoma (see Fig. 31.34). There is a significantly higher incidence of ocular and facial carcinomas in countries with long sunlight hours and outside management of the horses. Early dysplastic changes produced from a carcinogenic environment progress to more aggressive lesions and, in almost all classical cases, to variable levels of malignancy.

Why is it important to consider peer groups and in-contact horses and other animals?

In-contact horses provide an indicator of the management and feeding as well as exposure to common environmental and chemical insults. In theory at least, it is possible for more than one horse to develop a serious neoplasm as a result of common exposure. However, such circumstances are very rare. Clusters of tumour cases are encountered from time to time and then a putative carcinogenic circumstance can be justifiably sought.

The one circumstance when this is a significant issue is the potential for 'contagion' in respect of the equine sarcoid (p. 209). There have been strong suggestions, but no irrefutable proof, that the sarcoid is transmissible between horses (Fig. 27.7). Nonetheless, exposure to other horses with open sarcoid and possibly exposure to cattle infected with the bovine papilloma virus (BPV 1/2) can result in several horses becoming affected. The mechanisms behind this well-recognized clinical situation are not clear, but fly vectors may be involved either in 'spreading the virus' or in transfer of transformed cells across the gradient of the

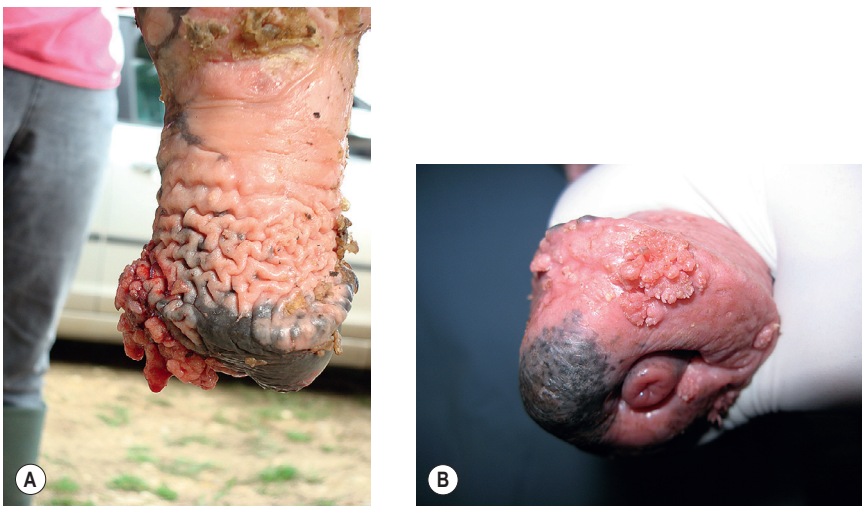


Figure 27.6 The history is a fundamental aspect of cancer medicine. The history is a fundamental aspect of cancer medicine and can provide extremely useful information regarding progression and recurrence in the event, for example, that there is history of previous treatment. Since a penile examination is not usually included in a pre-purchase examination, it might be easy to overlook the possibility of a penile carcinoma as in these two cases **(A,B)**, which both culminated in protracted litigation. Similarly, sarcoid or melanoma could easily be missed if there is no available history.

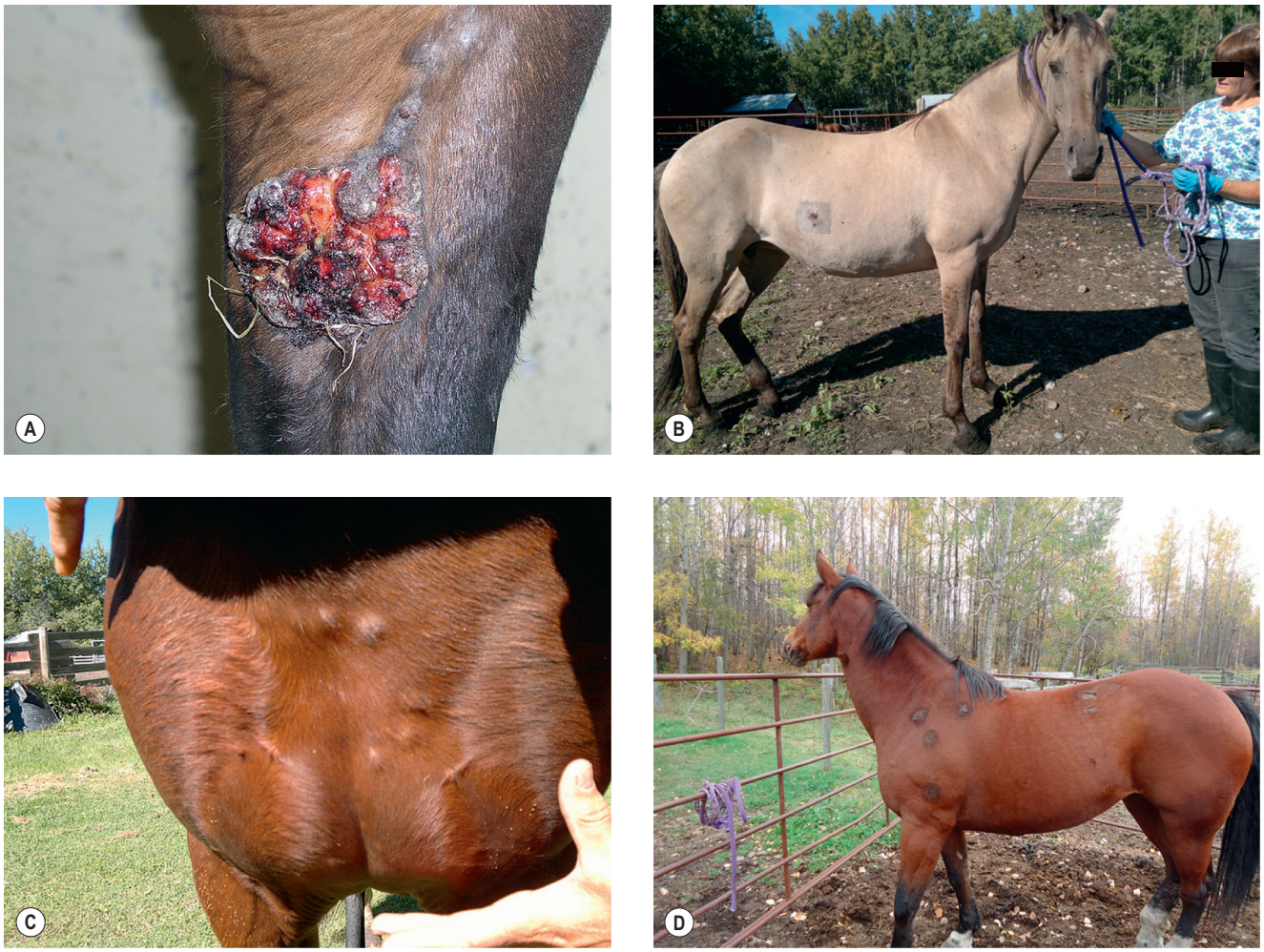


Figure 27.7 Contact with cattle affected by bovine papilloma virus tumours or other horses with sarcoid can result in significant outbreaks of the disease. Contact with cattle affected by bovine papilloma virus tumours or other horses with sarcoid can result in significant outbreaks of the disease. In the 'outbreak' illustrated here, there was no direct contact with cattle but 35 out of 40 horses all developed histologically confirmed sarcoid tumours of different types over a period of 1 year following the introduction onto the horse farm of one single case with several lesions **(A)**. **(B–D)** The lesions that developed on the horses were of a variety of sarcoid forms, ranging from nodular to occult (see p. 545) in various parts of the individual horse's anatomy – no fibroblastic types developed within the first 2 years but several had characteristic occult rims. The horses were unrelated to each other and of various colours and were geldings and mares. A few cases resolved spontaneously but most became 'typical' sarcoids and required treatment.

protective MHC class II mechanisms. Notwithstanding the conjectural, putative concept of transmission or simultaneous tumour transformation, it is always worth asking whether other horses in the same environment have similar tumours.

Why do routine procedures *such as worming, vaccination and dental and foot care matter?*

Removal of other factors that might also be responsible for some of the signs, or failure to remove them, might have a significant effect on the clinical state of the patient. Additionally, the signs associated with parasitism could easily be mistaken for paraneoplastic syndromes, such as weight loss and anaemia and vice versa. Furthermore, there are some parasitic infections that may be associated with some forms of neoplastic disease; a good example of this is the suggested relationship between gastric *Habronema*/*Draschia* infestations and gastric carcinoma or fibroma.

How does the previous disease, accident and injury history *affect the diagnostic process of cancer cases?*

Previous episodes of disease or previous injury can be significant. For example, tumour transformation with either sarcoid or squamous cell carcinoma (among other possibilities) can occur at wound sites and the resulting inhibited wound will not usually heal unless and until the tumour components have been eliminated (Fig. 27.8).

Repeated actinic dermatosis (sunburn) has been linked to the development of facial carcinoma, but this is by no means an invariable outcome.

Why is it important to know what medications *the horse has had and may be receiving concurrently?*

Concurrent medication may be related to the effects of the cancer condition (usually used when a diagnosis has not been achieved) or to the presence of comorbidity.



Figure 27.8 The key to a diagnostic conundrum is a good veterinarian who took a good history. **(A)** A large exophytic mass that developed at the site of a wound (the 'scar' can be seen running horizontally from the margin of the mass). This was thought at first to be granulation tissue but was in fact sarcoid; notice the occult sarcoid in the medial aspect of the forearm which had been present for some years without change (arrow). **(B)** A non-healing wound site on the dorsal aspect of the fetlock joint. Repeated attempts to repair the site failed and histology confirmed the presence of haemangiosarcoma at the site. In this case, it is impossible to guess whether the tumour transformation took place within a wound site or whether the tumour has developed at the site and then ulcerated. **(C)** This mare had this chronic non-healing wound site for 10 years. A biopsy was finally taken from several sites and squamous cell carcinoma was confirmed histologically. It is hard to guess when the transformation took place but any normal wound healing treatment would have been a waste of time and money; the key to the diagnostic conundrum was a good veterinarian who took a good history and established that there had been a complete failure to resolve the lesion for many years and then did the right thing and considered tumour transformation as a diagnostic option. *(Figure C courtesy of Mark Siddle.)*

Comorbidity is a serious hindrance in the effective diagnosis and therapy of the tumour state and the patient needs to be examined very carefully in all cases, to establish what is the true medical state of the patient. Additionally, and significantly, there may be drug interactions that will preclude certain therapeutic approaches. Again, at the present time, there is scant information about the possible interactions and synergies between non-cancer and cancer medications in horses.

The importance of the general history is summed up in Figure 27.9.

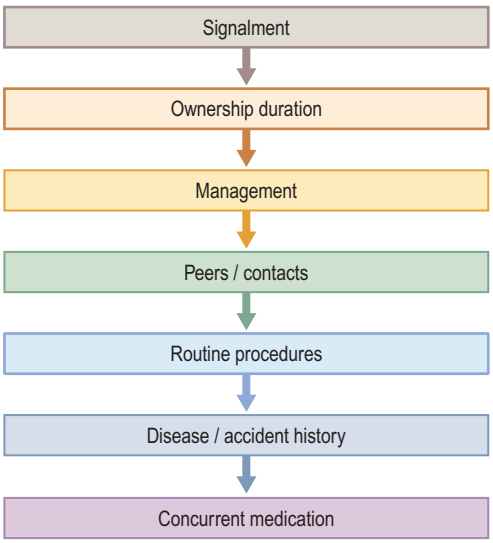


Figure 27.9 The general history. The general history is important, since each aspect may have a profound influence on the diagnostic process. Up to 50% of the clinically relevant material may be gleaned from the history alone. However, owners may not readily be aware of the overall importance and often view this as a waste of time.

The short-term or specific history

The specific or disease history relates to history of the particular complaint. Thus, if an owner complains that his horse has a 'lump' on its eyelid, the short-term history should relate to the course of that sign. Questions such as the date of onset, whether it was insidious or acute and the subsequent changes that have occurred since it was first noticed are important (Fig. 27.10). The treatment history is an important feature for several reasons. First, owners may well have attempted some sort of treatment themselves, either using 'left over drugs' from other cases or from human medications or from over-the-counter preparations. In all these circumstances, there may be significant information available. It is wise not to criticize the fact that these have been used (even though that is very tempting) but to ask whether any of the treatments attempted made any difference. This serves two useful purposes. First, the veterinarian is given hints as to anything that might have helped or exacerbated and, second, the owner will then feel able to be more forthcoming in respect of the history in general and may trust the veterinarian more.

The rate of progression of a tumour is a guide to its likely outcome. Tumours that remain static for long periods (often many years) are more likely to be benign or at least are less likely to metastasize. However, it is an important principle of cancer medicine that a tumour cell has an inherent

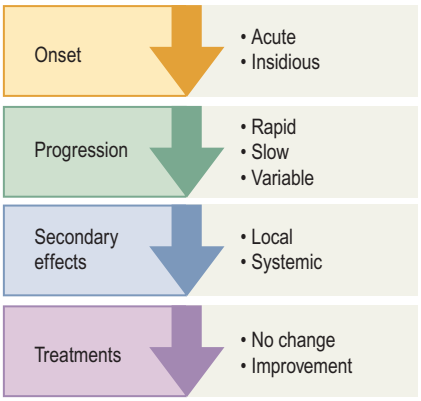


Figure 27.10 The short-term history. The short-term history provides useful information on the progression or deterioration of the tumour (whether with treatment attempts or not).

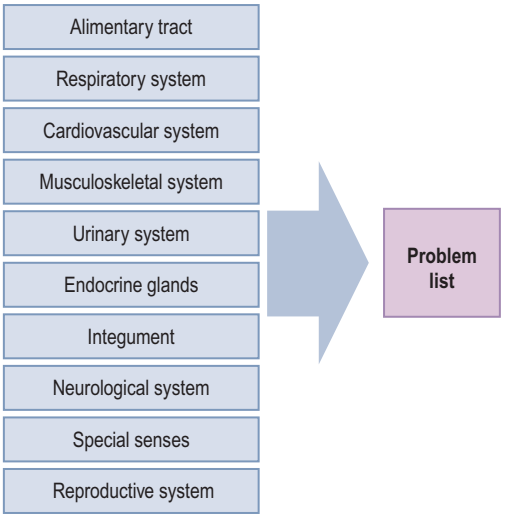


Figure 27.11 A body systems clinical examination technique. A body systems clinical examination technique is much more time consuming than a regional examination system but since many signs relating to cancer in horses are subtle, this is probably a better way of ensuring that every clinical abnormality is detected and every diagnostic possibility is considered. It is important to consider whether an observed/detected clinical abnormality is either: (a) SIGNIFICANT/primary; (b) SIGNIFICANT/secondary; (c) INSIGNIFICANT/primary; (d) INSIGNIFICANT/secondary; or (e) UNRELATED (whether significant or not). Cancer medicine will inevitably rely on the patient's own ability to limit the clinical effects and to tolerate the interventions that may be required.

genomic instability and so it is entirely possible that tumours that have remained static for a long time can suddenly burgeon and become a serious issue if they are subjected to any additional carcinogenic insult.

Clinical examination

Just as in the normal clinical investigation for disease of any type, the vital signs and a systematic full body systems examination are vitally important in cancer medicine (Fig. 27.11), even when intuitive supposition is used in cases when the diagnosis can be reasonably established very quickly.

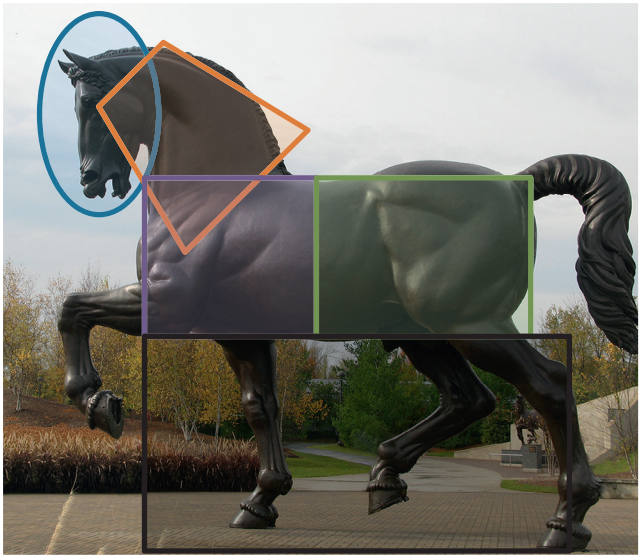


Figure 27.12 A regional examination system. A regional examination system requires the development of a strict logic so that nothing is missed. For example, a regional examination of the head needs to consider that each of seven relevant body systems may be reflected in changes. This is a common 'short-cut' system used by experienced clinicians; those with less experience should probably avoid this system in the investigation of cancer cases.

The vital signs include:

- Body temperature
- Pulse
- Heart rate
- Respiratory rate
- Mucous membrane colour
- Capillary refill time
- Bodyweight
- Body condition score.

It should be possible for a clinician to use either a body systems examination (this is preferred by the author since it has an inherent repetition that minimizes errors and omissions) or a regional examination. The latter is usually faster and is the approach many experienced veterinarians use (Fig. 27.12). However, it is easy to overlook some aspect of the regional anatomy and pathology and it is inherently less clinically efficient, as it is easy to overlook subtle changes in one or other body system when using a regional examination system, particularly by a less experienced clinician.

Many cases have multiple tumours and many tumour conditions of the horse affect multiple sites within an organ, whilst others can affect multiple organs/structures either primarily or secondarily. It is particularly easy to overlook the potentially more dangerous tumour when the case is presented with an overt readily visible mass. There may be subtle variations in the tumour type and there may be very deficient implications from their presence in different locations. A good example of this is the equine melanoma. Whilst the 'common' well-recognized melanoma state has largely been viewed historically as a cosmetic nuisance, an owner might be justifiably aggrieved when the horse suffers from a more serious sign at another site that has not even been considered. For example, a perineal melanoma may

look benign, but what is visible on the outside may belittle what is present internally. A simple, but thorough clinical examination should be able to identify potential sites for further methods to detect other tumours. In this circumstance, for example, a rectal examination and/or a guttural pouch endoscopy might be sensible steps to take.

Frequently, the case is initially presented for investigation of a 'paraneoplastic' sign (p. 70) and although it is probably equally wrong to overstate the role of cancer, for example when a horse has recurrent fever, it is equally wrong to overlook the possibility of a tumour being responsible. In this type of circumstance, the clinical examination needs to be efficient (so it does not waste time) and exhaustive, so that no body system is overlooked and no diagnostic possibility is excluded from consideration. Another good example of this may be when a case is presented with pyrexia of unknown origin and a chronic discharge from the prepuce. It might be assumed that 'infection' was the cause of both, but exhaustive examinations might identify a penile or preputial carcinoma and a high resting respiratory rate. This might be caused by secondary pulmonary tumours. The animal may also be mildly anaemic as result of paraneoplastic bone marrow suppression, so a tumour in one site might lead to overt signs in other body systems. A similar 'mistake' could be made when a middle-aged grey horse is presented with ataxia; the signs may quite rightly be attributable to a spinal cord compression from arthritic or degenerative orthopaedic disease, but especially in the case of grey horses, the possibility of a spinal or cerebral melanoma must be considered. Diagnosis can be really difficult and often the role of a neoplasm is deduced by the exclusion of other possibilities (Fig. 27.13).

No horse should leave the clinic without having had an exhaustive clinical assessment, so that the problem list can be completed effectively. At this stage, it is often possible to draw significant conclusions but the value of clinical examination lies in its ability to identify all the clinical abnormalities the horse has.

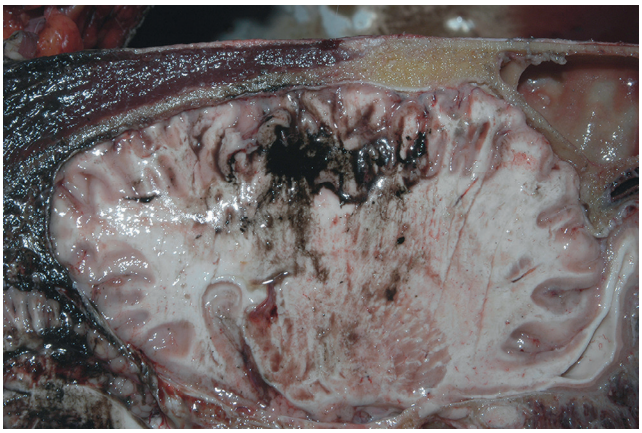


Figure 27.13 The alternative diagnosis. This 14-year-old grey gelding was presented for inexplicable ataxia that was attributed to spinal cord compression; no radiographic or scintigraphic confirmation could be found. A head MRI confirmed the presence of an extensive cerebral melanoma and this was finally considered to be the likely cause of the problem. The case was disappointing, in so far as enormous effort and finances had been devoted to investigation of 'orthopaedic/neurological disease', without any prior consideration of an alternative diagnosis – however rare that might be.

The 'problem list'

The third component of the clinical approach to the potential cancer case is the creation of the problem list (Fig. 27.14). This is made up from all the detectable or reported variations from 'normal' that are identified from the general and clinical history and the clinical assessment. No findings should be excluded, no matter how minor they might be. At this stage, the process of refinement of the diagnosis is the key issue.

Further clinical investigations

It is almost inevitable that a straightforward clinical examination may need to be expanded to include some more invasive procedures. A rectal examination is a good example of a test that can frequently be justified. In addition, of course, more sophisticated diagnostic aids may be required. These are considered below.

Diagnostic aids

It is almost certain that in the majority of cases, further tests will be carried out to establish the true nature of the problem and to establish the presence of secondary or metabolic effects and concurrent disease.

- *Haematology/biochemistry/serology/enzymology and tumour marker immunochemistry* (pp. 90 and 106): There are few specific haematological changes, but when taken with the clinical features, haematology and biochemistry can provide strong corroborative information. In spite of low specificity and generally low sensitivity, the combined pool of measured parameters can be very useful.
- In some circumstances, specific changes can be identified and then a diagnosis can be made with confidence. A good example of a specific finding is the presence of high numbers of circulating abnormal

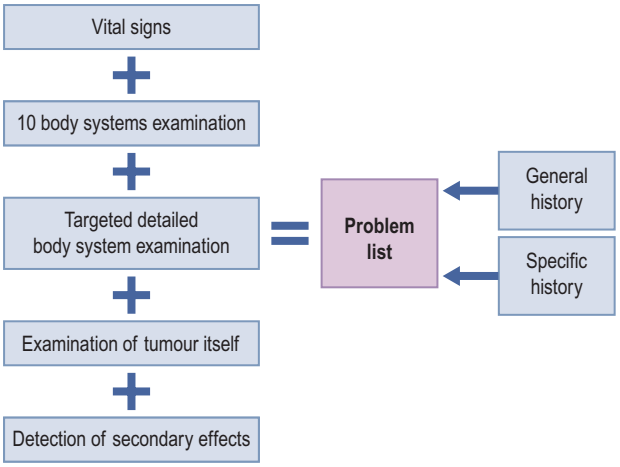


Figure 27.14 The problem list. The examination of a suspected cancer patient follows normal clinical principles that lead to the recognition of the *problems* that can be detected – the so-called 'problem list'. This is *not* synonymous with a diagnosis. It is important that any confounding influences, such as concurrent treatment with steroids or antibiotics, are taken into account at this stage. There is much to be gained by extra care with the history (anamnesis) of the case, since many cases have meaningful and helpful historical events and notes.

lymphocytes in some forms of leukaemic lymphosarcoma (see Fig. 7.7).

- *Endoscopy* (p. 103): Endoscopy through the use of a flexible endoscope or a rigid laparoscope can be singularly helpful in making a diagnosis in many cases. The specificity is high and the sensitivity is maximal – the tumour and the organ concerned are directly visible.
- *Radiography* (p. 101): The wide availability of sophisticated radiographic imaging means that many tumours that have either a solid structure or which have a destructive nature on surrounding bone tissues can be visualized with radiography. Of course, as might be suspected, bony tumours and those that fill body spaces are very easily diagnosed. The sensitivity is good, but many tumours cannot be differentiated on radiographic features alone, so the sensitivity of the procedure is variable. Some soft tissue tumours, such as melanomas are also radiodense and so can be visualized in some cases. The next stage in sophistication for the melanoma is computed tomography (CT).
- *Computed tomography* (p. 102): Increasingly this methodology is becoming more available to equine radiologists. The capture time of a few minutes and the ability to construct a full 3-D tissue-dependent image provides amazing diagnostic opportunities.
- *Magnetic resonance imaging (MRI)* (p. 102): MRI is not yet widely available, but together with CT, 3-D images of structures and subtle differentiation of bone and soft tissues provides the clinician with unrivalled imaging opportunities. The extra time that MRI requires to capture images is a major drawback and the costs of equipment mean that this is only available at very few centres worldwide at present. It is entirely possible that advances will be made that will allow the use of MRI in routine clinical imaging in horses.
- *Nuclear scintigraphy* (p. 102): Scintigraphy can be useful as a nonspecific test to identify deep-seated tumour-related inflammation. Although, when it works it is useful overall, it lacks both sensitivity and specificity.
- *Biopsy* (p. 87): Inevitably, the definitive diagnostic test is biopsy. Most of the well-recognized equine tumours have been characterized in detail and pathologists can recognize them in most cases. Biopsy has high sensitivity and specificity.

Different biopsy procedures are available for different tumours and, apart from very deep-seated tumours, they can usually be accessed by some means or another (often though this will require some form of imaging technique).

Factors that influence prognosis

Owners of horses diagnosed with a cancerous condition usually accept that the prognosis, for most, is guarded at best. In fact, usually they simply want to know what the likely course of events is and whether the tumour is treatable or not. This means that the clinician really needs to know what evidence there is for prognostic prediction. Clearly, many factors will influence the outcome of a tumour. These include:

- *Tumour type*: The primary influence on prognosis is the type of tumour involved. This also introduces aspects of the pathological behaviour and the extent of any related or paraneoplastic signs induced by the tumour itself. For most tumour types in horses, however, there is little evidence-based information beyond the extrapolations from other species and individual case and limited reports that have been published. Certainly, there are some tumour types that carry a bad prognosis, such as mesothelioma, non-cutaneous lymphoma and malignant carcinomas, and some that carry a good prognosis in general.
- *Extent*: Large tumours generally carry a worse prognosis than smaller ones, but some very small tumours have a profound clinical effect. Good examples of small tumours that have a profound effect on the animal or the function of the organ affected are phaeochromocytoma of the adrenal medulla and spinal cord melanoma. In the former case, it is the functionality of the tumour that creates the problem, whilst in the latter, it is the space-occupying aspect that is critical. Benign tumours that are very extensive also have a lower prognosis for any one of several reasons. Cosmetic acceptability, welfare issues and functional problems are significant aspects of this. For example, an extensive sarcoid over a wide area of the breast of a horse may have little effect on the horse itself but its extent will probably preclude any meaningful treatment, i.e. the prognosis is poor for the condition but better for the survival of the horse since it may remain much the same for the natural life of the horse (Fig. 27.15).



Figure 27.15 The prognosis for the various forms of cutaneous lymphosarcoma varies widely. This 16-year-old gelding was diagnosed with mycosis fungoides – an advanced tumour state with a very poor prognosis in any species. The name mycosis fungoides is misleading; loosely it is translated as 'mushroom-like fungal disease', but also, in its mildest form, it can mimic milder dermaphytosis. It is not a fungal disorder at all but a serious form of T-cell lymphosarcoma. The disease is an unusual expression of CD4 cells, which are skin-associated. This means that they are related biochemically and biologically to the skin. There are, however, many forms of cutaneous lymphosarcoma which are not related to mycosis fungoides; the prognosis for the various forms of cutaneous lymphosarcoma varies widely. *(Figure courtesy of Sarah Heathcote.)*

- *Location*: This is a fundamental aspect of cancer medicine. The location affects accessibility and this influences treatment options. Even some small tumours that are visible are a major threat to the function of an organ and therefore to the patient. A good example is the iridal melanoma. Here, when the tumour is small, it may have no material effect but as it expands it will have greater significance. If the tumour arises from the iris it might be accessible surgically but if it arises from the ciliary body, then it is likely not treatable and the prognosis for the eye is poor.
- *Duration*: In general, the longer a tumour has been in existence, the greater the difficulty of treatment and the greater the likelihood of tumour progression. Tumours have a strong tendency to expansion, making therapeutic options more challenging. However, some tumours can remain static for many years without any obvious change. It is the prediction of the future that is the problem.
- *Facility/availability of treatment*: Where treatment facilities are good, options for treatments will usually be wider. Normal equine practice will inevitably bring constraints as to what is feasible and what is within the experience and capability of the practitioner. Many cases can be managed well even in outpatient situations but some will clearly be impossible in some circumstances. In particular, chemotherapy and radiation will always require special facilities.
- *Patient compliance*: There is a general perception among owners that treatment must be 'pain free and complication free'. Almost all cancer treatment whether for benign masses or the more serious ones will have some adverse effect on the patient. Surgical procedures will be painful and chemotherapy may be both painful and have significant patient effects. Those are inevitable and the patient has to be in a physical and mental state to allow the procedures to take place. The patients, however, do not understand what is being done and so may actively resent treatment; alternative methods and strategies to overcome the compliance issue are generally possible in most circumstances. A good example of patient compliance problems is a sarcoid lesion on the belly of a wild zebra! Clearly, this represents the one extreme, whilst the other is the stoical and trusting nature of the donkey that probably will not show pain, no matter how severe it is.
- *Relative value of horse and cost of treatment*: The costs involved in most cancer treatment are high and when these exceed the actual value of the horse, the treatment may be viewed by the owner as unjustified. However, horses often (but by no means always) have an unquantifiable emotional value in addition to their pure market value. The more emotional value is attached to the horse, the more the owners have an expectation of success. Failure is not usually considered! A prognosis of 75% is often taken to mean 100% by owners. In other circumstances, the owner may simply request euthanasia and will then purchase another horse – hopefully without any tumour state.
- *Owner compliance*: One of the biggest issues in cancer medicine is owner compliance. The owner's perceptions of the effects of treatment on the wellbeing of the horse are often the first concern. Whilst a human may be very willing themselves to endure extremes of pain and discomfort during cancer treatment, owners of horses very often say 'I don't want to put him/her through a painful procedure'. This is an argument that veterinarians in practice will frequently have to consider. The second issue is the perception of the outcome. Cosmetic appearance is often critical to a horse owner. The owner may not consider that removal of an ear, eye or tail is an acceptable state, but this is purely a human sentiment. The horse will not worry at all about being cosmetically compromised and its peers will not ostracize the animal as a result of the 'disability', as humans might! Nevertheless, it is a serious issue that often results in decisions not to treat cancerous states and either to accept the status quo or to perform euthanasia, whether the animal needs it or not. Additionally, of course, owners often have preconceived ideas about 'cancer' in their animals – there is perception that cancer is 'not treatable' because veterinarians summarily 'execute' horses with cancer because the usual response from veterinarians is immediate euthanasia upon diagnosis – whether, actually, the horse needs it or not! This is a self-fulfilling prophecy that results in late presentation of cancer cases and then, of course, euthanasia *is* often the only option.

Finally, there are *financial constraints*. Given a circumstance with no financial constraints, many cancers can be treated or at least managed.[3] Chemotherapy methods are improving rapidly and so there are options for delaying euthanasia without compromising patient welfare even, for example, in some advanced lymphoma cases. Some tumour types are, however, currently at least, genuinely untreatable (e.g. disseminated melanoma and mesothelioma) and then other considerations need to be evaluated. Just because the horse has an advanced cancerous condition, it does not necessarily mean that its welfare is compromised to the point where it needs immediate euthanasia – it may be perfectly happy and may even be able to work in some way. Welfare is the issue and it is important to remember that not everyone has the same boundaries as to what is acceptable welfare and what is not acceptable welfare. In some circumstances, owners may not permit euthanasia when it is clearly in the animal's best interests and may make appeals for help both directly and to 'specialists' at other centres and via the internet. The single overriding aspect is the welfare of the patient and the attending veterinarian is the only person who has access to the whole case, so his or her opinions are paramount and provide a fundamental foundation for any subsequent decisions. It is entirely acceptable to subject an animal to a painful procedure (provided this can be mitigated to some extent at least) if it has a realistic chance of returning to an acceptable pain-free existence – by contrast, it is not acceptable to put an animal through any procedure, whether painful or not, without the prospect of an improvement in its health or its welfare status or both.

Close, frank and honest communication with the owner usually obviates most if not all the problems and 'team consensus decisions' can then be made in the best interests of the patient, taking account of the owners circumstances and sentiments. In the end, however, it is the responsibility

of the veterinarian alone to manage expectations and provide strong but sympathetic guidance, since veterinarians are the only people qualified to make decisions on animal welfare.

Client management (expectations/ complications)

Once a diagnosis is made, client communication is essential; the very word 'cancer' strikes fear in most owners. The fact that little is known about most cancers in horses simply adds to the level of the uncertainty that both the clinician and owner will experience. Individual owners will have very different attitudes towards the steps that might be suggested following the diagnosis. Some may wish to treat the horse no matter what the cost or the prognosis, whilst others may have a more ambivalent attitude and prefer to euthanize the horse immediately to avoid cost and future suffering implications. Others may wish to provide palliative care until the horse shows signs of suffering or compromised body function before taking action.

Risks and benefits of management

Inevitably, there are risks associated with cancer treatment and management, whether this is surgical or medical.

It is often hard to separate out the various aspects that an owner will consider so that a reasoned decision can be taken. It is probably wise to spend extra time explaining to the owner what the problems are and what is known about the tumour type; owners appreciate evidence but it is important to realize that most owners offered a 70% chance of success will mentally assume that this is actually 100% – a 70% success actually means a 30% failure and it is important to use both numbers when discussing the prognosis and complication rates with owners.

The biggest problem of all for the veterinarian is the general lack of controlled 'gold standard' evidence-based medicine from which to guide owners. Inevitably, there will be aspects of personal experience and owners may wish a second opinion or even referral to a specialist. This should not be viewed as a criticism but simply an indication that the client needs further support and guidance to make the best overall decision on the choices available.

Whether there is action to be taken to treat a patient, apply palliative care or to perform euthanasia, each of these steps will require client input. In the final analysis, the decisions taken following a diagnosis are a matter of teamwork and communication.

The future of cancer medicine in equine practice

Owner expectations are rising quickly and the veterinary profession needs to address these by advancing the science and practice of oncology. Whilst there are many established treatments that have been tested by time (and in a few cases by solidly conducted clinical trials), there is still much progress to be made in equine oncology. There is still far too little research being conducted into cancer in horses and far too few clinical trials being carried out. It is clear from the databases of veterinary refereed publications that cancer still features heavily in the literature and clearly is a major concern to practitioners. The large majority of publications, however, still involve case reports – often on single 'amazing' or unusual cases. Whilst this is clearly of clinical interest, it is not really pushing back the frontiers of equine oncology.

Additionaly there are far too few centres where oncological treatment can be carried out worldwide and even fewer centres carrying out fundamental research on the horse. When greater importance is placed on cancer in the equine species, we will be able to improve both our understanding of the major tumour states and also develop new and innovative treatments. Ideally, as in all species, prevention is far better than cure, but until we understand the conditions and the basic genetic and carcinogenic processes involved, we will always have to extrapolate from other species. Only when there is a solid will to improve the general and specific understanding of equine cancer will we make real progress.

References

1. Baker JR, Leyland A. Histological survey of tumours of the horse with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
2. Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: What it is and what it isn't. BMJ 1996; 312:71–72.
3. Dabarainer RM, Sullins KE, Goodrich LR. Large colon resection for treatment of lymphosarcoma in two horses. J Am Vet Med Assoc 1996; 208:895–897.

28

Tumours of the alimentary tract and abdominal cavity

Neoplasia of the oral cavity	429	Gastrointestinal neoplasia	457
Odontogenic neoplasia	430	Intestinal neoplasia	461
Incidental tumour-like dental masses	436	Smooth muscle tumours	465
Neoplasia of soft tissue origin	436	Hepatic neoplasia	467
Neoplasia of the tongue	449	Secondary hepatic neoplasms	470
Disorders of the mouth, jaws and teeth resembling neoplasms	452	Neoplasia of the spleen	470
Non-aneurysmal cystic lesions of bone	455	Pancreatic neoplasia	473
		Neoplasia of the peritoneum/omentum	474

Neoplasia of the oral cavity

Overview

Structures of the mouth, including the soft tissues, bone and teeth, may all develop neoplasia; this should be considered as a possible differential diagnosis of disorders of the oral cavity, especially those associated with swellings. Unfortunately, most published reports of specific neoplasms of the oral cavity involve single or few cases or are broad reviews based on these.[1–4]

Primary oral and dental tumours are usually classified by the tissue of origin as (Fig. 28.1)[3,5]:

1. Dental (odontogenic) tumours
2. Bone (osteogenic) tumours
3. Soft tissue tumours

and according to the clinical behaviour and pathological features:

1. Benign or malignant
2. Invasive or localized
3. Proliferative or ulcerative.

There is no meaningful information on tumour staging of equine orodental tumours. This is generally based on:

- *Tissue* of origin
- *Location* of tumour
- *Extent* of secondary tissue involvement
- *Clinical* behaviour
- *Pathological tumour* behaviour.

These features will all affect the feasibility and choice of treatment method, as well as the prognosis for the horse.

The majority of orodental neoplasms are well advanced, with extensive local infiltration, before clinical signs become apparent. Often, the secondary changes, such as weight loss or difficulty eating, are present and then become the reason for presentation. This makes the general diagnosis of neoplasia relatively straightforward but rather disappointing, since treatment options are then extremely limited.[6] Additionally, since the gross appearance of many neoplastic masses in their early and advanced states can be similar, the definitive diagnosis will often depend on histological examination.[7] Secondary tumours and invading tumours are rare but must be considered when investigating an oral mass, since the origin might be diagnostically helpful and may have therapeutic implications.

The lack of reported series of individual oral tumours and tumour-like masses testifies to the fact that most of these conditions are uncommon and that no significant attempt has been made to classify them and to quantify their prevalence through multicentre studies.[8–11] The specific difficulties that are presented by the tumours and their profound effects (whether benign or malignant) means, however, that veterinarians are expected to make prognostic decisions that are inevitably based on limited experience rather than sound evidence. Recommendations for treatment of rare conditions cannot be made with any certainty, and pathologists are often expected to provide information that simply does not exist.

Some non-neoplastic conditions, such as epulis, gingival hyperplasia, granulation tissue and hamartoma, can give the clinical suspicion of neoplasia. Some masses have histological features that support a diagnosis of neoplasia but are not, in fact, neoplastic.[12–14] For example, fibrous metaplasia of the nasal region and hard palate have been described and benign neoplastic growths are seen occasionally in association with abnormal germinal tissue of tooth roots (Fig. 28.2).[15,16]

These include:

1. Papilloma
2. Epulis
3. Polyp
4. Aneurysmal bone cyst
5. Fibrous dysplasia/metaplasia.

Clinical features

Clinical features of orodental neoplasia, which are often subtle in the early stages, include:

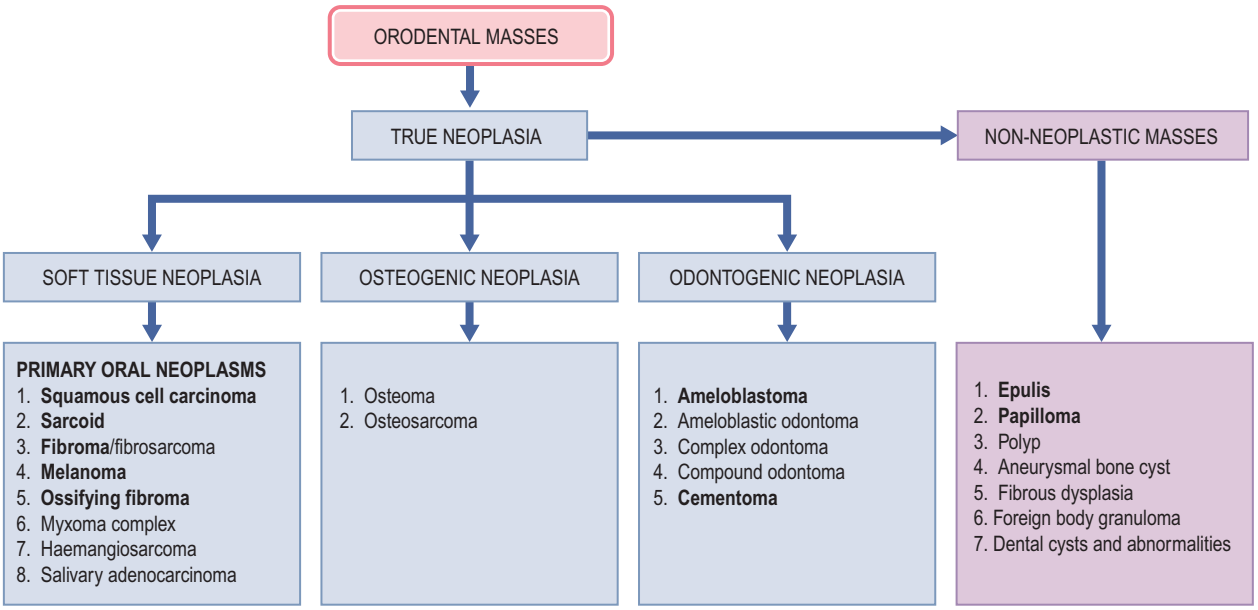


Figure 28.1 The classification of orodental masses in the horse. The conditions shown in bold font are the commoner ones.

1. Visible abnormal mass of tissue or secondary anatomical alterations (due to proliferation or destruction of tissue within the oral cavity or adjacent structures such as the jaws, cheeks, nasal cavity and paranasal sinuses)
2. Oral discharge/bleeding (haemosalivation or malaena with positive faecal blood)
3. Difficulty with prehension, mastication and swallowing (dysprehension, dysmasesis, dysphagia)
4. Weight loss
5. Recurrent fever and depression
6. Halitosis
7. Submandibular lymphadenopathy.

Some oral neoplastic conditions are very destructive. Additionally, extensive secondary changes, such as infection or trauma, may be more obvious than the underlying condition. For example, a destructive oral squamous cell carcinoma, involving the palate, may produce an oronasal fistula. The initial presentation might then be a nasal discharge with or without overt food material and a fetid odour. This might give the impression of a respiratory tract problem and so a careful scrutiny of the whole case is essential.

Odontogenic neoplasia

Overview

Tumours in this category are all rare, although it has been suggested that they are commoner in horses than in other species.[9] Odontogenic tumours are classified according to the inductive effect of one dental tissue on the others.[10,17] These tumours are almost always clinically benign, but are frequently locally invasive and aggressive. As a general rule, dental tumours are best treated by wide surgical removal (to ensure complete ablation of tumour and abnormal tissue)



Figure 28.2 This tumour-like mass developed in the incisive gingival of a 12-year-old gelding. Biopsy was inconclusive and only after full surgical removal was a diagnosis of an inflammatory reaction possible. Even then, there remained some doubt but, as the condition did not recur, the matter was not pursued. *(Figure reprinted from Easley J, Dixon P, Schumacher J. Equine Dentistry. Edinburgh: Saunders; 2011: 157 (Fig. 11.5), copyright 2011, reprinted with permission from Elsevier.)*

at an early stage in their development when such surgery has a chance of success. In most cases, however, the masses are not recognized sufficiently early and so local recurrences are common, in spite of attempts at wide surgical excision.[11] Most are benign but can have serious secondary effects, such as nasal obstruction and dental and facial deformity, resulting in difficulty eating and weight loss. There are some similar clinical conditions that resemble neoplasia but are in fact simply abnormal tooth formation (see Fig. 28.2). The important differential aspect in these cases is that the condition is present from the time of formation of the tooth. Odontogenic tumours are of variable histological appearance and are categorized currently on their morphologic basis.[18] Their features are summarized in Tables 28.1 and 28.2.

Table 28.1 Summary of features of odontogenic tumours based on published characteristics[17,19]

Tumour type	Age group (years)	Clinical	Best treatment option	Prognosis
Ameloblastoma	Wide range	Benign/locally invasive behaviour	Surgical excision/ hemimandibulectomy ± radiation	Fair–good; eating difficulties may be severe
Ameloblastic odontoma	<3	Benign/locally invasive	Surgical excision/ hemimandibulectomy ± radiation	Fair–good; eating difficulties may be severe
Cementoma		Benign; onset uncertain	Surgical removal	Good
Complex odontoma	<5	Benign malformation	Surgical removal	Fair (if removal feasible)
Compound odontoma				
Cysts/hamartoma		Various benign	Surgical removal	Fair (if removal feasible)

Table 28.2 Case reports/series of odontogenic tumours in the horse

Ref. No.	Age (years)	Sex	Breed	Presenting sign	Tumour type/ location	Treatment	Outcome
20	11	F	Oldenburg	3-month history of weight loss, swelling posterior right mandible	Ameloblastic odontoma	None	Euthanized
21	1.5	F	XB	Marked left mandibular swelling, profuse salivation and inability to eat/ drink. Painful, malodorous mass on mandible	Odontogenic myxoma	None	Euthanized
22			Pony		Ameloblastic odontoma		
23					Ameloblastic odontoma		
24	4 months	Colt	ArabX	Swelling right side face at 2 months, non-painful, firm, serous nasal discharge	Ameloblastic odontoma	Surgical resection	Euthanasia at surgery
25	5	G			Ossifying ameloblastoma		
26	4	F	QH	Hard mass right premaxilla slow growing for 2 years	Complex odontoma	Surgical excision	Survived
27	2	M	Morgan	Pain and irritation on using bit, swelling right maxillary region over 1st upper cheek tooth. Firm, non-painful	Complex odontoma	Surgical excision	No regrowth at 1 year
28	18(a)	G	SB	Multiple well-circumscribed round opaque masses surrounding roots of incisors (a+b) or premolars (c), deformation of bone, malocclusion and pain	Cementoma	Affected tooth removed by surgical extraction	Survived
	17(b)	M	SB				Survived
	2(c)	F	Holstein				Euthanized due to post-surgical complications
29	21	G	Arab	A 2-year history difficulty chewing, malodorous breath, severe tartar of maxillary and mandibular incisors, gingivitis and fractured 102	Cementoma	Surgical excision	Survived
30	9 months	Colt	QH	Chronic enlargement of right mandible present 6 months, no effect on mastication	Compound odontoma	Surgical removal	Survived, no recurrence at 3 years
	11 months	F	QH	Firm mass left maxilla of 7.5 months' duration, left mucopurulent nasal discharge, decreased airflow from left nostril, increased left SMLNs	Compound odontoma	Surgical removal	2nd surgical procedure, 5 months later, no recurrence at 4 years

Continued

Table 28.2 Case reports/series of odontogenic tumours in the horse – cont'd

Ref. No.	Age (years)	Sex	Breed	Presenting sign	Tumour type/ location	Treatment	Outcome
31	30	F	QH	Expanding mass L maxilla <1 month duration, firm, hard palate displaced medially, no history of dysphagia	Ameloblastic carcinoma: immunolabelling vimentin/CK+, CK5/6, CK14+ve	Cisplatin intralesional ×2 at 2-week intervals (conservative treatment opted for because of age)	No response – euthanized
32				See also Gardner DG. An orderly approach to the study of odontogenic tumours in animals. J Comp Pathol 1992; 107(4):427–438	Ameloblastomas in horse: critical review (published previous cases + 1 new case)		
33				L mandible	Ameloblastoma + hypercalcaemia of malignancy	Surgical removal, resolution of hypercalcaemia	
34	10	F	TB	Purulent nasal discharge, boney distortion over frontal and maxillary sinus, exophthalmus, obstruction of nasal passage and inspiratory/ expiratory stridor	Cementoma	Surgery	
	9	G	TB		Cementoma		

Ameloblastoma

See also page 323.

Disease summary

Notes

More common in older horses but can also be in younger ones.

Clinical features

Rapidly or slowly expanding boney swelling in upper or lower jaw with a progressive destructive behaviour. Early identification is unlikely.

Diagnostic confirmation

Radiography shows radiodense mass at the base of a tooth. Overt swelling noticeable late in course of disease. May cause malocclusion and oral pain late in course of disease. Biopsy is definitive.

Management

Removal of tooth and lesion in their entirety is usually curative. Chemotherapy is usually unrewarding.

Prognosis

Prognosis is very poor unless diagnosed very early and depends on the ability to remove affected tooth.

Description

These tumours are derived from odontogenic epithelium. True ameloblastoma produce no inductive changes in the connective tissue and so lack dentin and enamel.

These are commoner in the mandibular region of older horses, but can involve the maxilla and the medullary cavity of the mandible.[22,25,35–38] Several cases have also been reported in young foals.[23,24]

Clinical features

- May be overtly tooth-like or very mixed masses with no obvious dental tissue
- Often develop a central cystic region and cause bony/ solid swellings and abnormalities in the associated dental arcade
- Occasionally can present with a discharging sinus on the side of the face
- Late presentation shows an advanced and aggressively destructive fibroblastic tumour and embedded teeth with extensive bone loss (Figs 28.3, 28.4).

Differential diagnoses

- Ossifying fibroma and other tumours of the jaw, such as invasive squamous cell carcinoma and myxomatous tumours (although the latter tend to be destructive rather than proliferative)
- Osteosarcoma singularly rare in the horse
- Infections of tooth roots, radicular cysts and adjacent bone can be similar but are associated with extensive necrosis and typical radiographic features often complicated by maxillary reactive bone proliferation with obvious facial swelling
- Jaw fractures and other dental abnormalities, including malerupting and supernumerary cheek teeth, should also be considered.

Diagnostic confirmation

- Biopsy and radiographic findings are typical but can be similar to other tumour masses.

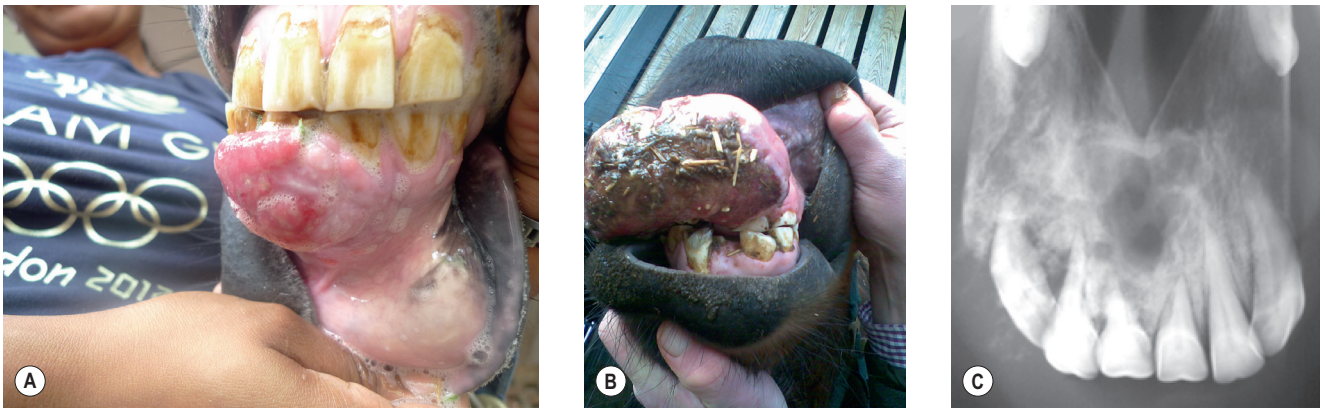


Figure 28.3 Ameloblastoma. Ameloblastoma is a progressive and potentially aggressive and destructive soft tissue tumour of the mouth. Typically, ameloblastomas start slowly and are often overlooked at the early stages. **(A)** This 13-year-old horse was presented with an ill-defined proliferative mass on the right rostral mandible that was identified incidentally during a routine dental examination and confirmed as an ameloblastoma by histological examination. **(B)** This more advanced ameloblastoma in an aged gelding caused extensive local tissue destruction with loss of the incisor teeth. **(C)** Radiographical evidence of bone destruction and tooth loosening is usually identified, as in this case of a 10-year-old Thoroughbred. Notice the characteristic multiloculated appearance with radiodense areas. *(Figure A courtesy of Fernanda Sepulveda; Figure B courtesy of Chris Green; Figure C courtesy of Bruce Bladon, reprinted from Easley J, Dixon P, Schumacher J. Equine Dentistry. Edinburgh: Saunders; 2011: 158 (Fig. 11.6B), copyright 2011, reprinted with permission from Elsevier.)*

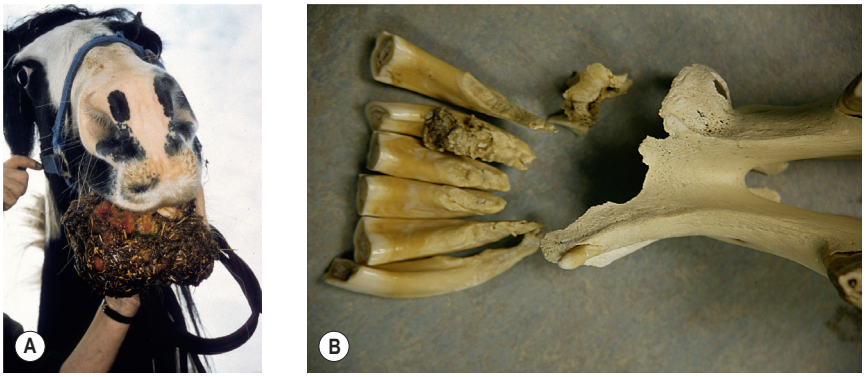


Figure 28.4 Ameloblastoma (advanced). **(A)** This 19-year-old Shire horse was presented with a massive neglected ameloblastoma, which had developed over a 3-year period from a small focal swelling that bled occasionally. The diagnosis was confirmed by biopsy. The horse had serious difficulty eating and had lost a significant amount of its bodyweight. No treatment was attempted. **(B)** The tumour caused extensive incisive/mandibular bone destruction and the teeth were loosely embedded within the tumour.

- Ameloblastoma usually has a rubbery consistency and a roughly spherical or multilocular shape with a cystic radiographic appearance. Odontomas are radiolucent or partially mineralized with foci of enamel tissue mixed throughout. Even when there is extensive ulceration, there should be little confusion between this and carcinomas or sarcomas, which are much more destructive than tumours of dental origin.

Management and prognosis

1. Surgical removal can be curative if treatment is initiated early and wide excision can be performed. Horses seem to cope well with rostral hemi-mandibulectomy and especially so if the mandibular symphysis is intact.
2. Bilateral rostral mandibulectomy can also be successful but special measures will be required to support adequate nutritional intake.
3. Radiation is probably the best option and has been used successfully.[39,40]
4. Topical chemotherapy is invariably unsuccessful.

The expansile nature of these tumours and their late recognition (particularly when they occur in foals and young horses, which would not necessarily be examined closely) make the outlook generally poor. Many horses are euthanized soon after they are diagnosed with the tumour, although the rate of growth may be slow and some useful quality of life may be possible even if surgery is not feasible.

Palliation is also possible with surgical tumour reduction using diathermy or laser procedures.

Cementoma

See also page 327.

Description

Cementoma is a very rare odontogenic neoplasm of mesenchymal origin without epithelial components. It is a slow-growing tumour arising from cementoblasts and was first described in humans in 1930.[28] It typically occurs in the root region of the developing tooth and is characterized by deposition of differentiated cemental matrix around the tooth root, proliferation of cementoblasts, and destruction of the lamina dura. In horses, there are few published reports, characterized as incidental radiological and macroscopic findings. More recently, a report described three cases in horses with multiple boney enlargements of the upper and lower jaw extending into the oral cavity, pain

and malocclusion.[28] It is possible that some of the features of this condition could be found in abnormal or supernumerary cheek teeth, where extensive distortion of the dental structures is encountered. However, it is often impossible to confirm the diagnosis or to differentiate it from dental abnormalities.

Based on a small number of case reports/series, ages reported have ranged from 2 years to 21 years old, with the majority being older horses.

Disease summary

Notes

Benign, odontogenic tumour.

Clinical features

Firm painless, slowly expanding swelling over maxillary cheek teeth or premaxilla.

Diagnostic confirmation

CT, radiography and biopsy (biopsy is difficult).

Management

Surgical removal is effective.

Prognosis

Prognosis is good provided that the tumour is accessible.

Clinical features

- Cementoma present clinically as boney swellings of the upper and lower jaw. However, the location of these tumours (at the base of the tooth) makes their early recognition and diagnosis unlikely. Only when there is overt swelling can the possibility be explored. Radiographically, they have a distinctive well-circumscribed opaque appearance without intact lamina dura and the tissue contains sheets of cementum-like material (Fig. 28.5).
- Secondary alveolar changes involving either infection or reactive bone proliferation may make them harder to recognize.
- Alterations in the crown structure are unusual but will make the condition more recognizable clinically.

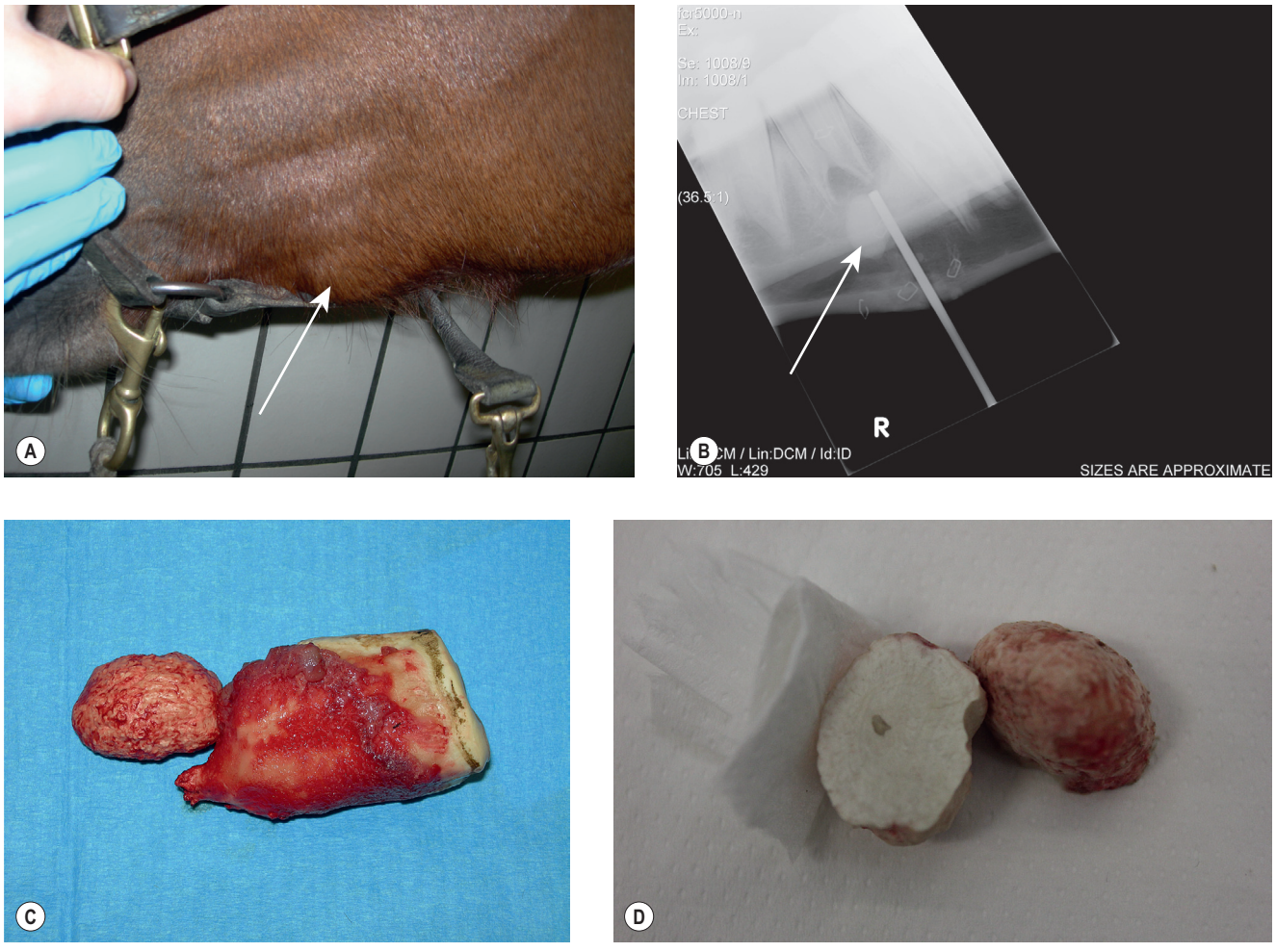


Figure 28.5 Cementoma. **(A)** During a routine dental examination, a solid swelling was identified in the left mandible at the position of 307 (second lower left cheek tooth) (arrow) in a 7-year-old Swiss mare. **(B)** An oblique projection radiograph was taken and revealed a solid well-defined mass (arrow). **(C)** The 307 premolar was removed and the tumour could then be removed in turn. **(D)** Typically, cementoma is a very solid mass with a dense bone-like structure. Histological confirmation can be difficult. *(Figures courtesy of Gabor Bodo and Christoph Koch, VetSuisse, University of Bern.)*

Management and prognosis

1. Removal of the tooth and lesion in its entirety is curative and feasible, but may be hindered by the ball-like aggregation of hard tissue at the tooth root.
2. Some cases remain unaffected for many years, with the condition being identified incidentally or at post-mortem examination.
3. May be associated with malocclusion of teeth and local pain, which may lead to clinically significant secondary effects, such as weight loss. Therefore, treatment should be attempted.
4. Prognosis will depend on the possibility of removal of the affected tooth.

Complex/compound odontoma

Disease summary

Notes

Rare tumour of dental structures.

Clinical features

Firm painless swelling over maxillary cheek teeth or premaxilla.

Diagnostic confirmation

CT, radiography and biopsy.

Management

Surgical removal can be effective but multiple surgical procedures may be necessary.

Prognosis

Prognosis is fair to good.

Description

Tumours in which epithelial components coexist with formation of dental matrix structures, such as dentin and enamel, are named 'odontoma'. Odontomas are further subdivided according to morphological features and degree of organization.[26,27] Compound and complex odontomas are the most differentiated of dental tumours. All features of normal odontogenesis, such as ameloblastic epithelium, organized dentin matrix formation and enamel matrix formation, are seen. Complex odontomas lack the formation of tooth-like structures, known as 'denticles', which are characteristic of compound odontomas. Complex odontoma contains all the elements of a normal tooth but the structure is chaotic. Compound odontoma is similar, except that the tissue is organized into recognizable tooth-like structures (denticles), although they may be grossly distorted. There is a marked inductive effect on mesenchymal tissue and there is some justification for considering some of them to be hamartomas of dental tissue rather than tumours. The aetiology of odontomas is unknown. Local trauma or infection has been suggested.

Occurrence

Both young and older horses may be affected, with a greater prevalence in younger animals.

Clinical features

See Figure 28.6.

- Many cases are identified incidentally.
- Firm painless swellings over the root regions of the maxillary cheek teeth or the premaxilla are characteristic.[26]
- Swelling may not be obvious if the more caudal four cheek teeth are involved as the expansion would be contained in the maxillary sinuses.
- Secondary sinusitis seems to be a rare complication.
- Other clinical abnormalities reported include lethargy, dysphagia and perialveolar swelling.[30]

Differential diagnoses

- Tumours of bone origin, such as osteoma
- Tumours of soft tissue origin, such as ossifying fibroma or other primary dental tumours

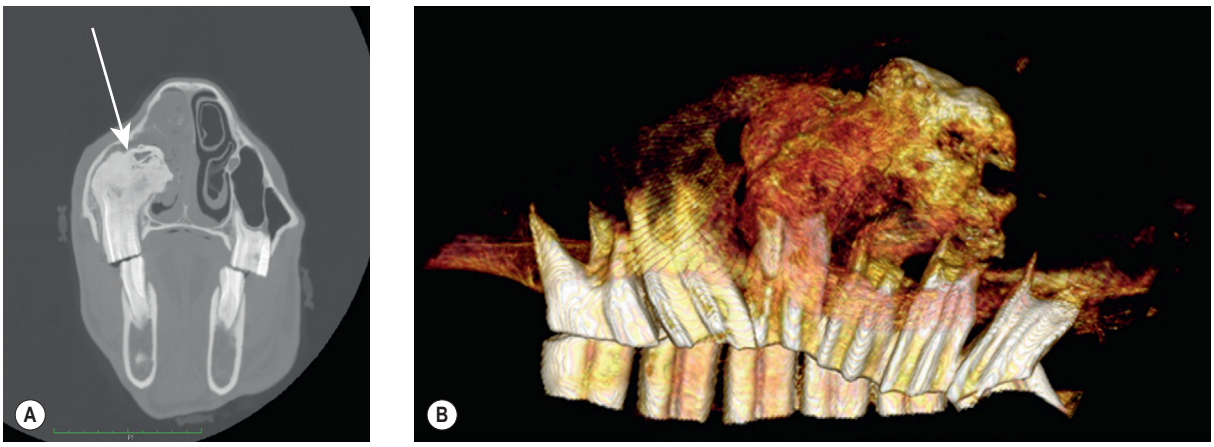


Figure 28.6 Compound odontoma. A 22-year-old Dales pony gelding was presented with a long history of a fetid left unilateral nasal discharge and facial swelling, associated with the region of the rostral maxillary sinus and rostral maxilla. The left nasal cavity was completely occluded. A preliminary radiographical study showed an ill-defined radiodense mass associated with 207 and 208. A computed tomography study was used to guide the choice of treatment. **(A)** A radiodense mass is visible intimately associated with the root of 207 (arrow). **(B)** A 3-D reconstruction confirmed the full extent of the tumour. The mass was relatively well-defined and was removed along with 207 and 208 and the pony recovered well, with no significant after-effects. A diagnosis of a complex odontoma was made histologically. This is a disorganized tumour containing the elements of a normal tooth.

- Primary dental disease with new bone formation and lysis should be considered
- Sinus cysts may be related to odontoma in some cases.

Diagnostic confirmation

Diagnosis can be confirmed by a combination of radiographic findings and histopathological examination. The radiographic and CT appearance is characteristic – multiple small lobulated masses within a well-defined cyst-like structure at the root of a maxillary tooth are typical (see Fig. 28.6). Interpretation of the area becomes difficult, as secondary changes occur in the adjacent teeth and sinuses.

Management and prognosis

1. Surgical removal may be feasible and curative, since the tumour is usually benign, but the extent of the tissue involvement will be an important factor. Multiple surgical procedures may be necessary and aftercare may be prolonged and complicated.
2. The outlook is reasonable or even good, although there are insufficient reports to establish a definitive prognosis.[30]

Incidental tumour-like dental masses

Description

This group includes radicular cysts and temporal teratoma. Temporal teratoma is a rare curiosity in the horse, in which dental tissue (which may be instantly recognizable as such) is located at sites away from the jaws (Fig. 28.7). The commonest site is in the temporal region where a sinus tract discharges glairy, milky material from a discrete opening on the leading edge of the pinna. The cystic structure may be situated some way from the ear itself but, sometimes, there is an obvious dental structure located against or attached to the temporal bone of the calvarium. Sometimes, the structure has no obvious dental tissue and comprises a smooth cystic lining lying below the ear.

Clinical features

These are rare lesions that present as open masses or cystic cavities of the temporal region ventral to the ear canal. They are lined by stratified squamous epithelium and often (but not always) contain abnormal dental structures (see Fig. 28.7).[41–44]

Diagnostic confirmation

1. The clinical features are distinctive.
2. Radiographs are used to establish the presence or absence and the location of any dental tissue. Contrast radiography can be helpful prior to surgical removal.
3. CT imaging is very helpful in establishing the presence and location of any dental remnant.

Management

1. *Surgery*: Temporal teratoma can carry a good prognosis with surgery, particularly where the condition is simply a cystic structure, although every part of the cystic lining must be removed to avoid recurrence. However, where aberrant tooth material is enclosed within a false alveolus originating from the calvarium (see Fig. 28.7B), surgery becomes much more of a challenge. Such cases must be fully assessed by CT scan if possible or at least by radiography (possibly with contrast material introduced via the sinus tract). In some cases, the cyst and the tooth-like structures are not obviously connected.
2. *Benign neglect*: Some cases can justifiably be left alone, since the discharging tract is usually a cosmetic and management nuisance rather than being clinically significant.

Prognosis

The prognosis is good.

Neoplasia of soft tissue origin

Overview

Soft tissue tumours of the mouth are far more common than those affecting the teeth and bones of the face, and those reported include squamous cell carcinoma, sarcoid, fibroma/sarcoma, melanoma, ossifying fibroma (juvenile mandibular ossifying fibroma, JMOF), myxoma complex neoplasms, haemangiosarcoma and salivary adenocarcinomas. Other secondary neoplasms may also develop in the mouth.



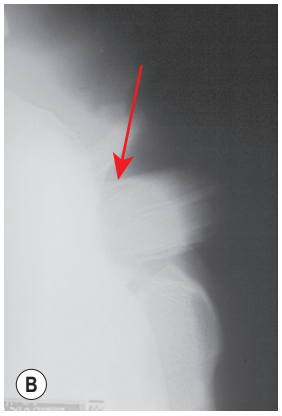


Figure 28.7 Temporal teratoma/cyst. **(A)** A temporal teratoma/cyst usually opens onto the skin on the leading margin of the ear (white arrow). In this case, there was no dental remnant. **(B)** Here, the discharging sinus was the same, but a solid mass was palpable below and slightly rostral to the ear. A pseudoalveolus and a tooth-like structure attached to the cranium was identified radiographically (red arrow).

Squamous cell carcinoma

See also pages 221, 575 and 630.

Disease summary

Notes

This is the most common oral neoplasm.

Clinical features

Initially proliferative mass, becoming destructive and ulcerative, infiltrating tissues of mouth; characteristic foul odour.

Diagnostic confirmation

CT and biopsy are definitive.

Management

Surgery on its own is usually unsuccessful; adjunctive local chemotherapy and/or radiation are essential.

Prognosis

The long-term prognosis is generally poor.

Description

Squamous cell carcinoma is a malignant neoplasm of stratified squamous epithelium that appears to have a predilection for mucosal junctions.

Occurrence

Squamous cell carcinoma (SCC) is probably the commonest oral neoplasm. Although mucocutaneous junctions are commonly involved outside the mouth, where there is an apparent correlation with non-pigmented skin and possibly with high levels of ultraviolet light, many of the most severe and aggressive tumours occur within the mouth.[10] The role of ultraviolet light in the pathogenesis of facial and lip carcinoma is uncertain but the Clydesdale breed and horses with non-pigmented skin of the face and lips are more often affected than other breeds and colours (Fig. 28.8). Putative carcinogens include chronic irritation such as epulis, foreign body reactions, chronic wounds and possibly dietary factors. Older horses are more likely to be affected.

There is often a suggestion that the primary tumour develops in the paranasal sinuses or nasal cavity and the destructive tissue involves the hard palate, but it may be difficult to identify whether the primary lesion is in the sinus or the palate.[45] SCC possibly arises in chronically irritated hyperplastic alveolar epithelium in cases of chronic periodontitis. The pathogenesis of squamous cell carcinoma remains uncertain.



Figure 28.8 Oral squamous cell carcinoma. This is a typical oral squamous cell carcinoma developing an invasive and destructive character in the lip region of an 18-year-old Clydesdale cross gelding. Note the lack of skin pigment at this site. Local lymph node involvement was obvious and confirmed on biopsy. The condition was managed on a palliative combination of intralesional chemotherapy using slow-release 5-fluorouracil and cisplatin and topical 5% 5-fluorouracil ointment, but the condition progressed over 3 years to this stage, by which time there was involvement of local and remote lymph nodes and the horse was systemically affected.

Clinical features

- Characteristically slow growing but occasionally show a more rapid course.
- May be proliferative, at least initially, but usually become very destructive, ulcerative and infiltrate widely into local tissues of the mouth, including the lips, buccal mucosa, hard palate and tongue.[46]
- Early lesions may simply resemble a non-healing wound, but more advanced, destructive carcinomas have a characteristic foul odour.
- Metastases to local lymph nodes can occur, although this is probably rare.[47] In theory, at least, they may disseminate to the lungs and elsewhere but this is also unusual.[48]
- Oral SCC may involve the lips or tongue (see Fig. 28.8), hard palate or gingiva and soft palate (Fig. 28.9).[49]
- Quite common for oral SCC to invade the nasal cavity and the paranasal sinuses (often to the point of gross distortion or obstruction to airflow).[50] Some involve the hard palate, base of the tongue (see Fig. 28.9G) or pharynx (see Fig. 28.9D,E) and can have serious physical effects on their function.
- When nasal cavity and paranasal sinuses are involved, there may be altered airflow (or even complete obstruction of the ipsilateral nostril).
- Pharyngeal and lingual cases may present with dysphagia of progressive, insidious onset. In all cases, weight loss and poor general health are common.
- More extensive spread may involve the orbit and the calvarium with secondary involvement, respectively, of the eye or the brain when the cribriform plate is eroded by tumour.
- It is also quite common for nasal SCC to invade the hard palate forming an oronasal fistula (see Fig. 28.9).
- In all cases, there may be extensive soft tissue disruption and consequent loosening/shedding of the teeth (see Fig. 28.9).
- The location of SCC often means that the tumours are frequently detected late in their course when a large invasive mass may already be present projecting from the gum or hard palate as a greyish, ulcerated and bleeding mass. Where the tumour surrounds a tooth, this may become dislodged.
- In almost all cases, there is a fetid odour from the mouth. Early tumours are often identified incidentally during routine dental procedures.
- Involvement of the lips and gums is usually clinically obvious but, nonetheless, late presentation is common.

Differential diagnoses

- Other proliferative and invasive lesions of the lips, including equine sarcoid, haemangiosarcoma, basal cell carcinoma and myxomatous tumours
- Non-healing oral wounds may be confused with early cases and carcinomatous changes may be a significant reason for incipient wound healing failure.

Diagnostic confirmation

- Biopsy provides a definitive diagnosis in all cases. Biopsy sites should be carefully chosen to obtain

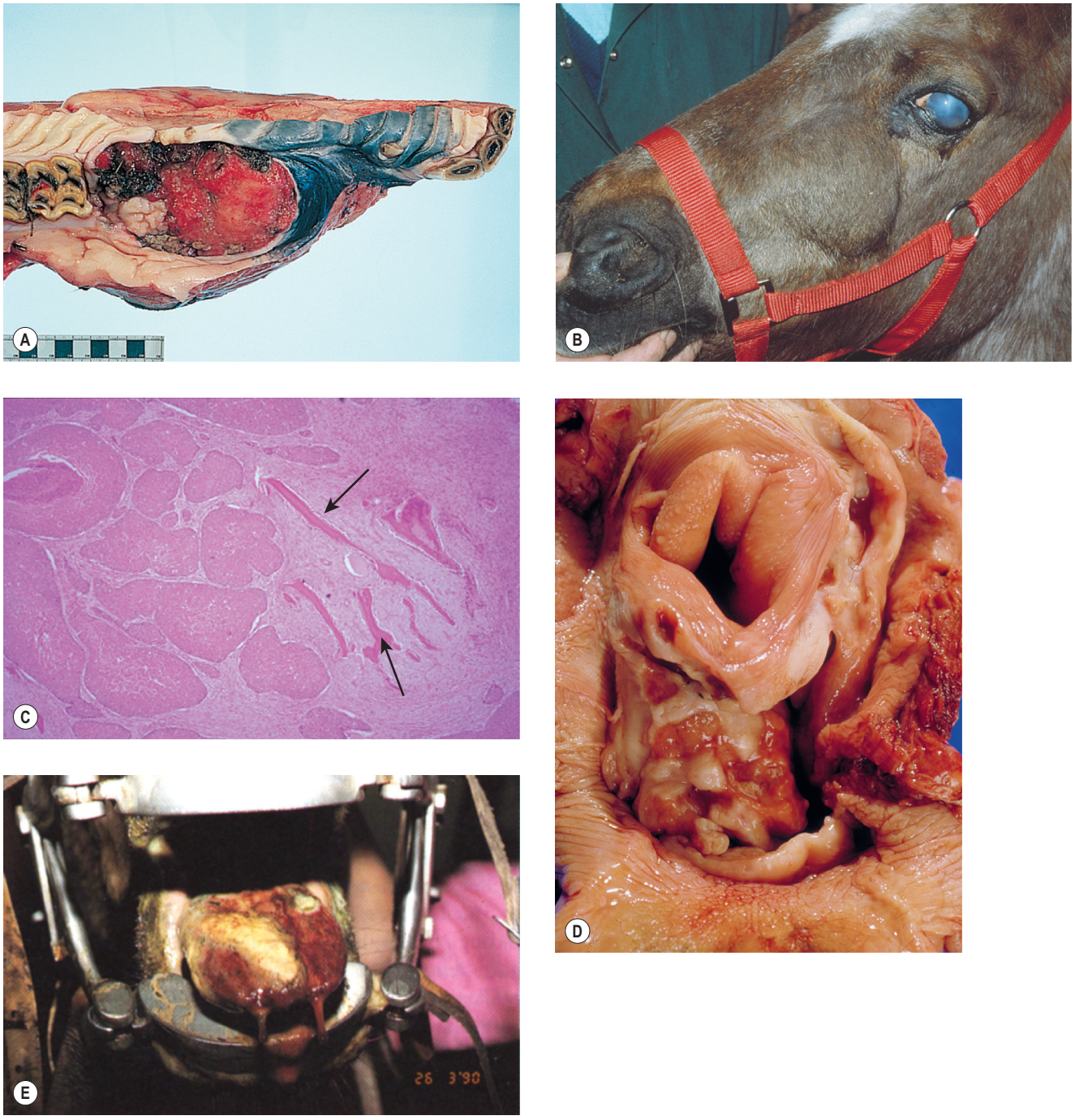


Figure 28.9 Carcinoma of the hard palate. A 23-year-old pony gelding was presented with a facial swelling and dysmasesis. There was extensive destruction of the palate and loss of the three rostral maxillary teeth with oronasal fistula. **(A)** A destructive carcinoma on the lip of a 23-year-old pony gelding. Note the extensive tissue destruction and the loss of the maxillary teeth. Treatment with intralesional cisplatin and topical 5-fluorouracil was not effective. **(B)** Facial distortion due to nasopalatine squamous cell carcinoma in a 12-year-old pony gelding. **(C)** A histological section of the endonasal carcinoma shown in (B). Solid cords of squamous carcinoma are surrounded by fibrous stroma and trabeculae of non-neoplastic reactive bone (arrows). **(D)** Squamous cell carcinoma of the pharynx, which was identified some 3 months after a lesion had been detected in the hard palate. It is possible that this developed independently or that it was an extension of the earlier lesion. **(E)** Carcinoma of the free portion of the tongue. The local lymph node was enlarged (see I).

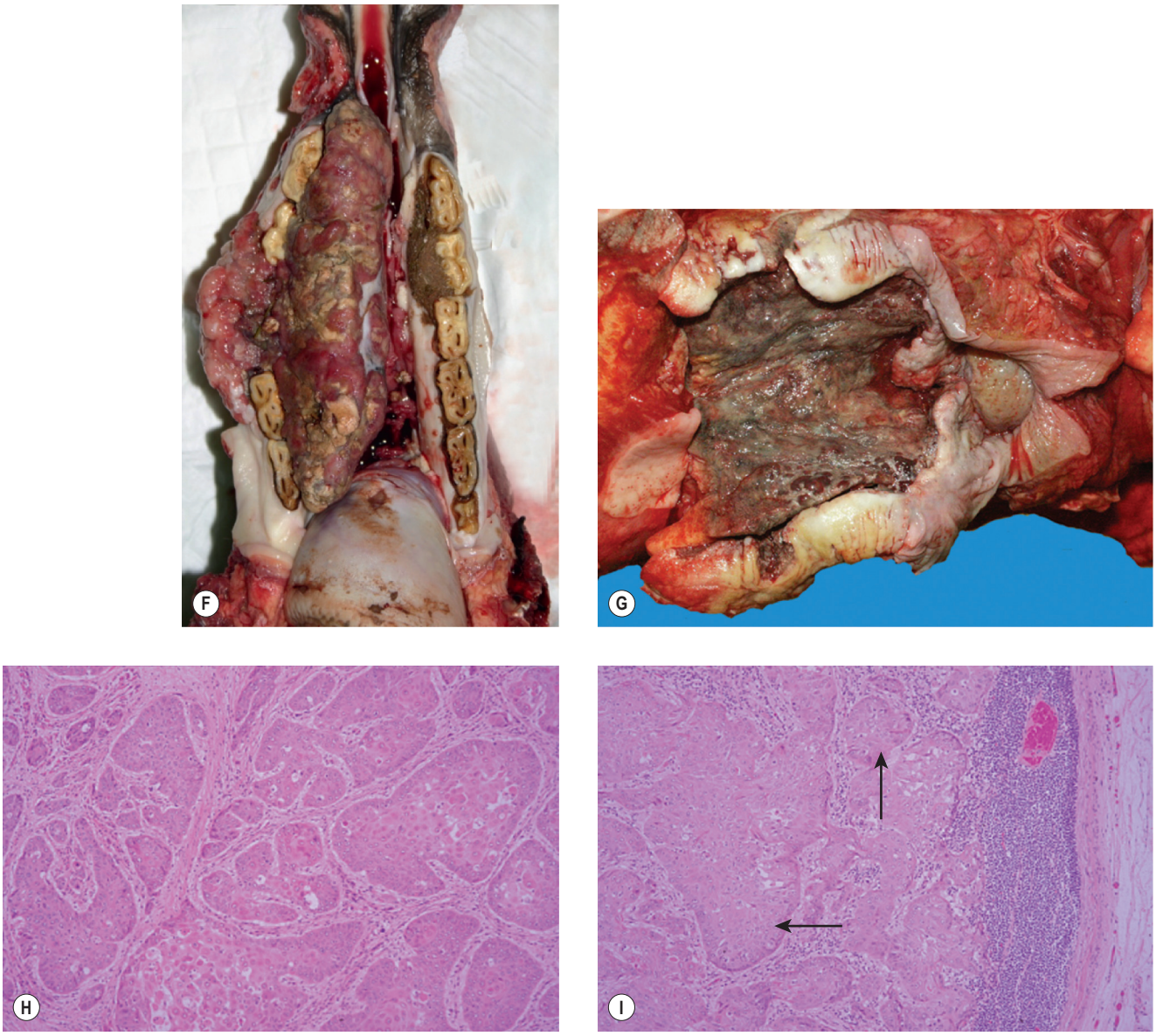


Figure 28.9 cont'd (F) This highly destructive oral carcinoma developed in a 4-year-old Warmblood. It involved the maxillary bone and resulted in dental problems. **(G)** This horse was presented with weight loss and dysphagia. The highly destructive oral and invasive carcinoma was not visible endoscopically from the pharynx and was only seen with difficulty during an oral examination. **(H)** A photomicrograph of cords of solid squamous cell carcinoma with deep invasion of the tongue. **(I)** Metastasis of squamous cell carcinoma to regional lymph node showing cords of tumour cells (arrows) beneath cortical lymphoid tissue. *(Figures reprinted from Easley J, Dixon P, Schumacher J. Equine Dentistry. Edinburgh: Saunders; 2011: 164–165 (Fig. 11.13), copyright 2011, reprinted with permission from Elsevier. Figure E courtesy of Dr RR Pascoe; Figure F courtesy of Chris Louf.)*

representative tissue with inclusion of a marginal (shoulder) zone. Punch or wedge biopsy sites should not be scrubbed or even washed before collection and should not be sutured afterwards since wound dehiscence is almost certain.

- Fine-needle aspirates and impression smears can be used but may be misleading, since they often consist mainly of stroma and inflammatory cells. Usually there is no need for this type of non-invasive sampling because the tumours are usually large and accessible.
- Radiographic examinations can be used to identify masses in the sinuses and the extent of bone destruction produced by invading carcinoma.
- CT and MRI are very useful, particularly for masses involving the pharyngeal/lingual regions and cases presenting with dysphagia. These methods help to identify and define the extent of the lesion, and also help to inform therapeutic choices.

Management

1. Surgery
   - While surgical excision of oral SCC lesions has been reported to be successful, complete surgical removal can be very difficult and, in certain inaccessible sites, it is clearly impossible. There is a very high rate of recurrence following such attempts.[51]

Small discrete tumours may, however, be amenable to surgical removal, and extensive excision involving hemimandibulectomy, such as has been described for other tumours of the jaw, will also possibly resolve the condition but may leave an unacceptable cosmetic or functional deficit.

2. Radiotherapy
   - Squamous cell carcinoma is relatively sensitive to gamma radiation and this offers the best prognosis, with a reasonably high success rate (DCK, unpublished observations).
   - Teletherapy is logical and can be finely controlled, but repeated fractionated doses need to be used. The horse therefore needs repeated general anaesthesia. The number of centres where this can be performed is very small and the procedure is necessarily expensive.
   - Simpler iridium-192 interstitial brachytherapy using linear platinum-sheathed sources has been used to good effect (DCK, unpublished observations) on small localized tumours. There are serious logistic and human health risks involved with the procedure, however, and limitations on the size and location of the tumours that can be treated. Placement of the sources within the highly mobile tissues of the mouth carries serious dangers if the horse were to dislodge the wires and swallow them.
3. Chemotherapy
   - Cisplatin, 5-fluorouracil and mitomycin-C have all been used in various intralesional or topical formulations for cutaneous and other carcinomas. Some SCCs respond well to intralesional cisplatin, either in water-soluble form using frequently repeated injections, or as a stable emulsion containing at least 3 mg/mL with an equal volume of sesame or almond oil (see p. 149), or in biodegradable bead or pellet forms.[52] The use in oral SCC has not been reported, but all these materials carry operator safety hazards. Their use should be restricted to specialist centres for oncology. There is no justification in human risk.
   - Topical applications of 5-fluorouracil cream have been reported to be successful or partially successful in the management of buccal, oral or other facial SCC.[53] Cures may, however, be difficult to effect using this alone. It is probably best viewed as an adjunctive or palliative approach with other forms of treatment, such as surgical tumour reduction, intralesional chemotherapy and cryotherapy. It may be particularly applicable to small, ulcerated, buccal and lip lesions because the accessibility of the site is clearly a major factor.

Prognosis

- Oral SCC is a low-grade locally invasive tumour that is usually slow to metastasize; while the clinical prognosis is inevitably poor, many cases can survive long periods even with quite extensive involvement (see Fig. 28.9).
- It tends not to metastasize beyond the local lymph node. However, it is probably unwise to assume that this will be the case in all affected patients.
- Secondary complications, such as facial or oral distortion and destruction, dysphagia, loosening of teeth and nasal obstruction, inevitably add significant complications and suggest a poorer prognosis.

Sarcoid

See also pages 204 and 545.

Disease summary

Notes

A common skin tumour that rarely affects the mouth itself.

Clinical features

Subcutaneous nodules on cheek or within lips, with an ulcerated surface, are the commonest oral manifestation of sarcoid.

Diagnostic confirmation

Characteristic features with lesions at other sites usually assumed to be sarcoid. Single lesions in the mouth are very rare and biopsy may be necessary to guide the treatment plan; biopsy may exacerbate the lesion.

Management

Surgical tumour reduction in combination with chemotherapy, immunomodulation or radiation.

Prognosis

Very guarded, since buccal sarcoids have a higher propensity for the development of the malignant form.

Description

There are usually two distinct forms of sarcoid that affect the mouth itself (as opposed to the skin of the lips and cheeks).

The nodular form remains subcutaneous, and is most often located at the angle (commissure) of the mouth or the cheeks and may extend into the mouth (see Fig. 28.10A). The verrucose form often involves the perioral skin. In the perioral skin and the tissues of the cheeks, in particular, it often has a highly invasive behaviour, then being classified as malignant sarcoid; it can also ulcerate into the mouth.

Clinical features

- Intracutaneous or subcutaneous nodules on the cheek or within the lips, with an ulcerated surface, are the commonest oral manifestation of sarcoid (Fig. 28.10). The nodules frequently ulcerate either on the cutaneous surface or into the mouth (see Fig. 28.10).
- The verrucose form is also a common type in the perioral skin but does not often involve the oral mucosa.
- Where the lesions are fibroblastic or mixed, a deeper component can be expected and should be considered carefully (see Fig. 28.10).
- Combinations of nodules within the skin and cutaneous involvement of verrucose sarcoid are also common (mixed sarcoid).
- The fibroblastic forms also occur in the perioral tissues and appear as a fleshy ulcerated mass of friable and

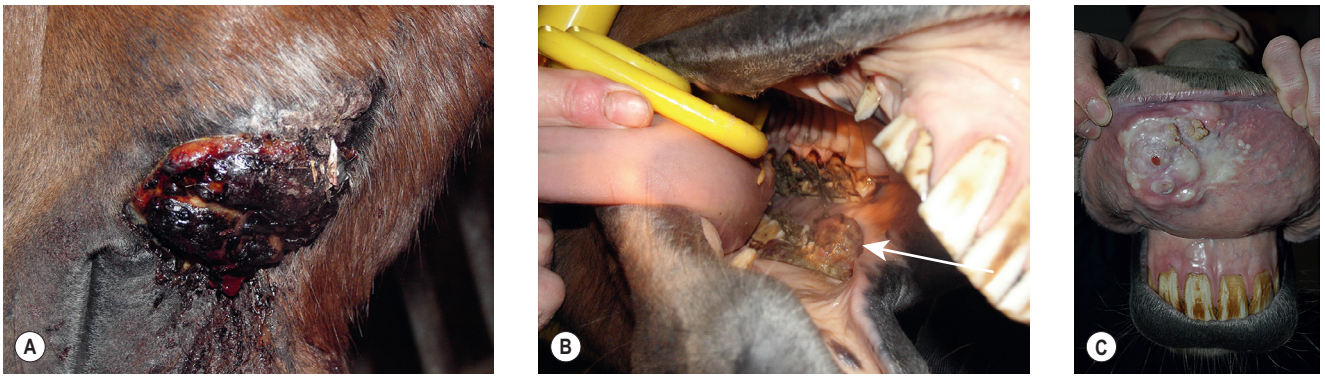


Figure 28.10 Oro-facial sarcoid. **(A,B)** Sarcoids occurring on the face commonly invade the muscles of the cheek and lips and may extend into the mouth. A 5-year-old gelding had a long history of a small localized facial sarcoid. This suddenly became aggressive and rapidly invaded into the mouth (arrow). **(C)** This lip sarcoid appeared to be predominantly nodular in type but it had a deep and aggressive base extending into the mouth.

easily traumatized tissue that is similar to granulation tissue; this form often develops subsequent to trauma or failed/partial treatment attempts of other types. They can extend rapidly into the mouth (see Fig. 28.10).
- The malignant form usually comprises various combinations of the sarcoid types but is highly invasive and nodules may be linked by cords of sarcoid tissue (see Fig. 31.12).

Primary sarcoid has not been reported on the tongue, gingiva or palate.

Differential diagnoses

- Viral papilloma
- Nodular forms may appear clinically similar to melanoma and mastocytoma or localized lymphoma
- Fibroblastic and nodular forms may resemble oral fibroma, basal cell carcinoma and inflammatory nodules (e.g. foreign body and parasitic granuloma) and granulation tissue arising from any cause.

Diagnostic confirmation

- Intuitive tentative clinical diagnosis is usually easily established:
  - Horses with a single sarcoid lesion located in the mouth without any other lesion are very unusual.
  - Horses that have the characteristic features and show lesions at other sites can usually be assumed to have sarcoid.
- The histological features are characteristic and, provided that a suitable contingency plan for treatment is ready prior to the results of biopsy, then it should be a logical diagnostic step. However, biopsy is not usually recommended because there are recognized dangers with biopsy of sarcoids.[54] Where the diagnosis is in significant doubt, a biopsy can be taken as long as there is a plan for treatment following diagnostic confirmation.

Management

See also page 555.

Treatment of buccal forms of the disease is notoriously difficult.

The options are limited and, in spite of countless anecdotal treatment successes, there is little established evidence for any treatment option.

Referral to a specialist centre is probably justified simply on the grounds that failure of a treatment may result in significant exacerbation of the lesion.

All treatments carry a guarded prognosis, with surgery being the most difficult.

Benign neglect

In some cases, the lesions can justifiably be left alone in view of the risks of exacerbation by incomplete excision. However, inadvertent trauma can also result in severe and rapid deterioration and so early treatment of small accessible lesions is strongly recommended in most cases.

Surgery

See also p. 120 and p. 556.

Surgical options include sharp tumour excision, laser surgical excision or diathermy. Surgical procedures are usually limited by the extent of the tumour and the regional complications that may be present. For example, excision of an oral/facial lesion may leave functional deficits or neurological compromises when branches of the facial nerve are involved. Surgical tumour reduction can be combined with other treatment, including chemotherapy, immunomodulation and radiation. Such combinations usually have a better prognosis than the basic procedure on its own. The use of *Smart surgery* (see p. 123) significantly improves the outcome of all surgical procedures used to treat equine sarcoid at all sites.

Cryosurgery

See also p. 126.

Hyperthermia carries some chance of success, but is naturally constrained by the need to ensure the margin of the tumour is incorporated in the treatment zone.

Radiotherapy

See also p. 165 and Figs. 9.35 and 9.36.

This is undoubtedly the best treatment for oral/facial sarcoids using brachytherapy based on interstitial linear or pelleted radioisotopes with a gamma emission capability. Radiation has a cure rate of over 95% and the cosmetics of the method are impressive. The most frequent isotopes used

include iridium-192 and gold-198. The former is presented in linear sources sheathed with platinum that renders the isotope effectively a total gamma emitter. Gold-198 is used as pellets and has a very short half-life (48 h) and so this is logistically easier to handle (the sources do not need to be removed, but clearly this method carries much higher operator risks than the lower emissions over a longer period characteristic of iridium. Linear iridium sources are left in situ for the calculated period to deliver the required radiation dose and are then removed). During the treatment time, the horse must be confined within an approved radiation unit. Complications involving wire displacement and injury or colic during the treatment period can add considerably to the logistic problems. Teletherapy is an ideal method of treatment but there are very few facilities for this at this time.

Chemotherapy

See also pages 129 and 558.

Intralesional cisplatin using stable emulsions with sesame oil has recently gained a good reputation, but the method carries very serious carcinogenic risks for operators and handlers alike and should be limited to specialist equine oncology centres.[52]

Biodegradable beads containing cisplatin (Matrix II, Royer Biomedical Inc., MD, USA) or sponges with 5–fluorouracil have been used to generally good effect but correct placement is critical and intralesional retention is sometimes a problem. The use of cisplatin should be restricted to specialist institutes where facilities for faecal and urine disposal ensure that human risks are minimized. The risks with the bead systems are significantly less (see p. 151).

Topical cytotoxic chemicals

See also pages 153 and 558.

Examples including 5-fluorouracil, imiquimod (Aldara, Graceway Pharmaceuticals, LLC, Bristol, UK) and Xxterra® (20% zinc chloride and *Sanguinaria canadensis* root extract paste) have also been used with variable results.

- They all require repeated applications and penetration of lesions is difficult, so failures are common.
- Scarring is a major hazard, particularly if the cheeks are involved, and functional difficulties can arise.

Immunomodulation

See also pages 189 and 559.

Intralesional immune 'stimulants', such as mycobacterial cell wall extracts or Bacillus Calmette-Guérin (BCG) can be effective in some nodular or fibroblastic forms but the prognosis is far worse than the corresponding results from treatment of periocular sarcoids of the same type.[55] Treatment is tumour volume-related and so large lesions require more BCG material and, of course, each individual lesion requires its own injections (see p. 559). Repeated injections are invariably required and each one carries the risks of causing anaphylaxis. The possibility of anaphylactic reactions can be reduced (but probably not eliminated) by premedication with flunixin meglumine and dexamethasone intravenously some 15–30 min before the procedure is carried out. Ensuring true intralesional injection can also reduce the risks.

Other options

1. Photodynamic therapy (see p. 160)
2. Phytotherapy (see p. 194).

Note

Typically, for all cancer conditions (and probably for all medical disorders), homeopathy and herbal medicine are not effective and cannot be justified even on placebo grounds because the patient cannot make the choice for itself. They are uniformly useless and delay intervention, often to the point of rendering the tumour untreatable. Regrettably, this is a particularly common approach for equine sarcoid.

Prognosis

- The prognosis for any sarcoid is very guarded and is worse for sarcoid on the face and mouth.
- Recurrences are common and new lesions also develop in the treated or other (adjacent or remote) sites.
- While the malignant form carries a very poor prognosis, it is less common than is the case with the other variants, although the cheek area seems prone to the malignant form.
- The prognosis for oral or facial sarcoids is also related to the loss of effective use as a result of interference with tack. Lesions and scarring as a direct result of treatments at the angle of the mouth or in the cheeks can adversely affect the use of bits and harness.
- Repeated trauma from harness or other damage results in continued exacerbation.

Melanoma

See also pages 237 and 568.

Disease summary

Notes

A common tumour of skin and other organs in grey horses; sometimes in horses of other colours, including bay, chestnut, cremello/albino horses.

Clinical features

Commonest site in oral cavity is lips, but also reported in cheek, tongue, gingiva and parotid salivary gland. Identified on clinical inspection but often not noticed until large.

Diagnostic confirmation

Clinical features alone are usually distinctive but biopsy or fine-needle aspiration is diagnostic. Histology is important because they vary in pathological behaviour.

Management

Surgical removal of small lesions or troublesome larger lesions is advised as early as possible to prevent lesions becoming a clinically significant problem.

Prognosis

Prognosis is good if treated early and regularly when small in size but outlook for larger complex or badly located lesions is always guarded since most become malignant in time.

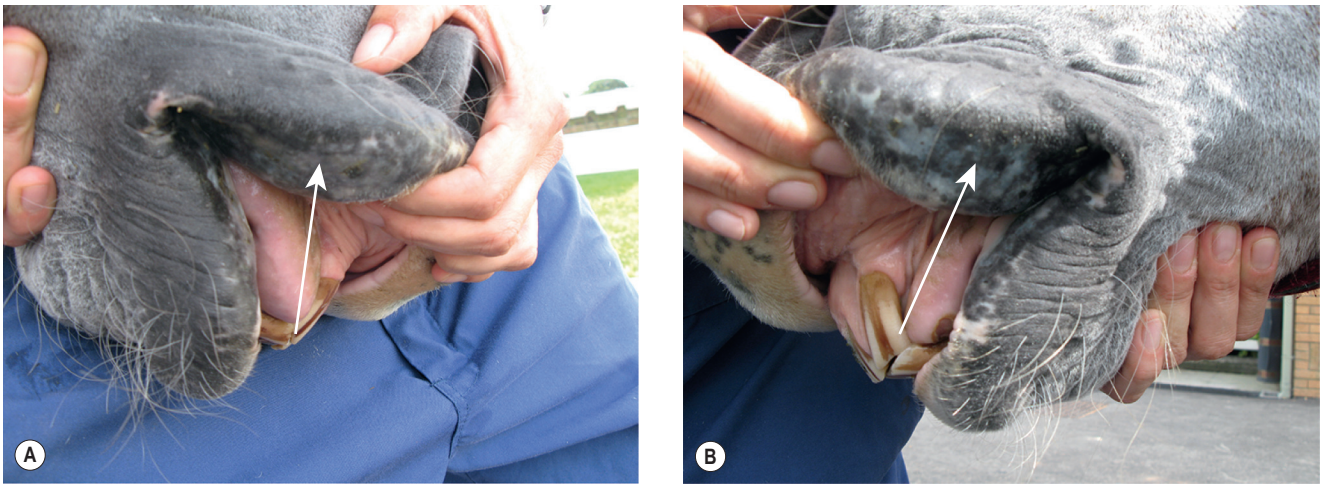


Figure 28.11 Multiple melanomas. (A,B) This 23-year-old grey gelding had multiple melanomas, including large more or less symmetrical tumours in both upper lips and a further ill-defined lesion in the lower lips on each side. They were asymptomatic and non-ulcerated.

Description

These are tumours of melanocytes occurring in the skin and in other organs (including the mouth and cheeks).

The majority of early melanomas are benign but some have an aggressive appearance and aggressive growth rate; these usually have a correspondingly aggressive pathological appearance. Generally, it is accepted that small early lesions are benign but that, with time, most become more malignant (whether or not they invade locally or metastasize to remote sites).

Clinical features

- Oral melanomas are usually benign initially and expand slowly but even histologically benign variants can reach considerable size. Surprisingly, tumours on the lips (Fig. 28.11) and gingivae are often only noticed when they are large.
- They mostly have no other systemic effects, although unrelated melanomas may develop simultaneously in other organs.
- Extensive lesions can develop in the parotid and pharyngeal lymph nodes and may extend into the parotid salivary gland either directly or by contiguous spread (Fig. 28.12).
- Melanomas affecting the masseter muscle and those that ulcerate into the mouth will usually affect mastication, even to the extent of causing weight loss and difficulty eating.
- In spite of the large size of some of these lesions, the clinical effects are usually minimal and relate simply to their space-occupying nature.

Differential diagnoses

- Equine sarcoid
- Mast cell tumour
- Lymphoma
- Parasitic and foreign body granuloma and oral penetration-induced abscesses/granuloma can produce a broadly similar outward appearance.



Figure 28.12 Pharyngeal melanoma. Melanoma tumours are frequently identified in the parotid region where they are associated closely with the parotid salivary glands or the parotid lymph nodes or both. They can become large and some can cause degrees of respiratory obstruction when they occupy the guttural pouch (see p. 496). The tumours are often found bilaterally and are identifiable as firm, multilobulated masses in the parotid region. They seldom ulcerate and usually expand slowly. In spite of massive enlargement, they seldom seem to cause any significant problem to the horse. It is likely that they will take the line of least resistance and expand laterally. This horse was apparently unaffected by large bilateral parotid salivary gland melanomas. *(Figure courtesy of Chris Riggs.)*

Diagnostic confirmation

- The diagnosis of melanoma is simple from clinical features and, if necessary, a fine-needle aspiration or hollow-needle biopsy (see p. 89).
- Biopsy is used to establish the pathological behaviour of an individual lesion and that may provide useful information for the prognosis.

Management

There is no uniformly useful treatment for melanomas in horses. Melanomas are traditionally left alone without any significant problems, apart from the cosmetic aspects, but

they will invariably become larger and more difficult if simply ignored. Therefore, it is no longer appropriate to advise benign neglect. However, spontaneous 'resolution' of small lesions can occur.

Surgery

See also pages 120 and 574.

For lip melanoma, surgical excision is sometimes feasible, especially in early cases, and is then usually effective, provided that a margin can be achieved.

Regrowth at the site can be a problem, because during surgery very small tumours may be seen within the surgical site. It is almost inevitable that some of these will be left to develop later.

By the time functional defects are present, surgical treatment options are usually very limited. This is complicated by the long-term 'conventional wisdom' that melanomas should be left alone and that there is a risk of metastatic dissemination if surgery is performed. Pathological descriptions generally confirm that very small lesions are usually benign and therefore are a reasonable surgical option. In contrast, advanced lesions often have a malignant histological appearance – often in localized areas within the main lesion – and provide a far higher risk. There is some justification, therefore, in the concept that small lesions in accessible sites should be removed as soon as feasible, so that at least these will not become a significant clinical problem and will not become malignant. The premise is that surgical tumour burden reduction reduces the overall long-term risk of malignancy.

Anatomical constraints are significant – surgical removal of tumours in inaccessible sites or sites that are complicated by anatomical obstacles to removal (such as in the parotid region) is probably contraindicated in most circumstances.

Chemotherapy

See also page 129.

Prolonged daily oral administration of cimetidine at doses of 7.5–15.0 mg/kg bodyweight has been suggested as being effective, but the results are not convincing in many cases (see pp. 146 and 574).[56,57] Treatment of single or few oral tumours on their own probably does not warrant this approach and there is probably no evidential justification in this approach.

The use of repeated intralesional cisplatin either in stable emulsion with sesame oil and water, or more sensibly as biodegradable beads (Matrix II), may bring improvements in some lesions, but cures are still not realistic. This may be a useful adjunct to surgical tumour volume reduction.

New treatments are currently being explored, including the use of 'vaccines' and cytokine mediators, such as interleukin-11. There is no evidence yet of the benefit of these in horses.

Radiotherapy

This is not usually effective against equine melanoma.

Prognosis

- The prognosis will largely depend on the location and extent of the tumour(s), the particular pathological characteristics and the extent of any secondary effects.
- The prognosis is usually regarded as relatively favourable, as the majority of tumours of this type have no metastatic tendency. However, occasionally, tumours are locally invasive and others are very aggressive with extensive metastatic spread and serious secondary effects. As might be expected, older lesions tend to be more malignant, at least in histological character and possibly also in clinical behaviour. Melanoma tumours developing in non-grey horses (and in particular cremello or albino horses) may be more inclined to be aggressive.

Oral fibroma/fibrosarcoma

See also pages 287 and 561.

Disease summary

Notes

Relatively commonly encountered (anecdotally) in practice but few reported cases.

Clinical features

Localized, fleshy, ulcerated mass usually seen alongside the maxillary cheek teeth.

Diagnostic confirmation

Biopsy is essential to differentiate from SCC, sarcoid and epulis.

Management

Surgery is the best option and laser surgery improves the prognosis and makes the procedure easier.

Prognosis

Prognosis is good, but theoretically it can progress to invasive fibrosarcoma.

Description

This is an exophytic fibroma that occurs with some regularity in the horse but may be even more common. The clinical similarity of the tumour with sarcoid and epulis confuses the diagnosis because they can appear to be very similar.

Possible causes include persistent inflammation at a defined site due to infection or tartar build-up, or foreign body reactions similar to epulis but many occur in otherwise normal mouths. Most are slow growing and symptomless; almost all early cases are detected incidentally during routine dental treatments. The benign forms may progress to invasive fibrosarcoma.

Occurrence

There are few reported cases, in spite of its relatively common occurrence. Older or mature horses appear to be more often affected. The buccal gingivae of the maxillary cheek teeth are the commonest site but, occasionally, they occur on the lingual margin and in the mandibular arcades.

Clinical features

- A localized fleshy, ulcerated and haemorrhagic mass is easily visualized, usually lying alongside the maxillary cheek teeth (Fig. 28.13).
- There may be some external distortion of the cheek outline if the mass reaches a suitable size.

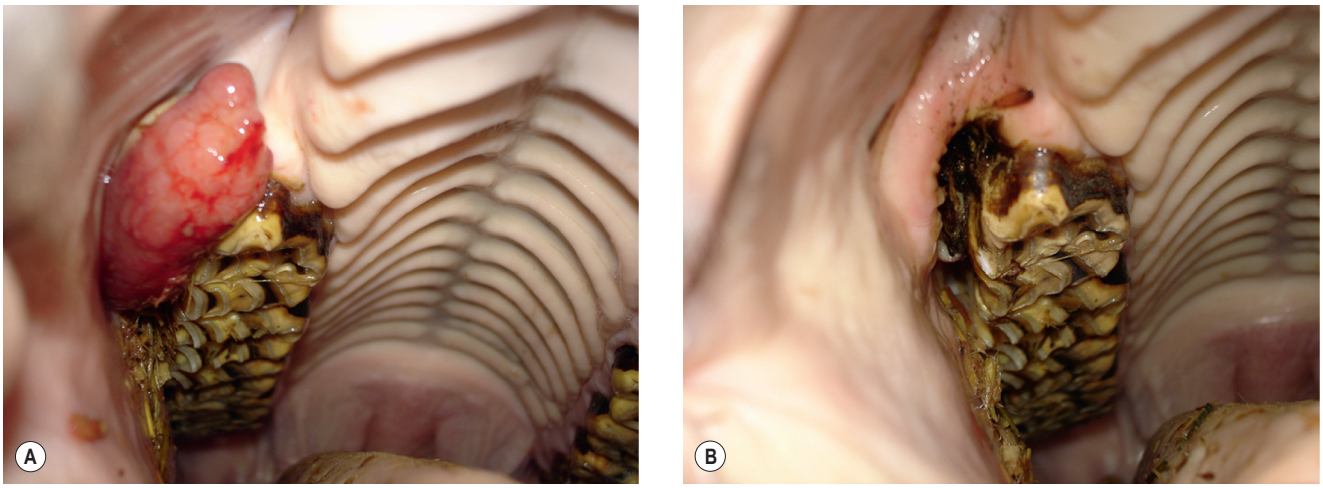


Figure 28.13 Oral fibroma. (A) This oral fibroma was noted during a routine dental examination. It created a visible swelling on the cheek but that had not been noticed by the owner. Saliva was positive for blood, as might be expected. **(B)** The tumour was removed under standing sedation and local analgesia using a diode laser and the diagnosis was confirmed on histology. No recurrence occurred for at least 6 years.

- Difficulty eating or haemoptyalism may be noticed by an astute owner.

Diagnostic confirmation

Biopsy is essential to differentiate it from squamous cell carcinoma, sarcoid and epulis in particular. Usually an excisional biopsy is performed if the mass is accessible. They are histologically distinctive and cannot really be confused with sarcoid or carcinoma.

Management and prognosis

Management options are limited.

Surgery carries a good prognosis.

- Laser surgical excision or diathermy are effective and produce a relatively bloodless surgical field. It is important to clean/de-scale the associated tooth at the same time in case this acts as a focus for a new mass.
- These tumours are commonly considered to be very benign in behaviour; most are slow growing. Multiple tumours do occur and so the suggestion is that there are environmental or circumstantial causes for them. Long-term prevention seems a possibility if dental hygiene can be maintained.
- There is no recorded suggestion that they are a precursor to squamous cell carcinoma, but in theory fibrosarcoma could develop.

Disease summary

Notes

Rare tumour mostly affecting younger horses.

Clinical features

Smooth, domed, expansile mass in rostral mandible of young horse, possibly causing distortion of lips and teeth.

Diagnostic confirmation

Radiography (CT if possible) and biopsy.

Management

Surgery – hemi- or rostral mandibulectomy, or radiotherapy as sole therapy or as an adjunct to extensive surgical tumour reduction (debulking).

Prognosis

Prognosis is fair, with appropriate treatment, but some do recur and some can be very problematic.

Equine juvenile mandibular ossifying fibroma

See also page 19.

Description

Benign proliferative fibro-osseous lesions of animals are uncommon. Osteoma, ossifying fibroma and fibrous dysplasia, all of which are predominantly found in the bones of the skull and mandible, are most frequent. In their early stages, they are intramedullary and destroy adjacent trabecular and cortical bone simply by expansion.

Productive bony lesions on the rostral mandible of young horses have been described as ossifying fibroma-osteoma, osteoma and osteosarcoma. Equine juvenile mandibular ossifying fibroma is the term used to describe these poorly-defined proliferative fibro-osseous, solitary lesions, which typically develop in the rostral mandible of younger horses.

Occurrence

Fibro-osseous lesions have been reported in a variety of other species, including human, Anglo-Nubian goat, cat and dog. In horses, most cases are reported at less than 1 year of age. They may, however, not be observed until the animal is handled at a later age, by which time there may be significant distortion and ulceration of the buccal mucosa.[58]

Historical evaluation of five cases suggested that trauma may be a predisposing factor. However, the young age observed both in humans and horses suggests a strong developmental connection.[7]

Clinical features

- The majority of these tumours are unilateral and situated in the rostral mandible.

- They rarely develop in the maxilla and in very rare cases can be bilateral.
- They may reach considerable size and, initially, at least, are covered by a domed, smooth/normal oral mucosa. Later, some ulceration is common (Fig. 28.14).
- Gross distortion of the lip and the associated teeth are likely.
- There is some variation in the clinical presentation, with some being flatter and more fleshy in appearance; they can then resemble other soft tissue tumours.
- The expanding lesion also causes loosening of the teeth and consequent difficulty with prehension.
- The tumour can predispose the mandible to pathological fracture.
- Although it is frequently obvious in the relatively early stages of development, they may only be identified late in their course, probably because there is little reason to examine the mouth of young horses.

Differential diagnoses

- Ameloblastoma
- Osteoma
- Osteosarcoma
- Fibrous dysplasia
- Other soft tissue tumours.

Diagnostic confirmation

- Radiographically, the dense tissue is obvious with only a few individuals showing the characteristic calcification more commonly encountered in other species; in the horse, dense fibrous tissue is more likely.
- The more ulcerated and secondarily infected lesions may resemble other soft tissue tumours.
- Biopsy is confirmatory.

Management

Surgery

Surgical excision is frequently curative, provided that sufficient attention is paid to the true extent of abnormal tissue. Cases subjected to this surgery should recover well and will usually cope well and lead active normal lives.[7,59] However, if extensive excision is required, it may leave unacceptable cosmetic and functional deficits. In a series of six cases, incomplete surgical resection resulted in local recurrence, while rostral mandibulectomies resulted in no recurrence in 5/5 cases receiving this treatment.[58]

Rostral mandibulectomy affords a simple and effective technique of treating tumours of the rostral portion of the mandible in horses[7] and is an effective option, particularly if the mandibular symphysis can be retained. Limited disabilities and acceptable cosmetic effects can be expected. The procedure involves preservation of the most caudal portion of the mandibular symphysis to maintain stability. There should be few surgical complications or recurrences, and the cosmetic and functional results are expected to be good.

Radiotherapy

Extensive surgical debulking followed by cobalt-60 teletherapy radiation has also been used successfully.[7] Radiation using cobalt-60 teletherapy alone in a standing sedated horse with a recurrent mass following surgical debulking alone, has also been used with a good outcome.[60] The mandible received a total midline dose of 4000 cGY in 10 fractions on a Monday, Wednesday and Friday protocol over 22 days. Despite minor acute side-effects of radiation, the filly continued to eat well. Clinical follow-up revealed progressive decrease in size of the mass over 1–2 years, at which point the owner reported no visible external evidence of the tumour. A further two cases have been treated successfully by the author (KS) using teletherapy, after surgical debulking, employing the same protocol.

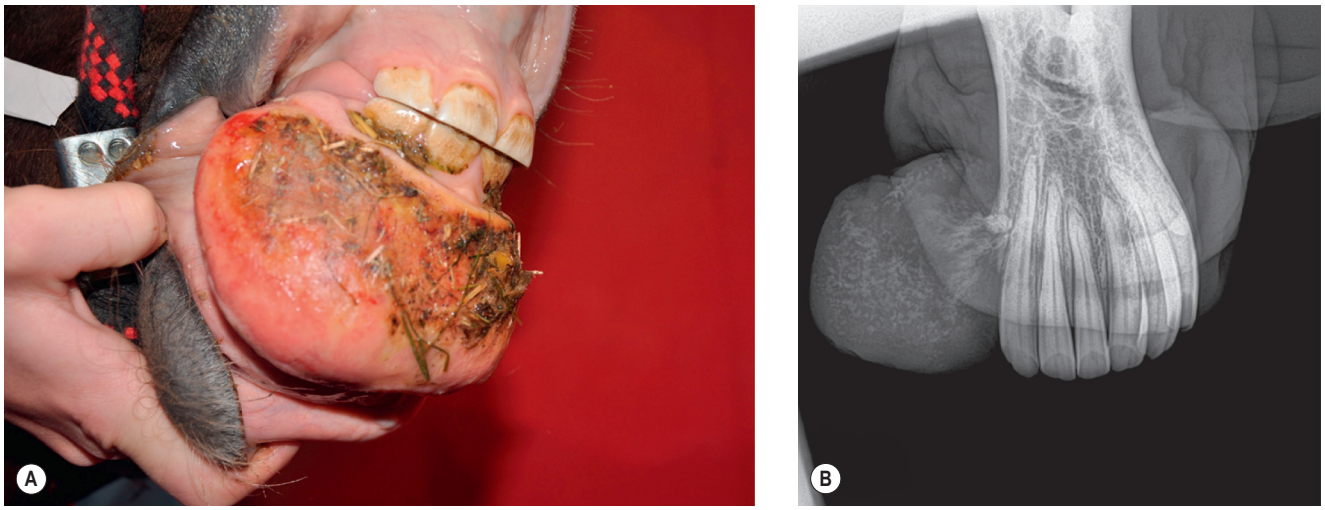


Figure 28.14 Slowly expanding ulcerated mass on the rostral mandible. **(A)** This 7-month-old Thoroughbred weanling was presented with a slowly expanding ulcerated mass on the rostral mandible. Radiography confirmed that the tumour was soft tissue density without any detectable bone involvement. A biopsy confirmed a diagnosis of ossifying fibroma. The tumour was resected surgically, with primary closure of the site. The wound broke down and the tumour recurred at the site. Radiotherapy was then used to treat the mass successfully. **(B)** A typical radiolucent, multiloculated radiographical appearance of an ossifying fibroma affecting the mandible. In this case, there is evidence of keratinization; note also the cortical thinning at the base of the tumour. *(Figure A courtesy of Chris Johansen; Figure B courtesy of Carmel Welsh.)*

Prognosis

- Regrowth of the tumour is common because of the difficulty of identifying the margins of the abnormal tissue.
- All resected tissue must therefore be submitted for histological examination, with particular attention to the surgical margins; these need to be identified and marked by the surgeon.
- Based on a very small number of reported cases, complete surgical excision, radiotherapy as sole therapy or a combination of radiation and surgical tumour reduction, the prognosis is fair.

Myxomatous neoplasms of the jaw and gingivae

See also page 315.

Disease summary

Notes

Very rare tumours derived from embryonal connective tissue.

Clinical features

Proliferative and destructive mass most commonly affecting incisor and molar dental arcades.

Diagnostic confirmation

Radiography (and CT where feasible) and biopsy are essential.

Management

Surgical excision is often difficult due to anatomical site; theoretically, radiation is effective but is not reported.

Prognosis

Prognosis is very poor or hopeless.

Description

These are very rare tumours derived from embryonal connective tissue. The tumours are identified by their characteristic histological appearance.

Occurrence

In the few reported cases, older or mature horses appear to be more often affected. The incisor and molar dental arcades of the maxilla are the commonest site.[61]

Clinical features

- These tumours are characteristically destructive (Fig. 28.15).
- The combined destruction and proliferation of tumour tissue creates obvious distortion of the maxilla, with possible secondary nasal and sinus obstruction.
- Loosening of teeth and infection of alveolar bone may result, but at least in the early stages there is little bone destruction (Fig. 28.16).

Differential diagnoses

- Ameloblastoma
- Ossifying fibroma
- Fibrosarcoma
- Squamous cell carcinoma.

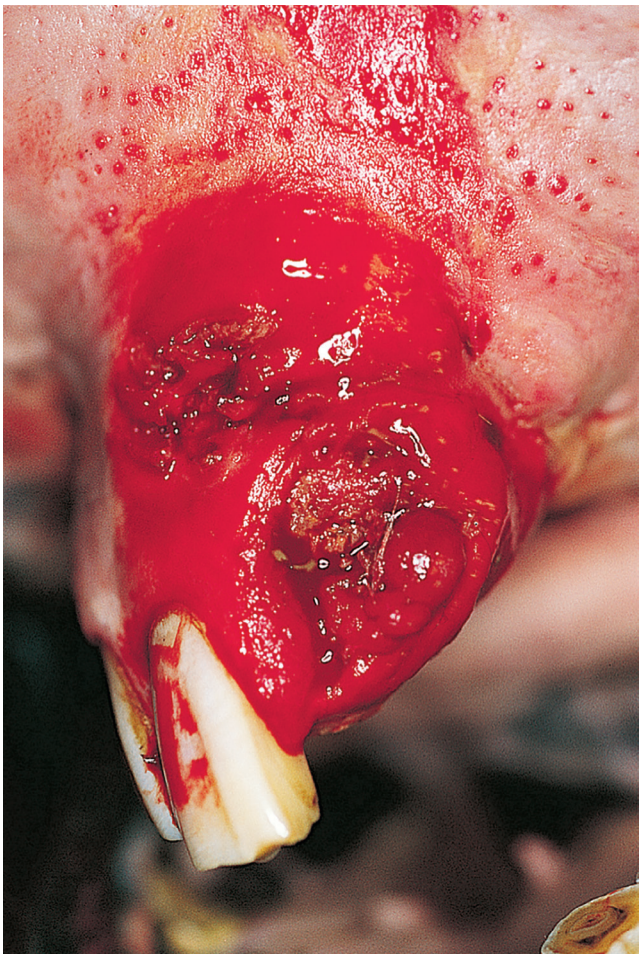


Figure 28.15 Myxomatous tumour of the premaxilla of a 14-year-old Hunter gelding. Note the extensive destruction that is clinically similar to the aggressive forms of carcinoma and the perilesional petechial haemorrhages; these were identified as micro-tumours. The condition can be differentiated histologically from carcinoma. *(Figure reprinted from Easley J, Dixon P, Schumacher J. Equine Dentistry. Edinburgh: Saunders; 2011: 175 (Fig. 11.21), copyright 2011, reprinted with permission from Elsevier.)*

Diagnostic confirmation

- Biopsy is essential.
- Radiographically, there is an aggressive lytic appearance with a diffuse mixture of bone and soft tissues often in a partially loculated form. The cardinal radiographic signs of the more malignant forms, however, are the combined destruction of normal bone and bizarre irregular new bone formation in a random distribution. The radiographic appearance can be very similar to osteosarcoma (see pp. 316 and 665) and squamous cell carcinoma.

Management

Management options are limited.

1. *Surgical excision/tumour reduction* is possible but the margins of the tumour and the usual anatomical site for them may make total surgical excision virtually impossible.
2. *Radiation* is a theoretical solution.

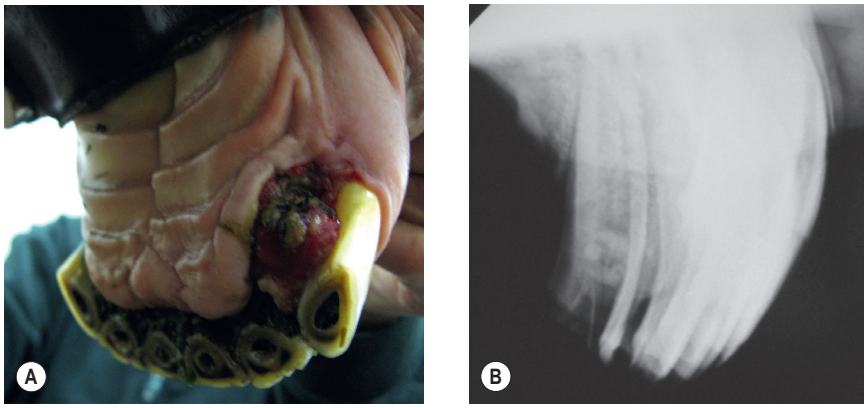


Figure 28.16 Malignant myxosarcoma. **(A)** This malignant myxosarcoma was identified incidentally during routine dental treatment. **(B)** Radiographs showed only limited alveolar and maxillary bone involvement. *(Figures reprinted from Easley J, Dixon P, Schumacher J. Equine Dentistry. Edinburgh: Saunders; 2011: 175 (Fig. 11.22), copyright 2011, reprinted with permission from Elsevier.)*

Prognosis

- These tumours are very unpredictable in behaviour; some are slow growing and remain relatively benign, others are highly aggressive and so carry a hopeless prognosis.
- There are no definitive reports of metastatic spread of the malignant forms of these tumours but this may reflect the short clinical course, which inevitably results in euthanasia, possibly before secondary tumours develop elsewhere.

Oral haemangiosarcoma

See also page 334.

Disease summary

Notes

A rare malignant neoplasm.

Clinical features

Red/purple ulcerated mass in oral mucosa, possibly with oral bleeding.

Diagnostic confirmation

Biopsy is definitive.

Management

Surgical tumour reduction or removal at an early stage may be feasible or can be used as local palliative treatment to keep the size under control.

Prognosis

Prognosis is poor.

Description

This is a malignant neoplasm of endothelial cells that can arise in any part of the body. They are reported to metastasize early and so tumours in any locality may be primary or secondary.

There are few reports of this tumour in the mouth.[62,63] Aged horses are more likely to develop them and there may be concurrent tumours at other sites, such as around the eye.

Clinical features

- A red or purple ulcerated, soft tissue mass in the oral mucosa (either on the sides of the tongue or on the gingiva) is typical.
- The mass is likely to be slow growing and, being subject to repeated trauma, there may be some oral bleeding.
- The lesions may be identified incidentally during a clinical examination, but where periocular lesions occur, the clinician should carefully examine all the visible mucous membranes, including the mouth, for other evidence of tumour.

Differential diagnoses

- Foreign-body reactions and ulceration arising from the attachments of *Gastrophilus* sp. may be similar
- Squamous or basal cell carcinoma/squamous papilloma with ulceration.

Diagnostic confirmation

- Biopsy is the only definitive way of establishing the diagnosis.

Management

1. *Surgery*: Surgical excision may be effective but there are considerable technical difficulties and risks of incomplete excision. Haemorrhage is a major issue.
2. *Palliative treatment*: Where other tumours are also present elsewhere, local palliative treatment is all that can be advised.

Prognosis

The presence of more than one lesion may not necessarily indicate that the tumour has spread metastatically, but haemangiosarcoma is a malignant tumour in horses and so this possibility must be considered.

Salivary adenocarcinoma

See also page 260.

Description

Salivary gland neoplasia is uncommon in horses.[64] For example, in one study of 687 necropsies and 635 biopsies, only three salivary tumours were described; two were carcinomas and one was a cystadenoma.[4]

Disease summary

Notes

Uncommon in horses.

Clinical features

Unilateral enlargement of affected gland, uncomfortable on palpation.

Diagnostic confirmation

Biopsy is definitive.

Management

Surgical removal is possible if diagnosis is made early but this is unlikely in most cases.

Prognosis

Prognosis is very poor.

A review of 1148 equine tumours included only two salivary adenocarcinomas.[65] Six of 14 equine salivary gland tumours were adenocarcinomas; where recorded, the sites of involvement were parotid gland (three cases) and submandibular glands (one case). The age range was 7–18 years.[66]

Their recognition is important because they are reported to be highly malignant (possibly up to 33% will develop secondary pulmonary tumours).

Clinical features

- Recognition is difficult but, clinically, the affected gland becomes enlarged (Fig. 28.17).
- Palpation is uncomfortable but not painful.
- Only one gland is usually involved and so the enlargement is asymmetrical and persistent, which differentiates it from the more usual very benign and transient parotid salivary gland swelling commonly encountered in grazing horses.

Differential diagnoses

- Benign swelling of the parotid salivary glands occurs frequently in grazing horses. This idiopathic condition is invariably transient and self-resolving.
- Obstruction of the salivary ducts by sialoliths (usually in the parotid gland) occurs within the gland substance or in the more rostral part of the duct. This results in a solid obstructive lesion with generalized glandular swelling. This remains hot and painful for some days before it subsides naturally as atrophy of the gland follows.
- Parotid melanoma is relatively frequently encountered in grey horses in particular (see p. 572)

Diagnostic confirmation

- Diagnosis is reliant upon biopsy but so few cases have been described that a characteristic histological appearance is not established.
- Post-mortem, gross and histological features are described.[5]

Management

Surgical excision is theoretically possible if diagnosis is made sufficiently early but this is unlikely in most cases. In any case, the tumour progression is usually rapid.

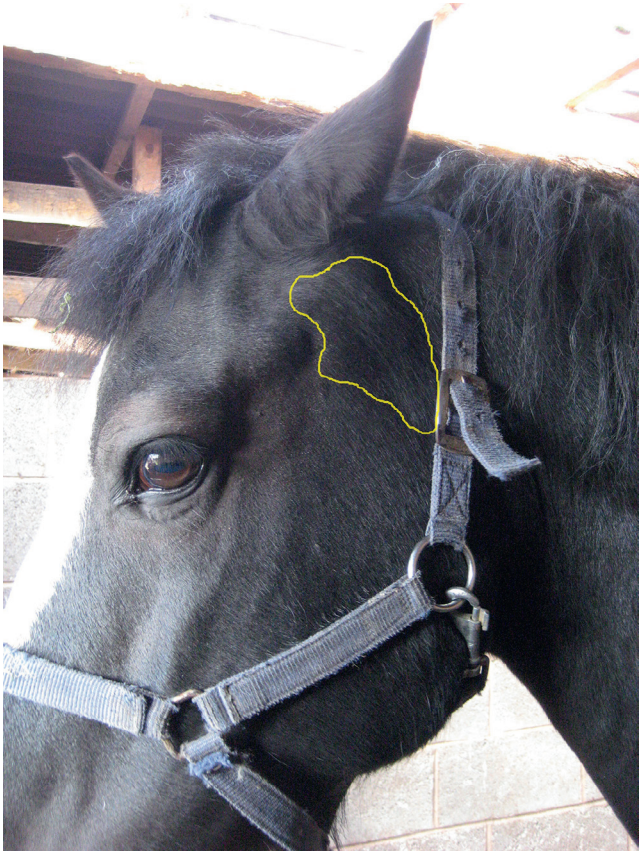


Figure 28.17 Salivary gland carcinoma. This 15-year-old pony gelding developed a rapidly expanding, warm swelling of the left parotid salivary gland. Ultrasonographic examination showed a diffuse area of mixed echogenicity, and biopsy confirmed a salivary gland carcinoma. The parotid saliva contained significant blood. The pony developed unilateral Horner's syndrome and facial paralysis over a 3-week period and was euthanized.

Prognosis

The high malignancy of most salivary gland carcinomas makes the prognosis very poor.

Neoplasia of the tongue

Overview

Tumours involving the tongue of the horse are uncommon. The gingivae, dental alveoli and lips are the most frequent sites of oral neoplasia. Primary tumours of the tongue reported in the horse include (see Table 28.3)[67–72]:

- Squamous cell carcinoma
- Rhabdomyosarcoma
- Perineurioma
- Mast cell tumour
- Lymphosarcoma
- Chondrosarcoma.

Several single case reports have been made of a variety of tumour types in the equine tongue (Table 28.3). This probably suggests that tumours are very rare and that a wide differential diagnostic possibility exists. Carcinoma is probably the commonest single tumour of the tongue but is still seemingly rare, with no published reports on it.

Table 28.3 Case reports of primary tumours of the equine tongue

Ref. No.	Age (years)	Sex	Breed	Presenting sign	Diagnosis	Treatment	Outcome
67	Adult	G	QH	4.5 cm diameter mass in tongue	Rhabdomyosarcoma	Incidental finding	Identified incidentally at necropsy with no evidence of metastases
	21	F	TB	2.0 × 2.0 × 5.0 cm slowly growing mass over 1 year	Rhabdomyosarcoma	Surgical excision	No recurrence at 1 year
68	5	F	Showhorse	Multiple coalescing masses on left dorsolateral aspect of tongue extending to tip of tongue, impeding mastication and causing reduced sensation in area of masses	Perineurioma	None	Unknown
69	20	F	Unknown	Nodular, firm, focal ulcerated mass ar right dorsobuccal face of tongue	Mast cell tumour	Surgery	No recurrence at 8 months post-surgery
71	4	G	Arab	Difficulty eating of 2–3 months' duration, only able to eat gruel, poor body condition, ptyalism, deviation of tongue and protrusion, 10×7×7 cm ulcerated mass on left mid tongue from mouth	Chondrosarcoma	Surgical resection	No recurrence or complications at 11 months post-surgery
70	10	F	Shetland	1 month history of unilateral food containing nasal discharge	T-cell-rich B-cell lymphosarcoma	None	Euthanasia
72	5	F	QH	6 month history quidding and nasal discharge with feed material, weight loss, DDSP by soft tissue mass at base of tongue	Rhabdomyosarcoma	Surgical resection orally	Successfully removed

Squamous cell carcinoma of the tongue

See also page 220.

Disease summary

Notes

Typically very rare.

Clinical features

Difficulty eating, quidding, protrusion of tongue and chronic weight loss; haemoptyalism.

Diagnostic confirmation

CT/MRI to identify extent of lesion. Definitive diagnosis is made by biopsy.

Management

Surgery with concurrent chemotherapy and/or radiation may be feasible.

Prognosis

Prognosis will depend on feasibility of tumour removal and absence of lymph nodes or remote spread. If rostral tongue lesions are detected early, there is some chance of successful intervention.

Description

Along with the other soft tissue primary tumours of the tongue, squamous cell carcinoma is typically very rare in horses.[3] The tumour may affect any part of the tongue and is characteristically invasive and restrictive, with tendency to malignancy and spread to local lymph nodes. However, there is no published evidence for this condition, specifically in horses.

Clinical features

(Figs 28.18, 28.19; see also Fig. 28.9E)

- Early signs are usually misleadingly innocuous and are often overlooked as trivial. Most cases are well advanced before they become clinically apparent
- Often, secondary changes such as weight loss or difficulty eating are the reasons for presentation.
- Based on the small number of case reports/series published, the most common presenting signs include difficulty eating, quidding, protrusion of the tongue and chronic weight loss.
- Visual identification of a mass on oral examination.[67–72]
- Some serious carcinoma lesions occur in the base of the tongue and may be difficult to visualize from the oral or pharyngeal aspects.

Differential diagnoses

- All soft tissue neoplasms must be considered as potential differential diagnoses.
- Foreign body and granuloma from those or other inflammatory conditions must also be considered. Early carcinoma of the tongue can be easily mistaken for a

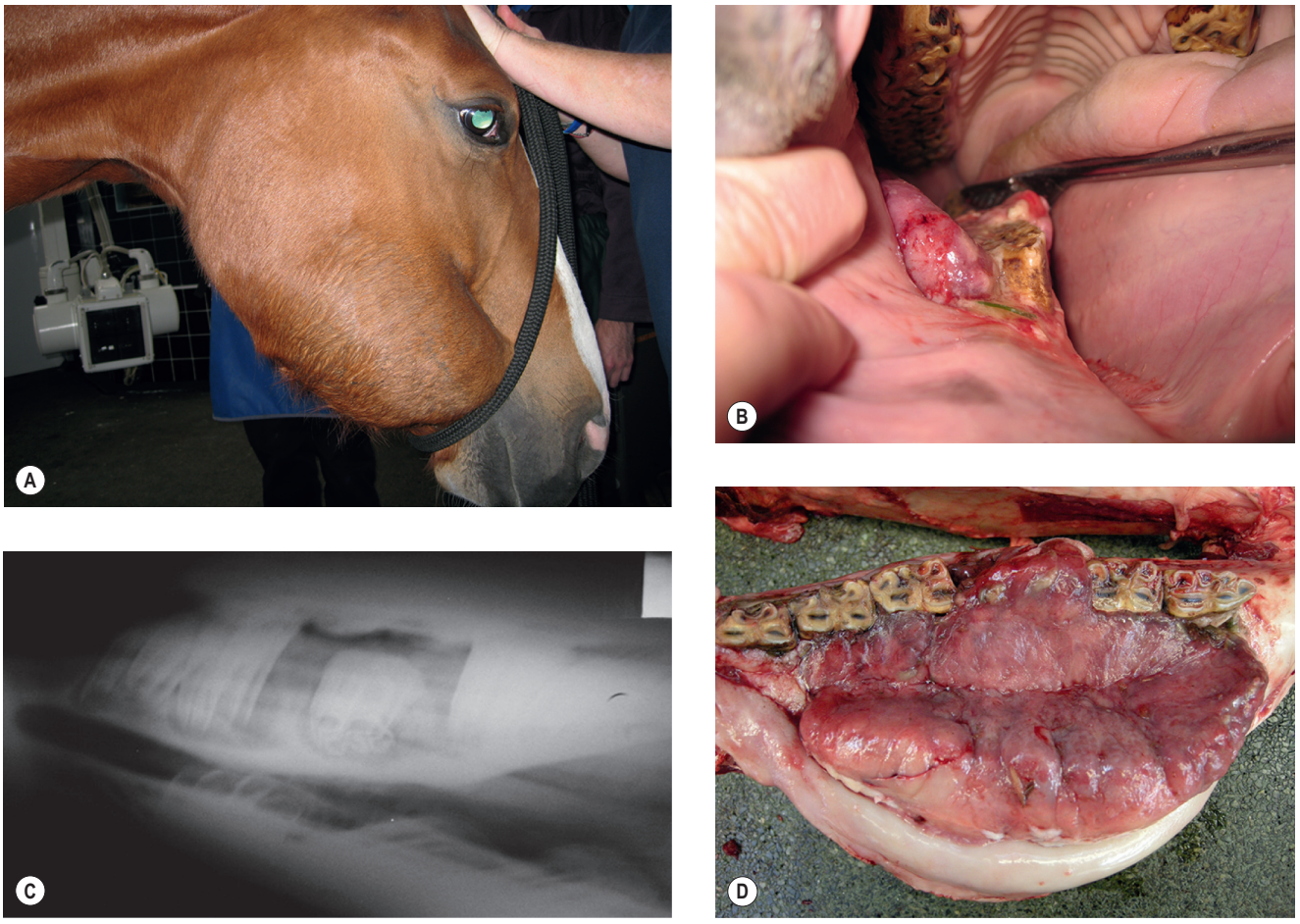


Figure 28.18 Oral/gingival carcinoma. **(A)** This 4-year-old Selle Français filly was presented with a rapidly progressive 'mandibular' swelling that had developed over a few weeks prior to presentation. **(B)** Oral examination confirmed a solid ulcerated soft tissue mass originating in the base of the tongue that caused mandibular distortion. **(C)** An oblique radiograph confirmed the loss of bony architecture and loss of 308 and displacement of 309. A biopsy confirmed carcinoma and the horse was euthanized on humane grounds. **(D)** The extent of the tumour was remarkable and local lymph node involvement with tumour cells was found in the submandibular and pharyngeal lymph nodes. *(Figures courtesy of Charles Louf.)*

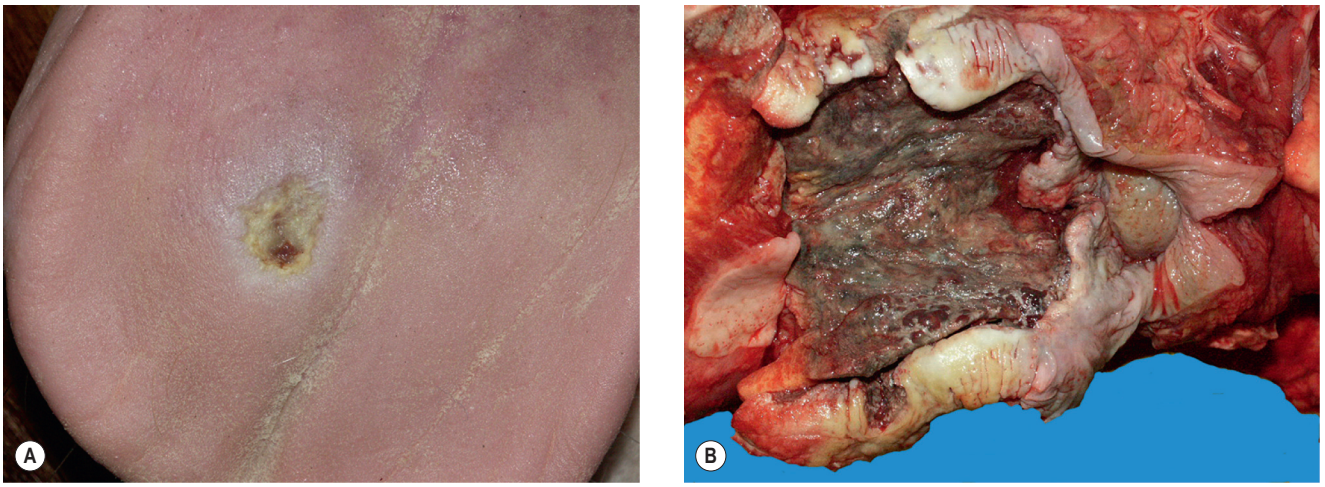


Figure 28.19 Carcinoma of the tongue. **(A)** This innocuous-looking lesion was identified by an observant owner on the rostral upper mucosa of the tongue of a 26-year-old pony. The submandibular and pharyngeal lymph nodes were grossly enlarged. The pony was anaemic and had lost weight significantly. Ultrasonographic examination revealed a destructive soft tissue region without evidence of foreign body. A biopsy confirmed a diagnosis of carcinoma with significant malignancy. **(B)** Carcinoma of the caudal parts of the tongue and oro-pharynx. Diagnosis can be difficult in the early stages when the patient may have subtle signs that are easily overlooked. This case was presented for veterinary examination because of haemoptyalism and weight loss with nasal return of food and halitosis over only a 7-day period.

trivial wound but wounds usually heal rapidly and seldom progress with destruction of tissue.

Diagnostic confirmation

- A detailed history, including timing of the last orodental examination and any features noted, is useful.
- A thorough clinical examination to identify any other primary or secondary changes is important, as a relatively small lesion on the tongue may be secondary to far more extensive lesions elsewhere.
- Oral endoscopy and ultrasonography may also be useful to visualize the mass within the oral cavity.
- Since many of these cases are destructive and proliferative, radiological examination or CT, if available, is always useful (see Fig. 28.18C).
- MRI may be extremely useful for identifying the extent of the lesion, assessing the feasibility of treatment for and surgical or radiotherapeutic planning.
- Biopsy and histopathology is the definitive means of diagnosis.

Management and prognosis

1. Treatment recommendations and prognostication cannot be made with any certainty based on the paucity of published data. In general, horses may do quite well after the free portion of the tongue is resected, but the tumour does appear to have an aggressive tendency so a full assessment is essential before embarking on any treatment.
2. Surgical resection via the oral cavity has been reported successfully with complete excision.[72]
3. Since carcinomas are known to be generally susceptible to radiation, radiotherapy and some forms of chemotherapy (such as intralesion's cisplatin or 5-fluorouracil) are probably worth considering.

Disorders of the mouth, jaws and teeth resembling neoplasms

Oral papilloma

See also page 247.

Disease summary

Notes

Relatively common.

Clinical features

Single or multiple discrete or coalescing verrucose, grey-pink papules around mouth and occasionally on the mucosa of the mouth. No material implications for the horse.

Diagnostic confirmation

Clinical appearance is typical – biopsy is definitive.

Management

Most oral papilloma lesions are persistent, but a few resolve spontaneously; older horses have more persistent lesions.

Prognosis

Prognosis is excellent.

Description

Viral papilloma is a relatively common occurrence on the skin of the mouth and lips and, in some cases, extends into the oral cavity. Host-specific equine papilloma viruses are the causative virus. Most often, young horses are affected in their first year or two at grass. Less commonly, they affect older horses and particularly those that have an immunocompromising disorder, such as pituitary pars intermedia dysfunction (PPID/equine Cushing's disease).

Clinical features

- Typically, papillomata appear as single or multiple, discrete or coalescing, verrucose, grey-pink papules around the mouth and, occasionally, on the mucosa of the mouth
- They seldom ulcerate unless they are traumatized.
- A few cases have lesions restricted to the oral mucosa and it is not known if these reflect a different manifestation of the same infection.
- In a few cases, there may be a severe oral infection and in these cases it is likely that some immunocompromising state exists.

Differential diagnoses

- *Equine sarcoid*: These seldom occur in the verrucous form in the mouth and so differentiation should be simple.
- '*Skin tags*' also occasionally develop in the mouth, particularly in old horses where they may easily be mistaken for papilloma and vice versa.

Diagnostic confirmation

- The diagnosis is usually simply based on epidemiology and clinical appearance.
- Biopsy is characteristic and most lesions resolve with age, although they may be very persistent in older horses.

Management

1. Most papillomata resolve spontaneously over some months but individual lesions may persist, often for many years – particularly in adult horses.
2. Therapeutic measures have included autogenous vaccines prepared from surgically excised lesions and various topical chemicals, such as podophyllin, formalin gels, etc.
3. Imiquimod can be helpful provided that the lesions are suitably accessible, but licking and rubbing reduce efficacy.
4. Many of these will be impractical within the mouth, and in those circumstances troublesome papillomata can be removed surgically or with cryonecrosis.

Prognosis

The prognosis is excellent. The majority resolve spontaneously, and those that do not, have no apparent harmful effect on the horse.

Epulis

Disease summary

Notes

Uncommon.

Clinical features

Nodule at gingival margin often associated with accumulation of dental tartar.

Diagnostic confirmation

Clinically distinctive, biopsy.

Management

Removal of causative factor.

Prognosis

Prognosis is good.

Description

The term 'epulis' is a clinical description of a smooth gingival nodule and can encompass different types of lesion, such as granuloma or neoplasia. These tumour-like masses develop from the fibrous tissue of the gingiva and are often but not always associated with the accumulation of dental tartar. In many cases, they arise from chronic local irritation due to persistent infection. They may therefore occasionally be an indicator of other disease. In horses, they are much less common than in some other species and seldom reach significant proportions (Fig. 28.20). They can easily be overlooked but are benign.

Clinical features

- Usually, epulis appears as a benign expansion of the gingival epithelium resulting in thickening and prominence of the gums, particularly evident at the gingival margin where it may be 'piled up' (Fig. 28.20A). In some older horses, there is a benign hyperplasia that has a more 'threatening appearance' (Fig. 28.20B), although there is no suggestion that it is in fact liable to tumour transformation.
- A few cases develop ulcerated proliferating masses at the site that can be much more like a true neoplasm and these may closely resemble oral fibroma.

Differential diagnoses

- Viral papilloma
- Sarcoid
- Proliferative forms of squamous cell carcinoma
- Oral fibrosarcoma.

Diagnostic confirmation

- The condition is distinctive clinically but refinement of the clinical diagnosis depends on histological examination of resected masses or a biopsy.
- Biopsy may, however, be misleading if granulation tissue is present, as they may be very similar histologically.
- The main differentials are, however, usually easily identified histologically.

Management

1. Removal of the causative factors usually results in complete resolution.
2. Many cases will resolve spontaneously after any dental tartar or damaged dental or soft tissue structures are removed.
3. Recurrence of both tartar and epulis should encourage a careful assessment of the whole horse in case there are any metabolic implications.

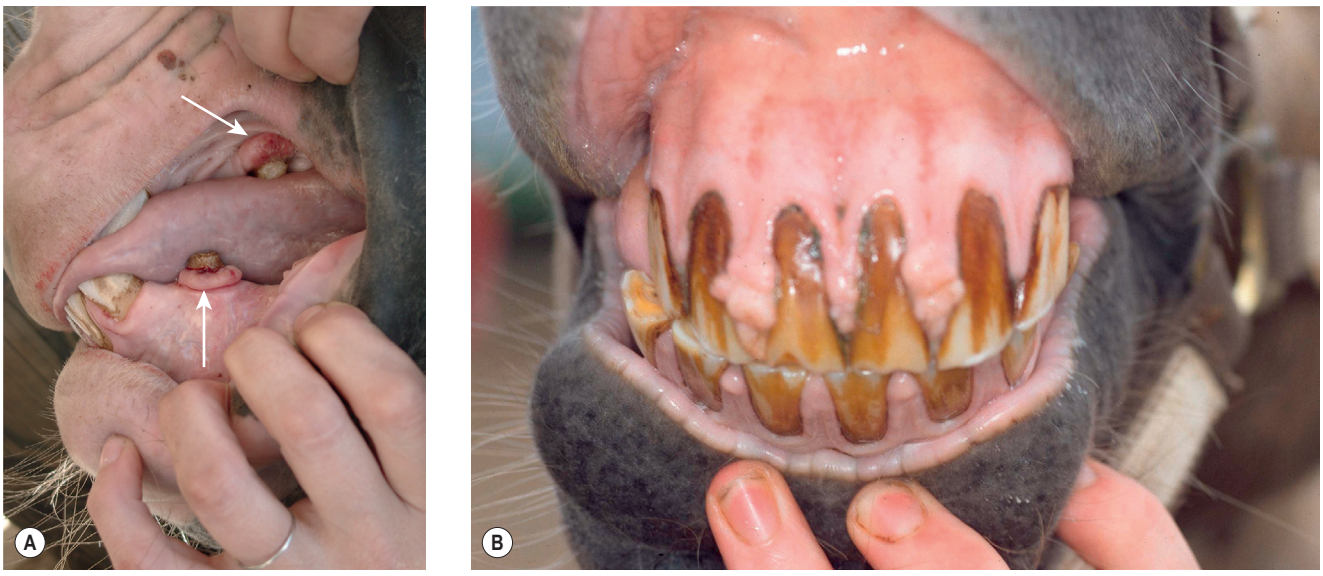


Figure 28.20 Epulis/benign gingival hyperplasia. (A) A small epulis-like gingival proliferation around the base of the upper and lower canine teeth (arrows). After removal of the tartar accumulation, the mucosa returned to normal. **(B)** A 20-year-old gelding with typical epulis/gingival hyperplasia between the upper incisor teeth. This is a benign state and there is no suggestion that it is a precursor to more aggressive tumours, such as carcinoma. *(Figure A reprinted from Easley J, Dixon P, Schumacher J. Equine Dentistry. Edinburgh: Saunders; 2011: 172 (Fig. 11.19B), copyright 2011, reprinted with permission from Elsevier.)*

Prognosis

- The prognosis is good.
- There are no reports that these masses are precursors to more malignant tumours such as squamous cell carcinoma, but one case developed a locally aggressive carcinoma some years after a benign epulis was removed from the base of a canine tooth (DCK, unpublished observation). It is probably unwise to draw any causative inference from this single case.

Mandibular aneurysmal bone cyst

See also page 672.

Disease summary

Notes

Rare.

Clinical features

Firm swelling on ventral aspect of horizontal ramus of mandible.

Diagnostic confirmation

Radiography.

Management

Deep surgical curettage and filling of defect with cancellous bone graft.

Prognosis

Prognosis is poor.

Description

While such structures might be expected in young horses, they may also occur in older horses, possibly as a result of trauma.[14] There is no evidence to suggest that these lesions are truly neoplastic, but diagnosis based on radiographic examination alone is probably unwise.

While there are no reports of concurrent neoplasia in the horse, complexes of tumours and cysts are reported in other species.

Clinical features

- These present as sterile, firm, expanding swellings usually on the horizontal ramus of the mandible (see Fig. 28.21A).
- The mandible becomes thickened from progressive destruction of cortical bone accompanied by reactive periosteal new bone formation.
- Some pain associated with mastication may develop and teeth may be shed abnormally as the alveoli are destroyed.
- The region may be warmer than the normal contralateral mandibular ramus.
- Aspiration reveals small volumes of yellow or red-orange fluid.[12]
- The rate of expansion may be sufficient to cause disruption and bleeding into the surrounding tissues and may easily suggest a neoplastic lesion.
- As the destruction becomes more aggressive, the mandible may suffer a pathological fracture. In advanced cases, the extent of bone destruction can be considerable (see Fig. 28.21) and then pathological fractures are likely.
- Although parotid duct obstruction can occur, this is usually a relatively insignificant clinical event (see Fig. 28.21). One report of a case of congenital aneurysmal bone cyst occurred in the mandible of a foal and resulted in a swelling large enough to prevent delivery.[14]

Differential diagnoses

- Congenital cysts of dental and sinus origin
- Tumours of dental origin such as ameloblastoma and odontoma
- Tumours of soft tissue origin such as ossifying fibroma
- Nutritional secondary hyperparathyroidism
- Fibrous dysplasia
- Paranasal sinus cysts have a similar radiographic appearance but will be in a very different location.

Diagnostic confirmation

- The radiographical appearance reveals a complex, loculated cyst-like structure containing bone fragments,

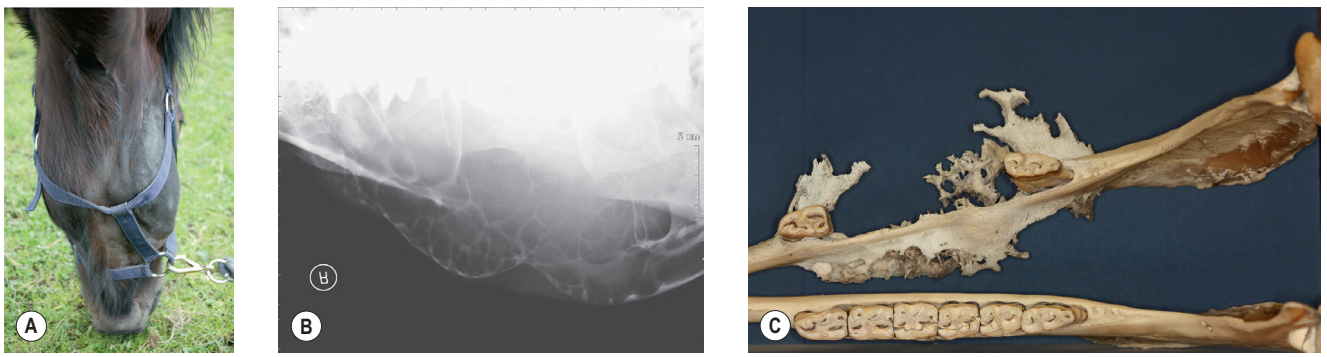


Figure 28.21 Thickening of the horizontal ramus of the mandible. (A) This 19-year-old pony mare developed a non-painful thickening of the horizontal ramus of the mandible. Gross distension of the proximal portion of the parotid duct and outward displacement of the masseter muscle were obvious. After some 12 months, she appeared to be in pain and ate slowly. **(B)** Radiographs showed a multilocular cyst-like condition, and aspiration produced around 250 mL of a clear yellowish fluid with low cell count. **(C)** Gross destruction of a mandible caused by an aneurysmal bone cyst. *(Figures reprinted from Easley J, Dixon P, Schumacher J. Equine Dentistry. Edinburgh: Saunders; 2011: 177 (Fig. 11.23), copyright 2011, reprinted with permission from Elsevier.)*

cartilage and soft tissue, usually with a fine rim of thin bone around the periphery (see Fig. 28.21). The structure closely resembles the complex of paranasal sinus cysts that may also arise congenitally or develop at later ages.

Management

1. The only effective treatment is deep and aggressive curettage of all abnormal tissue. The defect may be filled with cancellous bone grafts collected from a remote site. Repair may be slow and the site may be cosmetically compromised, but many cases can be cured effectively.
2. In most cases, treatment is not really justified and palliative care should be provided until euthanasia can be justified.

Prognosis

- The prognosis is poor unless the lesions are detected early and treated with aggressive surgical ablation and suitable reconstructive measures.
- The chances of an early diagnosis are low, so the outlook is generally poor.
- Complications, including dental shedding and pathological fractures, will reduce the prognosis considerably.

Non-aneurysmal cystic lesions of bone

See also page 674.

Overview

Cystic lesions of the jaws present as bony swellings, and may affect mastication. Radiographically, the cysts differ from the multiloculated destructive aneurysmal cysts in being rounded with a smooth bony lining and radiolucent centre. The generic term 'odontogenic cyst' is appropriate for these non-inflammatory cysts lined by epithelium.[17]

Radicular cysts occur adjacent to tooth roots. They are reactive lesions associated with oral inflammatory disease. Histologically, they are lined by stratified squamous epithelium with associated inflammatory cells. Additionally, there are occasional cystic 'tumour-like' conditions that affect the mandible in particular, and many of these have yet to be characterized (Fig. 28.22). They are rare anyway, and there is therefore no evidence on prognosis and treatment.

Fibrous dysplasia

See also page 674.

Description

Fibrous dysplasia of the bones of the skull has been reported in man and a clinically similar condition is recognized in horses as a smooth contoured bone deformity arising from loss of bone structure with extensive formation of fibro-osseous matrix.[73]

The lesion is probably not a true neoplasm. In the jaw/face region, major clinical effects are due to the expansive space-occupying nature of the slowly expanding mass.

Clinical features

The changes are easily recognized histologically but may be confused with neoplastic lesions both radiographically and clinically (Fig. 28.23). Suspicious masses should be subjected to the full range of diagnostic tests, including radiography, gamma scintigraphy, biopsy and, where feasible, computed tomography.

Management and prognosis

Surgical removal may be undertaken but many remain static and do not affect the horse.

Oesophageal carcinoma

See also page 221.

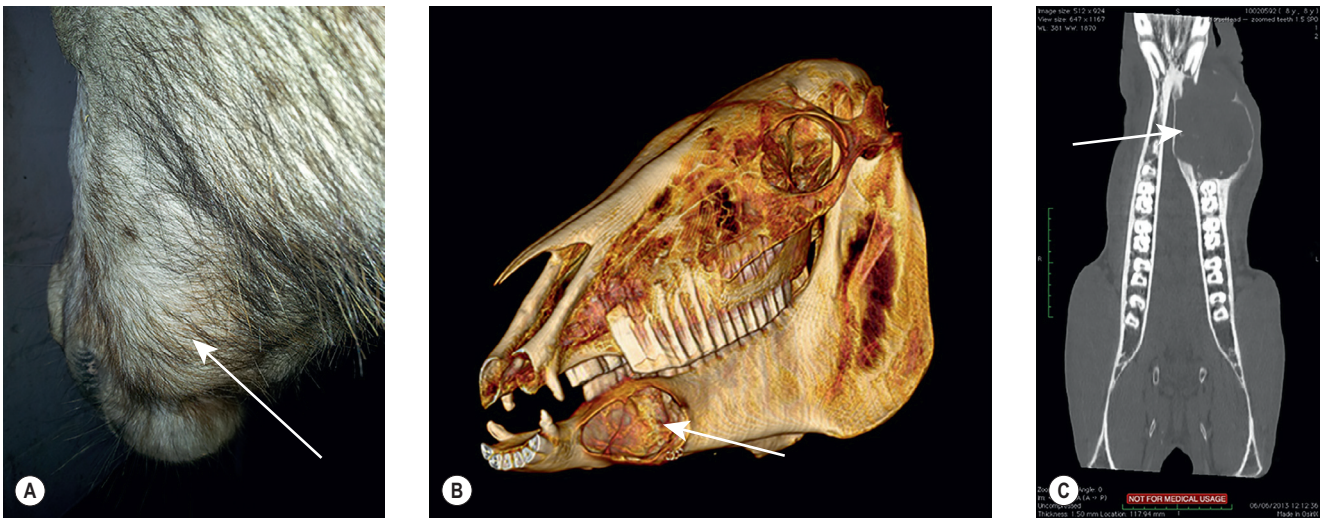


Figure 28.22 Unusual 'tumour' of odontogenic epithelial origin. (A) A small mandibular swelling was noted by an equine dental technician in this 8-year-old pony gelding. A standard lateral radiograph revealed a cystic 'cavity' around 306. The tooth was thought to be abnormal and so was removed along with the loose 307; this proved to be very easy to do and from that point on a progressive swelling developed over 3 months. A biopsy identified an unusual 'tumour' of odontogenic epithelial origin. **(B,C)** A CT scan with 3-D reconstruction was able to confirm the extent and location precisely.

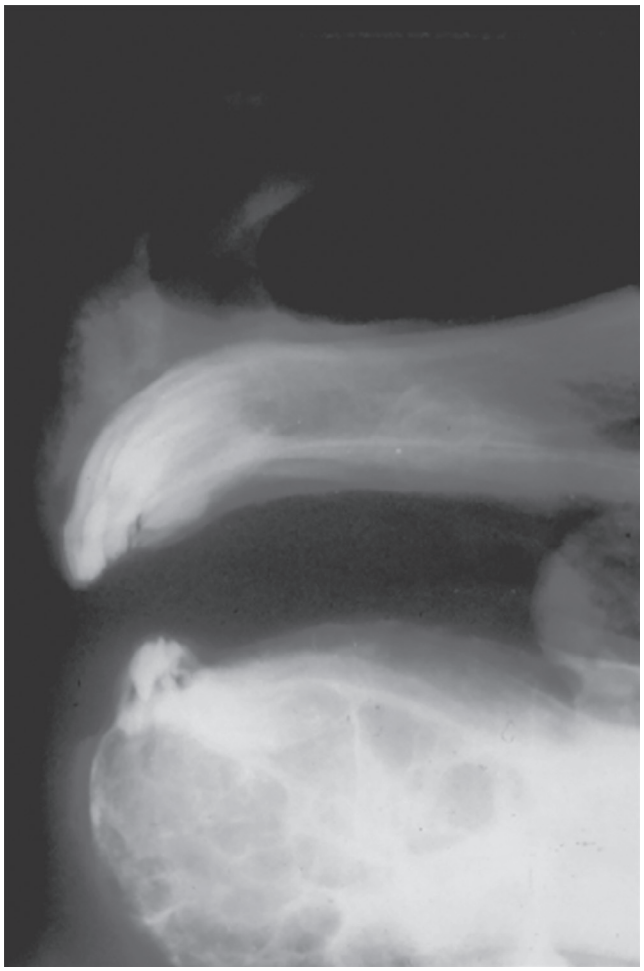


Figure 28.23 Fibrous dysplasia. A radiograph of fibrous dysplasia of the rostral portion of the mandible of a young horse. *(Figure reprinted from Easley J, Dixon P, Schumacher J. Equine Dentistry. Edinburgh: Saunders; 2011: 177 (Fig. 11.24), copyright 2011, reprinted with permission from Elsevier.)*

Disease summary

Notes

Carcinoma is the only reported primary oesophageal neoplasm. It is exceedingly rare.

Clinical features

Weight loss, recurrent choke and [haemo]ptyalism may be features.

Diagnostic confirmation

Endoscopy and grab biopsy, pleuroscopy of thoracic portion of oesophagus, biopsy.

Management

Treatment options are limited and, in any case, most cases are presented in an advanced and untreatable state.

Prognosis

Prognosis is hopeless.

Description

Neoplasia is a very rare cause of luminal distortion or obstruction of the oesophagus. Squamous cell carcinoma of the oesophagus, although of significance in human medicine, is the only reported neoplasm affecting the oesophagus of the horse.[9] In the few reported cases, there appear to be a predilection for the thoracic (smooth muscle) portion of the oesophagus, or more distally in association with gastric squamous cell carcinoma.[74,75] There are only two reports of involvement of the cervical portion of the oesophagus.[76,77] The aetiology is unknown. Most cases were mature horses and no sex or breed predilection is reported.

Clinical features

(Fig. 28.24)

- Generalized weight loss and depression
- Recurrent choke, ptyalism, eructation and 'gagging'
- Intermittent colic and abdominal guarding
- Rarely, a palpable mass may be present if the cervical portion of the oesophagus is affected
- Inability to pass a nasogastric tube may alert the clinician to a problem
- Early lesions may be subtle and it is expected that, with the more routine use of gastroscopic investigations, it might be recognized as haemorrhagic ulcerated areas within the oesophageal wall
- Oesophageal motility impairment may be recognized in the region of the neoplasm.

Differential diagnoses

- Non-neoplastic lesions presenting similarly include oesophageal ulceration, strictures and diverticuli or recurrent choke secondary to feed impaction
- Foreign body and perforation caused by them or other causes, leading to chronic mural abscessation
- Neoplasia involving the cervical region or thoracic cavity may cause extraluminal compression of the oesophagus and similar general clinical signs
- Congenital anomalies, such as oesophageal duplication cysts, may also present similarly. However, they tend to present in young animals, unlike reported cases of oesophageal squamous cell carcinoma, which have exclusively affected mature horses.

Diagnostic confirmation

- Visualization of the lesion via endoscopy enables a 'grab' biopsy of the mass to be taken; such biopsies need to be multiple, since they are very small and there is usually extensive local inflammatory reaction.
- Pleuroscopic examination and direct biopsy of the visible lesion have been reported for neoplasia involving the thoracic portion of the oesophagus.[75]

Management and prognosis

1. There are no successful reports of treatment of oesophageal neoplasia in the literature.
2. Treatment options are extremely limited because of the difficulty of access. Additionally, the cases are presented very late and so treatment is invariably



Figure 28.24 Oesophageal carcinoma. (A) This 14-year-old pony gelding was presented with a 4-month history of recurrent choking episodes and eructation and progressive swelling of the neck, particularly affecting the left side. The referring veterinarian had noted a foul smell on the stomach tube and some difficulty in passing the tube into the stomach. Gastroscopy revealed little of significance apart from distortion of the distal oesophagus and cardia with small bleeding ulcers. Radiography confirmed the presence of a mass in the caudal mediastinum. **(B)** At necropsy an oesophageal carcinoma was identified that affected the distal third of the oesophageal wall. There was remarkably little evidence of the tumour on oesophagoscopy.

impossible. Early lesions might provide opportunities for local chemotherapy or radiotherapy.

3. Prognosis is therefore probably hopeless.

Gastrointestinal neoplasia

See also page 305.

Overview

The gastrointestinal tract and abdominal organs are susceptible to a variety of primary tumours as well as metastatic tumours. The type of tumour is determined by the cell types present in the tissue and the distribution of blood flow and lymphatic flow to that tissue. With a few notable exceptions, neoplasia of the gastrointestinal tract is uncommon. It has generally been associated with geriatric horses presenting with signs including:

- Weight loss
- Intermittent, progressive or acute-onset, non-responsive, colic
- Variable faecal consistency with faecal blood
- Intermittent undulant pyrexia
- Lethargy and anaemia
- Anorexia and salivation.

However, there are also several tumours that occur within the abdomen in young/neonatal horses.

Gastric neoplasia is rare in horses, accounting for 1.5% of all equine neoplasms.[4] In humans, adenocarcinomas account for >90% of gastric neoplasms; risk factors associated with the development of human gastric neoplasia include *Helicobacter* spp. infection. *Helicobacter* spp. infection has been reported as a possible cause of equine glandular ulcers in horses, but its relationship to equine gastric neoplasia is unknown. The risk of adenocarcinoma in the horse is relatively low considering the 1:1 ratio of squamous:glandular epithelium.[78]

Other potential predisposing factors reported in horses include dietary excesses (nitrosamines) or deficiencies (proteins, trace minerals, riboflavin, vitamin A, vitamin E) and chronic irritation.[79,80]

In horses, squamous cell carcinoma (SCC) is the most common gastric neoplasm and accounts for 3–4% of all SCC cases.[4,9,10] One report suggests that gastric SCC is the most prevalent primary neoplasm of the gastrointestinal tract.[9] Another report suggested an equivalent prevalence of primary intestinal lymphoma.[78] Other gastric neoplasms previously reported in the horse include leiomyoma, leiomyosarcoma, gastrointestinal stromal tumour, papilloma, a benign polyp, mesothelioma and lymphoma.[4,81–83] The history and clinical signs associated with gastric neoplasia are frequently vague and seldom localize the disease process to the stomach (Table 28.4). The prognosis is grave because surgical resection of equine gastric neoplasms is impossible. Critically, the tumours are frequently advanced by the time a diagnosis is made and widespread transcoelomic and lymphatic/haematological spread has occurred. Metastasis is common. The condition is best regarded as fatal and most horses die or require early euthanasia. However, with the increasing use of gastroscopy, it is likely that earlier lesions will be detected and then some treatment options may open up.

In 24 gastric neoplasms in one report, 19 were squamous cell carcinoma, two were leiomyoma, and one lymphoma, one mesothelioma and one adenocarcinoma were reported. The mean age for gastric tumours in this study was 18 years, higher than previously reported. There was no sex or breed predilection; this also differs from previous reports.[78]

Since the early signs are usually very subtle or subclinical, there is wide variation in duration of clinical signs prior to presentation.

- *The most common presenting clinical sign is inappetence* (71%), which most likely occurs because of one or more of the following[78,84,85,87,88]:
  - Space-occupying mass in the lumen of the stomach, abdominal pain (colic), which may be associated with swallowing or after eating, gastric ulceration, oesophagitis, oesophageal obstruction and eructation.

Table 28.4 Summary of case reports/series of equine gastric neoplasia (SCC, squamous cell carcinoma)

Ref. No.	Tumour	Age (years)	Sex	Breed	Presenting sign	Outcome
78	SCC (*n*=19), leiomyoma (*n*=2), lymphoma (*n*=1), mesothelioma (*n*=1), adenocarcinoma (*n*=1)	Range: 9–25 Median: 18	58% G 38% F 4% M	38% QH, 21% Arab, 16% QHX, 25% other	Inappetence (71%), weight loss (58%), lethargy (29%), hypersalivation (29%), colic (21%), pyrexia (21%), halitosis (8%), choke (4%)	22 euthanized 2 died
84	SCC	12	M	SB	Anorexia, cough, colic, 2 weeks	Euthanasia
85	SCC	10	F	Walking Horse	Colic, anorexia, 10 days	Died
	SCC	9	G	TB	Anorexia, weight loss 3 months	Died
	SCC	15	F	Appaloosa	Anorexia, weight loss 1 months	Died
	SCC	10	G	XB	Anorexia, weight loss 3 months	Euthanasia
	SCC	14	F	Palomino	Anorexia, weight loss 2 weeks	Euthanasia
	SCC	13	F	TB	Lethargy, fever, anorexia, weight loss 3 weeks	Euthanasia
75	SCC	15	G	QH	Chronic intermittent colic	Euthanasia
83	Hyperplastic polyp	13	G	Arab	Acute colic	Euthanasia
81	Leiomyosarcoma	12	G	TB	Anorexia, weight loss, intermittent fever	Euthanasia
86	SCC (*n*=5)					
87	SCC	20	G	XB	Anorexia, cough, colic 2 weeks	Euthanasia
88	SCC	17	G	Paint	Respiratory distress, severe weight loss, anorexia, lethargy	Euthanasia
	SCC	9	M	QH	Lethargy, weight loss 2 months	Euthanasia
	SCC	17	G	Arab	Weight loss, anorexia, lethargy 2–3 weeks	Euthanasia

  - Eructation is usually accompanied by a necrotic odour.
  - Repeated bruxism and gagging and arching of the neck after swallowing, and very slow eating are likely.
- Other clinical signs reported:
  - *Weight loss* is generally associated with inappetence and cachexia and is commonly reported in gastric and intestinal neoplasia.
  - *Colic* may be associated with pain because of impaired gastric outflow and/or abdominal metastases.
  - *Tachycardia* is associated with anxiety, abdominal pain and anaemia.
  - *Hypersalivation* is associated with narrowing of distal oesophageal lumen into the cardia because of either distal oesophageal hypertrophy or neoplastic infiltrates.
  - *Fever* is commonly associated with SCC and is likely associated with inflammation secondary to neoplasia, immune response to a necrotic mass or leakage of ingesta into the peritoneum.[78]
  - *Lethargy/anaemia*
  - *Oesophageal obstruction*.[78]

Diagnostic confirmation

The diagnostic evaluation of gastric or gastrointestinal neoplasia is appropriate in any horse presenting with any of the clinical symptoms outlined above and should consist of a detailed history, complete physical examination including careful rectal examination, routine haematology and biochemistry, and peritoneal fluid analysis. Endoscopy, transabdominal ultrasonography, laparoscopy and laparotomy can be used to further evaluate the case.[89]

Notes

Most cases of equine gastric neoplasia were reported before gastroscopy was readily available. Gastroscopy may appear normal in cases with smooth muscle or serosal tumours since the mucosa is typically unaffected. However, a mural mass may create a convex bulge, which may be investigated with contrast radiography or laparoscopy.

Gastroscopy may reveal an abnormal proliferative mass (single, multinodular or diffuse and irregular) in the squamous portion of the stomach, and all of these are suggestive of gastric SCC.

- *Rectal examination* may reveal abnormal findings in up to 67% of abdominal neoplasia cases; findings may include abnormal mass(es), small intestinal distension and caecal impaction.[78] Rectal palpation is therefore valuable, but negative findings do not exclude metastatic disease because the tumours may be too small or may be restricted to inaccessible parts of the abdominal cavity.
- *Routine haematological analyses* usually show nonspecific markers of chronic inflammation, such as hypoalbuminaemia, hyperglobulinaemia and hyperfibrinogenaemia. Anaemia tends to be the most

common clinical pathological abnormality.[78,85] In one case series, 19% of cases showed elevation in liver specific enzymes and all of these had liver metastases. Hypercalcaemia of malignancy has been reported in cases of gastric neoplasia.[78]

- *Endoscopic biopsy* is frequently non-diagnostic, but should still be performed.
- *Gastroscopy* should be performed if clinical signs and clinical pathological data suggest gastric disease, but failure to identify an abnormality does not rule out gastric neoplasia. Gastric ultrasonography has been used for diagnosis of gastritis, impaction, distension and neoplasia. Ultrasonographic findings may include a heterogenous mass in the left side of the abdomen associated with the greater curvature of the stomach. Metastatic lesions may be identified in the liver, spleen, omentum and peritoneum, and peritoneal effusions may also be identified. In one study, ultrasound findings strongly correlated with post-mortem findings, making it a valuable diagnostic tool for investigation of gastric disease.[78] Abdominocentesis will vary from normal if the mass is confined within the stomach, to an exudate if the mass has spread. Neoplastic cells from a primary gastric SCC will only rarely be observed in peritoneal fluid. Therefore, the absence of inflammatory or neoplastic cells in peritoneal fluid does not exclude a diagnosis of gastric neoplasia.[78,89]

Management and prognosis

No successful treatment of any gastric neoplasia has been reported.

Treatment of most abdominal neoplasia is restricted in horses because of poor accessibility of much of the abdominal viscera, financial constraints of extensive surgical procedures and chemotherapeutics, but mostly because of the advanced stage of disease by the time diagnosis is reached. However, focal lesions and, more particularly, focal benign lesions, can sometimes be surgically corrected.

Prognosis is poor.

Gastric squamous cell carcinoma

See also page 230.

Disease summary

Notes

Rare highly malignant tumour predominately occurring in middle-aged and older horses.

Clinical features

Weight loss, fetid/necrotic odour on the breath, especially after eructation, dysphagia/slow eating with pain during and after feeding, recurrent colic.

Diagnostic confirmation

Gastroscopy is important; biopsy may be possible.

Management

No treatment is possible.

Prognosis

Prognosis is hopeless.

Description

There are two types of SCC based on growth characteristics – erosive and productive/proliferative – and some cases have both types of morphology.

The majority of gastric SCCs are locally aggressive and invasive but are slow to metastasize to local lymph nodes and lung. Transcoelomic spread is common and haematogenous spread to the liver is a feature of some cases.

One study reported a 4:1 male:female ratio.[90] A mean age range of 8.6–14.6 years old has been suggested.[79] Breeds reported to be at increased risk included Draft breeds, Appaloosa, Paint, Pinto and mixed breed horses.[79,91] Some studies have, however, shown no sex or breed predisposition.[78]

The potential role of *Gasterophilus* spp. or *Draschia* spp. larvae in the pathogenesis of gastric carcinoma is uncertain.

Clinical features

- Progressive weight loss
- Malodorous breath and eructation
- Slow eating pattern, dysphagia, intermittent choke and frequent attempts to swallow (gagging)
- Undulant pyrexia
- Recurrent low-grade colic, particularly occurring post-prandially or associated with feeding
- Signs of respiratory distress associated with pleural effusion and metastasis
- Paraneoplastic signs, including anaemia and hypercalcaemia, may be the first clinical evidence in early cases.

Differential diagnoses

- Gastric ulceration syndrome
- Oesophageal neoplasia/obstruction/foreign body/perforation and diverticulum
- Parasitism (gastric/intestinal).

Diagnostic confirmation

- Gastroscopy with biopsy is most useful in making an ante-mortem diagnosis (Fig. 28.25).
- Rectal examination may reveal an abdominal mass or caudal displacement of the spleen. Enlarged mesenteric lymph nodes or even small coelomic tumours may be identified per rectum.
- Contrast radiography can be helpful also but requires powerful radiography equipment for adult horses.
- Abdominocentesis may occasionally reveal neoplastic cells or an exudative effusion.

Management and prognosis

- No treatment is possible. No successful treatment options have been reported in the literature. No attempts should be made to remove any gastric tumours in horses.
- The rate of progression is usually high and from an early diagnosis to death/euthanasia on humane grounds is usually only a matter of months.
- All gastric SCCs are primary neoplasms and the majority occur as a single mass[75,78,84,86,88,92,93]; with a metastasis rate of 68% in one study.[78] Neoplastic

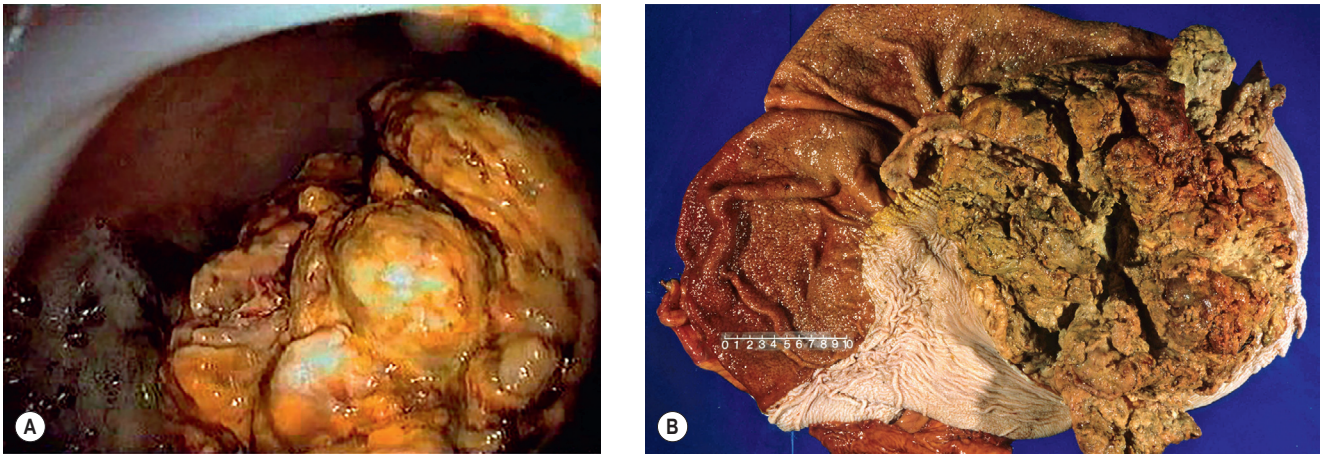


Figure 28.25 Gastric (squamous cell) carcinoma. (A) Gastroscopy is extremely helpful in making a diagnosis of gastric carcinoma. When the lesions are large, biopsy of diagnostic tissue can be difficult, and when they are small, the tumours may be overlooked unless careful examination is made. **(B)** At necropsy, the gross proliferative and ulcerative nature of the carcinoma is very obvious.

transmural (transcoelomic) extension to the serosa is common, highlighting the need for early diagnosis.[78]

Leiomyoma/sarcoma

See also page 307.

Disease summary

Notes

Very rare.

Clinical features

Nonspecific signs, including anorexia, weight loss and intermittent fever.

Diagnostic confirmation

Gastroscopy if extension to gastric mucosa has occurred, ultrasonography, exploratory laparotomy, biopsy.

Management

No treatment is currently possible.

Prognosis

Prognosis is hopeless, but progression may be slow and the tumour has a benign pathological behaviour.

Description

Gastric leiomyoma is a benign tumour of gastric smooth muscle. It mainly causes clinical signs associated with a space-occupying lesion. In one study, leiomyoma presented as a large solitary mass arising from the muscularis of the squamous region of the stomach.[78]

In some cases, it is reported to extend into the mucosa, where it may be identified at gastroscopy, but it has not been reported to invade the serosa or to metastasize.

Gastric leiomyosarcoma is a malignant neoplasm originating from smooth muscle that is locally slowly invasive and slow to metastasize.

Unlike SCC, gastroscopy may not detect the intramural mass, making ante-mortem diagnosis difficult. The single reported case was identified during an exploratory laparotomy.[81]

Clinical features

- Clinical signs are nonspecific and associated with the presence of a space-occupying mass.
- Nonspecific signs include weight loss, inappetence, intermittent fever and recurrent colic.

Differential diagnoses

- Other gastric neoplasms
- Gastric ulceration syndrome
- [Chronic] Gastric impaction.

Management and prognosis

- No successful treatment is reported and it is best regarded as untreatable.
- Prognosis is hopeless, but both the benign and malignant forms are very slowly progressive.

Gastric adenocarcinoma

See also page 265.

Disease summary

Notes

Very rare tumour of the glandular structures of the stomach.

Clinical features

Nonspecific signs of weight loss, inappetence, intermittent fever and colic.

Diagnostic confirmation

Gastroscopy, transabdominal ultrasonography, exploratory laparotomy, biopsy.

Management

No treatment is possible.

Prognosis

Prognosis is hopeless – most cases are presented very late in the course.

Description

Gastrointestinal adenocarcinoma is rare in the horse, with the majority of cases involving the colon.[94] Adenocarcinoma originates from glandular crypt epithelium, and has only been reported in older horses.

Cotchin (1977) cites a report published in 1941 by Thoonen and Ide of a primary gastric adenocarcinoma.[9] One other primary gastric adenocarcinoma presented with encephalopathy secondary to portal vein metastasis and thrombosis.[92]

Clinical features

Clinical signs are vague and, by the time of diagnosis, invasion of regional lymph nodes and metastasis to mesenteric lymph nodes, liver and lungs is likely. In one case, necropsy revealed multiple masses on the serosa of the stomach, with other small masses on the parietal peritoneum, omentum, spleen and liver, appearing to originate from the pancreas or biliary tree and not from the glandular epithelium of the stomach.

Differential diagnoses

- Other gastric/intestinal neoplasia
- Gastric ulceration syndrome.

Diagnostic confirmation

- Difficult to make ante-mortem diagnosis
- Exploratory laparotomy and biopsy.

Management and prognosis

There have been no successful reports of treatment of gastric adenocarcinoma in the horse.

Surgical excision has not been attempted in the horse.[78,92]

The prognosis is best regarded as hopeless.

Intestinal neoplasia

See also pages 307 and 346.

Overview

Intestinal neoplasia is generally rare in horses.[5] Lymphoma (alimentary form) is the most common equine intestinal neoplasm.[4,95–104] Lipoma is, however extremely common in older horses where it has a significance in causing strangulating obstructions of the small and large intestine.

Intestinal neoplasms reported in the horse include:

- Lipoma[105–107]
- Lymphoma
- Adenocarcinoma[108–114]
- Leiomyoma[115]
- Leiomyosarcoma[116–119]
- Haemangiosarcoma
- Myxosarcoma[82,120–122]
- Ganglioneuroma[123,124]
- Nerve sheath tumour[125,126]
- Carcinoid.[127]

Diagnosis of intestinal neoplasia in the horse is frequently a challenge, as presenting signs are very similar to many other clinical conditions. The general clinical signs will include one or more of the following:

- Weight loss
- Decreased appetite
- Chronic/recurrent acute colic
- Diarrhoea
- Intermittent fever
- Tachycardia/tachypnoea
- Hypoalbuminaemia.

Differential diagnoses

- Inflammatory bowel diseases
- Non-intestinal, intra-abdominal neoplasia
- Internal abscessation
- Hepatic disease, e.g. cholangiohepatitis
- Parasitism
- Renal disease.

Diagnostic confirmation

A definitive diagnosis is important because the treatment options and management of these diseases is variable.

- A complete haematological and biochemical profile usually reveals nonspecific markers of chronic inflammation, such as hypoalbuminaemia, hyperglobulinaemia and hyperfibrinogenaemia. Anaemia may be present, as may leukocytosis and a mature neutrophilia.
- Rectal examination may reveal abnormal findings, including a palpable intra-abdominal mass/masses in around half of the cases.
- Abdominocentesis frequently reveals a transudate or modified transudate with mild elevations in total nucleated cell counts and total protein concentrations. In one study, a diagnosis of lymphoma was confirmed by cytological examination in 21% of cases.[14]
- Complete transabdominal ultrasonography is very useful in all the tumour types, with subtle and obvious variations that support the diagnosis. Abnormalities of the small intestine, including increased wall thickness (4–15 mm), hypomotility and intraluminal masses, may be identified in up to 73% of cases; in most they are located in the ventral abdomen. Abnormalities of the large colon may be found in 54% of cases. Other abnormalities identified may include evidence of hepatopathy (rounded margins, enlargement or masses), splenic masses and increased peritoneal fluid.
- Rectal biopsy is a simple diagnostic test that may support a diagnosis, although it lacks specificity and sensitivity. However, it should always be performed as it may reveal a diagnosis. Similar support may be obtained from transendoscopic duodenal biopsies.
- Exploratory coeliotomy or exploratory laparoscopy and collection of intestinal biopsies is a routine approach to many of the cases. A definitive pathological diagnosis can usually be made from biopsies collected at the time of surgery.
- A definitive ante-mortem diagnosis is made in only one-third of cases, despite extensive diagnostic work-up. However, of those cases diagnosed at post-mortem, almost all had shown ultrasonographic abnormalities.

Management

Treatment options are frequently limited by the late stage at presentation and the presence of metastases. However, treatment of lymphoma with corticosteroid drugs has been reported to be successful, particularly in T-cell-rich B-cell lymphoma either solely or in conjunction with complex chemotherapy regimens, including doxorubicin (see p. 152). Single or focal or regional masses, such as adenocarcinoma, may be amenable to surgical resection and the outcome will depend on the nature and pathological behaviour of the tumour and the ability to remove the entire problem. An early diagnosis is clearly a fundamental requirement but that is often difficult in itself.

Prognosis

Prognosis is generally poor to hopeless for most serious intestinal cancers. One study reported the time from onset of clinical signs to euthanasia or death as 1.9 months, and although some cases may be treated, all cases are ultimately euthanized because of the intestinal neoplasia.[14]

Intestinal lymphoma

See also page 346.

Disease summary

Notes

Rare, but still the most common haematopoietic neoplasm; 19% of lymphoma cases affect the alimentary tract.

Clinical features

Weight loss, lethargy and anorexia. Chronic/recurrent or in some cases more acute colic and/or diarrhoea depending on the location and nature of the tumour.

Diagnostic confirmation

Biopsy of affected lymph node or mass, or cytological examination of peritoneal. Immunophenotyping will identify the precise tumour type.

Management

There is no sensible treatment for extensive or advanced lymphoma, but surgical resection or radiotherapy may be applied to solitary or localized tumour. Systemic chemotherapy centred on doxorubicin and other agents can be attempted.

Prognosis

Therapy should be viewed as palliative. Short-term prognosis for cases with localized or regional lymphoma is fair, but long-term prognosis is likely hopeless.

Description

Lymphoma, although rare, is the most common malignant neoplasm and the most common haematopoietic neoplasm in the horse. Primary alimentary lymphoma appears to arise from intestinal lymphoid tissue in the mucosal lamina propria. leading to an abundance of neoplastic cells in the mucosa and submucosa.

Lymphoma is conventionally classified into[128]:

- Multicentric
- Alimentary
- Mediastinal
- Cutaneous
- Solitary.

Multicentric lymphoma is the commonest form, and in one study, 19% of all lymphoma cases were the alimentary form.[96] Previous studies have reported age at diagnosis to be 8–10 years for all forms of lymphoma.[129,130] An older mean age at presentation of 16 years has also been suggested.[109] This may indicate that the alimentary form of lymphoma tends to occur at an older age compared with other forms of lymphoma.

Alimentary lymphoma is likely to affect multiple segments of intestine in young horses (<10 years), while focal intestinal lesions are often more likely to occur in older horses.[109] Immunohistochemistry may be helpful in differentiating B-cell lymphoma from T-cell lymphoma in some cases. Metastases are common by the time a definitive diagnosis is made and few studies have reported an absence of metastases.

Clinical features

(Fig. 28.26)

- Weight loss
- Lethargy/anaemia
- Anorexia/pica
- Recurrent, chronic or occasionally acute colic
- Diarrhoea, possibly with faecal blood.

Differential diagnoses

- Other intestinal neoplasms
- Other intra-abdominal non-intestinal neoplasms
- Other causes of intestinal and non-intestinal abdominal pain:
  - Hepatic disease
  - Renal diseases
  - Inflammatory bowel diseases
  - Internal abscessation
  - Parasitism.

Diagnostic confirmation

- Investigation of a horse with suspected lymphoma should include a complete physical examination, including palpation of peripheral lymph nodes and palpation of accessible abdominal organs by rectal examination.
- Horses with lymphoma are usually anaemic as a direct result of premature destruction of antibody-coated erythrocytes, inadequate production of erythrocytes due to myelophthisis and chronic inflammation or blood loss through intestinal ulceration. Leukocytosis with neutrophilia occurs as a result of tumour necrosis. Circulating lymphocytes may be normal in number in intestinal lymphoma – lymphocytic leukaemia is extremely uncommon unless there is extensive bone marrow involvement. Nonspecific biochemical abnormalities include hypoalbuminaemia, hyperglobulinaemia and hyperfibrinogenaemia. Hypoalbuminaemia is most likely associated with protein-losing enteropathy, or if there is metastasis to the liver, may be a result of decreased production by

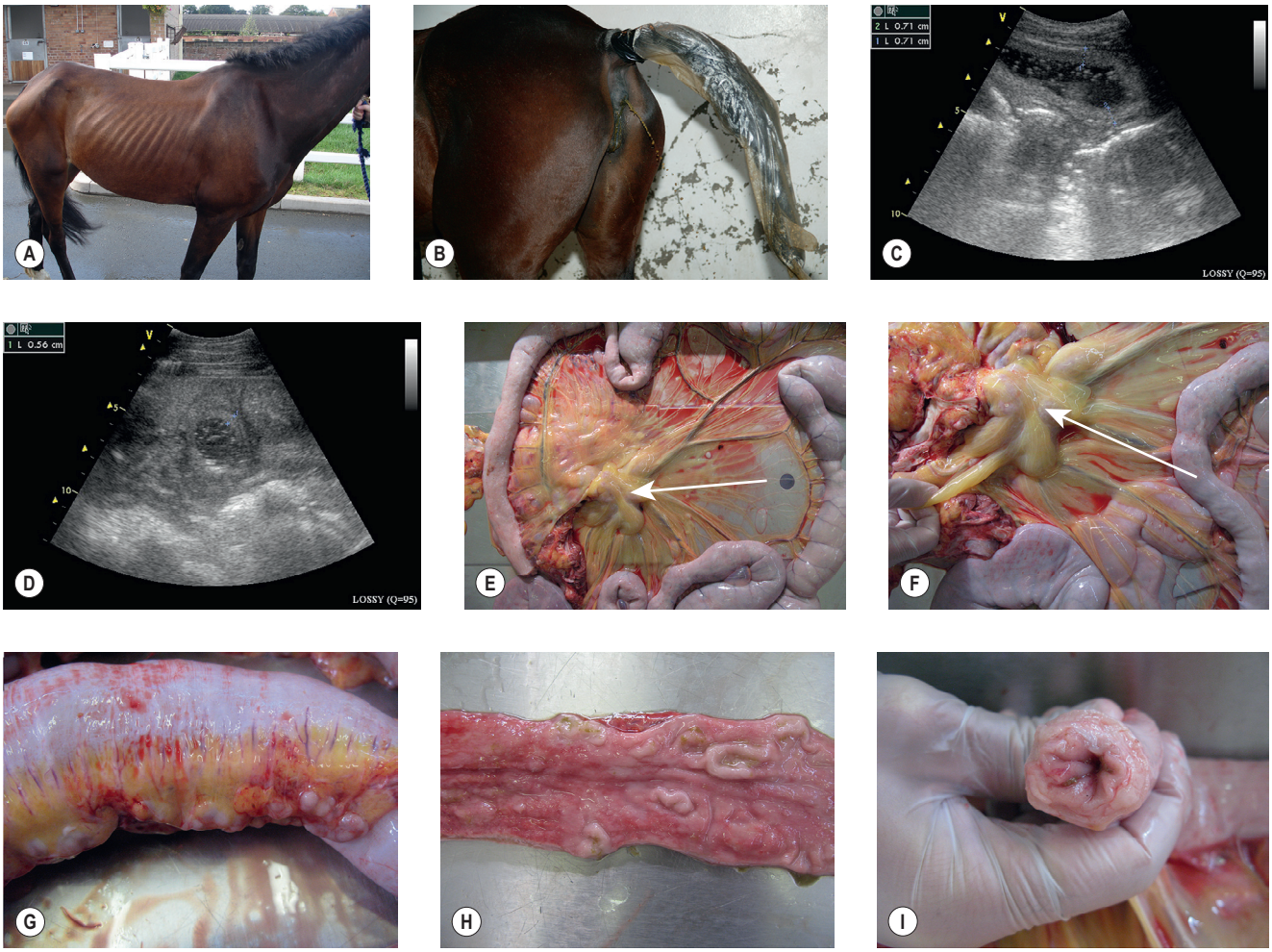


Figure 28.26 Intestinal lymphoma. (A,B) This 12-year-old part-bred mare was presented with weight loss and progressively severe diarrhoea. She showed intermittent pyrexia and mild abdominal pain but was otherwise quite bright. Apart from a low albumin and moderate hypergammaglobulinaemia, she showed few other signs of a major problem. **(C,D)** Ultrasonography revealed generalized echodense thickening of the large and small intestine and myriad focal solid areas. The latter were also identified by rectal examination. Abnormal lymphocytic cells were identified in the peritoneal fluid. **(E–I)** At necropsy, a diffuse intestinal lymphoma was diagnosed. Focal intestinal tumour masses were distributed throughout the tract and extended into the mesenteric lymph nodes (arrows). Immunostaining confirmed this to be a T-cell lymphoma and was restricted to the intestinal tract.

the liver. Although hypercalcaemia of malignancy may be observed, horses with intestinal lymphoma are frequently hypocalcaemic because they are hypoalbuminaemic.
- Ultrasonography of thorax and abdomen is very useful.
- Aspiration or biopsy of affected lymph nodes or masses identified by ultrasonography.
- Cytological examination of peritoneal fluid.
- Immunophenotyping by immunohistochemistry and flow cytometry, to categorize lymphoma into B- or T-cell origin. Alimentary lymphomas are generally T-cell origin and generally more aggressive and carry a poorer prognosis than B-cell lymphoma.

Management

- It is important to consider the horse's overall physiological status, location and extent of disease and the client's financial and emotional commitment to treatment.
- Staging of lymphoma may help determine appropriate treatment options, if any.
- If a solitary mass is identified, surgical resection may be appropriate (Fig. 28.27). However, by the time of diagnosis, metastasis is common, and surgical therapy is not warranted. Surgical resection of lymphoma of the large colon has been reported.[6] In one case, the horse was reported to be healthy at 18 months post-surgery. The other horse was euthanized 14 months post-surgery because of development of multicentric lymphoma.
- Several multi-drug chemotherapeutic protocols including doxorubicin have been reported for treatment of equine lymphoma with varying success (see p. 152). Anecdotal reports of remission of 1–2 years are present in the literature, while therapy is continued. However, once therapy is discontinued, the lymphoma usually returns.

Prognosis

- Treatment responses and outcomes are not yet established. However, most cases diagnosed are at a late stage and therefore short-term prognosis may be fair with therapy, but long-term prognosis at present is

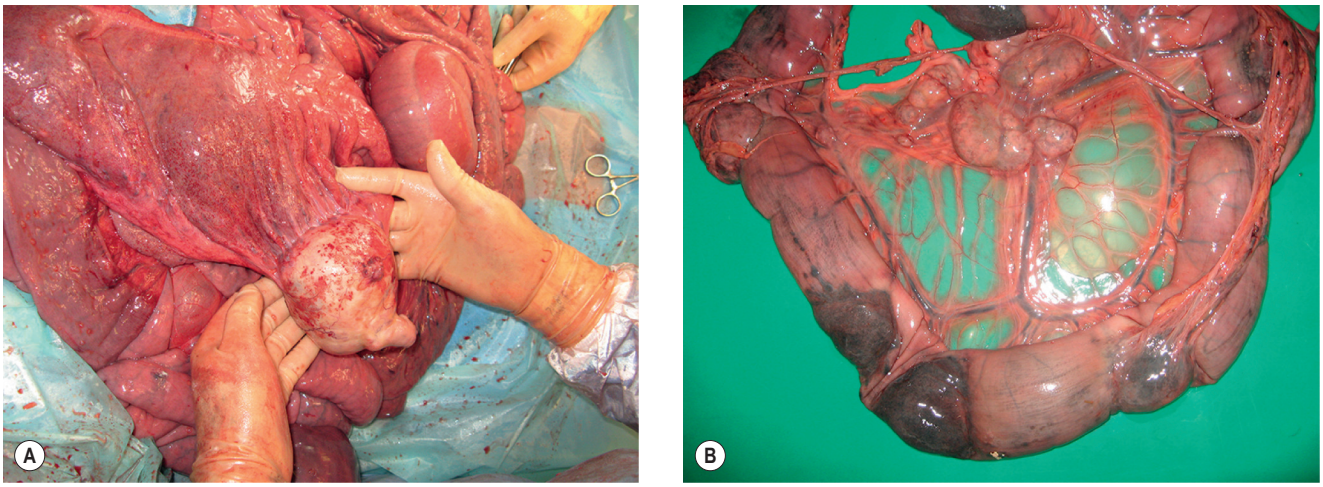


Figure 28.27 Focal intestinal lymphoma. Intestinal lymphoma can be focal or regional and these do then offer some opportunity for effective surgical therapy. **(A)** This focal mass was identified in a horse with recurrent mild colic over 8 months. No other problem was identified and the mass was resected. The horse survived for at least 5 years without any problem. This was a B-cell lymphoma. **(B)** A 14-year-old Thoroughbred mare presented with severe colic following several milder episodes over 14 months. A regional T-cell lymphoma was identified and an enterectomy of the affected segment was carried out. The mare recovered well but developed weight loss and succumbed to a further undiagnosed colic episode some 14 months later.

poor, with any treatment being palliative rather than curative.

Adenocarcinoma

See also pages 265 and 266.

Disease summary

Notes

Very rare.

Clinical features

Weight loss, inappetence, lethargy, intermittent fever and recurrent colic.

Diagnostic confirmation

Transabdominal ultrasonography may reveal the presence of intra-luminal masses, exploratory laparotomy allows direct examination and biopsy.

Management

Surgery may be feasible if the condition is focal and detected very early and it is situated in an anatomically convenient location.

Prognosis

Early cases carry a better prognosis, but a poor prognosis is advised even if the affected gut can be resected. Most cases are presented in an advanced state and recurrence and early metastatic spread are likely.

Description

Adenocarcinoma is an uncommon tumour of the gastrointestinal tract originating from the glandular crypt epithelium, and accounts for <1% of all equine neoplasms.

The small intestine is possibly the predominant site, but some studies have reported that either no predominant location was noted or the large intestine was the predominant location.[109,111,112]

Adenocarcinoma affects older horses for the most part, but some younger horses may be affected also. By the time clinical signs are noted, there has usually already been significant invasion of regional lymphatics as well as metastasis to mesenteric lymph nodes, liver and lungs.

Clinical features

(Fig. 28.28)

- Recurrent colic is a the common presenting clinical sign, and is likely associated with obstruction caused by the increasing size of an intraluminal mass

Some reports of adenocarcinoma of the large colon include the caecum.[131] Tumours have been reported at the base of the caecum near the caecocolic junction.

1. Mass lesions have been found affecting the following:
   a. Right ventral colon[132]
   b. Right dorsal colon and the transverse colon.[113,133]
2. One case of osseous metaplasia resulted in intestinal obstruction and colic secondary to osteoid production.[133]

Diagnostic confirmation

- The presence of an intraluminal mass can be identified by complete transabdominal ultrasonography in most cases of intestinal adenocarcinoma.[1]
- Collection of intestinal biopsy by exploratory laparotomy will provide a definitive diagnosis.

Management

There are few reported cases with a successful treatment outcome.

Surgical resection of three cases of jejunal adenocarcinoma has been reported.[109] Owing to the pattern of invasion, adenocarcinoma often has annular infiltration. Caecal rupture at surgery secondary to a spherical caecocolic

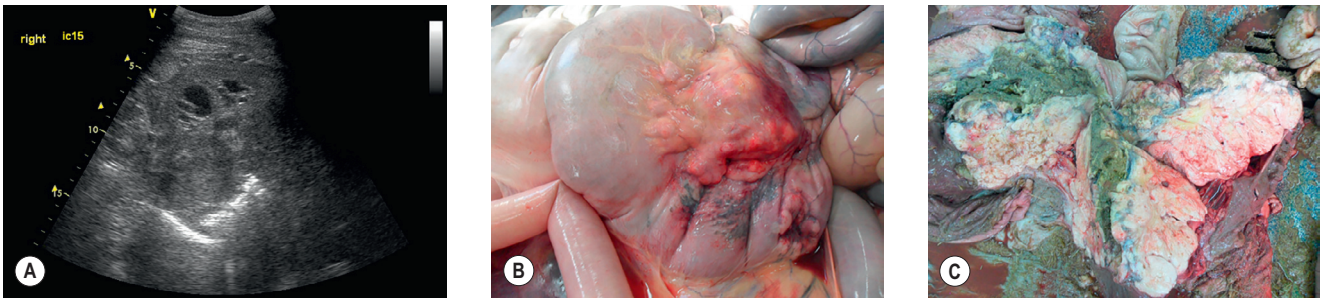


Figure 28.28 Intestinal adenocarcinoma. A 12-year-old Warmblood mare was presented with weight loss and increasingly severe colic. A mass was identified per rectum associated with the head of the caecum and this was also demonstrated by ultrasonography. **(A)** The mass was of variable echodensity and had an ill-defined margin. Peritoneal fluid showed active mesothelial cells and evidence of inflammation but no abnormal cells. **(B,C)** At necropsy, an intestinal adenocarcinoma was identified involving the caecocolic and ileocaecal regions with extensive necrosis within the mass. The caecal and mesenteric lymph nodes were infiltrated but no remote sites were involved.

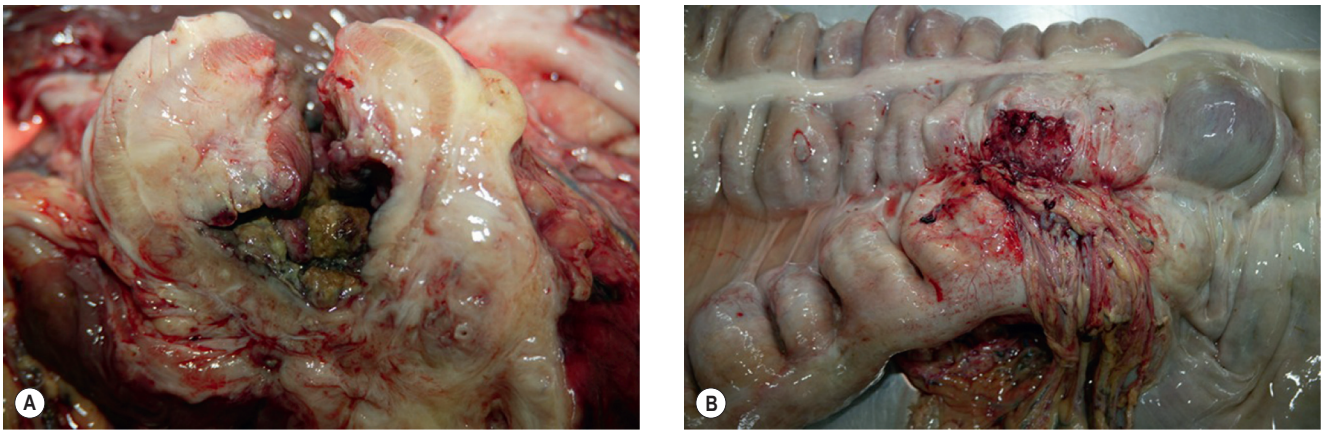


Figure 28.29 Intestinal leiomyosarcoma. A 12-year-old TBx mare was presented with intermittent colic, intermittent melaena and persistently positive faecal haemoglobin and albumin. An ultrasound examination showed a focal, ulcerated echodense mass in the right ventral colon. A mass that was diagnosed histologically as a malignant leiomyosarcoma was identified at laparotomy. The mass was removed by segmental enterectomy but the horse failed to thrive and, at necropsy, the tumour had metastasized to the liver and lung.

adenocarcinoma in a 13-year-old mare with colic has been reported.[134]

In cases of jejunal adenocarcinoma, recurrence is likely, although it may be several years after the original surgery.[109]

Prognosis

The prognosis is therefore guarded but will depend heavily on the stage of detection and the efficiency of removal of the tumour.

Smooth muscle tumours

See also page 305.

Overview

Smooth muscle tumours affecting the intestinal tract are very rare. Leiomyoma is a benign tumour of the intestinal smooth muscle that has been associated with clinical signs of recurrent colic. Colic signs are usually secondary to intestinal obstruction.[80] In one study, three out of four cases were located in the jejunum.[109] Whilst most smooth muscle tumours present with colic and are euthanized, surgical resection with a favourable outcome is possible because they are often pedunculated, well encapsulated and extraluminal. These tumours do not metastasize to distant sites.[135,136]

One report of a jejunal leiomyoma in a 16-year-old mule found an intussusception of the jejunum associated with a mass lesion. The mule was euthanized but surgical excision would have been expected to be curative.[137]

Leiomyosarcoma is a rare malignant tumour of the smooth muscle lining the gastrointestinal tract (Fig. 28.29). It tends to be locally invasive and slow to metastasize. This is the second most common primary malignant neoplasm to affect the gastrointestinal tract after adenocarcinoma.[80] Two horses reported in one study were both euthanized but, again, surgical excision may have been curative.[138]

Lipoma

See also page 294.

Description

Lipoma is a very benign tumour arising from mesenteric adipocytes that remain attached by a pedicle of variable length.

Pedunculated lipomas start as localized plaques of fat between two serosal layers of mesentery. As these aggregations enlarge, the overlying serosa stretches, forming a pedicle, which lengthens as the weight of the lipoma increases. Whilst many old ponies and horses have one or more lipomas (and often many) attached to the

mesentery, only a very small proportion cause strangulation obstructions.[106] Older horses are more commonly affected, with a mean age of 16.6–17.6 years, and geldings are over-represented.[106,107]

Clinical features

- Acute colic secondary to small intestinal obstruction or strangulation by the pedicle of a lipoma requires immediate surgical intervention (Fig. 28.30A,B). There appears to be an increased risk of pedunculated lipoma in ponies and that may be related to genetic predisposition because lipid metabolism of ponies differs from that of horses.
- Lipoma may also cause small colon obstruction and strangulation; however, this is uncommon.[139,140]
- There has only been a single case report of a lipoma causing strangulation of the rectum.[141]
- On occasion, non-strangulating intestinal obstructions can occur also.
- Necrosis of the fat is sometimes encountered but it is not known whether this is a problem within the tumour itself or if it is the pedicle that is compromised. It is possible that mild pain or other effects may arise from this.

Disease summary

Notes

A very common incidental and very benign tumour of the mesentric and intestinal fat of older horses with, possibly, very serious secondary effects.

Clinical features

Most signs are associated with acute or peracute onset of strangulating intestinal obstructions, mostly from pedunculated lipomas.

Diagnostic confirmation

The diagnosis is usually implied and confirmed on exploratory coeliotomy.

Management

Surgical resection is standard procedure for lipomas causing strangulation – removal of other lesions during the surgery may be prophylactic to some extent but, since time is vital, this is seldom performed to any significant extent.

Prognosis

Prognosis is usually excellent provided that the secondary strangulating effects are amenable to some form of correction.

Differential diagnoses

Other causes of strangulation obstruction of the small intestine vary, depending on the population of horses treated. Some of the commoner causes include:

- Epiploic foramen entrapment
- Inguinal herniation
- Incarceration of intestine in a mesenteric rent
- Incarceration by adhesions, intussusception
- Diaphragmatic hernia
- Umbilical hernia
- Others.

Diagnostic confirmation

- Exploratory laparotomy; identification of characteristic extraluminal mass causing strangulation of intestine
- Biopsy is not necessary.

Management and prognosis

Surgical resection is often curative, barring complications associated with intestinal compromise (see Fig. 28.30).[80]

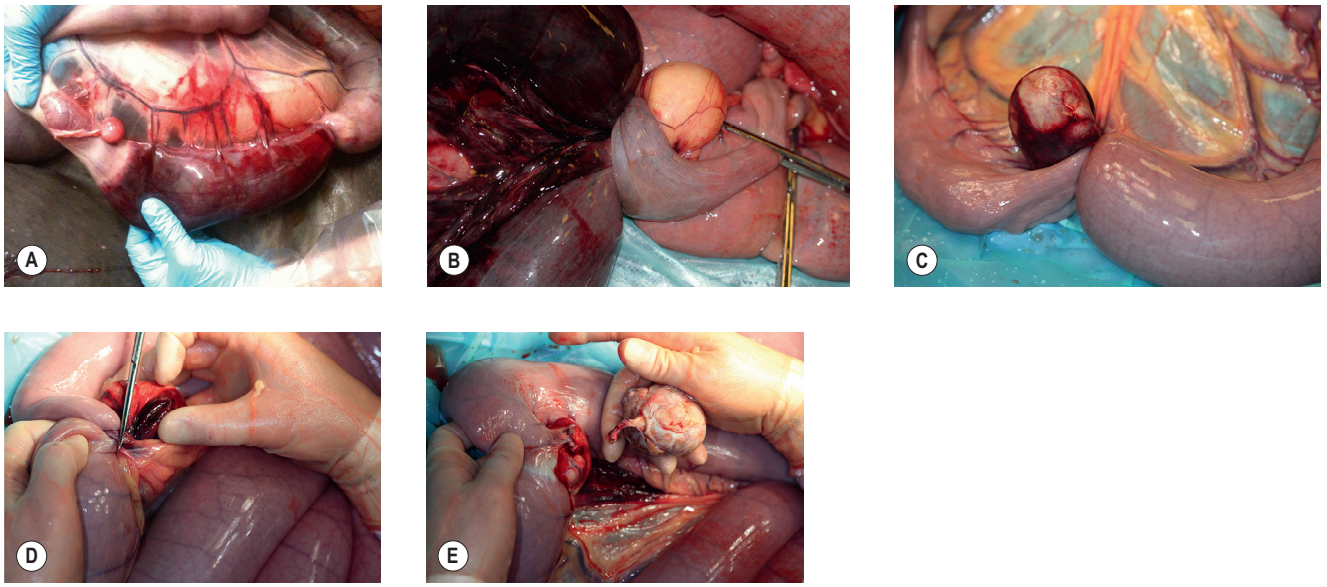


Figure 28.30 Mesenteric lipoma. Pedunculated lipoma is very common in older horses and is one of the commonest causes of strangulating intestinal obstruction. **(A)** The size of the tumour is not always the issue. Here, a very small lipoma with a long pedicle caused a strangulating obstruction of a 30 cm length of jejunum. Surgical enterectomy was simply achieved. **(B)** A longer-standing strangulation of a much greater length has correspondingly more serious implications. **(C–E)** This lipoma caused a strangulation without significant circulatory compromise, although its own blood supply was affected. Simple section of the pedicle resolved the issue without any need for enterectomy. Fortunately, the case was diagnosed very promptly.

Notes

- Lipomatosis is an uncommon benign infiltrative form of lipoma causing massive local invasion and expansion.
- Infiltrative lipomas are uncommon neoplasms which have been reported to occur in the subcutaneous and muscular tissues of dogs and other species.

They are considered to be benign histologically, and often cause massive tissue invasion as they grow by infiltration and expansion. There has been a single case report of a 7-year-old Quarter Horse gelding presenting with colic secondary to muscular and neural compromise to the intestinal wall. The transverse and small colon were dramatically affected and the horse was euthanized.[142]

Hepatic neoplasia (See p. 268)

Overview

Primary equine liver tumours are extremely rare.[143] However, metastatic disease is not uncommon in the equine liver.[80] Only 21 cases of primary liver tumours have been reported to date, of which 11 are classified as hepatoblastoma.[144–157]

Other reports of primary hepatic tumours in young horses include:

- Mixed hamartoma[156]
- Mesenchymal hamartoma[145]
- Hepatocellular carcinoma.[143,148,155]

In mature horses, cholangiocellular carcinoma and hepatocellular/cholangiocellular carcinoma have also been reported.[149,152,158] Horses with primary hepatic neoplasia range in age from later-term aborted fetuses to 3 years, and genetic influences on their formation are unknown. There is currently no classification scheme, as they are so rare. In humans, most primary liver tumours are classified as hepatoblastoma or hepatocellular carcinoma. Hepatoblastoma is more common in neonates or young children, while hepatocellular carcinoma occurs more frequently in juveniles.[143]

The clinical features will usually be nonspecific, but extensive involvement by any of the primary or secondary tumours that affect the liver will inevitably be profound.

1. Biochemical profiles of horses with hepatic neoplasia may reveal elevations in gamma glutamyl transferase, alkaline phosphatase and other hepatic enzymes, as well as elevations in bilirubin and total serum bile acids. However, no elevation or mild elevations have also been reported even in extensive neoplastic infiltration of the liver.[80,159]
2. Neoplasms of the equine liver do not commonly exfoliate into the abdominal cavity, but it is still advisable to perform abdominocentesis for cytology on multiple occasions. A non-septic peritonitis is the most common finding.[80]
3. Although ultrasonographic abnormalities are a reliable indicator of the presence of severe pathology, the sensitivity of ultrasound for the detection of hepatic disease is low and assessment is subjective.[159] Neoplastic infiltration of the liver occurs more frequently with secondary neoplasms; liver infiltration is reported in up to 40% of lymphoma cases.[129] Ultrasonographic examination of hepatic lymphoma usually presents with a diffuse increase in the echogenicity of the liver associated with the diffuse cellular infiltrate, with loss of the normal parenchymal architecture. Hepatomegaly and rounded liver margins are common. Larger discrete masses in an otherwise normal liver have been reported occasionally in horses with lymphoma. In horses with more aggressive neoplasms, such as cholangiocarcinoma and hepatocellular carcinoma, complex masses containing a heterogenous echogenicity may be imaged ultrasonographically.[155] Multifocal masses scattered throughout the hepatic parenchyma are consistent with metastatic neoplasia of other origin, such as carcinoma, haemangiosarcoma and melanoma.[160] Obvious sites for biopsy can be defined if focal pathology is identified on ultrasound examination. Hydatid cysts or hepatic abscess can possibly be confused with tumours but in these conditions biopsy is contraindicated.[159]
   - There are no possible treatments for primary or secondary/metastatic hepatic tumours.
   - The prognosis is dependent on the tumour type and how much functional compromise there is.
   - Pain is not usually a feature of hepatic tumours in horses and the early signs are subtle and nonspecific, so usually cases are presented very late.

Hepatoblastoma (HB)

See also page 270.

Disease summary

Notes

Very rare embryonic tumour.

Clinical features

Weight loss, pyrexia, congested mucous membranes, altered faecal consistency, icterus and respiratory signs if other organs are involved.

Diagnostic confirmation

Ultrasonography and guided biopsy are the only way to make an ante-mortem diagnosis.

Management

No surgical or chemotherapeutic treatment options have been described in the horse.

Prognosis

Prognosis is hopeless.

Description

Hepatoblastoma is an extremely rare malignant embryonic tumour of the liver and is of unknown aetiology. It is the most common primary hepatic tumour in human infants, but is rarely described in domestic animals.[144] However, there are a few reports of the tumour in young horses from birth to 3 years of age (Table 28.5).

Table 28.5 Summary of findings reported for primary equine hepatoblastoma

Ref. No.	Diagnosis	Age (years)	Sex	Breed	Clinical presentation	Outcome
144	HB epithelial type	10 months	F	TB	Recurrent fever, congested mucous membranes, pleural effusion	Euthanasia
147	HB epithelial type	1	F	TB	Fever, diarrhoea, inappetence	Euthanasia
151	Mixed HB with teratoid features	Stillborn	–	TB	Stillborn full-term fetus, history of dystocia	Stillborn
	Mixed HB with teratoid features	Neonate	–	–	Neonate, history of dystocia	Died
	Mixed HB with teratoid features	Neonate	–	–	Neonate, wry nose	Euthanasia
146	Mixed HB without teratoid features	10 months	M	TB	Anorexia, variable faecal consistency, tachycardia, dyspnoea, pyrexia, venous congestion	Died
150	HB epithelial type	2.5	F	TB	Lethargy, anorexia, weight loss	Euthanasia
153	HB mixed	Fetus	M	TB	Fetus	Died
154	HB mixed	3	G	Appaloosa	Tachypnoea, tachycardia, pleural effusion	Euthanasia
143	HB epithelial type	Aborted fetus	M	SB	Aborted fetus at 8.5 months' gestation	Died
	HB epithelial type	4	F	TB	Depression, malaena, tachycardia, tachypnoea, injected mucous membranes	Euthanasia

The tumour is often associated with a variety of other congenital abnormalities.[146] Reported cases of hepatoblastoma in animals include mice, sheep, pigs, horse, dogs and cattle.[146] In humans, several subtypes are recognized and are referred to as pure epithelial or mixed (epithelial and mesenchymal) types.

The mixed type can include patterns with teratoid features.[146]

Clinical features

Hepatoblastoma in horses is reported to be associated with nonspecific signs, including:

- Weight loss
- Pyrexia
- Congested mucous membranes
- Altered faecal consistency
- Dyspnoea and pleural effusion; this reflects other organ system involvement.

More specific signs of liver disease, such as icterus, may also be seen.[144,146,150,154]

Clinicopathological features are consistent with an inflammatory process, liver disease or erythrocytosis.

Diagnostic confirmation

- *Ultrasonographically*, there is hepatomegaly, single to multifocal masses with heterogenous echogenicity, encapsulation and cavitation.[143]
- Paraneoplastic polycythaemia vera, hypoglycaemia and thrombocytosis have been described in horses.[144,147,150]
- *Histological examination* of affected hepatic tissue is the only definitive method for diagnosis of hepatoblastoma.
- *Immunohistochemistry* is a further diagnostic technique used in both human and equine hepatic tumour classification.[144,146,147,150] Concentrations of alpha-fetoprotein (α-FP) in serum or affected hepatic tissue may serve as a tumour marker but cannot be used alone to confirm a diagnosis.[143]

Management and prognosis

Neither surgical nor chemotherapeutic treatment options have been attempted in equine hepatic tumours and the prognosis, therefore, remains extremely poor.[143]

Hepatocellular carcinoma

See also page 268.

Disease summary

Notes

Extremely rare neoplasm affecting younger horses.

Clinical features

Vague and nonspecific signs include lethargy, weakness, weight loss, inappetence, fever, diarrhoea, ventral oedema.

Diagnostic confirmation

Ultrasonography and guided biopsy are the only way to make an ante-mortem diagnosis.

Management

No reported treatment.

Prognosis

The condition carries a hopeless prognosis.

Description

Hepatocellular carcinoma has been reported in only three young horses (1–2 years old): a Thoroughbred, a Paint horse

and an Arab have been the subject of individual case reports.[80,148,155]

Clinical features

(Fig. 28.31)

- Lethargy
- Weakness and anaemia
- Weight loss
- Inappetence
- Fever
- Ventral oedema, secondary to hypoproteinaemia and hypoalbuminaemia
- Terminal massive haemoperitoneum and icterus.

Diagnostic confirmation

- Erythrocytosis with tumour production of erythropoietin is a likely feature
- Persistent hypoglycaemia with normal serum insulin concentrations. Hypoglycaemia is a feature of hepatic failure. However, hypoglycaemia may occur secondary to a paraneoplastic syndrome involving insulin-like growth factor production by the neoplastic liver or increased uptake of glucose by neoplastic cells.[80]
- Serum alpha-fetoprotein (normally present only during fetal life) may be elevated in some cases. However, this may not be present due to limited release of α-FP or pulsatile release.
- Ultrasonography may show a markedly enlarged liver containing a focal mass of mixed echogenicity.
- Histopathological findings are varied; three variants noted – trabecular, adenoid and solid. No classification scheme has been devised in horses because such tumours are so rare, but extrapolation from their human correlates can possibly be applied.

Diagnosis is confirmed at necropsy. Massive haemoperitoneum, hepatomegaly and metastases to the omentum, spleen, abdominal wall, left kidney, diaphragm, lungs and bronchial lymph nodes were found in a young Thoroughbred.[148] A yearling Arabian filly with hepatocellular carcinoma collapsed with hepatic capsular rupture and haemoperitoneum.[155] A 15-month-old Paint filly that presented with a 2-week history of lethargy, erythrocytosis, fever, elevated serum protein and icterus with an excess of serosanguineous peritoneal fluid was diagnosed at necropsy with hepatocellular carcinoma.[143]

Management and prognosis

There have been no attempts at treatment and the prognosis is hopeless.

Cholangiocellular carcinoma

See also page 270.

Disease summary

Notes

Extremely rare tumour of biliary duct cells of older horses.

Clinical features

Depression, inappetence, intermittent fever and colic.

Diagnostic confirmation

Ultrasonography and biopsy.

Management

No treatment is possible.

Prognosis

Prognosis is hopeless, with rapid progression to death or euthanasia.

Description

Cholangiocellular carcinoma or intrahepatic bile duct carcinoma is a malignant hepatic neoplasm of older horses arising from and affecting the epithelium of the biliary tree. There are only five reported equine cases in the literature to date.

Clinical features

Cholangiocellular carcinoma is most common in horses older than 10 years old and is difficult to diagnose because the progression is slow and the clinical presentation is nonspecific[149,152,158,161,162]:

- Inappetence
- Intermittent fever
- Depression
- Intermittent colic

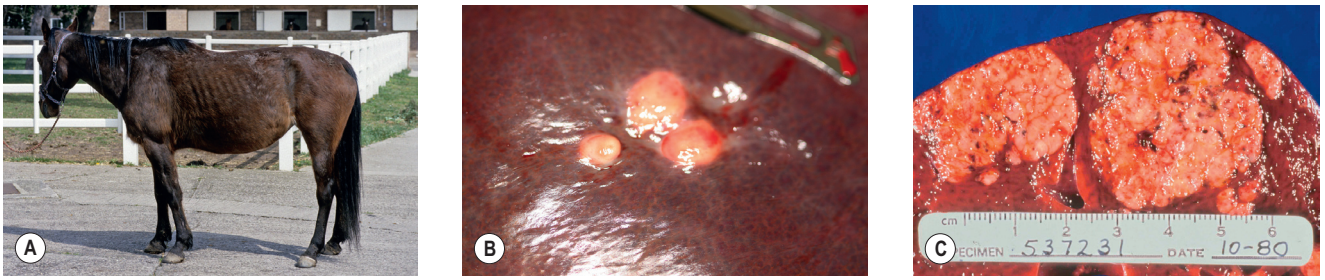


Figure 28.31 Hepatocellular carcinoma. (A,B) A 5-year-old Thoroughbred cross mare was presented with rapid weight loss, inappetence and anaemia with intermittent colic signs. Peritoneocentesis revealed a large amount of sanguineous fluid with a high cell count – predominantly neutrophils. Ultrasound scan revealed several solid masses within the liver and biopsy from one of these confirmed carcinomas. At necropsy, several ill-defined solid histologically definitive carcinomas were identified. **(C)** The typical appearance of a hepatocellular carcinoma. *(Figure courtesy of Dr RR Pascoe.)*

- Icterus
- Lameness.

The clinical signs of intermittent colic, fever and diarrhoea are most likely related to cholangitis. It is suggested that chronic diseases of the bile duct epithelium in horses may predispose to neoplastic change.[162]

A 10-year-old Tennessee Walking Horse gelding was evaluated for intermittent fever, lethargy and anorexia. Initial laboratory analyses revealed anaemia and hyperfibrinogenaemia. Abdominocentesis and thoracentesis yielded fluid samples with high nucleated cell counts and total protein concentrations. The tentative diagnosis was non-septic peritonitis. The horse did not improve after 4 days of antimicrobial treatment, and pitting oedema of the ventral midline developed. Thoracic radiography and ultrasonography revealed consolidation of the ventral aspect of the lung fields and pleural effusion. Pleuroscopy of the right hemithorax revealed pleural effusion and a soft tissue mass in the caudal portion of the mediastinum. Biopsy of the liver and mediastinal mass led to a presumptive diagnosis of metastatic cholangiocellular carcinoma. The horse was euthanized, and the diagnosis was confirmed at necropsy.[152]

Septic cholangiohepatitis was diagnosed in an 11-year-old Warmblood gelding with a history of intermittent colic and fever. Antibiotic treatment (gentamicin) was unsuccessful. Five months after initial examination, the horse had a sudden onset of severe right forelimb lameness. The horse responded to treatment with antibiotics and phenylbutazone, but lameness and fever recurred 7 months later, and the horse was euthanized. Post-mortem findings revealed nodules throughout the liver and a mass associated with the right metacarpophalangeal joint. Histological and immunohistochemical examination revealed carcinomatous infiltration of the liver and metacarpophalangeal joint, confirming a diagnosis of cholangiocellular carcinoma with metastasis to the metacarpophalangeal joint.[158]

A 20-year-old mare presented with a prolonged history of recurrent colic, diarrhoea, inappetence, mild intermittent fever and progressive weight loss. Ultrasonography revealed hepatomegaly and multiple nodules with mixed echogenicity. Histopathology confirmed a cholangiocellular carcinoma.[162]

There has also been one report of a combined hepatocellular carcinoma and cholangiocellular carcinoma in an 18-year-old Thoroughbred mare, who presented with depression, anorexia and icterus.[149]

Diagnostic confirmation

- The clinical signs and biochemical parameters are nonspecific
- Ultrasonography may identify multiple nodules with mixed echogenicity
- Biopsy of the liver under ultrasound guidance is definitive but it can still be difficult to sample truly representative tissue

Diagnosis is usually reliant upon necropsy.[152]

Management and prognosis

There has been no successful treatment reported and prognosis is hopeless.

Secondary hepatic neoplasms

Overview

Secondary/metastatic tumours of the liver are actually more common than primary tumours and are most frequently associated with lymphoma (including hepatosplenic lymphoma), melanoma and haemangiosarcoma (Table 28.6). In theory at least, almost all malignant/metastatic tumours can affect the liver, including carcinomas and sarcomas – usually the signs of all these tumours are related to their tissue of origin and the original primary site, but the deposition of metastatic tumours in the liver is not invariable even in the most aggressive tumour forms. Evidence of concurrent hepatic damage alongside a primary tumour should alert the clinician to the possibility of liver involvement.

Neoplasia of the spleen

The naturally high blood supply to the spleen and its intense haematopoietic and lymphatic functions make it a prominent site for primary and secondary/metastatic neoplasia. The major primary tumours that affect the spleen include haemangiosarcoma and lymphoma. Apart from lymphoma, melanoma is the commonest metastatic tumour of the spleen.

Lymphoma

See also page 350.

Disease summary

Notes

Primary (hepato-) splenic lymphoma is rare but it is encountered with some regularity. The spleen may be involved in multicentric lymphoma or as a metastatic site for other forms of lymphoma.

Clinical features

Cases are usually presented for weight loss or recurrent/intermittent colic and anaemia (this may be primary or immune-mediated haemolytic anaemia).

Diagnostic confirmation

Ultrasonography and biopsy are very feasible due to the prominent/accessible location of the spleen. Rectal examination may identify an enlarged 'lumpy' spleen. Serum IgM may be low.

Management

Splenectomy may be possible if no evidence of metastases is found.

Prognosis

Prognosis is very poor.

Description

The spleen is a fairly common site for infiltration of equine lymphoma. However, the literature contains very few reports of lymphoma isolated solely to the spleen, although anecdotally there are cases that are attributed to the spleen

Table 28.6 The clinically significant features of the more common secondary hepatic tumours in the horse

Secondary hepatic neoplasms	Lymphoma[163]	Hepatosplenic lymphoma[164]	Haemangiosarcoma[165]	Melanoma[166]
Definition	Most common tumour to metastasize to liver, often not possible to determine whether primary or secondary	Single report in a mare. Extranodal lymphoma characterized by infiltration of hepatic sinusoids and splenic red pulp sinuses predominantly by CD-8-positive cells	Hepatic spread is not as common as splenic, musculoskeletal, pulmonic or pleural forms	Rarely metastasizes to the liver. Most metastasis involves lymph nodes, surrounding or within blood vessels throughout the body, spleen, skeletal muscle. Most horses have dermal melanomatosis for years (range 1–6 years) before succumbing to metastatic disease
Clinical features	Anorexia Weight loss Lethargy Ataxia Depression	Weight loss Weakness Anaemia/thrombocytopaenia Evidence of hepatic disease	Haemorrhage into body cavities, skeletal muscle or subcutaneous locations. Elevated heart and respiratory rates. Pale or icteric mucous membranes	Multiple organ involvement. Variety of clinical syndromes depending on organ involvement
Diagnostic confirmation	Biopsy Variable ultrasound findings including hypoechoic nodules, or diffuse hyperechogenicity	Biopsy; post-mortem diagnosis in 1 reported case revealed diaphragmatic rupture, severe hepatosplenomegaly and no other nodal or extranodal site affected	Ultrasonography and guided biopsy	Ultrasonography and guided biopsy. Histological characteristics of dermal masses are not predictive of malignancy in majority of cases
Treatment/outcome	Palliative systemic chemotherapy possible (see p. 130)	Systemic chemotherapy theoretically (see p. 130). Aggressive clinical course and likely very poor response to chemotherapy	None reported for involvement of liver	None reported. Cimetidine appears to be ineffective and vaccines and mediator treatments are not useful in disseminated forms (see p. 146)

Table 28.7 Case reports of primary splenic lymphoma

Ref. No.	Diagnosis	Age (years)	Sex	Breed	Clinical presentation	Outcome
167	Splenic lymphoma	7	M	TB	Splenic mass identified at ex lap for acute abdominal crisis	Euthanasia
168	Splenic lymphoma	5	G	TB	Weight loss, depression, polydipsia, polyuria (hyperparathyroidism)	Euthanasia
169	B-cell splenic lymphoma	4	M	TB	Incidental finding at post-mortem	Euthanasia for fractured forelimb (racehorse)
170	B-cell splenic lymphoma	5	–	Mule	Lethargy, anorexia, anaemia, haemoabdomen	Splenectomy, survived, 7 months follow-up
171	Splenic lymphoma	10	G	Tennessee Walker	Weight loss, intermittent colic, lethargy, fever, tachycardia, tachypnoea, pallor, ascites and ventral oedema	Resection of splenic mass; died shortly after surgery. Metastasis to liver and lung

only (Table 28.7). The likelihood is, however, that many of these will actually be multicentric lymphoma cases with more significant/identifiable splenic masses.

Horses of all ages are reported to be affected, so this differential diagnosis should be considered even in young foals.

Clinical features

(Fig. 28.32)

- Frequently nonspecific signs, including:
  - Weight loss
  - Lethargy
  - Anorexia
  - Intermittent colic
  - Anaemia – may be seen in cases of splenic neoplasia due to immune-mediated disease, as a result of altered surface antigen exposure of erythrocytes with subsequent antibody production, or increased destruction of erythrocytes in the enlarged congested spleen.

Diagnostic confirmation

- *Ultrasound*: Transabdominal ultrasonography on the left side of the abdominal wall assists in the

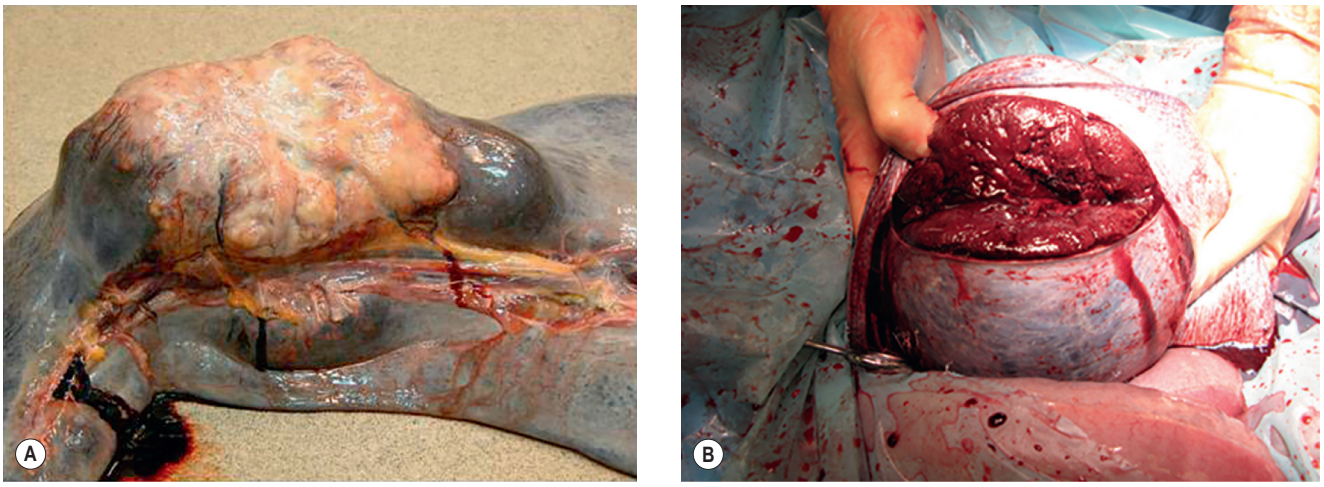


Figure 28.32 Splenic lymphoma. (A) A splenic lymphoma that was restricted to the spleen in a 12-year-old mare presented with weight loss and anaemia. **(B)** A 6-year-old Thoroughbred gelding had a long history of intermittent colic, persistent mild anaemia and progressive mild weight loss. He was presented with a more acute colic episode. Rectal examination quickly revealed a grossly enlarged spleen with a well-defined single large mass. Ultrasonographic diagnosis is relatively easily achieved. A presumptive diagnosis of neoplasia (probably lymphoma) was made and confirmed on laparoscopic examination and frozen section histology. On economic grounds, the owner declined the option of splenectomy, which probably had a good chance of being successful. At necropsy, no other masses were identified and the tumour was typed as a B-cell lymphoma. *(Figure A courtesy of Hal Schott.)*

identification of splenic enlargement or hypo- and/or hyperechoic masses within the spleen in a number of cases[80]

- *Transabdominal (ultrasound-guided) biopsy and histopathology*
- *Laparoscopy* is a reasonable way of eliminating multicentric lymphoma, where this is equivocal. It also allows accurate and safe biopsy.

Management and prognosis

There are several reports of splenectomy to treat splenic trauma, neoplasia and infection in horses. However, there is little known about the complications and post-surgical effects of such a procedure, particularly in young horses. There is a well-recognized condition known as 'post-splenectomy infection syndrome' in humans but it is not documented in horses.[172] However, in the author's (DCK) experience, splenectomy is well tolerated in horses and cases of solitary splenic lymphoma can be saved.

Splenectomy was reported for treatment of splenic lymphoma in a 5-year-old mule. A transthoracic approach utilizing a 16th rib resection was used after all other diagnostics failed to identify evidence of multicentric involvement. At the time of reporting, the mule had survived 7 months post-surgery.[170]

In future, the refinement of laparoscopic approaches may allow surgeons to use a variety of haemostatic techniques in a minimally invasive fashion.[172]

Haemangiosarcoma

See also pages 334 and 514.

Description

Haemangiosarcoma is a rare malignant tumour of vascular endothelial origin.

It may be focal, locally invasive, cutaneous or disseminated. A number of cases of disseminated haemangiosarcoma in the horse have been reported.[165] The condition is seldom limited to the spleen.

Haemangiosarcoma has been reported to occur particularly in middle-aged horses, with no apparent sex predilection.[165] Thoroughbreds seem to be over-represented, but a true breed predilection has not been established.

Disease summary

Notes

Rare tumour of vascular endothelium.

Clinical features

Very painful muscular swellings, elevated heart and respiratory rates, pale or icteric mucous membranes.

Diagnostic confirmation

Abdominocentesis, transabdominal ultrasonography and biopsy are the main diagnostic aids.

Management

Splenectomy is a feasible option but the tumour is seldom limited to the spleen.

Prognosis

Prognosis is very poor in all cases.

Clinical features

The respiratory and musculoskeletal systems are most commonly affected. The spleen was affected in 43% of cases.[165] The presenting signs include:

- Dyspnoea (26%)
- Subcutaneous or muscular swelling (24%)
- Epistaxis (17%)
- Lameness (12%)
- Heart and respiratory rates are usually increased and mucous membrane colour is usually frequently pale and/or icteric

- Capillary refill time and rectal temperature are usually unremarkable.

Haematological signs include:

- Anaemia (88%)
- Neutrophilic leukocytosis (62%)
- Thrombocytopaenia (48%).

Diagnostic confirmation

- *Abdominocentesis* may identify tumour cells since the tumours are frequently exfoliative.
- *Transabdominal ultrasonography and biopsy* can be easily performed in the splenic condition.

Management and prognosis

Since most splenic neoplasms are diagnosed late in the course, splenectomy is rarely an option due to the advanced stage of the disease. Additionally, splenic tumours may not be the primary problem – indeed, splenic haemangiosarcoma usually only becomes a significant problem when the tumours rupture into the abdomen causing significant haemoperitoneum. Extensive metastatic tumours involving the lymph nodes, liver and lungs are invariably present by the time haemangiosarcoma is identified in the spleen. Splenectomy is probably best regarded as a temporary palliative procedure.

The long-term prognosis for cases of splenic neoplasia is poor to grave, unless there is a solitary tumour amenable to surgical intervention.[173,174] Splenectomy is a major procedure and is little is known of the long-term consequences of such a procedure.[172]

Pancreatic neoplasia

See also page 267.

Pancreatic carcinoma

See also page 267.

Disease summary

Notes

Pancreatic adenocarcinoma or adenoma is extremely rare in horses.

Clinical features

The majority of clinical signs relate to abdominal disease, including weight loss, intermittent colic, diarrhoea, depression, inappetence and recurrent/persistent pyrexia.

Diagnostic confirmation

Definitive diagnosis is only made at necropsy. The pancreas is almost inaccessible to all ante-mortem diagnostic methods, although laparoscopy might be useful.

Management

No treatment is possible.

Prognosis

Prognosis is hopeless, with a rapidly progressive course.

Description

Pancreatic neoplasia is rare in horses, with only nine cases of exocrine pancreatic neoplasia (adenocarcinoma) reported in the literature to date and one further report of pancreatic adenoma (islet cell neoplasm) (see p. 267).[175–180]

Clinical features

In the published cases of exocrine pancreatic neoplasia in horses, the major presenting signs have been related to rapidly progressive abdominal disease. Signs are inconsistent, variable and nonspecific, and may partly explain the rare reports and diagnosis.[181]

- Depression
- Inappetence
- Acute diarrhoea[177]
- Weight loss[177]
- Intermittent abdominal pain/colic[177,178]
- Recurrent or persistent pyrexia
- Neutrophilia[177]
- Marked hypoalbuminaemia[177]
- Marked elevations in gamma glutamyl transferase, suggestive of biliary tract pathology[177]
- Exocrine pancreatic neoplasia might be expected to cause damage to endocrine cells of the islets of Langerhans, resulting in disorders of glucose metabolism. However, no reports of pancreatic adenocarcinoma have described this.

In a 16-year-old Thoroughbred mare with bilaterally reduced respiratory sounds ventrally, a small round mass in the centre of the abdomen was identified on rectal examination. Bilateral pleural effusion was noted and a mediastinal mass identified on thoracic ultrasonography, along with a 10 cm mass within the abdomen associated with the small intestine. Clinical pathology revealed a moderate neutrophilia and lymphopenia and mild to moderate elevations in liver parameters, including gamma glutamyl transferase and elevated bile acid concentrations. Cytology of pleural fluid was suggestive of exfoliative neoplastic cells and a diagnosis of metastatic neoplasia was made. At necropsy, a large multinodular mass was present in the proximal duodenum overlying the minor duodenal papilla, appearing to originate from the minor duodenal papilla where the accessory pancreatic duct empties into the duodenum. The pancreas was replaced by grey nodular tissue that was adherent to the stomach and liver. The major duodenal papilla is the site of discharge for both bile and the major pancreatic duct, but was unaffected in this case. Gamma glutamyl transferase (GGT) is of high concentration in equine pancreatic epithelial and renal cortical cells, as well as in biliary epithelial cells, and may explain the rise in GGT in this case, despite no involvement of the hepatic parenchyma or major duodenal papilla.[182]

Pancreatic adenocarcinoma with metastasis was also diagnosed at necropsy in an aged donkey stallion with a history of weight loss, chronic ingestion of *Senecio jacobea* (tansy ragwort), inappetence, depression and ascites. Signs progressed, with yawning and somnolence, and pyrrolizidine toxicity causing hepatic failure was presumed. At necropsy,

pancreatic adenocarcinoma was identified, with extension to the liver and mesenteric lymph nodes.[178]

Diagnostic confirmation

- Rectal palpation may reveal nodules throughout the peritoneum and a left perirenal mass.
- Peritoneal
- Transabdominal and transrectal ultrasonography may reveal evidence of metastasis and facilitate biopsy.
- Ante-mortem diagnosis has not been reported; definitive diagnosis is made post-mortem.

Management and prognosis

There have been no reports of ante-mortem diagnosis or treatment of pancreatic carcinoma in the literature. Prognosis is therefore grave.

Neoplasia of the peritoneum/omentum

See also page 281.

Overview

Tumours affecting the peritoneum relate, as might be expected, to the cells that form the structure. Secondary tumours can also extend to the peritoneal cavity and these include melanoma and gastric carcinoma in particular. Lymphoma and haemangiosarcoma can also be encountered.

There are three primary types of tumour, which are seen in the peritoneum/omentum. These are:

1. Mesothelioma
2. Leiomyoma: benign mesenchymal tumours arising from smooth muscle cells
3. Omental tumours: these have been reported in three horses[183–185]:
   a. Omental fibrosarcoma
   b. Peritoneal disseminated leiomyomatosis
   c. Omental leiomyoma.

Mesothelioma

See also page 281.

Description

Mesothelioma is a rare malignant mesodermal neoplasm arising from the mesothelial cells that normally form a single-cell lining covering the peritoneal, pericardial and pleural surfaces.[5]

Mesotheliomas have been classified into three main histological types[5]:

1. Epithelioid
2. Biphasic
3. Sarcomatoid.

Since 1976, there have been 11 reports of mesothelioma in horses (Table 28.8). These include tumours arising in the pericardium, the pleural cavity, the peritoneal cavity, and those involving more than one of these sites.[161,186–191,193–195] The majority of reported cases have occurred in female horses from 2 to 27 years of age, but most affected horses were middle-aged to older horses. There is no obvious breed predisposition.

Disease summary

Notes

Very rare malignant tumour of mesothelial cells of the peritoneum (and less commonly the pleura or pericardium) affecting middle-aged horses. Inclined to direct transcoelomic metastasis.

Clinical features

Marked abdominal distension due to ascites arising from multiple well-defined masses on the parietal and visceral peritoneum, colic, weight loss and ventral oedema.

Diagnostic confirmation

Diagnostic tests include abdominocentesis (cytology), transabdominal ultrasonography, ultrasound-guided fine-needle aspirate of mass(es), biopsy.

Management

No treatment is possible.

Prognosis

Prognosis is hopeless; the course is usually insidious to start with and then rapidly progressive.

Clinical features

The clinical presentation depends on the location and extent of the nodules and the physical and metabolic effects of the fluid accumulation (Fig. 28.33, Table 28.8).

- Cases of mesothelioma affecting the peritoneal cavity usually present with marked abdominal distension and colic; this is the most common presentation.
- Rectal examination will usually confirm the presence of multiple masses of variable size associated with the parietal or peritoneal surfaces, but some may be very small.
- Others signs include lethargy, ventral and/or peripheral oedema, anaemia, weight loss and respiratory difficulty.

Differential diagnoses

Other differential diagnoses for abdominal distension in the horse include:

- Overweight (fat)
- Intestinal accumulation of gas (flatus)
- Ascites due to liver failure, circulatory problems or hypoalbuminaemia
- Haemoabdomen secondary to trauma or other abdominal tumours
- Exudates secondary to bacterial disease, rupture of the gastrointestinal tract, neoplastic effusion or chylous effusion secondary to obstruction of lymphatic drainage
- Organ enlargement (including pregnancy) and fat
- Other tumours, particularly lymphoma and melanoma.

Diagnostic confirmation

- Most cases of mesothelioma have marked abdominal effusion and neoplastic mesothelial cells may be identified with abdominocentesis.

Table 28.8 Summary of 11 published cases of equine mesothelioma

Ref. No.	Age (years)	Sex	Breed	Presenting signs	Treatment/outcome
11	6	F	QH	Exercise intolerance of 5 weeks' duration; absent ventral lung sounds and severe respiratory distress	Euthanasia – malignant mesothelioma. Post-mortem – pleural and pericardial involvement, no extrathoracic involvement
186	6	F	Arab	Weight loss/intermittent ventral oedema of 8 weeks' duration, severe abdominal distension, pitting ventral oedema and distal hindlimbs, emaciated, diarrhoea, decreased lung sounds. Ultrasonography – marked ascites and bilateral pleural effusion	Euthanasia – generalized biphasic mesothelioma Post-mortem – primary pericardial spread through lymphatics. Calretinin was used as immunohistochemical marker
187	9	F	Haflinger	Weight loss, ascites and azotaemia	Drainage of abdominal fluid followed by exploratory laparotomy – euthanasia. Post-mortem – multiple nodular and papillary nodules distributed throughout peritoneal cavity; disseminated lipid-rich mesothelioma
188	6	F	TB	Late pregnant, presented with acute severe colic, distended abdomen greater than expected for pregnancy, ascites and abnormal cells identified on abdominal paracentesis, suspicious of neoplasia	Exploratory laparotomy identified numerous small raised white lesions on visceral and parietal peritoneum, involving the greater omentum and spreading to peritoneal surfaces. No abnormalities detected in pleural cavity. Euthanasia – mesothelioma confirmed
189	8	G	Hanoverian	Ascites identified on transabdominal ultrasonography	Euthanasia. Peritoneal mesothelioma
190	13	F	Icelandic pony	Recurrent ascites	Euthanasia – malignant biphasic epithelioid mesothelioma. Post-mortem – ascites and hydrothorax; multifocal and coalescing laminar masses and nodules in peritoneal and pleural cavities. Positive immune staining for cytokeratin and vimentin
191	11	F	Lipizzaner	Lethargy, abdominal distension, coughing and weakness of 1 month duration; presented in thin body condition with ventral oedema; ultrasonography revealed large volume of anechoic fluid in peritoneal cavity with multilobular masses adherent to abdominal wall at many locations, multiple metabolic derangements and acute renal failure, consistent with tumour lysis syndrome	Euthanasia – peritoneal mesothelioma. Post-mortem – multilobular friable masses up to 20 cm+ scattered throughout parietal peritoneum; no intrathoracic masses; IHC-positive for cytokeratin and vimentin
192	27	F	QH	Presented with old age and weight loss	Euthanasia – pericardial mesothelioma. Post-mortem – 3 L serosanguineous fluid in pericardial sac with numerous nodules on epicardial surface. No lesions elsewhere
193				Respiratory distress, depression and pleural pain. Copious effusion with neoplastic mesothelial cells	Euthanasia – pericardial mesothelioma. Euthanasia – pleural mesothelioma
194		F		Pleural effusion with neoplastic cells	Pleural mesothelioma

- Transabdominal ultrasonography (see Fig. 28.33A) may reveal a large volume of anechoic abdominal fluid and multiple irregular cauliflower-like masses adherent to the abdominal wall at many locations, usually fused to the peritoneum and characterized by mixed echogenicity.
- Ultrasound-guided fine-needle aspirate of a representative intra-abdominal mass is definitive.
- Biopsy of masses via exploratory laparotomy or laparoscopy will provide all the confirmation required.

Management and prognosis

Treatment is impossible.

The prognosis is hopeless for all forms of mesothelioma – progression is rapid in most cases over a 4–6-week period.

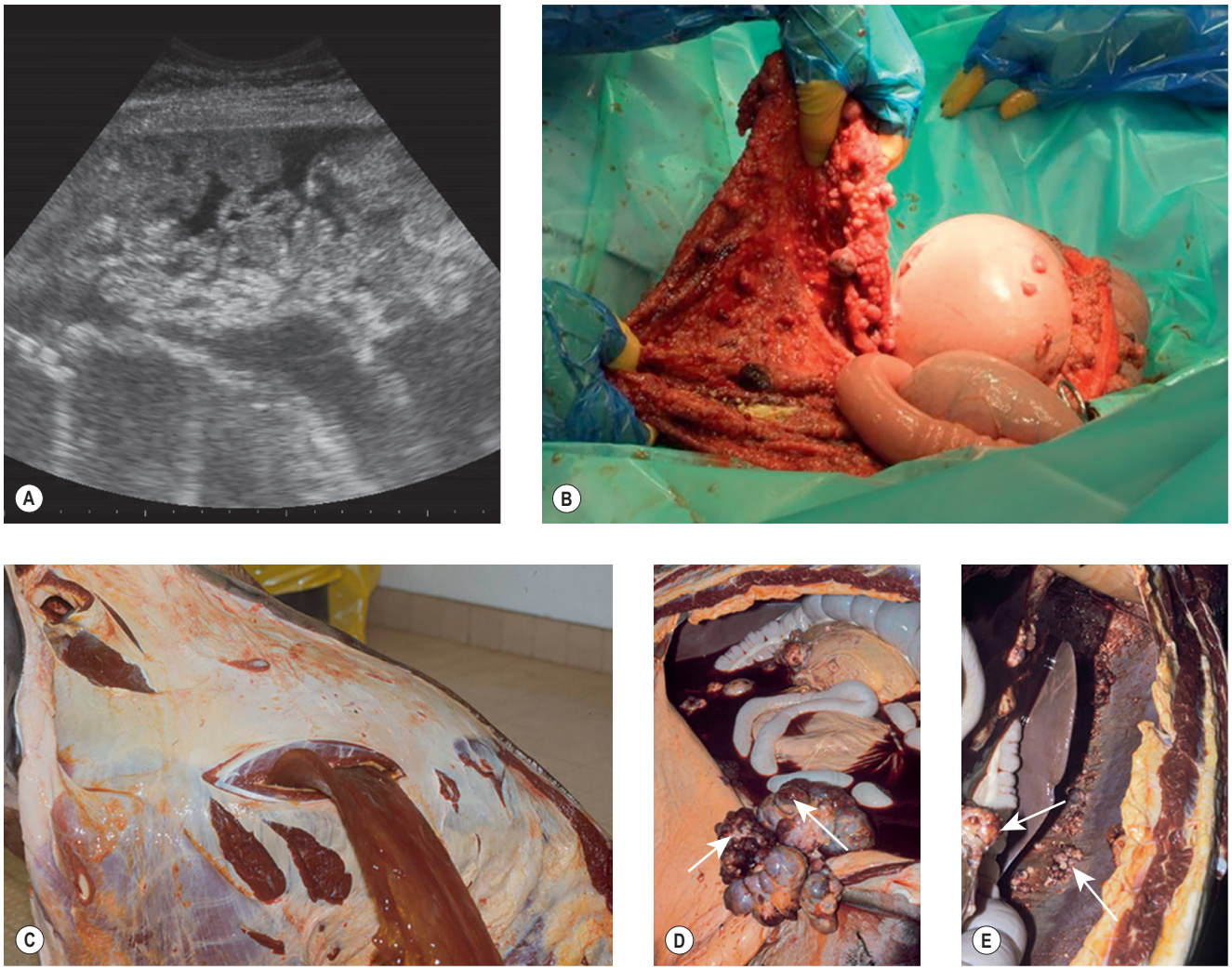


Figure 28.33 Mesothelioma. A middle-aged Thoroughbred mare was presented with colic and gross fluid distension of the abdomen. **(A)** Ultrasonography revealed a large volume of anechoic fluid and multiple well-defined nodules within the peritoneal cavity – most were associated with visceral peritoneal surface. Further nodules were identified in the pleural space and pericardium. Peritoneocentesis revealed a dark brown opaque fluid with an elevated protein and a massive cell count. Cytology confirmed the presence of abnormal mesothelial cells and plentiful mononuclear and polymorphonuclear cells. **(B)** Laparotomy revealed the full extent of the problem, with extensive involvement of the visceral and parietal surfaces of the abdomen. **(C–E)** The nodules can be very much larger and often there is an enormous volume of brownish peritoneal fluid. In this case, the horse had a recent history of weight loss and progressive respiratory difficulty with anaemia and abdominal distension. A diagnosis of mesothelioma was based on peritoneal cytology and ultrasonography. Over 100 litres of brown fluid was present and the nodules were very extensive, involving parietal and visceral peritoneum (including both surfaces of the diaphragm and the pleura) and ranged in size from a few millimetres to 8–9 cm in diameter (arrows). *(Figures A and B courtesy of Victoria Coppas.)*

References

1. Jackson C. The incidence and pathology of tumours of domesticated animals in South Africa. Onderstepoort J Vet Sci Anim Ind 1936; 6:1–460.
2. Hagdoost IS, Zakarian B. Neoplasms of Equidae in Iran. Equine Vet J 1985; 17:237–239.
3. Pirie RS, Tremaine WH. Neoplasia of the mouth and surrounding structures, 4th edn. In: Robinson NE, ed. Current therapy in equine medicine. Philadelphia: WB Saunders; 1997: 153–155.
4. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
5. Head KW. Tumors of the alimentary tract. In: Moulton JE, ed. Tumors in domestic animals, 3rd edn. Berkeley: University of California Press; 1990: 347–374.
6. Baker GJ. Oral examination and diagnosis: Management of oral diseases In: Harvey CE, ed. Veterinary dentistry. Philadelphia: WB Saunders; 1999: 217–220.
7. Richardson DW, Evans LH, Tulleners EP. Rostral mandibulectomy in five horses. J Am Vet Med Assoc 1991; 199:1179–1182.
8. Baker JR, Leyland A. Histological survey of tumours of the horse with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
9. Cotchin E. A general survey of tumours in the horse. Equine Vet J 1977; 9:16–21.
10. Strafuss A. Squamous cell carcinomas in horses. J Am Vet Med Assoc 1976; 168:61–62.
11. Turrel JM. Oncology. In: Kobluk CN, Ames TR, Geor RJ, eds. The horse: diseases and clinical management. Philadelphia: WB Saunders; 1995: 1128–1130.
12. Purdy CM. Mandibular aneurysmal bone cyst in a horse. Equine Pract 1985; 7:22–24.
13. Verstraete FJ, Ligthelm AJ. Excessive granulation tissue of periodontal origin in a horse. Equine Vet J 1988; 20:380–382.
14. Lamb CR, Schelling SH. Congenital aneurysmal bone cyst in the mandible of a foal. Equine Vet J 1989; 21:130–132.
15. Gibbs C. The equine skull; its radiographic investigation. J Am Vet Radiol Soc 1974; 15:70–78.
16. Wyn-Jones G. Interpreting radiographs 6: Radiology of the equine head (part 2). Equine Vet J 1985; 17:417–425.
17. Dubielzig RR. Tumors of the alimentary tract. In: Meuten DJ, ed. Tumors in domestic animals, 4th edn. Ames: Iowa State Press; 2002: 402–410.
18. Tremaine WH. Dental endoscopy in the horse. Clin Tech Eq Pract 2005; 4:181–187.
19. Pindborg JJ, Kramer IR, Torlini H. Histological typing of odontogenic tumors, jaw cysts and allied lesions. Geneva: World Health Organization; 1971: 145–154.

20. Knowles S, Blas-Machado U, Butler AM, et al. Ameloblastic fibro-odontoma associated with a retained molar in an Oldenberg mare. J Vet Diagn Invest 2010; 22:987–990.
21. Chandra AMS, Buergelt CD, Ethell MT. Odontogenic myxoma of the mandible in a filly. J Vet Diagn Invest 1999; 11:274–277.
22. Peter CP, Myers VS, Ramsey FK. Ameloblastic odontoma in a pony. Am J Vet Res 1968; 29:1495–1498.
23. Lingard DR, Crawford TB. Congenital ameloblastic odontoma in a foal. Am J Vet Res 1970; 31:801–804.
24. Roberts MC, Groenendyk S, Kelly WR. Ameloblastic odontoma in a foal. Equine Vet J 1978; 10:91–93.
25. Summers PM, Wells KE, Adkins KF. Ossifying ameloblastoma in a horse. Aust Vet J 1979; 55:498–500.
26. Dillehay DL, Schoeb TR. Complex odontoma in a horse. Vet Pathol 1986; 23:341–342.
27. Dubielzig RR, Beck KA, Levine S, et al. Complex odontoma in a stallion. Vet Pathol 1986; 23:633–635.
28. Kreutzer R, Wohlsein P, Staszyk C, et al. Dental benign cementomas in three horses. Vet Pathol 2007; 44:533–536.
29. Levine DG, Orsini JA, Foster DL, et al. What is your diagnosis? Benign true cementoma (benign cementoblastoma). J Am Vet Med Assoc 2008; 223: 1063–1064.
30. Brounts SH, Hawkins JF, Lescun TB, et al. Surgical management of compound odontoma in two horses. J Am Vet Med Assoc 2004; 225:1423–1427, 1393.
31. De Cock HE, Labelle P, Magdesian KG. Ameloblastic carcinoma in a horse. J Comp Pathol 2003; 128:210–215.
32. Gardner DG. Ameloblastomas in the horse: a critical review and report of an additional example. J Oral Pathol Med 1994; 23:41–44.
33. Rosol TJ, Nagode LA, Robertson JT, et al. Humoral hypercalcaemia of malignancy associated with ameloblastoma in a horse. J Am Vet Med Assoc 1994; 204:1930–1933.
34. Schaaf KL, Kannegieter NJ, Lovell DK. Calcified tumours of the paranasal sinuses in three horses. Aust Vet J 2007; 85:454–458.
35. Wahl P. Adamantinoma polycysticum ossificans am Unterkiefer eines Pferdes. Dtsch Tierarztl Wochenschr 1936; 46:113–117.
36. Vaughan JT, Bartels JE. Equine mandibular adamantinoma. J Am Vet Med Assoc 1968; 153:454–457.
37. Hanselka DW, Roberts RE, Thompson RB. Adamantinoma of the equine mandible. Vet Med Small Anim Clin 1974; 69:157–160.
38. Jones SL, Brumbaugh GW. Ameloblastoma in mandible of horse. What is your diagnosis? J Am Vet Med Assoc 1991; 199:630–631.
39. Théon AP. Radiation therapy in the horse. Vet Clin North Am Equine Pract 1998; 14:673–688.
40. French DA, Fretz PB, Davis GD. Mandibular adamantinoma in a horse; radical surgical treatment. Vet Surg 1984; 13:165–171.
41. Mason BJ. Temporal teratomata in the horse. Vet Rec 1974; 95:226–228.
42. Fessler JF. Heterotopic polyodontia in horses: nine cases (1969–1986). J Am Vet Med Assoc 1988; 192:535–538.
43. Lindshaw WA, Bech KA. Temporal teratoma in a horse. Compend Contin Educ Pract Vet 1986; 8:168–171.
44. Kramer IRH, Pindborg JJ, Shear M. Histological typing of odontogenic tumors, 2nd edn. Berlin: Springer-Verlag; 1993: 151–156.
45. Howie F, Munroe G, Thompson H, et al. Palatine squamous cell carcinoma involving the maxillary sinus in two horses. Equine Vet Educ 1992; 4:3–7.
46. Schuh JCL. Squamous cell carcinoma of the oral, pharyngeal and nasal mucosa in the horse. Vet Pathol 1986; 23:205–207.
47. Johnson PJ. Dermatologic tumors (excluding sarcoids). Vet Clin North Am Equine Pract 1998; 14:625–658.
48. Barker IK, van Dreumel AA, Palmer N. In: Jubb KV, Kennedy PC, Palmer N, eds. Pathology of domestic animals, 4th ed. New York: Academic Press; 1993: 27.
49. Knottenbelt DC, Pascoe RR. Diseases and disorders of the horse. London: Wolfe; 1994: 303.
50. Leyland A, Baker JR. Lesions of the nasal cavity and paranasal sinuses of the horse causing dyspnoea. British Vet J 1975; 131:339–346.
51. Orsini JA, Nunamaker DM, Jones CJ, et al. Excision of oral squamous cell carcinoma in a horse. Vet Surg 1991; 20:264–266.
52. Théon AP. Cisplatin treatment for cutaneous tumors. In: Robinson NE, ed. Current therapy in equine medicine, 4th edn. Philadelphia: WB Saunders; 1997: 372–377.
53. Paterson S. Treatment of superficial ulcerative squamous cell carcinoma in three horses with topical 5-fluorouracil. Vet Rec 1997; 141:626–628.
54. Broström H. Equine sarcoids. A clinical and epidemiological study in relation to equine leucocyte antigens (ELA). Acta Vet Scand 1995; 36: 223–236.
55. Knottenbelt DC, Kelly DF. The diagnosis and treatment of periorbital sarcoid in the horse: 445 cases from 1974 to 1999. Vet Ophthalmol 2000; 3:169–191.
56. Goetz TE, Ogilvie GK, Keegan KG, et al. Cimetidine for the treatment of melanoma in 3 horses. J Am Vet Med Assoc 1990; 196:449–452.
57. Goetz TE, Long MT. Treatment of melanoma in horses. Compend Contin Educ Pract Vet 1993; 15:608–610.
58. Morse CC, Saik JE, Richardson DW, et al. Equine juvenile mandibular ossifying fibroma. Vet Pathol 1988; 25:415–421.
59. Kawcak CE, Stashak TS, Norrdin RW. Treatment of ossifying fibroma in a horse by hemimaxillectomy. Equine Pract 1996; 18:22–25.
60. Robbins SC, Arighi M, Ottewell G. The use of megavoltage radiation to treat juvenile mandibular ossifying fibroma in a horse. Can Vet J 1996; 37: 683–684.
61. Barakzai SZ, Dixon PM. Sinonasal myxoma in a four-year-old thoroughbred gelding. Vet Rec 2003; 152:210–211.
62. Fry FL, Knight HD, Brown S. Hemangiosarcoma in a horse. J Am Vet Med Assoc 1983; 182:287–289.
63. Sweigard KD, Hattell AL. Oral hemangiosarcoma in a horse. Equine Pract 1993; 15:10–13.
64. Dunkel BM, Del Piero F, Kraus BM, et al. Congenital cutaneous, oral, and periarticular haemangiosarcoma in a 9-day-old Rocky Mountain horse. J Vet Intern Med 2004; 18:252–255.
65. Stackhouse LL, Moore JJ, Hylton WE. Salivary gland adenocarcinoma in a mare. J Am Vet Med Assoc 1978; 172:271–273.
66. Head KW. Salivary gland disease in domestic animals. In: Norman JE, McGurk M, eds. Salivary glands color atlas and text. Philadelphia: Mosby-Wolfe; 1995: 367–389.
67. Castleman WL, Toplon DE, Clark CK, et al. Rhabdomyosarcoma in 8 horses. Vet Pathol 2011; 48:1144–1150.
68. Vashisht K, Rock RW, Summers BA. Multiple masses in a horse's tongue resulting from an atypical perineurial cell proliferative disorder. Vet Pathol 2007; 44:398–402.
69. Seeliger F, Hess O, Pröpsting MJ, et al. Confocal laser scanning analysis of an equine oral mast cell tumour with atypical expression of tyrosine kinase receptor C-KIT. Vet Pathol 2007; 44:225–228.
70. Rhind SM, Dixon PM. T cell-rich B cell lymphosarcoma in the tongue of a horse. Vet Rec 1999; 145:554–555.
71. Wilson GJ, Anthony ND. Chondrosarcoma of the tongue of a horse. Aust Vet J 2007; 85:163–165.
72. Hanson PD, Frisbie DD, Dubielzig RR, et al. Rhabdomyosarcoma of the tongue in a horse. J Am Vet Med Assoc 1993; 202:1281–1284.
73. Jacobson SA. The comparative pathology of the tumors of bone. Springfield: Thomas; 1971: 164–211.
74. Pommer A. Carcinomstenose des oesophagus Beim Pferd. Wien Tier M 1947; 34:193–197.
75. Ford TS, Vaala WE, Sweeney CR, et al. Pleuroscopic diagnosis of gastroesophageal squamous cell carcinoma in a horse. J Am Vet Med Assoc 1987; 190:1556–1558.
76. Roberts MC, Kelly WR. Squamous cell carcinoma of the lower cervical oesophagus in a pony. Equine Vet J 1979; 11:199–201.
77. Campbell-Beggs CL, Kiper ML, MacAllister C, et al. Use of esophagoscopy in the diagnosis of esophageal squamous cell carcinoma in a horse. J Am Vet Med Assoc 1993; 202:617–618.
78. Taylor SD, Haldorson GJ, Vaughan B, et al. Gastric neoplasia in horses. J Vet Intern Med 2009; 23:1097–1102.
79. McFadden KE, Pace LW. Clinical manifestations of squamous cell carcinoma in horses. Comp Cont Ed Pract Vet 1991; 13:669–676.
80. East LM, Savage CJ. Abdominal neoplasia (excluding urogenital tract). Vet Clin North Am Equine Pract 1998; 14:475–493.
81. Boy MG, Palmer JE, Heyer G, et al. Gastric leiomyosarcoma in a horse. J Am Vet Med Assoc 1992; 200:1363–1364.
82. Del Piero F, Summers BA, Cummings JF, et al. Gastrointestinal stromal tumours in equids. Vet Pathol 2001; 38:689–697.
83. Morse CC, Richardson DW. Gastric hyperplastic polyp in a horse. J Comp Pathol 1988; 99:337–342.
84. Wrigley RH, Gay CC, Lording P, et al. Pleural effusion associated with squamous cell carcinoma of the stomach of a horse. Equine Vet J 1981; 13:99–102.
85. Tennant B, Keirn DR, White KK, et al. Six cases of squamous cell carcinoma of the stomach of the horse. Equine Vet J 1982; 14:238–243.
86. Olsen SN. Squamous cell carcinoma of the equine stomach: a report of five cases. Vet Rec 1992; 131:170–173.
87. Aronoff N, Reed AL, Aronson E. Radiographic diagnosis – gastric tumor in a horse. Vet Radiol Ultrasound 1997; 38:185–186.
88. McKenzie EC, Mills JN, Bolton JR. Gastric squamous cell carcinoma in three horses. Aust Vet J 1997; 75:480–483.
89. Murray MJ. Diseases of the stomach. In: Mair TS, Divers T, Ducharme NW, et al., eds. Manual of equine gastroenterology: Harcourt Publishers Ltd; 2002: 241–248.
90. Moore JN, Kintner LD. Recurrent esophageal obstruction due to squamous cell carcinoma in a horse. Cornell Vet 1976; 66:590–597.
91. Burney DP, Theisen SK, Schmitz DG. Identifying and treating squamous cell carcinoma of horses. Vet Med 1992; 87:588–594.
92. Patton KM, Peek SF, Valentine BA. Gastric adenocarcinoma in a horse with portal vein metastasis and thrombosis: a novel cause of hepatic encephalopathy. Vet Pathol 2006; 43:565–569.
93. Keirn JM, White KK, King JM, et al. Endoscopic diagnosis of squamous cell carcinoma of the equine stomach. J Am Vet Med Assoc 1982; 180: 940–942.
94. Barker IK, van Dreumel AA, Palmer N. The alimentary system. In: Jubb KV, Kennedy PC, Palmer N, eds. Pathology of domestic animals, 4th edn. San Diego: Academic Press; 1993: 73.
95. Baker JR, Ellis CE. A survey of post mortem findings in 480 horses 1958 to 1980: (1) causes of death. Equine Vet J 1981; 13:43–46.
96. Van den Hoven R, Franken P. Clinical aspects of lymphosarcoma in the horse: a clinical report of 16 cases. Equine Vet J 1983; 15:49–53.
97. Sanz MG, Sellon DC, Potter KA. Primary epitheliotropic intestinal T-cell lymphoma as a cause of diarrhea in a horse. Can Vet J 2010; 51:522–524.
98. Nunes J, Mackie JT, Kiupel M. Equine histoplasmosis presenting as a tumor in the abdominal cavity. J Vet Diagn Invest 2006; 18:508–510.
99. Herraez P, Berridge B, Marsh P, et al. Small intestine large granular lymphoma in a horse. Vet Pathol 2001; 38:223–226.
100. La Perle KMD, Piercy RJ, Long JF, et al. Multisystemic, eosinophilic, epitheliotropic disease with intestinal lymphosarcoma in a horse. Vet Pathol 1998; 35:144–146.
101. Humphrey M, Watson DA, Edwards HG, et al. Lymphosarcoma in a horse. Equine Vet J 1984; 16:547–548.

102. McConnell S, Katada M, Fiske RA, et al. Equine lymphosarcoma diagnosed as equine infectious anaemia in a young horse. Equine Vet J 1982; 14: 160–162.
103. Wiseman A, Petrie L, Murray MJ. Diarrhoea in the horse as a result of alimentary lymphosarcoma. Vet Rec 1974; 95:454–457.
104. Pinkerton ME, Bailey KL, Thomas KK, et al. Primary epitheliotropic intestinal T-cell lymphoma in a horse. J Vet Diagn Invest 2002; 14: 150–152.
105. Freeman DE, Schaeffer DJ. Age distributions of horses with strangulation of the small intestine by a lipoma or in the epiploic foramen: 46 cases (1994–2000). J Am Vet Med Assoc 2001; 219:87–89.
106. Edwards GB, Proudman CJ. An analysis of 75 cases of intestinal obstruction caused by pedunculated lipomas. Equine Vet J 1994; 26:18–21.
107. Blikslager AT, Bowman KF, Haven ML, et al. Pedunculated lipomas as a cause of intestinal obstruction in horses: 17 cases (1983–1990). J Am Vet Med Assoc 1992; 201:1249–1252.
108. Moran JA, Lemberger K, Cadoré J-L, et al. Small intestine adenocarcinoma in conjunction with multiple adenoma causing acute colic in a horse. J Vet Diagn Invest 2008; 20:121–124.
109. Taylor SD, Pusterla N, Vaughan B, et al. Intestinal neoplasia in horses. J Vet Intern Med 2006; 20:1429–1436.
110. Honnas CM, Snyder JR, Olander HJ, et al. Small intestinal adenocarcinoma in a horse. J Am Vet Med Assoc 1987; 191:845–846.
111. Spoormakers TJ, IJzer J, Sloet van Oldruitenborgh-Oosterbaan MM. Neurological signs in a horse due to metastases of an intestinal adenocarcinoma. Vet Q 2001; 23:49–50.
112. Harvey-Micay J. Intestinal adenocarcinoma causing recurrent colic in the horse. Can Vet J 1999; 40:729–730.
113. Rottman JB, Roberts MC, Cullen JM. Colonic adenocarcinoma with osseous metaplasia in a horse. J Am Vet Med Assoc 1991; 198:657–659.
114. Patterson-Kane JC, Sanchez LC, MacKay RJ, et al. Small intestinal adenomatous polyposis resulting in protein-losing enteropathy in a horse. Vet Pathol 2000; 37:82–85.
115. Kasper C, Doran R. Duodenal leiomyoma associated with colic in a 2-year-old horse. J Am Vet Med Assoc 1993; 202:769–770.
116. Haven ML, Rottman JB, Bowman KF. Leiomyoma of the small colon in a horse. Vet Surg 1991; 20:320–322.
117. Clem MF, DeBowes RM, Leipold HW. Rectal leiomyosarcoma in a horse. J Am Vet Med Assoc 1987; 191:229–230.
118. Hanes GE, Robertson JT. Leiomyoma of the small intestine in a horse. J Am Vet Med Assoc 1983; 182:1398.
119. Mair TS, Davies EV, Lucke VM. Small colon intussusception associated with an intraluminal leiomyoma in a pony. Vet Rec 1992; 130:403–404.
120. Hafner S, Harmon BG, King T. Gastrointestinal stromal tumours of the equine caecum. Vet Pathol 2001; 38:242–246.
121. Muravnick KB, Parente EJ, Del Piero F. An atypical equine gastrointestinal stromal tumour. J Vet Diagn Invest 2009; 21:387–390.
122. Edens LM, Taylor DD, Murray MJ, et al. Intestinal myxosarcoma in a Thoroughbred mare. Cornell Vet 1992; 82:163–167.
123. Porter BF, Storts RW, Payne HR, et al. Colonic ganglioneuromatosis in a horse. Vet Pathol 2007; 44:207–210.
124. Allen D, Swayne D, Belknap J. Ganglioneuroma as a cause of small intestinal obstruction in the horse: a case report. Cornell Vet 1989; 79:133–141.
125. Kirchhof N, Scheidemann W, Baumgärtner W. Multiple peripheral nerve sheath tumours in the small intestine of a horse. Vet Pathol 1996; 33: 727–730.
126. Pascoe PJ. Colic in a mare caused by a colonic neurofibroma. Can Vet J 1982; 23:24–27.
127. Orsini JA, Orsini PG, Sepesy L, et al. Intestinal carcinoid in a mare: an aetiologic consideration for chronic colic in horses. J Am Vet Med Assoc 1988; 193:87–88.
128. Taintor J, Schleis S. Equine lymphoma. Equine Vet Educ 2011; 23:205–213.
129. Neufeld JL. Lymphosarcoma in the horse: a review. Can Vet J 1973; 14:129–135.
130. Mair TS, Hillyer MH, Taylor FG, et al. Small intestinal malabsorption in the horse: an assessment of the specificity of the oral glucose tolerance test. Equine Vet J 1991; 23:344–346.
131. Dart AJ, Hodgson DR, Snyder JR. Caecal disease in equids. Aust Vet J 1997; 75:552–557.
132. Traub JL, Bayly WM, Reed SM, et al. Intra-abdominal neoplasia as a cause of chronic weight loss in the horse. Compend Contin Educ Pract Vet 1983; 5:S526–S534.
133. Kirchhof N, Steinhauer D, Fey K. Equine adenocarcinoma of the large intestine with osseous metaplasia. J Comp Pathol 1996; 114:451–456.
134. Wright JA, Edwards GB. Adenocarcinoma of the intestine in a horse: an unusual occurrence. Equine Vet J 1984; 16:136–137.
135. Livesey MA, Hulland TJ, Yovich JV. Colic in two horses associated with smooth muscle tumours. Equine Vet J 1986; 18:334–337.
136. Collier MA, Trent AM. Jejunal intussusception associated with leiomyoma in an aged horse. J Am Vet Med Assoc 1983; 182:819–821.
137. Wilson T, Modransky P, Savage CJ. Small intestinal intussusception in a mule. Equine Pract 1994; 16:36–38.
138. Mair TS, Taylor FGR, Brown PJ. Leiomyosarcoma of the duodenum in two horses. J Comp Pathol 1990; 102:119–123.
139. Dart AJ, Snyder JR, Pascoe JR, et al. Abnormal conditions of the equine descending (small) colon (1979–1989). J Am Vet Med Assoc 1992; 200:971–978.
140. Dart AJ, Snyder JR, Pascoe JR. Resection and anastomosis of the small colon in four horses. Aust Vet J 1992; 69:5–7.
141. Mason TA. Strangulation of the rectum of a horse by the pedicle of a mesenteric lipoma. Equine Vet J 1978; 10:269.
142. Henry GA, Yamini B. Equine colonic lipomatosis. J Vet Diagn Invest 1995; 7:578–580.
143. Beeler-Marfisi J, Arroyo L, Caswell JL, et al. Equine primary liver tumors: a case series and review of the literature. J Vet Diagn Invest 2010; 22:174–183.
144. Axon JE, Russell CM, Begg AP, et al. Erythrocytosis and pleural effusion associated with a hepatoblastoma in a Thoroughbred yearling. Aust Vet J 2008; 86:329–333.
145. Brown DL, Anderson M, Cullen JM. Mesenchymal hamartoma of the liver in a late-term equine fetus. Vet Pathol 2007; 44:100–102.
146. Cantile C, Arispici M, Abramo F, et al. Hepatoblastoma in a foal. Equine Vet J 2001; 33:214–216.
147. Gold JR, Warren AL, French TW, et al. What is your diagnosis? Biopsy impression smear of a hepatic mass in a yearling Thoroughbred filly. Vet Clin Pathol 2008; 37:339–343.
148. Jeffcott LB. Primary liver-cell carcinoma in a young thoroughbred horse. J Pathol 1969; 97:394–397.
149. Kato M, Higuchi T, Orita Y, et al. Combined hepatocellular carcinoma and cholangiocarcinoma in a mare. J Comp Pathol 1997; 116:409–413.
150. Lennox TJ, Wilson JH, Hayden DW, et al. Hepatoblastoma with erythrocytosis in a young female horse. J Am Vet Med Assoc 2000; 216:718–721.
151. Loynachan AT, Bolin DC, Hong CB, et al. Three equine cases of mixed hepatoblastoma with teratoid features. Vet Pathol 2007; 44:211–214.
152. Mueller PO, Morris DD, Carmichael KP, et al. Antemortem diagnosis of cholangiocellular carcinoma in a horse. J Am Vet Med Assoc 1992; 201:899–901.
153. Neu SM. Hepatoblastoma in an equine foetus. J Vet Diagn Invest 1993; 5:634–637.
154. Prater PE, Patton CS, Held JP. Pleural effusion resulting from malignant hepatoblastoma in a horse. J Am Vet Med Assoc 1989; 194:383–385.
155. Roby KA, Beech JC, Black M. Hepatocellular carcinoma associated with erythrocytosis and hypoglycaemia in a yearling filly. J Am Vet Med Assoc 1990; 196:465–467.
156. Roperto F, Galatai P. Mixed hamartoma of the liver in an equine foetus. Equine Vet J 1984; 16:218–220.
157. Salvaggio A, Caracappa S, Gurrera A, et al. Hepatic biliary adenofibroma: a hitherto unrecognized tumor in equines. Report of a case. Vet Pathol 2003; 40:114–116.
158. Durando MM, MacKay RJ, Staller GS, et al. Septic cholangiohepatitis and cholangiocarcinoma in a horse. J Am Vet Med Assoc 1995; 206:1018–1021.
159. Rendle DI. Liver biopsy in horses. In Pract 2010; 32:300–305.
160. Reef VB. Adult abdominal ultrasonography. In: Reef VB, Virginia B, eds. Equine diagnostic ultrasound. Philadelphia: Saunders Company; 1998: 312–314.
161. Fry MM, Magdesian KG, Judy CE, et al. Antemortem diagnosis of equine mesothelioma by pleural biopsy. Equine Vet J 2003; 35:723–727.
162. Hilbert BJ, Little CB, Klein K, et al. Tumours of the paranasal sinuses in 16 horses. Aust Vet J 1988; 65:86–88.
163. Schnabel LV, Njaa BL, Gold JR, et al. Primary alimentary lymphoma with metastasis to the liver causing encephalopathy in a horse. J Vet Intern Med 2006; 20:204–206.
164. Chaffin MK, Schmitz DG, Brumbaugh GW, et al. Ultrasonographic characteristics of splenic and hepatic lymphosarcoma in three horses. J Am Vet Med Assoc 1992; 201:743–747.
165. Southwood LL, Schott HC, Henry CJ, et al. Disseminated haemangiosarcoma in the horse: 35 cases. J Vet Intern Med 2000; 14:105–109.
166. MacGillivray KC, Sweeney RW, Del Piero F. Metastatic melanoma in horses. J Vet Intern Med 2002; 16:452–456.
167. Browning AP. Splenic lymphosarcoma in a stallion associated with an acute abdominal crisis. Vet Rec 1986; 119:178–179.
168. Marr CM, Love S, Pirie HM. Clinical, ultrasonographic and pathological findings in a horse with splenic lymphosarcoma and pseudohyperparathyroidism. Equine Vet J 1989; 21:221–226.
169. Tanimoto T, Yamasaki S, Ohtsuki Y. Primary splenic lymphosarcoma in a horse. J Vet Med Sci 1994; 56:767–769.
170. Madron MS, Caston SS, Reintertson EL, et al. Diagnosis and treatment of a primary splenic lymphoma in a mule. Equine Vet Educ 2011; 23: 606–611.
171. Nyack B, Padmore CL, Dunn D, et al. Splenic lymphosarcoma in a horse. Mod Vet Pract 1984; 65:269–270.
172. Peroni JF. Equine splenectomy: Do we understand the consequences? Equine Vet Educ 2008; 20:371–372.
173. Rigg DL, Reinertson EL, Buttrick ML. A technique for elective splenectomy of Equidae using a transthoracic approach. Vet Surg 1987; 16:389–391.
174. Ortved KF, Witte S, Fleming K, et al. Laparoscopic-assisted splenectomy in a horse with splenomegaly. Equine Vet Educ 2008; 20:357–361.
175. Ross MW, Lowe JE, Cooper BJ, et al. Hypoglycemic seizures in a Shetland pony. Cornell Vet 1983; 73:151–169.
176. Carrick JB, Morris DD, Harmon BG, et al. Haematuria and weight loss in a mare with pancreatic adenocarcinoma. Cornell Vet 1992; 82:91–97.
177. Church S, West HJ, Baker JR. Two cases of pancreatic adenocarcinoma in horses. Equine Vet J 1987; 19:77–79.
178. Kerr OM, Pearson GR, Rice DA. Pancreatic adenocarcinoma in a donkey. Equine Vet J 1982; 14:338–339.
179. Priester WA. Data from eleven United States and Canadian Colleges of Veterinary Medicine on pancreatic carcinoma in domestic animals. Cancer Res 1974; 34:1372–1375.
180. Rowlatt U. Spontaneous epithelial tumours of the pancreas. Br J Cancer 1967; 21:82–107.
181. Mair TS. Pancreatic diseases. In: Mair TS, Divers T, Ducharme NW, eds. Manual of equine gastroenterology. London: WB Saunders; 2002: 248–350.

182. Rendle DI, Hewetson M, Barron R, et al. Tachypnoea and pleural effusion in a mare with metastatic pancreatic adenocarcinoma. Vet Rec 2006; 159: 356–359.
183. Harvey KA, Morris DD, Saik JE, et al. Omental fibrosarcoma in a horse. J Am Vet Med Assoc 1987; 191:335–337.
184. Johnson PJ, Wilson DA, Turk JR, et al. Disseminated peritoneal leiomyomatosis in a horse. J Am Vet Med Assoc 1994; 205:725–728.
185. Schaudien D, Müller JMV, Baumgärtner W. Omental leiomyoma in a male adult horse. Vet Pathol 2007; 44:722–726.
186. Stoica G, Cohen N, Mendes O, et al. Use of immunohistochemical marker calretinin in the diagnosis of a diffuse malignant metastatic mesothelioma in an equine. J Vet Diagn Invest 2004; 16:240–243.
187. Dobromylskyj MJ, Copas V, Durham A, et al. Disseminated lipid-rich peritoneal mesothelioma in a horse. J Vet Diagn Invest 2011; 23:615–618.
188. Ricketts SW, Peace CK. A case of peritoneal mesothelioma in a Thoroughbred mare. Equine Vet J 1976; 8:78–80.
189. Harps O, Brumhard J, Bartmann CP, et al. Ascites as a result of peritoneal mesotheliomas in a horse. Tierarztl Prax 1996; 24:270–274.
190. Ulrich R, Eydner M, Grün A, et al. A biphasic malignant mesothelioma of the peritoneum and pleura in a horse. Dtsch Tierarztl Wochenschr 2009; 116:186–191.
191. LaCarrubba AM, Johnson PJ, Whitney MS, et al. Hypoglycaemia and tumour lysis syndrome associated with peritoneal mesothelioma in a horse. J Vet Intern Med 2006; 20:1018–1022.
192. Carnine BL, Schneider G, Cook JE, et al. Pericardial mesothelioma in a horse. J Comp Pathol 1977; 99:105–107.
193. Colbourne CM, Bolton JR, Mills JN, et al. Mesothelioma in horses. Aust Vet J 1992; 69:275–278.
194. Kramer JW, Nickels FA, Bell T. Cytology of diffuse mesothelioma in the thorax of a horse. Equine Vet J 1976; 8:81–83.
195. Carnine BL, Schneider G, Cook JE, et al. Pericardial mesothelioma in a horse. Vet Pathol 1977; 14:513–515.

29

Tumours of the upper and lower respiratory tract

Upper airway neoplasia	480	Tracheal neoplasia	498
Other tumours in the sinonasal region	486	Neoplasia of the thoracic cavity	499
Tumour-like lesions	487	Primary thoracic tumours	499
Nasal polyp	488	Thymic tumours	501
Nasopharyngeal/laryngeal neoplasia	496	Metastatic thoracic tumours	506

Upper airway neoplasia

Overview

Neoplasia of the nasal cavity and paranasal sinuses comprises between 2% and 19% of all sinonasal disorders diagnosed at referral equine hospitals.[1–4] Squamous cell carcinoma is the most frequently identified primary tumour of the paranasal sinuses.

Considering the various cell types that are present in this anatomical region, equine sinonasal tumours include the following:

- Adenocarcinoma
- Fibrosarcoma
- Epithelial tumours (either surface or glandular origin)
- Haemangioma or haemangiosarcoma
- Mast cell tumour
- Myxoma or myxosarcoma
- Fibroma
- Undifferentiated carcinoma
- Bone and cartilage tumours (osteoma, osteosarcoma and chondroma)
- Lymphoma
- Haemangiosarcoma.

Additionally, the paranasal sinuses and the nasal cavity are relatively common sites for the development of 'tumour-like' conditions including:

- Epidermal inclusion cyst (atheroma)
- Maxillary and paranasal sinus cyst
- Progressive ethmoid haematoma (PEH)
- Nasal polyp.

Up to 75% of space-occupying masses of the nasal cavities and paranasal sinuses are tumour-like conditions, such as progressive ethmoid haematoma, paranasal sinus cyst or nasal polyp – sinunasal tumours are, therefore, relatively rare.[2]

Epithelial tumours tend to be found in older animals (median age 14 years) and fibro-osseous tumours more frequently occur in younger animals (median age 4 years).[5–10]

Clinical features

As a rule, neoplasia of the nasal and paranasal sinuses is generally characterized by an insidious onset with a protracted clinical course.[11] Unfortunately, the clinical signs of early sinus neoplasia are nonspecific, and similar to other inflammatory and space-occupying lesions in this region.

General clinical features of equine sinonasal neoplasia include:

- Nasal discharge
  - Unilateral, purulent or mucoid
  - Often treated as inflammatory sinus disease for a considerable time so the neoplastic process can be extensive before the diagnosis is made
- Facial swelling/deformity
- Epiphora
- Nasal obstruction
- Inspiratory and expiratory stridor with dyspnoea and cough
- Headshaking
- Exophthalmos/proptosis
  - Associated with presence of tumour infiltrating bony orbit, displacing the globe outwards
- Epistaxis
  - An uncommon clinical sign of sinus neoplasia
  - Absence of bleeding does not rule out neoplasia
- Neurological signs
  - Blindness
    - Associated with extension of mass into sphenopalatine sinus
- Submandibular lymphadenopathy
  - Tendency for local invasion rather than metastatic spread[12]
    - 20% of carcinomas spread to draining lymph node
    - 80% of carcinoma cases have clinical swelling of submandibular lymph nodes
    - Reactive lymphadenopathy may be associated with local infection and tumour necrosis.

Unilateral purulent or mucoid nasal discharge and facial swelling are the most commonly reported clinical signs in cases of sinus neoplasia, one study found, respectively, in

81% and 82% of cases.[8] These signs may be similar to those of a chronic primary sinus empyema, cyst or progressive ethmoidal haematoma, i.e. a putrid nasal discharge possibly mixed with blood. It is not uncommon for the presence of nasal discharge to be treated as being caused by inflammatory sinus disease and, consequently, the neoplastic process may be extensive before an accurate diagnosis is made. In most cases, the biological behaviour of sinonasal neoplasia is for local invasion rather than metastatic spread.[13]

With the exception of progressive ethmoidal haematoma (PEH), and in contrast to man and domestic animals, epistaxis of sinus origin is an uncommon clinical sign in horses with sinonasal neoplasia. In one study, epistaxis was present in only 10% of sinus neoplasia cases.[12] Therefore, absence of bleeding should not rule out neoplasia.[4]

If the lesion is extensive, facial asymmetry or deformity may be present. Both inspiratory and expiratory stridor with dyspnoea and coughing may also be evident. Evidence of nasal airflow obstruction is also reported to be common in cases of expansive intrasinus lesions; 31% prevalence of this clinical sign is seen in cases of paranasal sinus cyst and 40% in cases of sinus neoplasia.[12]

Due to their relatively aggressive nature and associated local tissue destruction and necrosis, secondary bacterial infection usually develops. Horses may have signs of chronic disease, including:

- Anorexia
- Weight loss
- Anaemia
- General poor condition.

Other less frequently reported signs include neurological signs, associated with extension into the sphenopalatine sinus, such as blindness. In addition, there may be proptosis when the tumour has infiltrated the bony orbit and displaced the globe outwards. Some tumours and nasal polyps protrude from the nostrils.

The literature confirms a predisposition for certain tumour types to occur at certain anatomical locations; squamous cell carcinoma (SCC) and unspecified carcinomas develop in the maxillary sinus, whilst adenocarcinoma tends to develop in the nasal and ethmoidal area.[14] More recent reports suggest a tumour predilection for the conchofrontal sinuses. No cases of adenocarcinoma appear to have been recorded in the maxillary sinuses.

Diagnostic confirmation

The histological differences between the mucosa at these sites may explain the variations in tumour incidence. In particular, the presence of Bowman's glands in the ethmoidal region could explain the higher incidence of glandular epithelial tumours of the ethmoidal/frontal area.[8] There is also consensus that tumours occur more frequently in the equine paranasal sinuses than in the nasal cavity itself.[15]

Squamous cell carcinoma has been said to be the most common tumour of the equine nasal cavity and paranasal sinuses, in particular of the maxillary sinuses. However, it is not always clear whether these lesions originate within the maxillary sinus or in the oral cavity.[16] Interestingly, a recent study using computed tomography (CT) of sinonasal neoplasia reported on 15 horses with sinonasal neoplasia. One-third of the tumours identified were neuroendocrine/neuroblastoma and none were identified as SCC.[17] Historically, a definite site of origin of sinonasal neoplasia was identified in 92% of cases. However, more recently, more than one site of origin has been suggested in 22% of cases.

Based on the recent CT study[17]:

- 1/15 horses had involvement of one paranasal sinus
- 6/15 involved both the nasal cavity and paranasal sinuses unilaterally
- 4/15 had bilateral involvement
- Conchofrontal sinus was the most commonly involved sinus (15/15)
- The caudal maxillary sinus was the next most commonly involved sinus (10/15)
  - The rostral maxillary sinus was involved in 9/10 horses with caudal maxillary sinus masses
  - No horse had rostral maxillary sinus involvement without caudal maxillary sinus involvement
- Extension into the retrobulbar space was noted in 10/15 horses.

Determining the origin of tumours by CT is challenging, but the most common point of origin of the tumours appears to be the retrobulbar area.[17]

Despite the locally aggressive nature of most sinonasal tumours, metastases have rarely been recorded. A study of 28 cases of sinonasal neoplasia found only 20% of 15 carcinomas had spread to draining lymph nodes and no metastases were recorded at distant sites. Despite a small number with local lymph node spread, clinical swelling of submandibular lymph nodes was present in 82% of affected animals. Therefore, lymphadenopathy is most commonly due to reactive lymphadenopathy associated with local infection and presumably tumour necrosis.[8]

Presenting signs for tumours of the nasal and paranasal sinuses in horses are often difficult to differentiate from other more common causes of chronic sinusitis. These may include primary sinusitis, i.e. sinusitis of no underlying cause, or sinusitis secondary to other disorders. These include[12]:

- Apical infection of the more maxillary cheek teeth
- Dental-related or maxillary fistula
- Paranasal sinus cysts
- Mycotic sinus infection
- Intrasinus progressive (ethmoidal) haematoma
- Sinus trauma.

A definitive diagnosis of sinus neoplasia is challenging, in part due to the similarity in clinical presentation of the more common inflammatory sinus disease; this commonly leads to delayed diagnosis.[4]

Diagnosis is generally achieved by a combination of:

1. Clinical/oral examination
2. Radiography/CT
3. Endoscopy/trephination-sinoscopy
4. Histopathological examination of biopsy specimens.

Management

Treatment options for sinonasal neoplasia are limited and include:

- Surgical excision or debulking
- Radiotherapy
- Local chemotherapy.

Well-circumscribed benign lesions, such as osteoma, can be surgically managed with success. However, treatment of carcinoma is particularly unrewarding, possibly due to the delayed diagnosis and the locally invasive nature coupled with an intolerant anatomy that precludes total or even significant surgical excision. The majority of horses diagnosed with sinonasal neoplasia are euthanized once a definitive diagnosis has been made.

Prognosis

The prognosis for most horses with sinonasal neoplasia, and in particular carcinomas (squamous cell, adenocarcinoma and undifferentiated carcinoma), is poor, mainly due to the advanced spread of these invasive tumours by the time of diagnosis.[18] Whilst use of multimodal therapy is limited in horses with sinonasal neoplasia, early diagnosis may allow the application of intralesional chemotherapy or radiotherapy, in conjunction with conventional surgery, to improve the currently poor outcomes.[19,20]

Squamous cell carcinoma

Disease summary

Notes

The most common primary sinunasal malignancy, but still rare. Usually in older horses.

Clinical features

Insidious onset of progressive nasal obstruction and stertor with a chronic serious or serosanguineous (unilateral) nasal discharge, fetid breath, facial deformity.

Diagnostic confirmation

Direct examination and biopsy combined is usually enough, but access to the tumours might require radiography/CT, endoscopy or ultrasonography.

Management

Surgical tumour reduction with concurrent chemotherapy or radiotherapy if indicated. Wide variety of chemotherapeutic approaches available.

Prognosis

Always guarded and, if inaccessible or extensive, prognosis is poor; metastasis is very rare.

Overview

See also pages 220 and 575.

Squamous cell carcinoma is generally considered the most common form of nasal and paranasal sinus neoplasia in horses and typically occurs in older horses.[8,16,21,22] It is usually unilateral.

It appears to have a predilection for the caudal maxillary sinus. However, squamous cell carcinoma may originate within the nasal cavities, paranasal sinuses and pharynx.[23–25] The origin of SCC has been the subject of considerable debate. Weisz (1944) stated, 'Carcinoma of the maxillary sinus is a misnomer since these tumours arise in the epithelium of the hard palate and grow into the maxillary sinus'.[26] However, Moulton (1990) believed that true primary SCC can occur in the paranasal sinuses.[27] Eight cases of oral SCC with invasion of the nasal cavities or sinuses have been described.[28] Non-keratinized SCC of the caudal maxillary sinus may extend to other sinuses, the nasal cavity, the orbit and cranium.[14,29]

Clinical features

- A wide variety of clinical presentations occurs (Fig. 29.1). The tumours may be destructive, in which case they would present with evidence of bleeding and malodourous breath or obvious distortion of anatomical integrity
- Tumours that only affect the skin and surface of the nasal cavity usually have a haemorrhagic and infected surface
- Chronic (usually unilateral) sanguineous-purulent nasal discharge with fetid breath
- An ulcerated and multilobular mass projecting from the affected mucosa, sometimes with significant nasal occlusion and possibly with nasal septal deviation that causes contralateral obstruction. Snorting and rubbing of the face may be present
- Secondary neurological changes may affect the function of the eye (CNIV, CNVI that innervate the extrinsic muscles of the eye, resulting in strabismus) or the trigeminal nerve (resulting in peripheral neuralgia, pruritus/numbness or headshaking and snorting) physical expansion of the orbit, resulting in exophthalmos. Invasion of the cribriform plate may result in significant central (cerebral) signs (Fig. 29.2).

Differential diagnoses

- Other neoplastic changes in the nasal cavity, such as adenocarcinoma and lymphoma
- Dental and bone tumours of the maxillary region, such as osteoma, cementoma and ameloblastoma
- Progressive ethmoid haematoma
- Nasal polyp
- Infections (bacterial or fungal) causing swelling or destruction of the intranasal structures.
- Glanders and epizootic lymphangitis – both of these can produce ulcerated areas with a serous/sticky discharges
- Foreign body granuloma, sinus infections and abscessation.

Diagnostic confirmation

- It is very important to examine the hard palate and adjacent gingiva for the characteristic epithelial defect
- Because of the proximity of the paranasal sinuses to the orbit, it is important to thoroughly examine the eye to ensure a primary SCC of the eye has not eroded the orbital bone and extended into the paranasal sinuses or vice versa[14]
- *Endoscopically*, squamous cell carcinoma within the nasal cavity and sinuses can vary in appearance – usually, there is an ulcerated mucosal surface and airway compromise – quite often they are large enough to preclude distal endoscopic examination



Figure 29.1 Squamous cell carcinoma in the nasal cavity. (A) Squamous cell carcinoma can affect any squamous epithelium in the respiratory tract, including the nostrils. **(B)** It can also occur in the nasal cavity (and paranasal sinuses), where it can involve the nasal punctum of the nasolacrimal duct. **(C)** In some cases, it is proliferative as well as destructive and can occlude the nostril completely.

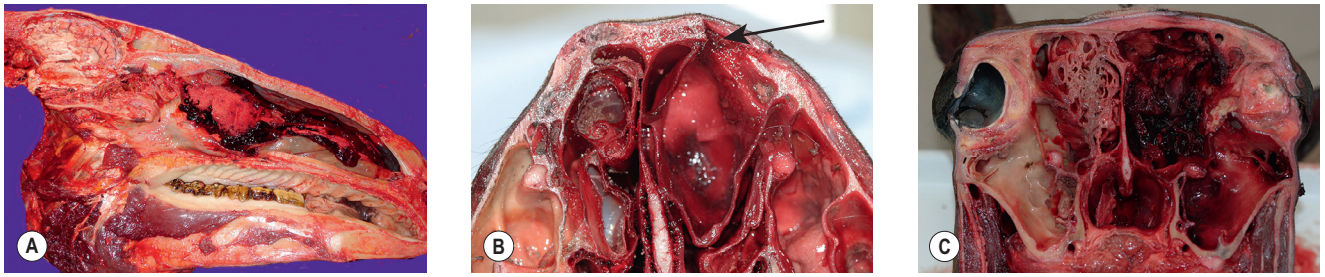


Figure 29.2 Maxillary squamous cell carcinoma. (A) This 6-year-old Thoroughbred cross gelding developed a persistent mild haemorrhagic left-sided nasal discharge with a fetid odour with mild facial/maxillary deformity. An area of bone loss was noted over the rostral maxillary sinus and maxilla (arrow) and this was scanned to reveal a heterogeneous mass. Lateral radiographs and CT identified a space-occupying soft tissue mass within the nasal cavity and the conchofrontal sinus and maxillary sinuses. The mass was investigated surgically and a biopsy was taken for immediate frozen section analysis and it was diagnosed with maxillary squamous cell carcinoma. **(A–C)** The carcinoma occupied the majority of the left nasal cavity and had obliterated much of the nasal anatomy.

- *Radiographically*, the tumours may appear as a slightly mottled to generalized soft tissue radiodensity with or without a fluid–gas interface within the sinus.

Despite their invasive growth, equine SCC metastases are rare and spread usually occurs in draining lymph nodes; these are best examined from within the guttural pouch.

An undifferentiated carcinoma has also been reported to occur in the rostral nasal cavity, ethmoid labyrinth and the frontal sinus.[30–32]

Management

1. *Surgical tumour reduction followed by chemotherapy,* such as slow release cisplatin, 5-fluorouracil or mitomycin-C or surgery accompanied by radiotherapy provide the only material options.
2. *Radiotherapy* as a sole treatment can be successful under very controlled conditions in early cases.

Prognosis

The prognosis is generally poor but will largely depend on the stage of diagnosis – most cases are presented late or are misdiagnosed and then proper treatment is delayed. Advanced cases carry a hopeless prognosis even though carcinoma is very sensitive to both chemotherapy and radiotherapy. Earlier diagnosis and better treatment will probably give a reasonable chance of recovery in future.

Adenocarcinoma

See also page 264.

Disease summary

Notes

Very rare rapidly expanding, invasive tumour of glandular epithelium occurring in older horses.

Clinical features

Depending on location of space-occupying mass, unilateral nasal discharge, facial swelling, exophthalmos, neurological deficits, respiratory noise.

Diagnostic confirmation

Biopsy is essential.

Management

No successful treatment options reported. Early diagnosis may give more opportunity for surgical debulking with adjunct radiotherapy or chemotherapy.

Prognosis

Prognosis is hopeless, but metastatic tumours are not reported.

Description

Adenocarcinoma usually affects older horses and generally arises from glandular epithelium.[33]

They are less commonly reported than tumours of surface epithelium and are preferentially found in the ethmoidal and frontal sinus regions.[16]

There have been five reports of cranial invasion of an adenocarcinoma.[34–38]

Clinical features

Clinical signs vary according to location of space-occupying neoplasm and include:

- Unilateral nasal discharge with fetid odour
- Facial swelling
- Multiple cranial nerve deficits may occur (Fig. 29.3)[37]
- Neurologic deficits include:
  - Strabismus
  - Blindness
  - Trigeminal neuralgia/headshaking (Figs 29.3, 29.4)
- Exophthalmos and persistent prolapse of the third eyelid (Fig. 29.4)
- Respiratory noises, a stridor, and possibly nasal obstruction
- Facial distortion and bone thinning, possibly leading to sinus tracts.

Diagnostic confirmation

- Endoscopy
- Radiography, CT
- MRI
- Biopsy.

Due to the preferential location of adenocarcinoma in the ethmoidal/frontal area, and the numerous reports of extension to the cranial cavity (see Figs 29.3, 29.4), careful neurological assessment, and 3D imaging to identify extension to the cranial vault are essential, prior to commencement of any type of treatment.

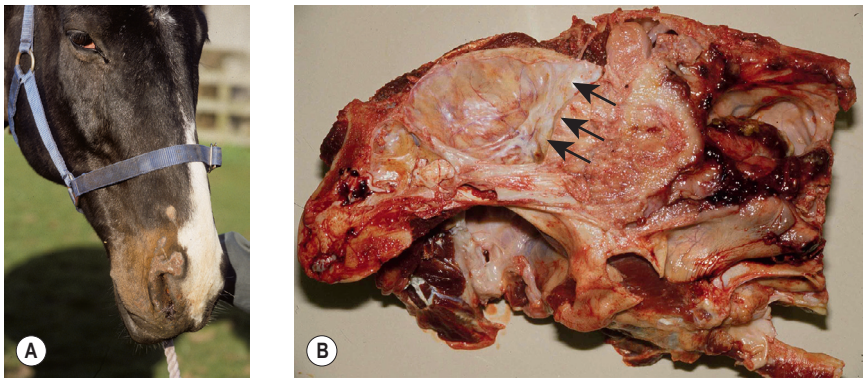


Figure 29.3 Adenocarcinoma in the ethmoid region of the nasal cavity. (A) This 12-year-old gelding developed an ethmoid haematoma, which was treated by surgical resection via a maxillary sinus flap. Some 14 months later, the gelding developed severe trigeminal neuralgia with ipsilateral facial self-trauma and low-grade epistaxis and halitosis. Endoscopic examination revealed an extensive dense, invasive and ill-defined mass in the ethmoid region of the nasal cavity. A biopsy revealed high-grade adenocarcinoma. Over the following 4 weeks, the horse developed progressive neurological signs and was euthanized on humane grounds. **(B)** At necropsy, the adenocarcinoma had eroded the cribriform plate and invaded the anterior region of the cerebral cortex (arrows).

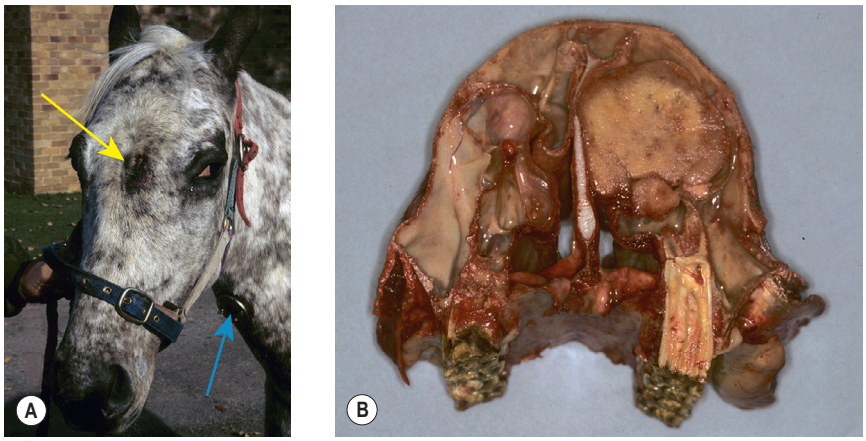


Figure 29.4 Sinus adenocarcinoma. (A) This 14-year-old grey mare was presented with a history of progressive respiratory difficulty and occlusion of the left nostril. A small amount of haemorrhagic nasal discharge and facial swelling strabismus of the eye (presumed to be of neurological origin) and prolapse of the nictitans developed over a period of around 3 weeks. An emergency tracheostomy tube (blue arrow) was required. A discharging sinus was noted on the forehead (yellow arrow). Radiography identified a space-occupying mass within the left maxillary sinus and nasal cavity and septal deviation. A biopsy of this mass confirmed a sinus adenocarcinoma and this was confirmed at necropsy. **(B)** The tumour occupied the large majority of the nasal cavity and had obliterated all sinus anatomy.

Management and prognosis

There have been no successful reports of treatment of sinonasal adenocarcinoma in the literature to date, and prognosis remains poor to hopeless. Hopefully, the more extensive use of CT in the investigation of sinonasal disease will enable earlier diagnosis and then the successful treatment.

Note

Undifferentiated (anaplastic) carcinoma has no squamous or glandular features and thus may arise from either surface or glandular epithelium.[16,39] Three cases of undifferentiated carcinoma were identified out of 28 cases of sinonasal neoplasia: two originated in the maxillary sinus and one in the hard palate.[8] Clinical signs were consistent with sinonasal disease, including facial distortion, nasal discharge and destructive changes on radiography. Two were euthanized on diagnosis. One pony was treated as a chronic sinus empyema, initially, followed by surgical removal 5 months later and recurrence of the lesion at 16 months, when it too was euthanized.

Mast cell tumour (intranasal)

Disease summary

Notes

Rare usually benign, solitary, space-occupying, slow-growing tumour of the nasal mucosa.

Clinical features

Space-occupying effects, but some cause irritation and snorting behaviour.

Diagnostic confirmation

Diagnosis is confirmed by biopsy.

Management

Surgical removal is effective; intralesional corticosteroids may be helpful.

Prognosis

Prognosis is good – disseminated forms are very rare.

Overview

Mast cell tumours are occasionally encountered in the skin of the nostrils, the nasal cavity and the pharynx.[40] They have a distinctive clinical and pathological character and are more commonly seen in male horses than females (see pp. 356 and 564). The tumour is probably not genuinely neoplastic in this site.[41] Arabians are probably over-represented but this applies more to cutaneous forms than nasal ones. Most tumours are well-differentiated, with low mitotic rates. Associated clinical disease is uncommon and malignant behaviour is extremely rare.

Clinical features

The signs are generally insignificant, but repeated bleeding and occasionally rubbing of the site can be significant.

The tumour may be ulcerated and reveal a yellowish, gritty content with distinctive yellow 'kunkers' (see Fig. 31.22C). A serous nasal discharge may be present when the lesions are situated in the nasal cavity. Endoscopically, a diagnosis can be very difficult. Some cause local pruritus and that might manifest as nasal or facial rubbing and irritation.

Differential diagnoses

1. Granuloma
2. Sarcoid
3. Polyp
4. Nasal amyloidosis.

Diagnostic confirmation

Ultrasonography shows a characteristic heterogeneic pattern (Fig. 7.10, p. 96). Biopsy provides a definitive diagnosis (see Fig. 7.5, p. 91).

Management

Despite the benign nature, incomplete excision leads to rapid recurrence due to local infiltration.

Prognosis

The prognosis is usually very good – mast cell tumours do not appear to be inclined to malignancy and (repeated) surgery will usually result in a good outcome.

Myxoma

See also pages 356 and 564.

Disease summary

Notes

Very rare, benign, space-occupying, slow-growing tumour, affecting the paranasal sinuses and sometimes the jaw and lungs. No metastasis.

Clinical features

Effects relate to space-occupying nature of the tumour, unilateral nasal discharge, facial swelling, exophthalmos, neurological deficits, respiratory noise.

Diagnostic confirmation

Diagnosis is confirmed by biopsy.

Management

Surgical removal may be feasible.

Prognosis

Prognosis is probably very poor.

Overview

Sinonasal myxoma is very rare. It is a benign tumour of primitive connective tissue cells, which grows by non-infiltrative expansion. Myxoma has been reported in the mandibular, bronchiolar and sinonasal regions of the horse. It has not been reported to metastasize either locally or systemically in the horse.[16] In humans, the gross appearance of sinonasal myxoma is an unencapsulated, gelatinous friable and infiltrative mass, as in the case in horses.[42] However, there have been variable reports of gross appearance from a firm round pale tumour, to a mucus-filled cavity. There are eight equine sinonasal myxoma and two myxosarcoma reported in the literature.[1,8,17,42–45]

Clinical features

The signs are directly attributable to the space-occupying and local pressure effects and secondary infection.

- Respiratory obstruction and facial deformity are the commonest features (Fig. 29.5)
- Secondary sinus infection and pressure necrosis may lead to nasal discharges and a fetid breath
- Other effects arise from organ interference, such as blindness, exophthalmos, glaucoma and neurological disturbances involving the infraorbital nerve.

Differential diagnoses

- Progressive ethmoid haematoma
- Nasal polyp
- Sinus cyst
- Sinus carcinoma/adenocarcinoma
- Sinus empyema/infection, including aspergillosis.

Diagnostic confirmation

- Imaging modalities, such as radiography and CT/MRI, provide nonspecific information
- Biopsy provides a definitive diagnosis – this may require sinus trephination.

Management

- Despite the benign nature, incomplete excision leads to rapid recurrence due to local infiltration. En bloc facial resection, as employed in humans to facilitate complete removal, is not considered feasible in the horse.[42]
- A combination of cryotherapy and levamisole (as an immunotherapeutic) was used successfully in the case of two horses.[44]

Prognosis

The prognosis is usually poor due to the late presentation and the anatomic difficulties of access. The advent of more readily available standing CT may assist early identification of the often more extensive nature of sinonasal myxoma and assist with surgical planning and prognostication.[17,42]

Other tumours in the sinonasal region

Overview

Other tumours reported in the nasal cavity and paranasal sinuses include:

- Neuroendocrine tumour (extra-adrenal paraganglioma)
- Dental tumours (see p. 312)
- Fibrosarcoma
- Melanoma
- Lymphoma
- Haemangiosarcoma
- Myxoma
- Meningioma.

A collision tumour occurs when two separate tumour types encroach on one another. A single case of a collision tumour has been reported; the tumour comprised glandular tissue and spindle cells growing concurrently within the frontal and caudal maxillary sinuses of a geriatric donkey.[46]

Neuroendocrine tumour/neuroblastoma/ extra-adrenal paraganglioma

See also pages 389 and 595.

Overview

These tumours are regionally invasive masses that affect older horses.[46–50] A recent CT-based study of cases of sinonasal neoplasia, unusually, had no cases of squamous cell carcinoma, but included several cases of neuroendocrine origin or neuroblastoma.[17] All cases involved the retrobulbar

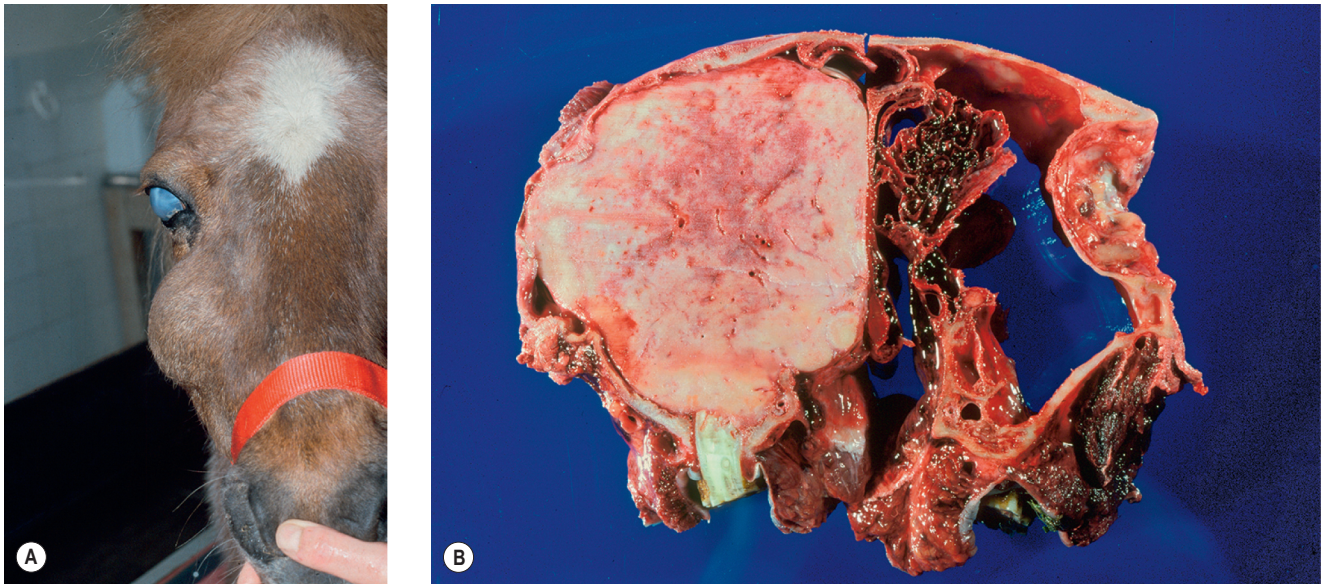


Figure 29.5 Myxoma. (A) This facial swelling developed over a period of about 4 months in a 6-year-old Welsh pony gelding. Concurrent signs of airway obstruction, blindness, glaucoma and exophthalmos developed simultaneously. A biopsy provided a diagnosis of myxoma. **(B)** At necropsy, the mass was a homogeneous solid but friable and gelatinous tumour that filled the maxillary sinus and obliterated the nasal cavity without any obvious displacement of the septum. All the signs were attributed to the space-occupying nature of the tumour.

space with various degrees of paranasal sinus involvement. Most cases originated from the retrobulbar space and one originated from the ethmoid turbinates. Most cases have marked erosion of the cribriform plate and clear extension into the cranial vault. MRI is suggested to be a better imaging modality for determining the involvement of brain parenchyma and the soft tissues of the orbit, in comparison to CT. MRI is useful for evaluation of horses with exophthalmos or neurological signs suggestive of orbital or intracranial disease (see p. 102).

Haemangiosarcoma

See also pages 334 and 514.

Overview

The clinical features of true vascular tumours and progressive ethmoidal haematoma can be similar, but their growth pattern and histology differ markedly.[51] Vascular tumours tend to grow by both expansion and infiltration, causing extensive bony destruction. There are very limited reports in the equine literature.

Chronic epistaxis and anaemia, with respiratory stridor and facial deformity, are the main nonspecific signs. Extensive involvement of the paranasal sinuses can be present, but metastasis does not appear to be a feature.[52,53]

Fibrosarcoma

See also pages 244 and 287.

Overview

Nasomaxillary fibrosarcoma has been reported in four horses and suggested to be a congenital lesion.[8,54,55] Affected horses tend to be young. One foal had an ulcerated mass over the nasomaxillary region at birth. The foal was euthanized after radiographs revealed a well-marginated soft tissue mass within the left maxillary sinus. Necropsy revealed a congenital nasomaxillary fibrosarcoma. The other two cases (11 and 20 months old) underwent surgical removal. One was euthanized during surgery due to the extensive nature of the mass; the other underwent surgical debulking and cryotherapy and demonstrated no recurrence at 18 months after surgery. One case of fibrosarcoma in a 9-year-old mare presented with headshaking, frontomaxillary swelling, third eyelid prolapse, exophthalmos, bilateral mucopurulent discharge and dyspnoea.[8] A tracheostomy was performed to resolve the dyspnoea and surgery was performed to remove the mass. This could not be removed fully. Recurrence occurred at 6 months' post-surgery and the horse was euthanized.

Tumour-like lesions

Epidermal inclusion cyst (atheroma)

See also page 260.

Description

Epidermal inclusion cysts (also previously referred to as atheroma or sebaceous cysts) are cysts of the skin restricted to the region of the nasal diverticulum. Epidermal inclusion cyst is a relatively common incidental (cosmetic) disorder. The term 'epidermal inclusion cysts' is preferred because it describes the keratinized and non-keratinized squamous epithelial cells and keratin debris (rather than sebaceous elements) that are found on microscopic examination of cyst contents.[56]

Disease summary

Notes

Common incidental anomaly – dermal inclusion cyst.

Clinical features

Tense, fluid-filled cystic structure of variable size in the dorsolateral aspect of the false nostril.

Diagnostic confirmation

Aspiration of the cyst produces milky grey-white viscous fluid.

Management

Surgical treatment is curative but probably not necessary.

Prognosis

Prognosis is excellent.

Clinical features

- Typically, unilateral, non-painful, fluid-filled, often tense, spherical mass in the dorsolateral aspect of the nasal diverticulum
- Vary in size from 2 to 5 cm diameter, but can be significantly larger
- Occurs predominantly in young animals (1–3 years)
- Some do gradually enlarge (Fig. 29.6), but most are very static and remain so for many years without any clinical consequence
- Contain opaque white or grey viscous material.[16,56]

Differential diagnoses

- Sarcoid
- Mast cell tumour
- Abscess
- Haematoma
- Foreign body reaction.

Although many owners are concerned in respect of respiratory obstruction, they very rarely, if ever, cause exercise intolerance or respiratory noise/abnormalities. Treatment is usually initiated for cosmetic reasons.

Diagnostic confirmation

The condition is characteristic:

- Aspiration of the cyst reveals a grey/creamy, thick fluid.

Management

- Establishment of drainage into the nasal diverticulum is feasible but concurrent sclerosis of the lining is necessary to prevent reformation of the cyst. This is usually achieved with daily application of strong iodine. Recurrence is still a frequent complication.

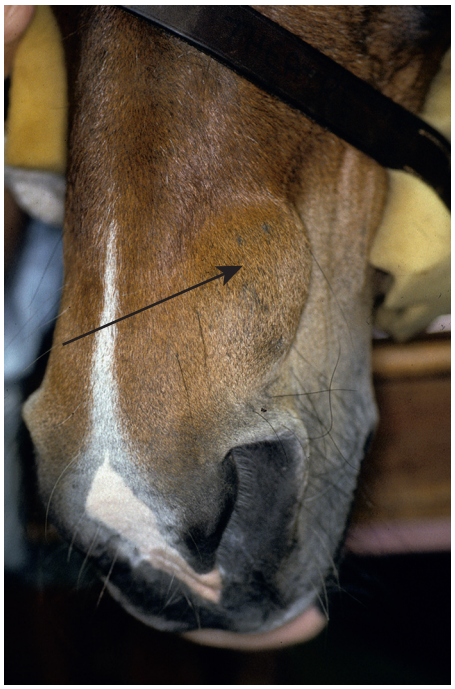


Figure 29.6 Atheroma/epidermal inclusion cyst. This 13-year-old Welsh cross gelding developed a non-painful, tense, fluid-filled swelling in the dorsolateral aspect of the false nostril (arrow) at age 2 years. The mass gradually enlarged over the following 11 years. It was not treated and caused no apparent problem to the horse. Most cysts are smaller than this and remain static. Surgical treatment options are available but are not strictly required.

- Surgical en bloc resection of the cyst can be performed in the standing, sedated horse. The skin and subcutaneous tissue over the cyst is incised and the cyst is dissected free of surrounding tissue. Careful dissection is necessary to prevent rupture of the cyst wall.[57]
- Surgical removal of the cyst lining is an alternative technique where the cyst is approached through a stab incision over the nasal diverticulum and a laryngeal burr is used to remove the lining.[58] Complications associated with this surgical extirpation include infection, dehiscence and recurrence.
- Intralesional formalin injection has been used to effect cyst obliteration; its effectiveness is believed to result from the desiccating and coagulation actions of formaldehyde. In a report of the treatment of five cases of epidermal inclusion cyst by intralesional formalin injection, the only effects were swelling of the cyst for 3–7 days after injection, nose rubbing and nasal irritation, mucoid nasal discharge and transient epistaxis. The procedure is simple, quick and inexpensive. A single injection of 10% formalin solution (3–5 mL depending on the size of the cyst), is adequate for complete desiccation of the cyst. The sclerosed remnant can be excised at a later date but may disappear or slough spontaneously.[59]

Prognosis

The prognosis is excellent.

Nasal polyp

See also page 259.

Disease summary

Notes

Rare benign tumour-like condition affecting middle-aged horses; usually unilateral and originating from caudal/ethmoidal respiratory mucosa.

Clinical features

Signs vary with location and extent; signs usually attributable solely to space-occupying effects within the airway, unilateral nasal discharge, respiratory noise and ultimately a fleshy mass at the nostril.

Diagnostic confirmation

Biopsy differentiates it from other similar conditions. Retrograde endoscopy via a tracheostomy site may identify the origin.

Management

Easily treated either by gentle direct traction or by cautery at its origin.

Prognosis

Prognosis is poor to hopeless.

Description

A polyp is a smooth, pedunculated growth on a mucosal surface. Polyps can be the result of hyperplasia of the mucosa or associated lymphoid tissue, usually attributed to inflammatory or allergic stimulation. The distinction between true benign neoplasia and inflammatory polyp may be difficult.[29]

Polyps are rare but occur in mature horses usually in the 7–19 years age range, with a median of 13.5 years. The duration of clinical signs prior to referral is usually around 26 weeks, although most are referred for acute nasal obstruction of rapidly developing tumour protruding from the nostril.

Clinical features

(Fig. 29.7)

- Single or multiple polyps, unilateral, arise insidiously from the mucosa of the nasal septum or conchae; most commonly they arise from the caudal aspect of the nasal conchae[55]
- Ipsilateral serous or serosanguineous nasal discharge is frequently present and often there is malodorous breath
- Facial swelling is very rare – most simply confirm to the nasal cavity, but within the sinuses they can cause some facial distortion
- Nasal airflow obstruction, with stertorous breathing and dyspnoea[56]
- Gross submandibular lymphadenopathy may be present (often ipsilateral only).

Differential diagnoses

1. Progressive ethmoid haematoma
2. Squamous cell carcinoma
3. Sinus cysts
4. Sinus empyema/conchal abscess/nasal aspergillosis.

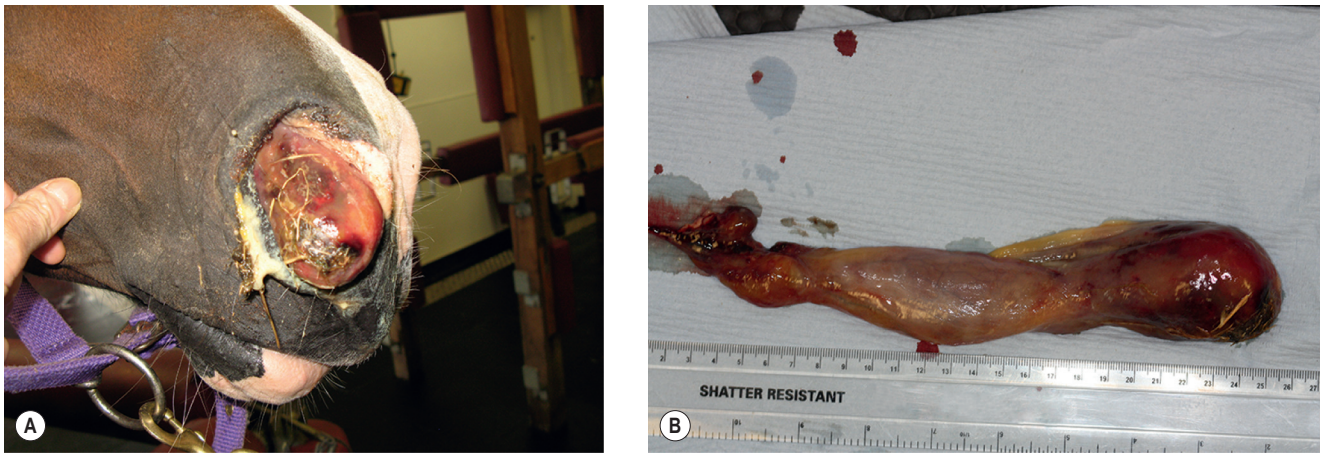


Figure 29.7 Nasal polyp. **(A)** A 12-year-old pony gelding was presented as an 'emergency' with a large soft mass at the right nostril. There was complete airway obstruction of the nostril but the pony was unaffected in any other way. **(B)** Following endoscopy via the left nostril, the attachment of the polyp was recognized at the caudal end of the nasal conchus and gentle traction released the polyp without any significant bleeding or difficulty. The condition did not recur at least for 6 years.

Diagnostic confirmation

- *Endoscopy*: Nasal cavity distortion/occlusion, occasionally with nasal septum displacement, is common. Abnormal secretions can be seen in the nasal cavity and sinus drainage may be seen from the caudal drainage angle in sinus polyp cases. Retrograde endoscopy via a tracheostomy site will usually identify the origin of nasal polyp
- *Radiography* (lateral and ventrodorsal projections) provides nonspecific evidence of nasal occlusion
- *Biopsy* specimens provide a definitive diagnosis.[60] Nasal polyps may show histological similarities to progressive ethmoid hematoma (see p. 258) but usually contain more organized granulation tissue. Progressive ethmoid haematoma has been described as a 'haemorrhagic polyp'.[61] Equine nasal polyps have some histological similarities to human nasal epithelial polyps, which are believed to result from polypoid epithelial proliferation in the presence of chronic inflammation[56]

Management

Most nasal polyps can be removed simply by gentle traction but in the event that this is not achieved/possible, a variety of surgical approaches can be made, depending upon their anatomic origin, including diathermy (snare or point), diode or Nd:YAG laser or sharp surgical incision.[60]

Prognosis

The prognosis is excellent.

Disease summary

Notes

Relatively common non-neoplastic proliferative (progressive) slow-growing expansile lesion originating from the ethmoidal nasal mucous or within the paranasal sinuses.

Clinical features

Space-occupying effects within the airway, unilateral serosanguineous nasal discharge, may extend to the nostril. May be multiple.

Diagnostic confirmation

Characteristic endoscopic and radiographical features.

Management

Surgical, laser or formalin ablation are effective; the former has severe haemorrhage.

Prognosis

Prognosis is guarded, since up to 30% recur and some are less accessible.

Progressive ethmoidal haematoma (PEH)

Description

Progressive ethmoidal haematoma (PEH) is a slowly progressive, expansive, non-neoplastic mass that arises beneath the mucosa in the ethmoid region or within the paranasal sinuses. The aetiology is not known.

The prevalence of progressive ethmoid haematoma has been reported at 0.03–0.04% (1 in 2500 horses).[62,63] Horses with PEH have been reported to represent 3.5–7.6% of horses with sinonasal disease and 10–27% of horses undergoing nasal or sinus surgery.[12,19,64] PEH has been reported in horses from 4 weeks to 20 years of age, with a median age of 5 years.[12] There may be an increasing likelihood of PEH developing as age increases.[58] Some reports suggest no sex predilection, whilst others suggest more frequent occurrence in male horses.[62,65] There may be a breed predisposition in Thoroughbreds and Arabian horses.

The pathophysiology of PEH is presumed to begin with haemorrhage in the submucosa of the respiratory epithelium, causing the mucosa to stretch, thicken and form a capsule around the slowly expanding haematoma.

Classification of PEH is useful because it will influence the choice of treatment.[66] PEH has been classified into four groups based on the primary location of the mass (site of origin):

1. Ethmoid turbinates
2. Maxillary sinus

3. Sphenopalatine sinus
4. Any other location.

Combinations of these groups also occur as PEH may arise at more than one site.

Clinical features

Duration of clinical signs prior to diagnosis ranges from 1 week to ≥5 years.[2,12]

- *Chronic low-grade unilateral, non-odorous sero-haemorrhagic discharge* is the most consistent clinical sign; this is due to ulceration of the respiratory epithelium covering the mass. Fresh haemorrhage is not usually seen and the blood is not associated with exercise (Fig. 29.8).
- *Nasal airflow obstruction* of varying degree is common and an adventitious respiratory noise may be present at exercise; in severe cases of nasal cavity PEH, a stertorous noise, obvious loss of airflow and respiratory distress may be present even at rest (Fig. 29.9).
- *Submandibular lymph node enlargement*.
- *Epiphora* is sometimes encountered and is assumed to be due to nasolacrimal duct obstruction by pressure.
- *Facial swelling* is rarely encountered but may occur as a late feature.
- *Dysphagia*: large masses may extend as far as the nasopharynx and cause dysphagia.
- *Central nervous signs*, including blindness, are very rarely associated with this condition.
- *Other signs* that may be presented include *coughing, purulent nasal discharge, exophthalmos and headshaking*.

The caudal and rostral maxillary sinus are also involved in 50% of cases, either alone (25%) or in conjunction with the ethmoid area (25%). These masses may extend into the nasal cavity. More rarely, PEH can also be found in the conchofrontal sinus, ventral conchal sinus and the sphenopalatine sinus.[18]

Differential diagnoses

The differential diagnoses of PEH include conditions that may result in persistent or intermittent epistaxis or blood-tinged nasal discharge. These include:

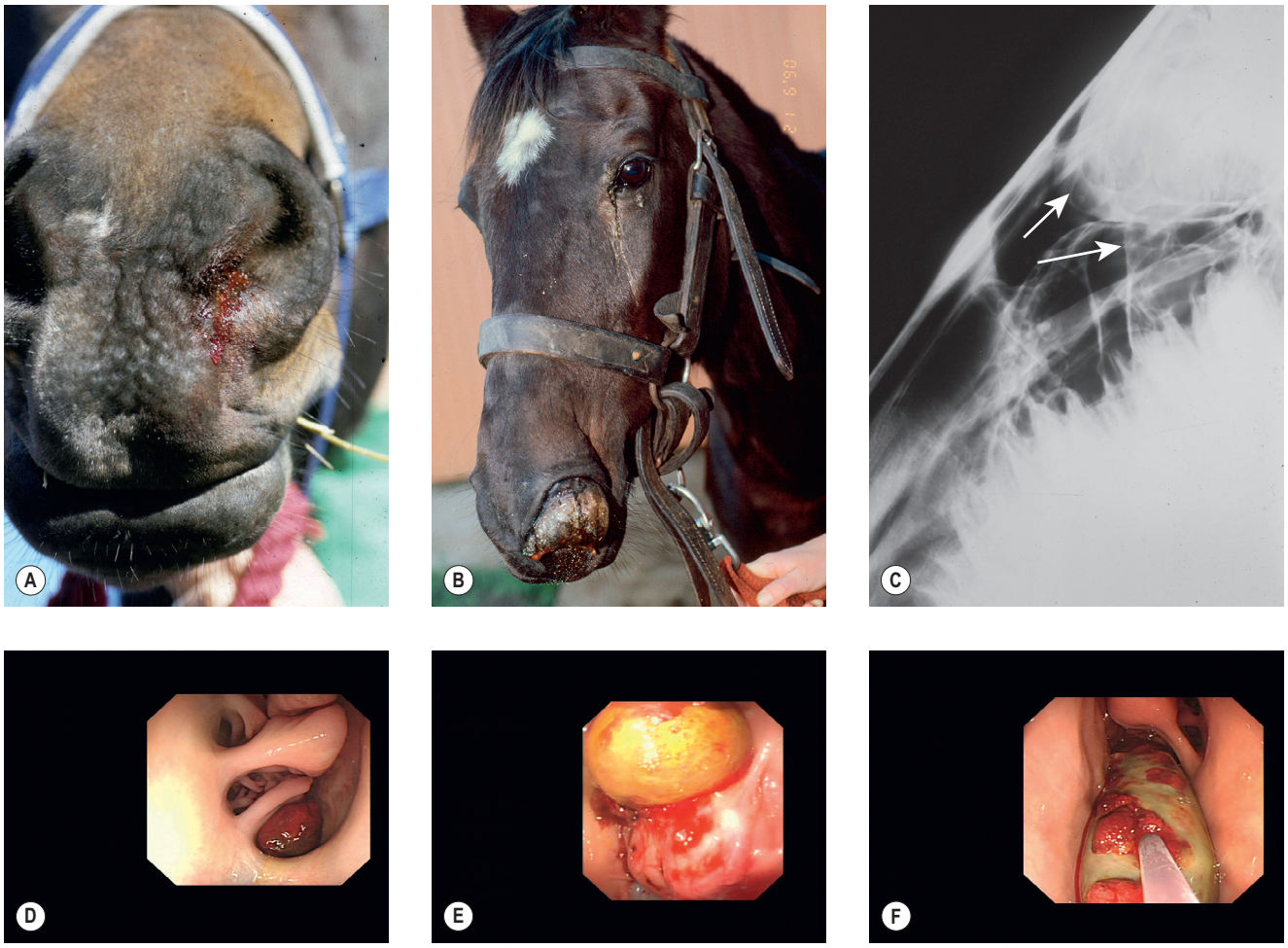


Figure 29.8 Ethmoid haematoma. **(A)** The first evidence of a progressive ethmoid haematoma is usually a unilateral serous nasal discharge that may have some evidence of haemorrhage. Gradually the amount of blood increases but it does have an intermittency in some cases. **(B)** It is unusual for the tumour to appear at the nostril but it can be occlusive. In this case, it has also occluded the nasal punctum of the nasolacrimal duct, causing secondary epiphora. **(C)** Even small masses can be detected radiographically (arrow) and CT and MRI are also good ways of imaging the mass and providing information for the treatment. Sinus tumours are more problematic radiographically. **(D–F)** There are a wide variety of endoscopic appearances of ethmoid haematoma, ranging from small lesions that have no material clinical effects **(D)**, to lesions that may occlude the nasal cavity **(E)**, to extensive lesions that occupy more of less of the nasal cavity **(F)**, and others that may extend into the nasopharynx. *(Figure B courtesy of Dr RR Pascoe; Figures D, E, F courtesy of Paddy Dixon.)*

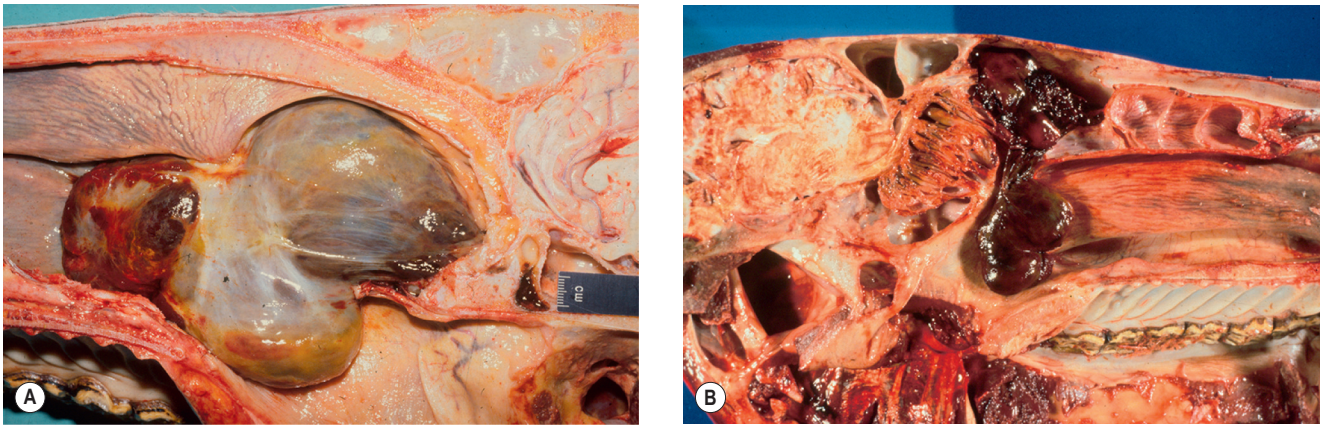


Figure 29.9 Two post-mortem specimens. It is easy to appreciate the extensive and occlusive nature of some of these tumours from these two post-mortem specimens **(A,B)**. The characteristic yellow/green colour is often present.

- Nasal (or sinus) polyp
- Exercise-induced pulmonary haemorrhage
- Osteoma, chondroma of the sinuses/turbinates
- Sinus or pharyngeal cyst
- Skull fracture/nasal trauma
- Nasal abscess or fungal rhinitis/sinusitis
- Nasal/sinus neoplasia such as carcinoma/adenocarcinoma
- Guttural pouch mycosis
- Sinus empyema
- Pulmonary abscess
- Pulmonary neoplasia
- Pleuropneumonia
- Foreign body granuloma.

Diagnostic confirmation

- PEH commonly presents with a very characteristic history and clinical examination (see Fig. 29.8A,B).[67]
- *Endoscopic examination* will invariably identify PEH arising from the nasal surfaces of the ethmoidal labyrinth in particular. The lesion usually appears as a smooth-walled mass pushing forward from the caudal nasal region. There may be surface haemorrhages and it may be ulcerated. PEH varies in colour from yellow/orange to grey/green.
  - Both nasal cavities should be examined in all cases because of the possibility of bilateral involvement.
  - If the PEH is very small and located deep within the ethmoid turbinate area or in the caudal maxillary sinus, endoscopic examination may only reveal a trickle of blood from the ethmoid region or middle nasal meatus. When blood is seen in the region of the ethmoid turbinates, close examination may reveal a small dark mass in the most caudal aspect of the ethmoid.
  - Direct sinus endoscopy through the caudal maxillary or frontal sinuses is often required for a definitive diagnosis of sinus PEH.[2]
- *Radiographical examination* (lateral and ventrodorsal projections) usually reveals a soft tissue mass extending rostral or dorsal to the ethmoidal labyrinth into the caudal maxillary sinus or frontal sinus, respectively. Fluid interfaces may be present due to secondary infection or haemorrhage into the sinuses. Small lesions, especially those within the ethmoidal labyrinth, may be obscured by superimposition of the eyes and the ethmoidal labyrinth and it is important to examine, at least, true lateral and a dorsoventral projections.
  - A PEH confined to the sphenopalatine sinus will not be visible on radiographs or on endoscopy per nasum; diagnosis can be achieved by direct sinus endoscopy in such cases.
  - Radiography, CT or MRI provide important information in selecting the most appropriate surgical approach (Fig. 29.10).[2,18]
  - Computed tomography is the best imaging technique for determining the precise origin, shape and size of PEH. CT eliminates all superimposition of ocular, oral and sinus structures that interfere with interpretation of routine radiographs. It also reveals bilateral lesions, which occur in around 16% of cases. In cases of bilateral PEH, it is not uncommon to find a very large PEH filling the entire maxillary sinus and a portion of the nasal cavity on one side and a very small PEH on the other side. The small lesion may not be detected simply with endoscopy and plain radiography, whereas it would be readily apparent on CT images.[66]
- Definitive diagnosis depends on histological examination of biopsy samples obtained with endoscopic guidance. Alternatively, a PEH located within the paranasal sinuses can be sampled through trephines. The distinctive histopathological features are the result of repeated local haemorrhage, subsequent breakdown of haemoglobin and organization of the breakdown products.[56] The lesions are composed of a thick fibrous capsule covered with respiratory epithelium. The fibrous stroma is filled with recent and old haemorrhage. There is an inflammatory infiltrate composed of haemosiderin-laden macrophages, plasma cells, lymphocytes and, less commonly, neutrophils and eosinophils. Some areas show necrosis.

Management

Techniques described for treatment of horses with PEH include surgical ablation through a frontonasal bone flap,

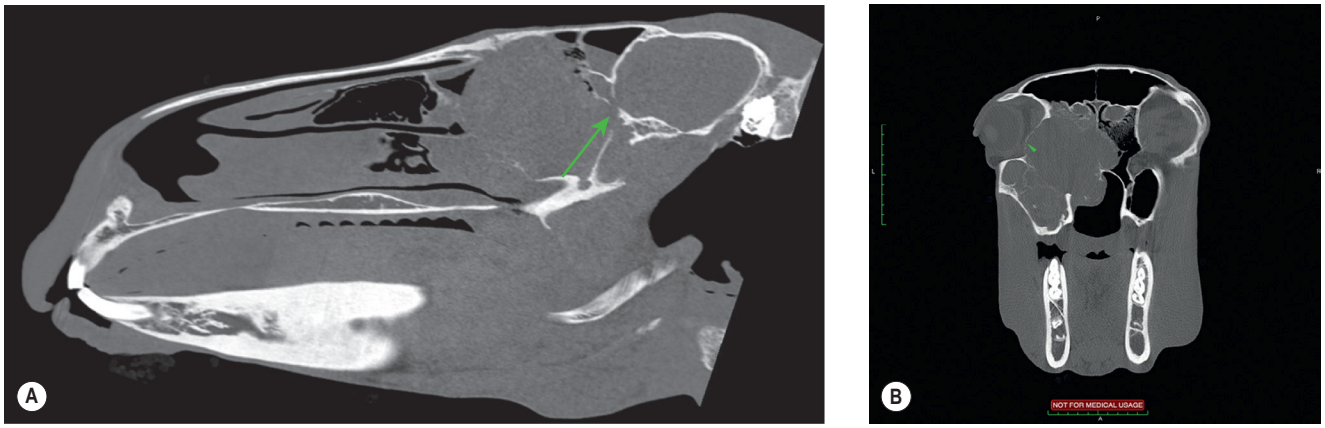


Figure 29.10 Diagnosis of ethmoid haematoma after endoscopy. This 8-year-old Thoroughbred gelding was diagnosed with ethmoid haematoma after endoscopy. A CT scan was performed and it was clear that the mass was very extensive and also involved the maxillary sinus (arrow). 3D-reconstruction helped in the surgical planning. *(Figures courtesy Veronica Roberts and Milosz Grabski.)*

Nd:YAG laser photoablation, surgical excision with cryogenic ablation of the base of the mass, cryogenic ablation alone, snare excision and intralesional injection of 10% formalin, or a combination of these.[58,63–65,68–74] The choice of treatment modality is dependent on the size, position and accessibility of the lesion, and available equipment.

Surgery

Surgical excision (either standing or under general anaesthesia) has been the treatment of choice for many years. The appropriate surgical approach depends on the size and location of the lesion. A frontonasal bone flap is generally the recommended approach. However, a maxillary bone flap may be required. Surgical techniques are described in standard surgical texts.

Intraoperative haemorrhage is the most common complication. Techniques to address intraoperative haemorrhage include:

- Bilateral temporary carotid artery occlusion
- Roll gauze packing of the sinuses or nasal cavity
- Cryotherapy applied to the base of the mass
- Cold saline sponges
- Photocoagulation with Nd:YAG laser
- Adrenaline-soaked sponges.

Other complications of surgical treatment include:

- Exophthalmos
- Encephalitis
- Fever
- Localized wound infection
- Facial bone sequestration
- Wound dehiscence
- Respiratory distress after endotracheal removal associated with significant nasopharyngeal oedema
- Blindness
- Colic
- Diarrhoea
- Fungal infection
- Suture periostitis
- Facial deformity.

Chemotherapy

Intralesional formalin (4% solution of formaldehyde) is a simple and relatively effective way to manage PEH lesions that are on the nasal side of the ethmoturbinates (i.e. those lesions that can be visualized endoscopically). Formalin desiccates and coagulates tissue by hydrolysing protein and results in direct necrosis of the mass (Fig. 29.11). PEH in the paranasal sinus may require a trephine hole for direct intralesional formalin administration.

Intralesional formalin technique

- The horse should normally be sedated for the procedure. Gloves and protective eyewear should always be used by both operator and the handler.
- 10 mL of 10% formalin solution (4% formaldehyde) is drawn up into a Luer lock syringe. The overall volume required depends on the size of the PEH. In most cases, 20 mL will be adequate (a smaller volume is used if a small PEH is being treated).
- An injection catheter with a swaged-on retractable, 17-gauge needle at the end is passed down the biopsy channel of the flexible endoscope and is used to inject formalin into the PEH.
  - A home-made injector can be made with a lavage/wash tube and a cut-off hypodermic needle – care should be taken not to draw the 'home-made' injection catheter through the biopsy channel of the endoscope, since it may damage the biopsy channel or get stuck in it
  - It is useful to drape a towel over the noseband of the headcollar, so that if the horse snorts, formalin will not be sprayed into the faces of the operator or the handler.
- The endoscope is passed until the PEH is clearly visible and the catheter and needle are then advanced into the lesion (see Fig. 29.11B). Formalin is injected slowly until it distends the mass and is seen to begin to leak out. It is common for the horse to snort at this point, and there may be mild or moderate haemorrhage from the mass.

Intralesional injections are probably best repeated at least 2 weeks apart for desired tissue sloughing between

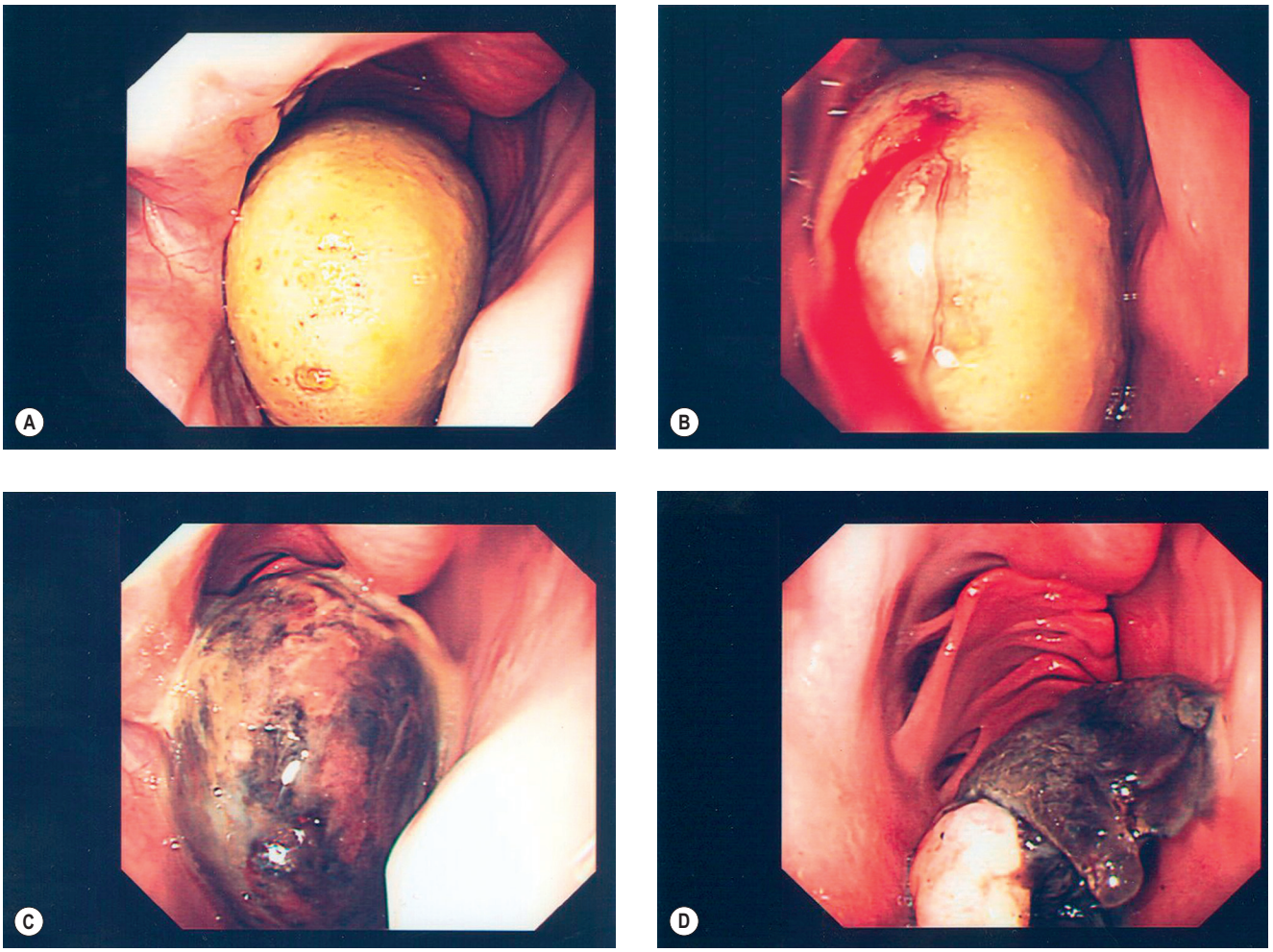


Figure 29.11 Progressive ethmoid haematoma. A 7-year-old Irish cross mare was presented with a long history of a progressively more obvious serosanguineous nasal discharge. **(A)** Endoscopic examination revealed a large yellow mass in the ethmoid region of the right nasal cavity. **(B)** This was injected with 8 mL of 10% formalin solution twice at 7-day intervals. **(C)** When the lesion was examined 2 weeks later, the mass had significantly reduced and the nasal discharge had ceased. **(D)** By 4 weeks after presentation, the mass was sloughing and the horse required no further treatment. Note the structural deformity of the ethmoidal region – this remained obvious for at least 18 months.

injections. Injections should be continued until the mass has apparently resolved or can no longer be injected.

Owners should be warned that repeated injections will be required, and that the number needed is impossible to predict.

A mucopurulent (and sometimes bloodstained) nasal discharge is expected over the following days to weeks as the mass necroses and sloughs (see Fig. 29.11C,D).

Owner compliance is important if the treatment is to be successful. Although intralesional formalin injection has proven largely to be successful, it is not without complications. These include:

- Copious nasal discharge for 5–7 days after injection.[64]
- Intralesional formalin injection of sinus PEH results in necrotic tissue, which may remain in the sinuses; in some horses, this can predispose to the development of chronic sinus empyema or mycosis.[18] It may be better to remove larger PEHs surgically by disrupting the PEH capsule and aspirating the semiliquid stroma and then injecting the base with formalin.
- A single case of a fatal complication has been reported; the cribriform plate had been damaged by the PEH, and formalin reached the frontal lobes of the brain, resulting in death. Damage to the cribriform plate was not identified by prior endoscopy or radiography.[74] CT scanning might be very helpful to avoid this complication in long-standing cases with large PEH.
- Careful case selection and specific imaging assessment are advised prior to injection.

Cryosurgery

Cryosurgery with liquid nitrogen can be performed via the nose or a bone flap. Repeated sequential freezing of small portions of the PEH with surgical removal of the frozen tissue until the base can be visualized and frozen is described. A lower incidence of recurrence for horses treated with a combination of surgical debulking and cryotherapy is reported than with cryotherapy alone.[63,70] However, other studies have reported no difference in recurrence among horses treated with cryotherapy and surgical removal and with other methods of treatment.[65]

Radiotherapy

Transendoscopic Nd:YAG laser ablation allows more accurate removal of PEH and significantly reduced surgical morbidity with reduced convalescent times.[71] Nd:YAG laser resection of PEH can be performed in the standing, sedated horse. Multiple treatments may be required to completely ablate a PEH. The most frequent complication after Nd:YAG laser resection of PEH is respiratory distress due to substantial inflammation within the nasal cavity and pharynx after laser use; 9/20 cases in one study required a temporary tracheostomy.[71] Surgical lasers are reported to reduce the amount of haemorrhage. Intraoperative blood transfusion is not usually required, since immediate bleeding is minimal. Other complications reported include meningoencephalitis, respiratory noise due to nasal and septal thickening and surgical site infection. Recurrence rates after Nd:YAG laser treatment are reported to be 20–22%.[71]

Prognosis

Complete remission can be expected in around 33% of cases and partial remission in 33% of cases.

Most PEH recur within the first 12 months of removal, so patients should be monitored frequently for the first 12 months post-treatment. Regardless of which treatment approach is used, frequent monitoring for recurrence, and aggressive treatment of any recurrent lesions while they are still small, is essential.

The best long-term results are possibly achieved when the owner commits to thorough diagnostic evaluation (including CT) and to a programme of frequent reassessment for at least 12 months after removal of the lesion. Repeated endoscopic examinations should be performed every 3–6 months after treatment for at least 5 years to monitor recurrence. In smaller, especially unilateral intranasal lesions, formalin injection appears to be a useful and inexpensive treatment. Even if PEH is not fully eliminated, the progression can usually be controlled by repeated injections.

A guarded to poor prognosis is still appropriate due to the high recurrence, despite treatment. However, with currently available medical and surgical treatments, PEH is not usually life-threatening and many affected horses are able to perform at their previous level of work.

The prognosis for athletic performance and survival without treatment is unfavourable, as the mass will progressively enlarge and eventually obstruct the nasal passages and distort the upper airway (see Fig. 29.9).

Paranasal sinus (PNS) cysts

See also page 259.

Description

Paranasal sinus cysts are single or multiloculated fluid-filled structures with an epithelial lining that most often develop in the caudal maxillary sinus; occasional cysts are found in the frontal sinus and in the ethmoid labyrinth.

Reviews of equine chronic sinus disease have shown that PNS cysts rank third most common behind primary and secondary (dental) sinusitis.[1,2,75]

The aetiology of sinus cysts is not known, but it has been suggested that they have a similar origin to progressive ethmoid hematoma.[76,77] However, there is some controversy over this.[56] The two conditions differ in that horses with PNS cysts have a very good prognosis, whereas recurrence is common in those affected with PEH.[9]

Early reports of horses with sinunasal cysts have suggested a biphasic age predisposition for the disease, with peaks at <1 year and >9 years old.[78–81] In a series of 37 cases of PNS, cysts were found in 256 cases of equine sinus disease, and in this series no age predisposition was evident and the age range was 3 months to 21 years, with a median of 7 years.[2] A second case series of 52 paranasal sinus cysts also found no biphasic age distribution[76]; the age range was 3 months to 23 years, with a median and mean age of 11 years, and three foals were affected.

Disease summary

Notes

Relatively common, benign, non-neoplastic condition affecting horses from foals to middle-aged horses; usually unilateral and situated in maxillary or frontal sinuses, but can be at other sites, including the nasal cavity and pharynx.

Clinical features

Signs usually attributable to space-occupying effects within the airway, unilateral nasal discharge, respiratory obstruction and facial distortion/swelling.

Diagnostic confirmation

Radiographically distinctive and aspiration reveals clear yellow, viscous fluid.

Management

Surgical ablation via a sinus flap is the treatment of choice.

Prognosis

Prognosis is very good, even if subtotal excision is done.

Clinical features

Sinus cysts usually arise in the region of the drainage ostium, so that expansion either occurs into the sinus or into the nasal meatuses. They typically contain clear viscid yellow fluid indicative of blood pigment degradation. The major presenting signs include[60]:

- *Facial swelling* (Fig. 12.12A)
  - PNS cysts cause pressure atrophy of the bone, producing maxillary or frontonasal swelling, which may be fluctuant if the bone is breached. Facial swelling generally occurs over the conchofrontal or maxillary sinuses, but a small number of cases have midline frontal distension. Rarely, proptosis may be observed.
- *Mucopurulent nasal discharge*
  - Sinus cysts are frequently referred after significantly longer duration than cases of primary sinusitis, which likely reflects the fact that mucopurulent nasal discharge is a less common clinical finding of PNS cysts.
- *Nasal airflow obstruction*
- *Abnormal respiratory noise* (50% of cases have airflow obstruction and respiratory noise)
- *Increased resonance on percussion* can be expected if there is thinning of the nasal bones.

- *Obstructive dyspnoea* at rest arises when the nasal meatuses are compressed or obliterated through cyst expansion, regardless of whether the cyst arises within the sinuses or the nasal meatuses.

Diagnostic confirmation

The presenting signs, physical examination, endoscopic examination and radiography provide the necessary diagnostic information. The spectrum of clinical signs reported can largely be attributed to the expansile nature of the lesion. Horses with PNS cysts may present with signs similar to those of primary sinus empyema, progressive ethmoidal haematoma and neoplasia. Needle aspiration of the cyst provides definitive confirmation of the diagnosis by the release of characteristic vivid yellow, translucent, seromucoid fluid.

Cysts that expand in a nasal direction can be seen via endoscopy as discrete rounded masses typically in the middle meatus. Those which are confined to the sinuses cause diffuse narrowing of the nasal airways to the point where passage of the endoscope to the nasopharynx is obstructed. Common endoscopic findings include narrowed nasal meatuses, a cyst in the nasal cavity, or a cyst visible caudal to the nasal septum viewed from the contralateral unaffected nasal meatus.

Radiological evaluation reveals a homogeneous soft tissue density with relatively well-demarcated margins (see Fig. 29.12C,D). On lateral standing projections, free gas/fluid lines may be observed, which indicate impeded sinus drainage. There may be dental distortion and displacement, flattening of the tooth roots, and soft tissue mineralization.[82] Ventro-dorsal projections demonstrate the limits of the lesion in a rostro-caudal dimension, as well as the extent of any nasal septum or vomer bone deviation. CT scanning or MRI may provide additional information, if these facilities are available.

Management

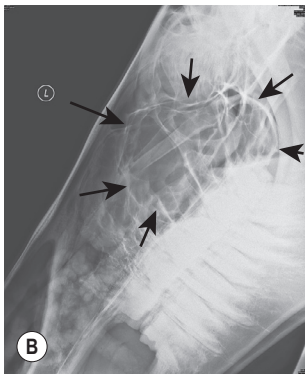
A frontonasal flap approach provides good access to the conchofrontal and maxillary sinus compartments; maxillary flaps give limited access due to the reserve dental crowns and infraorbital canal.[75]

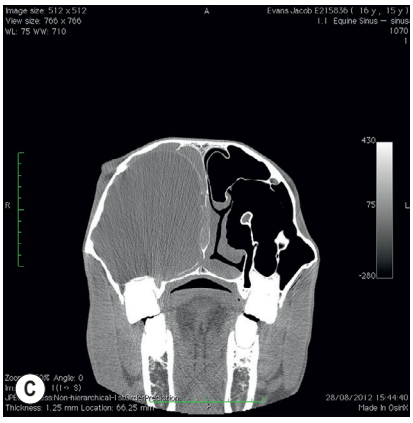
The cyst wall is peeled away from the inside of the sinuses. These types of cyst are highly amenable to treatment by sinusotomy, with most recent success rates of 92–100%.[12] In the event of incomplete ablation, small areas of residual cyst tissue do not appear to cause complications. Removal of all cystic lining that is tightly adhered to the sinus is not necessary, especially if attached to the medial aspect of the sinus (i.e. the concha), where its removal can cause marked epistaxis, or if attached to the infraorbital canal, where infraorbital nerve exposure can occur in up to 15% of horses with PNS cysts. One report described a less invasive sinoscopic removal of PNS cysts using a triangulation technique for instrument portals.[83] The prognosis for successful surgical ablation is excellent and recurrence is not likely. Facial deformity often resolves following surgery, especially in young horses.

Prognosis

The prognosis is good. Resolution can be expected in over 8% of cases.[3,80] In addition, subtotal resection also carries a good prognosis in most cases.[76]







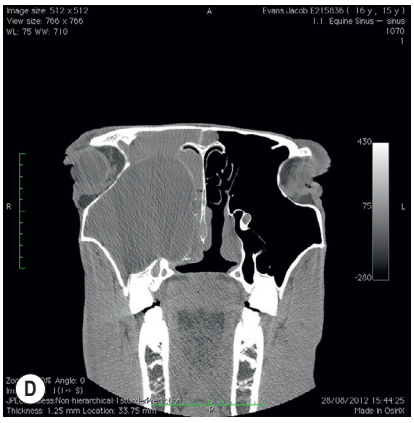


Figure 29.12 Sinus cysts. Sinus cysts may occur in very young foals – the soft, unfused facial and maxillary bones mean that distortion may be very marked. **(A)** In adult horses, a sinus cyst usually causes facial swelling but this tends to be more rounded. **(B)** Radiographically, the sinus cyst is very obvious in both lateral and ventrodorsal projections; usually a distinct bony lining can be seen (arrows). Aspiration from the cyst produces a clear viscous pale yellow fluid. **(C,D)** A CT scan was performed to establish the surgical boundaries – the cyst is very obvious. The entire cyst was removed successfully via a maxillary flap without any complications, in the standing sedated horse.

Guttural pouch neoplasia

Disease summary

Notes

Primary neoplasia of the guttural pouch is largely restricted to melanoma but secondary lymphoma, carcinoma, haemangiosarcoma and adenocarcinoma can develop in the prominent lymphoid tissue.

Clinical features

Signs are usually very subtle and nonspecific, with epistaxis and possible neurological signs. Swelling of the parotid region can occur.

Diagnostic confirmation

Endoscopy is the diagnostic procedure of choice (with biopsy is possible/indicated).

Management

No treatment for any tumours in the guttural pouch is described. Secondary tumours are very serious.

Prognosis

Prognosis depends on the condition and the implication of the tumour type. Guttural pouch melanoma can be very slow growing.

Description

Neoplasia of the guttural pouches is rare. Reported tumours at this site include squamous cell carcinoma, fibroma, haemangioma/haemangiosarcoma and melanoma.[25,84–90] Ectopic melanosis is a common feature of the mucosa of the guttural pouches of grey horses, and primary melanoma can arise here.

All regions of the horse richly endowed with lymphoreticular tissue are potential sites for development of lymphoma, and this can arise in the tissues abutting onto the guttural pouches (Fig. 29.13). The majority of horses identified with tumours in the guttural pouch have been older than 10 years, and most tumours have been malignant.[11,88]

Clinical features

Clinical signs are generally nonspecific but include:

- Mucopurulent (unilateral) nasal discharge
- Parotid swelling
- Epistaxis
- Cranial nerve dysfunction
- Dyspnoea
- Dysphagia.

Differential diagnoses

Other conditions to consider include:

- Guttural pouch empyema
- Guttural pouch mycosis
- Guttural pouch tympany.

Diagnostic confirmation

- *Endoscopy* is essential to identify the source of epistaxis, if present. Other causes of bleeding from the guttural pouches include mycosis, empyema and rupture of the longus capitis muscles of the neck. Endoscopy may reveal ventral compression of the dorsal pharyngeal wall and there may be evidence of drainage from the pharyngeal ostium.
- *Biopsy* of any identified mass is essential for making an accurate ante-mortem diagnosis. However, caution must be taken to avoid damage to vital structures within the guttural pouches.
- *Diagnostic imaging*
  - MRI and CT are the gold standard for imaging the equine head.[90–94]

Management and prognosis

At present, the prognosis for horses with tumours in the guttural pouch is poor and most horses are euthanized. Tumours in this location are usually not accessible due to invasion of surrounding soft tissue and vital anatomic structures. An attempt to remove a fibroma from the guttural pouch resulted in severe neurological signs necessitating euthanasia.[85] A (primary) squamous cell carcinoma within the guttural pouch was treated with cryotherapy and, although the initial response to treatment was encouraging, subsequent treatment failed, due to poor surgical exposure of the tumour and infiltrating fibrous tissue in the surgical site.[89]

Most reported tumours involving the guttural pouch are metastatic, and the prognosis is inevitably therefore grave.[11] With earlier diagnosis and better visualization of tumour location and extent, surgical options may have a more favourable prognosis.[95]

Nasopharyngeal/laryngeal neoplasia

Description

Neoplasia of the nasopharynx occurs infrequently in the horse.[11] Primary pharyngeal neoplasms are rare in the horse and most neoplastic conditions arise by extension of masses

Disease summary

Notes

True primary neoplasia of the pharynx is rare but significant tumours, such as lymphoma, carcinoma, chondroma and, more rarely, mastocytoma, do occur here.

Clinical features

Signs vary with location and extent and are usually attributable to functional compromise or tissue destruction/anatomical distortion. Space-occupying effects within the airway, unilateral nasal discharge, respiratory noise and dysphagia.

Diagnostic confirmation

Endoscopic visualization and biopsy will identify the nature of the mass(es).

Management

Treatment options are very limited – benign localized masses can be removed surgically or using diathermy or laser.

Prognosis

Prognosis is heavily dependent on the tumour type, extent and pathologic behaviour.

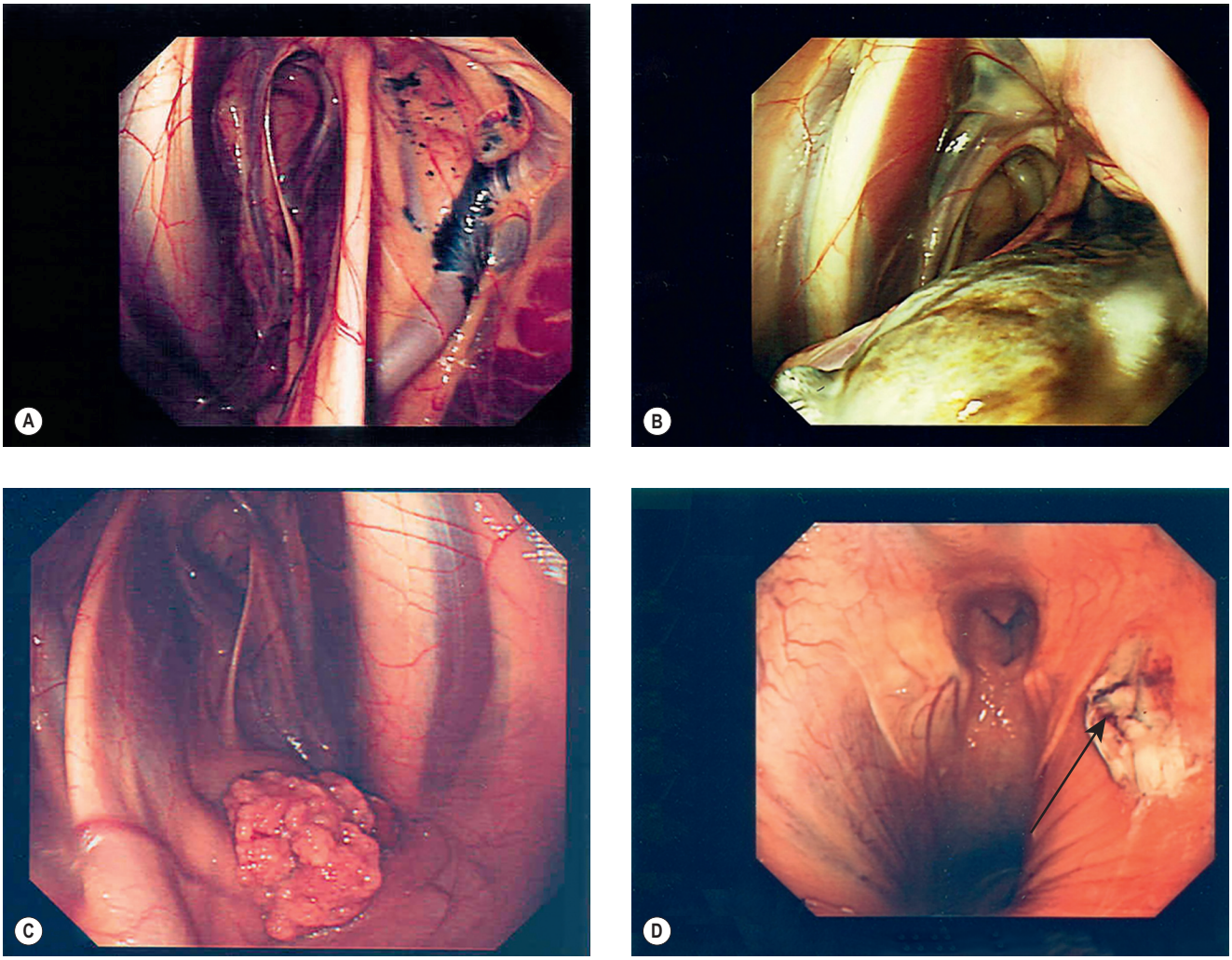


Figure 29.13 Milder forms of melanosis/melanoma. (A) Typical examples of the milder forms of melanosis/melanoma occurring in the guttural pouch. The striking thing about them is their close relationship to the external maxillary artery and the wide variety of morphology, ranging from very black flat plaques to distinct spherical nodules. **(B)** Both guttural pouches of the same 19-year-old grey Arabian mare with prominent parotid swellings showed large melanoma complex filling the ventral aspect of the pouch. **(C)** Secondary squamous cell carcinoma in the floor of the guttural pouch in an aged Thoroughbred cross gelding with a severe conjunctival carcinoma – it is always wise to try to check the regional lymph node in all cases of potential malignancy. **(D)** This innocuous discharging ulcerated area (white arrow) was associated with pharyngeal narrowing and submucosal swelling (red arrows). The horse had presented with apparent discomfort during swallowing, a mild cough and a scanty ipsilateral purulent nasal discharge flecked with blood. A diagnosis of undifferentiated pharyngeal carcinoma was based on histopathology of a biopsy taken from the site. Extensive local infiltration of the surrounding tissues was found at necropsy.

from neighbouring anatomical regions such as the oral and sinus cavities.[96–98] Squamous cell carcinoma appears to be the predominant reported tumour in the pharynx[87,99,100] and it may invade the nasopharynx from the nasal cavity, or it may metastasize to the retropharyngeal lymph nodes from a primary site in the oral cavity or orbit.

The pharyngeal mucosa hosts locally active oropharyngeal and nasal mucosa-associated lymphoid tissue, including nasopharyngeal, palatine, tubal, lingual and soft palate tonsils and diffusely distributed lymphoid cell accumulation. Solitary lymphomas, presumably originating from these tissues, have been reported in the palate, gingival and maxillary sinus.[101] Lymphoma has also been reported to arise in the nasopharynx.[101–103]

Other tumours at this location are very rare and previous reports include[40,98,104–107]:

- Mast cell tumour
- Chondroma
- Neuroendocrine tumour
- Fibrosarcoma
- Haemangiosarcoma
- Melanoma.

Clinical features

Clinical signs relate to the size and location of the tumour masses:

- Dyspnoea due to airway obstruction
- Dysphagia due to functional or space-occupying effects
- Malodorous nasal discharge secondary to extensive tissue necrosis
- Enlargement of submandibular lymph nodes
- Neoplastic destruction of the palate may lead to the formation of an oro-nasal fistula and ingesta-stained nasal discharge.

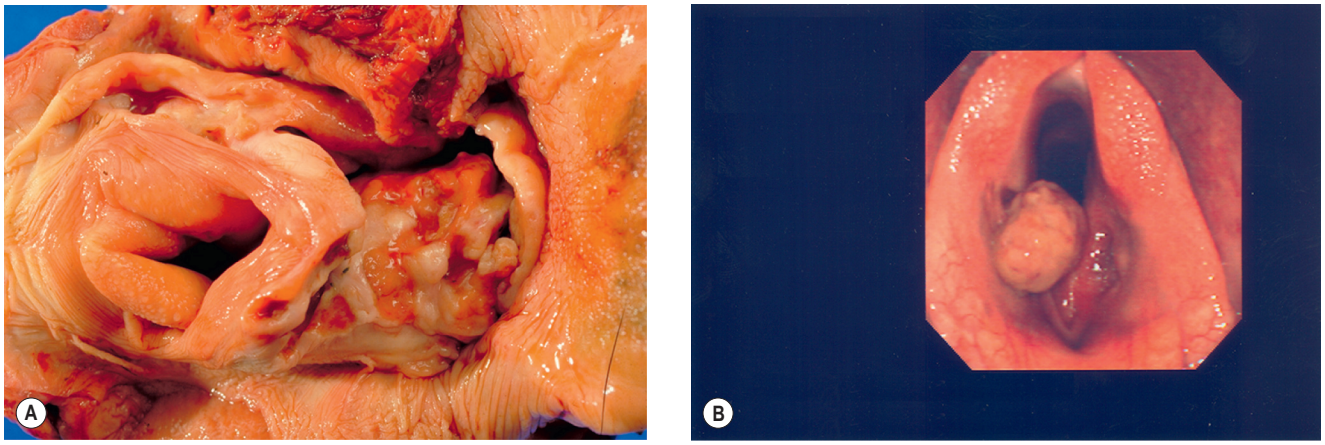


Figure 29.14 Pharyngeal carcinoma and laryngeal chondroma. (A) A destructive pharyngeal carcinoma that caused progressive weight loss and dysphagia. The lesion was very obvious from the pharyngeal aspect endoscopically. **(B)** Laryngeal chondroma that developed subsequent to a laryngeal surgery and caused a marked inspiratory dyspnoea and a biphasic snoring sound. This was removed successfully via a snared diathermy loop. *(Figure B courtesy of Paddy Dixon)*

Extensive infiltration of surrounding tissue and lymphatics may occur, due to the aggressive nature of these tumours, even if the mass is well-localized (Fig. 29.14).

Diagnostic confirmation

Tumours of the nasopharynx must be differentiated from more common pharyngeal disorders, including arytenoid chondritis and severe lymphoid hyperplasia.[11] Identification of these tumours can represent a considerable diagnostic challenge. Accurate diagnosis and assessment of the extent of tissue infiltration and organs affected is necessary to formulate a prognosis and establish a possible therapeutic plan.[101] In some cases, this can be achieved by endoscopic, radiographical and histopathological examination.

- *Endoscopically*, tumours may appear as irregular ulcerated masses or smooth thickened structures, depending upon tumour type. A report of a nasopharyngeal amelanotic melanoma showed that the slow onset of clinical signs (signs more consistent with commoner problems, such as retropharyngeal lymph node abscessation or tooth root infection), combined with the difficulty in visualizing or recognizing pharyngeal masses, can allow for severe enlargement and extensive tissue invasion of tumours prior to presentation for examination or treatment.[106]
- *Radiography* will help identify a soft tissue mass, but due to low soft tissue contrast and superimposition, precise location and origin of mass often cannot be determined. The anatomical complexity and superimposition of osseous, dental and soft tissue structures complicates radiographical interpretation and diagnoses.[108]
- *Ultrasonography* can be useful for examining superficial soft tissue structures, but is limited by a lack of penetration of bone and air-filled structures.[94,109] However, a laryngeal neuroendocrine tumour was identified by ultrasonography and allowed for ultrasound-guided biopsy of the mass.[107]
- *Magnetic resonance imaging*, although requiring a general anaesthetic and additional expense, can provide more information and exceptional evaluation of soft tissues as a result of the contrast achieved between tissues. Magnetic resonance imaging proved an exceptionally useful diagnostic tool to assess the precise localization, extent of tissue infiltration and presence of local metastasis in a case of extranodal T-cell-rich B-cell lymphoma.[101,110]
- *Computed tomography* scanning has limited value but it has been reported in the diagnosis of a cyst-like structure and a parapharyngeal aneurysm. CT provides information regarding the size and extent of the tumour, and can be performed standing, making it a less expensive and less invasive imaging method.[108]

Management

Treatment is rarely possible due to the aggressive nature of these neoplasms and resultant metastases, the anatomical location and the late stage at presentation.

Radiotherapy can be used to treat some tumours in this area. Alternatively, treatment by intralesional chemotherapy or laser excision might be considered in appropriate cases.

Prognosis

The prognosis for malignancy is very poor/hopeless, but for localized benign tumours and tumour-like masses the outlook is much better.

Tracheal neoplasia

Overview

Malignant tracheal tumours are singularly rare in the horse, but intratracheal squamous cell carcinoma has been diagnosed. More common benign lesions include:

- Papilloma
- Fibroma
- Chondroma
- Mastocytosis
- Adenoma.

Intratracheal polyps have also been reported, and include eosinophilic polyps. Benign tumours and polyps are usually amenable to surgical correction.[111]

Neoplasia of the thoracic cavity

Overview

Thoracic neoplasia in horses is rare and the true incidence in horses is unknown.[11,112–116] Surveys of post-mortem examinations indicate a very low incidence. A review of 1308 equine post-mortem examinations in an abattoir survey found only two cases of thoracic neoplasia, a granular cell tumour and a bronchiolar adenoma.[117] Two other surveys with a total of 931 post-mortem examinations revealed no cases of thoracic neoplasia.[96,118]

Thoracic neoplasia can be categorized into primary tumours of the lung, thymus and pleura lymphoma and tumours that originate in distant organs and metastasize to the thorax. The commonest tumours that metastasize to the thoracic cavity (usually the lungs) include adenocarcinoma (usually of renal or ovarian or thyroid origin), squamous cell carcinoma (usually of cutaneous primary origin), malignant melanoma, lymphoma and haemangiosarcoma.

Clinical features

The history often reveals:

- Depression
- Inappetence
- Weight loss
- Coughing
- Exercise intolerance.

Clinical signs depend on the type, origin, location and duration of the tumour and commonly include additional signs of tachycardia, tachypnoea, respiratory distress and ventral oedema. Most thoracic and pulmonary neoplastic disease induces pleural fluid accumulation – often in large volumes – and the effects of this are usually easily recognized clinically.

Differential diagnoses

Differential diagnoses for thoracic neoplasia include other lower respiratory tract conditions such as:

- Infectious disease (e.g. viral, bacterial or fungal pleuropneumonia, metacestode infection, fungal pneumonia, pulmonary abscess, bacterial endocarditis)
- Allergic conditions (e.g. recurrent airway obstruction)
- Congestive heart failure.

Diagnostic confirmation

Diagnostic procedures used to establish an ante-mortem diagnosis include:

- Clinical examination
- Auscultation and percussion of the thorax
- Haematology and serum biochemistry
- Endoscopy and collection of respiratory secretions
- Cytological analysis of pleural fluid
- Radiography
- Ultrasonography
- Thoracocentesis
- Thoracoscopy
- Percutaneous biopsy.

Prognosis

Generally, the prognosis for cases of thoracic neoplasia is poor or grave, although there are some well-recognized tumours that can be treated, or at least managed.

Primary thoracic tumours

Overview

Primary lung tumours occur rarely in horses.[112,119,120] Primary lung tumours constitute less than 10% of all thoracic neoplasms.[114] In a review of 38 cases of thoracic neoplasia, only three (7.9%) involved primary neoplasms,[115] thus strongly implying that secondary tumours of the lung are far more common. In another review of 35 cases, there were no primary lung tumours.[3]

Primary lung tumours reported to occur in the horse include:

- Pulmonary granular cell tumour[121–131]
- Pulmonary and bronchial carcinoma and adenocarcinoma[115,132–135]
- Bronchogenic squamous cell carcinoma[136,137]
- Bronchial myxoma[138]
- Pulmonary chondrosarcoma[139,140]
- Pulmonary leiomyosarcoma[141]
- Pleuropulmonary blastoma.[142,143]

Clinical features

The clinical signs of primary pulmonary neoplasms are often insidious in onset and vague/nonspecific, and depend on the tumour type and location.

Common presenting signs include:

- Depression
- Anorexia
- Persistent or undulant fever
- Ventral oedema
- Epistaxis
- Chronic coughing
- Weight loss
- Tachypnoea/dyspnoea
- Pleural effusion.

Older horses (>12 years) are most commonly affected, although pleuropulmonary blastoma has been reported in a neonate and a young mature horse.

In first opinion practice, the majority of the cases of thoracic neoplasia are initially diagnosed with recurrent airway obstruction (RAO), or low-grade pneumonia and pleuropneumonia. This is perhaps understandable because the signs are vague and, clinically, they are easily mistaken for far more common clinical disorders.

Management and prognosis

With the exception of granular cell tumours, therapeutic options are limited and prognosis is grave; the prognosis

is significantly affected by late presentation or by long-standing misdiagnosis.[144]

Pulmonary granular cell tumour

See also page 302.

Description

Granular cell tumours (syn. myoblastoma) appear to arise from Schwann cells, and are of mesenchymal origin. It is the most commonly reported primary lung tumour in the horse. The tumours are similar to the human endobronchial granular cell tumour. In other species (dogs, cats and man), these tumours are reported to occur at many different sites besides the thoracic cavity, most often the mouth and central nervous system.[145–148] Female horses are more commonly affected than males, no breed predilection has been reported and the mean age at presentation is 13 years (range 8–22 years).

The tumours typically occur as single or, less commonly, multiple nodules associated with the bronchi or bronchioles.[145] They are locally invasive, with no reports of metastasis. Although the majority of most tumours are submucosal, the mass commonly extends into a major airway, where it causes complete or partial obstruction. Predilection for the right hemithorax has been suggested, but this is not supported in the literature.[131] Bilateral disease occurs in less than 20% of case reports.

Clinical features

The duration of clinical signs ranged from 3 to 24 months. In some cases, granular cell tumours result in minimal clinical signs and can be identified incidentally at necropsy.[11]

In clinically-affected horses, signs commonly seen include:

- Chronic cough
- Tachypnoea
- Exercise intolerance
- Weight loss[144]
- Progressive respiratory distress[149]
  - Focal pneumonia distal to the airway obstruction, as a result of poor perfusion and poor clearance of respiratory secretions, and possibly even inhaled particulate material, may lead to additional signs of cough, fever, depression, abnormal lung sounds and leucocytosis
- Epistaxis is an infrequent late development
- Pleural effusion may be detected in a few cases, but is not a common feature
- Hypertrophic osteopathy (Marie's disease) reported as a paraneoplastic complication of granular cell tumour in some horses (see pp. 81 and 302)[121,129,150–152]
- Thoracic auscultation may reveal decreased or absent breath sounds over one hemithorax due to occlusion of one mainstem bronchus by the tumour
- A mainstem bronchus is the most commonly affected; the mass may directly obstruct the airway[148]

Differential diagnoses

1. Recurrent airway obstruction (RAO)
2. Inflammatory airway disease (IAD)
3. Tracheal/bronchial foreign body/granuloma
4. Tracheal trauma (previous) with scarring
5. Pulmonary abscess.

Diagnostic confirmation

Note

Horses with granular cell tumour are frequently misdiagnosed with recurrent airway obstruction (RAO), because the signs are easily confused; many have been treated for weeks or even years before the possibility of a granular cell tumour is considered.[126,131]

- *Haematology* usually reveals only nonspecific changes, including hyperfibrinogenaemia and leucocytosis with neutrophilia.[149]
- *Single or multiple radiopaque masses* close to the hilus of the lung may be detectable radiographically (Fig. 29.15), although in some cases, the mass may be obscured by the secondary focal pulmonary consolidation[149]
  - Focal pneumonia in an atypical pulmonary location (central or dorsal lung fields) may suggest the possibility of a tumour or inhaled foreign body.
- *Ultrasonographic examination* is not usually useful in diagnosis of these masses but decreased movement of the pleural surface over the affected hemithorax has been described in horses with large tumours.[131] Pleural thickening and 'comet-tail' irregularities may also be apparent.
- *Endoscopically*, an intraluminal mass with smooth, pale surface occluding or partially occluding a bronchus is usually easily seen (see Fig. 29.15). Frequently, the first evidence that is detected during bronchoscopy is a seromucoid or, occasionally, sanguineous discharge that can usually be tracked back to the lesion itself. Abnormal cells in the discharge or tracheal aspirate are seldom identified.
- *Biopsy*: small mucosal pinch biopsies may not be diagnostic, due to insufficient size and depth, since the mass is often covered by normal respiratory epithelium.[122,131] Biopsy may be unnecessary as the endoscopic appearance of the mass is distinctive
  - A larger biopsy specimen can sometimes be obtained using a longer, bigger biopsy instrument, such as uterine biopsy forceps, which are then passed into the affected bronchus via a tracheotomy incision performed at the thoracic inlet.[122]

Management and prognosis

1. *Conservative management* may produce an acceptable clinical outcome for several years in horses with undemanding workloads and non-progressive clinical signs[131]
   - Focal pneumonia may be treated/managed with suitable antibiotics.
2. *Surgical debulking* of the mass within the airway lumen may be possible using transendoscopic electrosurgery and/or laser ablation (Nd:YAG or diode), to coagulate

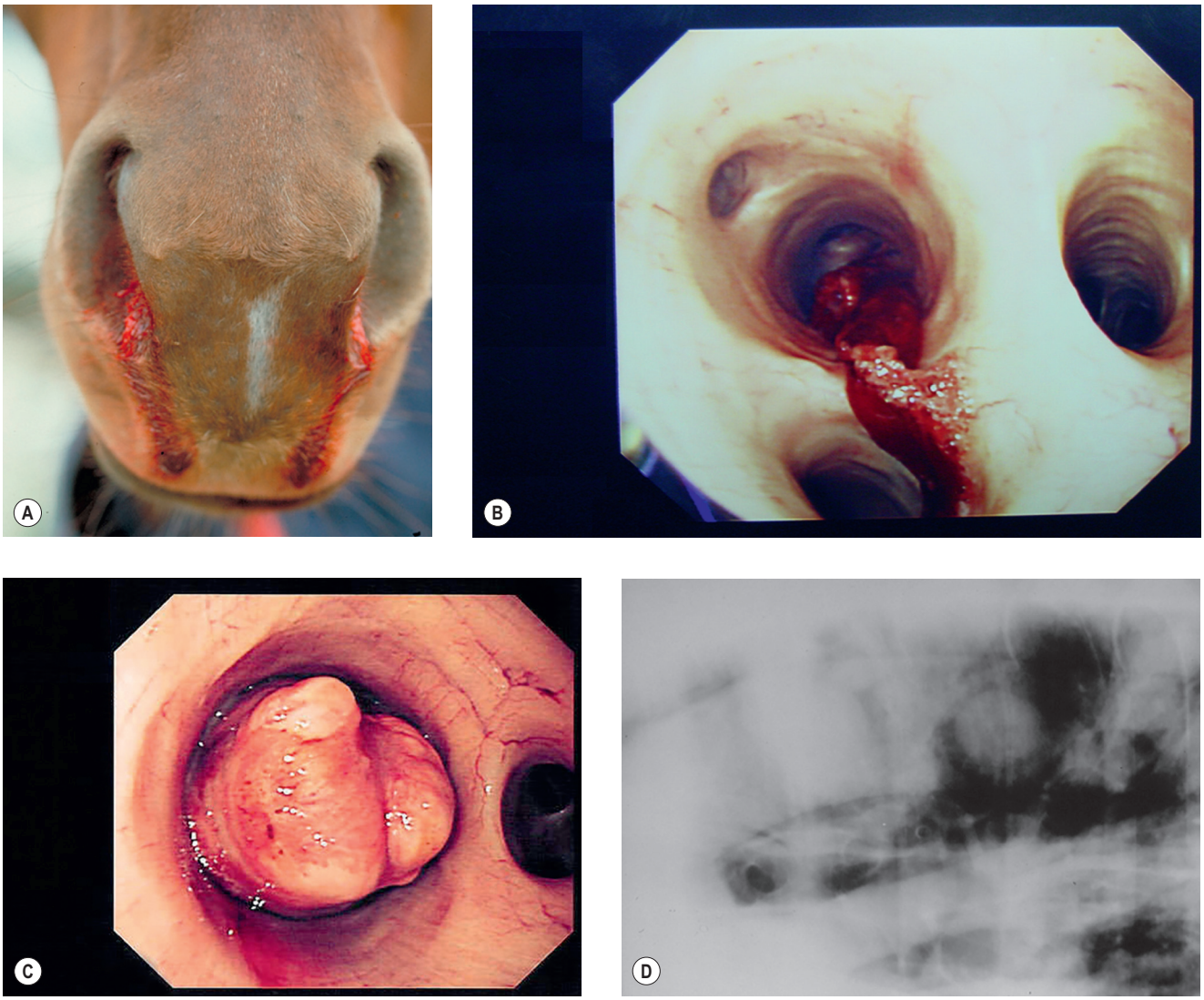


Figure 29.15 Pulmonary granular cell tumour. **(A)** A 12-year-old Welsh cross mare was presented with a 14-month history of a deep, harsh cough that had been visible endoscopically, and assumed from tracheal wash cytology and auscultation to be recurrent airway obstruction. She had shown no positive responses to the usual array of management alterations, systemic or oral steroids or bronchodilator medications. Finally, she developed bilateral epistaxis and haemoptysis. **(B)** Bronchoscopy identified a haemorrhagic 'trail' in the right bronchial tree. Notice that she showed no generalized oedema or narrowing of the airways. **(C)** The trail of blood could be followed to reveal a large mass occluding the major dorsal bronchus. **(D)** The mass was clearly visible radiographically. This mare had several others within the same area (visible radiographically), but no other lesions were found in other areas of the lung or the left lung. A presumptive diagnosis of pulmonary granular cell tumour was made and subsequently confirmed after the exposed mass was removed using a snared diathermy loop (see Fig. 29.16).

and kill residual tumour cells (Fig. 29.16).[123] However, in most cases, the tumour visible in the airway represents only a small proportion of the overall tumour mass; the large majority of most of these tumours usually lies deep to the mucosal surface, and progression of the disease and recurrence of the obstruction is usual.

3. *Surgical resection* of the affected lung lobe may also be possible.[122] In two published reports, there was no tumour recurrence at 2 years.

Thymic tumours

Description

Primary thymic tumours are very rare in horses.[153–157] These tumours may be benign or malignant and are derived from

Disease summary

Notes

Genuine thymic tumours are very rare; possible in younger adult horses.

Clinical features

Weight loss, inappetence, pyrexia, tachypnoea, ventral (sternal) or pectoral oedema/filling, jugular distension and 'pointing' of one (usually left) forelimb.

Diagnostic confirmation

Ultrasonography of cranial thorax and guided biopsy.

Management

No treatment is effective.

Prognosis

Prognosis is universally hopeless.

epithelial reticular cells of the thymus. Tumour classification has historically included those with a lymphocytic component, epithelial or mixed composition. Recently, the World Health Organization has described the classification of thymic tumours as types A, AB, B1, B2 and B3.[153] There is no equivalent equine classification as yet.

Clinical features

(Fig. 29.17)

- Most thymic tumours reported in horses have been incidental findings at post mortem. In one case, a malignant squamous cell thymoma was described in an 8-year-old cross bred mare, which presented with prescapular lymphadenopathy and sternal and forelimb oedema. Thoracic radiography revealed a mass cranial to the heart. On post-mortem examination, lesions extended from the intermandibular space to the thoracic inlet, with masses involving the mediastinum and pericardial sac, and diffuse pulmonary nodules.[155]

Thymic tumours would be expected to present with signs associated with a cranial mediastinal mass:

- Tachypnoea and dyspnoea
- Ventral sternal and/or pectoral oedema
- Bilateral jugular distension
- Change in heart sounds or caudal displacement of heart sounds on thoracic auscultation
- Weight loss
- Inappetence
- Pyrexia
- Pointing of a forelimb.

Differential diagnoses

1. Mediastinal lymphoma
2. Mediastinal melanoma
3. Mesothelioma
4. Metastatic disease
5. Cardiovascular disease or compromise
6. Cranial mediastinal abscess
7. Septic pleural effusion/pleuropneumonia.

Diagnostic confirmation

- *Thoracic radiography* may reveal mediastinal masses or pleural effusion, and radiography may be particularly useful after drainage of any effusion.
- *Thoracic ultrasonography* is now routinely helpful in determining the presence and volume of pleural effusion and, when the cranial thorax is imaged, the presence of cranial mediastinal masses. This requires the horse's forelimb to be extended cranially and the transducer directed cranially and dorsally in the 3rd intercostal space.
- *Thoracocentesis and cytology of pleural fluid*, under ultrasound guidance, may aid in making a distinction between septic and neoplastic disease. However, in

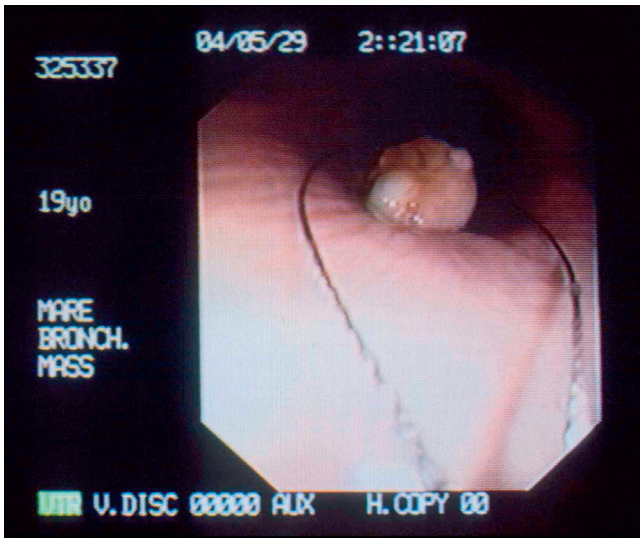


Figure 29.16 Bronchial granular cell tumour. This bronchial granular cell tumour was 'debulked' down to the mucosal level with the help of a snared diathermy loop. The mass grew back after 4 years and a repeat procedure was performed. *(Figure courtesy of Peter Clegg.)*

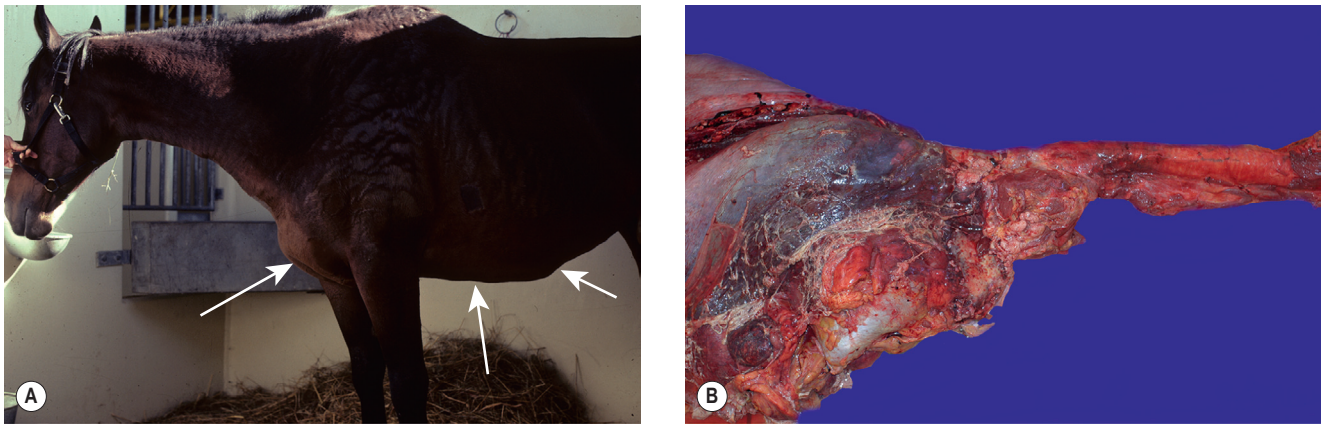


Figure 29.17 Thymic carcinoma. (A) This 9-year-old Thoroughbred brood mare was presented with progressive weight loss, bilateral jugular distension and ventral/sternal oedema (arrow). She showed prominent signs of Horner's syndrome on both sides and paraneoplastic pyrexia, anaemia and depression. A presumptive diagnosis of a malignant mass in her anterior mediastinum was made with a combination of clinical assessment, radiography and ultrasonography. **(B)** At necropsy, a thymic carcinoma that involved the vagosympathetic trunk on both sides was found (arrow) that had caused considerable pulmonary compromise.

patients with non-exfoliative neoplasia, this may not provide a definitive diagnosis. In the author's (limited) experience of thymic tumour, diagnostic cytology is not helpful.
- *Ultrasound-guided biopsy* with a hollow-needle biopsy instrument can be performed in the standing sedated or anaesthetized horse (see p. 89).

Management and prognosis

No ante-mortem treatment has been reported and the prognosis for almost all mediastinal and thoracic inlet tumours is universally hopeless.

Mesothelioma

See also pages 281 and 474.

Description

Mesothelioma is a rare primary malignant tumour arising from the mesothelial lining of the pleura, pericardium and peritoneum. There are a limited number of case reports of pleural and peritoneal mesothelioma in the horse[115,158–168] (see p. 281). In contrast to humans, cases of mesothelioma have not been associated with asbestos exposure in the few documented equine cases.[149]

There is no breed or gender predilection and reported cases have a mean age of 12 years.

Clinical features

The clinical presentation in horses includes:

- Weight loss
- Clinical signs consistent with large-volume pleural effusion:
  - Respiratory difficulty/distress
    - Tachycardia
    - Tachypnoea
    - Decreased breath sounds in the ventral lung fields
    - Increased breath sounds in dorsal lung fields
  - Oedema of the ventral thorax and abdomen
  - Various paraneoplastic signs, including anaemia and recurrent/undulant or persistent pyrexia.

Disease summary

Notes

Rare primary tumour of mesothelial cells of the pleura.

Clinical features

Weight loss, tachycardia, tachypnoea, dyspnoea, ventral sternal and/or pectoral oedema, decreased breath sounds ventrally associated with fluid within the pleural cavity.

Diagnostic confirmation

Thoracic ultrasonography and biopsy are definitive. Cytology of pleural fluid, for exfoliative neoplastic mesothelial cells, radiography and pleuroscopy are all strongly supportive.

Management

No treatment has been reported for pleural mesothelioma.

Prognosis

Prognosis is hopeless.

Differential diagnoses

1. Pleuropneumonia and pulmonary abscess
2. Thoracic trauma (including rib and lung damage)
3. Ruptured blood vessels (pulmonary arteries/veins)
4. Congestive heart failure.

Diagnostic confirmation

- *Ultrasonographically*, a pleural effusion is confirmed and mesothelioma usually has the appearance of multiple small nodules on a thick serosal surface.
- *Thoracocentesis* yields a modified transudate, sometimes haemorrhagic, and neoplastic cells may be identified in fluid samples.[162] However, differentiation of neoplastic mesothelial cells from reactive mesothelial cells is difficult.
- *Pleuroscopy and pleural biopsy* (obtained transcutaneously or via pleuroscopy) is diagnostic.

Management and prognosis

The malignant nature of the tumour and its rapid dissemination preclude any form of treatment, and affected horses are euthanized on diagnosis.[149]

Lymphoma

See also page 348.

Description

Equine lymphoma, although rare, is the most common haematopoietic neoplasm in horses. Lymphoma can be classified into five clinical forms:

1. Mediastinal
2. Multicentric
3. Alimentary

Disease summary

Notes

Rare, but lymphoma is the most common haematopoietic neoplasm and the most common thoracic neoplasm overall, mostly affecting younger adult horses.

Clinical features

Weight loss, lethargy, anorexia, ventral oedema, lymphadenopathy, cough, exercise intolerance, tachypnoea/dyspnoea, jugular distension, muffling of lung and cardiac sounds ventrally (associated with massive pleural effusion).

Diagnostic confirmation

Identification of pleural effusion or cranial mediastinal mass, ultrasonography and radiography (after fluid drainage), pleural fluid cytology, surgical or hollow-needle biopsy of any accessible tumour mass (using ultrasonographic guidance).

Management

Systemic chemotherapy is possible if diagnosis is made early, but is not curative; corticosteroids are commonly used in addition to chemotherapy.

Prognosis

Prognosis is poor or hopeless, depending on the facilities available for early diagnoses and treatment; therapy generally palliative, not curative.

4. Cutaneous
5. Solitary.

Lymphoma involving the mediastinum specifically is the commonest thoracic neoplasia identified in horses.[169] Thoracic lymphoma is, however, not considered to be a true primary thoracic neoplasm, since (more often than not) it originates from extra-thoracic tissue.[115]

Lymphoma is most commonly encountered in mature horses, without a breed or gender predisposition.[170] However, only one of 20 horses with thoracic lymphoma occurred in a pony; all other cases were in horses.[169]

In a series of 11 cases of thoracic lymphoma, the mean age at presentation was 7 years.

Classification of tumour type has become a routine aspect of the clinical evaluation of lymphoma.

Clinical features

Although the disease usually has an insidious progression, it is not uncommon for cases to present with a relatively acute onset of clinical signs.[171] However, the clinical course of disease in one case series of 11 horses with thoracic lymphoma was rapid, with a range of 1–8 weeks between onset of clinical signs and euthanasia.[169]

Cases of lymphoma typically present with a variety of clinical signs, which are usually related to the primary organ system involvement. Common general clinical features of the disease include[115,119,144,169,172–177]:

- Chronic weight loss
- Anorexia
- Lymphadenopathy
- Bleeding tendency
- Lethargy
- Subcutaneous/ventral oedema
- Colic
- Diarrhoea.

In addition to these nonspecific/general clinical signs, most horses with mediastinal lymphoma have signs that are consistent with large-volume pleural effusion and/or a mediastinal mass. These include:

- Ventral sternal and pectoral oedema (resulting from lymphatic obstruction). Very often, there is a history of a single leg (usually the right one) filling (oedema) before any other signs become apparent (Fig. 29.18)
- Persistent/undulating pyrexia of unknown origin
- Coughing is remarkably uncommon
- Exercise intolerance associated with dyspnoea/tachypnoea and tachycardia
- Distension of the jugular veins and possibly oedema and vascular engorgement of the head and forelimbs
- Auscultation of the chest reveals muffling of the lung sounds in the ventral thorax (usually bilaterally); removal of large volumes of pleural fluid (often over 20–30 L) is followed rapidly by reforming fluid and even continuous drainage can be inadequate to prevent fluid accumulation. This sign is invariably pathognomonic of pulmonary/thoracic neoplasia
- Cardiac sounds may be dispersed over a larger area than normal and there may be haemic murmur as result of anaemia[149]
- Less consistent signs relate to the presence of a space-occupying mass within the chest and include:
  - Single or bilateral mass expanding from the thoracic inlet at the base of the jugular groove
  - Dysphagia
  - Recurrent choke
  - Horner's syndrome.

One case presented with an exercise-induced respiratory noise of sudden onset, which was found to be related to a left-sided laryngeal hemiplegia, secondary to compression of the recurrent laryngeal nerve by an intrathoracic tumour.[20] Another case showed signs of Horner's syndrome caused by damage to the cervical sympathetic trunk by a lymphoma.[80] A further case report described mediastinal lymphoma in a 15-year-old pony gelding with complete atrioventricular

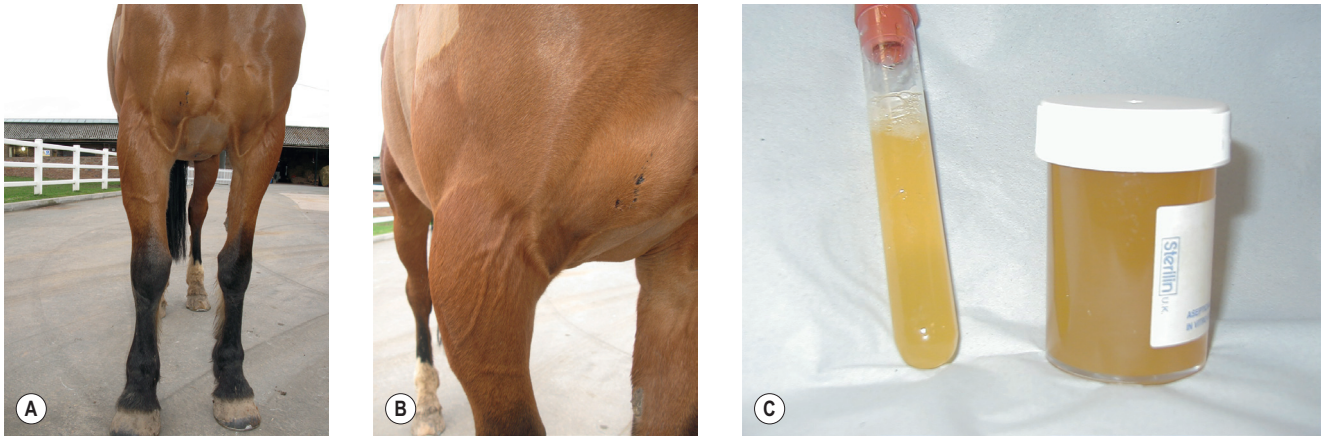


Figure 29.18 Lymphoblasts. This 7-year-old Irish Sport Horse was presented with a history of progressive poor performance over a period of 2 months. **(A)** The trainer reported that the front right leg was 'filled' (oedematous) at first and the horse showed profound tachypnoea and tachycardia on even minor exercise. Latterly, the horse developed mild ventral oedema and lost weight over a 14-day period. He held his elbows abducted. **(B)** He showed widespread venous distension on the right forelimb and was clearly anaemic. A persistent mild undulating pyrexia was notable. Auscultation, percussion and ultrasound of the chest revealed an elevated fluid line at the level of the mid-scapula. **(C)** Following insertion of chest drains, 20 and 16 L of fluid with a high cell count was drained from the left and right hemithoraces. The fluid was cytologically identical on both sides and contained abnormal mononuclear cells that were identified as lymphoblasts. Note the lack of red blood cells/haemogobin in the fluid.

block. There was no evidence of neoplastic infiltration of the cardiac conduction system. However, the vagus nerve and brachiocephalic trunk were embedded within the anterior mediastinal mass.[178]

Differential diagnoses

1. Thoracic lymphoma must be differentiated from other causes of chronic thoracic/pulmonary disease.
   - Dyspnoea, associated with pleural effusion, may be confused with that caused by lower airway obstruction in RAO. However, RAO does not generally cause weight loss or peripheral oedema.
   - Pneumonia and pleuropneumonia also cause dyspnoea. However, this is often accompanied by fever, stiffness and reluctance to move, and may be differentiated from lymphoma, based on cytological analysis of pleural fluid samples.
2. Other mediastinal or pulmonary primary or secondary tumours:
   - Thymic tumour
   - Melanoma
   - Mesothelioma.

Diagnostic confirmation

- Diagnosis of thoracic lymphoma is based on a combination of history, clinical examination, identification of pleural effusion, pleural fluid analysis and surgical biopsy of any accessible tumour masses.[149]
- Nonspecific haematological findings include leucocytosis, neutrophilia and hyperfibrinogenaemia. In a minority of cases, there may be a significant lymphocytosis in the peripheral blood, with the presence of abnormal circulating lymphoblastic cells. However, true myelophthisic leukaemia, representing bone marrow involvement, is very rare in the horse.[149]
- Paraneoplastic changes that are commonly found include hyperglobulinaemia, hypercalcaemia and anaemia.[179]
- Thoracic radiography may identify a pleural fluid line and, in some instances, reveals the presence of a mediastinal mass (Fig. 29.19A,B).
- Thoracic ultrasonography shows large amounts of pleural fluid due to compression of the lymphatic vessels and provides specific evidence regarding the presence, depth and character of pleural fluid (Fig. 29.19C).[144,180,181] Cranial mediastinal masses may be visible ultrasonographically, enabling ultrasound-guided biopsy to be performed. Visualization of the mass is improved by the presence of pleural fluid and by dorsal displacement of the lungs. In horses, ultrasound-guided biopsy of cranial mediastinal masses is difficult because the puncture site is located in the third intercostal space. The horse's leg needs to be extended cranially, ensuring immobilization of the horse during the procedure, with use of local and systemic analgesia, sedation and a nose twitch. Echocardiographic guidance during the biopsy is essential to avoid puncturing the heart or lungs.[181]
- Thoracocentesis is an important diagnostic procedure that will provide evidence of the nature of the fluid. Cytological examination often provides evidence of lymphoma (when the tumour is exfoliative) (Fig. 29.19D). In some instances, concurrent sepsis may be identified; therefore, careful examination of lymphocyte morphology should be performed. When overlapping conditions exist, a lack of response to appropriate medical therapy should alert the clinician to complicating factors and other diagnoses. The effusion in cases of lymphoma is typically a modified transudate or non-septic exudate and neoplastic cells are frequently, but not always, present in the fluid. A large number of the cells in such effusions will be mononuclear, mainly lymphocytic. Lymphoblasts with mitoses may be present.
- Thoracoscopy may be helpful in these cases and can be used to examine the pleural cavity and cranial mediastinum in horses with suspected mediastinal lymphoma as well as other forms of thoracic neoplasia.[182,183]
- Biopsy of suspect lesions can be undertaken during this thoracoscopy or ultrasonography.[182,184–186] When enlarged peripheral lymph nodes are present, biopsy is strongly recommended to aid in diagnostic confirmation of lymphoma. Fine-needle aspiration does not provide enough information regarding (disrupted) nodal architecture and are difficult to differentiate cytologically from reactive lymph nodes. Peripheral lymphadenopathy is an uncommon clinical feature of this disease, but a uni- or bilateral mass may be palpable at the base of the jugular groove.[187] When lymphadenopathy does develop, the pre-scapular and submandibular lymph nodes are most commonly enlarged. Rectal palpation should be considered to identify any concurrent abdominal lymphadenopathy or masses.[188]
- Diagnostic modalities utilized for tumour classification include immunophenotypic examination with flow cytometry and immunohistochemical staining on tissue samples (see p. 112).

Management and prognosis

In general, horses diagnosed with thoracic lymphoma are given a grave prognosis and subjected to human euthanasia immediately. Although there are no rigorous controlled clinical trials testing the efficacy of chemotherapeutic protocols in horses, systemic chemotherapy, including the use of doxorubicin and other combinations of anticancer medication, has been administered to many horses with lymphoma and has achieved good palliation (see p. 129). Horses seem to tolerate the drugs very well and often experience partial or complete remission or acceptable palliation of disease.[93]

There are many anecdotal reports of horses improving for periods of time on high doses of corticosteroids. However, cessation of therapy and potential side-effects, such as laminitis and increased susceptibility to infection, make this protocol only ever a short-term palliative solution. Several multidrug chemotherapeutic protocols have been reported for treatment of equine lymphoma with varying success (see p. 129). There are, however, strict guidelines on the handling and safe disposal of such drugs, and these protocols should be undertaken at specialist referral institutions.

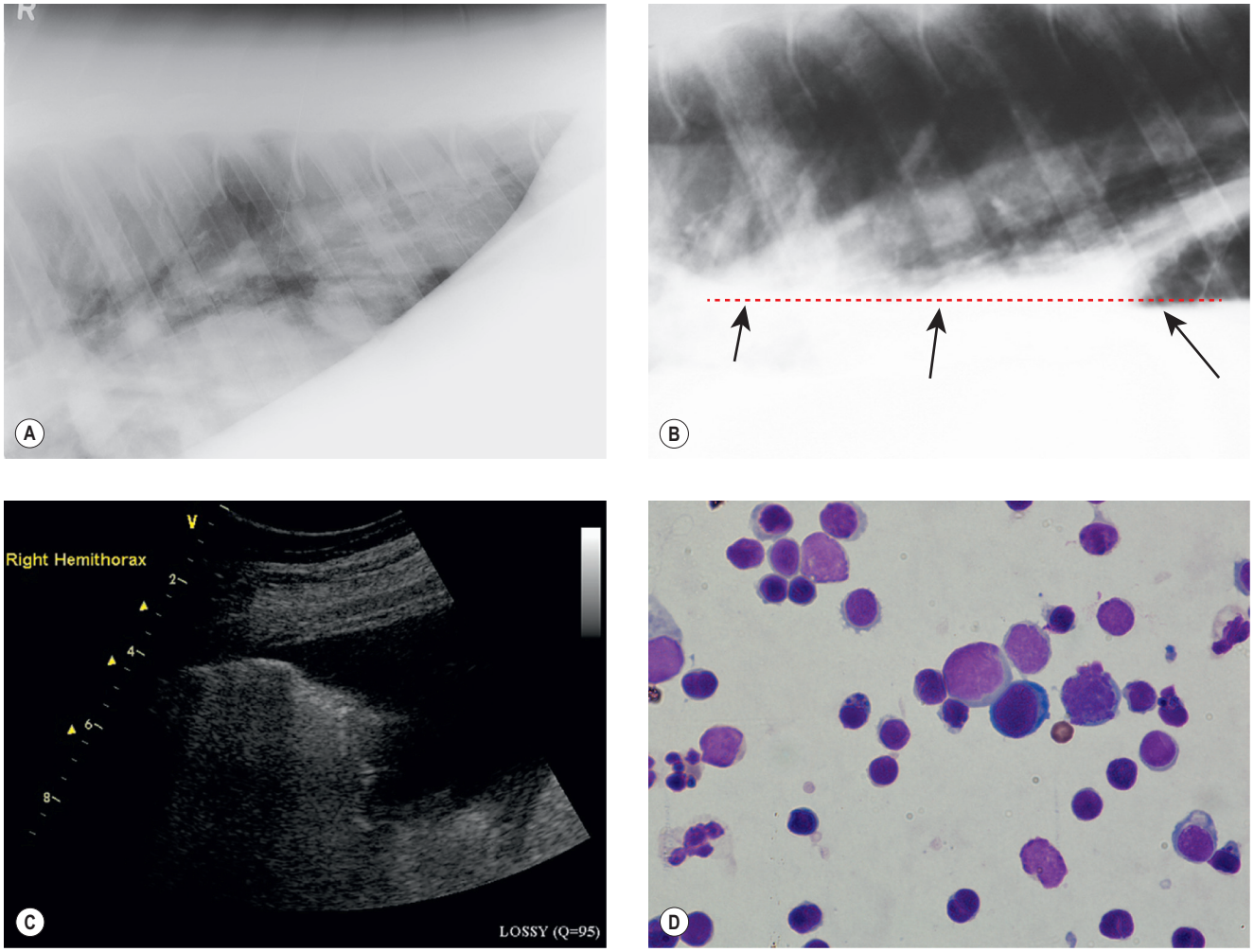


Figure 29.19 Thoracic lymphoma. **(A)** Thoracic radiography can reveal significant tumours in the lung tissue itself. **(B)** Most cases involving fluid accumulation produce copious pleural fluid that creates a percussible and radiographically identifiable fluid line (arrows). **(C)** Ultrasonographic examination provides nonspecific evidence of pleural fluid accumulation. The fluid is distinctly different from that which arises from inflammatory or haemorrhagic pathology in having a very uniform echolucency. **(D)** Pleural fluid cytology is a useful method of making a presumptive diagnosis. Most thoracic lymphoma cases are exfoliative into the pleural cavity to some degree, at least somewhat in contrast to abdominal lymphoma. Notice the variably sized lymphoblastic cells with prominent nucleoli. Some red cells are usually present as well (as in this case). Experienced cytopathologists may use cytological staining to confirm the true nature of the tumour. *(Figure A courtesy of Claudia Graubner.)*

Note

In one report of treatment of a mixed-cell thoracic lymphoma, a multidrug protocol was used:

- Over an 8-week period, cytarabine (179 mg/m^2 i.m.) every 2 weeks alternating with cyclophosphamide (142 mg/m^2 i.v.) every 2 weeks in conjunction with prednisolone 86 mg/m^2 p.o. q48 h.
- No adverse reactions were noted during the administration of chemotherapeutic agents and the horse was healthy 8 months later on continued prednisolone as sole therapy.[189]

For further detailed information on systemic chemotherapy for equine lymphoma, see page 137.

Outcomes for horses with thoracic lymphoma are poor, as might be expected, but, unfortunately, as most cases are diagnosed as late-stage disease, little evidence is available for early cases; it is likely that as earlier diagnosis is made, more effective treatments will be used and prognosis might improve significantly.

Metastatic thoracic tumours

Overview

As might reasonably be expected, the lung appears to be particularly susceptible to metastatic tumours, probably because of the dense vascular network. A variety of malignant tumours may metastasize to the lungs or cranial mediastinum from primary sites elsewhere in the body, but the 'soil and seed' hypothesis (see p. 52) may mean that metastatic tumour cells may not survive in or invade the lungs and then may bypass the capillary bed to lodge in any of the major organs. The commonest secondary tumours reported in the horse include:

- Haemangiosarcoma[114,190–198]
- Renal carcinoma[136–138]
- Fibrosarcoma[199,200]
- Mastocytoma[201]
- Adenocarcinoma[127–135]

- Squamous cell carcinoma[139,140,142,143,145–148,150,152]
- Melanoma[115,202–208]
- Undifferentiated sarcoma.[163,165,166]

Clinical features

The clinical features of these metastatic thoracic tumours are characteristically nonspecific and usually relate more to the primary site of tumour formation than to thoracic involvement.

Examination of other body systems may therefore reveal multi-systemic infiltration or may identify a primary neoplastic mass.

Diagnostic confirmation

- *Imaging*
  - Radiography, ultrasonography, thoracoscopy and thoracocentesis may all be helpful.
- *Neoplastic pleural effusion* is produced by some metastatic tumours.
- *Cytological evaluation* may or may not identify neoplastic cells.
- *Biopsy*, with the aid of thoracoscopy and ultrasonography, can help to obtain tissue to identify the tissue type.

In many cases, however, in practice thoracic tumour involvement will often rely on post-mortem examinations.

Haemangiosarcoma

Description

Haemangiosarcoma is a highly malignant neoplasm of (vascular) endothelial cells. After lymphoma, haemangiosarcoma is the second most common neoplasm to metastasize to the thorax and the lungs in particular. In a series of 35 cases of equine disseminated haemangiosarcoma, the pulmonary parenchyma and pleura were involved in 77% of cases.[192]

Middle-aged horses are most commonly affected (mean age 12 years, range 3–27 years), but it can affect young horses.

Disseminated haemangiosarcoma is aggressive and rapidly progressive.

Clinical features

(Fig. 29.20)

Clinical signs often appear suddenly, so most horses present in good body condition, with a short history of anorexia and depression. Some lose weight more rapidly. Clinical signs include[197]:

- Tachypnoea
- Respiratory distress
- Epistaxis/thrombocytopaenia
- Large volume of haemorrhagic or serosanguineous pleural effusion
- Anaemia and icteric mucous membranes
- Ventral oedema
- Subcutaneous, or intramuscular masses.

Differential diagnoses

1. Trauma causing hemithorax and haem abdomen
2. Pulmonary artery rupture
3. Lymphoma
4. Thoracic (malignant) melanoma
5. Thymic tumour (carcinoma).

Diagnostic confirmation

- A definite ante-mortem diagnosis is unlikely but may be helped by cytological evaluation of pleural fluid. Thoracocentesis reveals a large volume of pleural fluid that is serosanguineous. Cytological examination may or may not reveal neoplastic cells but they are often accompanied by a heavy neutrophilic cell count that confuses the diagnosis somewhat.
- Pleuroscopic guided biopsy may be feasible.
- Biopsy of another haemangiosarcomatous mass, if present, can support the diagnosis. This can, however, result in considerable further haemorrhage. Therefore, facilities to manage haemorrhage prior to performing a biopsy should be considered in suspect cases.

Management and prognosis

There is no effective treatment.

Disease summary

Notes

Rare; the second most common neoplasm to metastasize to the thorax; pulmonary parenchyma and pleura involved in 77% of disseminated haemangiosarcoma cases.

Clinical features

Rapidly progressive, so cases often present in good body condition; anorexia, depression, tachypnoea, pale or icteric mucous membranes, respiratory distress, epistaxis and subcutaneous, cutaneous or intramuscular mass are relatively common.

Diagnostic confirmation

Cytological evaluation of pleural fluid, pleuroscopic biopsy of mass, or biopsy of other haemangiosarcomatous mass (often in muscle).

Management

No effective treatment reported.

Prognosis

Prognosis is hopeless, the course is usually rapid.

Note

It is important to differentiate disseminated haemangioma from focal haemangiosarcoma of the distal limb in horses <3 years of age.[198] These tumours do not demonstrate the same aggressive biological activity and are unlikely to metastasize at the same rate, although they can reach considerable size and invade locally (see p. 512).

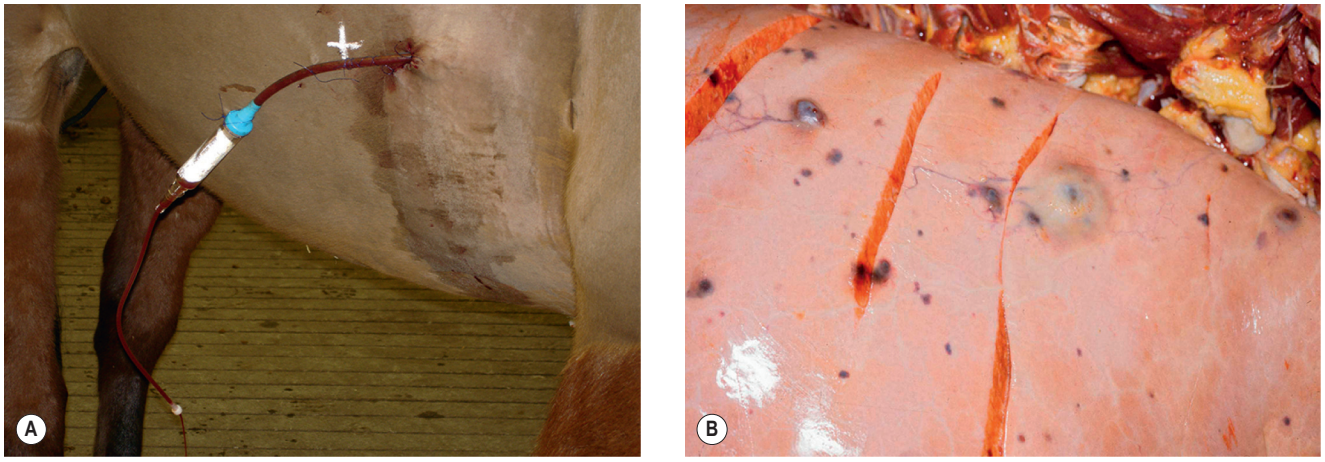


Figure 29.20 Pulmonary and pleural haemangiosarcomas. An 8-year-old part bred Hunter gelding was presented with a 4-week history of weight loss, increasing lethargy, recurrent pyrexia, ventral (sternal) oedema and progressive anaemia. Thoracic percussion and ultrasonography identified that, bilaterally, the chest contained a large volume of fluid. **(A)** Aspiration and drainage revealed a large volume (12 L right and 3 L left) of distinctly haemorrhagic fluid. Cytology revealed that the right lung fluid contained aggressive tumour cells consistent with haemangiosarcoma. Radiography failed to identify any convincing mass. **(B)** The horse was destroyed on humane grounds and multiple pulmonary and pleural haemangiosarcomas were identified; there were tumours in many of the major internal organs and a single focus (thought to be the primary lesion) in the semimembranosus muscle.

References

1. Boulton CH. Equine nasal cavity and paranasal sinus disease: a review of 85 cases. J Equine Vet Sci 1985; 5:268–275.
2. Tremaine WH, Dixon PM. A long-term study of 277 cases of equine sinonasal disease. Part 1: Details of horses, historical, clinical and ancillary diagnostic findings. Equine Vet J 2001; 33:274–282.
3. Tremaine WH, Dixon PM. A long-term study of 277 cases of equine sinonasal disease. Part 2: Treatments and results of treatments. Equine Vet J 2001; 33:283–289.
4. Witte TH, Perkins JD. Early diagnosis may hold the key to the successful treatment of nasal and paranasal sinus neoplasia in the horse. Equine Vet Educ 2011; 23:441–447.
5. Hilbert BJ, Little CB, Klein K, et al. Tumours of the paranasal sinuses in 16 horses. Aust Vet J 1988; 65:86–88.
6. Trotter GW. Paranasal sinuses. Vet Clin North Am Equine Pract 1993; 9:153–169.
7. Nickels FA. Diseases of the nasal cavity. Vet Clin North Am Equine Pract 1993; 9:111–121.
8. Dixon PM, Head KW. Equine nasal and paranasal sinus tumours: part 2: a contribution of 28 case reports. Vet J 1999; 157:279–294.
9. Freeman DE. Sinus disease. Vet Clin North Am Equine Pract 2003; 19:209–243.
10. Waguespack RW, Taintor J. Paranasal sinus disease in horses. Comp Cont Ed Pract Vet 2011; 33:E1–E12.
11. Scarratt WK, Crisman MV. Neoplasia of the respiratory tract. Vet Clin North Am Equine Pract 1998; 14:451–473.
12. Dixon PM, Parkin TD, Collins N, et al. Historical and clinical features of 200 cases of equine sinus disease. Vet Rec 2011; 169:439.
13. Baker GJ. Equine nasal and paranasal tumours. Vet J 1999; 157:220–221.
14. Noack P. Die Geschulste der oberen Atmungeswege bei den Haussaugetieren, Teile I, II; 1956.
15. Cotchin, E. Neoplasms of domesticated animals. Review series No. 4. Buckinghamshire: Commonwealth, Agricultural Bureau of Animal Health; 1967: 1926; 1–16.
16. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 1: Review of the literature and tumour classification. Vet J 1999; 157: 261–278.
17. Cissell DD, Wisner ER, Textor J, et al. Computed tomographic appearance of equine sinonasal neoplasia. Vet Radiol Ultrasound 2012; 53:245–251.
18. Dixon PM, Parkin TD, Collins N, et al. Equine paranasal sinus disease – a long-term study of 200 cases (1997–2009): Ancillary diagnostic findings and involvement of the various sinus compartments. Equine Vet J 2012; 44: 267–271.
19. Hart SK, Sullins KE. Evaluation of a novel post operative treatment for sinonasal disease in the horse (1996–2007). Equine Vet J 2011; 43: 24–29.
20. Walker MA, Schumacher J, Schmitz DG, et al. Cobalt 60 radiotherapy for treatment of squamous cell carcinoma of the nasal cavity and paranasal sinuses in three horses. J Am Vet Med Assoc 1998; 212:848–851.
21. Junge RE, Sundberg JP, Lancaster WD. Papillomas and squamous cell carcinomas of horses. J Am Vet Med Assoc 1984; 185:656–659.
22. Gaughan EM, Gift LJ, DeBowes RM, et al. Squamous cell carcinoma as a cause of dysphagia and blindness in a horse. Cornell Vet 1991; 81: 295–303.
23. Kemper DL, Walker MA, Morris EL, et al. What is your diagnosis? Squamous cell carcinoma of the paranasal sinuses in a horse. J Am Vet Med Assoc 1996; 209:1555–1556.
24. Madewell BR, Priester WA, Gillette EL, et al. Neoplasms of the nasal passages and paranasal sinuses in domesticated animals as reported by 13 veterinary colleges. Am J Vet Res 1976; 37:851–856.
25. Jones DL. Squamous cell carcinoma of the larynx and pharynx in horses. Cornell Vet 1994; 84:15–24.
26. Weisz L. Carcinoma of the maxillary sinus of the horse. Middlesex Veterinarian 1944; 4:16–17.
27. Moulton JE. Tumors of the respiratory system. In: Moulton JE, ed. Tumors of domestic animals, 3rd edn. Berkeley: University of California Press; 1990: 303–346.
28. Leuthold A. Equine Vet J 1938; 9:16–21. Cited in: Cotchin E. A general survey of tumours in the horse. Equine Vet J 1977; 9:16–21.
29. Cotchin E. Spontaneous neoplasms of the upper respiratory tract in animals. In: Muir CS, Shanmugaratnam K, eds. Cancer of the nasopharynx International Union Against Cancer, monograph series, Vol 1. Flushing: Medical Examination Publishing Co; 1967: 203–259.
30. Leyland A, Baker JR. Lesions of the nasal and paranasal sinuses of the horse causing dyspnoea. Br Vet J 1975; 131:339–346.
31. Dixon PM, Tremaine WH, Pickles K, et al. Equine dental disease part 1: a long-term study of 400 cases: disorders of incisor, canine and first premolar teeth. Equine Vet J 1999; 31:369–377.
32. Acland HM, Orsini JA, Elkins S, et al. Congenital ethmoid carcinoma in a foal. J Am Vet Med Assoc 1984; 184:979–981.
33. Mugera GM. Adenocarcinoma of frontal sinus in a horse. Bull Epizoot Dis Afr 1970; 18:171–173.
34. Hill FW, Moulton JE, Schiff PH. Exophthalmos in a horse resulting from an adenocarcinoma of the frontal sinus. J S Afr Vet Assoc 1989; 60:104–105.
35. Reynolds BL, Stedham MA, Lawrence JM, et al. Adenocarcinoma of the frontal sinus with extension to the brain in a horse. J Am Vet Med Assoc 1979; 174:734–736.
36. Zaruby JF, Livesey MA, Percy DH. Ethmoid adenocarcinoma perforating the cribriform plate in the horse. Cornell Vet 1993; 83:283–289.
37. Davis JL, Gilger BC, Spaulding K, et al. Nasal adenocarcinoma with diffuse metastases involving the orbit, cerebrum, and multiple cranial nerves in a horse. J Am Vet Med Assoc 2002; 221:1460–1463.
38. Hepburn RJ, Furr MO. Sinonasal adenocarcinoma causing central nervous system disease in a horse. J Vet Intern Med 2004; 18:125–131.
39. van Maanen C, Klein WR, Dik KJ, et al. Three cases of carcinoid in the equine nasal cavity and maxillary sinuses: histologic and immunohistochemical features. Vet Pathol 1996; 33:92–95.
40. Richardson JD, Lane JG, Nicholls PK. Nasopharyngeal mast cell tumour in a horse. Vet Rec 1994; 134:238–240.
41. Clarke L, Simon A, Ehrhart EJ, et al. Histologic characteristics and KIT staining patterns of equine cutaneous mast cell tumors. Vet Pathol 2014; 51:560–562.
42. Barakzai SZ, Dixon PM. Sinonasal myxoma in a four-year-old thoroughbred gelding. Vet Rec 2003; 152:210–211.
43. Rahko T, Alitalo I, Paatsama S. Myxoma in the nasal cavity of the Finnish bred horse. A report on three cases recently observed in Finland. Acta Vet Scand 1972; 13:131–133.
44. House PD, Farrell RK, Grant BD, et al. Cryogenic and immunotherapeutic treatment of myxoma in the horse. Can Vet J 1976; 17:216–219.

45. Pool RR. Tumors of bone and cartilage. In: Moulton MS, ed. Tumors of domestic animals, 3rd edn. Berkeley: University of California Press; 1990: 157–230.
46. Yamate J, Izawa T, Ogata K, et al. Olfactory neuroblastoma in a horse. J Vet Med Sci 2006; 68:495–498.
47. Basher AW, Severin GA, Chavkin MJ, et al. Orbital neuroendocrine tumors in three horses. J Am Vet Med Assoc 1997; 210:668–671.
48. Döpke C, Gröne A, von Borstel M, et al. Metastatic esthesioneuroblastoma in a horse. J Comp Pathol 2005; 132:218–222.
49. Matiesek K, Cronau M, Schmahl W, et al. al. Imaging features and decision making in retrobulbar neuroendocrine tumours in horses – case report and review of literature. J Vet Med A Physiol Pathol Clin Med 2007; 54:302–306.
50. Miesner T, Wilkie D, Gemensky-Metzler A, et al. Extra-adrenal paraganglioma of the equine orbit: six cases. Vet Ophthalmol 2009; 12:263–268.
51. Cook WR, Littlewort MC. Progressive haematoma of the ethmoid region in the horse. Equine Vet J 1974; 6:101–108.
52. Stencel E, Grotelueschen D. Haemangiosarcoma involving the frontal sinus of a horse. Equine Pract 1989; 11:14–16.
53. Chan CW, Collins EA. Case of angiosarcoma of the nasal passage of the horse – ultrastructure and differential diagnosis from progressive haematoma. Equine Vet J 1985; 17:214–218.
54. Schmotzer WB, Hultgren BD, Watrous BJ, et al. Nasomaxillary fibrosarcomas in three young horses. J Am Vet Med Assoc 1987; 191:437–439.
55. Hultgren BD, Schmotzer WB, Watrous BJ, et al. Nasal-maxillary fibrosarcoma in young horses: a light and electron microscopic study. Vet Pathol 1987; 24:194–196.
56. Tremaine WH, Clarke CJ, Dixon PM. Histopathological findings in equine sinonasal disorders. Equine Vet J 1999; 31:296–303.
57. Nickels FA. Nasal passages. In: Auer JA, Stick JA, eds. Equine surgery. Philadelphia: WB Saunders Co; 1999: 326–337.
58. Schumacher J, Moll HD, Schumacher J, et al. A simple method to remove an epidermal inclusion cyst from the false nostril of horses. Equine Pract 1997; 19:11–13.
59. Frankeny RL. Intralesional administration of formalin for the treatment of epidermal inclusion cysts in five horses. J Am Vet Med Assoc 2003; 223:221–222.
60. Watt BC, Beck BE. Removal of a nasal polyp in a standing horse. Can Vet J 1997; 38:108–109.
61. Platt H. Haemorrhagic nasal polyps of the horse. J Pathol 1975; 115:51–55.
62. Bell BT, Baker GJ, Foreman JH. Progressive ethmoid haematoma: background, clinical signs and diagnosis. Comp Cont Ed Pract Vet 1993; 15:1101–1110.
63. Bell BT, Baker GJ, Foreman JL. Progressive ethmoid haematoma: characteristics, cause and treatment. Comp Cont Ed Pract Vet 1993; 15:1391–1398.
64. Marriott MR, Dart AJ, Hodgson DR. Treatment of progressive ethmoidal haematoma using intralesional injections of formalin in three horses. Aust Vet J 1999; 77:371–373.
65. Specht TE, Colahan PT, Nixon AJ, et al. Ethmoidal haematoma in nine horses. J Am Vet Med Assoc 1990; 197:613–616.
66. Tate LP, Blikslager AT. New perspectives on diagnosis and treatment of progressive ethmoid haematomas. Annual Convention of the AAEP 2002; 233–239.
67. Conti MB, Marchesi MC, Zapulla F, et al. Clinical findings and diagnosis in a case of cholangiocellular carcinoma in a horse. Vet Res Commun 2008; 32(Suppl 1):S271–S273.
68. Schumacher J, Yarbrough T, Pascoe J, et al. Transendoscopic chemical ablation of progressive ethmoidal hematomas in standing horses. Vet Surg 1998; 27:175–181.
69. Colbourne CM, Rosenstein DS, Steficek BA, et al. Surgical treatment of progressive ethmoidal hematoma aided by computed tomography in a foal. J Am Vet Med Assoc 1997; 211:335–358.
70. Meagher DM. The evaluation of ethmoid haematomas in the horse. Vet Surg 1986; 15:128.
71. Rothaug PG, Tulleners EP. Neodymium:yttrium-aluminum-garnet laser-assisted excision of progressive ethmoid hematomas in horses: 20 cases (1986–1996). J Am Vet Med Assoc 1999; 214:1037–1041.
72. Laing JA, Hutchins DR. Progressive ethmoidal haematoma in horses. Aust Vet J 1992; 69:57–58.
73. Greet TR. Outcome of treatment in 23 horses with progressive ethmoidal haematoma. Equine Vet J 1992; 24:468–471.
74. Frees KE, Gaughan EM, Lillich JD, et al. Severe complication after administration of formalin for treatment of progressive ethmoidal hematoma in a horse. J Am Vet Med Assoc 2001; 219:950–951.
75. Lane JG. The management of sinus disorders: Part 2. Equine Vet Educ 1993; 5:69–73.
76. Woodford NS, Lane JG. Long-term retrospective study of 52 horses with sinunasal cysts. Equine Vet J 2006; 38:198–202.
77. Lane JG, Gibbs C, Meynink SE, et al. Radiographic examination of the facial, nasal and paranasal sinus regions of the horse: I. Indications and procedures in 235 cases. Equine Vet J 1987; 19:466–473.
78. Cannon JH, Grant BD, Sande RD. Diagnosis and surgical treatment of cyst-like lesions of the equine paranasal sinuses. J Am Vet Med Assoc 1976; 169:610–613.
79. Rush B, Mair T. Disease of the nasal cavity and paranasal sinuses. Equine respiratory diseases, 1st edn. Oxford: Blackwell Publishing; 2004.
80. Lane JG, Longstaffe JA, Gibbs C. Equine paranasal cysts: a report of 15 cases. Equine Vet J 1987; 19:537–544.
81. Freeman DE. Paranasal sinuses. In: Beech J, ed. Equine respiratory disorders, 1st edn. London: Lea and Febiger; 1991: 275–305.
82. Gilroy BJ, Lofstedt J, Pack L, et al. Paranasal sinus cyst as a cause of stridor in a standardbred colt. Can Vet J 1999; 40:49–51.
83. Silva LC, Zoppa AL, Fernandes WR, et al. Bilateral sinus cysts in a filly treated by endoscopic sinus surgery. Can Vet J 2009; 50:417–420.
84. Greene HJ, O'Connor JP. Haemangioma of the guttural pouch of a 16-year-old thoroughbred mare: clinical and pathological findings. Vet Rec 1986; 118:445–446.
85. Merriam JG. Guttural pouch fibroma in a mare. J Am Vet Med Assoc 1972; 161:487–489.
86. Trigo FJ, Nickels FA. Squamous cell carcinoma of a horse's guttural pouch. Mod Vet Pract 1981; 62:456–459.
87. Tuckey JC, Hilbert BJ, Beetson S, et al. Squamous cell carcinoma of the pharyngeal wall in a horse. Aust Vet J 1995; 72:227.
88. Baptiste KE, Moll HD, Robertson JL. Three horses with neoplasia including growth in the guttural pouch. Can Vet J 1996; 37:499–501.
89. McConnico RS, Blas-Machado U, Cooper VL, et al. Bilateral squamous cell carcinoma of the guttural pouches and the left middle ear in a horse. Equine Vet Educ 2001; 13:175–178.
90. Perrier M, Schwarz T, Gonzalez O, et al. Squamous cell carcinoma invading the right temporomandibular joint in a Belgian mare. Can Vet J 2010; 51:885–887.
91. Ferrell EA, Gavin PR, Tucker RL, et al. Magnetic resonance for evaluation of neurologic disease in 12 horses. Vet Radiol Ultrasound 2002; 43: 510–516.
92. Tietje S, Becker M, Böckenhoff G. Computed tomographic evaluation of head diseases in the horse: 15 cases. Equine Vet J 1996; 28:98–105.
93. Morrow KL, Park RD, Spurgeon TL, et al. Computed tomographic imaging of the equine head. Vet Radiol Ultrasound 2000; 41:491–497.
94. Tucker RL, Farrell E. Computed tomography and magnetic resonance imaging of the equine head. Vet Clin North Am Equine Pract 2001; 17:131–144.
95. Manso-Díaz G, García-Real MI, Casteleyn C, et al. Time-of-flight magnetic resonance angiography (TOF-MRA) of the normal equine head. Equine Vet J 2013; 45:187–192.
96. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
97. Hance SR, Bertone AL. Neoplasia. Vet Clin North Am Equine Pract 1993; 9:213–234.
98. Sullivan EK, Parente EJ. Disorders of the pharynx. Vet Clin North Am Equine Pract 2003; 19:157–167.
99. Jones SL, Langer DL, Sterner-Kock A, et al. Renal dysplasia and benign ureteropelvic polyps associated with hydronephrosis in a foal. J Am Vet Med Assoc 1994; 204:1230–1234.
100. Schuh JCL. Squamous cell carcinoma of the oral, pharyngeal and nasal mucosa in the horse. Vet Pathol 1986; 23:205–207.
101. Jakesova V, Konar M, Gerber V, et al. Magnetic resonance imaging features of an extranodal T cell rich B cell lymphoma in the pharyngeal mucosa in a horse. Equine Vet Educ 2008; 20:289–293.
102. Lane JG. Palatine lymphosarcoma in two horses. Equine Vet J 1985; 17:465–467.
103. Adams R, Calderwood-Mays MB, Peyton LC. Malignant lymphoma in three horses with ulcerative pharyngitis. J Am Vet Med Assoc 1988; 193: 674–676.
104. Trotter GW, Aanes WA, Synder SP. Laryngeal chondroma in a horse. J Am Vet Med Assoc 1981; 178:829–830.
105. Dawson DR, Scrivani PV, Schaefer DMW, et al. Epithelioid variant of haemangiosarcoma in a gelding. Equine Vet Educ 2009; 21:519–524.
106. Tyler RJ, R.I. F. Nasopharyngeal malignant amelanotic melanoma in a gelding age 9 years. Equine Vet Educ 2003; 15:19–26.
107. Koenig J, Silveira A, Chalmers H, et al. Laryngeal neuroendocrine tumour in a horse. Equine Vet Educ 2012; 24:12–16.
108. Garrett KS. Advances in diagnostic imaging of the larynx and pharynx. Equine Vet Educ 2012; 24:17–18.
109. Chalmers HJ, Cheetham J, Yeager AE, et al. Ultrasonography of the equine larynx. Vet Radiol Ultrasound 2006; 47:476–481.
110. Pekarkova M, Kircher PR, Konar M, et al. Magnetic resonance imaging anatomy of the normal equine larynx and pharynx. Vet Radiol Ultrasound 2009; 20:392–397.
111. Collins NM, Dixon PM. Disorders of the trachea. In: Robinson NE, Sprayberry KA, eds. Current therapy in equine medicine 6. Missouri: Saunders Elsevier; 2009: 261–263.
112. Monlux WS. Primary pulmonary neoplasms in domestic animals. Southwest Vet 1953; 6:131–133.
113. Gerber H. Chronic pulmonary disease in the horse. Equine Vet J 1973; 5:26–33.
114. Sweeney CR, Gillette DM. Thoracic neoplasia in equids: 35 cases (1967–1987). J Am Vet Med Assoc 1989; 195:374–377.
115. Mair TS, Brown PJ. Clinical and pathologic features of thoracic neoplasia in the horse. Equine Vet J 1993; 25:220–223.
116. Sweeney CR. Equine thoracic neoplasia. In: Smith BP, ed. Large animal internal medicine, 2nd edn. St Louis: Mosby; 1996: 582–584.
117. Cotchin E, Baker-Smith J. Tumours in horses encountered in an abattoir survey. Vet Rec 1975; 97:399.
118. Baker JR, Leyland A. Histological survey of tumours of the horse with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
119. Cotchin E. A general survey of tumours in the horse. Equine Vet J 1977; 9:16–21.
120. Priester WA, MacKay FW. The occurrence of tumours in domestic animals. Natl Cancer Inst Monogr 1980; 54:1–210.
121. Alexander JE, Keown GH, Palotay JL. Granular cell myoblastoma with hypertrophic pulmonary osteoarthropathy in a mare. J Am Vet Med Assoc 1965; 146:703–708.

122. Facemire PR, Chilcoat CD, Sojka JE, et al. Treatment of a granular cell tumour via complete right lung resection in a horse. J Am Vet Med Assoc 2000; 217:1522–1525.
123. Ohnesorge B, Gehlen H, Wohlsein P. Transendoscopic electrosurgery of an equine pulmonary granular cell tumour. Vet Surg 2002; 31:375–378.
124. Misdorp W, van Gelder NHL. Granular cell myoblastoma in the horse. A report of 4 cases. Pathol Vet 1968; 5:385–394.
125. Parker GA, Novilla MN, Brown AC, et al. Granular cell tumour (myoblastoma) in the lung of a horse. J Comp Pathol 1979; 89:421–430.
126. Nickels FA, Brown CM, Breeze RG. Myoblastoma. Equine granular cell tumor. Mod Vet Pract 1980; 61:593–596.
127. Turk MAM, Breeze RG. Histochemical and ultrastructural features of an equine pulmonary granular cell tumour (myoblastoma). J Comp Pathol 1981; 91:471–481.
128. Scarratt WK, Crisman MV, Sponenberg DP, et al. Pulmonary granular cell tumour in 2 horses. Equine Vet J 1993; 25:244–247.
129. Sutton RH, Coleman GT. A pulmonary granular cell tumour with associated hypertrophic osteopathy in a horse. N Z Vet J 1995; 43:123.
130. Goodchild LM, Dart AJ, Collins MB, et al. Granular cell tumour in the bronchus of a horse. Aust Vet J 1997; 75:16–18.
131. Pusterla N, Norris AJ, Stacy BA, et al. Granular cell tumours in the lungs of three horses. Vet Rec 2003; 153:530–532.
132. Dill SG, Moise NS, Meschter CL. Cardiac failure in a stallion secondary to metastasis of an anaplastic pulmonary carcinoma. Equine Vet J 1986; 18:414–417.
133. Uphoff CS, Lyncoln JA. A primary pulmonary tumour in a horse. Equine Pract 1987; 9:19–20.
134. Van Rensberg IB, Stadler P, Soley J. Bronchiolo-alveolar adenocarcinoma in a horse. J S Afr Vet Assoc 1989; 60:212–214.
135. Anderson JD, Leonard JM, Zeliff JA, et al. Primary pulmonary neoplasm in a horse. J Am Vet Med Assoc 1992; 201:1399–1401.
136. Schultze AE, Sonea I, Bell TG. Primary malignant pulmonary neoplasia in two horses. J Am Vet Med Assoc 1988; 193:477–480.
137. Lavoie JP, Carlson GP, George L. Hypertrophic osteopathy in three horses and a pony. J Am Vet Med Assoc 1992; 201:1900–1904.
138. Murphy JR, Breeze RG, McPherson EA. Myxoma of the equine respiratory tract. Mod Vet Pract 1978; 59:529–532.
139. Sullivan DJ. Cartilaginous tumours (chondroma and chondrosarcoma) in animals. Am J Vet Res 1960; 21:531–535.
140. Clem MF, O'Brien TD, Feeney DA, et al. Pulmonary chondrosarcoma in a horse. Compend Contin Educ Pract Vet 1986; 8:964–969.
141. Rossdale PD, Greet TRC, McGladdery AJ, et al. Pulmonary leiomyosarcoma in a 13-year-old Thoroughbred stallion presenting as a differential diagnosis to recurrent airway obstruction. Equine Vet Educ 2004; 16:21–28.
142. Pérez-Ecija RA, Mendoza FJ, Zafra R, et al. Clinical, pathological and immunohistochemical features of a pulmonary blastoma in a horse. Vet Rec 2009; 164:182–183.
143. Woolford L, Staniek G, Blunden AS. Pleuropulmonary blastoma in an equine foetus. Vet Pathol 2010; 47:1086–1089.
144. Davis EG, Rush BR. Diagnostic challenges: Equine thoracic neoplasia. Equine Vet Educ 2013; 25:96–107.
145. Bouchard PR, Fortna CH, Rowland PH, et al. An immunohistochemical study of three equine pulmonary granular cell tumours. Vet Pathol 1995; 32:730–734.
146. Kagawa Y, Hirayama K, Tagami M, et al. Immunohistochemical analysis of equine pulmonary granular cell tumours. J Comp Pathol 2001; 124: 122–127.
147. Patnaik AK. Histologic and immunohistochemical studies of granular cell tumours in seven dogs, three cats, one horse, and one bird. Vet Pathol 1993; 30:176–185.
148. Kelley LC, Hill JE, Hafner S, et al. Spontaneous equine pulmonary granular cell tumours: morphologic, histochemical, and immunohistochemical characterization. Vet Pathol 1995; 32:101–106.
149. Mair TS, Rush BR, Tucker RL. Clinical and diagnostic features of thoracic neoplasia in the horse. Equine Vet Educ 2004; 16:30–36.
150. Godber LM, Brown CM, Mullaney TP. Polycystic hepatic disease, thoracic granular cell tumor and secondary hypertrophic osteopathy in a horse. Cornell Vet 1993; 83:227–235.
151. Mair TS, Dyson SJ, Fraser JA, et al. Hypertrophic osteopathy (Marie's disease) in Equidae: a review of twenty-four cases. Equine Vet J 1996; 28:256–262.
152. Heinola T, Heikkilä M, Ruohoniemi M, et al. Hypertrophic pulmonary osteopathy associated with granular cell tumour in a mare. Vet Rec 2001; 149:307–308.
153. Dadmanesh F, Sekihara T, Rosai J. Histological typing of thymoma according to the new World Health Organization classification. Chest Surg Clin N Am 2001; 11:407–420.
154. Migaki G. Hematopoietic neoplasms of slaughter animals. Natl Cancer Inst Monogr 1969; 32:121–151.
155. Whiteley LO, Leininger JR, Wolf CB, et al. Malignant squamous cell thymoma in a horse. Vet Pathol 1986; 23:627–629.
156. Furuoka H, Taniyama H, Matsui T, et al. Malignant thymoma with multiple metastases in a mare. Jpn J Vet Sci 1987; 49:577–579.
157. Shahriar F, Moore J. Thymic epithelial tumor with heart metastasis in a horse. Vet Med Int 2010; Aug 8: doi: 10.4061/2010/386378.
158. Straub R, von Tscharner C, Pauli B, et al. Pleural mesothelioma in a horse. Schweiz Arch Tierheilkd 1974; 116:207–211.
159. Kramer JW, Nickels FA, Bell T. Cytology of diffuse mesothelioma in the thorax of a horse. Equine Vet J 1976; 8:81–83.
160. Wallace SS, Jayo MJ, Maddux JM. Mesothelioma in a horse. Compend Contin Educ Pract Vet 1987; 9:210–216.
161. Carnine BL, Schneider G, Cook JE, et al. Pericardial mesothelioma in a horse. J Comp Pathol 1977; 99:105–107.
162. Mair TS, Hillyer MH, Brown PJ. Mesothelioma of the pleural cavity in a horse: diagnostic features. Equine Vet Educ 1992; 4:59–61.
163. Colbourne CM, Bolton JR, Mills JN, et al. Mesothelioma in horses. Aust Vet J 1992; 69:275–278.
164. Fry MM, Magdesian KG, Judy CE, et al. Antemortem diagnosis of equine mesothelioma by pleural biopsy. Equine Vet J 2003; 35:723–727.
165. Stoica G, Cohen N, Mendes O, et al. Use of immunohistochemical marker calretinin in the diagnosis of a diffuse malignant metastatic mesothelioma in an equine. J Vet Diagn Invest 2004; 16:240–243.
166. LaCarrubba AM, Johnson PJ, Whitney MS, et al. Hypoglycaemia and tumour lysis syndrome associated with peritoneal mesothelioma in a horse. J Vet Intern Med 2006; 20:1018–1022.
167. Ulrich R, Eydner M, Grün A, et al. A biphasic malignant mesothelioma of the peritoneum and pleura in a horse. Dtsch Tierarztl Wochenschr 2009; 116:186–191.
168. Dobromylskyj MJ, Copas V, Durham A, et al. Disseminated lipid-rich peritoneal mesothelioma in a horse. J Vet Diagn Invest 2011; 23:615–618.
169. Mair TS, Lane JG, Lucke VM. Clinicopathological features of lymphosarcoma involving the thoracic cavity in the horse. Equine Vet J 1985; 17:428–433.
170. Platt H. Observations on the pathology of non-alimentary lymphomas in the horse. J Comp Pathol 1988; 98:177–194.
171. Lawn K. Sudden death due to thoracic lymphoma in a standardbred racing horse. Can Vet J 2005; 46:528–529.
172. Neufeld JL. Lymphosarcoma in a mare and review of cases at the Ontario Veterinary College. Can Vet J 1973; 14:149–153.
173. Neufeld JL. Lymphosarcoma in the horse: a review. Can Vet J 1973; 14:129–135.
174. Theilen GH, Madewell BR, eds. Equine leukaemia complex. Veterinary cancer medicine, 1st edn. Philadelphia: Lea and Febiger; 1979: 272–279.
175. Van den Hoven R, Franken P. Clinical aspects of lymphosarcoma in the horse: A clinical report of 16 cases. Equine Vet J 1983; 15:49–53.
176. East LM, Savage CJ. Abdominal neoplasia (excluding urogenital tract). Vet Clin North Am Equine Pract 1998; 14:475–493.
177. Taintor J, Schleis S. Equine lymphoma. Equine Vet Educ 2011; 23:205–213.
178. Sugiyama A, Takeuchi T, Morita T, et al. Mediastinal lymphoma with complete atrioventricular block in a horse. J Vet Med Sci 2008; 70: 1101–1105.
179. Mair TS, Yeo SP, Lucke VM. Hypercalcaemia and soft tissue mineralization associated with lymphosarcoma in two horses. Vet Rec 1990; 126:99–101.
180. Garber JL, Reef VB, Reimer JM. Sonographic findings in horses with mediastinal lymphosarcoma: 13 cases (1985–1992). J Am Vet Med Assoc 1994; 205:1432–1436.
181. De Clercq D, van Loon G, Lefère L, et al. Ultrasound-guided biopsy as a diagnostic aid in three horses with cranial mediastinal lymphosarcoma. Vet Rec 2004; 154:722–726.
182. Vachon AM, Fischer AT. Thoracoscopy in the horse: diagnostic and therapeutic indications in 28 cases. Equine Vet J 1998; 30:467–475.
183. Pollock PJ, Russell T. Standing thoracoscopy in the diagnosis of lymphosarcoma in a horse. Vet Rec 2006; 159:354–356.
184. Peroni JF, Horner NT, Robinson NE, et al. Equine thoracoscopy: normal anatomy and surgical technique. Equine Vet J 2001; 33:231–237.
185. Mannsmann RA, Bernard-Strother S. Pleuroscopy in horses. Mod Vet Pract 1985; 66:9–17.
186. Lee WL, Tennent-Brown BS, Barton MH, et al. Two horses with thoracic lymphoma diagnosed using thoracoscopic biopsy. Equine Vet Educ 2012; 25:79–83.
187. Meyer J, DeLay J, Bienzle D. Clinical, laboratory and histopathological features of equine lymphoma. Vet Pathol 2006; 43:914–924.
188. Asahina M, Murakami K, Ajito T, et al. An immunohistochemical study of an equine B-cell lymphoma. J Comp Pathol 1994; 111:445–451.
189. Saulez MN, Schlipf JW Jr, Cebra CK, et al. Use of chemotherapy for treatment of a mixed-cell thoracic lymphoma in a horse. J Am Vet Med Assoc 2004; 224:733–738.
190. Valentine BA, Ross CE, Bump JL, et al. Intramuscular haemangiosarcoma with pulmonary metastasis in a horse. J Am Vet Med Assoc 1986; 188: 628–629.
191. Johnson JE, Beech J, Saik JE. Disseminated hemangiosarcoma in a horse. J Am Vet Med Assoc 1988; 193:1429–1431.
192. Southwood LL, Schott HC, Henry CJ, et al. Disseminated haemangiosarcoma in the horse: 35 cases. J Vet Intern Med 2000; 14:105–109.
193. Gruys E, Kok HA, Van Der Werff YD. Dyspnoea due to intrathoracic haemorrhage and haemangiosarcoma in a horse (author's transl.) Dutch. Tijdschr Diergeneeskd 1976; 101:310–312.
194. Frye FL, Knight HD, Brown SI. Haemangiosarcoma in a horse. J Am Vet Med Assoc 1983; 182:287–289.
195. Freestone JF, Williams MM, Norwood G. Thoracic haemangiosarcoma in a 3-year-old horse. Aust Vet J 1990; 67:269–270.
196. Collins MB, Hodgson DR, Hutchins DR, et al. Haemangiosarcoma in the horse: three cases. Aust Vet J 1994; 71:296–298.
197. Jean D, Lavoie JP, Nunez L, et al. Cutaneous haemangiosarcoma with pulmonary metastasis in a horse. J Am Vet Med Assoc 1994; 204:776–778.
198. Johns I, Stephen JO, Del Piero F, et al. Haemangiosarcoma in 11 young horses. J Vet Intern Med 2005; 19:564–570.
199. Reinertson EL. Fibrosarcoma in a horse. Cornell Vet 1974; 64:617–621.
200. Jorgensen JS, Geoly FJ, Berry CR, et al. Lameness and pleural effusion associated with an aggressive fibrosarcoma in a horse. J Am Vet Med Assoc 1997; 210:1328–1331.
201. Tan RHH, Crisman MV, Clark SP, et al. Multicentric mastocytoma in a horse. J Vet Intern Med 2007; 21:340–343.

202. Kirker-Head CA, Loeffler D, Held JP. Pelvic limb lameness due to malignant melanoma in a horse. J Am Vet Med Assoc 1985; 186:1215–1217.
203. Kunze DJ, Monticello TM, Jakob TP, et al. Malignant melanoma of the coronary band in a horse. J Am Vet Med Assoc 1986; 188:297–298.
204. Milne JC. Malignant melanomas causing Horner's syndrome in a horse. Equine Vet J 1986; 18:74–75.
205. Murray MJ, Cavey DM, Feldman BF, et al. Signs of sympathetic denervation associated with a thoracic melanoma in a horse. J Vet Intern Med 1997; 11:199–203.
206. MacGillivray KC, Sweeney RW, Del Piero F. Metastatic melanoma in horses. J Vet Intern Med 2002; 16:452–456.
207. Tarrant J, Stokol T, Bartol J, et al. Diagnosis of malignant melanoma in a horse from cytology of body cavity fluid and blood. Equine Vet J 2001; 33:531–535.
208. Traub JL, Schroeder WG. Malignant melanoma in a horse. Vet Med Small Anim Clin 1980; 75:261–263.

30 Tumours of the cardiovascular system

Overview 512
Vascular neoplasia 512
Cardiac neoplasia 522
Neoplasia of the haematopoietic system 523
Leukaemia 539

Overview

Neoplasms of vascular origin may originate from either blood vessel or lymphatic endothelium and include haemangioma, haemangiosarcoma, lymphangioma, lymphangiosarcoma and angiosarcoma.

Neoplasms affecting the cardiovascular system are very rare in horses, with an estimated prevalence of approximately 0.25%, although some well-defined tumour types occur more than others.[1,2]

Vascular neoplasia

Haemangioma/vascular hamartoma/ cavernous haemangioma

See also page 339.

Description

Haemangioma is a benign neoplasm derived from vascular endothelium. It is frequently thought that haemangiomas may not be neoplastic and, in fact, may be hamartomas, or developmental malformations of vascular tissue, even though they may not always be easily recognizable from birth (see p. 339). Cutaneous haemangioma accounts for about 1–4% of all dermal neoplasms.[3]

In one case series of 21 vascular tumours, 18 were diagnosed with haemangioma. Of those, 12/18 were <1 year old and six of those were congenital, i.e. noted at birth.[1] In another review of 10 cases of vascular malformations, six were diagnosed as haemangioma and 4/6 were <18 months old, consistent with the view that these lesions are probably developmental in origin.[4]

Haemangiomas have most frequently been reported in the skin, particularly the extremities of young animals.[1,5] They can in fact be situated anywhere on the skin surface.[1,4,6] Haemangioma has also been recorded in the following[4,7–12]:

- Ocular tissues (conjunctiva, eyelid, limbus, cornea and canthus)
- Ovary
- Guttural pouch
- Pleura
- Peritoneum
- Rectum
- Male external genitalia
- The synovium of the deep digital flexor tendon.

It is also reported rarely in tendon sheaths of young horses between 1 and 3 years old.[13] Synovial haemangioma shows infiltrative growth, but shows no cytological features of malignancy and does not metastasize.

The aetiopathogenesis of these tumours in horses is unknown, but in cases involving the skin and eye, exposure to ultraviolet light may be important.[11] In humans, synovial lesions may be associated with previous trauma, but this is not reported in the horse.[12] The dorsal carpal region of three young TB horses had tumours classified as vascular hamartoma.[14]

Clinical features

See Figures 30.1 and 30.2.

Presenting signs depend on the site of the lesion:

- Cutaneous lesions, mainly affecting the extremities[4,6,15]
  - Alopecia
  - Generalized limb swelling

Disease summary

Notes

Rare, usually benign congenital tumour-like, non-metastatic mass derived from vascular endothelial cells. Most cases affect the limb or body skin of young foals; often thought to be a vascular anomaly.

Clinical features

Cutaneous blue/red/black nodular/multinodular masses (usually small fleshy, exophytic) that bleed easily and progressively enlarge; frequently small and commonly found on distal extremities. Ocular lesions are raised fleshy masses with conjunctival swelling.

Diagnostic confirmation

Biopsy and histopathology with immunohistochemistry Factor VIII-related antigen as vascular endothelial cell marker.

Management

Surgical excision should be curative; may be problematic, depending on location and if very large. Alternatives include cryotherapy and radiotherapy. Recurrence has been reported.

Prognosis

Prognosis is good.



Figure 30.1 Vascular hamartoma/cavernous haemangioma. The distal limb is a common site for these tumours in young foals – any are present at birth. They are easily mistaken for congenital papilloma. **(A)** A typical (cavernous) haemangioma on the distal limb of a 3-week-old Arabian foal. The lesion was noticed at birth and grew slowly. It was successfully removed surgically with some difficulty, since it involved the digital sheath. **(B)** A less typical type of haemangioma in a newborn foal showing extensive skin involvement. *(Figure B courtesy of Gil Riley.)*

- Round, nodular or wart-like appearance
- Progressively enlarging blue/red/black nodular/multinodular masses
- Frequently small (2–5 cm) but can be large and multiple
- Ulceration of the skin
- Locations reported predominantly include distal limb, in particular fetlock and pastern region, but also reported in hock, withers, metacarpal region, lip, tibial region, coronary band and perineum

- Ocular lesions
  - Serosanguineous ocular discharge
  - Conjunctival swelling
  - Raised, fleshy, red mass
  - Synovial lesions: slow-growing lesions may infiltrate adjacent structures, including synovial sheaths and joints, resulting in progressive lameness and tendon sheath effusion or subcutaneous swelling[12]
  - Non-painful mass, localized pain, or pain on palpation, depending on their size, location and physical alterations in neighbouring structures
  - One case report describes a synovial haemangioma of the digital flexor tendon sheath in a 15-year-old gelding
- Other lesions
  - Haemangioma of the guttural pouch has been reported in a 16-year-old TB gelding with dysphagia and nasal reflux of ingesta.[9]

Differential diagnoses

1. Lymphangioma
2. Haemangiosarcoma
3. Squamous cell carcinoma (particularly for ocular lesions)
4. Sarcoid
5. Congenital papilloma
6. Other proliferative deformities and abnormalities encountered at birth such as meningocele or encephalocele
7. Exuberant granulation tissue.

Diagnostic confirmation

Diagnostic confirmation is made by a combination of thorough clinical examination, biopsy and histopathology. In cases of synovial and ocular haemangioma, diagnostic imaging modalities such as ultrasonography and radiography may be helpful.

- Diagnostic imaging, including skull radiographs, may help identify soft tissue masses within the paranasal sinuses or evidence of bone lysis
- CT may provide greater information regarding the extent of the mass and features of malignancy (in cases of haemangiosarcoma)[16]
- If the mass is located within a soft tissue structure, ultrasonographic examination may be appropriate to evaluate the extent of the lesion; Doppler flow ultrasonography can help a great deal to identify the abnormal blood flow patterns
- Biopsy and histopathology
  - Immunohistochemistry, using markers such as factor VIII-related antigen (von Willebrand factor) as a vascular endothelial marker
  - It may in some circumstances be appropriate to perform local lymph node biopsy to eliminate the possibility of infiltration or metastasis associated with haemangiosarcoma.

Management

Treatment is by excision or by ablation of abnormal vascular bed with laser.

Surgery

- Complete surgical excision should be curative.
- This may be problematic with very large lesions, depending on location.[6]
- In one case series of cutaneous haemangioma, 4/7 cases showed no recurrence at 1 year, 3/7 required a second resection and, of those, 3/3 were curative.[15]
- Metastasis has not been documented. However, although it is characterized as benign, infiltrative and invasive growth and recurrence after removal are recognized.
- Synovial haemangiomas, despite their benign nature, are not well demarcated; there is no capsule and their shape usually follows that of the anatomical structure where they are located. They may also extend across normal tissue barriers. They may therefore become difficult to excise, because they may spread through the entire synovium and infiltrate the surrounding muscles and fat and haemostasis may be a challenge. Following complete excision, recurrence is unlikely[12]

Cryosurgery or laser ablation

May assist destruction of the abnormal vascular bed.[11]

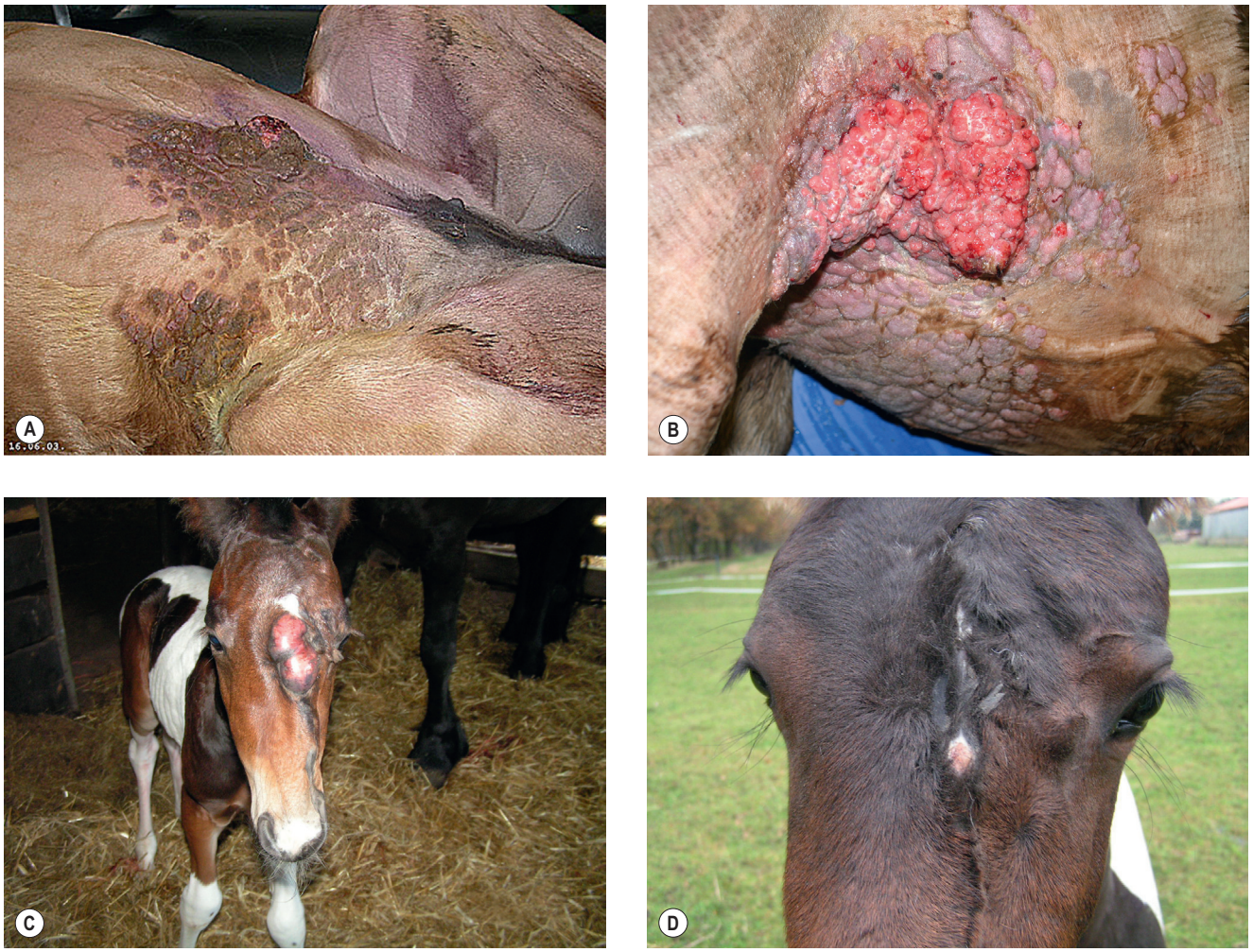


Figure 30.2 (Congenital) haemangioma. These two cases illustrate the difference in outcome and emphasize the need to keep a guarded prognosis. **(A)** A foal was examined at 3 days of age with an assumed 'iodine burn' around its umbilical region. A presumptive diagnosis of cavernous haemangioma was made on clinical examination and confirmed on biopsy. No treatment was given and over the next 3 months, the foal deteriorated badly with thickening of the tumour and widening of the involved region. **(B)** At 5 months of age the tumour had become very aggressive with invasion of the associated deep musculature and the surface of the tumour was easily traumatized and bled profusely. The foal was euthanized. **(C)** A congenital vascular hamartoma/cavernous haemangioma was diagnosed histologically on this 3-day-old foal. Surgical removal was problematic but successful. **(D)** The wound healed well, leaving a large but insignificant scar without any recurrence. *(Figures C and D courtesy of Nils Telerup.)*

Radiotherapy

A conjunctival haemangioma in an American Albino gelding was treated by surgical removal and application of strontium-90 plesiotherapy.[8]

Prognosis

The prognosis for the vascular hamartoma/haemangioma complex appears to be fair to good, as they grow slowly and usually present as well-defined vascular lesions, making them generally amenable to surgical excision.[8,11] However, not all are at suitable places and some have secondary involvement of other structures, such as the tendon sheaths and deep tissues.

Note

An epithelioid variant of cutaneous haemangioma has been described in two horses.[17] This variant can be viewed as a cutaneous endothelial tumour/benign haemangioma of well-formed, sometimes thick-walled, vessels. The diagnosis of such neoplasms poses a significant diagnostic challenge for the pathologist. One case presented with a mass in the dermis of the right cranial neck in a 13-year-old Morgan gelding. Surgical excision was curative. A second case presented in a 3-year-old TB gelding on the lateral metatarsus. Punch biopsy confirmed the diagnosis and, again, surgery was curative.[17]

Haemangiosarcoma

See also page 334.

Description

Haemangiosarcoma is an uncommon, highly malignant tumour of the vascular endothelium.[18] Haemangiosarcomas may affect horses of any age, including foals, but are most frequently reported in middle-aged to older horses.[18,19] No breed or sex predilection has been reported.[18]

Haemangiosarcomas may occur as focal (cutaneous) masses, masses with local infiltration, internal masses restricted to one organ or disseminated neoplasia affecting multiple organs.[18–21] Cutaneous vascular lesions are more commonly less aggressive (haemangiomas) but even these

Disease summary

Notes

Rare, highly malignant tumour of vascular endothelium usually affecting adult horses without sex or breed predilection. Skin, conjunctiva and muscle are the main primary sites. Possible cause of incipient wound healing failure when tumour develops in a wound site.

Clinical features

May be focal cutaneous masses, masses with local infiltration particularly affecting major muscles or disseminated neoplasia. A combination of anaemia, neutrophilic leucocytosis, thrombocytopaenia and normal bleeding times is suggestive of the tumour.

Diagnostic confirmation

Diagnostic imaging, biopsy, histopathology and immunohistochemistry for vascular endothelial markers confirm the diagnosis.

Management

Surgical removal of early lesions may be effective, but early diagnosis is not often made. Surgery or radiotherapy can be used for localized tumours if not disseminated. Systemic chemotherapy has not yet proven effective.

Prognosis

Prognosis is very poor unless localized accessible tumours are identified. High malignancy rate with rapid metastasis in most cases.

can be malignant and locally invasive. In addition to disseminated disease, local invasion of the vertebrae and spinal cord, oral cavity, eye, tarsal sheath and frontal sinus has been reported.

There may be a subpopulation of young horses (<3 years) with haemangiosarcoma, in which dissemination is less common.[21] Many of these are congenital and most are external as opposed to the internal disseminated form seen in older animals. Haemangiosarcoma of young animals appears to be slowly progressive or aggressive and these cases appear to primarily affect the musculoskeletal system.[21]

Haemangiosarcoma is relatively uncommon in horses and affected horses often present a major diagnostic challenge. Haemangiosarcoma is mainly a disease of the middle-aged horse without a breed or sex predilection.[18,21] Presenting clinical signs vary according to the body system or systems involved and include cutaneous masses, leg swelling and lameness, epistaxis, depression and poor performance.

Disseminated haemangiosarcoma is a disease of mature, particularly middle-aged horses, although a wide range (3–27 years) of ages was found. The mean and median age of affected animals in one case series was 12 years.[18] Haemangiosarcoma affecting young horses is very uncommon.[21]

Clinical features

These tumours generally present with clinical signs referable to the body system affected. The most prominent presenting signs are referrable to the respiratory and musculoskeletal systems and external tumours may be recognized on the skin or visible mucous membranes.[18] Secondary involvement of the spleen and liver are common. Haemangiosarcoma represents a major cause of haemoabdomen and may involve other tissues, including skeletal muscle, lung, synovium, paranasal sinuses, guttural pouches, pericardium and oral cavity.[22,23]

- Painful, often marked and progressive muscle swelling. Lameness/diffuse unilateral limb swelling or joint effusion where the primary involvement is of the musculoskeletal system[21]
- Anorexia/weight loss
- Depression/lethargy/poor performance
- Oedema (pectoral, ventral, preputial or distal limb)
- Tachycardia/tachypnoea/dyspnoea, chronic cough (possibly with haemoptysis)
- Epistaxis/cough (haemoptysis)
- Pale or icteric mucous membranes
- Pyrexia
- Intermittent low-grade colic/haemoabdomen
- Abnormal lung sounds, including dull ventral lung sounds bilaterally (consistent with pleural effusion or haemothorax) and harsh lung sounds
- Behavioural and neurological signs
  - Ataxia[24–26]
  - Cranial nerve deficits, including reduced tongue tone, spontaneous nystagmus, head tilt, circling, dysphagia, proprioceptive deficits.[19]
- Cardiac signs
  - Ventricular arrhythmia.[27]
- Paraneoplastic bullous stomatitis[28]
- Single or multiple cutaneous masses or swelling involving the thorax, mandible/maxilla, oral cavity, prepuce and limbs.[23] Most are covered by normal, haired skin but some are ulcerated and haemorrhagic and some have a verrucose nature (Figs 30.3, 30.4).

Specific signs associated with ocular haemangiosarcoma include (see p. 622) (Fig. 30.5):

- Serosanguineous ocular and nasal discharge
- Conjunctival swelling and chemosis
- Vascularizing keratitis
- Red, fleshy mass on conjunctiva, sclera, third eyelid.[29–31]

Differential diagnoses

Differential diagnoses for disseminated haemangiosarcoma include:

Neoplastic

1. Lymphosarcoma
2. Lymphangiosarcoma
3. Epithelioid variant of haemangiosarcoma
4. Carcinoma
5. Plasma cell myeloma.

Non-neoplastic

1. Respiratory abnormalities, including pleuropneumonia and thoracic abscesses
2. Musculoskeletal abnormalities, including fracture or persistent haemorrhage from a vessel
   a. Lack of resolution of systemic signs, such as tachycardia should prompt further investigation

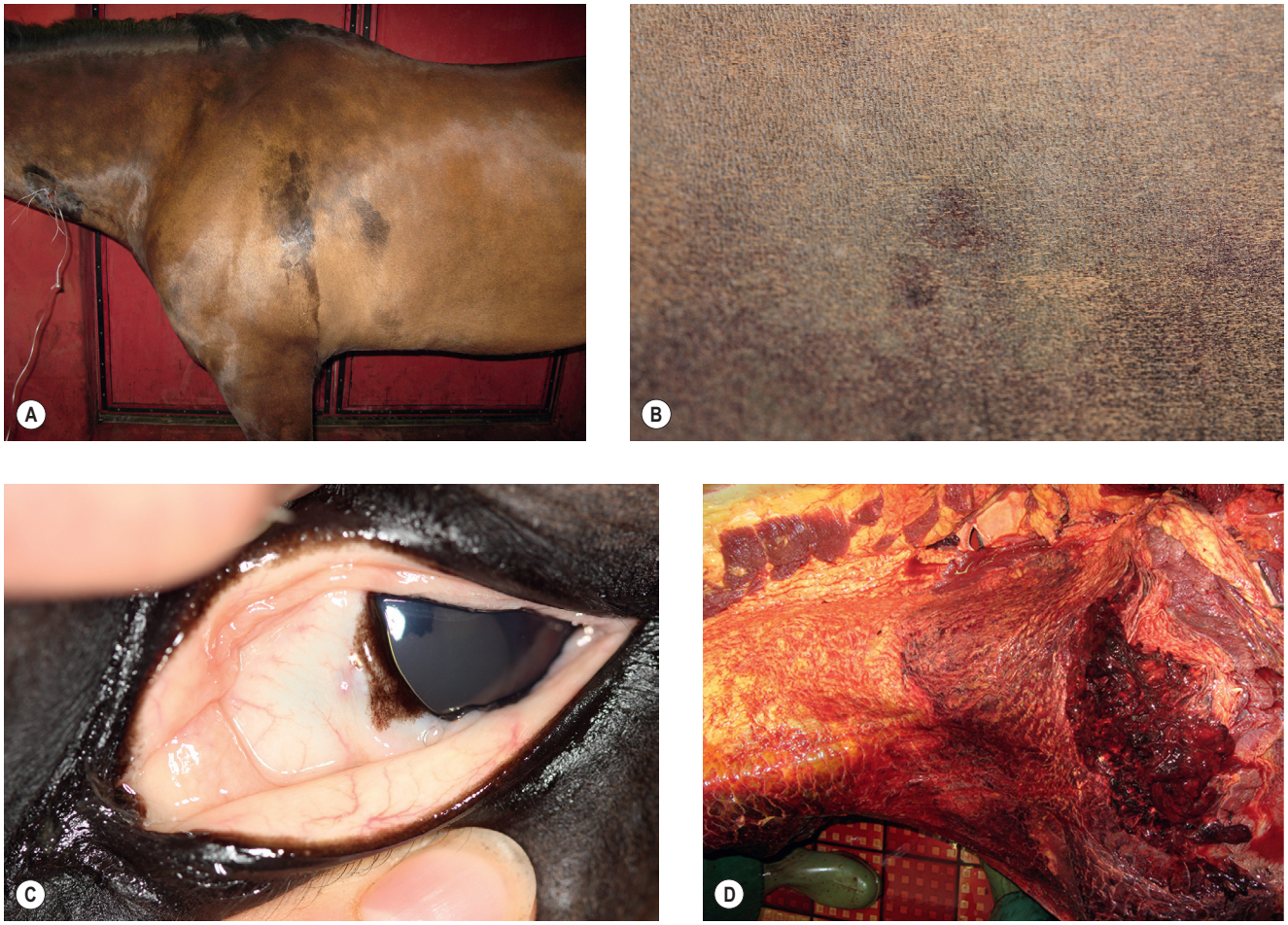


Figure 30.3 Haemangiosarcoma. (A) A 12-year-old gelding was presented with a 5-day history of a rapidly progressive very painful diffuse swelling on the left thoracic wall with a haemorrhagic (bruised) area over the triceps muscle **(B)**. There was associated localized sweating and extensive (haemorrhagic) oedema of the left forelimb and ventral oedema. The horse was febrile and patently anaemic, **(C)** with high cardiac and respiratory rates. **(D)** At necropsy, the horse was found to have a large invasive haemangiosarcoma of the triceps region that extended up into the neck. There were disseminated secondary tumours in the brain, lungs, spleen, kidney and intestinal wall.

3. Trauma causing haemoabdomen, splenic disorders (subcapsular splenic haematoma, splenic rupture), haemothorax or haematoma formation.

In suspected cases of musculoskeletal haemangiosarcoma in young horses presenting with cutaneous masses, limb swelling or joint effusion, the lack of physical examination findings, such as weight loss and depression, more typically associated with neoplastic processes, makes differentiation of musculoskeletal haemangiosarcoma from other, more common causes of limb swelling and cutaneous masses, such as haematoma, abscess, lymphangitis or cellulitis, more difficult.[21]

Differential diagnoses for ocular masses include:

1. Squamous cell carcinoma
2. Lymphoma
3. Granulation tissue
4. Habronema
5. Eosinophilic granuloma.

Diagnostic confirmation

Definitive diagnosis is based on biopsy and histopathology. In most disseminated forms of the disease necropsy multiple organ involvement involving the major organs is easily appreciated.

- *Haematology*
  - Anaemia, neutrophilic leucocytosis and thrombocytopaenia, although bleeding times may be normal.[18,21]
- *Serum biochemistry*[18]
  - Hypoproteinaemia, consistent with haemorrhage
  - Hyperglobulinaemia, consistent with chronic antigenic stimulation
  - Hyperbilirubinaemia
  - Hyperglycaemia
  - Elevated creatine kinase (CK)
  - Elevated aspartate aminotransferase (AST)
  - Electrolyte disturbances
  - Haematuria (micro or macro).
- *Abdominocentesis and thoracocentesis* may be helpful, but results of cytological examination generally reveal haemorrhage rather than evidence of neoplasia.
- *Diagnostic imaging*
  - Ultrasonography



Figure 30.4 Focal haemangiosarcoma. **(A)** The skin is a relatively common site for focal haemangiosarcoma – at this site, it may present as a fragile mildly painful expanding skin swelling that bleeds easily on handling. **(B)** It can also develop at the site of skin wounds, where it can be cause of incipient wound healing failure verrucose haemangiosarcoma. **(C)** Focal haemangiosarcoma in the jejunum can cause partial or complete non-strangulating obstruction of the gut and consequent intermittent low-grade colic, with more severe obstruction resulting in surgical colic. **(D)** Epithelioid variant/verrucose haemangiosarcoma on the caudal thigh of a 9-year-old Hunter-type gelding. The lesion was aggressive and associated with rapid metastatic developments. Notice the prominent vascular supply.

- Radiography is useful to assess presence of pleural effusion or abnormal lung pattern (metastasis to lungs), or possible bone involvement in cases of cutaneous masses or intramuscular swelling
- There are several reports of vertebral and spinal cord compression due to haemangiosarcoma without evidence of disseminated disease.[20,24,25,32] There are reports of soft tissue haemangiosarcoma infiltrating osseous tissue in distal limbs and the axial and limb skeleton.[21,33,34]
- *Endoscopy* of airway, bladder, abdomen and pleural cavity.[35]
- *Nuclear scintigraphy* was performed in one case presenting with left forelimb lameness that had failed to be localized with regional and intra-synovial anaesthesia; this case showed marked increased radiopharmaceutical uptake (IRU) in the region of the greater tubercle of the left humerus and radiography identified a large radiolucent area interspersed with sclerosis in the proximo-lateral humerus.

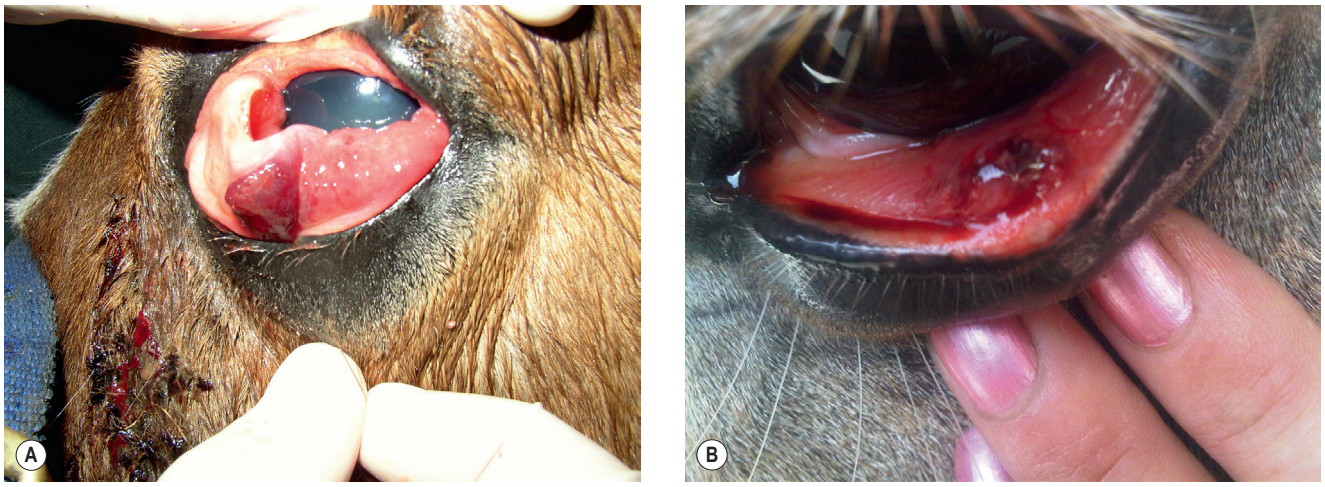


Figure 30.5 Ocular haemangisarcoma. Conjunctival haemangiosarcoma can be localized or part of wider disseminated problem. Highly vascular, often haemorrhagic localized or diffuse masses can be identified in the conjunctiva **(A,B)**. A lacrimal occult blood test will be very positive in all cases, and biopsy is definitive.

Ultrasonographically-guided biopsy confirmed the diagnosis[34]

- Scintigraphy may be useful to investigate the intestinal tract, using radiolabelled leukocytes.[36] However, this is not specific for neoplastic disease.

- *Biopsy and histopathology*
  - In one series of 35 cases of disseminated haemangiosarcoma, only 4/35 cases were diagnosed antemortem.[18]
  - The low number of ante-mortem diagnoses may be attributable to the mistaken initial diagnoses of trauma as a cause of haemorrhage into a body cavity or extensive haematoma formation in major muscle masses.
  - Collection of biopsy specimens and fine-needle aspirates is still rewarding and should be obtained if haemangiosarcoma is suspected.
  - General anaesthesia and/or use of a tourniquet may be required in some cases, for adequate haemostasis and collection of an appropriate sample.[18]
  - In a series of cases of haemangiosarcoma in young horses, a high percentage of cases was diagnosed ante-mortem (10/10 needle/excisional biopsies).[21]
  - The possible need for multiple biopsy specimens to confirm diagnosis should be emphasized, as tumours are not typically homogenous in nature and many areas may resemble haematoma or soft tissue trauma, snake bite or other conditions.
  - Use of immunohistochemical techniques for evaluation of biopsy specimens can confirm the endothelial origin of tumours
    - Factor VIII-related antigen is expressed in endothelial cells of both vascular and lymphatic origin, although it has significantly higher expression for vascular endothelium.
- *Necropsy*
  - Necropsy reveals that most tumours metastasize to the lung and pleura, skeletal muscle and spleen.[18]
  - Less commonly, haemangiosarcoma may be found in the heart, kidney, brain, gastrointestinal tract, mesentery, liver, diaphragm, lymph nodes, ovary, adrenal gland, larynx and mandible.[18] Joint involvement may be more common in younger animals.[21]
  - Other common post-mortem findings include large volumes of blood in the thoracic and abdominal cavities and within affected muscle groups. Accumulation of blood is usually a consequence of haemorrhage from tumours.
  - Tumours are usually fragile and easily traumatized, red to black in colour and ill-defined.
  - Despite the fact that the respiratory tract is the system most commonly affected, in relation to clinical signs and post-mortem lesions, in horses with disseminated haemangiosarcoma, primary tumour site in the thoracic cavity is relatively uncommon.[18]

Management

Treatment options are limited and are often considered palliative and cost-prohibitive for most horse owners.[21] Reported treatments include surgical resection of localized accessible masses with a wide margin, topical or systemic chemotherapy and radiation therapy.

Surgical excision

- Surgical resection can be curative if dissemination has not occurred and clean margins are achievable. However, many of these tumours are multifocal and extremely invasive and ill-defined, making complete excision unlikely.
- Surgical removal of haemangiosarcoma masses is often associated with recurrence of tumour or metastasis to other organs.[21,30]
- Surgical debulking may be done by sharp excision, or use of a surgical laser to photo-ablate cells.[36]
- Early diagnosis and complete surgical excision of locally invasive forms of haemangiosarcoma may result in long-term survival.[18]
- Surgical excision of multiple tarsal sheath haemangiosarcomas in one horse resulted in a successful return to racing.[37]

Chemotherapy

- Common chemotherapeutic drugs include doxorubicin, cyclophosphamide, vincristine and prednisolone. This should only be carried out by experienced clinicians with a full understanding of cytotoxic guidelines in use and handling of such medications.
- Side-effects are usually mild and include loss of normal tissue, erythema, local pain and burning and pruritus, but may be unacceptable, such as gastrointestinal, renal, neurological and cardiac abnormalities.[38]
- Topical or local chemotherapy with cisplatin or 5-fluorouracil has best success with small tumour bulk and therefore concurrent surgical debulking may be important.[21]

Radiotherapy

- Teletherapy (external beam radiotherapy) may be considered in some cases.
- Brachytherapy (iridium-192) has been used as an adjunctive treatment and produced complete gross local tumour resolution.[36] However, the case was complicated by widespread tumours.

Prognosis

The prognosis is best regarded as very poor in most forms, although it is clear that early recognition and aggressive treatment using multimodalities can be useful.[18] In most cases, supportive treatment was unrewarding and most horses show a rapid deterioration.

The overall prognosis for horses with juvenile haemangiosarcoma appears to be variable, based on a series of 11 cases.[21] Six of 11 horses were euthanized, with two surviving horses having only short-term follow-up and two surviving long term with apparent tumour resolution without treatment.

Epithelioid haemangiosarcoma is a variant of the histologically conventional haemangiosarcoma that has little or no morphological evidence of a vascular origin and has been reported rarely in domestic animals. The epithelioid variant of cutaneous haemangiosarcoma has been described in three single case reports and one case series.[17,39–41]

- One case presented with a mass in the deep dermis of the ventral neck in a 12-year-old Morgan gelding. Surgical excision was curative.[17]
- A second case presented in a 16-year-old Rocky Mountain horse gelding that was admitted for investigation of nasal discharge, fever and submandibular swelling. Subsequent histopathology provided a diagnosis of carcinoma; however, further post-mortem testing revealed an epithelioid variant of haemangiosarcoma. Despite cytology and surgical biopsy, the ante-mortem diagnosis of this tumour is difficult due to the lack of overt vascular differentiation. A post-mortem computed tomography helped characterize the invasive nature of the tumour.[39]
- A third case of a 15-year-old female grey Appaloosa horse was presented with a 7-month history of a mass over the right dorsal commissure of vulva. Based on histopathological examination and positive staining with factor VIII-related antigen, vimentin and Verhoeff-van Gieson stain, the vulvar mass was diagnosed as haemangiosarcoma with marked solar elastosis.[40]

One case series documents six cases of equine epithelioid haemangiosarcoma occurring in the ocular tissues of horses with a mean age of 19.8 years at the time of diagnosis. Microscopically, all of the lesions consisted of solid sheets or cords of epithelioid cells with rare narrow clefts or small spaces containing erythrocytes that were often the only feature indicating a vascular origin. Immunohistochemistry proved that the neoplastic cells expressed vimentin, CD31 and factor VIII-related antigen, but not cytokeratin, indicating an endothelial nature.[41]

Angiosarcoma

See also page 339.

Description

Malignant vascular tumours are classified as either haemangiosarcoma or lymphangiosarcoma, when the cell or origin is known and angiosarcoma when the cell of origin is uncertain. Trauma, solar radiation and X-irradiation have been suggested as aetiological factors.[42] There have only been a small number of cases reported in the equine literature to-date.[42–45] It is a tumour that is commoner in aged horses (9–25 years).

Angiosarcoma has been reported to affect:

- Ocular tissues
- Skin
- Paravertebral musculature
- Nasal passages.

Clinical features

Cutaneous and mucous membrane forms are usually localized but have a characteristic exophytic, fragile and friable nature that bleeds easily when handled (Fig. 30.6).

One case of angiosarcoma affecting the nasal passages has been reported in a 9-year-old Thoroughbred mare.[43] Clinical features identified included epistaxis, mucopurulent bilateral nasal discharge, facial swelling and stertor.

Disease summary

Notes

Very rare, highly malignant tumour of vascular origin usually affecting mature to older horses without known sex or breed predilection. Skin, conjunctiva and nasal mucous membranes are the main primary sites.

Clinical features

Localized invasive, fragile rapidly expanding mass with ill-defined margins.

Diagnostic confirmation

Biopsy, histopathology and immunohistochemistry.

Management

Surgery or radiotherapy can be used for localized tumours if not disseminated.

Prognosis

Prognosis is poor unless localized accessible tumours are identified.



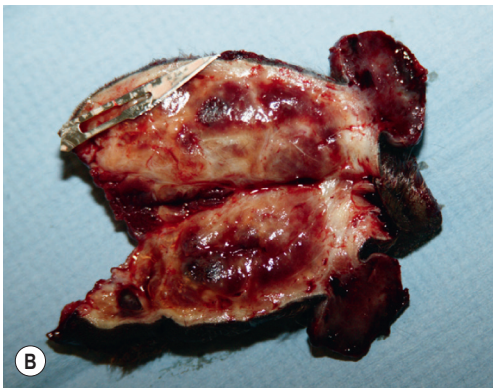


Figure 30.6 Focal cutaneous angiosarcoma. **(A)** This 21-year-old Welsh cob cross was presented with a progressively expanding focal swelling in the left axilla. The owner consulted soon after the lesion ulcerated and a 'mushroom' of friable highly haemorrhagic tissue developed. **(B)** A biopsy confirmed angiosarcoma and the tumour was removed with a wide margin, with the aid of diathermy. A safe margin was achieved and no further tumours developed for at least 8 years.



Figure 30.7 Angiosarcoma of the conjunctiva/cornea. This 18-year-old Thoroughbred cross Irish brood mare developed a rapidly progressive fleshy, haemorrhagic mass in the upper limbus of the right eye. The mass rapidly extended into the cornea over 3 weeks and had failed to respond to topical antibiotics and steroids. The eye was removed on suspicion of neoplasia and the diagnosis confirmed histologically. The horse developed clinical evidence of disseminated tumours and was euthanized without necropsy.

One case of angiosarcoma affecting the paravertebral musculature has been reported in an 18-year-old Quarter Horse gelding.[44] Clinical signs of ataxia and recumbency were noted.

The clinical features of equine ocular angiosarcoma (Fig. 30.7) include:

- Locally invasive fleshy, highly vascular and rapidly progressive mass within the limbal conjunctiva and cornea, with consequent corneal opacity
- Poorly circumscribed, firm, oedematous supraorbital swelling
- Exophthalmos/chemosis.

Differential diagnoses

Ocular angiosarcoma should be considered in the differential diagnoses of:

1. Causes of exophthalmos, such as trauma, foreign body, retrobulbar abscess and haematoma
2. Conjunctivitis
3. Orbital cellulitis
4. Other ocular neoplasms, including squamous cell carcinoma, haemangiosarcoma and lymphoma.

Diagnostic confirmation

- *Detailed ophthalmic examination*
- *Ultrasonography* may play an important role in imaging the eye and its surrounding structures, including the retrobulbar area. A case report of ocular angiosarcoma in a 25-year-old pony gelding with a proven angiosarcoma that had presented with exophthalmos revealed a hyperechogenic, homogeneous soft tissue space-occupying lesion around the eye and evidence of hyperechogenic irregular material within the vitreous. However, the caudal extent of the mass and the retrobulbar space could not be fully evaluated.[45]
- *Magnetic resonance imaging* (MRI) provides excellent soft tissue contrast, but there are few reports of MRI examination of neoplastic lesions on equine heads.[46–48] MRI provided the most definitive imaging modality in a case of locally invasive ocular angiosarcoma in a 25-year-old pony gelding, as it showed anatomical and physiological detail in both the osseous and soft tissue structures of the head.[45]
- *Biopsy and histopathology*
  - In a morphological and immunohistochemical study of malignant vascular ocular tumours, it was suggested that these neoplasms are classified as either haemangiosarcoma or lymphangiosarcoma if the cell of origin is known and as angiosarcoma if the origin is uncertain. Haemangioma and lymphangiosarcoma are often indistinguishable at light microscopy level, although blood-filled channels are more typical for haemangiosarcoma. Von Willebrand factor (factor VIII-related antigen) has been used as an immunohistochemical marker of blood vascular endothelium. Lymphatic endothelial cells probably synthesize less von Willebrand factor and therefore its expression is less consistent. This can help in the determination of the cell of origin. However, factor VIII staining alone cannot unequivocally discriminate between blood and lymphatic endothelium in normal tissue.[42]

Management

Of four cases of ocular angiosarcoma, two underwent surgical enucleation or extirpation, followed by radiation therapy, and one underwent radiation therapy alone. In the fourth case, treatment was not attempted, as the tumour had invaded the face and local lymph nodes. All cases recurred after treatment and all cases showed evidence of lymphatic metastasis.[42]

There have been no other reports of attempted treatment.

Prognosis

Based on the highly infiltrative growth pattern of angiosarcoma, prognosis is grave to hopeless.

Lymphangioma/lymphangiosarcoma

See also page 337.

Disease summary

Notes

Very rare benign but invasive tumour-like condition affecting lymphatic vessels in the limb, neck, axilla and peritoneal cavity of relatively young horses.

Clinical features

May be focal cutaneous involvement, but margins are ill-defined. Associated with extensive and persistent local oedema.

Diagnostic confirmation

Biopsy, histopathology and immunohistochemistry confirm the diagnosis.

Management

Surgical removal of early lesions might be effective, but early diagnosis is not often made.

Prognosis

Prognosis is very guarded unless the lesions are small and accessible.

Description

Lymphangioma consists of proliferating lymphatic vessels within a fibrovascular stroma. It can occur very rarely in both man and domesticated animals. Very early reports in horses involve the pleural cavity and small and large intestines. There is controversy over whether lymphangiomas are true neoplasms or hamartomas, i.e. a tumour-like proliferative disease originating from altered fetal development of the lymphatic system.

Lymphangioma occurs predominantly in the neck, axilla, retroperitoneal tissue, thighs and inguinal regions. It is assumed that alterations of these tissues during early fetal life cause disorders of normal remodelling and development of the lymphatic system, which does not communicate normally with the lymphatic system and proliferates in a tumour-like fashion.[49] There have been four cases reported in the literature in the past 30 years.[49–52]

Lymphangiosarcoma is a rare potentially malignant (metastasizing) tumour originating from endothelial cells of lymphatic vessels. The aetiology remains uncertain because it is not possible to determine whether chronic oedema is the result or the cause of the tumour. In general, these clinical signs indicate that the condition is grave.

There have been three cases reported in the horse to date.[53–55]

Clinical features

- Nodular masses in the inguinal and medial thigh or axillary regions associated with local and regional oedema (Fig. 30.8)[50,52]
- Chronic long-standing slowly progressive fluid-filled hygromatous 'sac'-like masses on the skin, particularly of the neck[51]
- The malignant form of lymphangiosarcoma may have additional signs including respiratory distress and anorexia. Bilateral pleural effusion and palpable masses per rectum.[53,54]

A 15-year-old Haflinger gelding was presented with a 4-week history of swelling of the left nictitating membrane. A biopsy was taken and the horse underwent surgical extirpation of the nictitating membrane. Postoperatively, the gelding developed progressive periocular swelling and serosanguineous nasal discharge for 5 months. A second biopsy was taken and the horse was euthanized, but further histology was not available. Histological examination of both biopsies and the extirpated nictitating membrane confirmed a lymphangiosarcoma.[55]





Figure 30.8 Lymphangioma. (A,B) This 4-year-old gelding developed a solely expanding thickening of the skin of the tibia with associated oedema. A biopsy of the abnormal skin provided a diagnosis of lymphangioma. *(Figures courtesy of Siobhan McAuliffe.)*

Differential diagnoses

1. Haemangioma
2. Lymphangiosarcoma
3. Haemangiosarcoma
4. Lymphangitis/cellulitis complex
5. Conditions associated with pleural effusion, such as pleuropneumonia and other thoracic neoplasia
6. Conditions associated with ventral oedema, such as vasculitis, congestive heart failure and protein-losing enteropathy/nephropathy and other causes of lymphatic obstruction.

Diagnostic confirmation

- *Ultrasonographic examination* may identify the full extent of the lesion and can be used to guide fine-needle aspiration of fluid or needle/punch biopsy.
- *Biopsy and histopathology*
  - Definitive diagnosis is only possible by histopathological examination. Small lymphatic vessels closely resemble capillaries and venules and are often only tentatively identified by the nature of their contents. However, the ultrastructure shows that the lymphatics are not surrounded by a continuous basement membrane or pericytes.
  - Discrimination between lymphangiosarcoma and haemangiosarcoma can be difficult, as both tumours arise from endothelial cells and develop channels or vessels.
  - Immunohistochemistry, using markers such as laminin, may confirm an absence of the basement membrane.[49]
  - Differentiation between lymphangioma and lymphangiosarcoma is critical, as they only differ in their cellular pleomorphism.[55]

Management

There has only been one successful report of treatment of lymphangioma.[51] Theoretically, if a mass was identified early enough, surgical excision would probably be curative. Therapeutic options are predominantly dictated by their location and clinical extent.[49]

Prognosis

There have been no successful reports of treatment of lymphangiosarcoma in the horse. Cases are frequently present at a late or terminal stage of disease, making treatment hopeless and prognosis grave.

Cardiac neoplasia

Description

Primary cardiac neoplasia is extremely rare, with only three cases reported in the literature.[56] Most cases of cardiac neoplasia of any sort are secondary neoplasms derived from another site,[57–59] but these are also extremely rare.

Lymphoma (B cell) is possibly the commonest of the cardiac tumours (Fig. 30.9). A primary T-cell-rich B-cell lymphoma was found in a 10-year-old Cob gelding presented with lethargy, weight loss and anorexia.[59] Cardiac assessment confirmed a sinus tachycardia and a grade 4/6 pansystolic decrescendo murmur and a grade 2/6 holodiastolic murmur. Echocardiography revealed an irregular mass surrounding the aorta and extending from the intraventricular septum, and the coronary artery was markedly enlarged. There was moderate aortic and mitral valve regurgitation. No abnormalities were identified on ultrasonography of the thorax or abdomen. Gross post-mortem findings included a poorly-circumscribed lesion surrounding the base of the aorta, hard mineralized plaques in the endothelium of the left ventricular outflow tract and right and left coronary arteries and a pale mass within the left ventricular wall. No other lesions were present.[59]

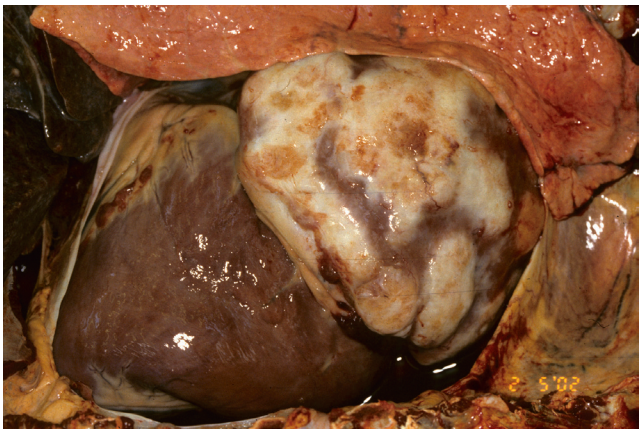


Figure 30.9 Primary cardiac lymphoma. This 16-year-old mare was presented with a history of lethargy, exercise intolerance and tachycardia. Multiple dense masses were identified on ultrasonography, and at necropsy extensive lymphoma masses were found in the walls of the left and right atria. Myriad tumours were identified in the liver – these were assumed to be metastatic.

A lipoma infiltrating into the myocardium apparently arose from the adipose tissue of the coronary groove, but associated clinical signs were not described.[56]

A malignant peripheral nerve sheath tumour in the proximal aorta and right atrium was found at necropsy in a horse presented with a 2-week history of weight loss, lethargy and weakness with tachycardia, pale mucous membranes, bounding peripheral pulses and a holosystolic grade 3/6 heart murmur.[58]

Cardiac disease arising as a result of secondary neoplasia is rare in horses. Only a few cases of neoplastic metastasis in the equine heart have been described; these include lymphosarcoma, melanoma, myxoma, granular cell myoblastoma, squamous cell carcinoma, testicular embryonal carcinoma, pulmonary carcinoma, rhabdomyosarcoma, mesothelioma and haemangiosarcoma.[27,60–62]

Cardiac failure in a 4-year-old Quarter Horse stallion secondary to tumour invasion, with a 5-week history of depression, dyspnoea, weight loss, weakness and intermittent fever, was found to be due to a large mass on the epicardial surface of the right atrium infiltrating both the atrial myocardium and the wall of pulmonary vein and a large botryoid mass attached to the endocardium within the left atrium. Tumour masses were also present throughout the pulmonary parenchyma and mediastinum, kidneys and several muscle groups. A diagnosis of

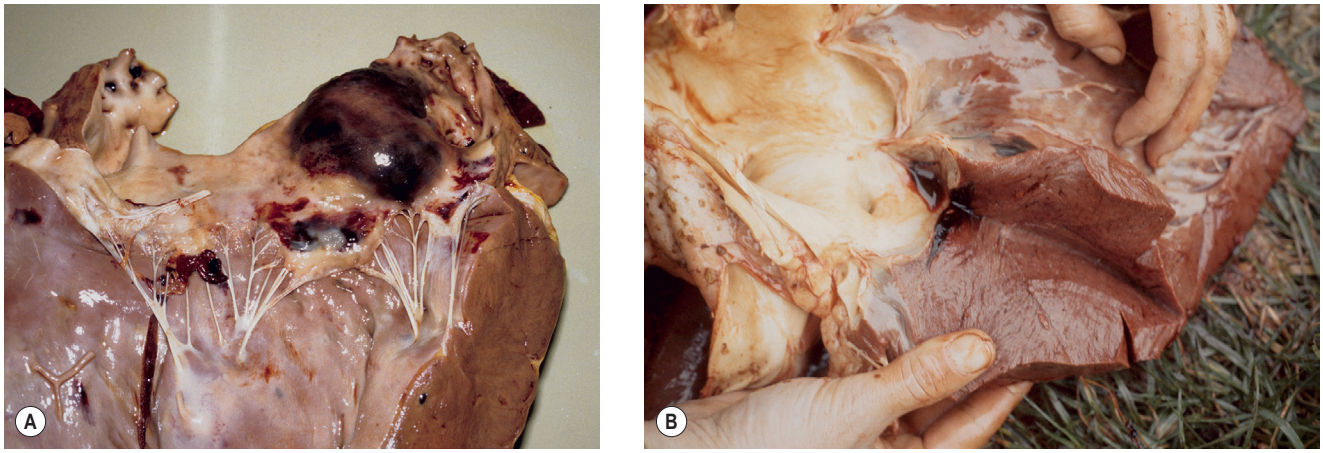


Figure 30.10 Melanoma. Disseminated melanoma is one of the commoner tumours identified in the heart. Most cases are asymptomatic but in some circumstances there can be dramatic effects. **(A)** A 16-year-old grey gelding with multiple cutaneous and parotid melanomas was presented with a severe heart systolic murmur. A mass was identified in the mitral valve and necropsy confirmed this mass to be a melanoma. **(B)** A 4-year-old grey Thoroughbred colt was found in extremis with a 3rd degree heart block. At necropsy, a discreet melanoma was found in the cardiac annulus and this was thought to have been responsible for the severe and fatal dysrhythmia. *(Figures courtesy of Dr RR Pascoe.)*

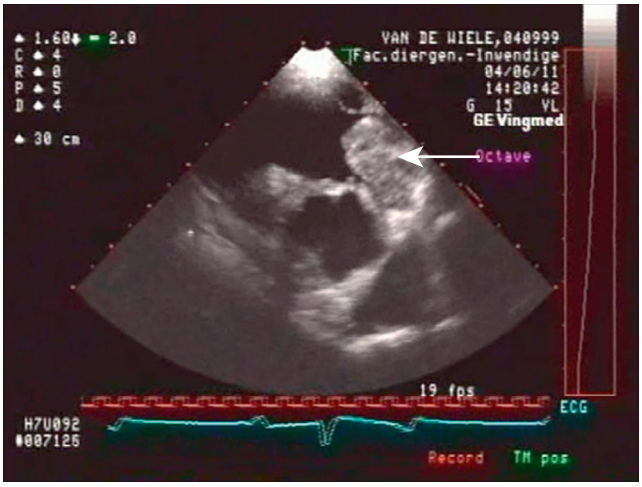


Figure 30.11 Myxoma. A 21-year-old mare was presented with bilateral jugular engorgement and ventral oedema. Cardiac ultrasonography revealed a discreet mass in the right atrium (arrow), which was thought to be a myxoma. No autopsy/biopsy results were available to confirm this however. *(Figure courtesy of Gunther van Loon.)*

anaplastic pulmonary carcinoma with metastasis to the heart was confirmed.[62]

Ventricular arrhythmia secondary to disseminated haemangiosarcoma was reported in a 15-year-old Belgian cross breed mare with a short history of increasing lethargy, pallor, pronounced tachycardia and arrhythmia.[27] Necropsy revealed haemangiosarcoma infiltrating the apical right ventricular myocardium and the myocardium of the apex of the left ventricular free wall. In a case series of disseminated haemangiosarcoma, 34% of cases had tumours located within the heart.[18]

Metastatic melanomas (Fig. 30.10) have been reported in many sites, including the heart, with various degrees of clinical implication; usually, however, they are found incidentally.[60] Echocardiography is therefore warranted in the detailed assessment of metastatic melanoma (Fig. 30.11).

Pericardial tumours are also only occasionally reported and they rarely involve the myocardium.[18,63] Mesothelioma has been reported to cause adhesive pericarditis and a pericardial haemangiosarcoma caused fatal thoracic haemorrhage.[22,64]

Neoplasia of the haematopoietic system

Description

Lymphoma, also referred to as lymphosarcoma, is the most common haematopoietic neoplasm in horses; it arises from lymphoid tissue (lymph nodes, spleen and gut-associated lymphoid tissue).[65] Lymphoma is usually classified in terms of the cell of origin as either B-cell or T-cell lymphoma. The large majority of the equine tumours are B-cell lymphomas. Very rarely NK-cell origin tumours are found. Most lymphoid tumours resemble some recognizable stage of B-cell or T-cell differentiation (precursor or peripheral cell) and these features are used in some classifications.

Leukaemia is the term given to a neoplasm arising from cells of the bone marrow, which results in neoplastic cells in the circulation. Each cell type present in the bone marrow has its own potential form of leukaemia. The term *lymphoma* has historically been used to describe the solid tumour in discrete tissue masses, but there are progressions and some cases will become leukaemic as they near the incurable stages. The differentiation is possibly therefore blurred. The terms *lymphoma* and *leukaemia* are simply used now to provide a description of the usual tissue distribution of each disease at presentation.

Equine lymphoma has been classified into several types, including:

1. Multicentric lymphoma
2. Alimentary lymphoma (focal or diffuse)
3. Mediastinal/thoracic/thymic lymphoma
4. Cutaneous lymphoma
5. Solitary or extra-nodal lymphoma, including hepatosplenic, ocular, nasopharyngeal and neurological.

Clinical features

Lymphoma can occur at any age in horses, but most cases occur within the 4–10-year range. There is no breed or sex predisposition.

Clinical signs of all forms develop insidiously and are typically nonspecific until progression of disease to end stage, when the signs may relate to the primary organ site affected.

Diagnostic confirmation

Clinical pathology is often not helpful with diagnosis, but nonspecific changes identified frequently include anaemia, hyperproteinaemia, hypoalbuminaemia and hyperfibrinogenaemia, with no evidence of infection.

A definitive diagnosis can sometimes be made through identification of neoplastic lymphocytes derived from body cavity effusion. Histopathological examination of biopsies of lymph nodes or a suspected lesion is confirmatory. Other diagnostic tests that can be useful include immunophenotyping and immunohistochemical analysis; these will often identify the specific tumour type involved.

Management

Treatment options currently available include surgical resection of solitary lesions, radiation therapy or systemic chemotherapy. Treatment is frequently palliative, however, although there are some published cases describing total resolution, particularly of 'cutaneous' T-cell-rich B-cell lymphoma.

Prognosis

The prognosis is always guarded and depends on the type and stage of disease at presentation.[66]

Multicentric lymphoma

See also page 342.

Disease summary

Notes

Multicentric lymphoma is the most common haematopoietic neoplasm but is still a rare clinical finding; most frequently found in young mature horses (4–12 years of age). Metastasis is common into many organs, including the spleen, kidney and liver.

Clinical features

Weight loss, depression, lethargy, ventral and limb oedema, recurrent fever and various degrees of lymphadenopathy.

Diagnostic confirmation

Identification of neoplastic lymphocytes during cytological examination of body cavity effusion or histopathological examination of biopsy of lymph node or a suspected lesion.

Management

Surgical excision of solitary lesions, radiation or systemic chemotherapy. Usually only useful in palliation, but occasionally can result in resolution of disease.

Prognosis

Prognosis depends on the stage of the disease and its specific type. Treatment is usually palliative only but may prolong useful life.

Description

Multicentric lymphoma is the most common form of equine lymphoma. It is characterized by widespread involvement of peripheral and internal lymph nodes, most likely through distribution of neoplastic lymphocytes via the lymphatic circulation. A variety of organs may be affected, most commonly liver, spleen, intestine, kidney and bone marrow (leukaemic lymphoma). Other organs reported to be involved include nasal and paranasal sinuses, central nervous system, heart, adrenal glands, reproductive organs and eye.[66]

Clinical features

See Figure 30.12.

Since the signs are insidious in onset for the most part, cases are usually presented late in the course when the signs are advanced. The disease may even be diagnosed by surprise during investigation of apparently minor clinical complaints, such as mild lethargy and subtle weight loss.

Clinical signs of multicentric lymphoma typically reflect the organs involved and include:

- Weight loss
- Abdominal distension/ventral body wall and limb oedema (often affecting the left frontlimb first)
- Elevated heart and respiratory rates and fever
- Widespread lymphadenoma
- Colic, recurrent or chronic
- Diarrhoea
- Respiratory abnormalities, including coughing and nasal discharges
- Polyuria/polydipsia/[micro-]haematuria
- Icterus.

Where there is central nervous system involvement, signs may include:

- Ataxia
- Urinary or faecal incontinence
- Cranial nerve deficits
- Seizures.

Ocular manifestations of multicentric lymphoma are frequently present and reported to occur in 27% of 79 cases.[67] Signs reported include:

- Eyelid swelling, frequently bilateral or shifting from one side to another[68]
- Chronic ocular discharge
- Oedematous third eyelid
- Unilateral exophthalmos
- Corneoscleral masses
- Chronic uveitis (frequently unresponsive to topical treatments).[69]

A range of paraneoplastic signs can be encountered, including intermittent/recurrent fever, anaemia, cachexia, pseudohyperparathyroidism with pruritus and alopecia and erythrocytosis.[70–72]

Diagnostic confirmation

See Fig. 30.13; see also Fig. 7.7.

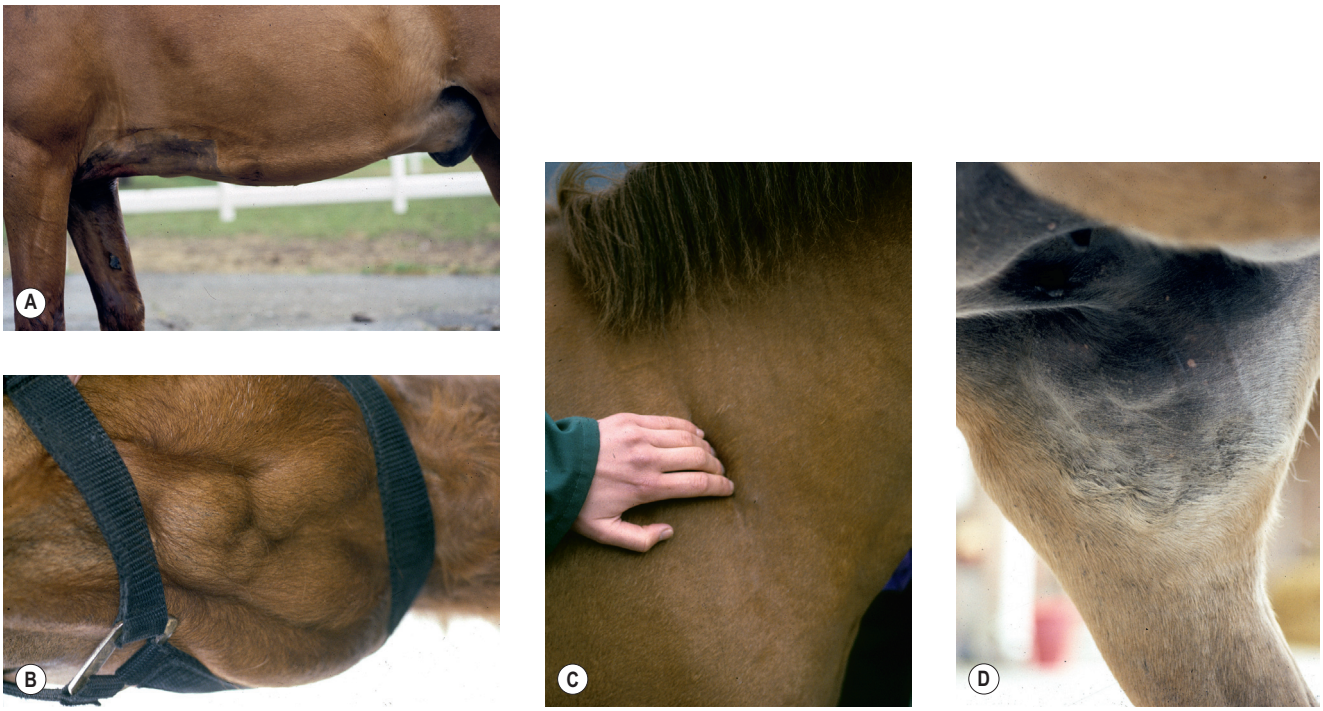


Figure 30.12 Multicentric lymphoma. **(A)** A 7-year-old Welsh pony gelding was presented with 5-week history of reduced exercise tolerance, inappetence and recurrent fever of unknown origin. He was reported to have lost a small amount of weight but was otherwise seemingly normal. He developed a prominent ventral oedema **(A)** and a clinical examination revealed lymphadenopathy of the submandibular **(B)** and prescapular **(C)** lymph nodes and extensive multilobular swelling in the inguinal and medial thigh regions of both hind legs **(D)**. Endoscopic examination showed extensive pharyngeal lymphoid proliferation and the pharyngeal lymph nodes within the guttural pouches were grossly enlarged. A diagnosis of multicentric lymphoma was made based on clinical and haematological findings and confirmed at necropsy. The owner declined any attempt to treat the horse. Mucous membranes of affected horses are often pale, due to anaemia, and have obvious petechiation.

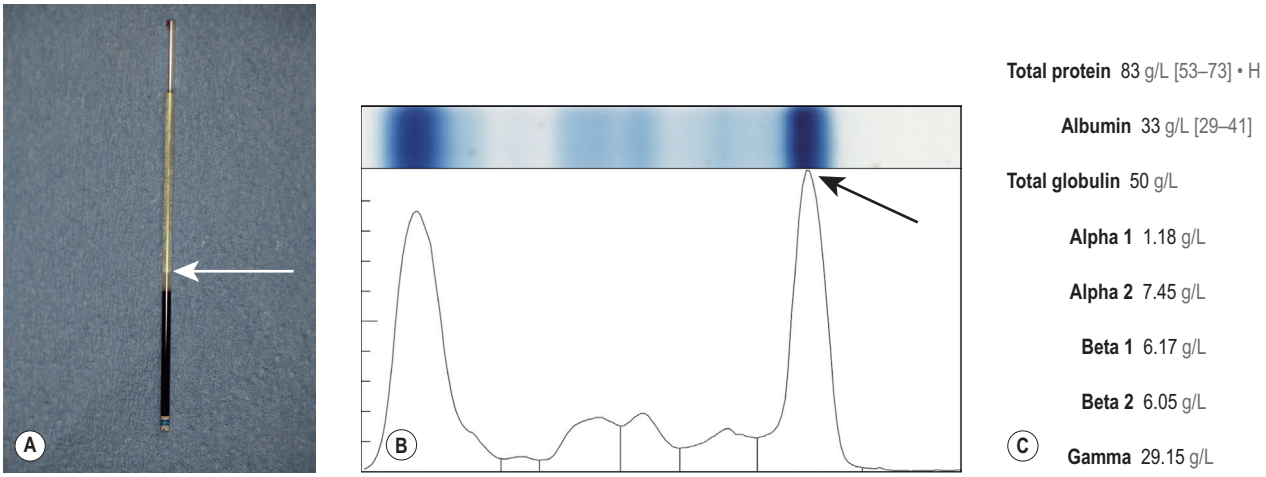


Figure 30.13 Leukaemic lymphoma/leukaemia. Leukaemia is rare in horses but is usually associated with massive circulating lymphocyte counts. **(A)** This can be rapidly identified from a microhaematocrit sample when a wide buffy coat later will be obvious. In this case, the total blood lymphocyte count was 172×10^9/L. The horse was marginally anaemic (PCV 27%) and had a slightly elevated absolute neutrophil count as well (9.3×10^9/L). The absolute levels are critical of course – percentage calculations would have indicated that the horse was neutropenic. A blood smear (see Fig. 7.7) showed vast numbers of abnormal lymphocytic cells with large nuclei and prominent nucleoli (see Fig. 7.7, p. 92). Flow cytometry and immunohistochemistry confirmed this to be a case of acute lymphocytic B-cell leukemia. **(B,C)** Plasma electrophoresis shows a prominent monoclonal spike in the gamma globulin region (arrow) and protein analysis confirms this as a significant but not massive monoclonal rise in gamma globulin. This is a feature of lymphoma. *(Figure B courtesy of Alistair Foote, Beaufort Cottage Laboratories.)*

- Multicentric lymphoma can usually be strongly suspected from the clinical features alone, but histological examination with immunohistochemical stains and/or flow cytometry are required for diagnosis.
- Complete blood count and serum biochemistry may reveal anaemia (red cell destruction/immune-mediated intravascular haemolysis) as a direct result of premature destruction of antibody-coated erythrocytes, inadequate production of erythrocytes due to

myelophthisis, chronic inflammation or blood loss. Leukocytosis, generally neutrophilia, as a result of tumour necrosis, may be present.
- When affected horses are leukaemic, atypical or abnormal immature lymphocytes are seen during cytological examination of the peripheral blood smear.
- Nonspecific biochemical abnormalities, including hypoalbuminaemia, hyperglobulinaemia (possibly with monoclonal gammopathy) and hyperfibrinogenaemia, are commonly reported.
- Ultrasonographic examination of the thorax and abdomen may aid in locating a mass and the extent of organ and/or localized lymph node involvement (see p. 93).
- Cytological examination of fluid collected from body cavities can reveal significant cell types but in general abdominal cytology is less productive than pleural cytology.
- Aspiration or biopsy of affected lymph nodes or masses identified by ultrasonography, endoscopy or at surgery is extremely useful and often diagnostic.
  - The morphology of neoplastic lymphocytes in horses is highly variable and normal reactive cells may be difficult to distinguish from well-differentiated neoplastic cells
  - Histological examination of a large (1–2 cm diameter) biopsy of the lymph node is recommended for ante-mortem diagnosis of all forms of lymphoma to permit examination of the architecture of the node for signs of neoplastic infiltration and effacement of normal structural relationships.
- Immunophenotyping by immunohistochemistry and flow cytometry allows categorization of lymphoma into B- or T-cell origin. Monoclonal antibodies (to CD5, CD8 in the case of T-cell lymphoma and CD10, 19, 20 in the case of B-cell lymphoma). Multicentric lymphomas are predominantly T-cell origin (see p. 112).

Management

The therapeutic approach to equine lymphoma includes assessment of the patient's physiological status, the extent and location of disease and the owner's personal and financial commitment to treatment.[66]

Staging the disease may aid in determining what treatment options, if any, are available. WHO developed a clinical staging system for lymphoma in domestic animals based on anatomical site and extent of organ involvement and clinical signs and clinicians should strive to use this, to aid and guide therapeutic interventions and as a guide to the prognosis (Table 30.1). Treatment is inevitably a difficult process that demands compliance from patient and owner alike, so it is not to be embarked upon lightly.

Since most cases of multicentric lymphoma are presented at or near end-stage disease, it is important to advise owners that treatment may not be warranted or will be palliative, rather than curative. A 'cure' should probably not be suggested in any real circumstance, since the disease is very difficult and there is little evidence-based information available.

Table 30.1 World Health Organization clinical staging system for lymphoma in domestic animals

Stage	Description
1	Limited to single node or lymphoid tissue within single organ
1a	Without systemic signs
1b	With systemic signs
2	Involvement of several lymph nodes within a regional area
2a	Without systemic signs
2b	With systemic signs
3	Generalized lymph node involvement
3a	Without systemic signs
3b	With systemic signs
4	Liver or spleen involvement with or without Stage 3 disease
4a	Without systemic signs
4b	With systemic signs
5	Manifestation in the blood and involvement of bone marrow and/or other organ systems with or without Stage 4 disease
5a	Without systemic signs
5b	With systemic signs

Surgery

In multicentric lymphoma, surgical resection of lymphomatous masses is unlikely to be beneficial. In cases of solitary lymphoma with no spread (such as isolated tumours in the conjunctiva or the skin or the gut), local surgical resection or radiotherapy can be curative.[73,74]

Systemic chemotherapy

- Systemic chemotherapy has been reported infrequently in adult horses and there are only limited reports of systemic chemotherapy for treatment of equine lymphoma.[66,75–79] The goals of chemotherapy are to maximize tumour cell destruction, while minimizing patient toxicity and avoidance of any drug exposure to healthcare personnel (see p. 163).
- Multiple drug protocols are usually advocated for treatment of lymphoma to minimize toxicity and the possibility of acquired drug resistance of tumour cells. The drugs that have been suggested/used include those shown in Table 30.2; they all have limitations and recognized side-effects. Most protocols used have included combinations of vincristine, cyclophosphamide, cytarabine (cytosine arabinoside), chlorambucil, doxorubicin, dactinomycin and prednisolone
  - Dosages are generally extrapolated from small animal and human studies and are calculated using the following formula: body surface area (m^2) = weight ($g^{2/3}$)×10.5/10^4 (see p. 134).[76]
- Corticosteroids alone, such as oral or parenteral dexamethasone or oral prednisolone, may be an economical option for palliation. There are anecdotal

Table 30.2 Systemic chemotherapeutic drugs used in treatment of lymphoma (see p. 129)

Agent type	Drug	Mechanism of action	Toxicity	Dose rate	Route	Frequency
Alkylating agent	Cyclophosphamide	Inhibits DNA, RNA and protein synthesis	Bone marrow suppression, bladder irritation (in canine)	200 mg/m^2	i.v.	Every 1–2 weeks
	Chlorambucil		Bone marrow suppression	20 mg/m^2	p.o.	Every 2 weeks
Antimetabolites	Cytarabine (cytosine arabinoside)	Kills cell in S-phase and blocks progression from G1 to S-phase of DNA synthesis	Thrombocytopaenia, neutropenia	200–300 mg/m^2	s.q., i.m., i.v.	Every 1–2 weeks
Antibiotics	Doxorubicin	Inhibition of protein synthesis, free radical formation	Bone marrow suppression, hypersensitivity reaction, cardiotoxic, nephrotoxic, pulmonary fibrosis	70 mg/m^2	i.v.	Every 3 weeks
Antitubulin	Vincristine	Inhibition of intracellular microtubules disrupting cell cycle	Perivascular tissue reaction, hepatotoxic	0.5 mg/m^2	i.v.	Weekly
Hormone	Prednisolone	Inhibits DNA synthesis	Laminitis	1 mg/kg	p.o.	q. 24h / q. 48h
Miscellaneous	L-asparaginase	Deprives cells of amino acid, inhibiting protein synthesis	Hypersensitivity reaction	10000–40000 IU/m^2	i.m.	Every 2–3 weeks

reports of palliation for months to years on lifelong therapy.
  - Corticosteroids may help reduce lymphoma masses and temporarily control some clinical signs for up to 18 months[80–83]
  - They may reduce peri-tumoral inflammation and oedema and therefore the severity of clinical signs
  - They are known to or suspected to induce apoptosis of lymphoid cells
  - Corticosteroids may usefully control certain paraneoplastic syndromes associated with lymphoma, including immune-mediated haemolytic anaemia and thrombocytopaenia and hypercalcaemia.
- Selection of chemotherapeutic drugs for use in a multi-drug protocol is based on the ability to administer the drugs at the maximum recommended dose without inducing severe toxicity; drugs that avoid overlapping toxicities and those that have a known effect against the neoplasm being treated are preferred (Box 30.1)[76,84]
  - After instituting chemotherapy, remission of equine lymphoma can be detected within 2–4 weeks and treatment is continued for an additional 2–3 months[76]
  - If remission is still evident at this time and side-effects are minimal, chemotherapy can be continued at a maintenance protocol, lengthening the intervals between doses. Intervals between treatments may be increased by 1 week for 2–3 months, then increased by an additional week. Prednisolone should still be administered daily or every alternate day.

Box 30.1 A suitable base CAP protocol for use in horses[76]

See also page 129.
- Cyclophosphamide 200 mg/m^2 (1 g/450 kg horse) i.v. every 2 weeks, alternating with below
  - cytarabine 1.0–1.5 g/treatment i.m./s.q. once every 1–2 weeks, alternating with above
- Prednisolone 1 mg/kg p.o. daily
- If no response, add vincristine (2.5 mg i.v.) on the weeks when cytarabine is administered

- Approximately 50% of multicentric lymphoma patients can be brought into remission for several months to a year using this protocol. Recurrence is likely once therapy is discontinued.[76]
- Side-effects of chemotherapy are not often encountered, but may include bone marrow suppression, gastrointestinal disturbances, alopecia and laminitis[76,84]
  - If significant abnormalities are observed during physical examination (evidence of sepsis, fever, identified focus of infection) or through haematology, it may be necessary to delay chemotherapy until those parameters return to acceptable levels, indicating resolution of the problem
  - Bone marrow suppression most commonly manifests as neutropenia within 7–10 days of dosing and fortunately is extremely uncommon in horses[76]
  - Full blood counts should be tested routinely before every treatment and weekly afterwards

- Horses may be relatively resistant to the myelosuppressive effects of more commonly used cytotoxic drugs. However, toxic profiles of all chemotherapeutic drugs are not yet established for the horse.

- Options for chemotherapy other than multi-drug protocols also include the administration of a single chemotherapeutic agent
  - Doxorubicin has been administered intravenously at a dose of 30–60 mg/m^2 every 2–3 weeks; it has been advised that this drug should be used with caution because myocardial damage and pulmonary fibrosis are potential side-effects , but the horse may be less sensitive to these effects than was previously thought[76,79,85]
  - A Phase I dose escalation and Phase II efficacy and biosafety study of doxorubicin chemotherapy in tumour-bearing horses has been published[79,85]
    - The maximum tolerated dose (MTD) was 75 mg/m^2
    - Recommended treatment dose of doxorubicin was 70 mg/m^2 given intravenously at 3-weekly intervals as a single agent
    - Adjuvant treatment with antihistamines and non-steroidal anti-inflammatory drugs is recommended to control hypersensitivity
    - No evidence of cardiotoxicity or pulmonary fibrosis was detected
    - Overall response rate was 47%; lymphoma and carcinoma were most responsive
    - In respect of the risk of exposure to drug residues, no detectable residues of doxorubicin were found in faecal samples at any time and in plasma and urine, after 2 and 3 days, respectively, Direct contact with urine-contaminated waste should therefore be avoided for 2 days after treatment.[79,85]

Prognosis

Treatment response and outcomes for equine multicentric lymphoma are currently unknown since the majority of horses are not diagnosed as having disease until end stage. There are very few reports of successful treatment, but many anecdotal reports of short-term palliation. The first Phase I and II dose safety and efficacy trials in horses for doxorubicin is encouraging and further studies of the safety and efficacy of individual cytotoxic drugs in horses is needed. Earlier diagnosis through improved imaging and better understanding of classification of lymphoma will guide appropriate therapeutic intervention.

Alimentary lymphoma

See page 346.

Description

Alimentary lymphoma is the most common equine intestinal neoplasm and the second most common form of lymphoma. Approximately 19% of all horses with lymphoma have the alimentary form.[66,86,87] Primary alimentary lymphoma arises from mucosal lymphoid tissue.

Disease summary

Notes

Rare tumour type but most common primary intestinal neoplasm; derives from the mucosal lymphoid tissue. Most frequently in older horses (>12 years of age). Metastasis is uncommon but may extend to abdominal cavity and major organs.

Clinical features

Commonest syndrome is diffuse forms associated with malabsorption, weight loss and recurrent fever but focal forms can cause non-strangulating obstruction.

Diagnostic confirmation

Identification of neoplastic lymphocytes during cytological examination of body cavity effusion or histopathological examination of biopsy of lymph node or a suspected lesion.

Management

Surgical excision of solitary lesions, radiation or systemic chemotherapy.

Prognosis

Prognosis depends on the stage of the disease and its specific type. Treatment is usually palliative only but may prolong useful life.

It typically occurs in older horses, with the most recent mean age reported as 16 years.[86]

Two forms are recognized. The commonest form is the diffuse form, which is associated with malabsorption syndromes in the small intestine or large and small colon – this type tends to affect the younger group of affected horses. The focal form occurs more often in the older age horses and involves small intestine or the caecocolic region; this form causes non-strangulating partial or complete intestinal luminal obstruction.

The small intestine is more commonly affected than the large intestine. However, multiple segments of intestine may be affected and lead to involvement of other organs and/or lymph nodes. This often makes it difficult to distinguish between alimentary and multicentric lymphoma.[86] Almost 75% of cases affect the small intestine, 50% affect the large intestine and 3% involve the small colon. About half of the cases have multiple areas of gastrointestinal tract affected.[86] Alimentary lymphoma is likely to affect multiple segments in young horses (<10 years), while focal lesions are more likely to occur in older horses.[86]

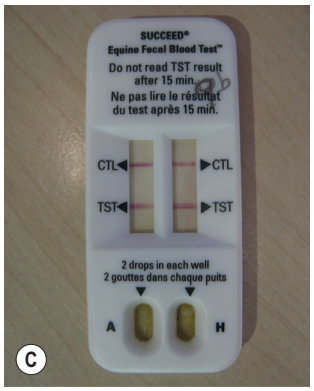
All forms may metastasize and particularly extend to regional lymph nodes (mesenteric and colonic), but this is less common than with other forms. Exfoliation into the peritoneal cavity is unusual but does occur. Metastases are common by the time a definitive diagnosis is made and few studies have reported an absence of metastases. In one study, 65% had evidence of metastasis to a regional lymph node and 76% had evidence of metastasis to other organs.[86]

Clinical features

Clinical signs most commonly associated with alimentary lymphoma include:

- Weight loss (Fig. 30.14A)
  - Most likely due to malabsorption of nutrients secondary to infiltration of the small intestinal







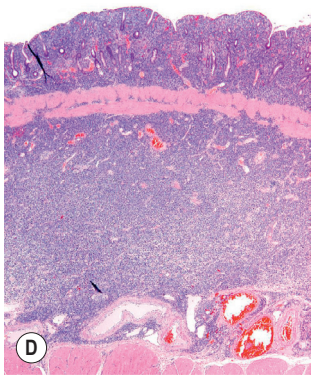


Figure 30.14 Intestinal lymphoma. **(A)** This 16-year-old pony mare was presented with a 4-week history of progressive weight loss and deteriorating diarrhoea **(B)**. **(C)** A fecal occult blood test SUCCEED FBT™, Freedom Health Uth, USA) was strongly positive for both albumin (left) and haemoglobin (right). A rectal examination identified diffusely thickened large colon with discreet nodules. Peritoneal fluid was unremarkable but haematology revealed a profound hypoalbuminemia and a regenerative anaemia. A rectal biopsy suggested that a lymphocytic infiltrative condition was present. **(D)** A hand-assisted laparoscopic large colon biopsy confirmed the presence of a severe aggressive highly anaplastic lymphoma that was affecting the wall of the colon. Treatment was not attempted. Reaching a definitive diagnosis is a fundamental requirement for most owners but it may take considerable effort.

mucosa with neoplastic cells and villous tip blunting,[88–91]

- Lethargy/pyrexia of unknown origin,
- Anorexia – this may also contribute to weight loss,
- Anaemia/melena,
- Hypoproteinaemia (combination of malabsorption/consumption and leakage into the lumen) may result in ventral and dependent oedema
  - Colic as result of partial bowel lumen obstruction by neoplastic tissue.[92] A retrospective study of recurrent colic showed that 20% of horses with recurrent, transient colic over a 1-month period were diagnosed with lymphoma; furthermore, 13% of those with recurrent prolonged colic (at least three prolonged episodes in 1 year) were diagnosed with lymphoma.[93]
- Chronic, profuse diarrhoea (Fig. 30.14B)
  - This is usually attributed to loss of fluid resorption when large and small colon are involved[94]
  - Faecal odour can be unusual due to malabsorption and maldigestion.
- Pyrexia
  - Inflammation secondary to neoplasia and release of cytokines from neoplastic cells.
- Ventral oedema
  - Secondary to lymphatic outflow obstruction associated with an intra-abdominal mass and hypoalbuminaemia.
- Bowel distension or palpable wall thickening on rectal examination
  - Most cases with a palpable intra-abdominal mass (including enlarged mesenteric lymph nodes) were diagnosed with lymphoma.[86]

Paraneoplastic signs are reported frequently and include:

- Hypereosinophilic syndrome
  - Neoplasia-associated eosinophilia is rare, but well-documented in humans in association with carcinomas, lymphoma and pancreatic islet cell tumours. Hypereosinophilia may be indicative that metastasis has occurred and may, therefore, infer a poor prognosis.[95,96]

Diagnostic confirmation

Differentiating between intestinal neoplasia and inflammatory bowel diseases, non-intestinal intra-abdominal neoplasia and internal abscessation can be a challenge, but since therapeutic management and prognosis vary considerably between these diseases, reaching an ante-mortem diagnosis is important. However, frequently, a definitive diagnosis is only reached postmortem.

- Palpation of peripheral lymph nodes and palpation of accessible abdominal organs by rectal examination.
- Complete blood count and serum biochemistry
  - Anaemia arises as a combined result of premature destruction of antibody-coated erythrocytes, inadequate production of erythrocytes due to myelophthisis, chronic inflammation or blood loss through intestinal ulceration

  - Faecal occult blood and albumin are frequently detected – this is indicative of intestinal protein and blood loss (Fig. 30.14C)
  - Leukocytosis with neutrophilia is a result of tumour necrosis
  - Hypoalbuminaemia, hyperglobulinaemia and hyperfibrinogenaemia
    - Hypoalbuminaemia is most likely associated with protein-losing enteropathy, or if there is metastasis to the liver, may be a result of decreased production by the liver
  - Although hypercalcaemia of malignancy may be observed, horses with intestinal lymphoma are frequently hypocalcaemic because they are hypoalbuminaemic[97]
  - Elevated liver enzymes may be an indicator of metastasis in horses, with concurrent clinical signs consistent with gastrointestinal disease.
- *Carbohydrate absorption tests* (oral glucose absorption test and D-xylose absorption test) have been used to assess small intestinal function, due to the limited accessibility of the small intestine for specific diagnostic tests.[98] Usually in cases of diffuse lymphoma, the absorption curve is abnormally flat, but this test is restricted to small intestinal disease. Furthermore, these tests are not specific for lymphoma.[99]
- Ultrasonography of abdomen
  - Transabdominal ultrasound findings have been shown to correlate closely with post-mortem and surgical biopsy findings. In one study, 82% of horses that underwent a complete ultrasound examination correctly identified the affected organs (Taylor et al. 2006). Only 40% of primary lesions were identified in horses undergoing partial abdominal ultrasound, confirming the importance of evaluating the entire abdomen. Small intestinal thickening is a common finding in lymphoma cases (Fig. 30.15A) Enlarged caecal mesenteric lymph nodes are often identified in horses with lymphoma (Fig. 30.15B).
- *Aspiration or biopsy* of affected lymph nodes or masses identified by ultrasonography, endoscopy or at surgery (Fig. 30.15D):
  - Duodenoscopy using a 3 m endoscope may enable duodenal biopsies to be obtained, although most biopsy specimens are too superficial and not diagnostic. Duodenoscopy permits examination of the proximal duodenal mucosa, bile duct papillae and facilitates duodenal mucosal biopsy.
  - Rectal biopsy is an easy and economic diagnostic procedure. In 50% of horses with weight loss ± diarrhoea, pathology is detectable. Although rectal biopsy has a low sensitivity (30%), it should always be performed, since it may provide a diagnosis. In one study, 100% of cases showed abnormalities; 50% of samples showed mild inflammation (proctitis) and 50% lymphoma. Interestingly, 66% of those with mild proctitis were subsequently found to have lymphoma.[86,100]
  - Exploratory coeliotomy or laparoscopy provides a good opportunity to sample abnormal intestinal tissue so that a diagnosis can be established definitively. Laparotomy is preferred to laparoscopy because a thorough examination and harvest of multiple full-thickness biopsies from all intestinal segments and associated lymph nodes can be achieved.
- Cytological examination of fluid collected from body cavities
  - Peritoneocentesis may be helpful in confirming a diagnosis if the neoplasm is exfoliative. Peritoneal fluid analysis has been reported to contribute to ante-mortem diagnosis of intestinal neoplasia in 21% of cases. In cases of intestinal lymphoma, 38–50% of cases have been reported to show abnormal lymphocytes in peritoneal fluid.[86,101] A negative finding does not of course preclude a diagnosis of lymphoma.
- *Immunophenotyping* by immunohistochemistry and flow cytometry allows categorization of lymphoma into tumours of B- or T-cell origin. Alimentary lymphomas are generally of T-cell origin and are generally more aggressive and carry a poorer prognosis than B-cell lymphomas.

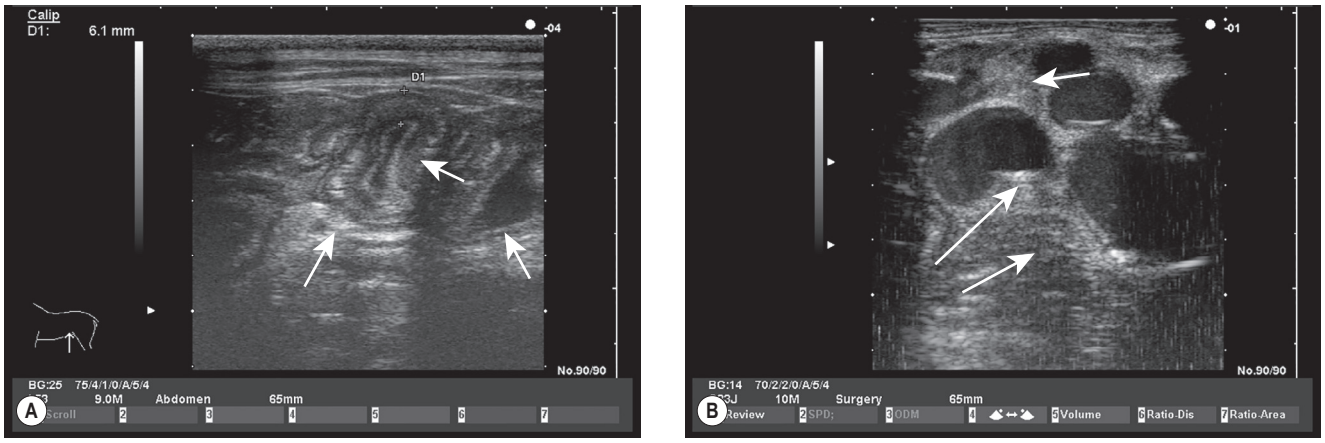


Figure 30.15 Intestinal lymphoma. (A) Thickened small intestinal wall over large or shorter lengths of gut can often be identified ultrasonographically (arrows). **(B)** Enlarged caecal lymph nodes (arrow) and focal isolated masses can also be identified attached to and involving the wall of the intestine (arrow). *(Figures courtesy of Barbora Bezdekova.)*

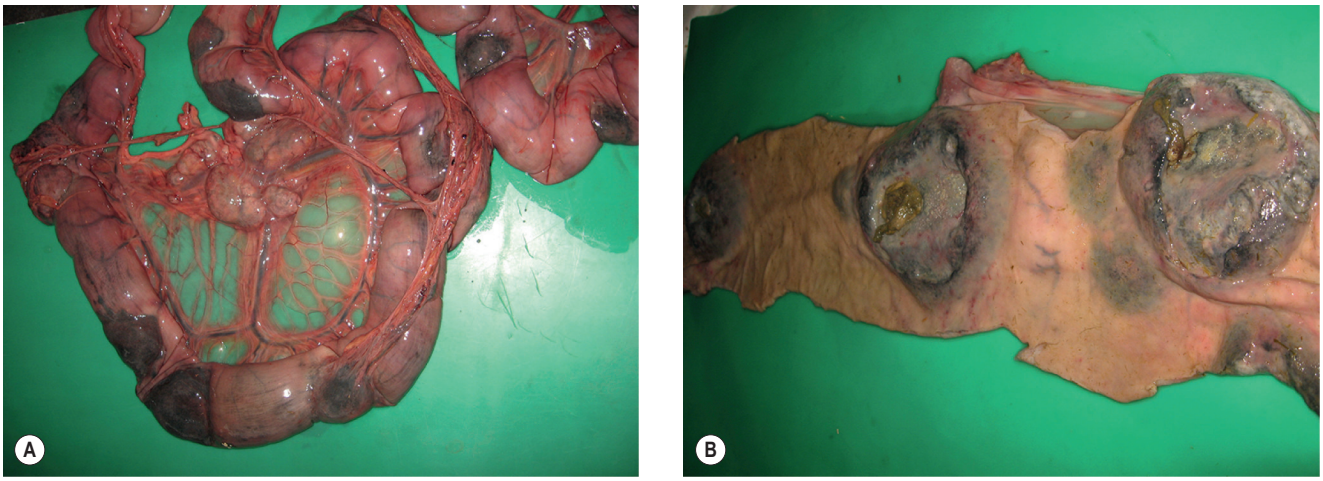


Figure 30.16 Intestinal lymphoma. (A) Focal involvement of segments of small intestine does provide an opportunity for surgical removal and restoration of intestinal integrity. **(B)** It is easy to appreciate the severity of the lesions visually during the surgery and at necropsy. *(Figures courtesy of Barbora Bezdekova.)*

Management

See Figure 30.16.

- *If a solitary mass is identified, surgical resection may be appropriate*. However, by the time of diagnosis, metastasis is usually widespread and surgical therapy is not warranted. Surgical resection of lymphoma of the large colon has been reported.[102] In one case, the horse was reported to be healthy at 18 months post-surgery. The other horse was euthanized 14 months after surgery because of multicentric lymphoma.
- Several *multi-drug chemotherapeutic protocols* have been reported for treatment of equine lymphoma with varying success. Anecdotal reports of remission of 1–2 years are present in the literature, while therapy is continued. However, once therapy is discontinued, the lymphoma returns.

Prognosis

Treatment responses and outcomes are not known. However, most cases are diagnosed at late stages and, therefore, whilst short-term prognosis may be fair with therapy, long-term prognosis is extremely poor. Treatment is best regarded as palliative rather than curative, at present.

Disease summary

Notes

Mediastinal lymphoma is the most common primary thoracic neoplasm of horses but is still very rare; horses of all ages can be affected.

Clinical features

Weight loss, depression, lethargy, ventral and limb oedema, recurrent fever and pleural effusion.

Diagnostic confirmation

Neoplastic lymphocytes found in pleural fluid or histopathological examination of biopsy of lymph node or a suspected lesion.

Management

No treatment is effective but palliative care can be provided by aggressive chemotherapy.

Prognosis

Prognosis is hopeless at the present time.

Mediastinal/thoracic/thymic lymphoma

See also page 348 and page 563.

Description

Mediastinal lymphoma is also referred to as *thoracic or thymic lymphoma*. It is reported to be the most common neoplasm affecting the thoracic cavity.[33,103–105]

Horses between 2 and 30 years of age can be affected, with a mean age of 10 years.[104,106] There is no breed predilection but geldings and stallions are seemingly affected more frequently. It may be less common in ponies than in horses.[104]

Clinical features

(Fig. 30.17A–C)

The most common clinical signs of the mediastinal form of lymphoma include:

- Depression
- Inappetence/weight loss
- Exercise intolerance
- Oedema of ventral thoracic, ventral abdominal, pectoral and proximal forelimb regions, resulting from lymphatic obstruction
- Cough/respiratory distress/tachypnoea/dyspnoea, due to presence of pleural effusion which causes severe pulmonary atelectasis and compromised pulmonary function
  - Abnormal sounds on lung auscultation, including muffled heart sounds and absence of pulmonary sounds ventrally
  - Dullness of thoracic percussion suggestive of evidence of pleural effusion



Figure 30.17 Mediastinal lymphoma. **(A)** This 9-year-old part bred mare was presented with a 5-week history of a progressive lethargy, depression, inappetence, weight loss (which was reported by the owner to affect only the hindquarters). The horse had a plaque of ventral oedema and elbow bilateral abduction – this was attributed to the accumulation of fluid within the pleural cavity. **(B)** Cutaneous vascular engorgement was noted. **(C)** A solid bilateral swelling in the thoracic inlet and jugular engorgement was present (arrow). Filling of the front right leg had been the first evidence that anything was wrong some 4–5 weeks previously. Mucous membranes were pale. The heart rate and respiratory rates were fast. **(D)** A total of 30 L of straw-coloured fluid was removed from each haemithorax using chest drains and one-way valves. **(E)** The fluid contained vast numbers of abnormal mononuclear cells.

- Bilateral distension of the jugular veins
- Bilateral firm masses at entrance to thoracic inlet.

Less common signs include:

- Fever – intermittent and recurrent
- Dysphagia
- Peripheral lymphadenopathy
- Respiratory noise (usually as result of bilateral laryngeal neuropathy/hemiplegia associated with involvement of recurrent laryngeal nerve in a mediastinal mass)[107]
- Severe bradycardia caused by complete atrioventricular block associated with mediastinal lymphoma has been reported in a single case.[108]

Diagnostic confirmation

Using a combination of routine diagnostic techniques, an ante-mortem diagnosis of thoracic neoplasia can be achieved in approximately 40% of cases described in two reviews.[33,104] Definitive ante-mortem diagnosis is most easily achieved when neoplastic cells are found in pleural fluid.[33,104]

- *Thoracocentesis*: This often reveals a large volume of blood-tinged frothy fluid. A horizontal fluid line in the chest can be identified using percussion, ultrasonography and radiography. Cytological examination of this fluid may reveal neoplastic lymphocytes, when the tumour is exfoliative.[106] In some instances, concurrent sepsis may be identified. Therefore, careful examination of the lymphocyte morphology should be performed by an experienced clinical pathologist. When overlapping conditions such as sepsis with mediastinal lymphoma exist, a lack of response to appropriate medical therapy should alert the clinician to other complicating factors and re-evaluation of the diagnosis (Fig. 30.17D,E).[109]
- *Clinical pathology*: Results of haematological and biochemical evaluations are frequently nonspecific.[106]
- *Radiography*: Thoracic radiography may reveal a pleural fluid line and, occasionally, a mediastinal mass. However, the muscular mass of the upper forelimb makes this difficult.[106,110]
- *Ultrasonography*: Thoracic ultrasonography provides specific evidence of the presence, depth and character of pleural fluid.[106] Ultrasonography of the cranial mediastinum may confirm the presence of a mediastinal mass.[109,111] Visualization of a cranial mediastinal mass is improved by the presence of pleural fluid and by the dorsal displacement of the lungs.[110]
- *Thoracoscopy*: Thoracoscopy, or pleuroscopy, is a minimally invasive procedure that allows endoscopic evaluation of the pleural space.[107,112,113] Representative biopsy samples of intra-thoracic masses can be obtained far more reliably in this way. Standing thoracoscopy allows access to and direct visualization of the dorsal and dorsolateral aspects of the equine thoracic cavity with minimal patient restraint and sedation.[114]

- *Biopsy*: Peripheral lymphadenopathy is an uncommon clinical feature of mediastinal lymphoma. However, when it develops, the prescapular or submandibular nodes are most commonly enlarged and biopsy is strongly recommended to support the diagnosis.

Management and prognosis

In most clinical reports of mediastinal lymphoma, no treatment is attempted and affected horses are euthanized. There is only one report in the literature of successful treatment of a thoracic lymphoma with systemic chemotherapy.[78]

Cutaneous lymphoma

See also page 349.

Description

Cutaneous lymphoma is an uncommon form of lymphoma. Cutaneous manifestations are frequently present as part of multicentric lymphoma, but there are reports of cutaneous and subcutaneous involvement as the solitary site.[115–124] The epitheliotropic form, also known as mycosis fungoides (which manifests as an infiltration by malignant lymphocytes, mainly of T-cell origin, into the epidermis and adnexa), giving the appearance of an exfoliating dermatitis, also occurs in horses; although it is extremely rare, there have been cases reported in the horse.[125,126] The nodular, non-epitheliotropic (histiocytic) form is the most recognized type in all domestic animals except the cat and dog. One retrospective study showed that the most common cutaneous lymphoma in the horse was the large cell type, which tended to be B cells and the tumours were characterized as T-cell-rich, large B-cell lymphomas with the T lymphocytes being non-neoplastic.[127]

Clinical features

In one recent study of 3351 cutaneous neoplastic biopsy specimens, 1.7% were diagnosed as lymphoma. Cutaneous lymphoma was 3.5 times as likely to be located on the body compared to other locations and mean age at presentation was 15.4 years. Thoroughbreds were 2.5 times as likely to have lymphoma compared to other breeds combined and males and females were equally affected in this study.[128] In earlier studies, mean age range was 5–12 years and females were over-represented.[129]

Cutaneous lymphoma is characterized by:

- Subcutaneous and cutaneous nodules (Fig. 30.18)
  - Usually slowly progressive development of solitary or multiple, non-painful, well-circumscribed, dermal or subcutaneous nodules or masses
- Overlying skin is usually intact without loss of hair
  - Some may have focal thickening of the affected skin, with ulceration and localized alopecia
- Commonest sites reported are the head, trunk, limbs and perineum
- Other reported sites include:
  - Shoulder
  - Pectoral region
  - Thorax
  - Flank
  - Thighs
  - Inguinal region
  - Scrotum
  - Periarticular[123]
- Peripheral lymph node enlargement
  - Primary cutaneous lymphoma without lymph node involvement is reported. However, lymphadenopathy is present in approximately 50% of cases[105,123,129]
- Subcutaneous nodules may infiltrate into underlying musculature[121]
- There are anecdotal observations of neoplastic nodules in some horses with subcutaneous lymphoma that wax and wane in conjunction with hormonal events such as oestrus, foaling and lactation[130]
  - In one report, regression of subcutaneous lymphoma in a mare was associated with administration of progesterone and removal of an ovarian granulosa–theca cell tumour[124]
  - In another reported case of equine cutaneous lymphoma, intralesional glucocorticoids and oral administration of progestins resulted in complete remission of the nodules[131]
- Clinical features of mycosis fungoides include: (Fig. 30.19)
  - Multifocal to generalized dermatitis, with widespread scaling, crusting, alopecia and perhaps ulceration



Figure 30.18 Cutaneous lymphoma. This 12-year-old Welsh pony mare had multiple firm cutaneous nodules over many areas of her body. Some had ulcerated but most were well-defined. She also had diffuse thickening of her gingiva. Biopsy from several of the nodules and the gingiva confirmed B-cell lymphoma. Cases may present with single isolated masses which may ulcerate in time but more usually they remain solid and well-defined. Multiple, sometimes coalescent, nodules are also a variant of the disease.





Figure 30.19 Mycosis fungoides. A 23-year-old gelding was presented with a 4-month history of cutaneous nodules that progressively enlarged and increased in numbers with prominent scaling over much of its skin. The horse suffered weight loss, hyperglobulinaemia, hypercalcaemia and anaemia. **(A,B)** The nodules ulcerated and discharged plasma-like fluid. Biopsy confirmed lymphoma. *(Figures courtesy of Sarah Heathcote.)*

- In humans, clinical features include location at mucocutaneous junctions, epidermal ulcers and progressive skin involvement
- One case report described a swollen, ulcerated, vulvar mass in a 17-year-old Quarter Horse mare, which enlarged over a period of 4 months to involve the skin of the perineum and ventral aspect of the abdominal wall[126]
- One case involved the mucous membranes of the mouth, nose and vulva.[125]

Differential diagnoses

1. Multicentric, thoracic or alimentary lymphoma with cutaneous metastases
2. Sarcoid (malignant and nodular forms)
3. Multiple insect bite reactions
4. Cutaneous mycetoma
5. Idiopathic collagen necrosis/eosinophilic collagen necrosis
6. Urticaria
7. Cutaneous histoplasmosis (epizootic lymphangitis)
8. Ulcerative lymphangitis (*Corynebacterium pseudotuberculosis*)
9. Equine cutaneous glanders.

Additional differential diagnoses for mycosis fungoides include:

1. Sarcoid of extensive verrucose or occult forms in particular
2. Pemphigus foliaceous
3. Sarcoidosis
4. Multisystemic eosinophilic epitheliotropic disease (MEED)
5. Systemic lupus erythematosus
6. Zinc-responsive dermatosis
7. Alopecia areata.

Diagnostic confirmation

- *Clinical features* are usually strongly suggestive.
- *Ultrasonography* allows accurate anatomical localization in relation to adjoining tissue, assessment of their internal structure, of involvement of adjacent muscles and of regional lymph nodes.[117] Ultrasonography also facilitates percutaneous fine-needle and hollow-needle aspiration.[117]
- *Biopsy, histopathology and immunohistochemical* methods of representative nodules to confirm infiltration with abnormal lymphocyte cells and T-cell nature of tumour.

Management

Reports of attempted treatment of cutaneous lymphoma are rare.[74,77,115,129,131] Local and systemic chemotherapy and radiation therapy have been described for treatment of solitary and multiple cutaneous lymphoma. It should also be noted that cutaneous lymphoma can remain static for some time – often some years – and there are sporadic reports in the literature of spontaneous resolution in young horses (<5 years).[129]

Surgery

Surgical removal for solitary lesions.

Systemic and local chemotherapy

- Prolonged high-dose corticosteroids (usually prednisolone) can have a dramatic effect on some cases. A dose of 1 mg/kg a 1 h for 35 days can be effective and bring about a dramatic improvement. Once the condition is in remission, the treatment is adjusted to 'pulse treatment' involving treatment for 7 days and no treatment for 14–21 days. Similar results can be achieved with dexamethasone at 0.1 mg/kg orally. The prolonged high-dose steroids can, however, have complications.
- Methotrexate and dexamethasone were used in one case, but the horse died after 14 days of therapy.[129]
- Immunotherapy using low-dose cyclophosphamide and an autogenous tumour cell suspension were used in a stallion with a subsequent halt in progression of tumour. The horse was clinically stable 19 months later.[77]
- Intralesional betamethasone combined with surgery and megestrol acetate were used successfully in the management of a horse with primary cutaneous lymphoma, but it was euthanized 3 months later as a result of exercise-related epistaxis. An 11-year-old mare with multiple cutaneous nodules was treated with intralesional corticosteroids and oral progestins and complete resolution of all nodules resulted.[131]
- Intralesional administration of cisplatin combined with sesame oil at a dose of 1 mg of cisplatin/cm^3 of tumour

injected in planes spaced 1 cm apart and repeated every 2 weeks resulted in a success rate of 96.2% for horses with cutaneous lymphoma lesions.[132]

Radiation therapy

Three horses diagnosed with cutaneous lymphoma (maxillary, perineal and lateral tarsocrural joint) were successfully treated with megavoltage radiotherapy and no recurrence of tumours was reported 29–114 months after treatment.[74] A single focal cutaneous lymphoma lesion on the jaw of a horse was treated with gamma irradiation via a linear accelerator with total remission.[73]

Prognosis

Survival rates of months to years have been reported and the cutaneous form is considered less aggressive than other forms of lymphoma, some persisting for years without apparent progression.[133] At the late stage of disease, metastasis to regional lymph nodes occurs, whereas widespread organ involvement is rarely reported.[134] In one study, the median survival time after diagnosis was 3.8 years (range 2–5 years).[116] Prognosis of the non-epitheliotropic form, mycosis fungoides, is poor.

Hepatosplenic/splenic lymphoma

See also pages 350 and 470.

Overview

The concurrent involvement of hepatic and splenic parenchyma is commonly reported as the result of the staging procedure of multicentric lymphoma in horses.[135] Although the restricted involvement of liver and spleen in lymphoma is rare, primary hepatosplenic lymphoma (HSPL) has been well-documented as a distinct disease in humans since 1990.[136] HSPL is an extra-nodallymphoma characterized by infiltration of hepatic sinusoids and splenic red pulp sinuses. Generally, in equine lymphoma and lymphoid leukaemia, there is distinctive infiltration of hepatic sinusoids and splenic white pulp by neoplastic cells predominantly, which is different from the distinctive infiltration of hepatic sinusoids and splenic red pulp in humans with HSPL.

The spleen is a fairly common site for infiltration of equine lymphoma. However, there are a few reports of lymphoma restricted solely to the spleen. A 7-year-old Thoroughbred stallion was reported to have a large splenic mass during an exploratory coeliotomy. The horse was euthanized and histopathology revealed no abnormalities other than a focal splenic lymphoma.[137] A 5-year-old Thoroughbred gelding was presented with polyuria and polydipsia. Post mortem revealed neoplastic cells confined to the spleen.[70] Paraneoplastic syndrome resulting in pseudohyperparathyroidism was suspected as a cause of polydipsia and polyuria, based on evidence of cardiovascular and renal mineralization. In the case of a 4-year-old Thoroughbred stallion racehorse, which presented for a fractured forelimb, post-mortem examination revealed a solitary splenic mass composed of neoplastic lymphocytes; no other gross abnormalities were identified.[138] The first successful treatment of a primary splenic lymphoma in a 5-year-old mule was reported in 2011.[139]

Clinical features

See Figure 30.20.

Clinical features commonly found in horses presented with hepatosplenic or primary splenic lymphoma include:

- Weight loss/ventral oedema
- Depression/weakness/lethargy
- Polydipsia and polyuria, possibly associated with pseudohyperparathyroidism
- Pale and/or icteric mucous membranes
- Petechial haemorrhage (associated with thrombocytopaenia).

Notes

- A large solid mass in the left to mid-abdomen or a palpably enlarged spleen on rectal examination is strongly suggestive of the diagnosis
- Liver tumours are far harder to identify and require the use of ultrasonography or laparoscopy.

Diagnostic confirmation

- *Transabdominal/transrectal ultrasonography* is exceptionally useful in the evaluation of splenic disease. The spleen normally lies immediately adjacent to the left body wall in the mid- and caudal abdomen and

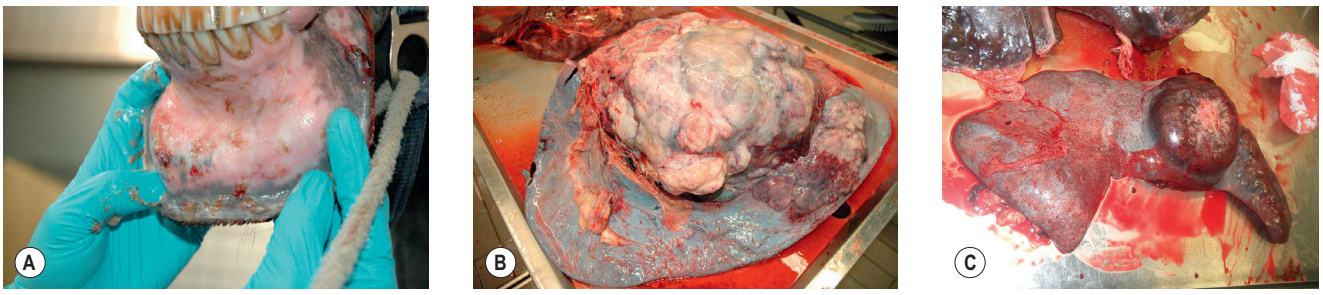


Figure 30.20 Splenic lymphoma. (A) A middle-aged mare was presented with a history of vague malaise and weight loss over some months. She developed haemoptyalism and obvious bullous changes in the mouth that were diagnosed as paraneoplastic bullous pemphigoid. **(B)** A splenic mass was palpated per rectum and identified ultrasonographically; at necropsy, this was found to be a very extensive splenic B-cell lymphoma. No other tumours were found. **(C)** This B-cell tumour was identified during rectal examination of a horse that was presented with dullness, anaemia and petechial haemorrhages. The single mass was identified by ultrasonography and a percutaneous hollow-needle biopsy confirmed the diagnosis. At necropsy no other tumours could be found; had splenectomy been possible in this case, there might have been a chance of resolution. *(Figures A and B courtesy of Vince Gerber and Lucio Unger, Vetsuisse University of Bern.)*

usually medial to the liver in the left cranial abdomen. It is one of the most homogeneous and echogenic of the abdominal organs and has few visible vessels. Therefore, diseases of the spleen associated with structural abnormalities are easily visualized using ultrasonography (see p. 93).[140]

- *Biopsy* of the spleen can be undertaken using a percutaneous cutting biopsy needle (with ultrasound guidance) or via laparoscopy.[140]
- *Laparoscopy* offers other advantages in the investigation of horses presenting with splenic lesions, as it allows visualization of other abdominal viscera.[140] This is particularly important in horses with neoplasia, as further intra-abdominal involvement would be expected more commonly and identification of this would significantly alter the treatment options available and the prognosis.

Management

There has only been one successful report of treatment of splenic lymphoma by surgical splenectomy.[139,141] Involvement of the liver, either as part of the syndrome or on its own, precludes any treatment attempt.

Prognosis

The prognosis is probably best viewed as poor or hopeless at the present time.

Plasma cell myeloma

See also page 355.

Description

Plasma cell neoplasia or multiple myeloma is a highly malignant neoplasm derived from plasma cells in the bone marrow, while plasmacytomas arise from plasma cells other than those of the bone marrow and are either solitary or multiple masses usually of the skin or mucous membranes. Plasma cells are the final differentiation of B lymphocytes.

Multiple myeloma is uncommon and has been reported in several species, including humans, cats, dogs and horses. In human beings, several predisposing factors have been proposed, including chromosomal translocation involving oncogenes, irradiation and chronic antigenic stimulation. Multiple myeloma is an extremely rare myeloproliferative disorder in the horse.[142–144] The neoplastic cells are responsible for an overproduction of a homogenous (monoclonal) immunoglobulin product known as paraprotein or M-component.

In humans, plasma cell myeloma has been characterized by:

- The presence (secretory myeloma) or absence (non-secretory myeloma) of serum or urine paraprotein
- Tumour location (solitary myeloma vs multiple myeloma vs plasma cell leukaemia).

The term 'multiple myeloma' is most appropriately used when there is diffuse multifocal bone marrow involvement with actual bone destruction.[65] Extra-medullary locations of myeloma reported in the horse include:

- Lymph nodes
- Lung
- Tongue
- Spleen
- Kidney
- Stomach and small intestine
- Liver
- Brain
- Orbit.

Multiple myeloma affects horses between 3 months and 25 years, with a median age at presentation of 18 years.[145] Quarter Horses seem most often affected (6/15) and there is no significant gender bias.[145–149]

Clinical features

The clinical signs of multiple myeloma vary with the level of plasma cell proliferation and are characteristically nonspecific: they vary with the location and effect of the neoplastic plasma cells and the nature and extent of the paraproteinaemia. The most definitive signs are found from bone marrow and blood analysis.

Clinical findings include:

- Weight loss
- Anorexia
- Fever
- Epistaxis and anaemia, possibly with icteric mucous membranes (Fig. 30.21A,B)
- Limb oedema
- Susceptibility to bacterial infections, in particular pneumonia, possibly due to deficiency of normal immunoglobulins, diminished bone marrow reserves, impaired neutrophil phagocytosis and a defective complement system
  - Neurological signs, such as hindlimb ataxia progressing to paralysis, have been reported in horses with plasma cell myeloma within the spinal canal compressing the spinal cord[150]

Disease summary

Notes

Very rare, highly malignant multifocal neoplasm of plasma cells in bone marrow.

Clinical features

Weight loss, anorexia, pale or icteric mucous membranes, fever, oedema of distal limbs, susceptibility to bacterial infections especially pneumonia, hindlimb paresis/ataxia or chronic lameness/bone pain, epistaxis and lymphadenopathy.

Diagnostic confirmation

Hyperproteinaemia and hyperglobulinaemia, monoclonal gammopathy identified by serum protein electrophoresis, plasmacytosis in peripheral blood smear or bone marrow aspirate, proteinuria, osteolytic lesions on radiography or scintigraphy, histopathology and immunohistochemistry.

Management

No treatment options are reported in the horse.

Prognosis

Prognosis is hopeless with a short course or progressive organ failure.

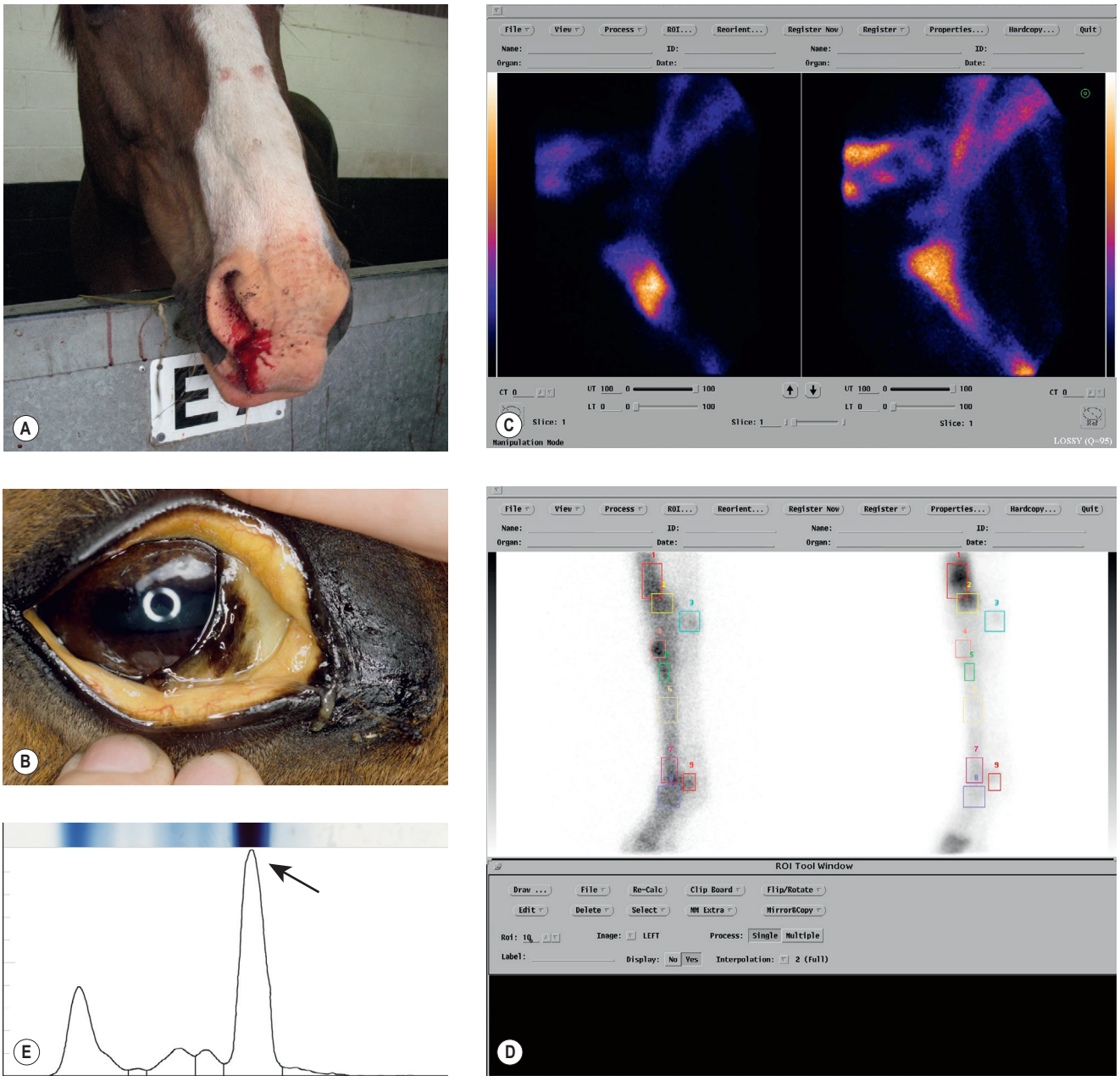


Figure 30.21 Plasma cell/multiple myeloma. Horses with plasma cell myeloma have characteristically vague clinical signs, including intermittent epistaxis **(A)**, pale or icteric mucous membranes **(B)**, and lameness that is hard to diagnose. Radiography and gamma scintigraphy can usefully identify multiple discrete focal pathology in the long bones in particular **(C,D)**. There is usually a profound hypoproteinemia attributable to a monoclonal gammopathy, which is identified by plasma electrophoresis (arrow) **(E)**. *(Figure E courtesy of Alistair Foote, Beaufort Cottage Laboratories.)*

- Palpable lymphadenopathy
  - Bone pain and lameness secondary to neoplasia is rare in horses, but has been reported secondary to an aggressive fibrosarcoma, osteochondroma, keratoma of the distal phalanx, intramuscular haemangiosarcoma, malignant melanoma and mastocytoma[149]
- Ptyalism and dysphagia have been reported in one case of extra-medullary plasmacytoma thought to be associated with neoplastic involvement of the trigeminal nerve.[151]

Differential diagnoses

1. Lymphoma
2. Leukaemia
3. Other causes of anaemia and jaundice
4. Other infectious and non-infectious causes of multilimb mild lameness and bone pain.

Note

Since the signs are extremely variable, this condition can easily be misdiagnosed or even overlooked completely.

Diagnostic confirmation

- *Radiographic evidence* of osteolysis in long bones and vertebral bodies and sternebrae.[145,146,150]
- *Gamma scintigraphic using ^{99m}Tc-MDP* shows evidence of focal radiopharmaceutical uptake in multiple sites associated with joint and long bone diaphyseal pain (Fig. 30.21C,D). Areas of uptake are much stronger than areas of uptake secondary to osteoarthritis or inflammation, but can be indistinguishable from fracture sites.[149]
- *Magnetic resonance imaging* remains the gold standard for diagnosis of myeloma in humans, but it is very difficult in horses as the modality is not readily available, is expensive and usually requires the additional risks of general anaesthesia.
- *Clinical pathology*
  - A normocytic, normochromic anaemia eventually develops in nearly all cases, mainly due to blood loss, reduced erythropoiesis secondary to myelophthisis and infection and the expansion of plasma volume secondary to the osmotic effect of the paraprotein.[146] Icterus can be profound in addition.
  - Pancytopenia develops as disease progresses, due to progressive myelophthisis.
  - Plasmacytosis in peripheral blood smear has not been documented in sufficient numbers to be termed 'plasma cell leukaemia', i.e. >20×10^9/L plasma cells.[65,145]
  - Hyperproteinaemia, hyperglobulinaemia and hypoalbuminaemia
    - Hyperglobulinaemia is a hallmark of multiple myeloma.[145] Monoclonal gammopathy is identified by serum protein electrophoresis (Fig. 20.21E). The mechanism of hypoalbuminaemia in horses is unknown, but in human cases it is primarily related to the extent of proliferation of myeloma and is therefore of diagnostic and prognostic importance
    - Serum protein electrophoresis.
- Monoclonal gammopathy in horses has been associated with multiple myeloma, malignant lymphoma and benign monoclonal gammopathies.[152]
- In horses and humans, subclasses of IgG are the predominant paraproteins associated with myeloma. (*In cases meeting human diagnostic criteria, IgG or an IgG fragment was the most common immunoglobulin identified by serum electrophoresis.*)[145]
- The non-secretory form of myeloma in humans is rare, accounting for 1–5% of all cases. In one equine case, the lack of Bence Jones proteins and the relatively mild hyperglobulinaemia were diagnostic of a non-secretory plasma cell myeloma. In the majority of equine cases, presence of hyperproteinaemia and monoclonal proteinaemia classifies them as secretory tumours[149,153]
  - Hypercalcaemia is not a common pathognomonic feature of the disease in horses. Horses with neoplasms other than multiple myeloma may have hypercalcaemia of malignancy[147,149]
    - Some cases are hypocalcaemic, probably secondary to hypoalbuminaemia
  - Bleeding diatheses as a result of impaired haemostasis caused by paraprotein binding to platelets and interference with various clotting factors[154,155]
  - Urinalysis
    - Proteinuria is a common finding in horses with myeloma
    - Bence Jones proteinuria.
- When the paraprotein is a light chain immunoglobulin, the fragments have the ability to pass through the glomerulus into the urine where they are referred to as Bence Jones proteins.
- These proteins are not detectable using a urine dipstick; detection requires electrophoresis of urine.
- Bence Jones proteins have been found in only one horse with multiple myeloma[145]
  - Azotaemia is rarely reported in horses with multiple myeloma, suggesting that renal disease is not a common clinical feature of multiple myeloma in horses, despite the proteinuria. The alkaline pH of horse urine may help to prevent the formation of tubular protein casts. Reduced protein precipitation is the proposed mechanism and basis for alkalinization of urine as a treatment for humans with myeloma cast nephropathy[146]
  - Bone marrow aspiration
    - In four of eight horses described in the literature, plasma cell numbers and/or morphology were consistent with diagnosis of multiple myeloma
    - The proportion of plasma cells in bone marrow aspirate may range from <5% to almost 100% because involvement of bone marrow is usually focal rather than diffuse. Repeated aspirates taken from several sites may therefore be necessary to confirm plasmacytosis in cases of multiple myeloma.
- *Histopathology*
  - Typically, multiple myeloma should not be diagnosed without evidence of bone marrow involvement; hence, bone marrow biopsies, often multiple, are required to establish a definitive diagnosis[65]
  - Immunohistochemistry may assist in diagnosing multiple myeloma in horses with monoclonal gammopathies
  - There is a single report of systemic light chain amyloidosis in a 16-year-old gelding secondary to multiple myeloma that presented with weight loss and ventral oedema.[148]

Management

Successful treatment of plasma cell myeloma in horses has not been reported. Melphalan, an alkylating agent, has been used extensively and successfully in the treatment of plasma cell myeloma in other species. Anecdotally, this drug may be used in horses (3.5–7.0 mg/m^2 orally once daily for 5–10 days then every 3 weeks).

Prognosis

The lifespan of horses with multiple myeloma will probably not exceed 2 years and most horses are euthanized much

sooner owing to the advanced stage of disease.[146] Negative prognostic indicators for multiple myeloma in other species include the presence of Bence Jones proteinuria (these are not encountered in horses), plasma cell leukaemia, pancytopenia, renal azotaemia and hypercalcaemia.

Leukaemia

See also page 352.

Overview

Leukaemia is defined as a progressive neoplastic transformation within the bone marrow of either the lymphoid or myeloid cell lines.[156] Leukaemia is characterized by the cell line of origin, the type and number of neoplastic cells within the circulation and the clinical course of the disease. All blood cells originate from a common pluripotent stem cell, from which it differentiates into either a lymphoid or myeloid stem cell. When the dominant cell population within the bone marrow is immature, the leukaemia is classified as acute. When the neoplastic transformation occurs at a later stage of differentiation, leukaemia is classified as chronic.

Although lymphoma is classified as a lymphoproliferative disorder, it originates in lymphoid tissue, but may progress to invade the bone marrow. This is termed *lymphoma with leukaemia, leukaemic lymphoma* or *secondary leukaemia*. Leukaemia in the horse is rare, with many single case reports or small case series describing horses affected with either myeloid or lymphoid cell lines (Table 30.3).

Disease summary

Notes

Very rare metastatic tumour characterized by profound circulating lymphocyte counts.

Clinical features

No specific clinical signs. Weight loss, lethargy, depression, intermittent fever, anorexia, ventral and distal limb oedema and peripheral lymphadenopathy.

Diagnostic confirmation

Diagnosis is suspected from elevated white cell count and abnormal cell morphology or maturation on peripheral blood smear; definitive diagnosis requires bone marrow aspirate or biopsy and cytochemical staining or immunophenotyping to identify cell line involved.

Management

No successful treatment. Corticosteroids and aggressive systemic chemotherapy with doxorubicin and other agents have anecdotally provided palliation and temporary remission. Treatment must be sustained.

Prognosis

Prognosis is hopeless.

Clinical features

Although there are no specific clinical signs for leukaemia, common observations, usually over a period of weeks, include:

- Weight loss
- Lethargy/depression
- Intermittent fever
- Anorexia
- Ventral and distal limb oedema
- Peripheral lymphadenopathy.

Other clinical signs reported in the literature include:

- Tachycardia
- Tachypnoea
- Poor performance
- Oral and skin ulceration
- Soft faecal consistency
- Mild abdominal pain
- Pale mucous membranes

Table 30.3 The accepted classification of the leukaemic state with the reported equine syndromes shown in **bold**. Acute leukaemia tends to have a short and rapidly progressive clinical course while chronic leukaemia has a gradual onset and longer clinical course

	Series	Stage	Type
Stem cell	Myeloid	Acute	1. **Acute myeloblastic (AML)** >90% myeloblasts (M1) **30 → 90% myeloblasts (M2)** 2. Promyelocytic (M3) 3. **Myelomonocytic (M4)** 4. **Monocytic leukaemia (M5)**[157–159] 5. **Erythroleukaemia (M6)**[160] 6. Megakaryocyte (M7)
		Chronic	1. **Chronic granulocytic leukaemia (CGL)**[161,162] 2. Chronic eosinophilic leukaemia 3. Chronic basophilic leukaemia 4. Polycythaemia vera 5. Essential thrombocytopaenia 6. Chronic myelomonocytic leukaemia 7. Chronic monocytic leukaemia
	Lymphoid		1. Primary lymphoid leukaemia 2. **Plasma cell neoplasm/multiple myeloma**[145] 3. Lymphoma Lymphoma with leukaemia[163]

(After Taintor, 2012.[156])

- Bleeding diatheses
  - Bleeding from venepuncture sites and wounds
  - Epistaxis
  - Haematuria
  - Mucosal petechial haemorrhage.

Differential diagnoses

1. Lymphoma
2. Plasma cell myeloma
3. Haemangiosarcoma.

Diagnostic confirmation

- Diagnosis of leukaemia can be difficult but should be suspected if there is:
  - Increased white cell count
  - Abnormal findings of cell morphology or maturation on clinical pathological examination of a peripheral blood smear
  - Confirmation of diagnosis is made by examination of a bone marrow aspirate or biopsy
  - Cytochemical staining or immunophenotyping can be performed on peripheral blood or bone marrow samples to aid differentiation of cell lines.
- Common findings on CBC include:
  - Anaemia
    - Most common finding in leukaemia: mild to severe, macrocytic or normocytic.
  - Cytopenia
    - May or may not be present, depending on stage of disease process
    - Pancytopenia or aplastic anaemia, secondary to reduced or absent erythropoiesis, granulopoiesis and thrombopoiesis, due to bone marrow suppression, has been reported in lymphoid leukaemia
    - Neoplastic cells may be present in bone marrow but not circulation (aleukaemic), may be present in scant numbers in circulation (subleukaemic) or be present in large numbers (leukaemic)
    - Thrombocytopaenia is a common finding in most leukaemic horses, resulting in clinical signs of bleeding and petechiation often reported.
- Contributes to anaemia.
- Coagulation profile results generally normal other than thrombocytopaenia.
- Serum biochemistry is generally nonspecific.
- Bone marrow aspiration or biopsy
  - Cytological assessment of nucleated cell population
  - Biopsy allows architecture of bone marrow to be assessed for disruption
  - Normal reference ranges for cellular components of bone marrow in the horse can be found in other texts.
- Immunophenotyping
  - Use of specific antibodies for differentiation of lymphoproliferative disease from myeloproliferative disease and to identify cell lineage such as T-cell or B-cell antigen
  - Immunohistochemistry uses all tissues
  - Flow cytometry uses peripheral blood, cavity fluid and cells in suspension
  - T-cell origin cells express CD3 on immunohistochemistry and CD4+ on flow cytometry
  - B-cell origin cells express CD79 on immunohistochemistry and B29A and E18A on flow cytometry
  - Additional immunological tests will help to improve our understanding of equine leukaemia and potentially provide therapeutic and better monitoring options and a more accurate prognosis.

Management

Corticosteroids, either prednisolone or dexamethasone, have provided palliative treatment to several horses with lymphoproliferative leukaemia. Two reports cite the unsuccessful use of cytarabine for treatment of myelomonocytic leukaemia.[164,165]

Prognosis

There have been no successful reports of treatment of leukaemia in the horse to date. All affected horses described have died or been euthanized following diagnosis or shortly after.

Lymphoid leukaemia

See also page 540.

Overview

Lymphoid leukaemia can be primary or secondary to lymphoma. Differentiation between the two types of lymphoid leukaemia can be difficult. Bone marrow involvement without peripheral lymphoid tissue involvement is indicative of primary lymphoid leukaemia.

Primary lymphoid leukaemia can be distinguished from secondary by examining the distribution of neoplastic cells in a bone marrow core biopsy; in primary lymphoid leukaemia, neoplastic cells are diffusely distributed and in secondary leukaemia, neoplastic cells are focal and located adjacent to paratrabecular blood sinuses. Primary lymphoid leukaemia can be further classified as acute lymphocytic leukaemia (ALL, or lymphoblastic leukaemia[166]) or chronic lymphocytic leukaemia (CLL, or lymphocytic leukaemia). Both types of leukaemia originate in the bone marrow, but may infiltrate highly vascularized structures such as the liver and spleen. Both types have been reported in the horse, but CLL has been reported more commonly.[156] ALL has been reported in three geldings, aged <8 years, and one 11-year-old female.[163,167,168] CLL has been reported mostly in geldings (7 geldings, 3 females), age >10 years (age range 10–23 years, median 20 years).[169–172]

Myeloid leukaemia

See also page 352.

Overview

Acute myeloid leukaemia (AML) is diagnosed from a bone marrow aspirate when >30% of nucleated cells are blast cells and >50% of nucleated cells are non-erythroid cells.

Cytochemical stains are used to determine the cell lineage and allow classification of the disease.[156]

Acute myeloid leukaemia is further categorized into multiple subgroups:

- Acute myeloblastic (M1 and M2)
  - Acute myeloblastic is either granulocytic or neutrophilic and is subdivided into M1, where >90% of non-erythroid cells are myeloblasts, and M2 where 30–90% of non-erythroid cells are myeloblasts[156]
  - M2 myeloid leukaemia was reported in an 18-year-old Morgan mare.[173]
- Promyelocytic (M3)
  - M3 promyelocytic leukaemia has not been reported in the horse.
- Myelomonocytic (M4)
  - Myelomonocytic (M4) leukaemia has been reported in nine horses to date, age 2–11 years (5 male, 1 gelding, 3 females).[157,159,160,165,174–177]
- Monocytic (M5)
  - Monocytic (M5) leukaemia has been reported in two horses, a mare and gelding both aged 6 years[158,178]
  - Acute monocytic leukaemia (M5) is characterized by peripheral monocytosis with neoplastic monocytes comprising >80% of non-erythroid cells in the bone marrow.
- Erythroleukaemic (M6)
  - There is one report of M6 erythroleukaemia in the literature, in a 10-week-old filly[161]
  - There is dual lineage with a coproduction of myeloblasts and erythroblasts and, clinically, this disease is characterized by a severe non-regenerative anaemia.
- Megakaryocytic (M7)
  - Megakaryocytic (M7) leukaemia is diagnosed when >30% of the nucleated cell population within the bone marrow are megakaryotypes
  - M7 has not, to date, been reported in the horse.

Myeloproliferative neoplasms are proliferations of immature and mature granulocytes, platelets and erythrocytes. They are commonly found in older animals, chronic in nature, but can progress to acute myeloid leukaemia.

Subgroups of chronic myeloid leukaemia include:

- Chronic granulocytic leukaemia (CGL)
- Chronic eosinophilic leukaemia[179]
- Chronic basophilic leukaemia
- Polycythaemia vera
- Essential thrombocytopaenia
- Chronic myelomonocytic leukaemia
- Chronic monocytic leukaemia
  - There are only two reports of chronic granulocytic leukaemia in the horse, both males aged 4 and 9 years.[162,180]

References

1. Hargis AM, McElwain TF. Vascular neoplasia in the skin of horses. J Am Vet Med Assoc 1984; 184:1121–1124.
2. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
3. Baker JR, Leyland A. Histological survey of tumours of the horse with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
4. Platt H. Vascular malformations and angiomatous lesions in horses: a review of 10 cases. Equine Vet J 1987; 19:500–504.
5. Sartin EA, Hodge TG. Congenital dermal haemangioendothelioma in two foals. Vet Pathol 1982; 19:569–571.
6. Vos JH, van der Gaag I, van Dijk JE, et al. Lobular capillary haemangiomas in young horses. J Comp Pathol 1986; 96:637–644.
7. Rhyan JC, D'Andrea GH, Smith LS. Congenital ovarian vascular hamartoma in a horse. Vet Pathol 1981; 18:131.
8. Vestre WA, Turner TA, Carlton WW. Conjunctival haemangioma in a horse. J Am Vet Med Assoc 1982; 180:1481–1482.
9. Greene HJ, O'Connor JP. Haemangioma of the guttural pouch of a 16-year-old thoroughbred mare: clinical and pathological findings. Vet Rec 1986; 118:445–446.
10. Crawley GR, Bryan GM, Gogolewski RP. Ocular haemangioma in a horse. Equine Pract 1987; 9:11–14.
11. Bolton JR, Lees MJ, Robinson WF, et al. Ocular neoplasms of vascular origin in the horse. Equine Vet J Suppl 1990; 10:73–75.
12. Holzhausen L, Nowak M, Junginger J, et al. Synovial haemangioma in an adult horse. J Vet Diagn Invest 2012; 24:427–430.
13. Pool RR, Thompson KG. Synovial haemangioma or vascular hamartoma in the tendon sheath of the horse In: Meuten DJ, ed. Tumors in domestic animals, 4th edn. Ames: Iowa State Press; 2002.
14. Colbourne CM, Yovich JV, Richards RB, et al. Vascular hamartomas of the dorsal carpal region in three young Thoroughbred horses. Aust Vet J 1997; 75:20–23.
15. Johnson GC, Miller MA, Floss JL, et al. Histologic and immunohistochemical characterization of haemangiomas in the skin of seven young horses. Vet Pathol 1996; 33:142–149.
16. Cissell DD, Wisner ER, Textor J, et al. Computed tomographic appearance of equine sinonasal neoplasia. Vet Radiol Ultrasound 2012; 53:245–251.
17. Warren AL, Summers BA. Epithelioid variant of haemangioma and haemangiosarcoma in the dog, horse and cow. Vet Pathol 2007; 44:15–24.
18. Southwood LL, Schott HC, Henry CJ, et al. Disseminated haemangiosarcoma in the horse: 35 cases. J Vet Intern Med 2000; 14:105–109.
19. Ladd SM, Crisman MV, Duncan R, et al. Central nervous system haemangiosarcoma in a horse. J Vet Intern Med 2005; 19:914–916.
20. MacGillivray KC, Graham TD, Parente EJ. Multicentric leiomyosarcoma in a young male horse. J Am Vet Med Assoc 2003; 223:1017–1021.
21. Johns I, Stephen JO, Del Piero F, et al. Haemangiosarcoma in 11 young horses. J Vet Intern Med 2005; 19:564–570.
22. Birks EK, Hultgren BD. Pericardial haemangiosarcoma in a horse. J Comp Pathol 1988; 99:105–107.
23. Dunkel BM, Del Piero F, Kraus BM, et al. Congenital cutaneous, oral and periarticular haemangiosarcoma in a 9-day-old Rocky Mountain horse. J Vet Intern Med 2004; 18:252–255.
24. Newton-Clarke MJ, Guffoy MR, Dykes NL, et al. Ataxia due to vertebral haemangiosarcoma in a horse. Vet Rec 1994; 135:182–184.
25. Berry S-L. Spinal cord compression secondary to haemangiosarcoma in a Saddlebred stallion. Can Vet J 1999; 40:886–887.
26. Hirsh JE, Grant BD, Linovitz R, et al. Diagnosis and surgical treatment of epidural neoplasms in two ataxic horses. Equine Vet Educ 2009; 21: 564–568.
27. Delesalle C, van Loon G, Nollet H, et al. Tumour-induced ventricular arrhythmia in a horse. J Vet Intern Med 2002; 16:612–617.
28. Williams MA, Dowling PM, Angarano DW, et al. Paraneoplastic bullous stomatitis in a horse. J Am Vet Med Assoc 1995; 207:331–334.
29. Sansom J, Donaldson D, Smith K, et al. Haemangiosarcoma involving the third eyelid in the horse: a case series. Equine Vet J 2006; 38:277–282.
30. Gearhart PM, Steficek BA, Peteresen-Jones SM. Haemangiosarcoma and squamous cell carcinoma in the third eyelid of a horse. Vet Ophthalmol 2007; 10:121–126.
31. Pinn TL, Cushing T, Valentino LM, et al. Corneal invasion by haemangiosarcoma in a horse. Vet Ophthalmol 2011; 14:200–204.
32. Kiupel M, Frank N, Stevenson GW, et al. Intrapelvic haemangiosarcoma in a horse. J Vet Diagn Invest 2000; 12:91–95.
33. Sweeney CR, Gillette DM. Thoracic neoplasia in equids: 35 cases (1967–1987). J Am Vet Med Assoc 1989; 195:374–377.
34. Cottle HJ, Hughes KJ, Philbey AW, et al. Primary haemangiosarcoma in the proximal humerus of a Clydesdale gelding. Equine Vet Educ 2008; 20: 575–579.
35. Rossier Y, Sweeney CR, Heyer G, et al. Pleuroscopic diagnosis of disseminated haemangiosarcoma in a horse. J Am Vet Med Assoc 1990; 196:1639–1640.
36. Burks BS, Leonard JM, Orsini JA, et al. Interstitial brachytherapy in the management of haemangiosarcoma of the rostrum of the horse: case report and review of the literature. Equine Vet Educ 2009; 21:487–493.
37. Van Pelt RW, Langham RF, Gill HE. Multiple haemangiosarcomas in the tarsal synovial sheath of a horse. J Am Vet Med Assoc 1972; 161: 49–52.
38. Knottenbelt DC. Basic principles of diagnosis and management of neoplasia in horses. Proceedings of the 9th International Congress, SIVE, 2003.
39. Dawson DR, Scrivani PV, Schaefer DMW, et al. Epithelioid variant of haemangiosarcoma in a gelding. Equine Vet Educ 2009; 21:519–524.
40. Gumber S, Baia P, Wakamatsu N. Vulvar epithelioid haemangiosarcoma with solar elastosis in a mare. J Vet Diagn Invest 2011; 23:1033–1036.
41. Arenas-Gamboa AM, Mansell J. Epithelioid haemangiosarcoma in the ocular tissue of horses. J Comp Pathol 2011; 144:328–333.
42. Moore PF, Hacker DV, Buyukmihci NC. Angiosarcoma in the horse: morphological and immunohistochemical studies. Vet Pathol 1986; 23: 240–244.

43. Chan CW, Collins EA. Case of angiosarcoma of the nasal passage of the horse – ultrastructure and differential diagnosis from progressive haematoma. Equine Vet J 1985; 17:214–218.
44. Kennedy FA, Brown CM. Vertebral angiosarcoma in a horse. J Vet Diagn Invest 1993; 5:125–127.
45. Bischofberger AS, Konar M, Posthaus H, et al. Ocular angiosarcoma in a pony – MRI and histopathological appearance. Equine Vet Educ 2008; 20:340–347.
46. Ferrell EA, Gavin PR, Tucker RL, et al. Magnetic resonance for evaluation of neurologic disease in 12 horses. Vet Radiol Ultrasound 2002; 43:510–516.
47. Dyson PK, Dunn KA, Whitwell K, et al. Ataxia and cranial nerve signs in a pony suffering a brainstem meningioma: clinical, MRI, gross and histopathological findings. Equine Vet Educ 2007; 19:173–178.
48. Naylor RJ, Dunkel B, Dyson S, et al. A retrobulbar meningioma as a cause of unilateral exophthalmos and blindness in a horse. Equine Vet Educ 2010; 22:503–510.
49. Gehlen H, Wohlsein P. Cutaneous lymphangioma in a young Standardbred mare. Equine Vet J 2000; 32:86–88.
50. Turk JR, Gallina AM, Liu IM, et al. Cystic lymphangioma in a colt. J Am Vet Med Assoc 1979; 174:1228–1230.
51. Platt H. Alimentary lymphomas in the horse. J Comp Pathol 1987; 97:1–10.
52. Junginger J, Rötting A, Stasyk C, et al. Identification of cutaneous lymphangioma by application of a lymphatic endothelial cell marker. J Comp Pathol 2010; 143:57–60.
53. Ijizer J, van den Ingh TS. Lymphangiosarcoma in a horse. J Comp Pathol 2000; 122:312–316.
54. Sanchez B, Nieto A, Ruiz de Leon MA, et al. Metastatic lymphangiosarcoma in a horse. Vet Pathol 2002; 39:266–268.
55. Puff C, Herder V, Philipp A, et al. Lymphangiosarcoma in the nictitating membrane of a horse. J Vet Diagn Invest 2008; 20:108–110.
56. Baker D, Kreeger J. Infiltrative lipoma in the heart of a horse. Cornell Vet 1987; 77:258–262.
57. Buergelt CD. Equine cardiovascular pathology: an overview. Anim Health Res Rev 2003; 4:109–129.
58. Quinn GC, Fews D, Pearson GR, et al. Malignant peripheral nerve sheath tumour of the heart in a horse. Vet Rec 2005; 157:847–849.
59. Penrose LC, Brower A, Kirk G, et al. Primary cardiac lymphoma in a 10 year old equine gelding. Vet Rec 2012; 171:20–21.
60. MacGillivray KC, Sweeney RW, Del Piero F. Metastatic melanoma in horses. J Vet Intern Med 2002; 16:452–456.
61. Castleman WL, Toplon DE, Clark CK, et al. Rhabdomyosarcoma in 8 horses. Vet Pathol 2011; 48:1144–1150.
62. Dill SG, Moise NS, Meschter CL. Cardiac failure in a stallion secondary to metastasis of an anaplastic pulmonary carcinoma. Equine Vet J 1986; 18:414–417.
63. Sweeney RW, Hamir AN, Fisher RR. Lymphosarcoma with urinary bladder infiltration in a horse. J Am Vet Med Assoc 1991; 199:1177–1178.
64. Carnine BL, Schneider G, Cook JE, et al. Pericardial mesothelioma in a horse. Vet Pathol 1977; 14:513–515.
65. Savage CJ. Lymphoproliferative and myeloproliferative disorders. Vet Clin North Am Equine Pract 1998; 14:563–578.
66. Taintor J, Schleis S. Equine lymphoma. Equine Vet Educ 2011; 23:205–213.
67. Rebhun WC, Del Piero F. Ocular lesions in horses with lymphosarcoma: 21 cases (1977–1997) J Am Vet Med Assoc 1998; 212:852–854.
68. Rendle DI, Hughes KJ, Farish C, et al. Multicentric T-cell lymphoma presenting as inferior palpebral swelling in a Standardbred mare. Aust Vet J 2012; 90:485–489.
69. Germann SE, Richter M, Schwarzwald CC, et al. Ocular and multicentric lymphoma in a young racehorse. Vet Ophthalmol 2008; 11:51–56.
70. Marr CM, Love S, Pirie HM. Clinical, ultrasonographic and pathological findings in a horse with splenic lymphosarcoma and pseudohyperparathyroidism. Equine Vet J 1989; 21:221–226.
71. Finley MR, Rebhun WC, Dee A, et al. Paraneoplastic pruritus and alopecia in a horse with diffuse lymphoma. J Am Vet Med Assoc 1998; 213:102–104.
72. Koch TG, Wen X, Bienzle D. Lymphoma, erythrocytosis and tumour erythropoietin gene expression in a horse. J Vet Intern Med 2006; 20:1251–1255.
73. Coumbe KM. Primary parotid lymphoma in a 10 year old Hanoverian gelding. Equine Vet Educ 1994; 6:91–94.
74. Henson F, Dixon K, Dobson J. Treatment of 4 cases of equine lymphoma with megavoltage radiation. Equine Vet Educ 2004; 16:312–314.
75. Mair TS, Couto CG. The use of cytotoxic drugs in equine practice. Equine Vet Educ 2006; 18:149–156.
76. Burns TA, Couto CG. Systemic chemotherapy for oncologic diseases In: Robinson NE, Sprayberry K, eds. Current therapy in equine medicine, 6th edn. St Louis: Saunders; 2009: 15–18.
77. Gollagher RD, Ziola B, Chelack BJ, et al. Immunotherapy of equine cutaneous lymphosarcoma using low dose cyclophosphamide and autologous tumour cells infected with vaccinea virus. Can Vet J 1993; 34:371–373.
78. Saulez MN, Schlipf JW Jr, Cebra CK, et al. Use of chemotherapy for treatment of a mixed-cell thoracic lymphoma in a horse. J Am Vet Med Assoc 2004; 224:733–738.
79. Théon AP, Pusterla N, Magdesian KG, et al. Phase I dose escalation of doxorubicin chemotherapy in tumor-bearing Equidae. J Vet Intern Med 2013; 27:1209–1217.
80. Schneider DA. Lymphoproliferative and myeloproliferative disorders. In: Robinson NE, ed. Current therapy in equine medicine, 4th edn. Philadelphia: WB Saunders; 1997: 295–299.
81. McClure JT. Leukoproliferative disorders in horses. Vet Clin North Am Equine Pract 2000; 16:165–182.
82. Carlson G. Lymphoma (lymphosarcoma) in horses. In: Smith BP, ed. Large animal internal medicine, 3rd edn. St Louis: Mosby; 2002: 1072.
83. Gerber V, Schott HC, Mullaney TP, et al. Glucocorticoid treatment for intestinal lymphomas of T-cell origin. Proceedings of the 7th International Equine Colic Symposium; 2002: 125.
84. Vail D, Young K. Hematopoietic tumors. In: Withrow S, Vail D, eds. Small animal clinical oncology, 4th edn. St Louis: Saunders; 2002: 699–784.
85. Théon AP, Pusterla N, Magdesian KG, et al. A pilot Phase II study of efficacy and biosafety of doxorubicin chemotherapy in tumor-bearing Equidae. Preventing occupational and environmental exposure to cytotoxic drugs in veterinary medicine, 2nd edn. ECVIM-CA; 2013. http://www.ecvim-ca.org/guidelines.
86. Taylor SD, Pusterla N, Vaughan B, et al. Intestinal neoplasia in horses. J Vet Intern Med 2006; 20:1429–1436.
87. East LM, Savage CJ. Abdominal neoplasia (excluding urogenital tract). Vet Clin North Am Equine Pract 1998; 14:475–493.
88. Wiseman A, Petrie L, Murray MJ. Diarrhoea in the horse as a result of alimentary lymphosarcoma. Vet Rec 1974; 95:454–457.
89. Roberts MC, Pinsent PJ. Malabsorption in the horse associated with alimentary lymphosarcoma. Equine Vet J 1975; 7:166–172.
90. Pinkerton ME, Bailey KL, Thomas KK, et al. Primary epitheliotropic intestinal T-cell lymphoma in a horse. J Vet Diagn Invest 2002; 14: 150–152.
91. Muñoz A, Riber C, Trigo P, et al. Haematopoietic neoplasms in horses: myeloproliferative and lymphoproliferative disorders. J Equine Sci 2009; 20:59–72.
92. Mair TS, Hillyer MH. Chronic colic in the mature horse: a retrospective view of 106 cases. Equine Vet J 1997; 29:415–420.
93. Hillyer MH, Mair TS. Recurrent colic in the mature horse: a retrospective review of 58 cases. Equine Vet J 1997; 29:421–424.
94. Love S, Mair TS, Hillyer MH. Chronic diarrhoea in adult horses: a review of 51 referred cases. Vet Rec 1992; 130:217–219.
95. Duckett WM, Matthews HK. Hypereosinophilia in a horse with intestinal lymphosarcoma. Can Vet J 1997; 38:719–720.
96. La Perle KMD, Piercy RJ, Long JF, et al. Multisystemic, eosinophilic, epitheliotropic disease with intestinal lymphosarcoma in a horse. Vet Pathol 1998; 35:144–146.
97. Mair TS, Pearson GR. Melanotic hamartoma of the hind brain in a riding horse. J Comp Pathol 1990; 102:239–243.
98. Mair TS, Hillyer MH, Taylor FG, et al. Small intestinal malabsorption in the horse: an assessment of the specificity of the oral glucose tolerance test. Equine Vet J 1991; 23:344–346.
99. Murphy D, Reid SWJ, Love S. Modified oral glucose tolerance test as an indicator of small intestinal pathology in horses. Vet Rec 1997; 140: 342–343.
100. Lindberg R, Nygren A, Persson SG. Rectal biopsy diagnosis in horses with clinical signs of intestinal disorders: a retrospective study of 116 cases. Equine Vet J 1996; 28:275–284.
101. Zicker SC, Wilson WD, Medearis I. Differentiation between intra-abdominal neoplasms and abscesses in horses, using clinical and laboratory data: 40 cases (1973–1988). J Am Vet Med Assoc 1990; 196:1130–1135.
102. Dabarainer RM, Sullins KE, Goodrich LR. Large colon resection for treatment of lymphosarcoma in two horses. J Am Vet Med Assoc 1996; 208:895–897.
103. Mair TS, Hillyer MH. Clinical features of lymphosarcoma in the horse: 77 cases. Equine Vet Educ 1991; 4:108–113.
104. Mair TS, Brown PJ. Clinical and pathologic features of thoracic neoplasia in the horse. Equine Vet J 1993; 25:220–223.
105. Van den Hoven R, Franken P. Clinical aspects of lymphosarcoma in the horse: a clinical report of 16 cases. Equine Vet J 1983; 15:49–53.
106. Scarratt WK, Crisman MV. Neoplasia of the respiratory tract. Vet Clin North Am Equine Pract 1998; 14:451–473.
107. Lee WL, Tennent-Brown BS, Barton MH, et al. Two horses with thoracic lymphoma diagnosed using thoracoscopic biopsy. Equine Vet Educ 2013; 25:79–83.
108. Sugiyama A, Takeuchi T, Morita T, et al. Mediastinal lymphoma with complete atrioventricular block in a horse. J Vet Med Sci 2008; 70: 1101–1105.
109. Davis EG, Rush BR. Diagnostic challenges: equine thoracic neoplasia. Equine Vet Educ, 2011.
110. De Clercq D, van Loon G, Lefère L, et al. Ultrasound-guided biopsy as a diagnostic aid in three horses with cranial mediastinal lymphosarcoma. Vet Rec 2004; 154:722–726.
111. Garber JL, Reef VB, Reimer JM. Sonographic findings in horses with mediastinal lymphosarcoma: 13 cases (1985–1992). J Am Vet Med Assoc 1994; 205:1432–1436.
112. Mackey VS, Wheat JD. Reflections on the diagnostic approach to multicentric lymphosarcoma in an aged Arabian mare. Equine Vet J 1985; 17:467–469.
113. Pollock PJ, Russell T. Standing thoracoscopy in the diagnosis of lymphosarcoma in a horse. Vet Rec 2006; 159:354–356.
114. Vachon AM, Fischer AT. Thoracoscopy in the horse: diagnostic and therapeutic indications in 28 cases. Equine Vet J 1998; 30:467–475.
115. Epstein V, Hodge, D. Cutaneous lymphosarcoma in a stallion. Aust Vet J 2005; 83:609–611.
116. de Bruijn C, Veenman JN, Rutten VPMG, et al. Clinical, histopathological and immunophenotypical findings in five horses with cutaneous malignant lymphoma. Res Vet Sci 2007; 83:63–72.
117. Kofler J, Kübber-Heiss A, Schilcher F. Cutaneous, multilocular T-cell lymphosarcoma in a horse. Zentralbl Veterinarmed A 1998; 45:11–19.

118. Grupta BN, Keahey KK, Ellis DJ. Cutaneous involvement of malignant lymphoma in a horse. Cornell Vet 1972; 62:205–215.
119. Neufeld JL. Lymphosarcoma in the horse: a review. Can Vet J 1973; 14:129–135.
120. Theilen GH, Madewell BR. Equine leukaemia complex. In: Theilen GH, Madewell GR, eds. Veterinary cancer medicine, 1st edn. Philadelphia: Lea and Febiger; 1979: 272–279.
121. Sheahan BJ, Atkins GJ, Russell RJ, et al. Histiolymphocytic lymphosarcoma in the subcutis of two horses. Vet Pathol 1980; 17:123–133.
122. Detilleux PG, Cheville NF, Sheahan BJ. Ultrastructure and lectin histochemistry of equine cutaneous histiolymphocytic lymphosarcomas. Vet Pathol 1989; 26:409–415.
123. Gerard MP, Healy LN, Bowman KF, et al. Cutaneous lymphoma with extensive periarticular involvement in a horse. J Am Vet Med Assoc 1998; 213:391–393.
124. Henson KL, Alleman AR, Cutler TJ, et al. Regression of subcutaneous lymphoma following removal of an ovarian granulosa-theca cell tumour in a horse. J Am Vet Med Assoc 1998; 212:1419–1422.
125. Hilbe M, Meier D, Feige K. A case of cutaneous epitheliotropic malignant lymphoma (mycosis fungoides) in a horse [German]. Berl Munch Tierarztl Wochenschr 1997; 110:86–89.
126. Potter K, Anez D. Mycosis fungoides in a horse. J Am Vet Med Assoc 1998; 212:550–552.
127. Kelley LC, Mahaffey EA. Equine malignant lymphomas: morphologic and immunohistochemical classification. Vet Pathol 1998; 35:241–252.
128. Schaffer PA, Wobeser B, Martin LE, et al. Cutaneous neoplastic lesions of equids in the central United States and Canada: 3,351 biopsy specimens from 3,272 equids (2000–2010). J Am Vet Med Assoc 2013; 242:99–104.
129. Johnson PJ. Dermatologic tumors (excluding sarcoids). Vet Clin North Am Equine Pract 1998; 14:625–658.
130. Henson KL, Alleman AR, Kelley LC, et al. Immunohistochemical characterization of estrogen and progesterone receptors in lymphoma of horses. Vet Clin Pathol 2000; 29:40–46.
131. Littlewood JD, Whitwell KE, Day MJ. Equine cutaneous lymphoma: a case report. Vet Dermatol 1995; 6:105–111.
132. Théon AP, Wilson WD, Magdesian KG, et al. Long-term outcome associated with intratumoral chemotherapy with cisplatin for cutaneous tumors in Equidae: 573 cases (1995–2004). J Am Vet Med Assoc 2007; 230:1506–1513.
133. Meyer J, DeLay J, Bienzle D. Clinical, laboratory and histopathological features of equine lymphoma. Vet Pathol 2006; 43:914–924.
134. Hermeyer K, Seehusen F, Gehlen H, et al. Cutaneous T-cell-rich B-cell lymphoma in a horse. Berl Munch Tierarztl Wochenschr 2010; 123: 422–424.
135. Roccabianca P, Paltrinieri S, Gallo E, et al. Hepatosplenic T-cell lymphoma in a mare. Vet Pathol 2002; 39:508–511.
136. Weidmann E. Hepatosplenic T cell lymphoma. A review on 45 cases since the first report describing the disease as a distinct lymphoma entity in 1990. Leukaemia 2000; 14:991–997.
137. Browning AP. Splenic lymphosarcoma in a stallion associated with an acute abdominal crisis. Vet Rec 1986; 119:178–179.
138. Tanimoto T, Yamasaki S, Ohtsuki Y. Primary splenic lymphosarcoma in a horse. J Vet Med Sci 1994; 56:767–769.
139. Madron MS, Caston SS, Reinertson EL, et al. Diagnosis and treatment of a primary splenic lymphoma in a mule. Equine Vet Educ 2011; 23:606–611.
140. Ralge CA, Mair TS. Evaluating the equine spleen. Equine Vet Educ 2007; 19:11–13.
141. Rigg DL, Reinertson EL, Buttrick ML. A technique for elective splenectomy of Equidae using a transthoracic approach. Vet Surg 1987; 16:389–391.
142. Cornelius CE, Goodbary RF, Kennedy PC. Plasma cell myelomatosis in a horse. Cornell Vet 1959; 49:478–493.
143. Markel MD, Dorr TE. Multiple myeloma in a horse. J Am Vet Med Assoc 1986; 188:621–623.
144. MacAllister C, Qualls C, Tyler R, et al. Multiple myeloma in a horse. J Am Vet Med Assoc 1987; 191:337–339.
145. Edwards DF, Parker JW, Wilkinson JE, et al. Plasma cell myeloma in the horse. A case report and literature review. J Vet Intern Med 1993; 7: 169–176.
146. Pusterla N, Stacy BA, Vernau W, et al. Immunoglobulin A monoclonal gammopathy in two horses with multiple myeloma. Vet Rec 2004; 155: 19–23.
147. Barton MH, Sharma P, LeRoy BE, et al. Hypercalcemia and high serum parathyroid hormone-related protein concentration in a horse with multiple myeloma. J Am Vet Med Assoc 2004; 225:409–413.
148. Kim DY, Taylor HW, Eades SC, et al. Systemic AL amyloidosis associated with multiple myeloma in a horse. Vet Pathol 2005; 42:81–84.
149. Morton AJ, Davis JL, Redding WR, et al. Nonsecretory multiple myeloma in a horse. Equine Vet Educ 2007; 19:564–568.
150. Drew RA, Greatorex JC. Vertebral plasma cell myeloma causing posterior paralysis in a horse. Equine Vet J 1974; 6:131–134.
151. McConkey S, López A, Pringle J. Extramedullary plasmacytoma in a horse with ptyalism and dysphagia. J Vet Diagn Invest 2000; 12:282–284.
152. Geelen SN, Bernadina WE, Grinwis GC, et al. Monoclonal gammopathy in a Dutch warmblood mare. Vet Q 1997; 19:29–32.
153. Seide RK, Jacobs RM, Dobblestein TN, et al. Characterization of a homogeneous paraprotein from a horse with spontaneous multiple myeloma syndrome. Vet Immunol Immunopathol 1987; 17:69–77.
154. Jacobs RM, Kociba GJ, Ruoff WW. Monoclonal gammopathy in a horse with defective haemostasis. Vet Pathol 1983; 20:643–647.
155. Henry M, Prasse K, White S. Haemorrhagic diathesis caused by multiple myeloma in a three-month-old foal. J Am Vet Med Assoc 1989; 194: 392–394.
156. Taintor J. Equine leukaemia. Equine Vet Educ 2012; 24:604–609.
157. Bienzle D, Hughson SL, Vernau, W. Acute myelomonocytic leukemia in a horse. Can Vet J 1993; 34:36–37.
158. Monteith CN, Cole D. Monocytic leukaemia in a horse. Can Vet J 1995; 36:765–766.
159. Brumbaugh GW, Stitzel KA, Sinkl KG, et al. Myelomonocytic myeloproliferative disease in a horse. J Am Vet Med Assoc 1982; 180: 313–316.
160. Blue J, Perdrizet J, Brown E. Pulmonary aspergillosis in a horse with myelomonocytic leukaemia. J Am Vet Med Assoc 1987; 190:1562–1564.
161. Forbes G, Feary DJ, Savage CJ, et al. Acute myeloid leukaemia (M6B: pure acute erythroid leukaemia) in a Thoroughbred foal. Aust Vet J 2011; 89:269–272.
162. Searcy GP, Orr JP. Chronic granulocytic leukaemia in a horse. Can Vet J 1981; 22:148–151.
163. Bernard W, Sweeney C, Morris F. Primary lymphocytic leukaemia in a horse. Equine Pract 1988; 10:24–30.
164. Buechner-Maxwell V, Zhang C, Robertson J, et al. Intravascular leukostasis and systemic aspergillosis in a horse with subleukaemic acute myelomonocytic leukaemia. J Vet Intern Med 1994; 8:258–263.
165. Ringger NC, Edens L, Bain P, et al. Acute myelogenous leukaemia in a mare. Aust Vet J 1997; 75:329–331.
166. Bezdekova B, Faldyna M, Zapletal O, et al. Acute B-lymphoid leukemia in a mare. Vet Med 2009; 54:249–255.
167. Roberts MC. A case of primary lymphoid leukaemia in a horse. Equine Vet J 1977; 9:216–219.
168. Lester GD, Alleman AR, Raskin RE, et al. Pancytopenia secondary to lymphoid leukemia in three horses. J Vet Intern Med 1993; 7:360–363.
169. Cian F, Tyner G, Martini V, et al. Leukaemic small cell lymphoma or chronic lymphocytic leukaemia in a horse. Vet Clin Pathol 2013.
170. Rendle DI, Durham AE, Thompson JC, et al. Clinical, immunophenotypic and functional characterization of T-cell leukaemia in six horses. Equine Vet J 2007; 39:522–528.
171. Dascanio JJ, Zhang CH, Antczak DF, et al. Differentiation of chronic lymphocytic leukaemia in the horse. A report of two cases. J Vet Intern Med 1992; 6:225–229.
172. Schwarz B, Gruber A, Benetka V, et al. Concurrent T cell leukaemia and equine multinodular pulmonary fibrosis in a Hanoverian Warmblood mare. Equine Vet Educ 2012; 24:187–192.
173. Clark P, Cornelisse CJ, Schott HC, et al. Myeloblastic leukaemia in a Morgan horse mare. Equine Vet J 1999; 31:446–448.
174. Boudreaux MK, Blue JT, Durham SK, et al. Intravascular leukostasis in a horse with myelomonocytic leukaemia. Vet Pathol 1984; 21:544–546.
175. Spier SJ, Madewell BR, Zinkl JG, et al. Acute myelomonocytic leukaemia in a horse. J Am Vet Med Assoc 1986; 188:861–863.
176. Mori T, Ishida T, Washizu T, et al. Acute myelomonocytic leukaemia in a horse. Vet Pathol 1991; 28:344–346.
177. McClure JT, Young KM, Fiste M, et al. Immunophenotype classification of leukaemia in 3 horses. J Vet Intern Med 2001; 15:144–152.
178. Burkhardt E, Saldern FV, Huskamp B. Monocytic leukemia in a horse. Vet Pathol 1984; 21:394–398.
179. Morris DD, Bloom JC, Roby KA, et al. Eosinophilic myeloproliferative disorder in a horse. J Am Vet Med Assoc 1984; 185:993–996.
180. Johansson AM, Skidell J, Lilliehöök I, et al. Chronic granulocytic leukaemia in a horse. J Vet Intern Med 2007; 21:1126–1129.

31

Tumours of the skin

Overview
Primary cutaneous tumours
Equine sarcoid 545
Occult sarcoid 546
Verrucose sarcoid 547
Nodular sarcoid 548
Fibroblastic sarcoid 550
Mixed (verrucous, nodular and fibroblastic) sarcoid 552
Malignant sarcoid 553
Fibroma and fibrosarcoma 561
Neurofibroma (schwannoma, neurilemmoma, neurinoma, nerve sheath tumour/perineural fibroblastoma) 562
Basal cell carcinoma 563
Mastocytoma (equine cutaneous mastocytosis/mast cell tumour) 564
Malignant fibrous histiocytoma (extra-skeletal giant-cell tumour) 566
Lipoma (liposarcoma) 567
Melanoma and melanosarcoma 568
Squamous cell carcinoma 575
Sebaceous gland tumour/carcinoma 580
Sweat gland tumour 581
Trichoepithelioma 581
Keratoma 582
Neoplastic conditions with cutaneous manifestations
Haemangioma/haemangiosarcoma 583
Cutaneous lymphoma 583
Lymphangioma 583
Mycosis fungoides (malignant cutaneous T-cell lymphoma 583
Pituitary pars intermedia dysfunction (PPID) (equine Cushing's disease) 583

OVERVIEW

The skin is by far the most common location of tumours in horses – many of the surveys of tumours carried out over the last century attest to the high numbers of skin tumours relative to other tumours. Although there are many tumour types, three primary skin tumours dominate the literature and practical case circumstances:

- Sarcoid
- Melanoma
- Squamous cell carcinoma.

These three tumour types make up over 95% of cutaneous tumours in the horse.[1,2] The remainder include various forms of lymphoma, basal cell carcinoma, haemangiosarcoma and mastocytoma and a multitude of lesser recognized tumours with rare or very rare incidence.

The most significant aspect of cutaneous neoplasia is the fact that the tumours can be seen or felt, or both. Their generally benign impression has, however, led to a general philosophy of indifference to their existence and this has significantly hindered therapeutic progress. Certainly, it is far easier to understand why an internal neoplasm without any external indicators of pathology can be overlooked to the point of late presentation. It is very hard to understand the 'thought process' that allows a visible, obvious and significant tumour on the skin to become a disaster. The rather casual approach to skin neoplasia from owners, in particular, has led to an unhelpful and rather introspective attitude to the conditions whereby veterinarians are, in turn, inclined to advise benign neglect: 'Monitor its progress and let me know when it gets bad'. This attitude is certainly counter to all recognized approaches to neoplastic disease in any other species. The owner could justifiably ask the veterinarian, 'Is this small tumour on my horse going to get smaller, easier and less dangerous with time, or is it going to get bigger, more difficult and more dangerous?' The next question that can be asked after the obvious answer is given can be, 'Would you prefer to do something about it now while it is small, easy and relatively safe, or would you prefer to have to operate when it is larger, difficult/impossible and pathologically dangerous?' Given that the melanoma, in particular, is almost invariably very benign when it is early and small and almost invariably becomes larger and/or malignant, the choice is obvious and stark.

Tumours that are 'out of context' in location and type are usually taken more seriously. Thus, where a melanoma occurs in non-grey horses, it usually has a more malignant implication and usually triggers a more positive approach from both owner and veterinarian. Squamous cell carcinoma is an aggressive, often invasive tumour but only rarely does it metastasize to other organs. Cutaneous lymphosarcoma is a serious problem but the cutaneous form has a much better prognosis than the multicentric forms (see p. 349). What is treatable depends primarily on the tumour type and extent and also on the available technology and the skill and experience of the veterinarian.

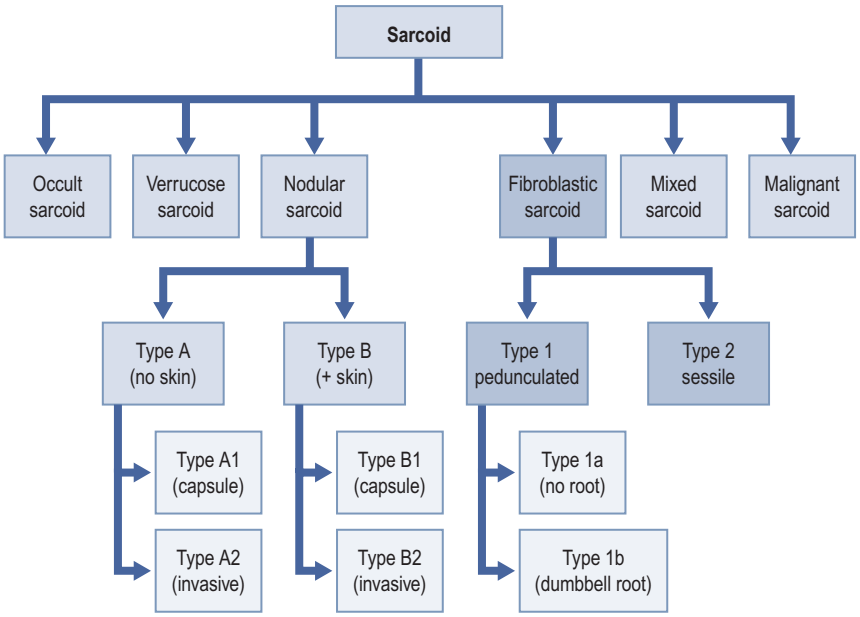


Figure 31.1 Classification of the equine sarcoid. The equine sarcoids can be classified into defined types based upon their morphological appearance and pathological characteristics. The type allocated is the predominate type of an individual lesion. The mixed sarcoid type is only used when no other single predominate type can be applied.

PRIMARY CUTANEOUS TUMOURS

Equine sarcoid

See also page 203.

Disease summary

Notes

Most common skin tumour of horses worldwide. Associated with the bovine papilloma virus-1. The tumour is locally invasive in all its forms but non-metastatic.

Clinical features

Six different morphological forms are recognized – each has its own characteristics. Progression from earlier mild forms to more severe forms is common.

Diagnostic confirmation

Diagnosis is by biopsy (although this can cause exacerbation).

Management

The full range of treatment options are available, ranging from simple surgical excision to radiotherapy, but no treatment is consistently effective.

Prognosis

Recurrence following treatment is very common. The prognosis is generally good, provided that the tumours are controlled. The condition seldom 'kills', but many horses are destroyed as a direct result of untreatable or unacceptable sarcoid tumours.

Overview

The sarcoid is the most common cutaneous tumour of Equidae worldwide; it can affect all Equidae, including horses, mules, donkeys, ass, onagers and zebras.

Clinically and pathologically, sarcoids present most of the features of a true neoplasm. The predominant cell type is a malignant/transformed fibroblast with characteristic in vitro appearance and histological features.

Sarcoids generally have a high capacity for local tissue invasion into the dermis and subcutis. However, true metastatic dissemination does not occur. Tumours can appear in freshly healing wounds in previously normal horses or re-occur at the same site following apparent complete surgical removal even up to 10 or more years later.[3,4]

Sarcoid is a locally aggressive fibroblastic tumour occurring in six clinically recognizable forms, all of which have a high propensity for recurrence (Fig. 31.1).[5,6] An individual horse may have more than one sarcoid type but there are, however, some individual horses that have a predominate type – sometimes exclusively. Although each of these forms is commonly identifiable, it is important to recognize that the 'less severe' forms can rapidly progress to the more aggressive types, particularly if they are traumatized. Furthermore, the specific types may not be clearly identifiable in every case and then the 'mixed' category is applied. It is, however, usually obvious that even the mildest forms are indeed sarcoid – in vitro cell cultures derived from these are typical and indistinguishable from those taken from the more aggressive lesions. These factors suggest that both cell and host factors are responsible in combination for the variety of forms.

Classification of the lesion type is important because the different types have different therapeutic demands and different prognostic implications (see Fig. 31.1). What may suit a small occult lesion in one site may not be applicable to the aggressive fibroblastic lesion in another. This classification is supported by pathological descriptions and is important because treatment options and prognosis vary for the different types of sarcoid. Furthermore, there is a general tendency towards progression from the milder superficial types to the more aggressive forms, either as a result of natural development or as a result of accidental or iatrogenic interference. The latter tends to cause a more aggressive and rapid exacerbation. However, it is important to recognize that the sarcoid does not have defined boundaries between the various types. Usually, the lesions have some aspects of other types and many do progress

from one type (usually occult or verrucose) to the more aggressive types (fibroblastic and malignant). There is, however, no predictable progression, except to emphasize the dramatic changes that can follow interference or injury of a sarcoid.

The malignant form is rare but, as a form of the disease, it is a serious complication, given that there are no effective treatments for this form and that the nature of the condition is likely to have a significant systemic and local effect on the horse.

The number of sarcoids affecting individual horses is very variable. Single lesions are encountered both spontaneously and associated with wound sites. Sarcoids commonly multiply on the individual horse, sometimes very rapidly. Some lesions remain relatively, or even completely, static for years and then may suddenly expand without any apparent reason.

A few individuals show spontaneous full and permanent self-cure and a very few disappear spontaneously after being accidentally or intentionally (by biopsy) traumatized, but both of these circumstances are exceptions rather than the rule. Interestingly, spontaneous remission usually means that the horse will not develop further lesions. However, the course of the condition is entirely unpredictable and it is unwise to make any firm predictions on the course or the likelihood of a successful treatment.

The clinical implications of sarcoid are, potentially at least, serious. Whilst a few superficial sarcoids may have no immediate effect on the horse or its performance, there is real potential for both individual lesion exacerbation and an increase in the number of sarcoids on the horse. Fortunately, sarcoid is a non-metastatic tumour, but it can be very aggressive locally. The condition has a serious implication on the commercial value of the horse and may compromise the use of the horse due to the anatomical location or size and appearance of the tumours.

- The individual lesions have a tendency to exacerbation (although this may not be invariable and it can occur over a very variable time).
- More sarcoids are likely to develop over time and these may not necessarily be of the same type as the original lesion(s).
- The lesions will probably require some form of treatment and this is likely to be problematic and expensive.
- Failure of any chosen treatment method represents a major setback and subsequent treatments are likely to be even more difficult.
- The condition may directly affect the performance of the horse or at least there will be periods of time during treatments or during fly seasons when the horse will not be useable.
- The likely sale value of an affected horse will be lower than it would have been had it not had any sarcoids and, when the horse is sold on at a later date, the sarcoids may be a significant deterrent to purchase.

The condition has become a major aspect of pre-purchase examination and insurance complications; it is unlikely that an insurance company will provide insurance cover for skin diseases and neoplastic conditions, if, at the time of proposal, there is any evidence at all of sarcoid.

In many neglected cases, the disease becomes a significant welfare issue. As flies pester the horse, secondary infection and fly strike occur and serum and blood loss can be significant. Apart from these aspects, the cosmetic aspects are significant for many owners. Finally, severe sarcoid has been a common cause of legal charge on the grounds of cruelty and neglect.

Clinical features

The clinical recognition of the equine sarcoid is considerably complicated by the spectrum of variously recognizable skin lesions that are included in the clinical and pathological classification. Each of the recognized types has several variations and individual horses can have several different types at the same time. There is nothing prescriptive about what types of sarcoid occur in particular types of animal and in particular locations. However, there are broad principles that can be useful in some cases. The size of lesions is not related to the type and it is entirely possible to have small or large lesions of each recognized type and that there may be a wide variety of lesions and sizes on a particular animal. The presence of several different types on the same horse is a strong diagnostic support, but of course other concurrent conditions can be very similar and can then complicate the diagnostic process.

The variation in clinical presentation means that each type of sarcoid has its own set of different differential diagnoses.

Occult sarcoid

Clinical features

- Occult sarcoids manifest as hairless areas, often roughly circular and with a thinned skin in the affected area (Fig. 31.2).
- They usually contain one or more small cutaneous nodules (2–5 mm diameter) or roughened areas with a mild hyperkeratotic appearance but these may or may not be present or obvious in every case. Careful palpation of the skin between thumb and forefinger will, however, usually confirm their presence, even when very small.
- Some occult lesions are extensive, covering very large areas of skin. The typical appearance is still the same, but invariably nodules or verrucose areas can be identified within the affected skin (see Fig. 31.2).
- In some cases, the skin will feel diffusely thickened and, in others, the thickened areas are distributed almost randomly within the changed area.
- An area of changed/altered, slightly thickened skin, with thin hair coat and slight changes in hair pigment, may be all that is seen; these changes may be difficult to identify in winter-coated animals.
- The lesions are characteristically slowly progressive but they may develop 'warty' verrucous growths or, if

injured (or subjected to biopsy or ill-advised treatment attempts), may develop rapidly into fibroblastic lesions.
- Pain and pruritus are not features of occult sarcoids and there is no discernible systemic effect, regardless of the extent or number of lesions.



Figure 31.2 Occult sarcoid. A typical occult sarcoid on the medial thigh of a 14-year-old Thoroughbred mare. There is obvious alopecia and slight scaling – the lesions have a characteristic circular appearance. Notice the relationship of the lesions to major cutaneous blood vessels. In some cases, the skin changes are more or less prominent and may include small areas of ulceration. In this case, there are small areas of ulceration resulting from persistent fly worry but the circular, alopecic nature is clear. The skin may be palpably thickened and/or loses its natural elasticity. Changes in hair pigmentation (paler or darker) can also sometimes occur.

- Predilection sites include the skin around the mouth and eyes, the neck and other relatively hairless areas of the body, including the medial aspects of the forearm and thigh. It is rare on the limbs and main body trunk but they can be found at any site in individual cases.
- Cases may remain static for many years; however, extensive development of verrucose sarcoid or conversion into fibroblastic-type sarcoid usually demands immediate attention. This can occur at any time with or without apparent insult.

Note

While the lesion remains as a static/quiescent hairless patch, showing no evidence of progression in either size or number of nodules, it may be wise not to interfere. However, this represents the earliest stage of the condition and, as such, may be the best time to institute treatment.

Differential diagnoses

- Idiopathic alopecia/hypotrichosis
- Dermatophytosis (ringworm)
- Bullous disorders: including pemphigus foliaceus, vasculitis (immune-mediated and autoimmune forms)
- Rub marks, chronic skin rubbing and scarring resulting from obvious cause such as rug or harness contact
- Alopecia areata.

Verrucose sarcoid

Clinical features

- Verrucose sarcoids have a characteristic wart-like appearance in and on the skin (Fig. 31.3A) and this appearance is the main reason for referring to sarcoids







Figure 31.3 Verrucose sarcoid. (A) A wart-like circular verrucose sarcoid that had progressed from an occult area over a 2–3-week period. This lesion also overlies a prominent cutaneous vein. Notice the feint occult margin, which is pathognomonic of sarcoid. **(B)** This case has typical multifocal verrucose sarcoids. Notice the wart-like appearance of the individual lesions and the distinctive (pathognomonic) occult margin/halo around most of but not all of these sarcoids. **(C)** Verrucose sarcoid can be very extensive, as in this case – similar extensive changes were present on both medial thighs and the side of the face.

as 'warts'. The surface is scaly and it is often easy to dislodge the superficial accumulated keratinized material easily, without pain or haemorrhage.
- The lesions are invariably alopecic when they occur on normal, haired skin.
- Some ulcerate and may bleed.
- They are not painful unless infected and are not pruritic.
- In many individual lesions, the area involved is relatively localized and, in some, there is an occult margin extending around the affected area, imparting an obvious halo around the wart-like centre (Fig. 31.3B). There may, however, be many lesions, each with subtle variations in the amount of occult rim and the amount of 'piled up keratin' and even some extensive lesions may be missed under long-hair cover.
- Many start out roughly circular, reflecting possible progression from occult lesions, but extensive changes (Fig. 31.3C) that have no defined margins are common. Extensive areas of skin can be affected and some can be surrounded by an area of slightly thickened/changed skin with an altered, thin hair-growth pattern (occult halo), possibly reflecting a surrounding area of early occult sarcoid.
- When examined closely, individual lesions may be sessile (flat-based) or pedunculated (with a narrow neck), but coalescing lesions are more common than isolated small ones. Small nodules may appear at any stage or over any area of the affected skin. Some areas may become ulcerated and crusting can be somewhat misleading.
- They are most often slow growing and not usually very aggressive until injured/insulted. Rubbing, biopsy, partial excision or minor or major trauma to the surface commonly results in a dramatic exacerbation to a true fibroblastic character over variable areas of the lesion. They may, however, develop, whether or not they are insulted or traumatized.
- Pain and pruritus are not features of the verrucose sarcoid and secondary infections are uncommon, even when superficial ulceration occurs.
- The history and clinical examination will rapidly establish the natural progression, but the changes may be limited to smaller or larger areas of the verrucose sarcoid.
- Predilection sites include the face (and particularly the eyelids and periorbital skin), body, axillae and groin/sheath areas. This form is rare on the limbs.

Differential diagnoses

- Papillomatosis (warts)
- Linear keratosis/epidermal naevus
- Dermatophytosis
- Chronic 'therapeutic' vesicant blistering
- Hyperkeratosis from chronic pruritic disease, skin irritation/rubbing (responsive hyperkeratosis)
- Equine sarcoidosis (chronic granulomatous disease)
- Equine (cutaneous) systemic lupus: erythematosus-like syndrome (dermal form)
- Squamous cell carcinoma.

Nodular sarcoid

Clinical features

The nodular lesions are easily recognizable as firm, well-defined subcutaneous, usually spherical nodules of 10–75 mm diameter, but individual nodules can be much larger and there can be many nodules of varying size, complexity and location.

Nodules fall into two distinct categories based upon the relationship/involvement of the overlying skin (Table 31.1). Each of these is further divided into two based upon the extent of involvement with surrounding tissues.

Type A nodules

Type A nodules have no cutaneous involvement. The skin can be moved freely over the nodule and there are no changes in the overlying skin (except in a few very long-standing cases in sites where there is very thin skin, such as the eyelid when the overlying skin can become atrophied and very thin).

These are then usefully subdivided into two subtypes:

- *Type A1* nodules (Fig. 31.4):
  - The nodule is enclosed in a loose fibrocellular capsule and can be moved independently of the skin *and* the underlying structures.
  - In some cases, the weight of the nodule creates a skin pedicle – this can only occur with a Type A1 nodule because binding into subcutaneous tissue will more often preclude the weight from hanging on the skin alone.
- *Type A2* nodules:
  - These have no cutaneous involvement but are locally invasive with a 'bound-down' character – this precludes independent movement of the nodule

Table 31.1 The clinical and pathological features of nodular sarcoids

Nodular sarcoid		Clinical and gross pathological features
Type	**Subtype**	
A: No cutaneous involvement Single or multiple Individual or multilobular No occult changes directly associated with nodules	1	No deep tissue involvement Loose fibrocellular capsule Defined margins
	2	Deep tissue involvement Invasive 'bound-down' character Ill-defined margins
B: Cutaneous involvement Single or multiple Individual or multilobular Possible occult and occasionally verrucose margin on skin	1	No deep tissue involvement Loose fibrocellular capsule Defined margins
	2	Deep tissue involvement Invasive 'bound-down' character Ill-defined margins

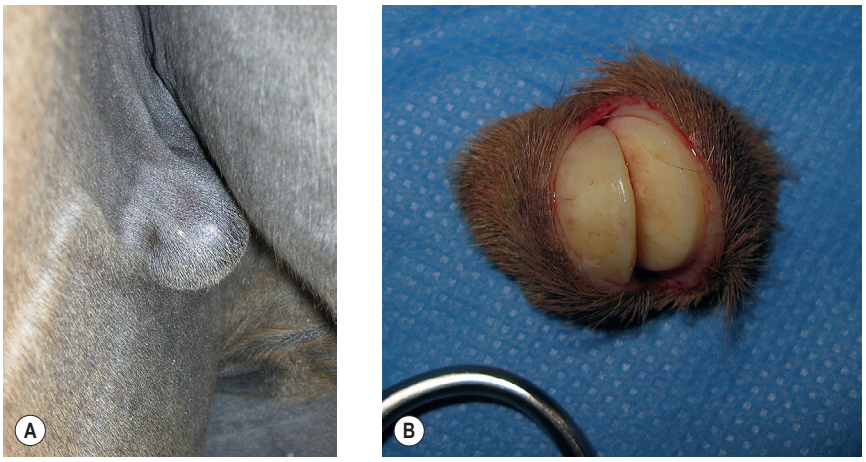


Figure 31.4 Type A1 nodular sarcoid. **(A)** A typical Type A1 nodular sarcoid on the medial thigh. The skin can be moved freely over the mass and the mass can be moved freely over the subcutaneous tissues. **(B)** A Type A1 nodule excised from the belly skin of a 6-year-old gelding. Notice the loose fibrocellular capsule that allows the sarcoid itself to 'shell out' easily from the capsule. Sometimes the skin overlying the mass is thin but there is no connection between the lesion and the skin itself.



Figure 31.5 Type A2 nodular sarcoid. The lower lid masses in this case are good examples of Type A2 nodules. The skin can be moved over the top of the nodules, but the nodules cannot be moved independently of the tissues below and around the nodule, i.e. the nodules are 'bound down'. This is a very common event with eyelid nodules. *(Figure reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 393 (Fig. 18.19), copyright 2009, reprinted with permission from Elsevier.)*

relative to the deeper structures in the subcutis and beneath.
- This is a very common type around the eye (Fig. 31.5).

Type B nodules

- These have visible or palpable cutaneous involvement that means the overlying skin cannot be moved over the nodule.
- Usually, the overlying skin is obviously abnormal (either hyperkeratotic or thinned and alopecic) and occasionally ulcerated. In some cases, the skin is ulcerated completely and then a fibroblastic lesion can develop (Fig. 31.6).
- This type is also divided into two subtypes according to the deeper pathological nature:
  - *Type B1* nodules have no deep tissue invasion
  - *Type B2* are 'bound-down', seemingly attached to the surrounding and deeper tissues.
- The firm involvement of the skin may preclude a proper test of its deeper invasive nature.
- All Type B nodules are potentially dangerous and this is particularly so around the eye and the side of the mouth, where invasion can be extensive (Fig. 31.6B).

The overlying skin of any of the types may become thin/hypoplastic or atrophied over larger nodules of both A and B types. Type B nodules may have some adjacent occult changes in the skin, but this does not occur with Type A1 or A2 nodules.

When the skin ulcerates, the masses quickly take on a more aggressive fibroblastic character. A similar aggressive fibroblastic response commonly follows iatrogenic or accidental damage.

The number of nodules varies widely – single, few, several or even hundreds are common. Many cases of both Type A and Type B nodules have multiple interlinking nodules (see Fig. 31.5 and Fig. 31.6B).

Pain and pruritus are not common features – the condition is often very benign in this form, but some can become extremely complex and invasive.

Predilection sites include the groin, sheath or eyelid regions. Nodular sarcoids are very rarely found on the distal limbs, possibly because they are rarely associated with wounds.

Differential diagnoses

- Fibroma/fibrosarcoma
- Neurofibroma (schwannoma)
- Equine eosinophilic granuloma/collagenolytic granuloma
- Melanoma
- Equine cutaneous mastocytosis/equine malignant cutaneous mastocytosis/congenital equine mastocytoma
- Lymphosarcoma/lymphoma/cutaneous histiocytic lymphoma
- Dermoid cyst
- *Hypoderma* spp. (warble fly) cysts:
  - Foreign body/fly bite reaction.

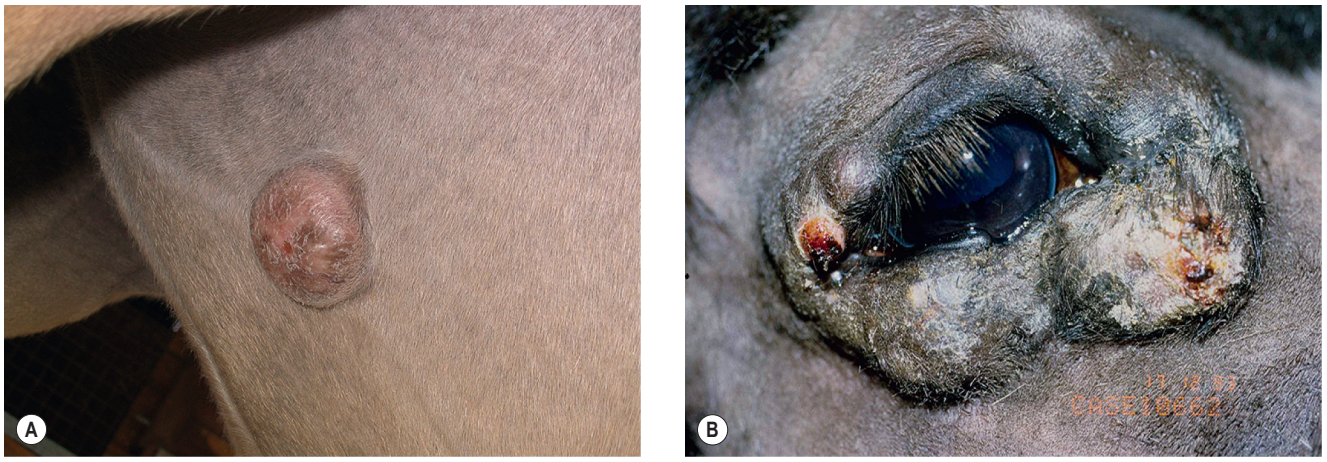


Figure 31.6 Type B nodular sarcoid. (A) The skin over this firm Type B1 sarcoid nodule could not be moved independently of the nodule but the nodule can be moved freely over the underlying tissue. Notice the definite cutaneous changes typical of sarcoid. Sometimes the lesions can be multilobulated. **(B)** Commonly, the nodules are complex and linked, as in this case. Note the marked secondary cutaneous involvement with extensive verrucose changes and focal areas of ulceration. The nodules that cannot be moved independently of the deeper structures (including the bone of the orbit) are Type B2 nodules.

Table 31.2 The clinical and pathological features of fibroblastic sarcoids

Fibroblastic sarcoid		Features
Type	**Subtype**	
1: Pedunculated	a	Distinct pedicle No deep tissue involvement
	b	Distinct pedicle Wide/palpable 'root' Invasive 'bound-down' character Ill-defined margins of root
2: Sessile/ broad-based	'Bound-down' character Ill-defined margins	



Where these lesions occur on the distal limb regions in particular they are a major problem and are often associated with a previous wound. As the clinical appearance can be very similar to granulation tissue it is important to establish when and if a wound occurred and to biopsy the tissue.

Fibroblastic sarcoid

Clinical features

Fibroblastic sarcoid can be conveniently divided into two broad clinically recognizable groups (Table 31.2).

- *Type 1* (pedunculated) *fibroblastic sarcoid*: These have a narrow skin 'pedicle' with a fleshy ulcerated (often bleeding) crown. Quite often, it is possible to palpate normal, thin skin adjoining the lesion but sometimes the pedicle is very short and then the true nature of the lesion can only be defined by ultrasonography or after a surgical or other procedure to debulk the external mass. This group has two clinically significant and recognizable subgroups.
  - *Type 1a* (pedunculated) sarcoids have no discernible root – the base feels free of any thickening or palpable tumour and there are no histologically detectable deep extensions of the sarcoid tissue. The detection of deep extensions is clearly difficult in early lesions but usually it is possible to get an impression of normality both within and deep to the pedicle (Fig. 31.7A).
  - *Type 1b* (*pedunculated and rooted*) sarcoids have a distinctive root that is palpable beneath the narrow pedicle; it may not be extensive on palpation but the significance of any deep thickening either within or below the pedicle can be used to confirm the Type 1b fibroblastic sarcoid. The difference between these and the Type 1a (non-rooted pedunculated sarcoid) can be visible, but sometimes can be better appreciated by palpation (Fig. 31.7B). In some cases, the pedicle can be very short (particularly where there is little loose skin, such as on the distal limb and face). The term 'dumbbell' form gives a good impression of the clinical and pathological nature of the Type 1b (*pedunculated*) fibroblastic sarcoid.
- *Type 2* (sessile) *fibroblastic sarcoid*: In this case, the lesions are sessile; they have a broad base without any detectable narrowing at the skin level. This type invariably has extensive involvement beneath the visible lesion and this may extend some distance from the apparent skin margin. Deep and lateral cutaneous involvement occurs and so the sarcoid may be bound down to the deep tissues and a diffuse ill-defined margin in the dermis/epidermis. Frequently, these lesions are exudative and bleed easily (Fig. 31.8).

These tumours have a characteristic aggressive, fleshy, ulcerated appearance, commonly with a fibrocellular scab over the surface and secondary infection. There is commonly superficial infection, serum exudation and the lesions are easily traumatized, causing haemorrhage. Both pedunculated and extensive sessile tumours with prominent

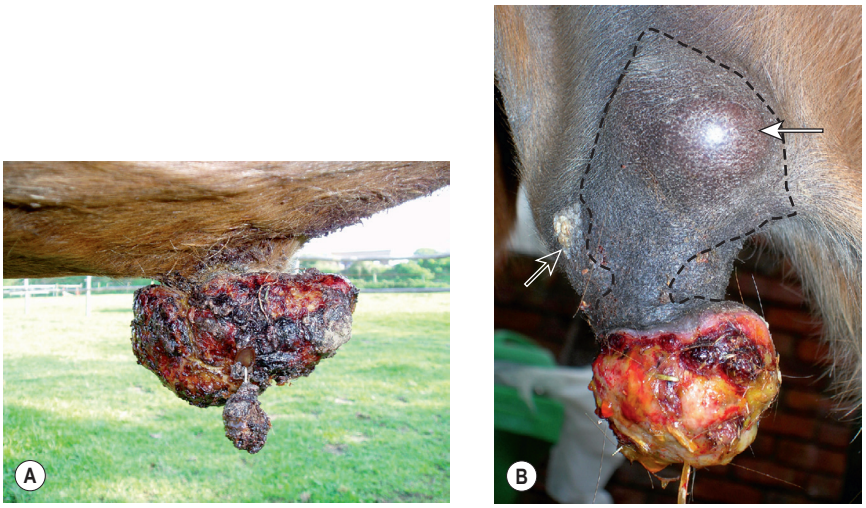


Figure 31.7 Fibroblastic sarcoid. (A) A typical Type 1a (pedunculated, non-rooted) fibroblastic sarcoid. Note the fleshy and aggressive-looking mass but the relatively narrow pedicle. From a clinical perspective alone, it is sometimes impossible to be sure that there is no deep extension beyond the skin level. **(B)** This fibroblastic sarcoid fulfils the criteria for classification as a Type 1b (it is pedunculated but rooted) or dumbbell form. The main lesion is the ulcerated mass, whilst the narrow stalk expanded proximally to a large nodular and invasive mass in the subcutis above (arrow). The palpable form of the sarcoid is shown in the dotted lines. This has involved the skin surface and could, on its own, be classified as a Type B2 nodule (see above). Note also the adjacent small verrucose lesion, which was incidental (open arrow). The horse had many such verrucose lesions but only one fibroblastic sarcoid. *(Figures reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 395 (Fig. 18.25), copyright 2009, reprinted with permission from Elsevier.)*

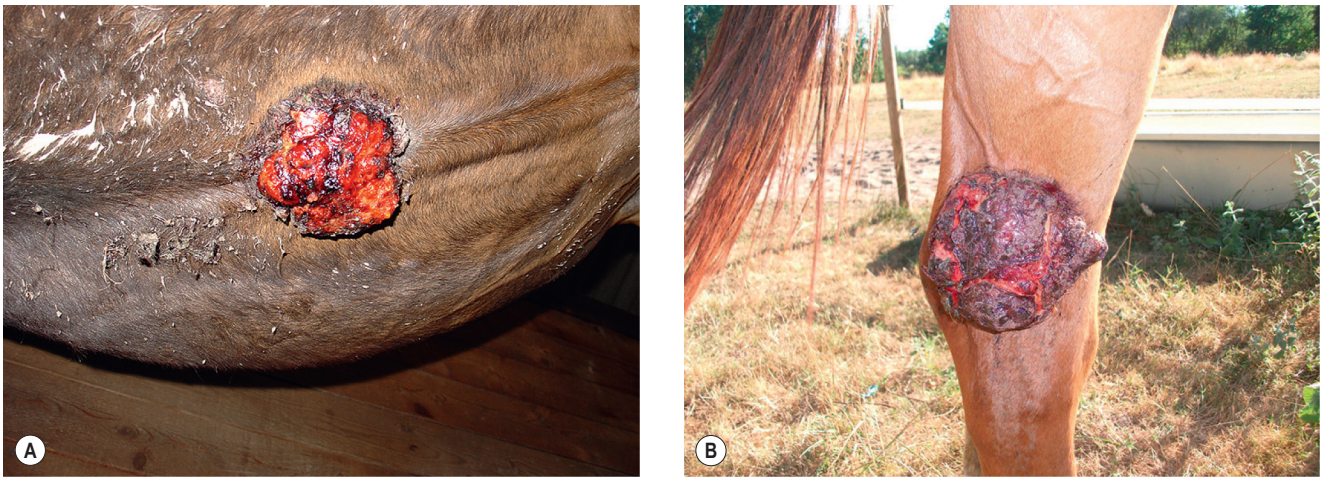


Figure 31.8 Fibroblastic sarcoid. (A) A typical flat/broad-based fibroblastic sarcoid on the ventral midline. Notice that there is no pedicle; the attachment to the underlying tissues occupies the whole area of the sarcoid. **(B)** Broadly based, non-pedunculated fibroblastic sarcoid over the tarsus. The extent of attachment means that treatment is severely constrained at this anatomical site.

ulceration and serum exudation are commonly encountered. The latter may reflect single or repeated insults to the 'lesser' forms but may develop spontaneously.

Fibroblastic sarcoids of both broad types are common at sites of wounds and particularly on distal limb wounds, especially if other sarcoids are present elsewhere. Repeated insult (accidental or iatrogenic) appears to encourage local subdermal and dermal invasion. Therefore, tumours that have had previous unsuccessful treatment attempts can be extremely difficult to manage and become progressively more sessile and malignant in nature.

Concurrent (excessive) granulation tissue growth serves to confuse the diagnosis. Accidental wounds which fail to heal may contain significant sarcoid components in the wound margins and are irregularly and unpredictably mixed with granulation tissue. One of the common features of this type of sarcoid is the history of interference, either intentionally or accidentally. Even minor trauma can trigger an expansion of the lesion and repeated insults can result in a challenging clinical position (Figs 31.9, 31.10). This form is particularly attractive to surface-feeding flies and in the summer months they can cause considerable extra surface ulceration and infection. In spite of their open nature, myiasis seldom seems to occur in this type of sarcoid (in contrast to the pedunculated form where this is a much more frequent occurrence).

Even when the lesions are highly ulcerated and aggressive, pruritus and pain are rarely present. Very large pendulous sarcoids may irritate the horse and repeated trauma can cause heavy bleeding.



Figure 31.9 Type 2 (sessile) fibroblastic sarcoid. The history of this aggressive Type 2 sessile fibroblastic sarcoid included several vain attempts to remove the expanding lesion by surgical excision. After each attempt, healing was disrupted and the sarcoid returned with increasing aggression. Treatment was very problematic and prolonged. *(Figure courtesy of Dr Martin Stokli; reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 396 (Fig. 18.28), copyright 2009, reprinted with permission from Elsevier.)*

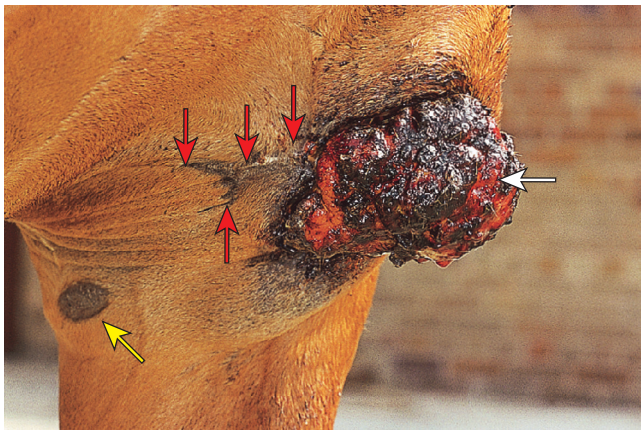


Figure 31.10 Highly aggressive, sessile, rooted fibroblastic sarcoid. This pony developed a highly aggressive, sessile, rooted fibroblastic sarcoid (white arrow) at the site of a relatively trivial wound that appeared to heal well until 6 weeks' post-injury (red arrows show the 'healed scar'). Several smaller focal sarcoid lesions were present along the wound. Clinical examination revealed an occult sarcoid in the axilla (yellow arrow) that had been present for 5 years without apparent change. *(Figure reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 396 (Fig. 18.29), copyright 2009, reprinted with permission from Elsevier.)*

Surgical wounds are also liable to sarcoid development. Dehiscence of the suture line within 2–7 days (or up to 5 years afterwards) for no apparent/obvious reason may be suggestive of sarcoid development.

Predilection sites include the groin, eyelid, lower limbs and coronet, sites of skin wounds at any location and sites of any other types of sarcoid subjected to trauma or insult.

At some anatomical sites, such as the distal limb, coronary band and eyelid, this type of sarcoid can carry a very poor prognosis.

In spite of their aggressive appearance and in common with other types of sarcoid, they do not metastasize. However, they can spread locally in the dermis by local invasion/extension and then they may justifiably be classified as malignant.

Differential diagnoses

- (Exuberant) granulation tissue
- Botryomycosis/pyogranuloma/pseudomycetoma
- Neurofibroma (schwannoma)/neurofibrosarcoma (ulcerated)
- Squamous cell carcinoma
- Haemangioma/haemangiosarcoma
- Cavernous haemangioma/vascular hamartoma
- Habronemiasis
- Pythiosis ('swamp cancer')
- Fibrosarcoma
- Sweat gland tumour
- Giant cell sarcoma
- Mycosis fungoides.

Mixed (verrucous, nodular and fibroblastic) sarcoid

Overview

In clinical circumstances, almost every lesion could be classified as mixed, in that most if not all sarcoids have several different types within the affected site. The mixed classification is, however, reserved for those lesions where there is no predominant type. This type of sarcoid probably represents a progressive/transient state between the verrucous/occult types and fibroblastic/nodular types and, in many cases, there are obvious sarcoid types visible. It is entirely possible that a single area actually contains all the available types to varying extents (Fig. 31.11).

Clinical features

- Variations in proportion of the types is infinite and complex mixtures of any or all of the above types (containing both verrucous and fibroblastic elements) are common in long-standing lesions or those subjected to repeated minor trauma (such as rubbing by tack or harness or those that are subjected to partial or irrational treatment attempts).
- They become progressively more aggressive as more fibroblastic transformation takes place – a common consequence also of biopsy or injury.
- Predilection sites include the face, eyelid, groin and medial thigh, but the reality is that most lesions at most sites could justifiably be termed 'mixed sarcoid'.

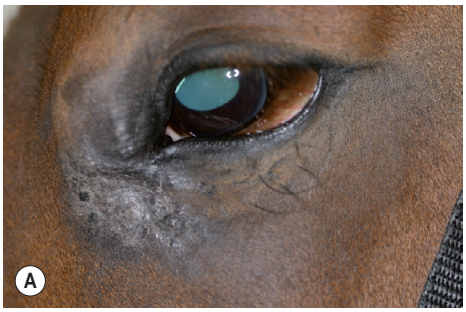




Figure 31.11 Many sarcoids are mixed, but usually it is possible to identify a predominant type. The mixed classification is restricted to those lesions in which a predominant type is not definable. **(A)** This mixed periocular sarcoid contains approximately equal elements of verrucose and nodular sarcoid. **(B)** A mixed lesion containing elements of fibroblastic and verrucose, as well as nodular sarcoid in the axilla of a young Welsh pony. *(Figures reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 398 (Fig. 18.31), copyright 2009, reprinted with permission from Elsevier.)*





Figure 31.12 The malignant form of sarcoid has particularly aggressive clinical behaviour, although it does not necessarily have to be extensive. Common sites for this form are the side of the face **(A)** and the elbow region, particularly in the region of the olecranon **(B)**. *(Figures reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 399 (Fig. 18.32), copyright 2009, reprinted with permission from Elsevier.)*

Differential diagnoses

There is little problem with recognition of the mixed sarcoid – the presence of more than one form of sarcoid in a single lesion is virtually pathognomonic.

- Complex mixtures of *granulation tissue* in verrucose and/or fibroblastic sarcoid. (The fibroblastic forms of sarcoid can contain granulation tissue in various proportions and so biopsy should be taken carefully.)
- *Habronemiasis* (particularly if affecting ulcerated verrucose sarcoid).
- *Pemphigus complex*.

Malignant sarcoid

This is a recently described rare variation of the equine sarcoid.[6,7] A history of repeated trauma to other types of sarcoid, e.g. repeated surgical interference or applications of inappropriate medications, is commonly involved. However, some cases have no such history and the clinical presentation varies. The malignant classification can justifiably be given to a development of typical multiple, locally invasive sarcoids of nodular and fibroblastic character. They can, however, be very much more localized (Fig. 31.12).

Clinical features

- Cords of nodules and ulcerated lesions over a wide area could be simply large numbers of unconnected nodules or fibroblastic lesions, but where connections occur subcutaneously, the classification of malignant sarcoid should be used. Individual horses may have a single area involved, such as around the eye or in the groin, but others have multiple severely affected areas at some or all of the characteristic locations.
- Locally malignant sarcoid is a possible sequel to surgical excision and to wounds – particularly where the latter are subjected to repeated trauma.

- Whilst most of these remain reasonably local, some track down lymphatic vessels and invade local tissues.
- Others show extensive infiltration of lymphatics (cords of tumour are commonly palpable), with numerous ulcerative nodules and surface involvement. Although the local lymph nodes can be enlarged, there are no reports of sarcoid tissue within them.
- No disseminated metastases have been reported for any sarcoid.
- Predilection sites include the jaw, face, elbow and medial thigh areas in particular.
- A rare particular form of malignant sarcoid that is relatively under-recognized and very dangerous occurs in the neck/jugular (Fig. 31.13A) and occasionally elsewhere, including over the buttock region. In this form, a ring of nodules surrounds a 'relatively normal' verrucose or occult central zone. This ring of nodules expands progressively, leaving larger areas of verrucose and occult change in the middle (Fig. 31.13B). On occasion, the whole area erupts into a malignant invasive complex (Fig. 31.13C).

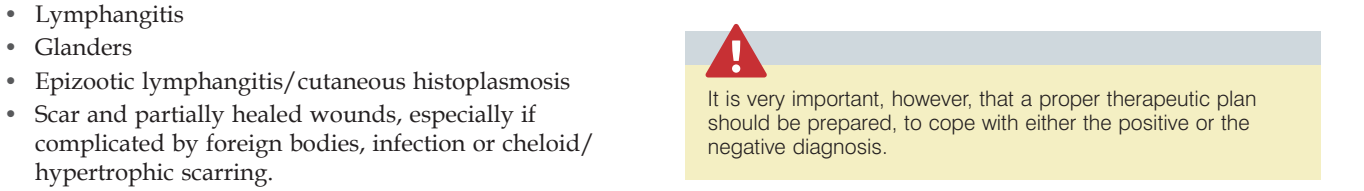
Differential diagnoses

- Squamous cell carcinoma
- Lymphoma/lymphosarcoma (generalized or cutaneous histiocytic lymphosarcoma)
- Subcutaneous mycosis
- Lymphangitis
- Glanders
- Epizootic lymphangitis/cutaneous histoplasmosis
- Scar and partially healed wounds, especially if complicated by foreign bodies, infection or cheloid/hypertrophic scarring.

Diagnostic confirmation

The clinical features of sarcoid, in general, are usually clearly recognizable, but confirmation of the diagnosis is not always straightforward. Multiple tumours with the characteristic features of more than one type of sarcoid on an individual horse make the diagnosis relatively simple – there is no other disease with the same range of clinical features and types. However, it is also easy to assume that all the lesions are in fact variants of sarcoid, when in fact there may be other coexisting conditions. It is always wise to assess each suspicious area and consider the full range of differential diagnoses for that single lesion before moving on to the next one.

- *Partial or excisional biopsy* will almost always provide a definitive diagnosis, but there is a recognized risk of exacerbation following surgical biopsy. The attendant risks are probably minimal if a fine-needle aspirate is taken from the margin of a suspected lesion, but the interpretation of these is much more difficult (and more usually inconclusive) and so in exchange for the safety, there is a risk of a false-positive or -negative diagnosis. A total excisional biopsy rather than a sample biopsy should therefore be performed if this option is to be used and is feasible.



It is very important, however, that a proper therapeutic plan should be prepared, to cope with either the positive or the negative diagnosis.





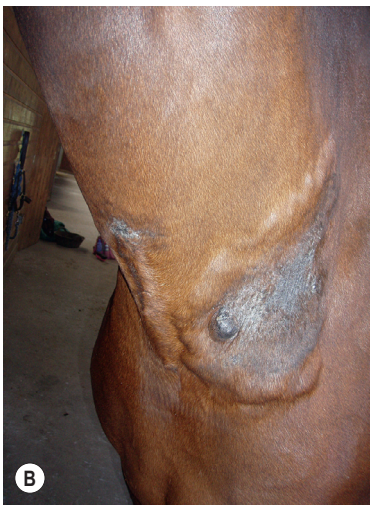


Figure 31.13 Malignant sarcoid – expanding ring nodular form. (A) A typical early case of the unusual expanding ring nodular form of sarcoid. Notice the distinct ring of nodular masses that surround the central verrucose area. This case started with a very limited ring of connected nodules some 12 months previously. **(B)** This is a more advanced case of the malignant ring form – notice how the ring of nodules expands, leaving a verrucose or sometimes even a near-normal central part. The horse also had a similar lesion on the right neck. In this case, there is a Type B nodule within the central zone. **(C)** A severe form of the malignant expanding nodular form of sarcoid. The nodules have ulcerated and extended to involve most of the neck.

Biopsy with no plan is dangerous – the risks are too high and if no definitive therapeutic plan can be made, then a biopsy should probably *not* be taken at all. A biopsy should not be taken if it is not going to influence the subsequent management in any way.

- *Superficial swabs* taken from the surface of a suspected lesion can be subjected to PCR testing. Identification of the BPV genome in these swabs is reported to be highly significant.[8] However, the virus can be found on the normal skin surface and in sites of other skin pathology.

Management

Treatment should follow as soon after diagnosis as possible. Suspicious lesions can justifiably be treated immediately after biopsy using an appropriate regimen (see below). The different forms of sarcoid all require subtly different approaches – some are easier and some are more complex, but it is not only the type of sarcoid that makes a difference. Aspects of extent and location and previous interferences are at least as significant in terms of treatment selection. Aspects of logistics, horse and owner compliance and cost have also to be considered. What might suit one circumstance might not suit another.

General treatment considerations

- The prognosis for all cases is very guarded and owners must be made aware of the possible serious complications which can arise from this disease. Owners must be apprised of the limitations, cost and likely/possible outcome of the various treatment options.
- No case of sarcoid can be considered to be free of the disease, even following apparently successful treatment (Fig. 31.14). Remission periods of 5 years are usually considered reasonable in many neoplastic conditions, but the sarcoid is complicated by a known tendency for longer periods of dormancy and by the genetic predisposition to the disease.

Note

A horse [donkey, mule or zebra] that has even one sarcoid lesion is, *ipso facto*, liable to the disease and remains so for life. New lesions and recurrence at sites of previous lesions should be expected throughout the life of the affected animal.

- There is a strong likelihood, therefore, that prolonged or repeated treatments will be required. However, complete, spontaneous regression of tumours is occasionally encountered (Fig. 31.15) and owners can then be reasonably assured that the condition is *unlikely* to recur.[9] This does *not*, however, apply when every single lesion on an individual is treated 'successfully' – in these cases, there is probably no immunological response and so they are in fact still liable to develop more lesions and recurrences at the site of previously treated lesions.



Figure 31.14 'Wart' – massive sarcoid. Surgical removal of a localized 'wart' from this site was thought to be successful when the wound appeared to be healing well. The original location of the surgical incision is shown by the dotted line. However, the wound broke down distally at 8 days – 1 day after suture removal – and this massive sarcoid developed over the following 2 months. Biopsy confirmed the diagnosis. Note the smaller lesions in the more proximal parts of the wound. *(Figure reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 400 (Fig. 18.35), copyright 2009, reprinted with permission from Elsevier.)*

Treatment methods

Many treatment methods, including conventional and non-conventional approaches, have been used with varying reported success. Where there is a multitude of different treatments, the implication is clear – either they have severe restrictions or none is universally effective. In the case of the sarcoid, both of these factors are important. Only those treatments which are documented and reported to have a benefit and those that the author has personal experience of are considered here.

The various treatment methods described below may be more or less applicable to specific types of sarcoid. Currently, there is no effective treatment regimen for the malevolent form of the disease – treatment is invariably palliative only.

Benign neglect

Benign neglect is a realistic option in some cases where either the lesions are so small as to make the cost and procedure of treatment seem disproportionate or so extensive as to make any method impossible. For the former cases, this option should always be viewed with some caution, as many cases become progressively worse.

The option of benign neglect may be suitable for the affected horse(s), but it does of course mean that the existing sarcoids could be a problem in terms of spread to other sites on the horse or (to a far lesser degree admittedly) to other horses. A photographic record is very useful and, of course, is very accurate. The record should enable another veterinarian, who might attend the case in the future, to make a sensible judgement on the rate of progression.

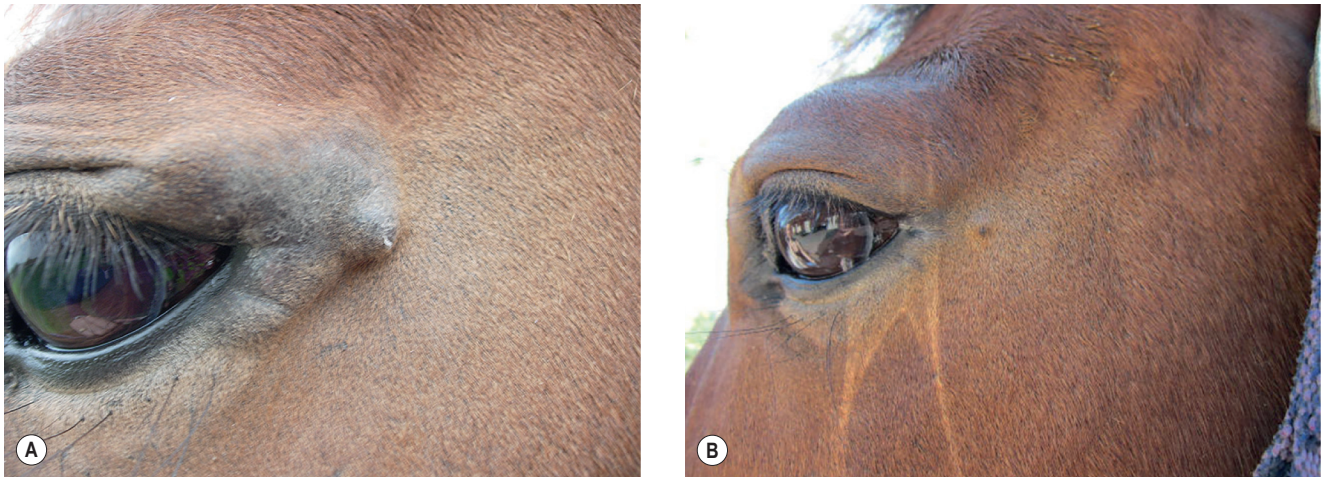


Figure 31.15 Spontaneous resolution of a Type B nodular sarcoid. (A) This complex Type B nodular sarcoid developed at the lateral canthus of the eye over a period of 8 months from a small verrucose plaque that had been present for some 12 months. At 4 weeks after diagnosis, the lesion showed an improvement and so treatment was delayed. One month later, there was a definite reduction in both extent and severity. **(B)** After a total of 4 months, the lesion disappeared, leaving a very limited 'localized area'. One year later, nothing could be seen and the horse never developed any other sarcoids. *(Figures courtesy of Georgie Critchley.)*

Careful owner counselling is also an important aspect of this option; in the event that the owner recognizes deterioration, then of course immediate veterinary attention should be sought. Owners will also benefit from careful advice on fly control, wound management and the need for regular reassessments.

For the most part, the option of benign neglect should only be used when the case can be monitored for progression or when a proposed treatment method/interference cannot expect to resolve the problem at all. Some lesions even resolve spontaneously (see Fig. 31.15).

Palliative treatment

Palliative treatment of the equine sarcoid is usually counterproductive but any method that slows down the deterioration could be viewed as reducing the severity of the problem and prolonging the life of the horse. For extremely large and 'impossible' lesions, this can be an effective approach for a temporary benefit.

Surgical methods

Ligation

See also page 127.

- This is limited to small nodular lesions (Type A1 and Type B1) or fibroblastic lesions with a well-defined 'neck' (Type 1a, *pedunculated*).
- A convenient method for this is the use of lamb castration/elastration bands. These are cheap, effective and convenient but are limited in size. Ligation with plastic 'ties' or with suture material is far less effective and tends to cut rather than squeeze, and so recurrence rates are far higher. Quite often, it is helpful to place several of the bands around the base of the lesion – each being applied closer to the body of the horse than the preceding one. In this way, extra tissue is incorporated and the risks of recurrence are correspondingly less.
- Occult, verrucose, sessile fibroblastic (Type 2), invasive nodules (Types A2 and B2), mixed sarcoids and malignant sarcoids are usually not amenable to this treatment. Results with Type A1 and Type B1 nodular lesions in the groin, in particular, are satisfactory.
- Partial ligation of a large lesion is a high-risk strategy, unless there is a definite plan for treatment of the remaining sarcoid tissue immediately following the sloughing of the necrotic part. This is more likely, however, to result in exacerbation and a reduced prognosis, unless the second phase is instigated immediately and treatment is persistent thereafter.

Surgical excision

- Although this is an easy, attractive, fast and effective option in some cases, there is a high rate of recurrence in all except the most confined and defined lesions. Recurrence rates can be over 70% within 6 months and often the recurrences are more aggressive and in larger numbers.[10,11]
- In many circumstances, this is, however, the only practical option available and then it is important that the best possible technique is applied to maximize the benefit. Wide excision carries the best prognosis where surgery is used. Nonetheless, it is wise always to give a very guarded prognosis when surgery is used. The concept of SMART surgery, in which cell contamination is minimized (or preferably eliminated) remains the standard approach in most cases. This also improves the prognosis significantly (see Fig. 9.3 and p. 120).
- Superficial (occult and verrucose) lesions can be effectively treated by wide excision provided that the wound can be closed and then protected during complete healing. Any delay in healing may be due to sarcoid regrowth. Complete or partial failure of the wound to heal is early evidence that there is residual tissue in the wound site. Wound breakdown within days of surgery is a common immediate indicator of failure to excise all the sarcoid tissue, but sarcoid regrowth can take up to ≥5 years to recur at the site. Rapid development of fibroblastic sarcoid commonly follows and, indeed, removal of a single lesion may be followed by development of several new sarcoids at the

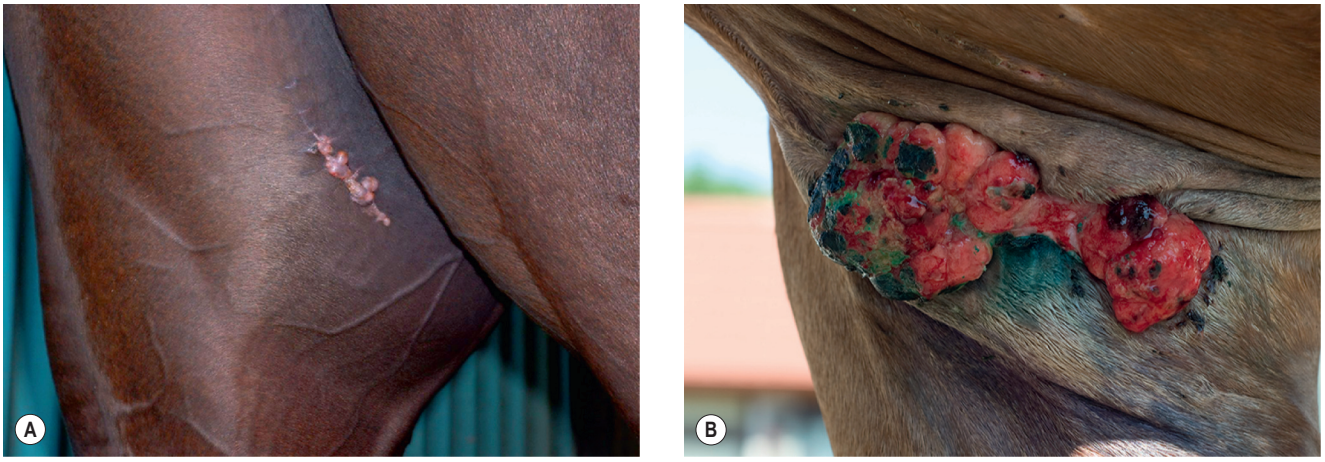


Figure 31.16 Recurrence of a Type B sarcoid. (A) A Type B sarcoid was removed from this caudal thigh some 14 weeks previously. The wound healed well initially but then it became obvious that several new lesions were developing in the site. Surgical pathology of the original mass and biopsy of the new lesions confirmed both were sarcoid. The reason for recurrence of this type may be the seeding of the operative site with cells from the original lesion or may be due to incomplete excision. **(B)** An apparently superficial linear verrucose sarcoid was removed surgically from this axilla of an 8-year-old gelding. Recurrence occurred rapidly over the following 4 weeks, with a marked proliferation of fibroblastic sarcoid. *(Figure A reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 404 (Fig. 18.36), copyright 2009, reprinted with permission from Elsevier; Figure B courtesy of Zoltan Zagyi.)*

site – this possibly reflects that the tumour was not completely excised and/or that the wound site was seeded with desquamated transformed (tumorous) fibroblasts. It is wise to protect the sarcoid lesion with plastic adhesive dressings or a swab over the main lesion prior to starting the surgery (Fig. 31.16).

- Notwithstanding the limitations of surgery, excision of nodular lesions carries a somewhat better prognosis provided that the lesion is not attached to the skin and provided that the operative site is not contaminated with sarcoid tissue released by cutting into the lesion itself. Where these criteria can be met, the prognosis is usually fair. Nodular lesions in the eyelids, however, are potentially very dangerous, as they commonly have extensive ramifications through adjacent tissues and often extend into the muscles of the eyelids.[12] Surgery almost always fails in these sooner or later.
- Type 1b (*pedunculated/dumbbell*) and Type 2 (*sessile*) fibroblastic sarcoids and mixed and malevolent sarcoids are not generally suitable for surgical excision alone. The prognosis following surgery can be improved somewhat by combining it with other modalities in a combination of cryosurgery, cautery, hyperthermia, topical cytotoxic compounds, immunotherapy with BCG, intralesional slow release cisplatin or 5-fluorouracil injections or radiation.

Should recurrence occur, an alternative method should be used as quickly as possible. Combination methods are usually the best option if recurrence occurs.

Cryosurgery

See also page 126.

- Cryosurgery is commonly used but suffers from the same limitations as sharp excision. On its own, it has a relatively poor success rate, except in the smallest and most defined lesions, which carry a reasonable success rate provided that the procedure is controlled and correct. The margins of the lesion need to be defined and thermocouples placed so that the whole lesion is destroyed without unnecessary damage to underlying or adjacent tissues. Furthermore, it is particularly difficult to apply in a controlled fashion to large areas and infiltrative lesions.
- Aggressive cryosurgery involving the crude application of liquid nitrogen is not an acceptable method. There is uncontrolled tissue destruction and often this fails to resolve the larger lesions in any case.
- The reported benefit from cryoantigens released into the bloodstream, which results in a resolution of lesions remote from the treated one, has not subsequently been substantiated.[13] However, reports of up to 100% success have been made, but this is likely to be the result of a combination of careful case selection and meticulous procedure.
- Combination therapy (usually with surgical debulking prior to cryonecrosis) may carry a better prognosis, but the freezing process following surgical debulking may do little more than destroy seeded cells in the wound bed. Heavy bleeding complicates cryo-destruction, with a general loss of efficacy.

Hyperthermia/radiofrequency hyperthermia

See also page 129.

Hyperthermia relies upon the extra sensitivity of tumour cells to temperature rises and the method is reported to produce some good results, albeit in a very few cases. Repeated procedures are required and the extent of the tumour has to be defined, so that every sarcoid cell can be effectively treated. Tissue is heated to 50°C for 30 s and the procedure repeated weekly for up to 5 weeks.[14] The method has not gained general acceptance. High-frequency therapeutic ultrasound has a similar effect in raising the temperature of tumour masses but there are no reports of its application in sarcoids.

Electrocautery

Surgical electrocautery has advantages in that the margin of the lesion is effectively cauterized and so is extended beyond

the incisional line. Furthermore, bleeding from the margins of the wound is minimal. However, its efficiency depends on the extent of the tumour and its locality. Scarring can be limited if primary closure of the wound is possible. It is one of the few possibilities for treatment of pinnal sarcoids (especially those on the skin of the inside of the ear). In this site, there are particular difficulties with treatment, such as the lack of any subcutaneous or supportive connective tissue or muscle and the close proximity of the lesions to major blood vessels in the ear flap. The practical options are extremely limited and this method does seem to work in a reasonable number of cases.

Laser surgery (CO_2-YAG laser/diode laser excision)
(See p. 124)

- Laser excision is reported to have a higher success rate than sharp surgery; up to 80% of treated cases may be successful.[11] Again, selection of the most appropriate lesions is very important. Laser surgery may be even more effective in donkeys and mules than in horses, but it is likely that the nature of the lesion and the location are major factors in the prognosis. Typically, the prognosis will depend on careful case selection.
- The major benefit appears to lie in the bloodless field of surgery and the low rate of recurrence may reflect the destruction of marginal cells, which might be left viable by surgery or cryosurgery. Postoperative swelling and pain are minimal and primary closure may be possible.
- Laser surgery is often the only effective alternative to diathermy for treating localized lesions on the pinna – especially where the lesion is on the medial wall. *Non-rooted, pedunculated (Type 1a)* fibroblastic eyelid tumours can also be successfully treated in this way.
- CO_2 laser surgical equipment is expensive initially and to maintain, but the development of diode lasers has made this less of a consideration. Special safety precautions are required when lasers are used – these include eye protection, shielding all reflective surfaces and careful use of the laser pulses.

Local/topical medication with cytotoxic or antimitotic compounds/chemotherapy

Topical chemotherapeutic agents including cytotoxic and antimitotic compounds such as 5-fluorouracil or cisplatin can be used effectively. They are limited, however, by their overall efficacy and the need to sustain medication over prolonged periods. However, when topically applied or injected into lesions, they seem to have little or no untoward systemic effects.

- *Heavy metal compounds* (inorganic arsenic/antimony/mercury salts): (see p. 140) These induce extensive tissue necrosis and scarring. Combinations of these compounds can limit the toxicity of each individual one but still maintain the efficacy. They are easy to apply and some complex mixtures of these with antimitotic, corticosteroid and cytotoxic drugs, such as AW4-LUDES, have a reasonable reputation (Fig. 31.17).
- *5-Fluorouracil*: (see p. 153) This can be applied as a 5% ointment under a bandage or topically on a twice-daily basis for some weeks. It can be successful on single, small occult or verrucose sarcoids and is also a useful material for controlling large areas of verrucose or occult sarcoid, which cannot effectively be treated by any other means. Scarring is usually minimal, although the treated area can show marked reaction, as cells are destroyed over a wide area of the surface of the skin.
- *Podophyllum*: There are few reports of the use of this material, which is used to treat human viral papilloma. Disappointing and unreliable results are reported anecdotally, with a few good reports. The material needs to be applied at least daily and some cases may not respond at all, while others may be exacerbated.
- *Imiquimod* (Aldara 3M): (see p. 154) This material is used to treat human genital warts and is said to be an immune response modifier with potent antiviral and anti-tumour properties. A preliminary study involving 19 cases resulted in a detectable and worthwhile benefit. Some 80% of lesions showed a 60–75% improvement.[15] The material is applied to the surface of the tumour three times a week for between 16 and 32 weeks. The therapeutic benefit is slow to develop and is accompanied by alopecia, inflammation and depigmentation in the treatment site. It is not clear which of the major properties brings the benefit. There are reports of serious human side-effects but none of these has so far been reported in horses.

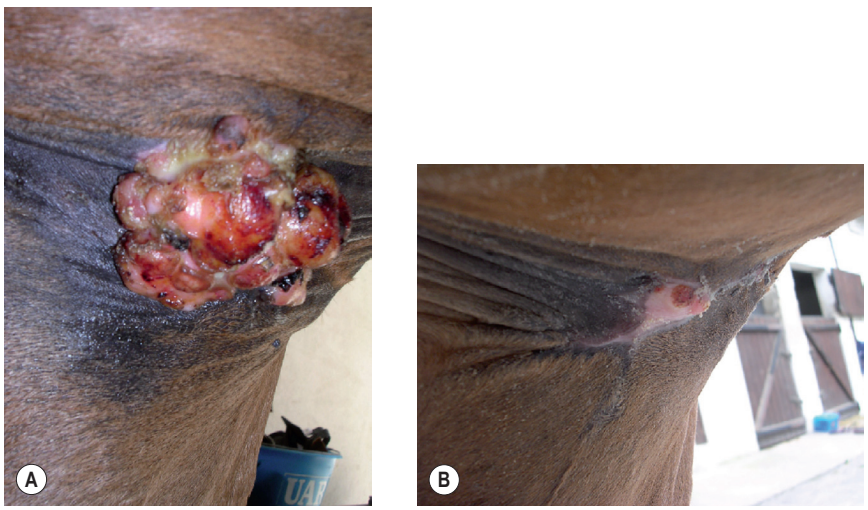


Figure 31.17 Type 2 (sessile) fibroblastic axillary lesion. (A) This highly invasive Type 2 (sessile) fibroblastic axillary lesion was treated with repeated courses of AW4-LUDES over a period of 12 months. **(B)** The outcome was very encouraging, although there was a small recurrence after 2 years. This site is always problematic, no matter what treatment is selected. *(Figures reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 405 (Fig. 18.37), copyright 2009, reprinted with permission from Elsevier.)*

- *Silver nitrate* (caustic pencil) application: This is a rather old-fashioned method that relies upon the direct tissue destructive effects of silver nitrate. It is applied by means of a 'styptic/caustic' pencil to very small localized lesions only.
- *Formalin-based gels* (Lotagen, Hoechst): This is a derivative of the human wart treatment and is only applicable to very few small, superficial sarcoids. There are no reports of clinical trials but some anecdotal reports of successes.

Intralesional anti-mitotic/cytotoxic chemicals

See also page 145.

- *Bleomycin*: 5–7 weekly repeated intralesional injection of 1.5 mg bleomycin (Blenoxane, Bristol Meyers Oncology, USA) has been reported to be an effective regimen for small localized tumours.[16] However, other attempts to use the same regimen have failed to show any material advantage over other intralesional and topical compounds.[17]
- *Cisplatin* (cis-diaminedichloro-platinum; DDP) (Platinol, Bristol Myers Oncology, USA; Cisplatin Injection, David Bull Laboratories, Warwick, UK and Mulgrave, Victoria, Australia): (see p. 146) Good results are reported for small fibroblastic and nodular lesions in particular but it requires repeated injection into the site of the lesion. In some cases it can be used in conjunction with surgical debulking to improve the overall outcome. Cisplatin has a broad spectrum effect against epithelial and fibroblastic (mesenchymal) tumours and this is used to treat sarcoid tumours.

  Results indicate that up to 93% of sarcoid tumours <5 cm diameter are resolved by this method. Tumours >5 cm may require surgical debulking prior to injection and that when this is performed, the results are reported to be better than simple wide surgical excision – indeed results in difficult sites are said to be up to 100% successful.[17]
- *Intralesional cisplatin* infiltration can be significantly enhanced by the procedure of electrochemotherapy (see p. 147); this method relies upon the increased tissue permeability arising from direct application across the site of an electrical current. Although there are no reports of other chemicals being used in this way, it is quite likely that some improvement will be achieved.
- *5-Fluorouracil injections*: Repeated intralesional infiltration of a sarcoid lesion with this material can have significant benefit. However, there are no reported control studies. The best doses and frequency of injections are not yet clear. Slow release biodegradable emulsions, sponges and beads are being developed and these systems will provide better controlled release of the chemicals so less drug and better results can be expected.

Electrochemotherapy

See also page 158.

- Electrochemotherapy has been shown to be effective in localized individual tumours. It has limited applications because of the need for repeated general anaesthesia and specialist equipment.

Photodynamic therapy

See also page 160.

- This method relies upon defined wavelength light to an area that has been pre-treated with a photodynamic agent. The agent can be applied topically and then the light source is applied to that area or the agents can be administered parenterally and the lesion then exposed to the required wavelength of light. Results are not widely reported but the technique is being used with increasing frequency in other species for other tumour types. Ultimately, it is likely that the agent can be delivered to the tissues in an antibody bound form and so the procedure would specifically target the tumour cells.

Phytotherapy

See also page 194.

- The use of various plant extracts either topically or by injection, has gained some popularity in spite of very poor results. The only material that has been subjected to a proper clinical trial (in both humans and horses) is an extract of mistletoe (*Viscum album*). In the treatment of sarcoid this material (Iscador® P) subcutaneous injection of this material had a poor overall outcome but some cases were treated successfully.[18]

Immunological methods

- Treatment attempts with 'vaccinations' has been undertaken by several research workers and is still performed by some practitioners. Bovine 'wart vaccine' has been used and was found valueless. It may indeed make the condition worse. Pox vaccines administered intralesionally are also unsuccessful. The studies involving 'vaccination' have been consistently disappointing and the general consensus is that they cannot be supported at the present time.[19] Vaccination with bovine or equine papilloma virus vaccines have been ineffective.[20,21]

Vaccines (autogenous)

- The use of autogenous vaccines in treatment of the equine sarcoid is probably contraindicated. Many sarcoid cases which are treated with an autogenous vaccine are worse afterwards, with some cases developing several thousand lesions. However, the cases do resolve spontaneously, suggesting that there is some 'immunological' response available but autogenous vaccines do not appear to be the most appropriate way of inducing this.
- Subcutaneous autologous transplantation of liquid nitrogen frozen blocks of sarcoid tissue has been reported as being an effective treatment but is fraught with hazard. Nevertheless, there are reported positive outcomes (see also p. 191).

Immunomodulation

- Immunomodulating proteins including various types of protein cell-wall fractions derived from Bacillus Calmette-Guérin (BCG) or other mycobacteria, or live, freeze-dried (lyophilized) BCG have been used widely. Other proteins and 'stimulating' materials have also been used.
  - *Bacillus Calmette-Guérin* (BCG) (and related protein derivatives) (see p. 189): The reconstituted purified protein extract or preferably lyophilized live bacteria,

is injected intralesionally at repeated intervals. The technique carries a fair to good prognosis for treatment of nodular and some fibroblastic lesions in and around the eyelids in particular.[12] The prognosis seems to be worse away from this area and some fibroblastic lesions on the limbs appear to be aggravated rather than treated and in fact, become worse. The method is probably not appropriate for mixed, verrucose or occult lesions because the diffuse nature of the tumours precludes effective intralesional injection. There is an ill-defined (slight, but definite) risk of an occasional anaphylactic reaction that is significantly higher with repeated injections and highest if a repeat course is carried out after some months/years.

- *Nonspecific immunostimulation*: A crude extract of *Propionibacterium acnes* (Eqstim®, Neogen, USA) is marketed in the USA as a safe but potent stimulator of cell-mediated immunity. Although there is no data sheet indication for sarcoid treatment, it has been used both by intramuscular injection and intralesional injection. There are anecdotal reports of successes and failures and it is suggested that this is an inappropriate method for treatment of equine sarcoids.[22] A similar, nonspecific oral product known as Equimune® is advertised in USA as a means of stimulating immunity. The suggestion is that this results in an immunological restoration and the ability to specifically treat a wide variety of medical disorders. Until there are properly controlled, double-blinded clinical trials suggesting genuine evidence of efficacy, these products have no indication in the management of sarcoid tumours.
- *Interferon and interleukin*: (see p. 186) Trials in the treatment of sarcoid with high dose systemic and intralesional interferon and interleukins are being carried out in several centres. The preliminary results are disappointing, but the approach may be found to be helpful in some particular early cases.

Radiation methods

See also page 179.

Radiation is by far the most effective method of treatment but has severe limitations of availability and cost. Radiation (brachy- or tele-) therapy using gamma radiation carries a very good prognosis within the limits of the technology. It is usually limited by cost and availability as well as the need to consider operator safety. It is therefore usually restricted to smaller lesions in areas for which no other method is suitable, such as the eyelids and over joints, etc. (Fig. 31.18) The value of beta radiation delivered to superficial lesions by plesiotherapy (see p. 184) is doubtful in view of its poor penetration through tissues. It is therefore not applicable to larger tumours with extensive tissue involvement (see p. 184).

Typically for any radiation treatment, the beneficial responses are slow to appear and it may take up to 14 months for example in cases treated with iridium-192 linear interstitial brachytherapy. In the interim, the treated site often develops purulent discharging sinus tracts or moderate to severe inflammation. Some cases however, respond faster and without significant superficial necrosis. The outcome is cosmetically excellent in most cases but as might be expected, there is a degree of scarring, some pigmentary loss and frequently alopecia. Radiation does not discriminate between neoplastic cells and normal cells, so some collateral damage is likely and this can be significant, e.g. the cornea may become cloudy, cataract may develop and even underlying bone may sequestrate.

General comments

Particular problems are encountered when treating sarcoids at difficult sites, such as the eyelids, face, lips, coronary band and over joints and other synovial structures. Notwithstanding the risks of surgery, it is sometimes the only viable option. For example, topical applications on the medial thigh can be highly problematic with possible contact with the unaffected adjacent limb and belly wall. Axillary lesions are often particularly difficult with slow healing and a high rate of recurrence. There is also a significantly increased difficulty with sarcoid transformation at wound sites.

In all cases, whether at a difficult site or not and whether complicated by the extent and type of the lesion(s), the best possible treatment *must* be applied on the first occasion. Failures make the likelihood of future success much less and progressive difficulty is likely with repeated failures of treatment. The choice of treatment remains a clinical decision that should be taken only after all the aspects of the condition are considered. Specialist advice is often available from referral centres and equine dermatologists.



Figure 31.18 Severe malignant periorbital sarcoid. (A) This horse was presented with severe malignant periorbital sarcoid that had been treated by surgical excisions and by application of various topical concoctions. **(B)** At 14 months following treatment with low dose iridium-192 brachytherapy. **(C)** Note the secondary/consequential corneal fibrosis and the alopecia and pigmentary changes. There is also a small anterior capsular cataract. The horse had other lesions at other sites but no recurrences occurred at this site over 6 years.

Prognosis

The prognosis for any sarcoid must be guarded. There is strong tendency both from the veterinary profession and owners to belittle the disease through the terms 'wart' and 'Angleberry'. These imply some sort of benign nature akin to normal viral papilloma on cattle and horses, but there is little predictable about the equine sarcoid and it is unwise to ignore it.

The prognosis is significantly reduced with each sequential failure to resolve the lesions and this applies also to other lesions on the horse that are not subjected to treatment at the time.

It is highly likely that recurrences will occur at treatment sites at any time, between days and 20–30 years after treatment, and that new lesions will likely develop in any (genetically) susceptible horse. The only cases that appear to be unlikely to develop any more lesions are those that spontaneously resolve without any treatment. The same does not, however, apply to horses that are treated to the point of having no apparent lesions at all.

Fibroma and fibrosarcoma

See also page 287.

Disease summary

Notes

Rare, usually solitary tumour of fibroblast cells, with a range of malignancy. Older horses more often affected.

Clinical features

Firm or soft ill-defined locally invasive subcutaneous tumour.

Diagnostic confirmation

Biopsy is important to differentiate it from sarcoid and neurofibroma.

Management

Surgical excision plus concurrent local chemotherapy if the surgical margins are not safe.

Prognosis

Malignant forms do occur but metastasis is rare.

Overview

This is an uncommon tumour arising from dermal or subcutaneous fibroblasts. Older horses are more liable to be affected, with predilection sites on the head, legs, neck and flanks. Lesions are usually solitary, well-defined nodular subcutaneous masses that range in size from 3 to 25 cm diameter.

Fibroma of the sole is one area where the diagnosis can probably be justified in most cases. It is one of the commonest neoplasms encountered in the frog of the horse's foot. However, it is also possible to confuse this form with dense granulating frog fibrous tissue at the site of a wound or chronic foreign body reactions.

Myxofibroma or fibromyxoma is also applied to some tumours with focal areas of mucinous degeneration but, again, they are clinically indistinguishable from sarcoid.

Fibrosarcoma is very rare and represents the malignant form of the fibroma – a high proportion of these cases will, in fact, be aggressive fibroblastic or malignant sarcoid.

Clinical features

- Often, single, firm or soft, well-circumscribed, dermal or subcutaneous nodules, which may ulcerate or develop into a flattened, verrucous or fleshy, cauliflower-like lesion, especially when the fibrosarcoma form develops (Fig. 31.19).
- The surface may be hyperkeratotic in the early stages.
- The large majority of tumours that are classified as 'fibroma' or 'fibroma durum' are, in fact, clinically typical of nodular sarcoids (see p. 548) and the differentiation of the two is probably unnecessarily justified on clinical or therapeutic grounds.
- A particular form of fibroma occurs on the sole of the foot.

Differential diagnoses

- Sarcoid
  - From a clinical perspective, the differentiations from sarcoid are extremely difficult, although most genuine fibrosarcomas are very solid, slow growing and ill-defined
- Lymphoma/lymphosarcoma
- Other tumours (including keratoma of the foot)
- Exuberant granulation tissue
- Foreign body reaction.

Diagnostic confirmation

Histological section of biopsy or whole tumour is essential for diagnostic confirmation.

Management

- 'Total' surgical excision or cryotherapy of the invasive forms of fibrosarcoma carries a poor success rate – possibly because most of these cases are, in fact, sarcoids. Repeated surgical procedures or laser surgery can improve the success rates.
- Excision of fibroma lesions is feasible with the same caveats as nodular sarcoid.
- The best results are obtained by radiation (teletherapy), but this is not widely available as an option.

Prognosis

- Most genuine fibromas are benign and remain localized.
- Fibrosarcomas may be multiple and are usually locally invasive, but normally have little tendency to metastasize.

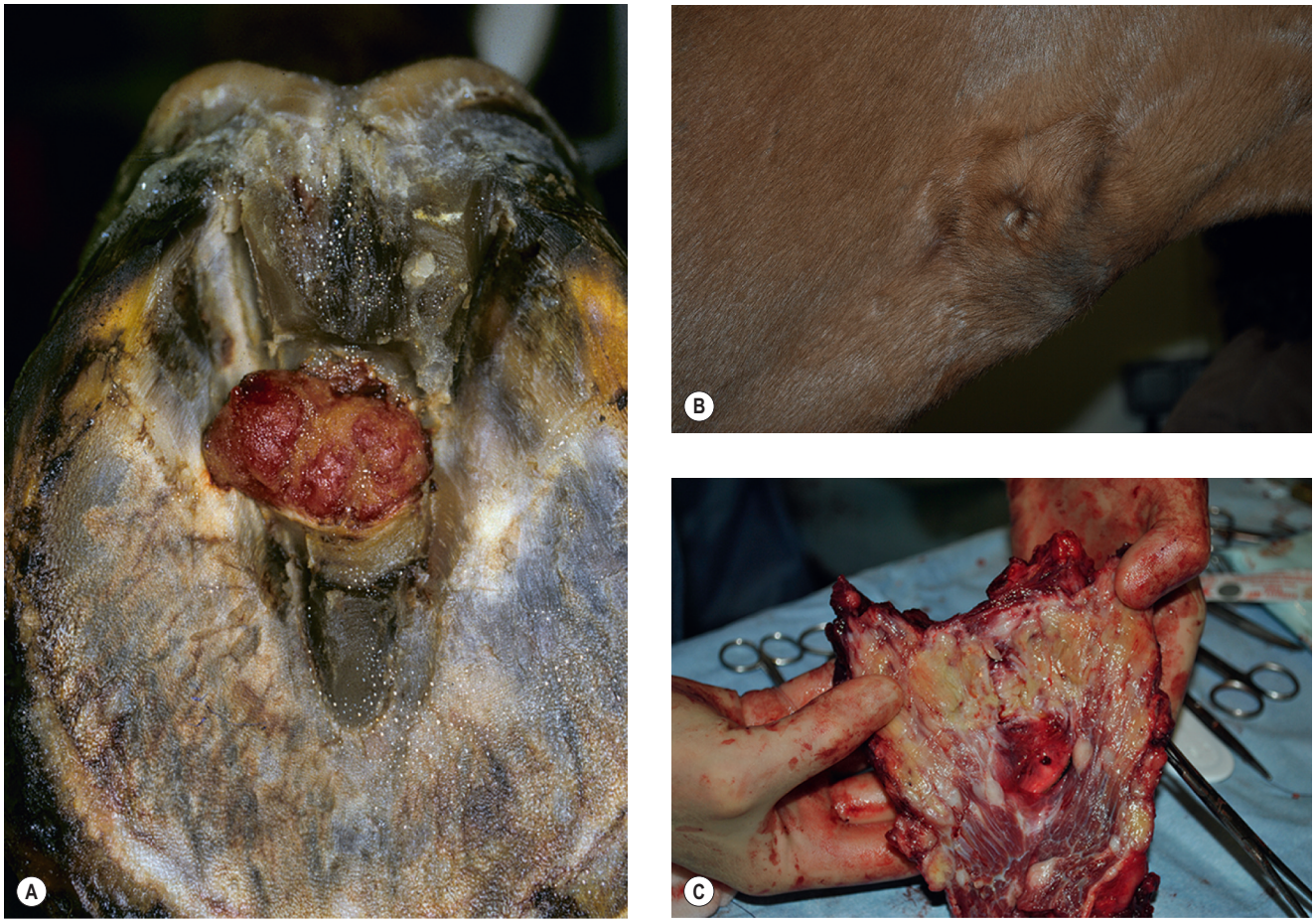


Figure 31.19 Fibrosarcoma. (A) A solar fibroma that developed spontaneously and which required surgical removal on two occasions. **(B,C)** This very dense fibrosarcoma developed in the jugular region of a 12-year-old Thoroughbred gelding. The mass enveloped the jugular vein and vago-sympathetic trunk but was removed successfully using careful surgery and concurrent intraoperative slow-release 5-fluorouracil. No further tumour-related complications arose but the horse had right-side laryngeal paralysis.

Neurofibroma (schwannoma, neurilemmoma, neurinoma, nerve sheath tumour/ perineural fibroblastoma)

See also page 299.

Disease summary

Notes

Rare benign, locally invasive fibrous tumour of nerve sheath. Most occur on the face or sheath regions.

Clinical features

Multiloculated coalescent or single, very firm, 'bound-down' nodules more often in the periorbital region and the sheath regions.

Diagnostic confirmation

Diagnosis requires special histological staining methods.

Management

Surgical excision and radiation are the best treatment options, but repeated recurrence is common.

Prognosis

Prognosis is guarded.

Overview

These are rare, discrete, localized fibrous cutaneous or subcutaneous tumours arising directly from nerve sheaths. They can occur anywhere associated with nerve tissue in horses of any age and type. The most common sites recorded include the upper and lower eyelids. Corded nodules extending from the parent tumour have been described (see p. 300).[23]

The relationship between these masses and nodular sarcoids is uncertain, but it seems likely that although the two tumours are clinically similar in many respects they are pathologically distinct. It does seem that sarcoids may have some neurofibroma-like inclusions that serve to confuse the diagnosis. It may be that these tumours have less effect on the overlying keratinocytes, so tend to mimic Type A (1 or 2) nodular sarcoids clinically.

The risk of malignant transformation is extremely small and most commonly are of cosmetic concern. A few do ulcerate, however.

Clinical features

- Small 1–10 mm hard *subcutaneous* nodules and, subsequently, very much larger multiloculated masses



Figure 31.20 Neurofibroma of the upper eyelid with multiple nodules of varying size. Eyelid distortion resulted in a purulent ocular discharge and intermittent corneal ulceration. *(Figure reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 409 (Fig. 18.40), copyright 2009, reprinted with permission from Elsevier.)*

(>25 mm diameter) develop. Multiple and cording lesions may be seen and larger lesions, in particular, cause erosion through overlying skin and develop into granulomatous-type lesions very similar in appearance and behaviour to fibroblastic sarcoid. However, they rarely show overlying hair loss until ulceration occurs. Some can be larger (Fig. 31.20).

Differential diagnoses

- Sarcoid (nodular and malevolent types)
- Equine cutaneous mastocytoma (mast cell tumour)
- Cutaneous histiocytic and generalized lymphosarcoma
- Cutaneous nodules caused by insect bites and allergic collagen necrosis.

Diagnostic confirmation

- *Biopsy or excisional histopathology*. They are immune-reactive for S100 but not for keratin, allowing them to be distinguished from epidermal tumours.
- *Fine-needle aspirates* are usually very difficult to obtain, owing to the extreme density of the tissues and the paucity of intercellular matrix, and seldom provide any definitive help.
- Recurrence is common, with almost identical nodular masses in chains.

Management

- *Complete surgical removal* carries a good prognosis but is extremely hard to achieve. Seeding nodules are easily overlooked and tumours recur in a different site on the eyelid in approximately 25–50% of cases where surgical excision is attempted.
- *Intralesional injection of BCG* (or similar immunomodulating proteins, see Ch. 9, p. 184) over an extended period can be effective but is far less effective than against nodular sarcoid in the same site.
- *Repeated intralesional cisplatin, or 5-fluorouracil*, in any form may be effective. Injections of 1 mg cisplatin or 3–5 mg 5-fluorouracil per mL of tumour are required every 1–2 weeks for 4–6 injections. Resolution may take a considerable time and there are no specific results published for neurofibroma (as opposed to sarcoid)
- *Gamma radiation brachytherapy using iridium-192* linear brachytherapy sources, or radio-gold-198 pellets or teletherapy is likely to be effective but is very limited in availability.

Prognosis

A very guarded prognosis is justified because complete resolution is almost impossible to achieve with a single surgical intervention. BCG therapy carries about 40% success for periorbital lesions. Radiation is very effective; iridium-192 linear brachytherapy or gold-198 treatments carry a good prognosis.[24]

Basal cell carcinoma

See also page 251.

Disease summary

Notes

Very rare locally aggressive tumour of basal cells more often on the face but any site can be affected. No metastatic tendency.

Clinical features

Ill-defined, ulcerated, frequently roughly circular tumour of skin. May be bound down in character.

Diagnostic confirmation

Biopsy is definitive.

Management

Surgical removal is usually effective.

Prognosis

Prognosis is good, provided it is excised fully – recurrence may occur but this remains local.

Overview

A very rare, sporadic, slow-growing, isolated ulcerative tumour most often found on the face, neck, pectoral regions and trunk of horses of all ages (4–26 years) of both sexes and all breeds.[25] Several different histopathological forms are recognized but the rarity of the tumour means that the classifications derived from other species are hard to justify and, in any case, the variants have no special aspects either clinically, therapeutically or prognostically.



Figure 31.21 Basal cell carcinoma. **(A)** An ulcerated basal cell carcinoma on the buttock region that has developed over some months from a small cutaneous nodule. **(B)** A basal cell carcinoma on the withers region showing the very typical feature of a prominent margin with a deeply ulcerated multinodular central area. **(C)** A slow-growing basal cell carcinoma on the tail of a 14-year-old gelding. *(Figure A courtesy of Patrick Martin; Figure B courtesy of Colin Mitchell; Figure C courtesy of Simone Herbert.)*

The tumour has a very benign nature and there is no established carcinogen.

Clinical signs

(Fig. 31.21)

- Solitary
- Well-demarcated
- Firm, freely moveable
- Nodular dermal mass
- Frequently ulcerates
- Tumours vary from 0.5 to 4–5 cm in diameter. The margins of the lesion commonly develop a 'piled-up' raised appearance giving the impression of a crater
- Non-ulcerating lesions may be alopecic and have a prominent blood supply.

Differential diagnoses

- Foreign body/parasitic or fungal granuloma
- Botryomycosis/pseudomycetoma/pyogranuloma
- Sarcoid (occult, nodular Type B or fibroblastic ulcerated types)
- Fibroma (fibrosarcoma)/neurofibroma
- Squamous cell carcinoma
- Melanoma
- Other ulcerating tumours.

Diagnostic confirmation

Biopsy (excisional) is usually justified in small tumours, particularly in view of the similarity with sarcoid and some melanomas.

Management

- Surgical ablation by excision is usually curative[25]
- Cryosurgery
- Laser excision
- Intralesional cisplatin.

Prognosis

Prognosis is good. These tumours seldom if ever metastasize or recur at the site of full surgical excision.

Mastocytoma (equine cutaneous mastocytosis/mast cell tumour)

See also pages 356 and 564.

Overview

An uncommon tumour occurring more frequently in young or middle-aged male horses than in females or older horses. Compared with many other veterinary species, mast cell tumours of any type are less common in horses.[26] There is debate about whether the condition is a true neoplasm and little is known about the condition or its aetiopathogenesis.

Three forms are recognized:

1. *Nodular equine cutaneous mastocytosis*: Solitary cutaneous nodules are histologically more representative of an accumulation of hyperplastic mast cells than a true neoplasm. Alternatively, the masses are referred to as benign mast cell tumours or focal mast cell dysplasia. Some opinions refer to the condition as being a reactive

Disease summary

Notes

Uncommon cutaneous nodular tumour affecting younger horses and more often males; possibly not genuine tumour in many cases, hence sometimes referred to as cutaneous nodular mastocytosis. Some can be malignant and disseminated.

Clinical features

Discrete slow-growing isolated nodule in skin or subcutaneously. Some are ulcerated and/or pruritic.

Diagnostic confirmation

Biopsy is definitive and circulating eosinophilia in malignant cases are significant aids.

Management

Excision of localized tumours is effective. Intralesional or systemic steroids can help.

Prognosis

Prognosis is good, apart from the disseminated form.

nodular disease with accumulations of mast cells rather than a true neoplasm.

2. *Malignant equine mastocytosis*: Malignant mastocytosis has been reported very rarely in horses.[26,27] When this form occurs, the cutaneous lesions may be clinically insignificant but provide a good opportunity for diagnosis provided that a careful clinical examination is performed.
3. *Congenital equine cutaneous mastocytosis*: This is possibly the rarest form of the condition and is detected at or soon after birth.[28]

Clinical features

Cutaneous nodular equine cutaneous mastocytoma

- Most mast cell tumours are between 2 and 20 cm diameter and usually involve dermal or subcutaneous layers. They rarely attach to underlying tissues but some do ulcerate and reveal the characteristic 'kunkers' (granular, firm, gritty masses in bunches) (Fig. 31.22A). Typically occur in young to middle-aged horses (1–18 years; mean approximately 7 years).
- Males are more often affected than females,
- Head is more often affected than the body and limbs, but all body sites can be affected (Fig. 31.22B). On the limb the condition is more common in close proximity to joints (especially the carpus), and on the limbs the nodules are often firmly bound down.
- Solitary, discrete, firm or slightly fluctuant, nodules (2–20 mm diameter) in the skin.
- Skin surface may be normal, hairless or ulcerated.
- A particular form appears to affect the conjunctiva (Fig. 31.22C).
- Multiple lesions can occur and appear to be less responsive to treatment.
- In some circumstances, there may be secondary space-occupying effects, such as corneal ulceration from a conjunctival mast cell tumour or restricted movement from a distal limb mastocytoma.
- A few cases are reported to be pruritic but seldom painful.
- A partial or complete capsule can be recognized ultrasonographically (and histopathologically).
- There is seldom any hair loss or pigment changes in the skin but some are ulcerated or alopecic.
- They seldom if ever metastasize.

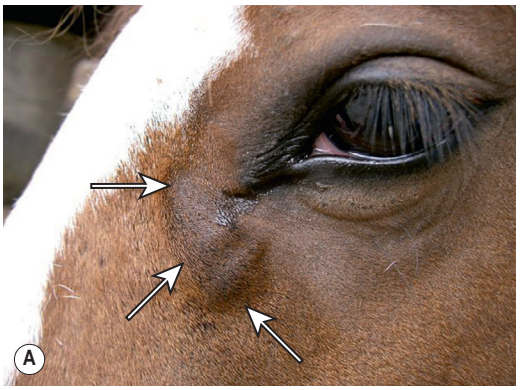






Figure 31.22 Mast cell tumour/mastocytoma. (A) This mast cell tumour was totally subcutaneous and involved multiple interconnecting nodules (arrows). **(B)** This ulcerated mast cell tumour in the nasal mucosa of a 9-year-old grey horse developed slowly and proved difficult to resolve (arrow). **(C)** Mast cell tumours are also relatively common on the conjunctiva and third eyelid (as in this case in a 6-year-old part Arab gelding). *(Figures A and C reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 411 (Figs 18.42C and D), copyright 2009, reprinted with permission from Elsevier.)*

Malignant equine cutaneous mastocytosis

- Very rare
- In the reported cases, clinical signs include pruritus at the site or generalized pruritus and lameness/pain associated with various joint and synovial structures

- Pathologically elevated circulating eosinophil counts and hyperfibrinogenemia
- Metastasis to local lymph nodes has been reported.

Congenital equine mastocytosis

- Very rare
- Widespread/disseminated raised ellipsoidal cutaneous nodules along the back and trunk, varying in size from 2–3 mm to 3–4 cm
- Larger nodules may have a fluctuant feel and there may be overlying skin ulceration
- May resolve spontaneously but there are too few cases to allow any sensible interpretation of the prognosis

Differential diagnoses

- Dermoid
- Squamous cell carcinoma
- Bacterial infection of non-healing wound/granulation tissue
- Fungal granuloma/deep dermal mycosis
- Insect bite/sting
- Sarcoid
- Habronemiasis (conjunctival)
- Botryomycosis/pseudomycetoma
- Eosinophilic dermatitis /collagenolytic granuloma complex
- Cutaneous amyloidosis.

Diagnostic confirmation

- Ultrasonographic examination may identify a heterogeneous 'gritty' echogenicity and will also serve to define any surrounding capsule to aid surgical decision-making.
- Fine-needle aspirate/biopsy or impression smears can help.
- Giemsa stain reveals heavy eosinophil and mast cell infiltration with metachromic granules.
- Biopsy or, preferably, surgical excision (excisional biopsy) and histopathology usually reveals focal aggregations of active mast cells, eosinophils, fibrinoid necrosis of collagen and, occasionally, mineralization. Accumulation of eosinophils is a common effect in mast cell tumours of all types.

Management

Surgery

Where possible, total, wide surgical removal can be an effective approach.[29]

There is apparently little risk of any immediate untoward response from handling the tumours or from residual cells within the operative site.

Intralesional anti-mitotic/cytotoxic chemicals

There are anecdotal reports of the use of intralesional sterile water injections – the mast cells are suggested to be more (highly) susceptible to variations in local osmotic pressure and this approach may at least be tried safely. Intralesional injection of distilled water (may require 2–4 treatments at 4–6 day intervals). The author has attempted this on a few occasions with some improvement but no resolution.

Intralesional injection of triamcinolone or methylprednisolone acetate can also be useful.

Prognosis

A good prognosis is usual for the benign form of the condition, although, where they are situated in difficult sites, some are very difficult to remove fully without damaging underlying tissues. Some lesions undergo spontaneous resolution without apparent reason.

The prognosis for the malignant form is very guarded, but there are too few cases to be confident about either the best choice of treatment or the likely outcome from either medical or surgical interventions.

Malignant fibrous histiocytoma (extra-skeletal giant-cell tumour)

See also page 290.

Disease summary

Notes

Rare, locally aggressive tumour of cutaneous and subcutaneous histiocytes most often in neck and body trunk regions.

Clinical features

Ill-defined, ulcerated, frequently roughly circular tumour of skin. May be bound down in character. Often very haemorrhagic.

Diagnostic confirmation

Biopsy is definitive.

Management

Surgical removal is usually effective but can be difficult in large lesions in problematic sites.

Prognosis

Prognosis is good, provided it is excised fully – recurrence may occur, but this usually remains local.

Overview

Very rare malignant tumours found in the neck and proximal regions of limbs. The term 'fibrous histiocytoma' is often used to cover a variety of sarcoma tumours that cannot be otherwise classified.

They are fibrohistiocytic tumours with variable cellular pleomorphism comprising mainly fibroblasts and macrophages (histiocytes) – the tumours usually relate to fibroblast transformation and so they may actually be a variant on the fibrosarcoma theme. Bizarre giant cells are a recognizable feature. There is debate about the true nature of these tumours. Many are associated with foreign bodies, necrotic tissue and repeated trauma.

There is no reported breed, sex or age predilection. Donkeys may also be affected.



Figure 31.23 Giant-cell tumour/malignant histiocytoma. (A) A slow-growing, mildly painful, warm swelling developed on the buttock of this 9-year-old TB cross gelding over a period of 6 months. The lesion ulcerated and bled significantly spontaneously and when handled or traumatized. The diagnosis was confirmed and the tumour removed surgically. No clear margin could be established and the tumour recurred. **(B)** This 18-year-old donkey developed a malignant histiocytoma at the carpus over a period of 3 months. No treatment was attempted. *(Figure B courtesy of the Donkey Sanctuary.)*

Clinical features

- Characteristically solitary, firm, poorly circumscribed but possibly multilobulated (See p. 53 and Fig. 4.27A,B)
- Locally invasive but very slow to metastasize
- The overlying skin may ulcerate and leave a large exposed, rapidly expanding and haemorrhagic tumour (Fig. 31.23A)
- In many cases, the tumour tissue is soft and easily damaged, causing moderate to severe haemorrhage (Fig. 31.23B).

Differential diagnoses

- Sarcoid
- Equine cutaneous mastocytoma
- Collagenolytic granuloma
- Neurofibroma/fibrosarcoma
- Melanoma
- Foreign body reactions.

Diagnostic confirmation

Biopsy shows characteristic histopathology with featured bizarre giant cells and abnormal fibroblasts in particular.

Management

- *Surgical excision* can be difficult owing to the invasive nature of the tumour, but if performed meticulously can result in resolution
- *Cryosurgery and laser excision* are, theoretically at least, possible treatment methods
- *Concurrent intralesional and perilesional chemotherapy* appears to be sensible but there is no report of their use.

Prognosis

Recurrence is common owing to the locally invasive nature of the tumour and the consequent difficulty in removal. Metastasis is not reported.

Lipoma (liposarcoma)

See also page 294.

Disease summary

Notes

Very rare, benign 'tumour' of fat.

Clinical features

Ill-defined, soft, rather diffuse mass lying subcutaneously.

Diagnostic confirmation

Biopsy is definitive.

Management

Surgical removal is usually effective, but is not always easy, and recurrence is common.

Prognosis

Prognosis is good, provided the tumour is excised fully – recurrence may occur.

Overview

Cutaneous lipoma is relatively uncommon when compared with other species and liposarcoma is very rare. The cutaneous tumours are formed from subcutaneous lipoid tissue, primarily in aged horses. Fat/obese animals are most affected, but significant lipoma can also be found in some thin horses. Donkeys may be more affected than horses.

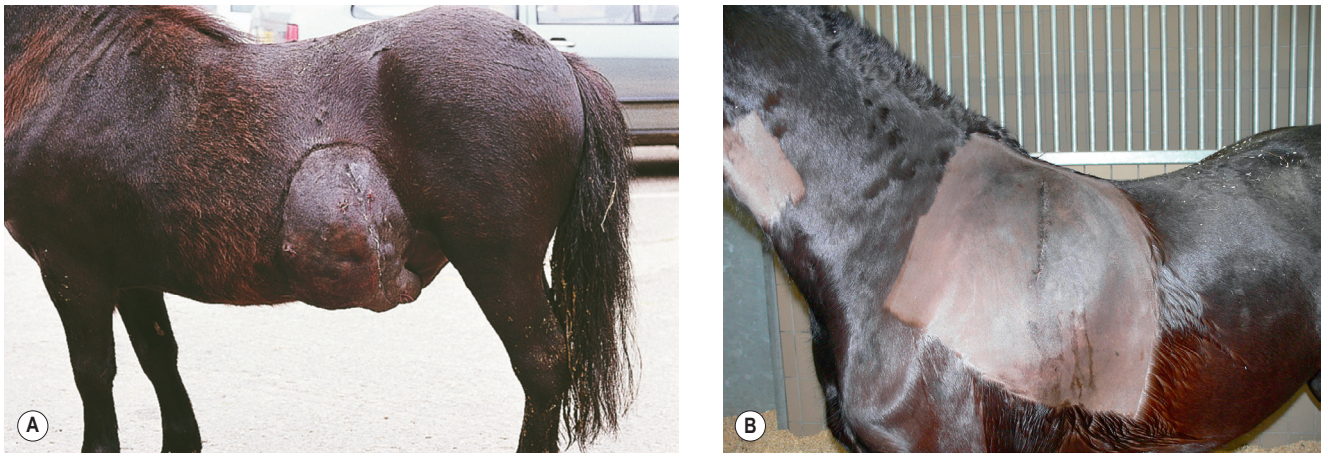


Figure 31.24 Lipoma. (A) Subcutaneous lipoma in the flank region of a 12-year-old Shetland pony mare. A surgical biopsy taken 2 weeks previously confirmed the nature of the multilobulated, soft, subcutaneous mass. It was removed uneventfully and did not recur for at least 6 years. **(B)** A 2-year-old Friesian gelding was presented with a large soft (non-fluctuant) swelling, approximately 35 × 30 × 10 cm over the upper part of the scapula following a kick some months previously. Ultrasound showed a large mass of 'unremarkable' soft tissue. Fine-needle aspiration biopsy gave only adipose cells. After removal, a diagnosis of lipoma was made. The tumour recurred quickly to its original size (as shown here) and texture and was re-operated. On this occasion, the lipoma was located not only subcutaneously but also had two large extensions under the latissimus dorsi muscle and over the top of the caudal part of the scapular cartilage and medial to the scapula. Surgery was completed successfully. *(Figure A reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 416 (Fig. 18.47), copyright 2009, reprinted with permission from Elsevier; Figure B courtesy of Jos M. Ensink.)*

Mesenteric lipomata are, however, very common in older horses where they can cause serious colic (see pp. 294 and 465); there is no apparent correlation between cutaneous/subcutaneous lipoma and internal lipoma formation.

Clinical features

- Entirely subcutaneous
- Soft but well-defined
- Lobulated or smooth mass which may be mobile under the skin
  - Usually on the trunk or neck (Fig. 31.24)

The tumours grow slowly and may fluctuate in size with body condition to some extent – even starvation does not, however, result in complete disappearance.

Differential diagnoses

- Body fat accumulation (fat pads)
- Foreign body reactions
- Haematoma
- Hernia
- Muscular, vascular or connective tissue hamartoma.

Diagnostic confirmation

- *Ultrasonographical examination* is very useful; there is a characteristic echo pattern typical of fat tissue
- *Biopsy* is definitive but not always easy to differentiate from simple fatty accumulation.

Management

Surgical removal is effective and it may help to limit dietary intake for some weeks before surgery to reduce the tumour as far as possible. As the skin is not involved, wound closure is not usually a problem. However, if the tumour is disrupted during surgery, the fat released may slow healing significantly.

Prognosis

Good prognosis, but other lipomas may develop locally or at other sites (internal and external). Recurrence may occur, but there are too few cases recorded to provide strong evidence for this.

Melanoma and melanosarcoma

See also page 237.

Disease summary

Notes

Very common melanocytic tumour of grey horses in particular. Cremello and other coloured horses are also affected. Strong tendency to enlargement and eventual histological malignancy. Can be disseminated.

Clinical features

Single isolated or multiple/coalescent dark nodules in the skin mainly around perineum, sheath, eyelid, mouth but all skin sites can be affected.

Diagnostic confirmation

Biopsy is definitive – fine-needle aspiration is simple and diagnostic but does not usually give an indication of malignant status.

Management

Surgical removal of early lesions is usually effective. Local chemotherapy and vaccines are being developed.

Prognosis

Prognosis is guarded, since many become malignant over time. Disseminated melanoma carries a hopeless prognosis (see p. 58, Fig. 4.31).

Overview

'Melanoma' is the term used to describe a spectrum of skin and deeper or generalized tumours that are readily recognized in clinical practice as affecting grey or colour-diluted horses ranging from newborn to aged.

The benign congenital (present at birth) and juvenile (acquired at <1 year of age) form could justifiably be termed 'melanocytoma' (benign melanoma) and the term 'melanoma' could be used to encompass all the other acquired tumours (including the malignant melanosarcoma) because they have a tendency to malignancy. However, the term 'melanoma' is the one that is most understood. Whilst some aspects of the condition are well recognized clinically, some are unpredictable and do not fall into any recognizable category.

A retrospective study of cutaneous melanocytic tumours in 53 horses revealed four identifiable clinical syndromes (Fig. 31.25)[30]:

1. *Melanocytic naevus* (melanocytoma): This form is histologically distinctive
2. *Dermal melanoma*
3. *Dermal melanomatosis*

   } Histologically similar but having distinctly different clinical behaviour
4. *Anaplastic malignant melanoma* (melanosarcoma): This form is histologically distinct.

All the common variations predominantly affect grey horses and to a lesser extent, non-pigmented (white/albino or cremello) horses. Other colours can be affected with typical melanomas but they are rarer by comparison with grey horses.

At least 80% of grey horses over 12 years of age will have one or more melanomas at some location. Attempts to draw similarities between the human melanoma and the common melanoma of horses, equine melanoma, have proven largely fruitless.[31]

Over 95% of cases are benign, at least at the time of early diagnosis, but a significant proportion (up to 30%) become malignant and may metastasize.[32,33] Over time, there is an increasing risk that the early benign hyperplastic melanoblasts will undergo malignant transformation. A high proportion of the early 'melanotic masses' have at least the potential to adopt an aggressive pathological behaviour. Melanomas in non-grey horses may be benign or malignant but appear to have greater tendency to malignancy.

They are usually non-invasive but can be coalescent. The clinical effects are largely due to their space-occupying bulk or to the cosmetic and debilitating effects of ulceration of the surface. A few cases are highly malignant and rapidly disseminate through the body via the blood and lymphatic circulations.

The common cutaneous sites include the underside of the tail and the skin of the tail itself, the perianal skin, the vulva and the prepuce. The eyelids and lips are probably less affected, but these sites are still common. Any cutaneous site can be affected. It also occurs internally in the linings of the guttural pouches, particularly overlying major blood vessels in the lateral compartment of the pouches, and somewhat less commonly in the parotid salivary and lymph nodes, and sporadically anywhere on or in the body (iris, mammary gland, paralumbar and neck musculature, legs, the foot or major internal organs). At least some of the latter are assumed to be metastatic.

There is no evidence that interference with the early benign forms will increase the likelihood of developing an aggressive malignant form. Similarly, superficial ulceration is neither a known precursor of, nor indicator for, transformation to malignancy.

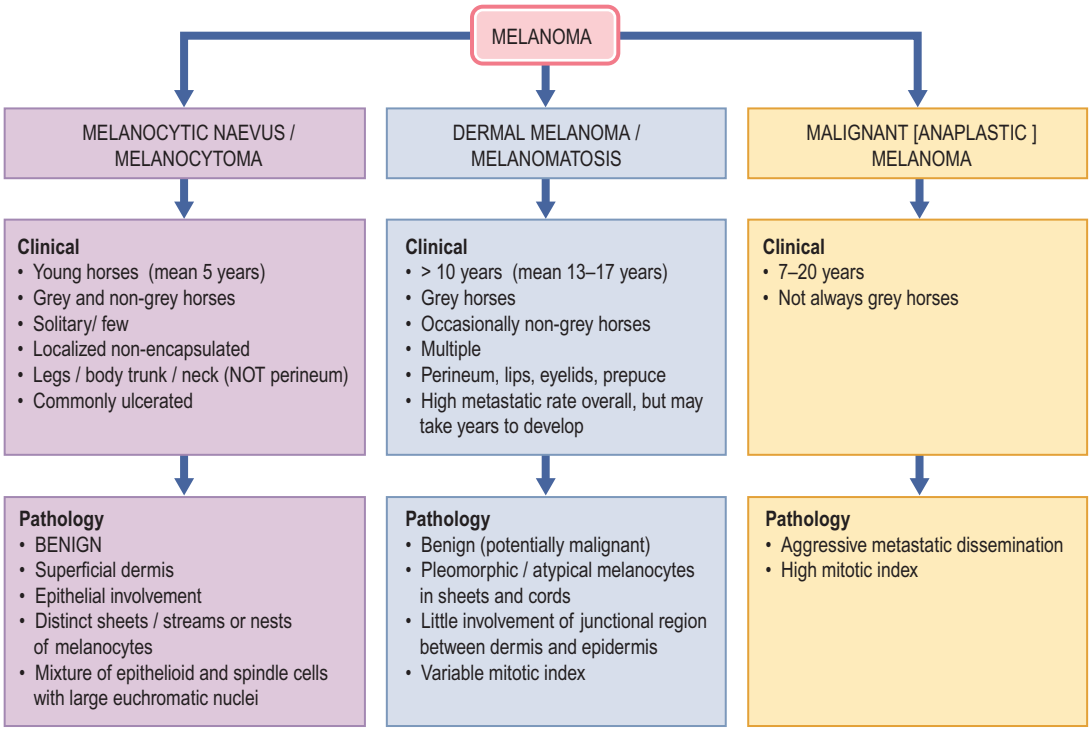


Figure 31.25 Classification of melanoma. Classification and clinical features of equine melanoma and melanoma-like conditions.

Clinical features

The clinical signs depend largely on the location, size and clinical behaviour of the lesion(s).

Melanocytic naevus/melanocytoma

- Isolated heavily pigmented, non-encapsulated cutaneous nodules, varying in size from 0.5 to 2–3 cm diameter, in the skin of grey or non-grey horses occurring in younger horses (birth to approximately 6–8 years of age), are typical
- Variable number but usually relatively few lesions are present. The legs, neck, facial skin and body trunk are more often involved; characteristically, this type does not affect the common perineal, penile, mouth and eyelid sites typical of dermal melanoma (see below)
- Individual nodules are often raised and commonly ulcerated to reveal the black/purple tumour tissue (Fig. 31.26).

Dermal melanoma/melanomatosis

This is the commonest form of melanoma and affects (older) grey horses almost exclusively. Single, multiple or coalescent cutaneous, often spherical nodules are characteristically most prevalent in the perineal skin. Primary tumours range widely in size from a few millimetres to over 20 cm (Fig. 31.27).

Growth is characteristically slow and can reach considerable size. Ulceration is common and then a tarry, black exudate (sometimes with haemorrhage) can be present. Single discrete nodules may have a pedicle or may be coalescent with many lesions (often hundreds or more of variable sizes). Some lesions are exudative and protein loss and debility can occur. Chronic blood loss can lead to mild regenerative anaemia. Ulcerated tumours often become infected and infested with fly maggots.

Those developing in the parotid lymph nodes and salivary glands and subcutaneous lesions are most obvious (Fig. 31.28).

Secondary signs are possible, including interference with any other organ, such as:

- Anal sphincter
- Eye (blindness or visual field deficits)
- Nerve fibre ('stringhalt')
- Spinal cord (ataxia and weakness)
- Trachea (dyspnoea/stertor)
- Jugular groove and guttural pouch (Horner's syndrome)
- Heart muscle (arrhythmias)

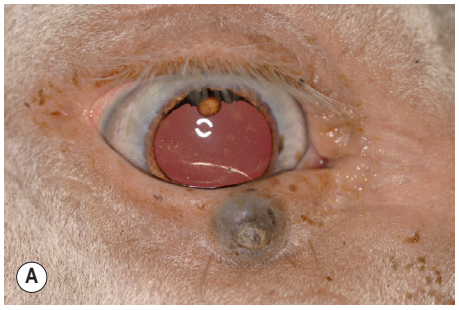
(see p. 523, Fig. 30.10).

Melanomas can be restricted to the subcutaneous tissues and then there is no particular dermal implication. Sometimes sweating and hair loss can be attributable to melanoma; for example, masses in the thoracic inlet or within the jugular groove may interfere with the cranial sympathetic trunk and induce Horner's syndrome (see p. 607, Fig. 33.4). Chronic cutaneous vasodilation causes sweating and gradual hair loss. The presence of isolated or even several secondary signs does not necessarily (nor even usually) mean that the condition has a certain malignancy. It is more likely that the simple space-occupying nature results in organ dysfunction. Any grey horse with a single or many defined cutaneous or subcutaneous nodules should be viewed as a potential melanoma case.

Malignant melanoma/melanosarcoma

This represents the most aggressive form of the disease. The malignant forms can be recognized by the topical features of a malignant tumour. The tumours grow rapidly, ulcerate and have a diffuse bound-down nature. Often, there is a grey or grey-pink heterogeneous nature to the surface of the tumour (Fig. 31.29).

- Malignant dissemination has the potential to affect any internal organ and can result in some paraneoplastic syndrome signs.
- Ultrasonographic features are reasonably well-defined and the malignant forms have a softer echogenicity, often with necrotic central portions, where the tumour has outgrown its blood supply.
- These cases will usually have other concurrent signs, such as colic, weight loss, cardiac arrhythmias, respiratory or neurological symptoms.



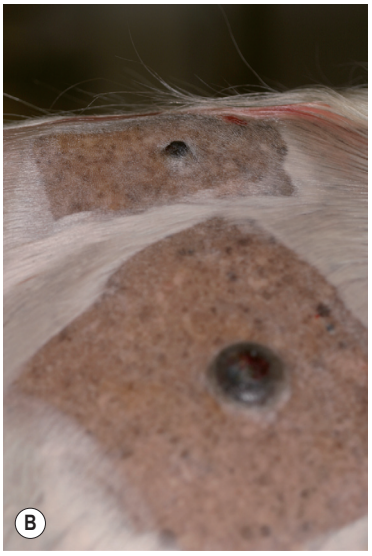


Figure 31.26 This young cremello pony had a variety of small black masses over its body from a very young age. Several remained static, but those on the eyelid **(A)** and shoulder **(B)** changed dramatically after 4 years and, so, all the visible lesions were removed surgically with a diode laser. *(Figures reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 422 (Fig. 18.53B and C), copyright 2009, reprinted with permission from Elsevier.)*



Figure 31.27 Cutaneous melanoma. Single or multiple cutaneous melanomas are common, particularly in grey horses. Some ulcerate but others do not. **(A)** A single ulcerated melanoma in the vulvar lip of a 9-year-old grey mare. **(B)** Multiple perianal and tail-base focal melanomas in a 16-year-old grey horse. **(C)** Extensive perineal melanoma in an 11-year-old mare; note that some regions are losing pigmentation. **(D,E)** Melanomas also occur in the eyelids. **(F,G)** The lips and sheath of this 18-year-old grey pony were severely affected by melanoma; these are also typical sites for the tumour. *(Figures A and B reprinted from Knottenbelt DC. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 423 (Fig. 18.54A and B), copyright 2009, reprinted with permission from Elsevier.)*

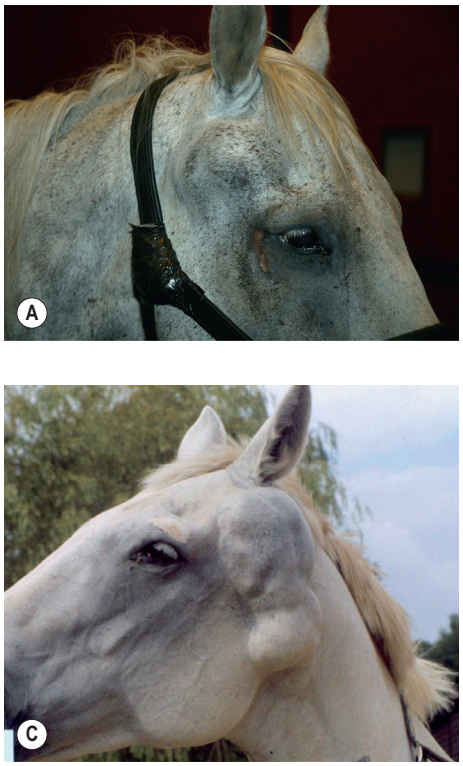


Figure 31.28 Melanoma. The head is another predilection site, with tumours commonly found in the subcutaneous areas and organs such as the zygomatic arch region **(A)** and the parotid salivary glands and guttural pouches **(B,C)** (see p. 496, and Fig. 29.13).

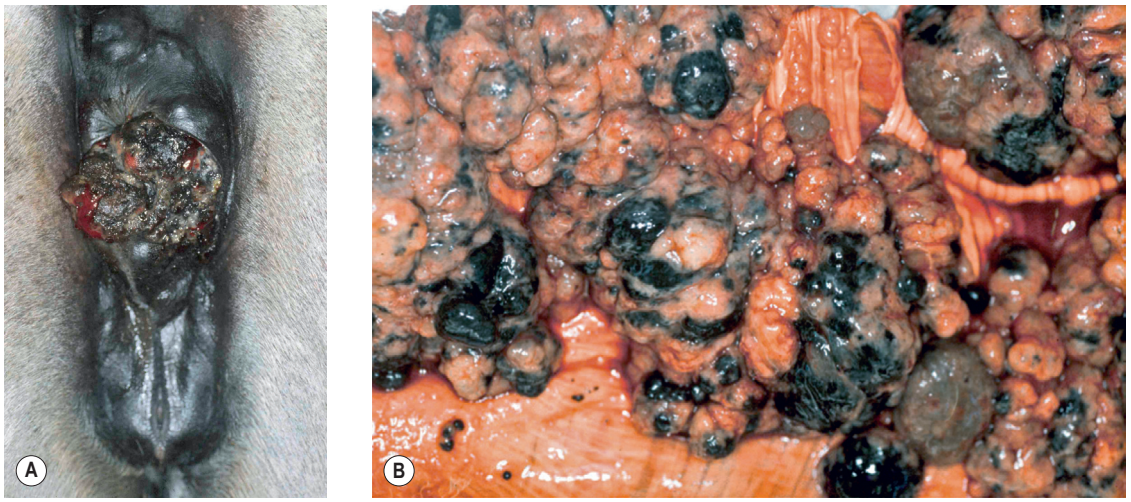


Figure 31.29 Aggressive malignant melanosarcoma. (A) This 9-year-old mare was presented for investigation of recurrent colic. During clinical examination, the ulcerated heterogeneous melanoma was identified. Peritoneocentesis produced copious fluid, with bizarre large cells and profuse melanocytic cells with a high mitotic index. **(B)** At laparotomy, the whole abdomen and the abdominal organs were infiltrated with tumours, some of which were black and some grey/pink or cream. At necropsy, a similar state existed in the chest and most major organs were involved in this extremely aggressive malignant melanosarcoma. *(Figures reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 424 (Fig. 18.55A), copyright 2009, reprinted with permission from Elsevier.)*

Notes

Not every melanoma is black in colour – some are amelanotic, and these are usually more aggressive than other lesions, since by definition they will then be anaplastic or at least undifferentiated. Suspicion must be aroused if a melanoma has red, grey or cream areas within it.

Melanomas that occur in non-grey horses tend to be more aggressive and are very easily overlooked or misdiagnosed (Fig. 31.30).

Notes

Where any clinical syndrome is presented in a grey horse, the possibility of (malignant) melanoma should be considered, even if the cutaneous evidence is limited.

It is very important to examine the surface of ulcerated melanomas and to perform guttural pouch endoscopy in all melanoma cases.







Figure 31.30 Melanoma in non-grey horses. **(A)** A 14-year-old bay gelding developed this large black multinodular neoplasm on the tail. The lesion progressed rapidly and a wedge biopsy confirmed a highly malignant melanoma. The tail was amputated at its base, but further tumours developed at the incision site and within the subiliac lymph nodes within some months of the surgery. **(B)** This isolated 'black tumour' was excised *in toto* with a wide margin and histology confirmed total removal of a malignant melanosarcoma. No recurrence occurred for at least 3 years. **(C)** This eyelid melanoma was the only tumour detected in a 14-month-old albino mare. It was removed successfully. *(Figure A courtesy of Lesley Rain.)*

Differential diagnoses

- Sarcoid (nodular form)
- Lymphoma/lymphosarcoma
- Haemangioma/haemangiosarcoma
- Warble fly (*Hypoderma bovis*)/other related parasitic cysts
- Cutaneous collagen necrosis/allergic collagenolytic granuloma
- Mast cell tumour
- Fibroma/fibrosarcoma
- Parotid salivary gland/guttural pouch disease
- *Gasterophilus* spp.-induced ulcerated lip granuloma.

Diagnostic confirmation

- Appearance and location are characteristic, but amelanotic melanoma can be more problematic.
- Biopsy by fine-needle aspirate is a very simple and very positive test – the black pigmented material is obvious and pathological examination is usually not then required, except to establish the true character of the cells themselves; fine-needle aspiration should be used very carefully as an initial screening method in tumours without pathognomonic appearance, e.g. in a subcutaneous nodule/tumour in a grey horse.
- Biopsy and excisional biopsy: mitotic indices vary widely from low to very high and reflect the potential or actual aggressiveness of the tumour.
- Malignant tumours may be recognized by the presence of pale grey or pink-creamy coloured areas within the black mass (see Fig. 31.29A). Blotting the ulcerated surface with a gauze swab or absorbent paper towel may reveal the mottled appearance.

Management

Melanocytic naevus/melanocytoma

- Surgical excision is curative. Partial excision may result in localized recurrence. There is no convincing published evidence that residual melanocytic tissue resulting from failure to remove all the 'tumour tissue' increases the risk of dissemination or increases the risk of malignant transformation.
- The lack of any effective alternative means that the decision for surgical removal should be taken early and all visible lesions should be removed when they are at an easily manageable size. This approach will limit the later numbers that become problematic, but it is accepted that this approach has its limitations. Any safe reduction in the number of tumours on an individual horse will reduce or delay the onset of unacceptable

ulceration and tissue distortions and will necessarily limit the development of malignancy to some extent.

Dermal melanoma/melanomatosis

Some tumours are reported to regress spontaneously but this is an extremely rare event. The large majority will expand and cutaneous lesions will eventually ulcerate. There is a significant risk of development of more aggressive forms and so treatment options should be considered carefully.

Benign neglect

Benign neglect has long been the 'treatment of choice', based on the premise that the tumours are benign and slow growing. This approach can justifiably be questioned – the tumours will only get bigger and less treatable with time, and once they are large it becomes virtually impossible to remove them safely and entirely by any known means. The owner will only be concerned about the visible lesions and so it is sensible to consider early removal of all accessible melanoma lesions by one means or another. Furthermore, there is an increasing risk of malignancy the longer the early benign lesions remain. At this late stage, interference is a major surgical challenge and most cases will be untreatable. It is difficult to answer an owner who asks, 'Why weren't the tumours removed when they were small and benign rather than when they became untreatable and troublesome later in life?'

Surgical removal

Surgical removal of troublesome lesions is possible. Single small tumours (<3–4 cm diameter) can usually be treated successfully by wide surgical excision or cryonecrosis therapy. Even larger areas of complex and coalescent melanomas can be removed surgically and so improve the quality of life for the affected horse.[34]

Ligation of isolated pedunculated lesions may be effective where this is feasible. Larger tumours will require reconstructive surgery, but even some severe cases can be helped significantly, although there is an obvious (but completely unproven) risk of both recurrence and, possibly, even metastatic spread.



Partial surgical excision alone can stimulate rapid tumour regrowth and possibly metastatic spread through stimulation to abnormal melanoblasts in proximity to the surgical site. Therefore it seems entirely logical to remove the tumours as soon as they are visible and at a stage when total excision can be safely achieved.

Cryosurgery

Cryonecrosis using a double or triple freeze–thaw cycle is effective in treating some localized small, ulcerated and discharging lesions and is useful for tumours which are inaccessible to total surgical excision, e.g. in the anal sphincter area. Better results are achieved when the tumour is surgically debulked as far as possible prior to cryonecrosis of the remaining inaccessible area. This rarely 'cures' the problem, but it allows a further useful life span for the treated horse. There is also a serious risk of exacerbation if the tumour is not eliminated completely.

Cisplatin (intralesional injection)

This is reported to be effective – some tumours appear to resolve following a single treatment, but others do not respond at all. Tumours >3 cm diameter should be debulked first and a vegetable oil-based emulsion of cisplatin injected into the base of the tumour at the rate of 1 mg/cm^3 of tissue every second week for 4 treatments (see p. 147). Repeat treatments may follow the same procedure.



Cisplatin is a very dangerous compound and human contact and environmental contamination must be avoided completely.

Cimetidine (oral administration)

Cimetidine is administered orally at 2.5 mg/kg three times daily, 3.5 mg/kg twice daily or (less satisfactorily) 7.5 mg/kg given once or twice daily for 6–12 weeks. Its successful use appears to be more applicable to tumours which are showing 'active growth'. Where growth has been minimal or even static, the response is reportedly poor. The reports of successful treatment (a 50–90% reduction in tumour size) are based on a small number of cases and varying doses and intervals and so there is little conclusion that can be drawn as yet from the current information. Subsequent studies have failed to show any convincing evidence of a benefit in the large majority of cases. An occasional tumour does, however, seem to respond. The clinical effects are hard to quantify in most cases and so it is useful to measure at least two dimensions of a single accessible lesion using skin calipers and then re-measure some weeks later. A response is indicated by a slow decline by 50–90% of the pre-treatment size and this response occurs during the first 6 weeks of treatment. If the drug is seen to have a beneficial effect, then it should be continued daily until there is no further improvement. If no significant effect is seen by 3–4 weeks, it is probably not worth continuing. The results are very variable but are now considered to be of no clinical value.[35]

The progression of the tumours is reported to be halted for months to years following cessation of treatment. Regrowth on cessation of treatment is also reported.

BCG immunostimulation/immunomodulation

The use of BCG immunotherapy (see p. 189) has not proven successful – a localized inflammatory response occurs but this is seldom helpful in stimulating tumour rejection in any meaningful way. A BCG cell-wall extract was used in conjunction with an X-irradiated autogenous vaccine but it is uncertain what extra effect that had.[36]

Autogenous vaccination

Injection of a crude autogenous whole melanoma cell 'vaccine' has been used successfully in one case.[36] Vaccination with X-irradiated autogenous vaccines have also been attempted following some successful reports in the human literature. However, in horses, the results are unconvincing at present, although in one report, 11 out of 12 cases showed a positive tumour regression without any apparent side-effect.[36] A tyrosinase antibody vaccine (Oncept™, MERIAL) for diogs has been used in horses also with uncertain results as yet. It may be more effective in slowing down tumour growth.

Prognosis

Although the majority of 'black' lumps are benign and almost every grey horse will eventually develop them, no melanoma should be belittled. Severe aggressive melanosarcoma may be very dangerous with widespread dissemination and then the prognosis is hopeless.

Individual tumours on other than grey horses can be surgically removed but a wider margin must be taken and histology to establish a safe margin must be performed. It is clinically sensible to perform all the surgeries as early as possible – there is little point in waiting for the tumours to get bigger and increasingly more difficult. Delays probably increase the possibility of developing malignancy.

Prevention is said to be possible by keeping susceptible horses out of the sunshine or applying copious high-factor sunscreen.[37] However, not only is this usually highly impractical but also sunshine is most unlikely to be a significant causative factor for equine melanoma, so this is probably not helpful.

Squamous cell carcinoma

See also page 220.

Disease summary

Notes

Relatively common locally aggressive tumour of squamous cells more often on the face (conjunctiva, eyelid and mouth) and genitalia (gelding penis) but any body site can be affected. Mucocutaneous junctions are most liable. Rarely has a metastatic tendency.

Clinical features

Ill-defined, ulcerated, proliferative or ulcerative/destructive mass with rapid progression. Early lesions may be papillomatous. Occasionally invasive and may extend to local lymph node or beyond.

Diagnostic confirmation

Biopsy is definitive.

Management

Surgical removal is usually effective – often best combined with some form of local chemotherapy. Several chemotherapeutic options and cryosurgery can also be effective.

Prognosis

Prognosis is usually fair but some do require repeated treatment – recurrence may occur, but this usually remains local. Some are very aggressive.

Overview

Squamous cell carcinoma is the second most prevalent skin tumour of horses. It is an invasive tumour of squamous cells of the skin and squamous mucosae with defined predilection sites. The condition does occasionally affect other squamous cell tissues, including the cornea (see pp. 616 and 614); hoof wall and respiratory (see pp. 482 and 496); reproductive (see pp. 630 and 648); and alimentary mucosae (see pp. 450 and 459).

Although it can develop at any site, it is certainly more common in non-pigmented skin and at mucocutaneous junctions such as the eyelids, mouth, vulva and clitoris, prepuce and facial skin around the nose. Penile forms are particularly common in geldings.

The prevalence in any geographical location may depend on many environmental and management factors, as well as the specific type of horses and individual susceptibility. If the condition is present on the eyelids/conjunctiva/cornea, there is a 10% probability that it will also be found at other cutaneous sites.[38]

Horses of all ages can be affected.

For each anatomical location, there are different possibilities for the aetiology and different epidemiological consequences.

- *The cutaneous forms* vary widely in their clinical behaviour from highly malignant and rapidly invasive and destructive forms to very benign, slow-growing mildly invasive tumours. Penile forms in younger horses tend to be much more aggressive and more commonly metastasize to regional lymph nodes and possibly remote organs, such as the lungs and vertebral bodies. Extension to involve preputial ring or primary preputial carcinoma is a serious complication. Most of the other cutaneous/superficial forms have little tendency to metastasize beyond the local lymph node.
- *Eyelid forms* vary widely but are more often static or slowly progressive and are usually fairly well localized. Some do, however, extend into adjacent structures such as the orbit or metastasize to the local (parotid and pharyngeal) lymph nodes and may then disseminate further. Certain forms, such as the gastric and respiratory mucosal forms are highly dangerous and may metastasize early (see pp. 227 and 459).
- The skin of the perianal region can develop an *ulcerative form* in horses with non-pigmented skin.
- *The facial forms* are probably commonest in the Clydesdale breed, especially where these are kept in tropical and subtropical areas, but all breeds can be affected – the restriction to non-pigmented skin may be a useful early indicator but later destruction can involve pigmented skin also.
- *Ocular forms* include:
  - Benign, proliferative
    - The benign types at all sites in the eye are usually slow-growing and proliferative
  - Aggressive ulcerative palpebral
    - The ulcerative forms are the preserve of the eyelids
  - Nictitans
    - The nictitans are faster and locally destructive.

Proliferative conjunctival squamous cell carcinomas are relatively common at the lateral limbus (corneo-scleral junction). The corneal form ('carcinoma in situ') is slowly invasive but usually remains very superficial. All types may be slow-growing or highly invasive but remain largely restricted to superficial tissues of the palpebral skin, conjunctival/corneal epithelium. In contrast to the bovine condition, ocular squamous cell carcinoma in the horse is only rarely malignant. The nictitans (third eyelid) form is usually slow-growing and proliferative, but can be aggressive and ulcerative.

Importantly, the clinical behaviour of different lesions on the same horse can be very different – each tumour needs to be assessed in its own right but, fortunately, tumours occurring at multiple locations are rare. In mares, the clitoral proliferative forms are commoner than the ulcerative labial forms.

Techniques of tumour grading/staging (see pp. 18, 19 and 21) can be used to guide the clinical decisions. Useful prognostic information on cell behaviour can also be derived from new techniques using indicators of nuclear mitotic activity measured from in vitro cell cultures from small biopsies; monoclonal antibodies directed at nuclear proteins associated with replicating cells are being used increasingly.

Clinical features

- Pre-cancerous changes may be present before patent carcinoma develops. The earliest of these changes is a squamous papilloma (Fig. 31.31A). In some cases, a pre-carcinomatous thickening and mild exfoliation and ulceration of the skin (leukoplakia) occurs – often (but not always), this is accompanied by significant preputial discharge; they are usually very obvious on the preputial and penile skin of older geldings (Fig. 31.31B). Initially, these early signs are usually not detected and a small, granulating 'sore' on the skin, which may be depressed below skin level, is often the first report.
- The penile forms may vary from single or multiple popular lesions to pedunculated or sessile 'cauliflower' type to smooth or ulcerated and highly invasive masses giving a wooden feel to the free end of the penis.
- Vulvar tumours are often slow-growing and proliferative in the clitoral form but are more often ulcerative in labial forms (Fig. 31.32).



Figure 31.31 Pre-carcinomatous squamous dysplasia. (A) This 17-year-old gelding developed several small papillomas on the penile shaft. After 7 years, these had transformed to a series of ulcerated and proliferative carcinoma lesions, although they remained localized and small. They were then removed surgically. PCR at both stages had revealed positive bovine papilloma viral DNA. **(B)** A 12-year-old gelding was presented with a history of preputial discharge. Clinical investigation revealed extensive multiple areas of leukoplakia (arrows) over the shaft of the penis and the glans penis. An excisional biopsy of one lesion confirmed squamous dysplasia and pre-carcinomatous changes. *(Figure B courtesy of Richard Frost.)*



Figure 31.32 Proliferative or papillomatous carcinoma. Proliferative changes are commonly encountered in genital carcinoma of geldings and mares. **(A)** A pedunculated proliferative carcinoma in the preputial reflection of a 21-year-old cream horse. **(B)** A highly malignant invasive and proliferative carcinoma of the penile glans with obvious leukoplakia (pre-carcinomatous dysplasia) on the penile shaft. The penis had a wooden feel and there were secondary tumours in the iliac lymph nodes and lungs. **(C)** A proliferative mass involving the clitoris of a 19-year-old pony mare showing ulceration and invasion around its base.



Figure 31.33 Destructive squamous cell carcinoma of the skin. **(A)** This is a good example of the smaller destructive type of carcinoma that occurs predominately on non-pigmented skin. **(B)** A destructive carcinoma of the skin of the muzzle – note that the lesion is restricted to the white-skinned area. **(C)** An extensive destructive carcinoma that originated in the clitoral and labial area of the vulva and extended to involve much of the skin of the right buttock. In this case, there was gross enlargement of the iliac lymph nodes and the mare was losing weight rapidly. No treatment was undertaken. **(D)** A highly invasive malignant carcinoma of the mouth in a 19-year-old, coloured cross bred pony. Attempts to treat the condition with intralesional slow-release cisplatin failed to halt progression and parotid and pharyngeal lymph nodes were progressively involved. Ultimately, the tumour spread to the lungs and spleen. *(Figures A, B and C reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 429–430 (Figs 18.59 and 18.60), copyright 2009, reprinted with permission from Elsevier; Figure B courtesy of Dr Ellen Singer.)*

- The skin at any site can be affected, but non-pigmented perineal skin (Fig. 31.33A) and nasal and facial skin (Fig. 31.33B) are probably commonest. Invasive forms are aggressively ulcerative and rapidly erode into normal tissue (Fig. 31.33C,D).
- Eyelid lesions often start as white, raised plaques recognizable histologically as squamous papilloma or pre-carcinomatous squamous dysplasia. They often start at the edge of the eyelid and proceed to extensive ulceration and destruction of the eyelid, rapidly and progressively invading the periorbital tissues (Fig. 31.34).
- Nictitans and conjunctival forms are very common and, here, the earliest stages may be noted as blood staining of the tears (see p. 616). They may progress rapidly as appearance changes to a granulomatous and ulcerated lesion.

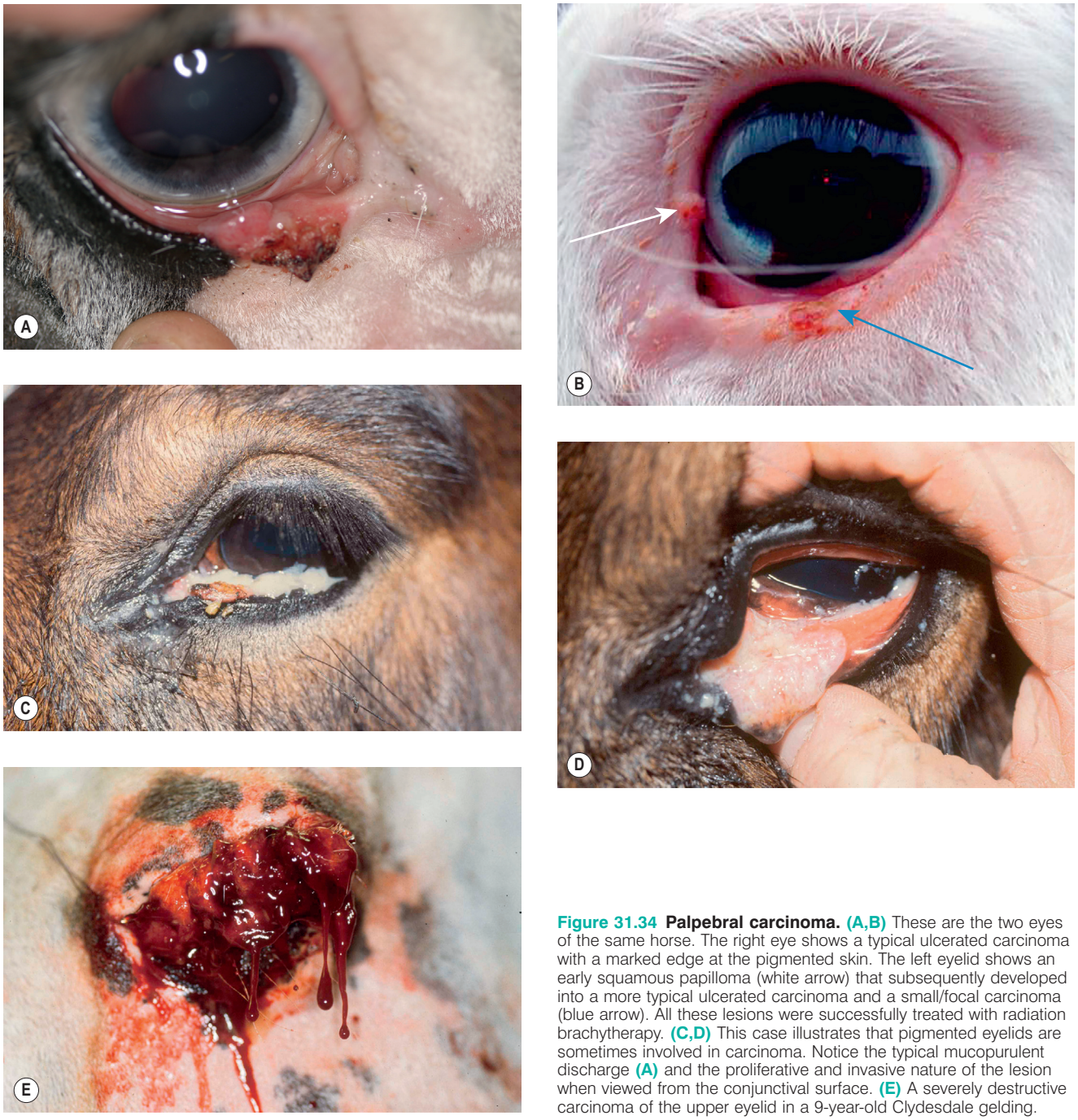


Figure 31.34 Palpebral carcinoma. (A,B) These are the two eyes of the same horse. The right eye shows a typical ulcerated carcinoma with a marked edge at the pigmented skin. The left eyelid shows an early squamous papilloma (white arrow) that subsequently developed into a more typical ulcerated carcinoma and a small/focal carcinoma (blue arrow). All these lesions were successfully treated with radiation brachytherapy. **(C,D)** This case illustrates that pigmented eyelids are sometimes involved in carcinoma. Notice the typical mucopurulent discharge **(A)** and the proliferative and invasive nature of the lesion when viewed from the conjunctival surface. **(E)** A severely destructive carcinoma of the upper eyelid in a 9-year-old Clydesdale gelding.

- All types have varying degrees of malodour, even with early lesions.
- Systemic signs may be relatively minor unless secondary metastatic spread has occurred. Weight loss, colic and chronic intestinal bleeding are signs of the gastric form, which carries a very poor prognosis and a short fulminating course. Secondary tumours can develop at any site (including the spinal cord, vertebral bodies, lungs, liver and spleen) from any form but, apart from the severe, malignant penile form and gastric squamous cell carcinoma, most are not malignant and even local lymph node involvement is unusual.
- Carcinoma can develop at sites of skin injury – biopsy is essential in such cases.

Differential diagnoses

- Sarcoid (fibroblastic and verrucose/mixed lesions)
- Melanoma
- Papilloma (especially nictitans and vulvar proliferative forms)
- Mast cell tumour
- Lymphosarcoma (cutaneous and generalized)
- Exuberant granulation tissue
- Botryomycosis/pyogranuloma

- Habronemiasis
- Phycomycosis and other fungal granulomas
- Other causes of colic/weight loss/anaemia and protein-losing enteropathy.

Diagnostic confirmation

- Surgical biopsy or even scrape cytology can be definitive
- Impression smears are possible for eye lesions
- Total excisional biopsy for histopathological examination usually can confirm both the diagnosis and the degree of differentiation.

Management

The main criteria for selection of treatment focus on the nature of the tumour (specifically its extent of invasion/localization) and its anatomical site and accessibility. A further major aspect is whether the tumour has already metastasized – if so, treatment will be palliative only. Prior to the application of any treatment method, a full clinical assessment must be performed to assess the extent of local and generalized spread of carcinoma.

Surgical ablation

See page 126.

- Where wide excision can be performed, the results are usually good, e.g. amputation of tail, enucleation/exenteration with complete removal of eyelids, amputation of penis.
- Very good results can usually be predicted on proliferative lesions at most sites. Less successful results are obtained with long-standing invasive tumours on eyelids, prepuce, mouth and, to a lesser extent, the vulva in the mare. Combination therapy is usually sensible and helpful in improving the prognosis when a safe/clear margin cannot easily be achieved.
- Due consideration should be given to the secondary effects of the surgery, including scarring and skin/tissue deficits.

Cryotherapy

See page 129.

- This can be performed on squamous cell carcinoma lesions either directly (facial, anal, nictitans, eyelid and conjunctival forms) or after surgical debulking. It is more likely to be successful in very early cases and is unsuccessful in rapidly or widely invasive tumours.
- The use of 2–3 freeze–thaw cycles is recommended.
- Cryosurgery gives only moderate results and is particularly poor around the eyes and mouth; while it can be very effective on limbal conjunctival and corneal lesions in these circumstances, the control of the freezing process has to be meticulous.
- Combination with intralesional chemotherapy improves the prognosis.

Cytotoxic chemicals and antimitotic drugs

- Topical application of antimitotic drugs, e.g. 5-fluorouracil and prednisolone (or other corticosteroids), may help but has a poor reputation in most cases.
- The best of the topical applications is 5% 5-fluorouracil cream applied twice daily for up to 21 days. There are reports of effective management of a variety of carcinomas in this way.[39,40] The successful treatments have been largely restricted to superficial forms in accessible locations and repeated applications over 30–20 days are required. This is not always feasible, but the results are impressive. Penile forms have considerable problems with topical treatments and twice-weekly or even weekly applications may be just as effective without the secondary problems.
- Intralesional chemotherapy using slow-release forms (biodegradable beads and slow-release oil emulsion) of cisplatin (see p. 147) and 5-fluorouracil (see p. 153) and topical chemotherapy with 5-fluorouracil cream have been proven effective.[17]
- Retinoids such as tazarotene may also be effective. The intralesional injection of cisplatin has been found to be effective in some cases.
- Topical mitomycin C has been used increasingly – particularly in corneal and palpebral carcinoma.[41] It can be used as sole treatment for smaller, more superficial carcinoma and as an adjunctive treatment with CO_2 laser ablation or surgery (see pp. 124 and 157).[42]

Immunomodulation

- BCG cell-wall extracts (or live BCG bacillus) have been used successfully in some forms of bovine ocular squamous cell carcinoma. The equine condition (at all sites) does not seem to be nearly as responsive, with very disappointing results. This treatment cannot be supported (see p. 189).

Radiation therapy

- This is probably the most reliably effective of all treatments, with good results expected in all cutaneous (and ocular) forms of the condition. These irradiation procedures usually require referral to specialist centres with qualified radiologists and specialized facilities for radiation protection (see p. 176).
- Radioactive implants with gold-198 and iridium-192 isotopes offer increased chances of resolution. Interstitial implants of cobalt-60, caesium-137, iridium-192 or gold-198 have all been successfully applied. Where the tumour mass is thin, e.g. corneal carcinoma in situ, or where debulking can be employed to reduce the mass of tumour tissue to <1–3 mm, strontium-90 probes/plaques (which are potent beta radiation emitters) can also be successfully used (see p. 184).
- The results of radiation brachytherapy are usually very satisfactory, with a good cosmetic effect and a low recurrence rate, although the full effects may not be obvious for some months.
- Teletherapy is a very effective treatment for most forms of the disease, which have no systemic dissemination, but is unlikely to be available except under very particular and specialized circumstances.
- As with all tumours, the radiation dose should be accurately calculated, and careful placement of the

implants can maximize the effect. Nevertheless, some tumours will recur in time.

Prognosis

Fortunately, most (but by no means all) cutaneous forms of the condition tend to remain fairly local in the early stages. Extensive local spread is rare but is still much more common than widespread metastatic dissemination. The major exception to this is the penile form, which occurs in younger geldings (<8 years of age). In these, the presence of a hard, wooden feel to the free end of the penis is a bad prognostic sign (see Fig. 31.32). Palpably enlarged inguinal and subiliac lymph nodes usually indicate a very poor prognosis. Preputial skin forms also carry a higher rate of malignancy than other forms.

Any secondary involvement of the local lymph nodes should be viewed with suspicion and it may be justifiable to biopsy this to check for metastatic tumour. If this is present, then the prognosis is very poor and it is not justifiable to subject the animal to surgery or other treatments.

Prevention

Penile forms can be prevented by regular sheath inspections and washing of suspected cases showing pre-cancerous changes or abnormal accumulations of smegma. The greater incidence of squamous cell carcinoma of the penis occurs in older geldings, usually ponies or work horses, which are less likely to receive regular cleaning of the prepuce and penis. Consequently, therapy should also be aimed at the regular cleansing of the prepuce and penis in this group of horses. This also particularly applies to the 'colour' dilute type of horse (Appaloosa, Piebald and Skewbald, Palomino and, to a lesser extent, grey horses). Regular washing of the clitoral region of mares may help to prevent occurrence.

Avoidance of other predisposing factors can be helpful but is usually difficult (avoidance of UV light in pale-skinned horses). Regular anthelmintic worming regimens and minimization of gastric ulceration may be useful, but the gastric condition is very rare and so these measures directed at prevention are probably disproportionate to the value.

Sebaceous gland tumour/carcinoma

See also page 255.

Overview

These are rare tumours arising from sebaceous gland cells in adult to aged horses. They may occur at any cutaneous site and the causative factors are unknown. There is no known age, sex or breed predilection.

Clinical features

- Solitary masses, which vary in form from nodules to alopecic lobulated growths
- They are usually slow-growing and benign in nature, but ulcerate early and become a fleshy, exophytic tumour mass (Fig. 31.35)

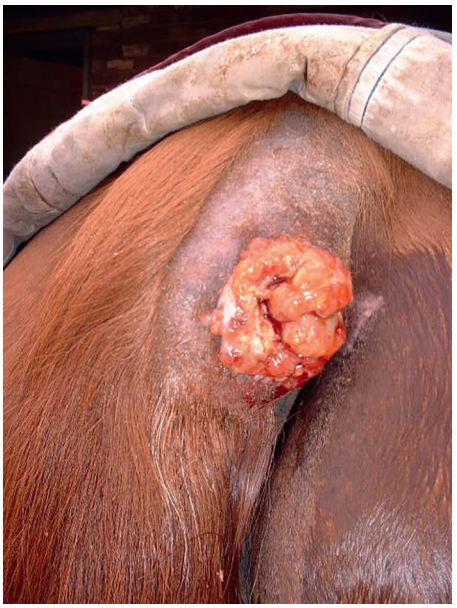


Figure 31.35 Sebaceous adenocarcinoma. An aggressive sebaceous gland carcinoma on the tail. The tumour had remained small for some months and then, following ulceration, rapidly deteriorated over a 6-week period. Surgical removal and local chemotherapy was successful.

Disease summary

Notes

Very rare, benign, usually solitary tumour of cutaneous sebaceous glands. Adenocarcinoma can be ulcerated and faster growing with some local destruction. No recognized metastatic tendency.

Clinical features

Focal nodular (possibly multinodular) mass in the skin itself.

Diagnostic confirmation

Biopsy (excisional) is definitive.

Management

Surgical removal is usually effective, but margins may not be easy to define.

Prognosis

Prognosis is good, provided it is excised fully – recurrence may occur but this remains local.

- Haemorrhage and a non-healing margin are major problems.

Differential diagnoses

- Sarcoid (nodular or fibroblastic)
- Squamous cell carcinoma
- Neurofibroma
- Dermoid cyst, nodular collagenolytic granuloma/eosinophilic collagen granuloma
- Insect and insect-bite reactions
- Foreign body reactions.

Diagnostic confirmation

Biopsy or surgical excision and histopathology.

Management

- Surgical excision or cryotherapy are effective, with little tendency to recurrence.
- The prognosis is good.

Sweat gland tumour

See also page 254.

Disease summary

Notes

Very benign, slow-growing localized tumour of the sweat gland. Any skin site can be affected. No metastatic tendency.

Clinical features

Well-defined, firm, nodular or multilobular mass in the skin.

Diagnostic confirmation

Biopsy is definitive.

Management

Surgical removal is usually effective.

Prognosis

Prognosis is good, provided it is excised fully.

Overview

Uncommon tumour of apocrine sweat glands that occurs in older horses, most commonly around ears and vulva. These tumour-like masses are usually very benign in character.

Clinical features

- Single, firm or cystic dermal nodules, which are non-painful, slow-growing and non-alopecic
- The lesions have a striking clinical resemblance to nodular sarcoid and neurofibroma but are histologically distinctive.

Differential diagnoses

- Nodular sarcoid/neurofibroma
- Foreign body reaction
- Insect bites/stings and migrations (e.g. *Hypoderma bovis*, warble fly)
- Collagenolytic granuloma (allergic/eosinophilic collagen necrosis).

Diagnostic confirmation

Biopsy/surgical excision and histopathology.

Management

Complete surgical ablation is curative.

Prognosis

A good prognosis can be given.

Trichoepithelioma

See also page 252.

Disease summary

Notes

Very rare, benign tumour-like condition of hair bulb cells occurring at any site on the body. No metastatic tendency is recognized.

Clinical features

Ill-defined, ulcerated, frequently roughly circular tumour of skin. May be bound down in character.

Diagnostic confirmation

Biopsy is definitive.

Management

Surgical removal is usually effective.

Prognosis

Prognosis is good, provided it is excised fully – recurrence may occur but this remains local.

Overview

Uncommon tumour of hair bulb cells that occurs in middle-aged horses at any skin site. It is very benign in character, remaining local, but may be invasive. The tumour is found most in areas where repeated mild skin trauma occurs, such as the girth region, so this may be an aetiological factor.

Clinical features

- Firm single or multilobular dermal and subcutaneous mass
- Non-painful, slow-growing and may have an alopecic thinned (atrophied) skin overlying the mass (Fig. 31.36)

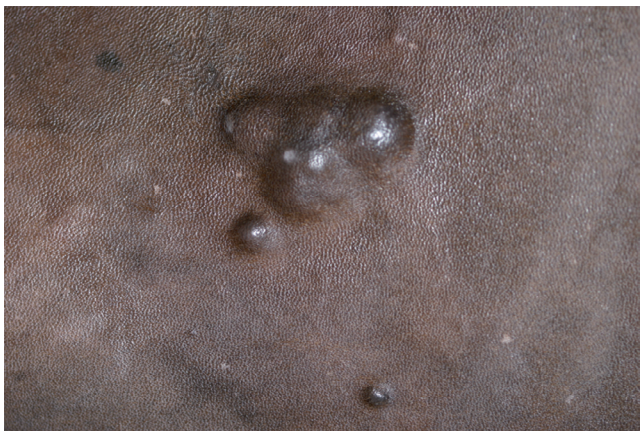


Figure 31.36 Trichoepithelioma. A cystic trichoepithelioma in the axillary/girth region. The mass was slow to expand and non-painful. A tentative diagnosis of nodular sarcoid was contradicted by excisional biopsy. The site healed without complication and no regrowth occurred. *(Figure reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 435 (Fig. 18.66), copyright 2009, reprinted with permission from Elsevier.)*

- The lesion has a striking clinical resemblance to nodular sarcoid and to axillary nodular necrosis
- The multinodular nature does, however, have an 'unusual' nature and experience helps to differentiate them
- The trichoepithelioma is histologically distinctive.

Differential diagnoses

- Nodular sarcoid/fibroma
- Basal cell carcinoma
- Dermal melanoma
- Foreign body reaction/girth gall
- Insect bites/stings and migrations (e.g. *Hypoderma bovis*, warble fly)
- Collagenolytic granuloma/girth gall/axillary nodular necrosis (allergic/eosinophilic collagen necrosis).

Diagnostic confirmation

- Biopsy
- Surgical excision
- Histopathology.

Management

Complete surgical removal is usually possible and should be curative. The margins are usually well-defined.

Prognosis

A good prognosis can be given.

Keratoma

See also page 256.

Overview

This is a tumour-like mass of keratin-producing cells in the inner surface of the coronary band, hoof wall or sole resulting in a keratin-containing 'core' between the wall and the pedal bone. The cause is not established but it may be more associated with a reactive response than a neoplastic one and so the term 'keratoma' (Fig. 31.37) may not strictly be correct.

They range in size from 1 to 4 cm in diameter, are either conical or cylindrical and grow distally, sandwiched between the wall of the hoof and the third phalanx.[43]









Figure 31.37 Keratoma. This usual tumour-like state is well recognized and occurs regularly. **(A)** Usually there is some form of lameness and hoof capsule or solar distortion. **(B,C)** Radiographical projections are often only subtle with indistinct changes, unless there are serious deformities in the hoof capsule or pedal bone. CT imaging helps enormously to establish the 3-dimensional extent of the secondary changes within the hoof and, in particular, the pedal bone. MRI, of course provides much more information about the extent and location of the mass. Here a sagittal image from a T1-weighted 3D gradient echo pulse sequence **(B)** and a frontal image from a T2-weighted 3D gradient echo pulse sequence **(C)** both show the solar keratoma protruding proximally from the solar corium (arrows). **(D)** Once removed, the tumour should be examined histologically for completeness and for the true nature of the mass (see p. 256). *(Figures A and D reprinted from Knottenbelt DK. Pascoe's Principles and Practice of Equine Dermatology. Edinburgh: Saunders; 2009: 436–437 (Figs 18.68 and 18.69), copyright 2009, reprinted with permission from Elsevier; Figures B and C courtesy of Merry Smith.)*

Disease summary

Notes

Relatively common expansile mass affecting the keratin-producing cells of the hoof wall. Uncertain whether this is a reactive condition or a true neoplasm.

Clinical features

Hoof wall distortion, lameness and visible alteration in the solar 'white line'.

Diagnostic confirmation

Radiographical evidence and clinical signs are definitive.

Management

Surgical removal is usually effective.

Prognosis

Prognosis is good, provided it is excised fully – recurrence may occur.

Diagnostic confirmation

- Characteristic changes in contour of the wall and sole
- Radiological, CT and MRI examinations will identify the mass and any underlying destruction or distortion of the pedal bone and may further guide the surgical procedure.

Differential diagnosis

Cysts in the pedal bone.

Management

Surgical removal of overlying wall with careful and complete resection and curettage of tumour from underlying bone is necessary. The method is described in all standard orthopaedic and surgical texts.

This tumour has a relatively high rate of recurrence, but it is not certain whether recurrences are the result of failure to remove the entire mass or genuine recurrence. Most authors report an excellent overall prognosis provided that the whole lesion is removed and any possible causative factors are eliminated. There may be a persistent hoof wall deficit, particularly if the coronary band was involved and/or was involved during surgery.

NEOPLASTIC CONDITIONS WITH CUTANEOUS MANIFESTATIONS

Haemangioma/haemangiosarcoma

See pages 332, 334 and 514.

Cutaneous lymphoma

See pages 349 and 533.

Lymphangioma

See pages 337 and 521.

Mycosis fungoides (malignant cutaneous T-cell lymphoma

See page 534.

Pituitary pars intermedia dysfunction (PPID) (equine Cushing's disease)

See page 585.

References

1. Baker JR, Leyland A. Histological survey of tumours of the horse with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
2. Jackson C. The incidence and pathology of tumours of domesticated animals in South Africa. Onderstepoort J Vet Sci Anim Ind 1936; 6:1–460.
3. Knottenbelt DC. Proceedings of the American College of Veterinary Internal Medicine (ACVIM), Orlando, 2007.
4. Broström H. Equine sarcoids. A clinical and epidemiological study in relation to equine leucocyte antigens (ELA). Acta Vet Scand 1995; 36:223–236.
5. Knottenbelt DC. A clinical classification of the equine sarcoid. Clin Tech Equine Pract 2005; 4:278–295.
6. Knottenbelt DC. A suggested clinical classification for the equine sarcoid. Clin Tech Eq Pract 2005; 4:277–295.
7. Knottenbelt DC, Edwards S, Daniel E. Diagnosis and treatment of equine sarcoid. In Pract 1995; 17:123–129.
8. Martens A, De Moor A, Ducatelle R. PCR detection of bovine papilloma virus DNA in superficial swabs and scrapings from equine sarcoids. Vet J 2001; 161:280–286.
9. Broström H. Equine sarcoids. A clinical, epidemiological and immunological study. PhD thesis, University of Uppsala; 1994: 36–37.
10. Goodrich L, Gerber H, Marti E, et al. Equine sarcoids. Vet Clin North Am Equine Pract 1998; 14:607–623.
11. Diehl M, Vingerhoets M, Stornetta D. Spezifische Methoden zur Enterfernung des Equinen Sarkoides [German]. Tierarztl Prax 1987; 7:14–17.
12. Knottenbelt DC, Kelly DF. The diagnosis and treatment of periorbital sarcoid in the horse: 445 cases from 1974 to 1999. Vet Ophthalmol 2000; 3:169–191.
13. Lane JG. The treatment of equine sarcoids by cryosurgery. Equine Vet J 1970; 9:127–128.
14. Hoffman KD, Kainer RA, Shideler RK. Radiofrequency current-induced hyperthermia for the treatment of equine sarcoid. Equine Pract 1983; 5: 24–28.
15. Nogueira SAF, Torres SMF, Malone ED, et al. Efficacy of imiquimod 5% cream in the treatment of equine sarcoids: a pilot study. Vet Dermatol 2006; 17:259–265.
16. Bouré L, Krawiecki J-M, Thoulon F. Essai de traitement des sarcoïdes du cheval par injection intratumorales de bléomycine (DCI). Point Vet 1991; 23:91–96.
17. Théon AP. Intralesional and topical chemotherapy and immunotherapy. Vet Clin North Am Equine Pract 1998; 14:659–671.
18. Christen-Clottu O, Klocke P, Burger D, et al. Treatment of clinically diagnosed equine sarcoid with a mistletoe extract (Viscum album austriacus). J Vet Intern Med 2010; 24:1483–1489.
19. Scott DW, Miller WH, eds. Neoplastic and non-neoplastic tumours. Equine dermatology. St Louis: WB Saunders; 2003: 730–731.
20. Roberts D. Experimental treatment of equine sarcoid. Vet Med Small Anim Clin 1970; 65:67–69.
21. Ragland WL. Equine sarcoid. Equine Vet J 1970; 2:168–172.
22. Studer U, Marti E, Stornetta D, et al. The therapy of equine sarcoid with a non-specific immunostimulator; the epidemiology and spontaneous regression of sarcoids [German]. Schweiz Arch Tierheilkd 1997; 139: 385–391.
23. Pascoe RR. Colour atlas of equine dermatology. London: Mosby; 1988.
24. Wyn-Jones G. Treatment of periocular tumours of horses using radioactive gold grains. Equine Vet J 1979; 11:3–6.
25. Slovis NM, McEntee MC, Fairley RA, et al. Equine basal cell tumours: 6 cases (1985–1999). J Vet Intern Med 2001; 15:43–46.
26. Tan RH, Crisman MV, Clark SP, et al. Multicentric mastocytoma in a horse. J Vet Intern Med 2007; 21:340–343.
27. Malikides N, Reppas G, Hodgson JL, et al. Mast cell tumours in the horse: four case reports. Equine Pract 1996; 18:12–17.
28. Cheville NF, Prasse K, van der Maaten M, et al. Generalised equine mastocytosis. Vet Pathol 1972; 9:394–399.
29. McEntee MF. Equine cutaneous mastocytoma: morphology, biological behaviour and evaluation of the lesion. J Comp Pathol 1991; 104:171–178.

30. Valentine BA. Equine melanocytic tumours: a retrospective study of 53 horses (1988 to 1991). J Vet Intern Med 1995; 9:291–297.
31. Seltenhammer MH, Heere-Ress E, Brandt S, et al. Comparative histopathology of grey-horse-melanoma and human malignant melanoma. Pigment Cell Res 2004; 17:674–681.
32. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
33. Dye V, Robinson JL, Aclund H, et al. Morphologic characteristics of equine melanomas and relationship to biologic behaviour. In: Rooney JR, Robertson JL, eds. Equine pathology. Ames: Iowa State University; 1993: 304.
34. Rowe EL, Sullins KE. Excision as treatment of dermal melanomatosis in horses: 11 cases (1994–2000). J Am Vet Med Assoc 2004; 225:94–96.
35. Warnick ID, Graham MF, Valentine BA. Evaluation of cimetidine treatment for melanomas in 7 horses. Equine Pract 1995; 17:16–18.
36. Jeglum KA. Melanomas In: Robinson NE, ed. Current therapy in equine medicine. Philadelphia: WB Saunders; 1997: 399–401.
37. Goetz TE, Long MT. Treatment of melanoma in horses. Compend Contin Educ Pract Vet 1993; 15:608–610.
38. Dugan SJ, Curtis CR, Roberts SM, et al. Epidemiologic study of ocular/adnexal squamous cell carcinoma in horses. J Am Vet Med Assoc 1991; 198:251–256.
39. Fortier LA, MacHarg MA. Topical use of 5-fluorouracil for treatment of squamous cell carcinoma of the external genitalia of horses: 11 cases (1988–1992). J Am Vet Med Assoc 1994; 205:1183–1188.
40. Patterson S. Treatment of superficial ulcerative squamous cell carcinoma in three horses with topical 5-fluorouracil. Vet Rec 1997; 141:626–628.
41. Rayner SG, van Zyl N. The use of mitomycin C as an adjunctive treatment for equine ocular squamous cell carcinoma. Aust Vet J 2007; 84:43–46.
42. Malalana F, Knottenbelt DC, McKane SA. Mitomycin C, with or without surgery, for the treatment of ocular squamous cell carcinoma in horses. Vet Rec 2010; 167:373–376.
43. Dyson SJ. Keratomas, neoplastic and non-neoplastic space occupying lesions in the hoof. In: Ross MW, Dyson SJ, eds. Lameness in the horse. St Louis: Saunders; 2003: 318.

32

Tumours of the endocrine and neuroendocrine systems

Endocrine tumours

Overview 585
Neoplasia of the pituitary gland 585
Neoplasia of the thyroid gland 586
Rare tumours of the thyroid gland 591

Neuroendocrine tumours

Overview 593
Neoplasia of the adrenal medulla (phaeochromocytoma/intra-adrenal sympathetic paraganglioma) 594

ENDOCRINE TUMOURS

Overview

Neoplasia of the endocrine system occurs mainly in older horses and most of the clinically significant tumours are benign; they can, however, be significantly hyperfunctional and that results in most of the clinical signs associated with them. Some are, however, important aggressive tumours that have abnormal functional and other pathological effects. Tumours are most commonly reported in the pituitary, thyroid and adrenal glands. Tumours of the interstitial cells of the testicle or ovary are technically endocrine tumours but are considered in the chapter on reproductive tumours (see p. 629).

Neuroendocrine tissue in horses is less well understood, with few case reports of neoplasia involving this system. A broad summary of the tumours that have been reported is shown in Table 32.1.

Disease summary

Notes

Genuine adenoma of the pituitary gland is probably very rare. Secondary hyperplasia as a result of pituitary pars intermedia dysfunction (PPID) is extremely common in older horses. The condition exclusively affects older horses.

Clinical features

Signs are varied but hypertrichosis is pathognomonic.

Diagnostic confirmation

Other causes of weight loss and polydipsia/polyuria are the main differentials.

Management

Treatment for genuine adenoma is not reported; hyperplasia is an endocrinology disorder.

Prognosis

Prognosis is fair – the progression is very slow for the most part.

Neoplasia of the pituitary gland

See also page 376.

Pituitary pars intermedia dysfunction (PPID/equine Cushing's disease)

Overview

Most equine pituitary adenomas arise in the *pars intermedia* (PI) of the pituitary gland where the melanotroph is the major cell type. There has been controversy as to whether these masses are, in fact, a benign neoplasm or actually represent adenomatous hyperplasia secondary to loss of dopaminergic inhibition of the PI.[1] Recently, however, a range of lesions have been described, from focal hypertrophy or hyperplasia, through diffuse adenomatous hyperplasia and microadenoma to adenoma.[2–4]

Pituitary adenoma typically affects older horses; 85% of cases are over 15 years of age; mean ages of 19–27 years have been documented.[5–8] The prevalence has been shown to increase with each year of age.[9] However, younger adults can occasionally be affected (7–12 years of age).[6]

Several breeds have been considered to be at greater risk for the development of PPID based on clinical case reports, including ponies and Morgan horses.

Clinical features

The clinical signs of PPID in horses are varied and include (Fig. 32.1):

- Hypertrichosis (hirsutism)
- Hyperhidrosis (sweating)
- Recurrent or persistent acute or subacute laminitis
- Polyuria/polydipsia
- Depression or behavioural abnormalities
- Lethargy
- Weight loss due to the catabolic effects of hypercortisolaemia and insulin resistance. Muscle atrophy, particularly of the epaxial, lumbar and abdominal muscles, is a common but nonspecific feature[10]
- Fat re-distribution gives the horse a pot-bellied appearance and bulging supraorbital fat pads. Large

Table 32.1 Summary of neoplasms affecting the endocrine and neuroendocrine system of horses

Endocrine	Pituitary thyroid	Adenoma/hyperplasia
		Adenoma
		Carcinoma
		C-cell (parafollicular) adenoma
		C-cell (parafollicular) carcinoma
		Ultimobranchial remnant (mixed) neoplasms
	Parathyroid	Chief cell adenoma
		Chief cell carcinoma
	Adrenal cortex	Adenoma
		Carcinoma
	Pancreatic islet cell	Adenoma
		Adenocarcinoma
	Multiple endocrine neoplasia syndrome	Appearance of benign and/or malignant neoplasms within ≥2 different endocrine glands (or paraganglia)
Neuroendocrine	Adrenal medulla	Phaeochromocytoma (intra-adrenal sympathetic paraganglioma)
	Extra-adrenal paraganglia	Orbital paraganglioma
		Chemodectoma
		Aortico-sympathetic paraganglioma
	Neuroendocrine tumours of dispersed neuroendocrine system	Carcinoids

deposits of fat at the tail-head, lumbar, neck and scapular regions contribute to the 'pot belly' appearance[10]
- Susceptibility to viral, bacterial or parasitic infections due to immunosuppression as a result of serum cortisol elevations and/or increased levels of potentially immunosuppressive hormones including ACTH, α-MSH and β-endorphin[11]
- Wound healing delays and variations, including non-healing oral ulceration
- Neurological impairments include blindness, ataxia, narcolepsy, collapse or seizures. In some horses, the pituitary mass compresses the optic tract, causing Wallerian degeneration and blindness[7,12]
- Pruritus that is not attributable to parasitism
- Reproductive acyclicity, irregular cyclicity and inappropriate lactation without pregnancy.

Differential diagnoses

- Other causes of weight loss, polydipsia and polyuria
- Other causes of laminitis
- Tumours affecting other body systems, including melanoma and lymphoma.

Diagnostic confirmation

- There are several static and dynamic tests that have been used to diagnose PPID, but few of these address the potential difference between a genuine adenoma of the pituitary gland and the functional secondary hyperplasia, which is undoubtedly much more common. The lack of a true gold standard has impaired the ability to validate diagnostic tests.[13] The diagnostic tests currently available are listed in Table 32.2. The technical details of these tests are described in standard medical texts.
- Current imaging modalities, including CT and MRI, provide some hope of a means of confirmation of the nature of the enlargement of the pituitary gland. Up to now, post-mortem confirmation with histology is the only definitive test of the true nature of the changes (Fig. 32.2).

Management and prognosis

There is no specific treatment for pituitary adenoma, but pergolide is a common medication for management of PPID syndrome.

The long-term prognosis for cases involving any tumour or hyperplasia of the pituitary gland will depend on the extent of the changes and the secondary effects. The prognosis for genuine adenomas is poor, since they seldom respond adequately to pergolide therapy.

Neoplasia of the thyroid gland

See also page 380.

Overview

Equine thyroid tumours have been described as 'moderately common', but they are seldom responsible for clinical disease or endocrinological dysfunction. In horses, thyroid adenoma, follicular carcinoma, C-cell adenoma, C-cell carcinoma, ultimobranchial adenoma and mixed C-cell (medullary) follicular carcinoma have been reported.[14–25]



Figure 32.1 Classically described signs of pituitary pars intermedia dysfunction/pituitary adenoma. **(A)** Weight redistribution/pot-bellied/ewe-necked body shape. **(A,B)** Hypertrichosis (hirsutism). **(B)** Hyperhidrosis/sweating, **(B)** laminitis, **(C)** opportunistic infection and immunosuppression leading to sinusitis, **(D)** non-healing oral ulcers, etc.

Thyroid tumours are notably more common in older horses; in a survey of thyroid glands in aged horses, no tumours were found in horses younger than 17 years of age and most tumours were microfollicular adenoma.[26]

They tend to occur more often in light-weight breeds than in Draft/heavy breeds.[27]

Three forms of thyroid tumour are described based on immunohistochemistry[28]:

1. Undifferentiated
2. Parafollicular (calcitonin-positive)
3. Follicular epithelial (thyroglobulin-positive).

The World Health Organization (WHO) classified malignant thyroid tumours of domestic animals as either variations of follicular or C-cell carcinoma but not mixed. In human medicine, the mixed forms are recognized and classified by WHO.[29] Mixed C-cell (medullary) follicular carcinoma has only been reported once in a horse.[25,30,31]

Thyroid adenoma

See also page 380.

Overview

Almost all thyroid adenomas in horses are follicular adenomas. They can be described as 'cold', 'warm' or 'hot', depending on their level of function; in horses they are usually considered 'cold' or non-functional. There are no papillary thyroid adenomata, i.e. they are all within the gland itself.

Adenoma is the most common neoplasm of the equine thyroid gland. It is age-related, and occurs mainly in horses older than 16–18 years of age. It is a benign tumour of follicular origin, usually unilateral and not usually associated with thyroid gland dysfunction or significant clinical signs.[18]

A thyroid adenoma was, however, reported to be associated with hyperthyroidism in a 23-year-old gelding

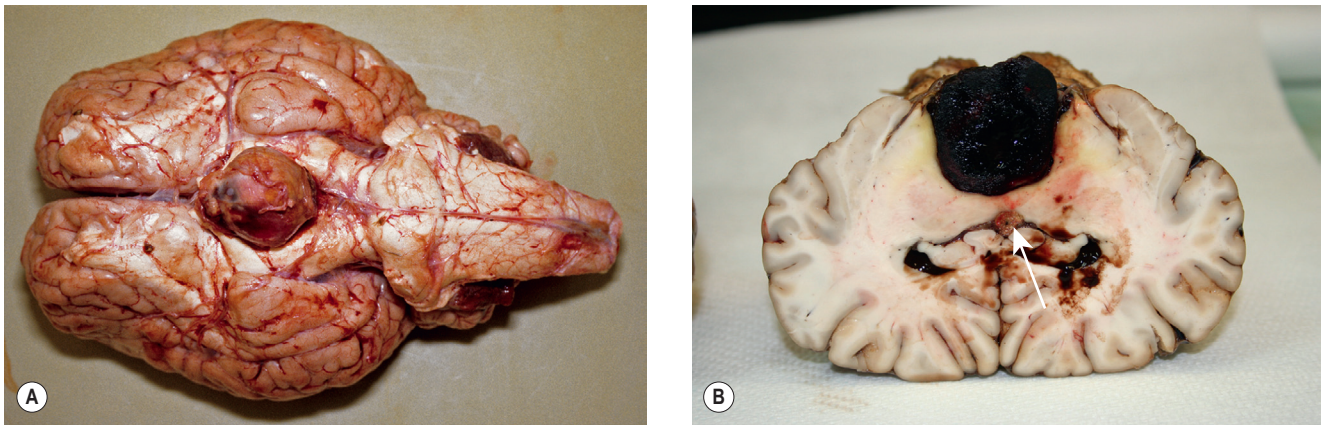


Figure 32.2 Pituitary adenoma. (A) Pituitary hyperplasia was confirmed histologically in this gland from a 25-year-old Welsh pony mare presented with all the signs of pituitary pars intermedia dysfunction (PPID/equine Cushing's disease). **(B)** A 13-year-old bay Thoroughbred mare was presented with a 3-week history of weight loss, inappetence and progressive central nervous signs including circling and left eye central blindness. MRI identified a well-defined (3×3×3 cm) mass in the pituitary gland. At necropsy, this was confirmed as a pituitary macroadenoma. Notice also the small (possibly insignificant) cholesterol granuloma in the third ventricle (arrow). *(Figures courtesy of Carney Jackson.)*

Table 32.2 Non-exhaustive list of direct and dynamic tests for diagnosis of PPID/pituitary adenoma

	Specificity	Sensitivity	Practicality
Simple tests			
Glucose	+	+	✓✓
Cortisol	++	+	✓✓
Urinary cortisol : creatinine ratio	++	+	✓
Insulin	+	+	✓
α-MSH	+++	++	✗
β-END	+	++	✗
ACTH	++	++	✓✓
Dynamic tests			
8 h cortisol difference	+	+	✓
Domperidone stimulation test	++	++	✗
ACTH stimulation test	++	++	✓
Overnight dexamethasone suppression test (ODST)	+++	+++	✓✓✓
TRH stimulation test (cortisol)	+++	+++	✓✓
Combined ODST/TRH stimulation test	++	+++	✓
TRH stimulation test (ACTH)	++++	++++	✓✓✓

The method for each of these tests is to be found in any standard equine internal medicine text. The tests are usually less convincing in genuine tumour cases, as might be expected. (The number of + marks indicates the extent of specificity band sensitivity of the tests and the number of tick marks indicates the clinical value.)

Disease summary

Notes

Relatively common benign (usually) unilateral, non-functional tumour of thyroid follicular cells that occurs in older horses (>17–18 years).

Clinical features

Gradual, non-painful, non-invasive expansion of one thyroid gland; usually asymptomatic, with no systemic or other signs. A very few can show more obstructive signs.

Diagnostic confirmation

Palpation is characteristic; ultrasonography and hollow-needle biopsy.

Management

Unilateral thyroidectomy is usually performed for cosmetic reasons.

Prognosis

Prognosis is excellent – few cases advance to carcinoma.

presenting with unilateral thyroid gland enlargement and emaciation, hyper-excitability, tachycardia, polyphagia, polydipsia and enophthalmos.[14] Diagnosis was achieved by percutaneous biopsy and a T_3 suppression test, in which T_4 concentrations were not suppressed after intramuscular administration of T_3. Hemi-thyroidectomy restored thyroid hormone concentrations to normal levels.

Clinical features

- Unilateral thyroid gland enlargement, with no obvious associated clinical signs is the most common presentation. Swelling is firm–hard, non-painful and warm only (Fig. 32.3). The mass can be moved relative to the surrounding skin and deep tissues
- Tracheal compression, gulping behaviour, stridor and exercise intolerance have been reported[32,33]

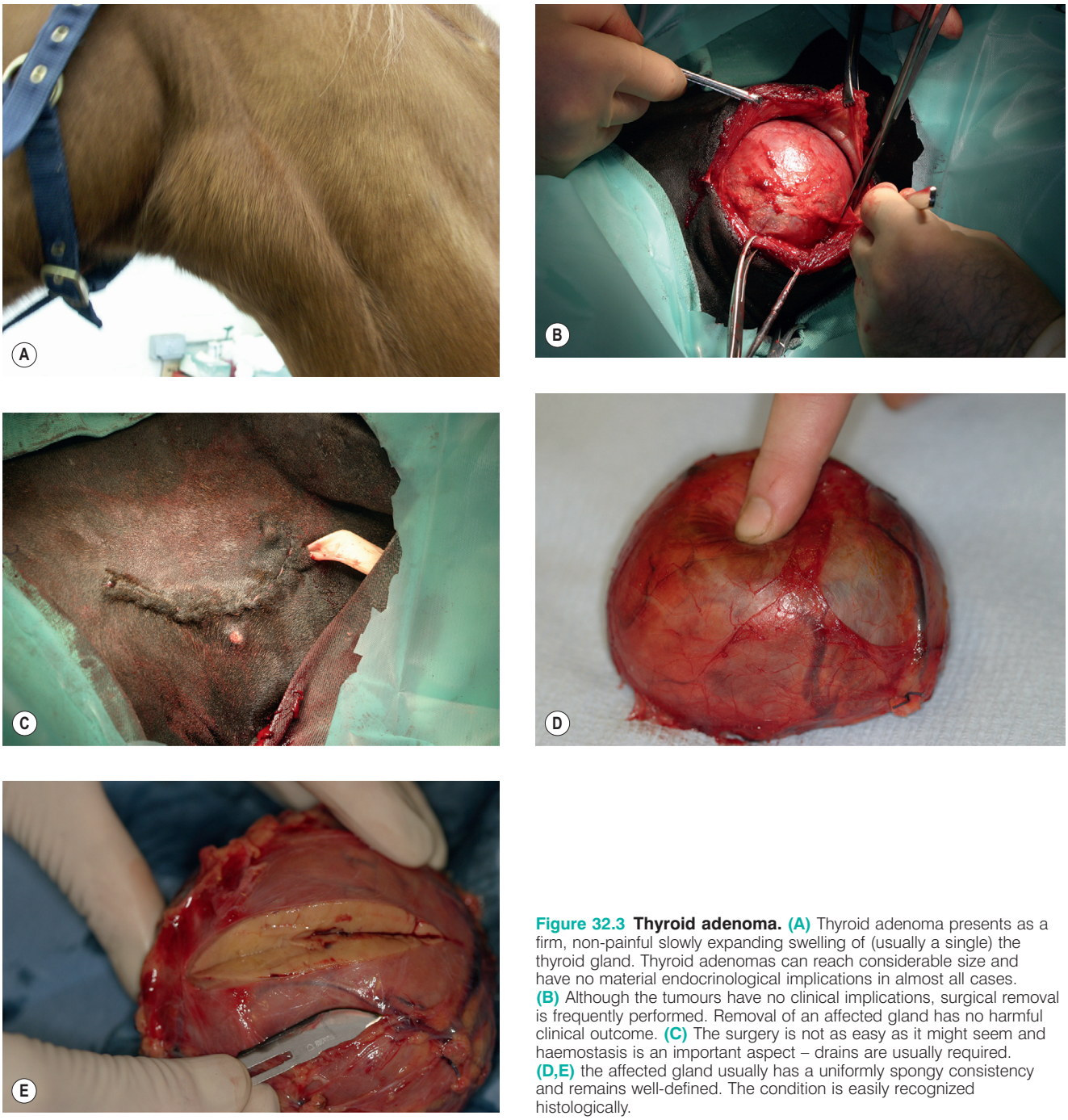


Figure 32.3 Thyroid adenoma. **(A)** Thyroid adenoma presents as a firm, non-painful slowly expanding swelling of (usually a single) the thyroid gland. Thyroid adenomas can reach considerable size and have no material endocrinological implications in almost all cases. **(B)** Although the tumours have no clinical implications, surgical removal is frequently performed. Removal of an affected gland has no harmful clinical outcome. **(C)** The surgery is not as easy as it might seem and haemostasis is an important aspect – drains are usually required. **(D,E)** the affected gland usually has a uniformly spongy consistency and remains well-defined. The condition is easily recognized histologically.

- Other clinical signs reported in association with functional tumours have been rarely reported, including those associated with hyperthyroidism – weight loss, hyper-excitability, polyphagia, tachycardia and polydipsia.[18]

Notes

- Thyroid adenoma is usually unilateral.
- Although the enlargement can cause some concern, these tumours are usually free of any apparent sign. Respiratory obstruction does not occur since the expansion takes the line of least resistance and so it does not compress any airway component. Surgery is usually performed for 'cosmetic reasons'.

Differential diagnoses

- Thyroid carcinoma
- C-cell adenoma/adenocarcinoma
- Parotid melanoma
- Salivary adenocarcinoma
- Branchial remnant/oesophageal cyst
- Salivary cyst
- Thyroiditis (inflammatory disease of the thyroid)
- Hyper- or hypothyroidism
- Iodine deficiency/goitre
- Neonatal hyperiodic goitre (paradoxical iodine-related hypothyroidism)

- Thyroid abscess
- Idiopathic thyroid enlargement.

Diagnostic confirmation

- Palpation is characteristic – the affected gland is easily mobile subcutaneously and is not warm
- Ultrasonography
- Fine-needle aspiration or hollow-needle (Tru-Cut) biopsy and histopathology provide definitive information
- Immunohistochemistry may be used to differentiate between parafollicular (calcitonin-positive) and follicular (thyroglobulin-positive) epithelial cells of the thyroid. Cell aggregations may contain undifferentiated cells that retained embryonic characteristics, such as those of the ultimobranchial remnant, and are classified as either an ultimobranchial remnant embedded in thyroid tissue without compression of adjacent cells, nodular hyperplasia of the ultimobranchial remnant causing compression of adjacent cells, or adenoma of the ultimobranchial remnant surrounded by fibrous capsule.[28]

Management

Occasionally the size of the tumour may warrant surgical excision – usually this is done on the erroneous belief that the swelling will cause respiratory obstruction or as a precaution against the possible development of thyroid carcinoma.

Surgery

Surgical excision may be considered, especially when the thyroid gland is unilaterally affected and no systemic disorder has been identified. Surgical thyroidectomy is a more challenging procedure than is usually thought (Fig. 32.3).

- Complications as a result of surgery may include haemorrhage, seroma formation and trauma to the recurrent laryngeal nerve, with resultant laryngeal hemiplegia.
- Hypocalcaemia may not occur as the parathyroid glands are not directly connected to the thyroid gland.
- A thyroid storm has been reported following hemi-thyroidectomy in a horse.[18] In cases of suspected functional tumours, it may, however, be prudent to establish the T_4 status prior to surgery.

Note

Phenylbutazone, which is commonly administered to horses prior to and after surgery, is known to decrease measured T_4 concentrations.[33] Therefore, it is recommended that thyroid hormone concentration assay is performed well before and after drug therapy is administered.

Radiotherapy

Radiotherapy is theoretically possible using radioiodine, but this is probably an unachievable goal in any case.

Prognosis

Thyroid adenoma is usually slow-growing and is very benign; it does not metastasize. Progression from hyperplasia to adenoma and then to adenocarcinoma has been reported in rodents, but this progression is not reported in the horse.[26] However, rapid expansion of the thyroid mass can occur, suggesting that these tumours may remain dormant or quiescent, but can suddenly enlarge.

Prognosis is good.[28] Most horses with benign adenoma or even early thyroid carcinoma remain clinically (endocrinologically) normal following unilateral thyroidectomy. In the rare bilateral cases, there may be other implications.

Thyroid adenocarcinoma (follicular carcinoma)

See also page 380.

Overview

Thyroid carcinoma is very rare, with few reports published.[15–19,26,34,35] The metastatic potential is low; however, metastases have been reported in the lung, skeletal muscles, heart, kidney, retropharyngeal lymph nodes and uveal tract. It is usually unilateral and amenable to surgical resection. The condition is usually found in older horses (usually without an apparent history of a prior adenoma). There is no reported sex or breed predisposition.

Thyroid carcinoma is usually follicular in origin, non-functional and, although it has been associated with exercise intolerance, typically it is not associated with clinical signs.

Clinical features

- Firm, hot (sometimes painful), rapidly expanding swelling of the thyroid gland (or the region of the gland) (Fig. 32.4A)
- 'Bound-down' nature with possible involvement of the overlying skin and other structures in the region, including the vagosympathetic trunk (possibly Horner's syndrome and/or ipsilateral laryngeal neuropathy)
- Exercise intolerance and an enlarged thyroid gland.[16] Possible airway narrowing through lateral pharyngeal compression.

Differential diagnoses

- Thyroid adenoma
- C-cell adenoma/adenocarcinoma

Disease summary

Notes

Very rare (usually unilateral), non-functional tumour of follicular cells (carcinoma) affecting middle-aged horses.

Clinical features

Exercise intolerance.

Diagnostic confirmation

Rectal palpation, ultrasonography and percutaneous biopsy.

Management

Unilateral nephrectomy (possibly by laparoscopy) if unilateral disease is confirmed and there is no evidence of metastatic disease.

Prognosis

Prognosis is very poor – possibly the most malignant tumour of horses.

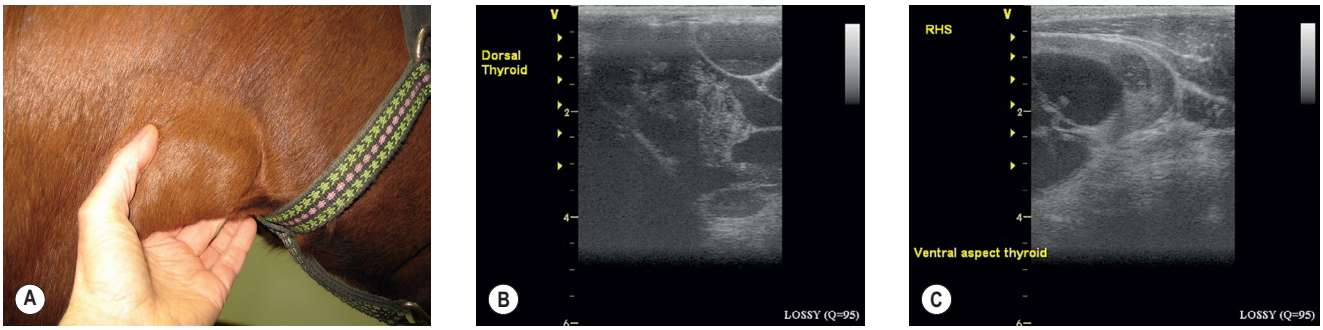


Figure 32.4 Thyroid carcinoma. (A) A hot, painful, multinodular swelling developed over a 4-week period in the right thyroid gland of a 12-year-old Thoroughbred cross gelding. **(B,C)** Ultrasonography confirmed that the mass was, in fact, the thyroid gland but that there was a very mixed echogenicity with a very high blood supply. The affected gland was removed surgically and histology confirmed a diagnosis of thyroid carcinoma. This was detected early and treated fast and the horse has had no further problems over at least 5 years.

- Oesophageal abscess
- Salivary or oesophageal cyst
- Thyroid abscess
- Parotid salivary gland melanoma
- Salivary adenocarcinoma.

Diagnostic confirmation

- Ultrasonography reveals a highly vascularized, ill-defined swelling with mixed echogenicity (possibly associated with tumour lysis/necrosis) (Fig. 32.4B,C)
- Nuclear scintigraphy may reveal displacement of the affected thyroid gland
- Percutaneous hollow-needle biopsy
- Serum biochemistry may reveal low T_3 and T_4, but most thyroid carcinomas are non-functional.[16] However, a case of a 21-year-old horse with a history of weight loss, tachypnoea, behavioural abnormalities and a progressively enlarging mass in the right cervical region was suggestive of hyperthyroidism associated with a thyroid tumour.[18] Baseline serum total thyroxine (tT_4) concentration was normal, but free thyroxine (fT_4) was significantly elevated. Surgical removal restored circulating thyroid hormone levels to normal and the horse competed successfully.[16]

Management

Surgical resection can be performed and, if carried out carefully, can be successful. A single case exhibited signs including seizures and hyperaesthesia.

Notes

Thyroid storm is a rare, life-threatening exacerbation of the hyperthyroid state described in humans, in which evidence exists of severe multiorgan dysfunction. The underlying mechanism is unknown. Surgical manipulation of the thyroid gland may stimulate the release of thyroid hormones, inciting the development of the condition. However, tT_4 and fT_4 concentrations are frequently normal after surgical removal of a hyperactive gland. Clinical signs of thyroid storm include pyrexia, tachycardia, sweating, seizures, coma, diarrhoea, vomiting, cardiac, collapse and occasionally death. Although hyperthyroidism appears to be rare in horses, it should be considered as a potential diagnosis when thyroid neoplasia occurs in association with weight loss, behavioural abnormalities, seizures or heat intolerance.[18]

Prognosis

Early recognition and surgical removal can carry a good prognosis. The prognosis in late presented cases is probably best regarded as guarded. Metastatic spread is extremely rare. However, a case of thyroid carcinoma in an 18-year-old Thoroughbred gelding presented with acute non-responsive colic and had metastases to multiple sites including the uveal tract, which led to the horse presenting with both ocular and abdominal pain. There was a progressively increasing swelling in the left lateral laryngeal region and a mass at the base of the iris of the right eye.[19] Rectal examination revealed a firm, soft tissue mass at the right ilium extending cranially into the abdomen. Ophthalmological examination revealed a 1 cm mass in the anterior chamber of the right eye, mild corneal oedema, hyphema, severe hyperaemia of corneal blood vessels and severe miosis, consistent with anterior uveitis. Abdominocentesis yielded haemorrhagic fluid. Ultrasonography of the right eye confirmed the presence of a mass within the eye. At post-mortem examination, a thyroid carcinoma was diagnosed with secondary metastases to the eye, lung, kidney and heart.

Rare tumours of the thyroid gland

C-cell adenoma and C-cell (medullary) carcinoma

See also page 382.

Overview

C-cell or parafollicular cell tumours have been reported in horses.[20–22,32,36] C-cell (parafollicular cell) tumours have been encountered most frequently in adult and aged bulls. Tumours derived from C cells are usually associated with excess secretion of calcitonin, which may cause slight hypocalcaemia. Little is known about these tumours in horses: they are occasionally identified incidentally at necropsy. Cattle with C-cell thyroid tumours frequently show lameness as a result of degenerative osteoarthropathy and ankylosing spondylosis with vertebral osteosclerosis. The pathogenesis of these lesions in relation to excess calcitonin production by the tumour is not understood.

Two horses with confirmed C-cell adenoma presented with constant gulping, which was relieved by surgical

removal of the enlarged glands.[32] It is likely in both animals that the paralaryngeal mass provoked discomfort, as indicated by constant gulping. Other cases show no clinical signs other than a palpably enlarged thyroid gland.[20,22]

Immunohistochemistry may be necessary to distinguish C-cell tumours from other thyroid neoplasms.[20,28] Most follicular epithelial cells and microfollicular adenomas are immunohistochemically positive for thyroglobulin, while parafollicular (C) cells and tumours derived from them are positive for calcitonin, calcitonin-gene-related peptide (CGRP), chromogranin A, neuron-specific enolase and synaptophysin. The majority of nodular lesions frequently found in the thyroid gland of older horses were C-cell adenoma, and these are usually non-functional and do not lead to calcitonin hypersecretion-related diseases.[21]

Ultimobranchial adenoma (mixed C-cell medullary microfollicular carcinoma)

See also page 383.

Overview

There is only one reported case in the literature at this time.

A mixed C-cell microfollicular carcinoma of the thyroid gland has been reported in a 15-year-old stallion presented with inappetence of 12 h duration and a cranio-ventral neck mass.[25]

Serum biochemistry revealed elevated ionized calcium and a normal total thyroxine level. Endoscopy revealed no oesophageal compression. Ultrasonographic examination showed a prominent left thyroid gland with heterogeneous hyperechoic centre, and normal right thyroid gland. Fine-needle aspirate of the mass was suspicious of a malignant process. Nuclear scintigraphy showed marked radiopharmaceutical uptake in the region of the left thyroid gland, consistent with metabolic hyperactivity.

A hemi-thyroidectomy was performed and histopathology of the mass revealed a lack of local invasion and a low anaplastic score, consistent with a benign classification as an adenoma. However, the presence of tumour emboli in the local lymphatics and veins confirmed malignancy. Immunohistochemistry confirmed a well-differentiated mixed C-cell microfollicular carcinoma of the thyroid gland.

Neoplasia of the parathyroid glands

See also page 384.

Overview

In the horse, primary hyperparathyroidism may result from a parathyroid adenoma or carcinoma, or parathyroid hyperplasia. This results in excessive and autonomous synthesis and secretion of parathyroid hormone (PTH). The parathyroid gland does not respond to the negative feedback of Ca^{2+}. Elevated PTH concentrations result in increased renal Ca^{2+} reabsorption (hypocalciuria), hyperphosphaturia, increased bone resorption, and increased vitamin D synthesis. The end result is loss of cortical bone and a condition known as 'osteodystrophia fibrosa'. Clinical features in these horses include enlargement of the facial bones, inspiratory noise associated with nasal passage stenosis, loosening of teeth, lameness and a poor body condition. Radiographic findings include osseous proliferation of the maxilla and mandible and loss of the lamina dura surrounding the molar teeth. Histopathological examination of the parathyroid gland is necessary to confirm primary hyperparathyroidism, but this can be difficult due to their small size and variable location.

There is only a very small number of primary hyperparathyroidism cases reported in the literature as an adenoma.[37–39] In two cases reported, a diagnosis of parathyroid gland adenoma was made based on clinical signs, but the parathyroid gland could not be identified at post mortem.[40,41] A 17-year-old pony mare was admitted for evaluation of progressive enlargement of the facial bones during the preceding 9 months. Laboratory testing revealed that the pony had hypercalcaemia, hypophosphataemia, high urinary fractional excretion of phosphorus and high serum concentration of intact parathyroid hormone (185.1 pmol/L; reference range, 0.25–2.0 pmol/L). On the basis of these findings, a diagnosis of primary hyperparathyroidism was made by ruling out nutritional secondary hyperparathyroidism, chronic renal disease and pseudohyperparathyroidism resulting from neoplasia. Surgical treatment was declined and the pony was euthanized. At post mortem, a functional lesion of the parathyroid tissue was not located. Difficulty localizing and grossly identifying parathyroid tissue in horses complicates definitive diagnosis and treatment of primary hyperparathyroidism.[41] Regression of bony lesions after surgical excision of a parathyroid adenoma has been reported.[37]

Pseudohyperparathyroidism has been used to describe a paraneoplastic syndrome known as 'humoral hypercalcaemia of malignancy', in which hypercalcaemia develops. Parathyroid hormone-related protein is the humoral factor responsible for hypercalcaemia. This paraneoplastic syndrome has been described in horses in association with gastric squamous cell carcinoma, lymphosarcoma, adrenocortical carcinoma, squamous cell carcinoma of the vulva and ameloblastoma (see p. 75).[39]

Neoplasia of the adrenal glands

See also page 384.

Overview

The adrenal gland comprises the medulla and the cortex; these differ in their embryological origin, type of secretion and function. The medulla is related functionally to the sympathetic nervous system and secretes adrenaline and noradrenaline in response to sympathetic stimulation. Tumours of the adrenal medulla are discussed in the section on Neuroendocrine: neoplasia (see pp. 384 and 387).

The adrenal cortex secretes corticosteroids and is involved in a variety of body functions, including maintenance of fluid and electrolyte balance, immunity, defence and energy metabolism.[42]

The adrenal cortex consists of three zones:

1. *The zona glomerulosa*: this secretes mineralocorticoids in response to the renin–angiotensin system and to changes in extracellular fluid osmolality

2. *The zona fasciculata*: this secretes glucocorticoids (cortisol) in response to adrenocorticotrophic hormone (ACTH) stimulation
3. *The zona reticularis*: this secretes androgens.

Adrenocortical neoplasia

See also page 386.

Overview

Cushing's syndrome in horses almost invariably originates from a pituitary pars intermedia adenoma (see pp. 587 and 376).[6] There are only four documented case reports of horses with a primary adrenocortical adenoma/carcinoma and none of these had demonstrably abnormal endocrine function.

There is one report of a functional adrenocortical neoplasm in a 12-year-old Warmblood gelding; the horse showed signs of pituitary-independent Cushing's syndrome, including a ravenous appetite, reduced muscle mass and increased body fat cover, delayed shedding of coat, hyperhidrosis and lethargy.[43–47]

Clinical signs progressed to include polyuria and polydipsia, and laminitis.

Clinical pathology revealed a persistent but variable hyperglycaemia, which induced paroxysmal elevation of corticosteroid concentrations. This was reflected by an increased urinary corticoid : creatinine ratio.

Neoplasia of the endocrine pancreas

See also page 386.

Overview

The islets of Langerhans are endocrine functional units of the pancreas. Histologically, four cell types can be identified: the α or A cells that secrete glucagon; the β or B cells that secrete insulin; the δ or D cells that secrete somatostatin; and the PP cells that secrete pancreatic polypeptide.

Exocrine pancreatic tumours (adenocarcinomas) are more frequent than endocrine (islet cell) tumours. One single case report on a pancreatic adenoma of pancreatic islet tissue in a 12-year-old Shetland pony mare has been published.[48] The pony had eight seizures over a 2-month period. Plasma glucose levels during three of these seizures were markedly depressed and serum insulin levels were elevated during two of the seizures. Gross and microscopic pathological evaluation of the pancreas revealed a single adenoma of pancreatic islet cell origin and hyperplasia of islet cells, predominantly beta cells.[48]

Multiple endocrine neoplasia

See also page 386.

Overview

The simultaneous occurrence of several endocrine tumours in a single individual is called multiple endocrine neoplasia (MEN) syndrome.

This syndrome is well described in humans, but less so in domestic animals. In humans, the appearance of benign or malignant proliferations within two or more endocrine glands is nearly always genetically determined. Two distinct forms of the human form of MEN have been described.

Type I MEN is characterized by hyperparathyroidism, pancreatic islet hyperplasia and/or adenomas and pituitary adenomas.

Type II MEN has two variants:

- *Type IIa* is characterized by:
  - C-cell (medullary) carcinoma
  - Hyperparathyroidism
  - Phaeochromocytoma
- *Type IIb* is characterized by
  - C-cell carcinoma
  - Phaeochromocytoma
  - Extra-endocrine changes, including multiple mucosal neuroma and ganglioneuroma.

MEN syndrome has not been diagnosed antemortem in the horse. However, one report describes the clinical presentation and post-mortem findings of a MEN-like syndrome in a horse (see also p. 386).[2] An 18-year-old Warmblood gelding presented with a history of progressive non-responsive colic. The horse was sweating profusely and tachycardic; a mass medial to the left kidney was palpated per rectum. Exploratory laparotomy revealed massive haemorrhage into the abdomen and a large, inoperable (20 cm diameter) mass in the region of the left kidney. A tear within the mass accounted for the massive bleeding. Post-mortem examination revealed a left adrenal gland phaeochromocytoma and a concurrent pituitary adenoma of the pars intermedia. However, since pituitary adenoma is quite common in aged horses, this presentation may simply represent a horse with pituitary pars intermedia dysfunction (PPID) that has coincidentally developed a phaeochromocytoma of the left adrenal gland. However, clinically, the simultaneous diagnosis of a phaeochromocytoma of the left adrenal gland and a pituitary adenoma of the pars intermedia fulfils the definition of MEN-like syndrome (see also p. 386).[49]

Another case was reported in a 22-year-old Thoroughbred mare.[36] The mare died as result of massive intrauterine haemorrhage during delivery of a live foal during an unattended parturition. At necropsy, a thyroid C-cell adenoma, a malignant phaeochromocytoma of the right adrenal gland, and multicentric bilateral nodular hyperplasia of both adrenal glands, were identified; this is similar to human MEN syndrome.

NEUROENDOCRINE TUMOURS

See also page 376.

Overview

Neuroendocrine tumours (NETs) are rare, slow-growing tumours derived from neuroendocrine cells, which are present throughout the body. In humans, they arise most commonly in the bronchopulmonary system and gastrointestinal tract.[50] Paraganglia are neural crest-derived neuroendocrine cells that are divided into adrenal (medulla) and extra-adrenal forms (see p. 376). Reports of NETs in the horse are rare.

Disease summary

Notes

Very rare but significant potentially malignant tumour of the adrenal medullary (chromaffin) cells.

Clinical features

Chronic weight loss with paroxysmal episodes of tachycardia, with hypertension, sweating and mydriasis. Often accompanied terminally by massive intra-abdominal haemorrhage and shock.

Diagnostic confirmation

Ultrasonography is the only current way of imaging the adrenal gland; measurement of catecholamine is currently almost impossible.

Management

No treatment is available.

Prognosis

Prognosis is hopeless.

Neoplasia of the adrenal medulla (phaeochromocytoma/intra-adrenal sympathetic paraganglioma)

Phaeochromocytoma

See also page 387.

Overview

Phaeochromocytoma is a rare tumour affecting the adrenal medullary chromaffin cells. It may be benign or malignant, non-functional or functional. Non-functional phaeochromocytoma is more common in horses and usually detected incidentally at post mortem.

Functional tumours produce excessive amounts of catecholamine. Signs are attributable to high concentrations of catecholamine.

There is no breed or sex predilection; the majority are unilateral and there is a low incidence of malignancy.

Most reports are in horses >12 years old, but there is one report in a foal diagnosed with the malignant form of the disease at 6 months of age.[51–57]

The onset of acute signs in horses with suspected functional phaeochromocytoma may be related to release of catecholamine from phaeochromocytoma. Pressure on the tumour from abdominal organs may cause expulsion of catecholamine-enriched blood from sinusoidal spaces in the tumour.

Clinical features

- Tachycardia
- Muscle tremors
- Mydriasis
- Variable appetite
- Polyuria and polydipsia
- Diarrhoea
- Exercise intolerance
- Tachypnoea
- Anxiety
- Pyrexia
- Weight loss
- Gastrointestinal ileus
- Cardiac arrhythmias.

Extreme shock with haemoabdomen has also been reported.

Differential diagnoses

Signs are variable and may be confused with other causes of abdominal pain and sweating.

- Excitement
- Colic and peracute laminitis
- Hypercalcaemic periodic paralysis
- Severe rhabdomyolysis/atypical myoglobinuria
- Cerebral piroplasmosis
- Digitalis or nitrate toxicity.

Diagnostic confirmation

- There are no definitive diagnostic procedures, since measurement of catecholamine is currently virtually impossible in practice
- Necropsy findings include a variably sized adrenal gland, with cystic foci and haemorrhage leading to haemoabdomen (Fig. 32.5).

Phaeochromocytoma in the horse presents a diagnostic challenge. Definitive ante-mortem diagnosis of a functional phaeochromocytoma in a horse has not been reported to date.

- Episodes of an acute onset of sweating, tachycardia, tachypnoea, muscle tremors and anxiety.
- Laboratory findings may support a diagnosis of phaeochromocytoma, but are not specific. Hyperglycaemia is a consistent finding.
- Other reported clinical pathological findings include neutrophilia, lymphopaenia, haemoconcentration, elevated creatine kinase and blood urea nitrogen.
- Plasma noradrenaline (norepinephrine) concentrations are routinely measured in human patients with suspected phaeochromocytoma; venous noradrenaline



Figure 32.5 Phaeochromocytoma. This large tumour was found in a mare showing signs of catecholamine surges. The mass comprised 10–20 round pale tan-coloured nodules 1–3 cm diameter, which resulted in a significant expansion of one pole of the left adrenal gland. This mare showed the typical multiple endocrine neoplasia combination (MEN) of phaeochromocytoma, pituitary adenoma and thyroid carcinoma (see pp. 386 and 593). *(Figure courtesy of Dr Guy Grinwis, University of Utrecht, the Netherlands.)*

levels in phaeochromocytoma patients are 10–50 times higher than those in other hypertensive patients. Venous noradrenaline levels have been measured in normal horses. Measurements are now required from equine phaeochromocytoma patients, especially whilst exhibiting clinical signs. If the same trend was present in equine patients, noradrenaline measurement could become a diagnostic test for catecholamine-producing tumours. This would be invaluable due to the nonspecific nature of presenting clinical signs.

- Hypertension, either paroxysmal or persistent, is expected, so indirect blood pressure measurement could be included in part of a clinical evaluation and hypertension may strongly support a tentative diagnosis of phaeochromocytoma, and warrant measurement of plasma noradrenaline levels.

Management and prognosis

No treatment is possible – surgery has been attempted but invariably fails (Table 32.3). Pending a diagnosis, the horse should be kept as stress free as possible – sedation may help, but since the release is independent of any stimulus, this may not help at all.

No horse has been successfully treated for a functional phaeochromocytoma. Most cases have a rapid clinical course, with profound circulatory collapse that necessitates euthanasia.

Equine orbital extra-adrenal paraganglioma

See also page 389.

Overview

Primary tumours of the equine orbit, including neuroendocrine tumours such as extra-adrenal paraganglioma, are rarely reported. They are also rare in humans and non-chromaffin paraganglionic tissue has not been identified as a normal structure in this location. In the retrobulbar region, extra-adrenal paraganglioma likely originates from the ciliary ganglion within the orbital muscle cone in a ventro-lateral position adjacent to the optic nerve.[58] The major reported features of extra-adrenal paraganglioma are shown in Table 32.4.

Clinical features

The main clinical feature of equine orbital paraganglioma is progressive, non-painful exophthalmia of an extended duration (Fig. 32.6). Of eight cases where the eye affected was recorded, 7/8 cases affected the right eye. There is no known anatomical or physiological reason for this.

Duration of clinical signs prior to presentation ranged from 1 month to 5 years.[58–60]

Vision may be normal or impaired.

Ophthalmic and neuro-ophthalmic examination may identify:

- Chemosis and inability to repulse the globe
- Conjunctival hyperaemia
- Epiphora
- Exposure keratopathy
- Third eyelid prolapse
- Anisocoria
- Decreased menace response
- Optic nerve atrophy
- Hyperaemia or pallor of optic nerve
- Vascular attenuation.

Other signs may include epistaxis (where the tumour breaks into the nasal cavity or maxillary sinus) or central nervous signs attributable to forebrain compression

Table 32.3 Summary of 13 reported cases of equine phaeochromocytoma

Ref. No.	Age (years)	Sex	Breed	Presenting signs	Outcome
51	25	F	Unknown	Pregnant, muscle tremors, profuse sweating, mydriasis, tachycardia, tachypnoea	Euthanized
54	25	F	TB	Muscle tremors, profuse sweating	Died
	15	F	Cob	Sweating, tachypnoea, weight loss, apprehensive	Euthanized
	21	G	TB	Diarrhoea	Euthanized
	6 months	F	SB	Spinal cord disease	Euthanized
	17	F	QH	Abdominal pain	Euthanized
	15	G	Grade	Left maxilla swelling	Euthanized, adenocarcinoma of nasal mucosa
	15	G	Shetland	Oesophageal obstruction	Died
	20	G	American Saddlebred	Abdominal pain	Euthanized
	12	F	QH	Laminitis, mastitis	Euthanized
	13	M	TB	Exercise intolerance, tachypnoea, abdominal pain	Euthanized
56	12	F	SB	Abdominal pain, sweating, muscle fasciculation, ataxia	Euthanized
	21	G	QH	Abdominal pain, sweating	Died

Table 32.4 Clinical, diagnostic, treatment and outcome features of some reported cases of equine orbital paraganglioma

Ref. No.	Age (years)	Sex	Breed	Eye	History	Clinical signs	Diagnosis	Treatment/Outcome
59	13	F	Belgian	Left	Epiphora, swelling 1 month	Epiphora, exophthalmos, anisocoria, ↓ PLR	US – 5 cm diameter hypoechoic lobulated mass caudal to zygomatic process	Exenteration; histopathology – NET by IHC and Grimelius' technique. No recurrence 2 years post-surgery
	29	F	Unknown	Right	Blindness 3 years' duration initially diagnosed secondary to glaucoma	Painful, third eyelid prolapsed, phthisis bulbi, chemosis, conjunctival hyperaemia, pigmented cornea	Surgery	Exenteration; histopathology – Grimelius' technique and IHC positive for chromogranin diagnosed NET. Excision not complete. No problems 19 months post-surgery
	24	G	Appaloosa	Right	Exophthalmos 15 months' duration	Exophthalmos, exposure keratopathy, endophthalmitis	None	Euthanasia. PM – soft tissue mass in retrobulbar space extending caudally through optic canal into cranial vault. Also extended rostrally to caudal aspect of right nasal turbinates. Numerous nodules throughout lung. NET
60	25	G	Haflinger	Unknown	Chronic progressive unilateral exophthalmos	Exophthalmos	US – retrobulbar space-occupying lesion. MRI – infiltrative intracranial growth pattern but sparing of orbital soft tissues	None – histopathology – poorly-differentiated NET
58	16	F	SB	Right	Exophthalmos 4 years' duration	Exophthalmos, negative menace, hyperaemic optic nerve	None	Exenteration – extensive haemorrhage intraop. Follow-up at 2 years – no problems
	24	G	QH	Right	1.5 years' duration	Exophthalmos, epiphora, third eyelid prolapsed, perforated corneal ulcer, ruptured lens	None	Exenteration – extensive haemorrhage intraop. Euthanized 14 months post-surgery for unrelated colic
	14	F	Trakehner	Right	1.5 years' duration	Exophthalmos, negative menace, pale optic nerve attenuated vasculature, cataract	None	Exenteration, extensive haemorrhage intraop. 2.5 years later – exophthalmos other eye, 4 years later – died at home – no post mortem
	15	G	Tennessee Walking Horse	Right	5 years' duration	Wax/waning exophthalmos	US – 2 soft tissue masses. Radiography – no bony involvement, ST mass	Exenteration, extensive haemorrhage intraop. Euthanized

Table 32.4 Clinical, diagnostic, treatment and outcome features of some reported cases of equine orbital paraganglioma – cont'd

Ref. No.	Age (years)	Sex	Breed	Eye	History	Clinical signs	Diagnosis	Treatment/Outcome
	15	G	TB	Right	2 years' duration	Exophthalmos, third eyelid prolapsed, chemosis, negative menace and PLR, pale optic nerve with vascular attenuation	US – 2 years prior to surgery – soft tissue mass, no bony involvement	Exenteration, extensive intra-op haemorrhage, extension – orbital Tru-Cut – carcinoma. No problems at 6 months' post-surgery
	23	G	Missouri Fox Trotter	Right	1 month duration	Exophthalmos, epiphora	None	Exenteration, extensive intraop. haemorrhage; no problems 22 months post-surgery

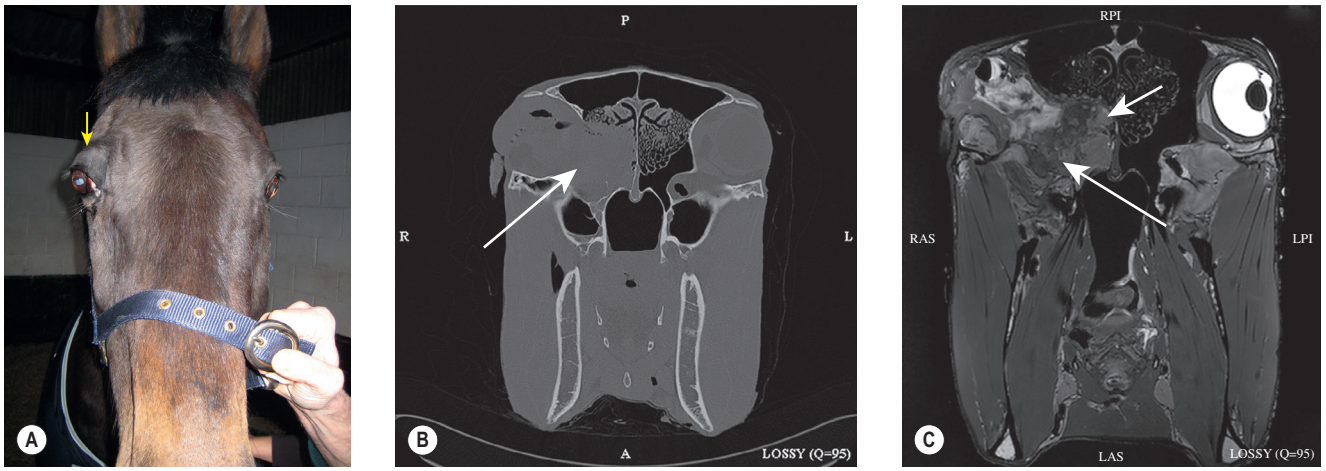


Figure 32.6 Extending space-occupying mass. **(A)** This 14-year-old mare was presented with an 8-month history of progressive right-side exophthalmos and visual compromise. Some temperament changes were noted, with the horse becoming very dull and occasionally appeared startled and hyper-responsive. Over the previous 2 weeks, a serosanguineous mildly malodorous nasal discharge was reported. Ultrasonography and endoscopy revealed a space-occupying mass in the orbit and a bleeding ill-defined mass in the caudal nasal cavity, respectively. **(B)** Standing CT showed an extensive space-occupying mass behind the eye, with extension into the caudal nasal cavity (arrow). **(C)** A T2-weighted MRI identified that the mass extended into the cribriform plate and cerebrum (arrow).

and inflammation (arising from erosion/invasion of the cribriform plate), including dullness, strabismus and seizures.

Differential diagnoses

Neoplastic

- Orbital fibroma
- Retrobulbar melanoma
- Lipoma
- Adenocarcinoma
- Metastatic lymphosarcoma
- Chondroma rodens
- Malignant rhabdoid tumour
- Microglioma
- Medulloepithelioma
- Neuroepithelial tumour of optic nerve
- Multiple osteoma and melanoma
- Extension of squamous cell carcinoma
- Meningioma
- Progressive ethmoid haematoma.

Non-neoplastic

- Orbital cellulitis
- Abscess
- Extension of a sinus cyst
- Retrobulbar haemorrhage
- Mycotic infections of sinus/guttural pouch
- Hydatid cyst
- Fracture of the orbit.

Diagnostic confirmation

- *Ultrasonography* often reveals a retrobulbar soft tissue mass of variable size and consistency, within the muscular cone, extending towards the optic foramen. This confirms the presence of a mass, but does not provide a definitive diagnosis.
- *Radiography and CT*. Radiography may be helpful to show evidence of bone lysis or sclerosis and the extent of the tumour.
- *MRI* is probably the definitive procedure, particularly if any attempt is to be made to remove the tumour.

In one study, the most useful diagnostic technique was considered to be a thorough ocular examination to rule out other causes of exophthalmia, ultrasonography to confirm presence of a retrobulbar mass and CT to identify the extent of tumour involvement.[58]

Definitive diagnosis depends on electron microscopic demonstration of membrane-bound neurosecretory granules or on demonstration of granules by means of Grimelius' staining, or on immunohistochemistry for neuron-specific enolase and chromogranin.

Management

Early surgical removal may allow complete removal of the tumour. However, it is hard to justify removal of a visually healthy globe, and tumours may have a protracted course and not be identified until obvious exophthalmia is apparent.

1. Exenteration is the usual surgical intervention due to the intimate association of the tumour with the optic nerve. Seven of nine cases, where an exenteration was performed, showed no recurrence between 6 and 30 months' post-surgery.[58,59]
2. An unsuccessful tumour removal via orbitotomy has been discussed in one report.

Notes

- Massive intraoperative haemorrhage is consistently reported.[58] Preoperative blood volume expansion has been suggested.
- Before embarking on any surgery, a full imaging investigation must be performed.

Prognosis

Orbital paraganglioma frequently extends beyond the orbital cavity by the time diagnosis is possible. However, recurrence within the orbit is rare if the tumour can be removed successfully. Equine orbital paraganglioma tends to grow slowly, as shown by the prolonged period of slowly progressive clinical signs prior to veterinary intervention.

Metastasis has only been reported in one horse.[59]

Chemodectoma

See also page 389.

Overview

Aortic and carotid body tumours in domestic animals are uncommon and reported most frequently in the dog. Other species are rarely affected. Tumours arise from chemoreceptor cells in the aortic and carotid bodies, usually known as chemodectoma, and belong to a group of non-chromaffin paraganglioma.

An aortic body adenoma was reported in a 5-year-old mare as an incidental finding post mortem. An 8 cm diameter round mass was identified at the heart base located between the aorta and pulmonary artery.[61]

A chemodectoma was reported in a 13-year-old Quarter Horse gelding with a history of exercise intolerance and sternal oedema. At presentation, the horse was pyrexic, inappetent and intolerant of exercise at walk and at pasture.

Further investigations revealed a pleural effusion and a multilobulated mass caudal and lateral to the heart. Cytology of pleural fluid revealed no neoplastic cells or infectious agents. An ultrasound-guided aspirate of the cranial mediastinal mass was consistent with a neoplastic process and the horse was euthanized.

Necropsy revealed a multilobular mass involving the base of the heart and mediastinum. A chemodectoma was confirmed from immunohistochemistry and ultrastructural features.[62]

Aortico-sympathetic paraganglioma

See also page 390.

Overview

A malignant retroperitoneal paraganglioma was reported in a 10-year-old Quarter Horse mare.

The mare initially presented with colic. Progression of clinical signs over a period of weeks included anorexia, ataxia, blindness, aimless wandering and finally recumbency, with continuous thrashing attempts to stand.

The mare was euthanized. At necropsy, a large encapsulated mass was identified in the sublumbar region. Numerous nodules were also dispersed through the brain, lungs, both kidneys and spleen. Histopathologically, all tissue was similar. Gross, histological and immunohistochemical examination confirmed a malignant extra-adrenal retroperitoneal paraganglioma. The sublumbar mass was considered the primary neoplasm and thought to originate in the aortico-sympathetic ganglion.[63]

A metastatic extra-adrenal sympathetic paraganglioma was reported in a 20-year-old Selle Français Warmblood gelding.

The horse presented with signs of colic and died during transport to a referral facility.

Post-mortem examination revealed haemoperitoneum and an encapsulated mass in the sublumbar region, cranial to the left kidney and adherent to the large colon. Lesions were also present in the spleen and one thyroid gland.

Immunohistochemistry showed tumour cell expression of chromogranin A, synaptophysin and neuron-specific enolase, but no expression of cytokeratin. These findings confirmed a metastatic extra-adrenal paraganglioma originating from the superior para-aortic paraganglia. The functional status of this tumour was unknown, as the horse was dead on arrival. No serum was collected for catecholamine from this case, but may be advisable in similarly presenting cases. However, the clinical features of the case are likely to be related to the adherence of the tumour to the colon, and the severe intra-abdominal blood loss is the likely cause of death.[64]

Neoplasia of the dispersed neuroendocrine system

See also page 391.

Overview

Carcinoids are considered to be derived from cells of the diffuse neuroendocrine system. This is a cell population with comparable functional characteristics and is widely

distributed throughout the body. Carcinoid tumours produce a variety of amines and peptides, such as serotonin, insulin, gastrin, somatostatin, glucagon, vasoactive peptide and calcitonin. Carcinoid syndrome has not been confirmed in horses.[65]

Intestinal carcinoid should be considered in the differential diagnosis of horses with chronic colic. A mare referred with a history of chronic colic was found at exploratory coeliotomy to have internal herniation with simultaneous volvulus of the jejunum and accompanying carcinoid.[66]

Three cases of carcinoid tumour in horses (aged 16, 16 and 26 years), all originating from the maxillary sinuses and the retrobulbar region and all causing exophthalmos, have been reported.[65] One horse presented with left-sided exophthalmos and a well-circumscribed mass in the left maxillary sinus. Post-mortem examination revealed destruction of the orbital wall. The second case also presented with exophthalmos and an enucleation was performed. The horse re-presented 18 months later, with continuing intermittent epistaxis. At post-mortem examination, a tumour mass was present in the left caudal nasal cavity, causing compression of the nasal turbinates. The third case presented with exophthalmos and a CT scan revealed a large mass in the left ethmoid region extending to the orbit, maxillary sinus and both sphenopalatine sinuses.[65] This is the only report of carcinoid in the sinus of domestic animals and it is unclear which neuroendocrine cells give rise to such tumours. The origin of the carcinoid tumour in these three horses was unclear.[65] None of the tumours had metastasized, although one tumour showed localized expansive growth and destruction of surrounding bony structures, resulting in exophthalmos and epistaxis.[65]

A single case of a neuroendocrine tumour in the larynx of a horse has been reported in a 13-year-old Quarter Horse mare presented for evaluation of severe inspiratory and expiratory stridor and a firm swelling lateral to the left parotid gland, with pain on palpation of the throat region of 12 months' duration.[67] A soft tissue mass between the aryepiglottic fold and the corniculate process was evident on endoscopic examination. Radiography and ultrasonography also confirmed a large mass localized between the thyroid and arytenoid cartilages. MRI was performed post mortem and showed a well-defined mass situated between the left thyroid and arytenoid cartilages, creating severe axial obstructive displacement of the left arytenoids into the airway. No metastases were identified. Positive staining for synaptophysin, chromogranin A and neuron-specific enolase (NSE), which are conventional markers of neuroendocrine differentiation, confirmed the diagnosis.[67]

The classification systems used for neoplasia of the dispersed neuroendocrine system in humans are not considered applicable in veterinary medicine, due to the very limited number of reported cases.[68]

References

1. Paradis MR. Tumors of the central nervous system. Vet Clin North Am Equine Pract 1998; 14:543–561.
2. van der Kolk JH, Heinrichs M, van Amerongen JD, et al. Evaluation of pituitary gland anatomy and histopathologic findings in clinically normal horses and horses and ponies with pituitary pars intermedia adenoma. Am J Vet Res 2004; 65:1701–1707.
3. McFarlane D, Miller LM, Craig LE, et al. Agreement in histologic assessments of the pituitary pars intermedia in aged horses. Am J Vet Res 2005; 66: 2055–2059.
4. Miller MA, Pardo ID, Jackson LP, et al. Correlation of pituitary histomorphometry with adrenocorticotrophic hormone response to domperidone administration in the diagnosis of equine pituitary pars intermedia dysfunction. Vet Pathol 2008; 45:26–38.
5. Brosnahan MM, Paradis MR. Demographic and clinical characteristics of geriatric horses: 467 cases (1989–1999). J Am Vet Med Assoc 2003; 223:93–98.
6. Heinrichs M, Baumgärtner W, Capen CC. Immunocytochemical demonstration of proopiomelanocortin-derived peptides in pituitary adenomas of the pars intermedia in horses. Vet Pathol 1990; 27:419–425.
7. van der Kolk JH, Kalsbeek HC, van Garderen E, et al. Equine pituitary neoplasia: a clinical report of 21 cases (1990–1992). Vet Rec 1993; 133: 594–597.
8. Pilsworth RC, Knottenbelt DC. Hirsuitism. Equine Vet Educ 2006; 18:120–121.
9. McGowan TW, Pinchbeck GP, McGowan CM. Prevalence, risk factors and clinical signs predictive for equine pituitary pars intermedia dysfunction in aged horses. Equine Vet J 2013; 45:74–79.
10. Scott DW, Miller WH. Equine dermatology, 2nd edn. Maryland Heights: Elsevier Saunders; 2011.
11. McFarlane D, Paradis MR, Zimmel D, et al. The effect of geographic location, breed, and pituitary dysfunction on seasonal adrenocorticotropin and α-melanocyte-stimulating hormone plasma concentrations in horses. J Vet Intern Med 2011; 25:872–881.
12. Loeb WF, Capen CC, Johnson LE. Adenomas of the pars intermedia associated with hyperglycemia and glycosuria in two horses. Cornell Vet 1966; 56:623–639.
13. McFarlane D. Equine pituitary pars intermedia dysfunction. Vet Clin North Am Equine Pract 2011; 27:93–113.
14. Alberts MK, McCann JP, Woods PR. Hemithyroidectomy in a horse with confirmed hyperthyroidism. J Am Vet Med Assoc 2000; 217:1051–1054.
15. Hillidge CJ, Sanecki RK, Theodorakis MC. Thyroid carcinoma in a horse. J Am Vet Med Assoc 1982; 181:711–714.
16. Held JP, Patton CS, Toal RL, et al. Work intolerance in a horse with thyroid carcinoma. J Am Vet Med Assoc 1985; 187:1044–1045.
17. Hovda LR, Shaftoe S, Rose ML, et al. Mediastinal squamous cell carcinoma and thyroid carcinoma in an aged horse. J Am Vet Med Assoc 1990; 197:1187–1189.
18. Ramirez S, McClure JJ, Moore RM, et al. Hyperthyroidism associated with a thyroid adenocarcinoma in a 21-year-old gelding. J Vet Intern Med 1998; 12:475–477.
19. Bradley AE, Pirie RS, MacIntyre N. Thyroid carcinoma with multiple metastasis in a horse. Equine Vet Educ 2000; 12:170–174.
20. Kuwamura M, Shirota A, Yamate J, et al. C-cell adenoma containing variously sized thyroid follicles in a horse. J Vet Med Sci 1998; 60:387–389.
21. Ueki H, Kowatari Y, Oyamada T, et al. Non-functional C-cell adenoma in aged horses. J Comp Pathol 2004; 131:157–165.
22. van der Velden MA, Meulenaar H. Medullary thyroid carcinoma in a horse. Vet Pathol 1986; 23:622–624.
23. Turk JR, Nakata YJ, Leathers CW, et al. Ultimobranchial adenoma of the thyroid gland in a horse. Vet Pathol 1983; 20:114–117.
24. Tateyama S, Tanimura N, Moritomo Y, et al. The ultimobranchial remnant and its hyperplasia or adenoma in equine thyroid gland. Nihon Juigaku Zasshi 1988; 50:714–722.
25. Saulez MN, Viljoen A, Kafka U, et al. The use of nuclear imaging for a mixed C cell microfollicular carcinoma of the thyroid gland in a mature horse. Equine Vet Educ 2012; 12:170–174.
26. Dalefield RR, Palmer DN. The frequent occurrence of thyroid tumours in aged horses. J Comp Pathol 1994; 110:57–64.
27. von Sandersleben J, Hänichen T. Tumours of the thyroid gland. Bull World Health Organ 1974; 50:35–42.
28. Toribio RE, Duckett WM. Thyroid gland. In: Reed SM, Bayly WM, Sellon DC, eds. Equine internal medicine, 2nd edn. St Louis: Saunders; 2004: 1340–1356.
29. Neracher H, Hedinger C. Classification of thyroid gland tumors in accordance with 1974 WHO nomenclature. Histological follow-up examination of 327 malignant thyroid gland tumors. Schweiz Med Wochenschr 1975; 105:1000–1006, 1052–1056.
30. Brown PJ, Reina A, Gartner DN. Thyroglobulin, calcitonin, Ki67, and CEA immunohistochemistry staining of dog thyroid carcinomas. Eur J Vet Pathol 2001; 7:11–16.
31. Tucker RL, Fidel J. The diagnosis, characterisation and treatment of a mixed C cell microfollicular thyroid carcinoma in a horse. Equine Vet Educ 2012; 25:126–128.
32. Lucke VM, Lane JG. C-cell tumours of the thyroid in the horse. Equine Vet J 1984; 16:28–30.
33. Elce YA, Ross MW, Davidson EJ, et al. Unilateral thyroidectomy in 6 horses. Vet Surg 2003; 32:187–190.
34. Joyce JR, Thompson RB, Kyzar JR, et al. Thyroid carcinoma in a horse. J Am Vet Med Assoc 1976; 168:610–612.
35. Haeni H, vonTscharner C, Straub R. Thyroideacarcinoma mit knockenmetastasen beim pferd. Schweiz Tierheilk 1979; 121:413–420.
36. De Cock HE, MacLachlan NJ. Simultaneous occurrence of multiple neoplasms and hyperplasias in the adrenal and thyroid gland of the horse resembling multiple endocrine neoplasia syndrome: case report and retrospective identification of additional cases. Vet Pathol 1999; 36:633–636.
37. Bienfet V, Dewaele A, van Essche R, et al. Un trouble parathyroidien primaire? Un case d'osteofibrose chex le poney Shetland par adenoma parathyroidien. Guerison par ablation chirurgicale. Ann Med Vet 1964; 108:252–256.
38. Peauroi JR, Fisher DJ, Mohr FC, et al. Primary hyperparathyroidism caused by a functional parathyroid adenoma in a horse. J Am Vet Med Assoc 1998; 212:1915–1918.

39. Toribio RE. Calcium disorders. In: Reed SM, Bayly WM, Sellon DC, eds. Equine internal medicine, 2nd edn. St Louis: Saunders; 2004: 1295–1327.
40. Roussel AJ, Thatcher CD. Primary hyperparathyroidism in a pony mare. Comp Cont Ed Pract Vet 1987; 9:781–783.
41. Frank N, Hawkins JF, Couëtil LL, et al. Primary hyperparathyroidism with osteodystrophia fibrosa of the facial bones in a pony. J Am Vet Med Assoc 1998; 212:84–86.
42. Toribio RE. The adrenal glands. In: Reed SM, Bayly WM, Sellon DC, eds. Equine internal medicine, 2nd edn. St Louis: Saunders; 2004: 1356–1361.
43. van der Kolk JH, Ijzer J, Overgaauw PAM, et al. Pituitary-independent Cushing's syndrome in a horse. Equine Vet J 2001; 33:110–112.
44. van der Kolk JH, Mars MH, van der Gaag I. Adrenocortical carcinoma in a 12-year-old mare. Vet Rec 1994; 134:113–115.
45. Evans LH, Siegel ET, Hubben K. Clinico-pathologic conference. J Am Vet Med Assoc 1968; 152:1778–1786.
46. Raker CW, Fegley H. Clinico-pathologic conference. J Am Vet Med Assoc 1965; 147:848–860.
47. Fix AS, Miller LD. Equine adrenocortical carcinoma with hypercalcemia. Vet Pathol 1987; 24:190–192.
48. Ross MW, Lowe JE, Cooper BJ, et al. Hypoglycemic seizures in a Shetland pony. Cornell Vet 1983; 73:151–169.
49. Germann SE, Rütten M, Derungs SB, et al. Multiple endocrine neoplasia-like syndrome in a horse. Vet Rec 2006; 159:530–532.
50. Ferlito A, Devaney KO, Rinaldo A. Neuroendocrine neoplasms of the larynx: advances in identification, understanding, and management. Oral Oncol 2006; 42:770–788.
51. Buckingham JD. Case report. Pheochromocytoma in a mare. Can Vet J 1970; 11:205–208.
52. Gelberg H, Cockerell GL, Minor RR. A light and electron microscopic study of a normal adrenal medulla and a pheochromocytoma from a horse. Vet Pathol 1979; 16:395–404.
53. Yovich JV, Ducharme NG. Ruptured pheochromocytoma in a mare with colic. J Am Vet Med Assoc 1983; 183:462–464.
54. Yovich JV, Horney FD, Hardee GE. Pheochromocytoma in the horse and measurement of norepinephrine levels in horses. Can Vet J 1984; 25:21–25.
55. Duckett WM, Snyder JR, Harkema JR, et al. Functional pheochromocytoma in a horse. Comp Cont Ed Pract Vet 1987; 9:1118–1121.
56. Johnson PJ, Goetz TE, Foreman JH, et al. Pheochromocytoma in two horses. J Am Vet Med Assoc 1995; 206:837–841.
57. Froscher BG, Power HT. Malignant pheochromocytoma in a foal. J Am Vet Med Assoc 1982; 181:494–496.
58. Miesner T, Wilkie D, Gemensky-Metzler A, et al. Extra-adrenal paraganglioma of the equine orbit: six cases. Vet Ophthalmol 2009; 12:263–268.
59. Basher AW, Severin GA, Chavkin MJ, et al. Orbital neuroendocrine tumors in three horses. J Am Vet Med Assoc 1997; 210:668–671.
60. Matiasek K, Cronau M, Schmahl W, et al. Imaging features and decision making in retrobulbar neuroendocrine tumours in horses – case report and review of literature. J Vet Med A Physiol Pathol Clin Med 2007; 54: 302–306.
61. de Barros CS, dos Santos MN. Aortic body adenoma in a horse. Aust Vet J 1983; 60:61.
62. Levy M, Stegelmeier BL, Hudson LM, et al. Chemodectoma in a horse. Can Vet J 1990; 31:776–777.
63. Kim D-Y, Hodgin EC, Lopez MK, et al. Malignant retroperitoneal paraganglioma in a horse. J Comp Pathol 1994; 110:407–411.
64. Herbach N, Breuer W, Hermanns W. Metastatic extra-adrenal sympathetic paraganglioma in a horse. J Comp Pathol 2010; 143:199–202.
65. van Maanen C, Klein WR, Dik KJ, et al. Three cases of carcinoid in the equine nasal cavity and maxillary sinuses: histologic and immunohistochemical features. Vet Pathol 1996; 33:92–95.
66. Orsini JA, Orsini PG, Sepesy L, et al. Intestinal carcinoid in a mare: an etiologic consideration for chronic colic in horses. J Am Vet Med Assoc 1988; 193:87–88.
67. Koenig J, Silveira A, Chalmers H, et al. Laryngeal neuroendocrine tumour in a horse. Equine Vet Educ 2012; 24:12–16.
68. Kiupel M, Capen C, Miller M, et al. Histological classification of tumours of the endocrine system of domestic animals. Second Series, Vol. XII. Washington DC: Armed Forces Institute of Pathology, CL Davis DVM Foundation and The World Health Organization Collaborating Centre for Comparative Oncology; 2008.

33

Tumours of nerves and nervous tissue

Overview 601
Primary nervous tissue tumours 601
Secondary tumours of the nervous system 605
Other secondary tumours affecting the central nervous system 609
Tumours of the peripheral nervous system 610

Overview

Neoplasia of the central and peripheral nervous system of the horse is very rare, with the exception of pituitary pars intermedia dysfunction/pituitary adenoma, which is discussed elsewhere (see pp. 376 and 587), and peripheral nerve sheath tumours (see pp. 299 and 562).[1]

The clinical signs exhibited by horses with tumours of the central nervous system are dictated by the anatomical location of the lesion. The central nervous system is particularly intolerant of any space-occupying or invasive lesion but it is remarkable how often the conditions are presented late in the course; this suggests that slow-onset disease of the central nervous system is less likely to be detected by veterinarians either because the cases are not presented (the signs are viewed as 'insignificant' to owners) or because the signs are attributable in error to other differential diagnoses.

Reported primary tumours in the central nervous system appear to involve lymphoma, melanoma and haemangiosarcoma.

Secondary tumours are a significant clinical event, with notable involvement of lymphoma, melanoma, haemangiosarcoma and, again, the clinical signs will be highly dependent on the location, extent and progression of the tumours.

In addition, tumours of the paranasal sinus and nasal cavity and conchae, such as nasal sinus and adenocarcinoma, can extend into the brain via the cribriform plate. In these circumstances, the signs of central nervous disease usually affect the horse late in the course of the disease (see p. 483). Tumours within the orbit, including squamous cell carcinoma (see p. 575) and extra-adrenal paraganglioma (see p. 595), can extend directly into the calvarium and cause significant brainstem signs.

Brainstem and forebrain signs include:

- Cranial nerve deficits
- Behavioural changes – including head pressing and seizures.

Lesions restricted to the thoracolumbar spine cause:

- Hindlimb ataxia
- Weakness.

The prognosis for any tumour of the central nervous system is very poor, although some are identified at necropsy incidentally, implying perhaps that not every tumour causes significant clinical signs and not every tumour is inevitably progressive. The options for therapy of central nervous neoplastic disease are extremely limited in horses, in particular, and as a result, all reported cases involving ante-mortem diagnosis of primary or secondary central nervous neoplastic disease have so far had a fatal outcome.

Note

Since there is very little literature relating to central nervous neoplasia in the horse, the various conditions are discussed below in a somewhat different format, which simply describes the cases that have been reported in brief so that they can be borne in mind when any horse is presented with a suspect central nervous disorder. It is of course impossible to provide any evidence-based interpretation of these, apart from simply recognizing the generally poor outcome for most of these conditions.

Primary nervous tissue tumours

Astrocytoma

See also page 363.

Disease summary

Notes

Extremely rare tumour of astrocytes.

Clinical features

Signs attributable to multifocal central nervous disease mainly in the cerebrum and brainstem.

Diagnostic confirmation

CT and MRI imaging are the best aids.

Management

No treatment is possible.

Prognosis

The prognosis is probably hopeless.

Overview

Apart from the retinal/fundic astrocytoma (see p. 625), which is a rare but recognized (incidental finding), only one case affecting the cerebrum has been reported.[2,3]

Case review

A 4-year-old Dutch Warmblood mare

- Presented with a 10-month history of ataxia and proprioceptive deficits.[3]
- Neurological examination was suggestive of a multifocal brain disorder with clinical findings, including:
  - Decreased sense of smell
  - Decreased facial sensation of the right muzzle
  - Mild right-sided facial paresis
  - Right head tilt
  - Leaning to the right but circling to the left
  - Grade 4/5 assymetric ataxia of all four limbs.
- Neurological deficits rapidly progressed until the mare was unable to move and became stuporous.
- CSF cytology was unremarkable.
- Brainstem auditory evoked response test revealed increased latencies in several peaks on both sides, but worse on the right.
- Computed tomography defined a large, non-contrast-enhancing, expansile mass in the left cerebral hemisphere that compressed and displaced the lateral ventricle to the right.
- Post-mortem examination revealed a tumour that effaced much of the piriform and temporal lobes.
- Histopathology classified the mass as an astrocytoma with an oligodendroglioma component.

The mass was further classified as a Grade IV glioblastoma, with an oligodendroglial component (GBM-O), according to histological criteria established for the international WHO classification of tumours of the human central nervous system.[3,4]

Oligodendroglioma

Overview

Oligodendrocytes are one of several neuroglial cells in the nervous system with fewer and shorter processes than astrocytes. They are found in both grey and white matter and maintain myelin in the CNS. There has been only one report in the literature of an oligodendroglioma in a horse.[5]

Disease summary

Notes

Extremely rare tumour of oligodendrocytes.

Clinical features

Pre-mortem clinical signs are not known.

Diagnostic confirmation

CT and MRI imaging are likely to be the best aids.

Management

No treatment is possible.

Prognosis

The prognosis is probably hopeless.

Case review

A 10-year-old Thoroughbred mare

This mare was found dead, drowned in a dam[5]:

- There was no history of previous illness and the animal had been observed normal the day prior to presentation.
- A necropsy revealed:
  - Diffuse enlargement of the left cerebral hemisphere principally affecting the parietal, temporal and occipital lobes
  - The left occipital lobe contained a large circumscribed poorly-encapsulated 6.5 cm mass with flattening of the overlying gyri, extending almost to the meningeal surface
  - The mass compressed the adjacent brain and lateral ventricle.

Ependymoma

See also page 365.

Overview

Ependymal cells are epithelial lining cells of the ventricles of the brain or central canal of the spinal cord. In domestic animals, ependymoma is an extremely rare tumour of the central nervous system.

Case reviews

There are three reports of ependymoma in the horse.[6–8]

A 2-year-old Standardbred gelding

This Standardbred gelding presented with[6]:

- Adipsia.
- Hypernatraemia, which was not correctable by intravenous fluid therapy.
- Prolapsed third eyelid.
- Myoclonus of muscles of head, neck and forelimbs.
- Persistent tail swishing
  - Necropsy revealed a mass compressing the neurohypophysis; this was probably the cause of the adipsia and resultant hypernatraemia.

Disease summary

Notes

Extremely rare epithelial tumour of the ventricles of the brain.

Clinical features

Signs include bizarre behavioural signs, ataxia and possibly some cranial nerve signs consistent with brainstem disease.

Diagnostic confirmation

CT and MRI imaging are the best aids.

Management

No treatment is possible.

Prognosis

The prognosis is probably hopeless.

A 17-year-old Arab gelding

This Arab gelding presented with[7]:

- Progressive ataxia.
- Dog sitting, spinning and falling
  - Necropsy revealed a papillary ependymoma on the ventral aspect of the hypothalamus impinging on the optic chiasm and caudally displacing the pituitary gland
  - Lesions were confined to the CNS with multifocal haemorrhage throughout the spinal cord; this was most severe at the lumbosacral nerve roots.

A 19-year-old Dutch Warmblood gelding

This Dutch Warmblood gelding presented with[8]:

- Neurological signs anatomically localized to T3–L3 (abnormal pelvic limb gait).
- Xanthochromia identified on CSF analysis was considered indicative of subarachnoid haemorrhage
  - Necropsy revealed that the entire surface of the brain and spinal cord appeared discoloured orange-brown and a large extramedullary mass, identified as a myxopapillary ependymoma, was found at the left side of the cerebellomedullary angle
  - Histologically, the orange–brown discoloration was due to leptomeningeal and superficial parenchymal haemosiderosis
  - The combination of pigmentation, superficial tract degeneration and clinical signs of spinal cord disease confirmed a diagnosis of marginal siderosis of the spinal cord
  - In this horse, significant degenerative changes were localized to the spinal cord despite the fact that siderosis was extensive within the brain and spinal cord, and clinical signs reflected this.

Choroid plexus tumour

See also page 366.

Overview

Choroid plexus papillomas are rare, slow-growing and histologically benign intracranial neoplasms of the choroid plexus. There are many reported cases of choroid plexus papillomas in dogs and man. In horses, despite reference to their existence,[1] only three cases have been reported.[9–12] All reported cases have occurred in young horses (4–5 years old), except most recently in an 11-year-old horse.[12]

Disease summary

Notes

Extremely rare, very benign but clinically significant tumour of the choroid plexus largely of younger horses.

Clinical features

Signs include cranial nerve abnormalities, ataxia and circling.

Diagnostic confirmation

CT and MRI imaging are the best aids.

Management

No treatment is possible.

Prognosis

The prognosis is probably hopeless.

Case reviews

A 5-year-old Warmblood mare[11]

- Presented with a history of depression and circling.
- Clinical findings were consistent with a focal lesion in the left forebrain and included:
  - Poor body condition
  - Moderate depression with intermittent circling and head pressing
  - Head and neck deviation to left and circling to left
  - Right facial hypalgesia
  - Poor thoracolaryngeal (slap) reflex on the left side
  - Poor postural reactions on the right forelimb
  - Slow feeding.
- Routine haematological, serum biochemical and cerebrospinal fluid analysis revealed no significant changes.
- Three days following initiation of symptomatic treatment, the horse deteriorated with signs of compulsive persistent box walking and altered behaviour, including aggression and seizure
  - An exploratory craniotomy was performed under general anaesthesia to utilize intraoperative ultrasonography to help identify the lesion and determine whether surgical therapy was feasible
    - Ultrasonography using a 5 MHz transducer revealed an echogenic mass in the region of the ventral forebrain and midbrain overlying the floor of the calvarium.
- Due to the extensive size of the mass and inaccessibility, the mare was euthanized.
- Histopathology of the mass confirmed a choroid plexus papilloma.

An 11-year-old Andalusian stallion[12]

- Presented with a 1-week history of hindlimb ataxia.
- Clinical findings included:
  - Grade ¾ ataxia in hindlimbs
  - Grade ¼ ataxia in forelimbs
  - Proprioceptive deficits in all four limbs
  - Paresis on circling to the right
  - Decreased tail tone and cutaneous sensation over the hindlimbs were consistent with a focal or multifocal cervical lesion.
- Cervical radiographs, myelogram and CSF analysis were normal.
- Treatment with corticosteroids and dimethyl sulfoxide provided no improvement in clinical signs and the horse was euthanized.
- Histopathology and immunohistochemistry confirmed a diagnosis of choroid plexus papilloma affecting the fourth ventricle.

Olfactory neuroblastoma

See page 367.

Disease summary

Notes

Extremely rare malignant tumour arising in the ethmoidal region of the nasal cavity.

Clinical features

Signs attributable to space-occupying, invasive tumour in the caudal nasal cavity, i.e. epistaxis, exophthalmos and strabismus.

Diagnostic confirmation

CT and MRI imaging are the best aids.

Management

No treatment is possible.

Prognosis

The prognosis is probably hopeless.

Overview

Olfactory neuroblastoma is an extremely rare, malignant, invasive neoplasm arising in the ethmoturbinate region of the nasal cavity (Fig. 33.1). There have been three reports in the horse.[13–15]

Case reviews

An 11-year-old Thoroughbred gelding[15]

- Presented with:
  - A 3-month history of lacrimation
  - Exophthalmos of the right eye
  - Right-sided epistaxis.
- Endoscopic examination revealed a large nodule obstructing the right nasal cavity
  - The mass increased in size over a 2-month period, with worsening proptosis of the right globe and ongoing epistaxis.
- No further diagnostics were undertaken and the horse was euthanized
  - At necropsy the nodule occupied the olfactory region of the right nasal cavity and right frontal sinus. There was no invasion into the cranium or metastases to regional lymph nodes

A 17-year-old Hanoverian gelding[14]

- Presented with a severe proptosis of the left eye; unfortunately, clinical and diagnostic findings were not reported.
- Diagnostic imaging, including radiography and CT, suggested the mass was not amenable to surgical removal and the horse was euthanized
  - At necropsy, an irregular mass was identified involving the left ethmoid region, maxillary sinus, superior turbinate and orbit and extending posterior to the left orbit
  - The mass displaced the cribriform plate into the cranial cavity. The nasal septum was displaced to the right and the left nasal turbinates were compressed and atrophied
  - Metastatic involvement was identified in the choroid and retina.

No metastatic involvement was present in the other cases. Metastases of olfactory neuroblastoma are frequently reported in humans, with primary sites being the lymph nodes, lung, brain and bone. In dogs and cats, metastases have been found in regional lymph nodes.

Differential diagnoses

- Neuroendocrine carcinoma
- Squamous cell carcinoma
- Rhabdomyosarcoma
- Malignant melanoma[15]
- Adenocarcinoma
- Fibrosarcoma
- Lymphoma.

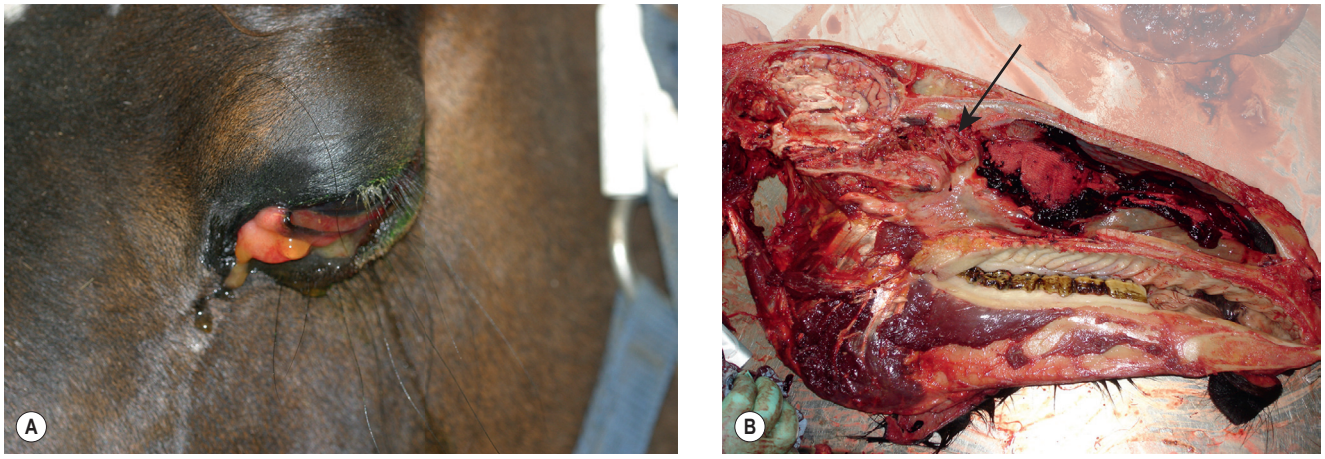


Figure 33.1 Olfactory neuroblastoma. (A) This 9-year-old gelding was presented with a chronic persistent haemorrhagic left-side nasal discharge. Advice was sought when the eye showed exophthalmos and conjunctival oedema and haemorrhage. Limited imaging facilities were available but a mass could be seen endoscopically that was largely occluding the left nasal chamber. On the assumption that this was an ethmoid haematoma or similar condition, an attempt was made to remove it via a maxillary sinus flap. Only part of the tumour was accessible and its nature gave cause for concern. Surgical pathology made a diagnosis of (olfactory) neuroblastoma and the horse was accordingly euthanized. **(B)** At necropsy, the remains of the tumour were focussed around the ethmoidal region (arrow) and extended into the orbit. No other pathology was identified. Notice the sinus and nasal packing that was used to control postoperative haemorrhage. CT and MRI imaging would have assisted a great deal.

Meningioma

See also page 367.

Overview

Meningioma is believed to arise from meningeal arachnoid cells that are trapped within or outside bone during development of the skull and facial bones. It presents as slow-growing, expansile masses.[16] There are a small number of equine cases reported in the literature.[16–19]

Clinical signs relating to meningioma are usually due to the space-occupying nature of the mass, which compresses tissues or interferes with CSF flow and thus increases intracranial pressure.[18]

The aetiology of meningiomas is unknown, but in some species there is a strong (female) sex predisposition, suggesting that these tumors may be under some hormone drive. However, no such association has been found in horses.[18]

Case reviews

A 5-year-old Appaloosa gelding (paranasal meningioma)[16]

Diagnosed at necropsy with paranasal meningioma.

- Presented with a 5-day history of right-sided epistaxis and facial swelling.
- Clinical examination revealed:
  - No airflow through the right nostril
  - Bloody and mucopurulent right-sided nasal discharge
  - Non-painful facial swelling rostral and ventral to the right eye.
- Radiography revealed an extensive soft tissue mass within the right paranasal sinuses, especially the maxillary sinus.
- Endoscopic examination of the right nostril was impeded by the mass.
- A tissue biopsy obtained by trephination of the maxillary sinus was non-diagnostic but suspicious of a spindle cell neoplasm.
- The horse was euthanized.
- A post-mortem CT scan revealed:
  - Tumour invading the right maxillary and right and left frontal and sphenopalatine sinuses
  - The ethmoid plate was breached and the nasal septum was deviated to the left
  - There was extensive bone lysis in:
    - Nasal septum, hard palate, maxillary bone and bones of the orbit
  - No other abnormalities were identified.

An 18-year-old Welsh Mountain pony (brainstem meningioma)[18]

- Clinical and neurological examination findings, including cranial nerve deficits and ataxia. consistent with an anatomic localization of a brainstem lesion.
- Symptomatic treatment partially resolved some symptoms for a short period, but signs recurred and the pony was euthanized.
- A post-mortem MRI scan revealed a soft tissue mass of mixed signal intensity 20×20×30 cm ventral to the brainstem, causing elevation and compression of the brainstem.

A 16-year-old Thoroughbred gelding (retrobulbar meningioma)[19]

- Presented with unilateral left-sided exophthalmos and apparent blindness.
- MRI identified a well-defined soft tissue mass intimately associated with the optic nerve, suggestive of a meningioma.
- Histopathology confirmed the diagnosis and the horse underwent a course of adjuvant radiotherapy.
- The eye was enucleated under general anaesthesia and partial excision of the mass was achieved.
- 12 months following surgery the horse was back in work with no neurological abnormalities
  - Follow-up CT imaging of the skull revealed mild bone sclerosis, with no remnants of the mass identified.

Pineoblastoma/medulloblastoma

See also page 368.

Overview

Pineoblastoma is an extremely rare tumour of primitive neuroectodermal cells in the pineal gland; they are always in the midline, and do not involve the cerebellum. In contrast, medulloblastoma usually originates in the cerebellum.[20] A single case has been reported and there is little clinical information in that description.

Case review

An adult Quarter Horse stallion[20]

- Presented with progressive central nervous system signs. Including weakness and incoordination of 4–5 months' duration.

Secondary tumours of the nervous system

Overview

Although many tumours circulate through the bloodstream, few gain access to the central nervous system. Most metastatic tumours with neurological implications involve structures around nervous tissue and the signs are a direct result of their space-occupying nature. The central nervous tissue is very intolerant of compression and so the signs will relate strongly to the location and nature of the tumour (see Figs 37.2, 37.3 and 37.4).

Lymphoma

See also page 342.

Overview

A total of 12 cases of CNS lymphoma have been reported between 1970 and 2013 (Table 33.1). Most lymphoma cases involving the central nervous system arise as part of

Table 33.1 Central nervous system lymphoma cases reported between 1970 and 2013

Ref. No.	Age (years)	Location	Compressive or invasive	Clinical signs	CSF	Single or multiple
21	15	T2, T9, T15	Compressive (epidural)	Swelling left mandible, ataxia 4 days	N/A	Multiple
22	13	T12	Compressive (epidural)	Hindlimb paresis, ataxia 4 weeks	Xanthochromia	Single in spinal cord; multiple in body
23	1.75	T17, T18, brain	Compressive (epidural)	Acute-onset hindlimb ataxia	Normal	Multiple
24	7	Thoracic, lumbar, cauda equine	Compressive	Hindlimb ataxia progressing to recumbency, death (6 weeks)	N/A	Multiple
25	2	L1	Compressive	Hindlimb paresis, transient abnormal head and neck posture, recumbency	Normal	Multiple – spleen, mesenteric lymph nodes
26	6	Leptomeninges of cerebrum, cerebellum, pia mater of C1–L3	Invasive of white and grey matter (subdural, subarachnoid, pia mater)	Lethargy, mild weight loss, skin nodules, lameness, mild hindlimb ataxia	WBC count 8190 cells, 49% neutrophils, 41% lymphocytes/blast cells, 8% small lymphocytes, 3% macrophages. Protein 599 mg/dL	Multiple
	3	Diffuse infiltrates in meninges, CN VII 7, spinal nerves, nerve root ganglia	Compressive and invasive (subdural, extradural)	Facial paralysis, dysphagia, ataxia, recumbency	WBC count 2733, predominantly large round cells. Protein <2.5 mg/dL	Multiple
27	18	Thickening of leptomeninges along spinal cord, neuropil of cerebrum, thalamus, cerebellum, medulla	Compressive and invasive (white matter)	Miotic left pupil, ptosis of left eyelid, muscle atrophy over left C1–C3, paresis, ataxia worse in hindlimb	WBC count >100, 59% neutrophils, 28% lymphocytes, 11% mononuclear cells, 2% plasma cells	CNS only
28	20	Brainstem, medulla, spinal cord, meninges	Compressive and invasive	Hyperaesthetic, hyperexcitable, head pressing, hindlimb ataxia, left CN VII 7	WBC count 2750, 86% neutrophils, 14% mononuclear	Unknown but suggestive of multiple
29	9	Thoracolumbar vertebra, nerve root	Compressive (epidural, dura mater)	Acute hindlimb ataxia, worse on left	N/A	Multiple
30	12	All regions of brain and spinal cord	Invasive	Sudden-onset ataxia, seizures and recumbency	N/A	CNS only
31	9	C2–C3	Compressive	6 weeks stumbling, Grade 2.5/5 ataxia, neck stiffness	Normal	Single

multicentric disease or by local invasion from an adjacent site.

Clinical features

Clinical signs of nervous system lymphoma typically relate to progressive expansion of the tumour and compression of adjacent neurological structures. The spinal cord is more frequently involved than the brain, although both sites may be affected in multicentric disease (Fig. 33.2) (see p. 342).

Melanoma

See also page 237.

Overview

Melanomas are slow-growing, locally invasive dermal tumours commonly found in ageing grey horses.

These tumours most commonly involve:

- The ventral tail
- External genitalia

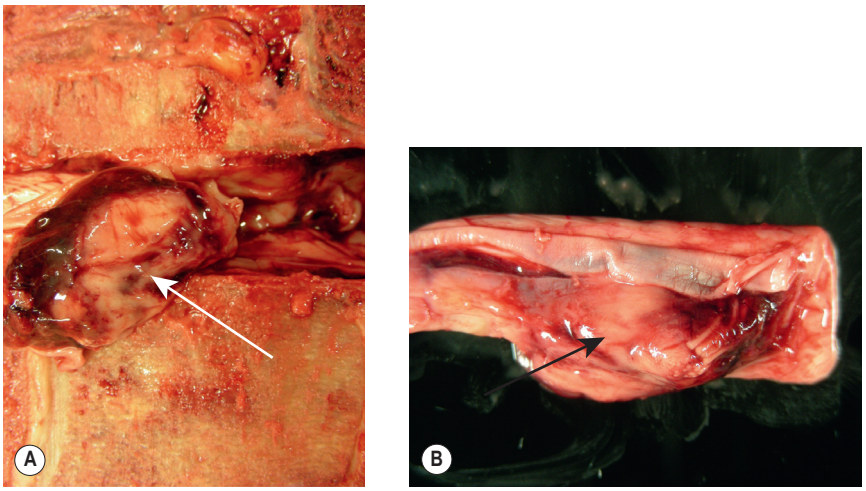


Figure 33.2 Secondary spinal lymphoma. A middle-aged mare was presented with chronic weight loss, generalized alopecia and focal vasculitis. Additionally, there were profound neurological deficits relating to lumbar spinal compression. Generalized lymphadenopathy and consistent haematological changes supported a diagnosis of lymphoma. **(A)** At necropsy, the diagnosis was confirmed and significant lymphoma lesions were also identified in the vertebral bodies and spinal canal. **(B)** Somewhat unusually, there were lesions within the spinal cord itself. *(Figures courtesy of Harry Carslake.)*

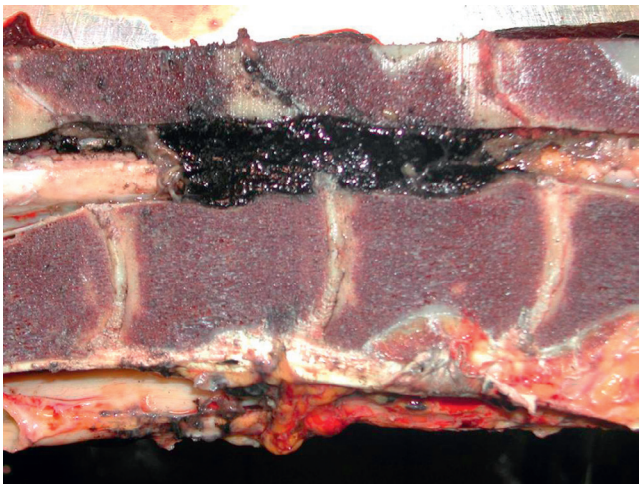


Figure 33.3 Secondary melanoma. A middle-aged grey horse was presented with progressive hindlimb ataxia, tail paralysis and urinary incontinence attributable to spinal compression or pathology in the mid-lumbar region. A spinal fluid sample revealed abnormal melanocytes. At necropsy, a significant melanotic mass was present within the spinal canal, wrapping around and invading the spinal cord. *(Figure courtesy of Lucia Unger and Vince Gerber, Vetsuisse Bern.)*



Figure 33.4 Melanoma affecting peripheral nerves. Although melanoma within nerves is unreported, some melanomas do interfere with peripheral nerve pathways. This 19-year-old grey mare had a single, large rapidly expanding melanoma in the right jugular furrow. The jugular vein was displaced (arrow). She developed a profound Horner's syndrome with ipsilateral facial sweating and ptosis and complete right-sided laryngeal paralysis. There were multiple melanomas, including within the guttural pouches. She was presented because she developed an inspiratory stridor and, on presentation, she had profound right-side laryngeal paralysis and Horner's syndrome. The tumour had wrapped around the vagosympathetic trunk and it was impossible to follow it through the mass.

- Neck
- Perineum
- Around the head
- Parotid gland.

Malignant melanomas can arise from normal melanocytes in the epidermis and oral epithelium or from the junctional or dermal elements of melanomas. Metastasis is often widespread and occurs via lymphatic and vascular routes. Equine malignant melanomas have been reported to cause neurological deficits in horses, and are the most common tumours affecting the spinal cord (Fig. 33.3; see also Fig. 27.13).

Melanoma can also affect the path of peripheral nerves and, in particular, this occurs when melanomas are located in the thoracic inlet or the jugular groove where they can cause impairment of function in the vago-sympathetic trunk in particular. Horner's syndrome and/or ipsilateral laryngeal paralysis can then occur (Fig. 33.4). Any nerve can be involved (see p. 99, Fig. 7.13).

Clinical features

Melanomas invading the central nervous system present with a wide variety of neurological deficits, depending on location of lesion and clinical signs reported. They are described in Table 33.2.

Haemangiosarcoma

See also pages 334 and 487.

Overview

There have been only six reports of haemangiosarcoma affecting the central nervous system.[31,39–43]

Two cases of disseminated haemangiosarcoma were reported to involve the heart, lungs, skeletal muscle and the brain.[1] No CNS signs were reported in association with the brain metastases.

Although haemangiosarcoma more commonly affects other body systems (see p. 334), it may involve the CNS,

Table 33.2 Central nervous system melanoma cases reported between 1970 and 2013

Ref. No.	Age (years)	Location	Compressive or invasive	Clinical signs	CSF	Single or multiple
32	17	L5–6 (epidural)	Compressive	Progressive hindlimb paresis and ataxia, flaccid tail and anus, perineal anaesthesia and urine dribbling	1+ Pandy	Extension from 12 cm mass in right paralumbar musculature
33	21	Sacral nerves, dorsal ganglia, proximal ischiatic nerve and gluteal muscle fibres	Compressive and invasive	Rapidly deteriorating lameness of right hindlimb	N/A	Multiple
34	13	C7–T1	Compressive	Progressive symmetrical bilateral ataxia, worse in hindlimbs	Normal	Multiple
	22	C4, C7–T1, L5–S2	Compressive	Recumbency	Normal at AO, Melanin granules at LS tap	Multiple
35	10	Brainstem over medulla and fourth ventricle	Compressive	Lack of cough reflex and pneumonia	N/A	Multiple
36	12	L2–L4	Compressive and invasive	Hindlimb paresis and ataxia, recumbency, faecal and urinary incontinence, flaccid tail	CSF – AO and LS – normal	Multiple
37	12	T10–T11	Compressive and invasive	PUO and anaemia of 5 days' duration followed by ataxia and recumbency	N/A	Multiple
38	13	Dorsal to brainstem at foramen magnum	Compressive	Recurrent choke, weight loss and mucopurulent nasal discharge, CN V, IX, X and XII, mild hypermetria and ataxia	N/A	Cutaneous masses confirmed melanoma on ventral tail and perianal, single brainstem melanoma

resulting in progressive neurological signs, and should be considered as a differential diagnosis for horses that present with signs consistent with an intracranial CNS lesion (Fig. 33.5).

Case reviews

A 25-year-old Saddlebred stallion[42]:

This Saddlebred stallion presented with:

- A 12-month history of difficulty balancing when breeding,
- Ataxia and intermittent knuckling of the hindlimbs
  - Anatomical lesion localization was consistent with a single cervical lesion or multifocal spinal cord lesions. The decision was made to euthanize the horse
  - Necropsy revealed an extradural compressive mass in the dorsal spinal canal at C7–T1
  - Immunohistochemistry was positive for endothelial cell marker, factor VIII antigen, consistent with a diagnosis of haemangiosarcoma.

An 18-year-old Percheron cross gelding

This Percheron cross gelding presented with[43]:

- Acute onset of neurological signs, including depression, right head turn and circling to the right and spontaneous nystagmus.
- Ataxia of all four limbs.
- Decreased tongue tone and right facial hypalgesia, consistent with a diffuse brainstem lesion.
- Diagnostic tests were negative for EHV and WNV.
- Lumbosacral CSF tap was pink and tested positive for antibodies to *Sarcocystis neurona*
  - However, this was consistent with blood contamination.
- Despite symptomatic therapy, clinical signs progressed and the horse was euthanized on day 6
  - An atlanto-occipital CSF tap taken immediately post mortem was moderately xanthochromic
  - Necropsy revealed multiple variably sized nodules throughout the lungs and myocardium and multiple expansile and compressive red-grey nodules focally within the brain
  - Histopathology confirmed the masses in the brain were identical to those in the lungs and heart. Immunohistochemistry, using endothelial cell marker confirmed a diagnosis of disseminated haemangiosarcoma involving the lungs, heart and brain
  - It is likely the source of blood in the CSF was haemorrhage associated with the CNS haemangiosarcoma.

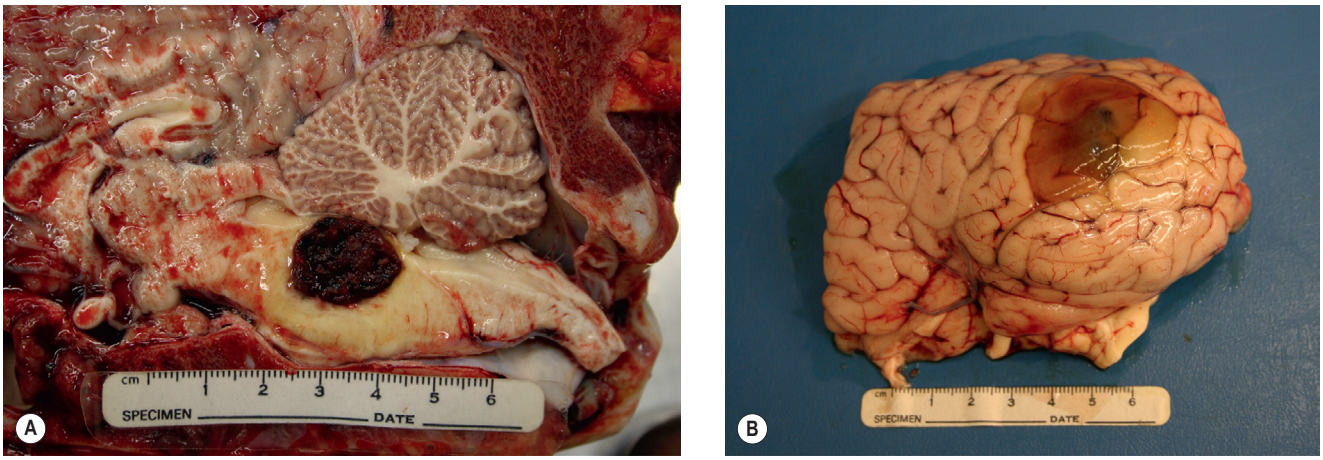


Figure 33.5 Intracranial haemangiosarcoma. A 6-week-old foal was presented with anaemia and central nervous signs attributable to both the brainstem and the cerebrum. At necropsy, a primary pulmonary haemangiosarcoma was identified. **(A,B)** Additional well-defined haemangiosarcoma masses were present in the brainstem and the cerebrum. *(Figures courtesy of Vince Gerber and Lucia Unger, VetSuisse Bern.)*

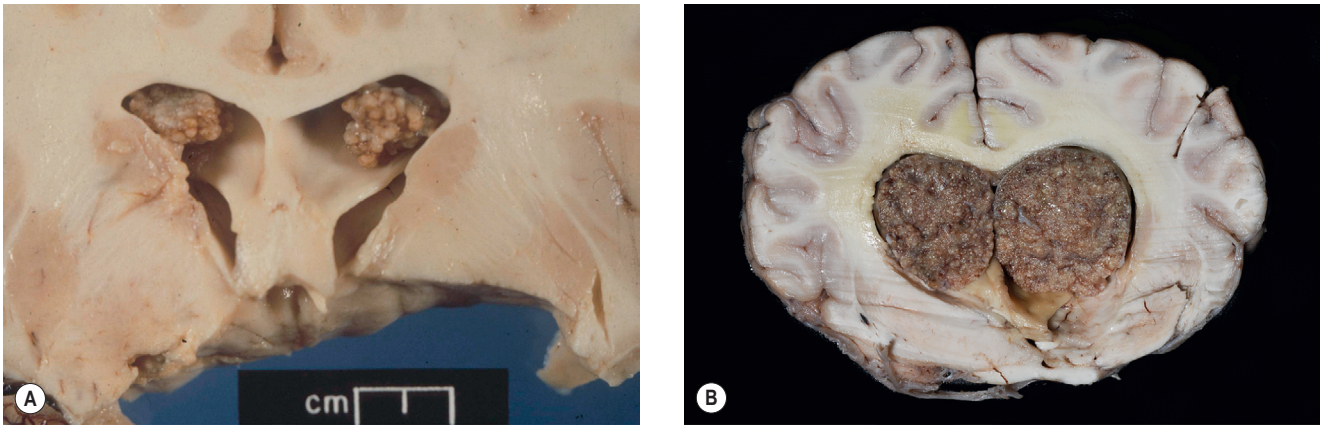


Figure 33.6 Cholesterol granuloma. (A) Cholesterol granuloma in the ventricles of the brain of a 19-year-old horse destroyed for other reasons. They can be found incidentally with some frequency and it is not certain whether small lesions like this can cause any significant clinical signs or pathology. **(B)** This horse had significant progressive central nervous signs, including dullness, yawning and compulsive walking. Liver function tests were normal. At necropsy, this very extensive pair of approximately symmetrical cholesterol granulomas were found. It is not certain they caused the problem, but no other explanation could be found. *(Picture B courtesy Gail Leeming.)*

A 14-year-old Welsh pony gelding[31]:

- Presented with a 3-day history of ataxia in all four limbs (Grade IV/V); a spinal cord compressive lesion was suspected in the cervical region.
- Radiography and myelography identified a compressive lesion at mid-C2.
- Surgery was performed to remove the mass, but the horse never recovered to standing.
- Histopathology showed characteristics consistent with haemangiosarcoma.

Other secondary tumours affecting the central nervous system

Overview

Other secondary tumours that have been reported occasionally in the central nervous system include:

- Carcinomatosis[44]
- Lipoma[45]
- Adenocarcinoma[46]
- Plasma cell myeloma[47]
- Phaeochromocytoma[48]
- Fibrosarcoma[49]
- Squamous cell carcinoma[50]
- Undifferentiated sarcoma.[51]

Non-neoplastic masses within the nervous system

Cholesterol granuloma

See also page 370.

Description

Cholesterol granulomas are tumour-like masses of the choroid plexuses of the ventricles of the equine brain (Fig. 33.6). They are an inflammatory granulomatous process affecting the choroid plexus of, especially, the lateral ventricles with marked infiltration and deposition of cholesterol within the tissues.[52] The choroid plexus has an

epithelial cuboidal cell lining and the inflammation occurs within the choroid plexus membrane, resulting in expansion of the membranes and filling of the space. Reported prevalence has been reported up to 15–20% in older horses.[52]

Clinical features

Most reported cholesterol granulomas are small and do not cause any clinical signs. However, if the cholesterol granuloma reaches a significant size, reported clinical signs are very variable and intermittent. This could be due to intermittent hydrocephalus and/or oedema formation within the cerebral parenchyma, with remission taking place once pressure of the CSF returns to normal. However, Johnson et al. suggested that it could be due to intermittent release of irritant substances from the cholesterol granuloma.[53]

- The most frequently reported clinical sign is depression.[53–58]
- Additional signs, the majority of which indicate forebrain pathology, include:
  - Behavioural changes
  - Apparent intermittent blindness
  - Compulsive walking
  - Syncope-like attacks and weakness
  - Circling
  - Head turn or head tilt.
- Mentation alterations, including:
  - Mania and aggression
  - Tremors and lack of response to stimuli can be present
  - Yawning and head pressing may give the impression of hepatoencephalopathy
  - Seizure
  - Vague colic signs.

Various cranial nerve signs, including facial paralysis, anisocoria and bilateral dorsal strabismus, are reported.

The development of cholesterol granulomas could be related to chronic or intermittent oedema and congestive haemorrhages in the choroid plexuses.[52] However, they might represent a chronic granulomatous reaction to cholesterol crystal deposition, associated with chronic choroid plexus vascular leakage.[58]

Diagnostic confirmation

As might be expected, a pre-mortem diagnosis can be a serious challenge, particularly because of the wide range of signs and the nonspecific findings in cerebrospinal fluid.

Imaging techniques, including MRI and CT, can be major help, but availability is usually problematic.

- *MRI* appearance of cholesterol granulomas has been described[59]
  - As with many other intracranial conditions, MRI provides a highly precise image and localization of any abnormal structure and may even provide a specific diagnosis.[59]
- *CT* appearance of cholesterol granulomata has also been described[57,60,61]
  - CT can be very useful in achieving a diagnosis.
- *Guided biopsy* has also been used without significant problems.

Management

Most horses with cholesterol granuloma have been euthanized soon after diagnosis, based on a perceived poor prognosis. However, two cases, in which high-quality diagnostic images were obtained in the sedated animal (avoiding general anaesthesia), showed improving neurological signs, allowing discharge from the hospital. Follow-up after 1 year in a single case showed a reduction in the size of the mass. Since the presenting signs are thought to be due to inflammation, treatment directed towards reduction of inflammation, such as long-term use of non-steroidal anti-inflammatory drugs, might be indicated.[61]

Tumours of the peripheral nervous system

Overview

Tumours of the peripheral nerves of horses are singularly rare in all species, but both benign and malignant tumours can develop from any elements of the nerve sheath. For the most part, only two conditions occur with any frequency. These are the so-called 'neuroma', which is a frequent complication of surgical neurectomy or traumatic nerve damage in horses, and the cutaneous neurofibroma, which is very similar in behaviour and clinical appearance to some forms of nodular sarcoid (see pp. 549 and 662).

Neuroma

Overview

Following neurectomy (and in particular palmar digital neurectomy), a condition that is referred to as a 'neuroma' quite commonly develops. This is a painful expansion of the severed proximal end of the nerve. It is uncertain whether this is a neoplasm or whether it is a reactive response to damage. Overall, the consensus is that it is not a neoplasm.

Neurofibroma/schwannoma

See also pages 299 and 562.

Overview

These tumours develop from cells in the peripheral nerve sheath, including Schwann cells, perineural cells and most commonly fibroblasts. Most true neurofibroma lesions express Schwann cell characteristics, including the S100 antigen expression. They also have a capability of melanocytic differentiation and so may be accompanied by apparent hyperpigmentation.

The most common form of neurofibroma in horses is the cutaneous schwannoma. These are tumours that arise from Schwann cells and these are slowly-expanding, well-encapsulated, space-occupying masses with a firm well-defined nodular or multinodular form (see p. 562). The tumours vary in the amount of extracellular matrix and

so there is a spectrum of tumour texture, from very firm masses with highly collagenized matrix and little myxoid material to rather soft masses with much more myxoid interstitial matrix. The expanding tumour displaces the axons and so, most often, no nerve fibres are found in the masses.

The cutaneous form is the commonest peripheral nerve tumour in the horse and usually manifests as a single discrete localized mass within a capsule. A few have a more plexiform nature, with an infiltrative behaviour. Their significance lies mostly in their similarity with some forms of sarcoid and in their difficulty with treatment (see p. 562).[62]

A study describing 22 cases of cutaneous schwannomas in horses aged between 8 and 25 years showed that most affected horses had solitary, multinodular or single nodular cutaneous masses, the majority of which were on the head and neck. The tumours were well-demarcated and solely but progressively expansile.

A single case of intracranial schwannoma has been described in a young horse presented with slowly progressive neurological signs, including changes in mentation and circling, suggesting pathology in the cerebrum. Visual impairment and unilaterally decreased facial sensation were noted. A solitary schwannoma, which compressed the left cerebrum, was found at necropsy.[63]

They are seldom malignant, but there are reports of malignant transformation when the condition can be more problematic and requires sophisticated treatment, including radiation brachytherapy.[64]

References

1. Paradis MR. Tumors of the central nervous system. Vet Clin North Am Equine Pract 1998; 14:543–561.
2. Gelatt KN, Leipold HW, Finocchio EJ, et al. Optic disc astrocytoma in a horse. Can Vet J 1971; 12:53–55.
3. Gericota B, Aleman M, Kozikowski TA, et al. A grade IV glioblastoma with an oligodendroglial component (GBM-O) in a horse. J Comp Pathol 2010; 142:332–335.
4. Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumours. Brain Pathol 1993; 3:255–268.
5. Reppas GP, Harper CG. Sudden unexpected death in a horse due to a cerebral oligodendroglioma. Equine Vet J 1996; 28:163–165.
6. Heath SE, Peter AT, Janovitz EB, et al. Ependymoma of the neurohypophysis and hypernatraemia. J Am Vet Med Assoc 1995; 207:738–741.
7. Carrigan MJ, Higgins RJ, Carlson GP, et al. Equine papillary ependymoma. Vet Pathol 1996; 33:77–80.
8. Huxtable CR, de Lahunat A, Summers BA, et al. Marginal siderosis and degenerative myelopathy: a manifestation of chronic subarachnoid haemorrhage in a horse with a myxopapillary ependymoma. Vet Pathol 2000; 37:483–485.
9. Fankhauser R, Luginbühl H, McGrath JT. Tumours of the nervous system. Bull World Health Organ 1974; 50:53–69.
10. Sohrabi Haghdoost I, Zakarian B. Neoplasms of equidae in Iran. Equine Vet J 1985; 17:237–239.
11. Pirie RS, Mayhew IG, Clarke CJ, et al. Ultrasonographic confirmation of a space-occupying lesion in the brain of a horse: choroid plexus papilloma. Equine Vet J 1998; 30:445–448.
12. Sardon D, Vazquez F, Cabrera P, et al. Choroid plexus papilloma of the fourth ventricle of the plexus in a horse. J Equine Vet Sci 2008; 28:545–548.
13. Loupal G, Mikula M. Olfaktorius Neuroblastom bei einem Pferd. Pferdeheilkunde 1985; 1:65–69.
14. Döpke C, Gröne A, von Borstel M, et al. Metastatic esthesioneuroblastoma in a horse. J Comp Pathol 2005; 132:218–222.
15. Yamate J, Izawa T, Ogata K, et al. Olfactory neuroblastoma in a horse. J Vet Med Sci 2006; 68:495–498.
16. Kreeger JM, Templer A, Turnquist SE, et al. Paranasal meningioma in a horse. J Vet Diagn Invest 2002; 14:322–325.
17. Lüginbühl H, Fankhauser R, McGrath JT. Spontaneous neoplasms of the nervous system in animals. Prog Neurol Surg 1968; 2:85–164.
18. Dyson PK, Dunn KA, Whitwell K, et al. Ataxia and cranial nerve signs in a pony suffering a brainstem meningioma: clinical, MRI, gross and histopathological findings. Equine Vet Educ 2007; 19:173–178.
19. Naylor RJ, Dunkel B, Dyson S, et al. A retrobulbar meningioma as a cause of unilateral exophthalmos and blindness in a horse. Equine Vet Educ 2010; 22:503–510.
20. Holshuh HJ, Howard EB. Pineoblastoma, a primitive neuroectodermal tumour in the brain of a horse. Vet Pathol 1982; 19:567–569.
21. Neufeld JL. Lymphosarcoma in a mare and review of cases at the Ontario Veterinary College. Can Vet J 1973; 14:149–153.
22. Shamis LD, Everitt JI, Baker GJ. Lymphosarcoma as the cause of ataxia in a horse. J Am Vet Med Assoc 1984; 184:1517–1518.
23. Kannegieter NJ, Alley MR. Ataxia due to lymphosarcoma in a young horse. Aust Vet J 1987; 4:377–379.
24. Rousseaux CJ, Doige CE, Tuddenham TJ. Epidural lymphosarcoma with myelomalacia in a seven year old Arabian gelding. Can Vet J 1989; 30: 751–753.
25. Zeman DH, Snider TG 3rd, McClure JJ. Vertebral lymphosarcoma as the cause of hind limb paresis in a horse. J Vet Diagn Invest 1989; 1:187–188.
26. Williams MA, Welles EG, Gallor RJ, et al. Lymphosarcoma associated with neurological signs and abnormal cerebrospinal fluid in two horses. Progr Vet Neurol 1992; 3:51–56.
27. Lester GD, MacKay RJ, Smith-Meyer B. Primary meningeal lymphoma in a horse. J Am Vet Med Assoc 1992; 201:1219–1221.
28. Bentz BG, Van Winkle TJ, Bernard WV. Lymphosarcoma involving the brainstem and spinal cord in a horse. Equine Vet Educ 1995; 7:124–126.
29. Gliatto JM, Alroy J. Cutaneous amyloidosis in a horse with lymphoma. Vet Rec 1995; 137:68–69.
30. Morrison LR, Freel K, Henderson I, et al. Lymphoproliferative disease with features of lymphoma in the central nervous system of a horse. J Comp Pathol 2008; 139:256–261.
31. Hirsch JE, Grant BD, Linovitz R, et al. Diagnosis and surgical treatment of epidural neoplasms in two ataxic horses. Equine Vet Educ 2009; 21: 564–568.
32. Traver DS, Moore JN, Thornburg LP, et al. Epidural melanoma causing posterior paresis in a horse. J Am Vet Med Assoc 1977; 170:1400–1403.
33. Kirker-Head CA, Loeffler D, Held JP. Pelvic limb lameness due to malignant melanoma in a horse. J Am Vet Med Assoc 1985; 186:1215–1217.
34. Schott HC, Major MD, Grant BD, et al. Melanoma as a cause of spinal cord compression in two horses. J Am Vet Med Assoc 1990; 96:1820–1822.
35. Kenney DG, Divers TJ. A brainstem melanoma associated with loss of the cough reflex, resulting in aspiration pneumonia in a horse. Prog Vet Neurol 1993; 4:11–13.
36. Rodriguez F, Forga J, Herráez P, et al. Metastatic melanoma causing spinal cord compression in a horse. Vet Rec 1998; 142:248–249.
37. Patterson-Kane JC, Sanchez LC, Uhl EW, et al. Disseminated metastatic intramedullary melanoma in an aged grey horse. J Comp Pathol 2001; 125:204–207.
38. Covington AL, Magdesian KG, Madigan JE, et al. Recurrent oesophageal obstruction and dysphagia due to a brainstem melanoma in a horse. J Vet Intern Med 2004; 18:245–247.
39. Waugh SL, Long GG, Uriah L, et al. Metastatic haemangiosarcoma in the equine: report of 2 cases. J Equine Med Surg 1977; 1:311–315.
40. Newton-Clarke MJ, Guffoy MR, Dykes NL, et al. Ataxia due to vertebral haemangiosarcoma in a horse. Vet Rec 1994; 135:182–184.
41. Johnson JE, Beech J, Saik JE. Disseminated hemangiosarcoma in a horse. J Am Vet Med Assoc 1988; 193:1429–1431.
42. Berry S-L. Spinal cord compression secondary to haemangiosarcoma in a Saddlebred stallion. Can Vet J 1999; 40:886–887.
43. Ladd SM, Crisman MV, Duncan R, et al. Central nervous system haemangiosarcoma in a horse. J Vet Intern Med 2005; 19:914–916.
44. Wright JA, Giles CJ. Diffuse carcinomatosis involving the meninges of a horse. Equine Vet J 1986; 18:147–150.
45. Anderson WI, King JM. Incidental meningeal lipoma in a horse. Vet Pathol 1988; 25:530–531.
46. Reynolds BL, Stedham MA, Lawrence JM, et al. Adenocarcinoma of the frontal sinus with extension to the brain in a horse. J Am Vet Med Assoc 1979; 174:734–736.
47. Drew RA, Greatorex JC. Vertebral plasma cell myeloma causing posterior paralysis in a horse. Equine Vet J 1974; 6:131–134.
48. Froscher BG, Power HT. Malignant pheochromocytoma in a foal. J Am Vet Med Assoc 1982; 181:494–496.
49. Reinertson EL. Fibrosarcoma in a horse. Cornell Vet 1974; 64:617–621.
50. Patterson LJ, May SA, Baker JR. Skeletal metastasis of a penile squamous cell carcinoma. Vet Rec 1990; 126:579–580.
51. Van Biervliet J, Alcaraz A, Jackson CA, et al. Extradural undifferentiated sarcoma causing spinal cord compression in 2 horses. J Vet Intern Med 2004; 18:248–251.
52. Jubb KV, Huxtable CR. The nervous system. In: Jubb KV, Kennedy PC, Palmer N, eds. Pathology of domestic animals, Vol. 1, 4th edn. San Diego: Academic Press Inc; 1993: 267–440.
53. Johnson PJ, Lin TL, Jennings DP. Diffuse cerebral encephalopathy associated with hydrocephalus and cholesterinic granulomas in a horse. J Am Vet Med Assoc 1993; 203:694–697.
54. Ooms L, Muylle E, van den Hende C. Choroid plexus cholesteatoma in a horse. Vlaams Diergeneeskundig Tijdschrift 1975; 45:87–98.
55. Jackson CA, deLahunta A, Dykes NL, et al. Neurological manifestation of cholesterinic granulomas in three horses. Vet Rec 1994; 135:228–230.
56. King JM. Bilateral choroid plexus cholesteatomas. Vet Med 1997; 92:514.
57. Vink-Nooteboom M, Junker K, van den Ingh TS, et al. Computed tomography of cholesterinic granulomas in the choroid plexus of horses. Vet Radiol Ultrasound 1998; 39:512–516.
58. Hahn CN, Mayhew IG, Mackay RJ. Diseases of the forebrain. In: Colahan PT, Merritt AM, Moore JN, et al., eds. Equine medicine and surgery, 5th edn. St Louis: Mosby; 1999: 904–913.
59. Maulet BEB, Bestbier M, Jose-Cunilleras E, et al. Magnetic resonance imaging of a cholesterol granuloma and hydrocephalus in a horse. Equine Vet Educ 2008; 20:74–79.

60. Vanschandevijl K, Gielen I, Nollet H, et al. Computed tomography-guided brain biopsy for in vivo diagnosis of a cholesterinic granuloma in a horse. J Am Vet Med Assoc 2008; 233:950–954.
61. Finding E, Fletcher N, Avella C, et al. Standing CT and clinical progression of equine cholesterol granulomata. Vet Rec 2012; 170:289–290.
62. Schöniger S, Valentine BA, Fernandez CJ, et al. Cutaneous schwannomas in 22 horses. Vet Pathol 2011; 48:433–442.
63. Williamson LH, Farrell RL. Intracranial schwannoma in a horse. Cornell Vet 1990; 80:135–141.
64. Saulez MN, Voigt A, Steyl JC, et al. Use of Ir192 interstitial brachytherapy for an equine malignant dermal schwannoma. J S Afr Vet Assoc 2009; 80:264–269.

34 Tumours of the eye

Neoplasia of the eyelids 613
Tumours of the conjunctiva, the globe and the orbit 613
Other corneal, conjunctival and ocular tumours 626

Neoplasia of the eyelids

See page 299.

Tumours of the conjunctiva, the globe and the orbit

Overview

Primary tumours of the equine orbit are reportedly rare.[1] Irrespective of their origin, nearly all reported orbital tumours in horses have already invaded the orbital soft tissues, the calvarium or adjacent cavities of the skull at the time of admission. The majority of orbital tumours occur in older horses, which inevitably influences the prognosis and owner willingness to pursue therapy.[2]

Orbital tumours may arise as primary neoplasms or may be secondary to primary tumours of the paranasal sinuses or as extension of ocular/adnexal structures. For example, orbital carcinoma can develop directly from the nasal cavity or paranasal sinuses or from carcinoma of the conjunctiva or third eyelid.[2] Previously described equine orbital tumours include a series of extra-adrenal paraganglioma (neuroendocrine tumour) and single cases of a variety of tumour types (Table 34.1).

Apart from lipoma, virtually all these masses are capable of invading the bone and, thereby, entering the multiple cavities of the skull. Some, such as neuroendocrine tumours, can metastasize[1,11]; the risks associated with tumour dissemination via the bloodstream are, however, probably minimal compared with the probability of local destructive expansion.

The clinical presentation of primary orbital tumours usually consists of progressive non-painful exophthalmia of an extended duration – often over some years but occasionally more acutely. Affected horses may be blind in the ipsilateral eye and there may be some ocular discharge and conjunctival oedema chemosis. A fundamental feature is the 'filling' or expansion of the supraorbital fossa and the inability to repulse the eye back into the orbit. The third eyelid may not prolapse in response to this test. If the eye is displaced sufficiently to preclude blinking, there may be an exposure keratitis.

As might be expected, there may be secondary intraocular effects, including anisocoria (unequal pupil size), mydriasis, scleral indentation, optic nerve atrophy, pallor or hyperaemia and varying degrees of blindness with absent or decreased direct and consensual light and menace responses.

There may be concurrent paraneoplastic peripheral neuropathies that are not attributable to local effects of the tumour but rather to an immune-mediated neuropathy.[11]

In secondary tumours, clinical signs related to the primary origin of the tumour may be noted. Extension of sinus tumours may be accompanied by other clinical signs, including unilateral nasal discharge and diminished airflow. Orbital tumours originating from extension of ocular/adnexal tumours usually have obvious adnexal neoplasia accompanying the exophthalmos.

Differential diagnoses

- Retrobulbar/orbital neoplasia
- Orbital cellulitis and abscess
- Sinus cysts
- Hydatid cyst
- Myositis of extraocular or masticatory muscles
- Retrobulbar haematoma
- Zygomatic salivary gland mucocele
- Congenital malformations (e.g. retrobulbar dermoid cyst).[17]

Since there are several important differential diagnoses, the investigation of a suspected of retrobulbar mass should include a detailed full clinical and neuro-ophthalmic examination. Nasal endoscopy, radiography and CT with MRI and ultrasonography provide the basis for diagnostic confirmation.[11,15,18]

The true prevalence of equine intraocular neoplasms is unknown, but they are rare.[19–21] The most common primary intraocular tumours in animals originate from melanocytic (melanoma) or neuroepithelial cells.[22] The most prevalent intraocular tumour is probably melanoma, which occurs most commonly in grey horses.[20,23,24] Astrocytoma is recorded in horses but appears to be restricted to the optic disc region.[25] Primary intraocular tumours of neuroectodermal origin, including medulloepithelioma and retinoblastoma, are rare but significant (see pp. 372 and 623).

Table 34.1 Reported ocular and periocular tumours

Tumour type	Ref. No.
Extra-adrenal paraganglioma (neuroendocrine tumour)	1,3,4
Malignant rhabdoid tumour	5
Orbital fibroma	6
Retrobulbar melanoma	7
Lipoma	8
Nasal and paranasal adenocarcinoma	9–11
Squamous cell carcinoma	12
Metastatic lymphosarcoma	8
Chondroma rodens	13
Neuroepithelial tumour	14,15
Unclassified tumour	16

Disease summary

Notes

Relatively common potentially malignant tumour of the conjunctiva or corneal epithelium.

Clinical features

Highly vascularized proliferative and/or ulcerative/destructive tumours with a chronic characteristic mucopurulent ocular discharge.

Diagnostic confirmation

Clinical and histological features are typical.

Management

A variety of surgical and chemotherapeutic options are available. Some are highly effective and others are less so in individual animals. Surgery with some form of chemotherapy appears to be the best option in most circumstances but radiation is a very effective.

Prognosis

The prognosis is good for early cases, but poor for later presented cases with advanced invasion.

Most intraocular tumours exert their effects through their space-occupying nature, either in the globe itself or within the optic nerve or retina. As horses adapt well to progressive, unilateral, slowly deteriorating vision, blindness can be easily overlooked by an owner in the absence of ocular pain or abnormal discharges. It is entirely reasonable that an owner may not notice an intraocular mass until it becomes visually obvious.[24]

Prognosis

The prognosis for horses with orbital or intraocular neoplasia remains generally very guarded. Early clinical suspicion and aggressive preoperative investigations will improve prognosis in some cases. Ultrasonography and biopsy of suspicious masses, in conjunction with lymph node biopsy, thoracic radiography and abdominal ultrasound, CT and MRI of the head, may clarify the prognosis when malignant tumours are suspected. However, practitioners should be aware of the marked difference in prognosis for orbital neoplasms compared with ocular or localized eyelid neoplasia.[26]

Squamous cell carcinoma

See also pages 220 and 575.

Overview

Squamous cell carcinoma (SCC) is the most common neoplasm of the equine cornea, conjunctiva and third eyelid, representing 48–75% of neoplasms involving this region.[8,12,19,27–36] The nictitating membrane (third eyelid) and conjunctiva are the most frequent sites. It is also the commonest eyelid neoplasm (see p. 578).[37]

Intrinsic factors that predispose to SCC include ocular pigmentation, age, gender and genetics. Ocular and periocular pigmentation are the most obvious predisposing factors, in that horses with the least pigmentation have the highest incidence of SCC, such as Appaloosas, Paints and Pintos. Draft breeds, such as Clydesdales, Shires and Belgians, also have a higher incidence of corneal and conjunctival SCC, despite having pigmented periocular skin and eyelid margins[8,38]; more commonly, however, the interpalpebral conjunctiva is non-pigmented in these Draft breeds.[2]

Prevalence increases with age, and most affected horses are between 7 and 10 years of age. However, age of onset is frequently unknown, as many horses are not diagnosed as having lesions for months to years. A higher incidence in geldings has been reported.[34] The specific pathophysiological mechanism responsible for this is unknown, but could have an endocrinological basis.[39]

Extrinsic factors include ultraviolet radiation, chronic irritation or infection causing tissue metaplasia, viral infection and parasites. Actinic influences are noted, as geographic locations having more sunshine and higher altitudes are likely to have an increased incidence of SCC.[2] The harmful effects of solar ultraviolet radiation in the development of SCC may be mediated through the overexpression or dysfunction of the *p53* tumour suppression gene, in horses and other domestic species.[40]

Chronic irritation or infection leading to tissue metaplasia with subsequent ocular SCC is seen in horses with recurrent or neglected ocular habronemiasis or onchocerciasis. Horses that have chronic conjunctivitis, chronic nasolacrimal duct obstruction and congenital or acquired lid abnormalities are also at risk.[2]

Clinical features

Clinical signs of conjunctival/corneal/nictitating membrane SCC can be quite variable, but classic appearance includes:

- White-pink, raised, cobblestone mass that bleeds easily (Fig. 34.1A); these can be located at any part of the conjunctiva and may extend across the limbus into the corneal epithelium (as corneal carcinoma in situ) (Fig. 34.1D, and Fig. 34.2) and may also involve the caruncle medially.
- Large lesions may often have a white necrotic 'cake frosting' appearance (Fig. 34.1B).

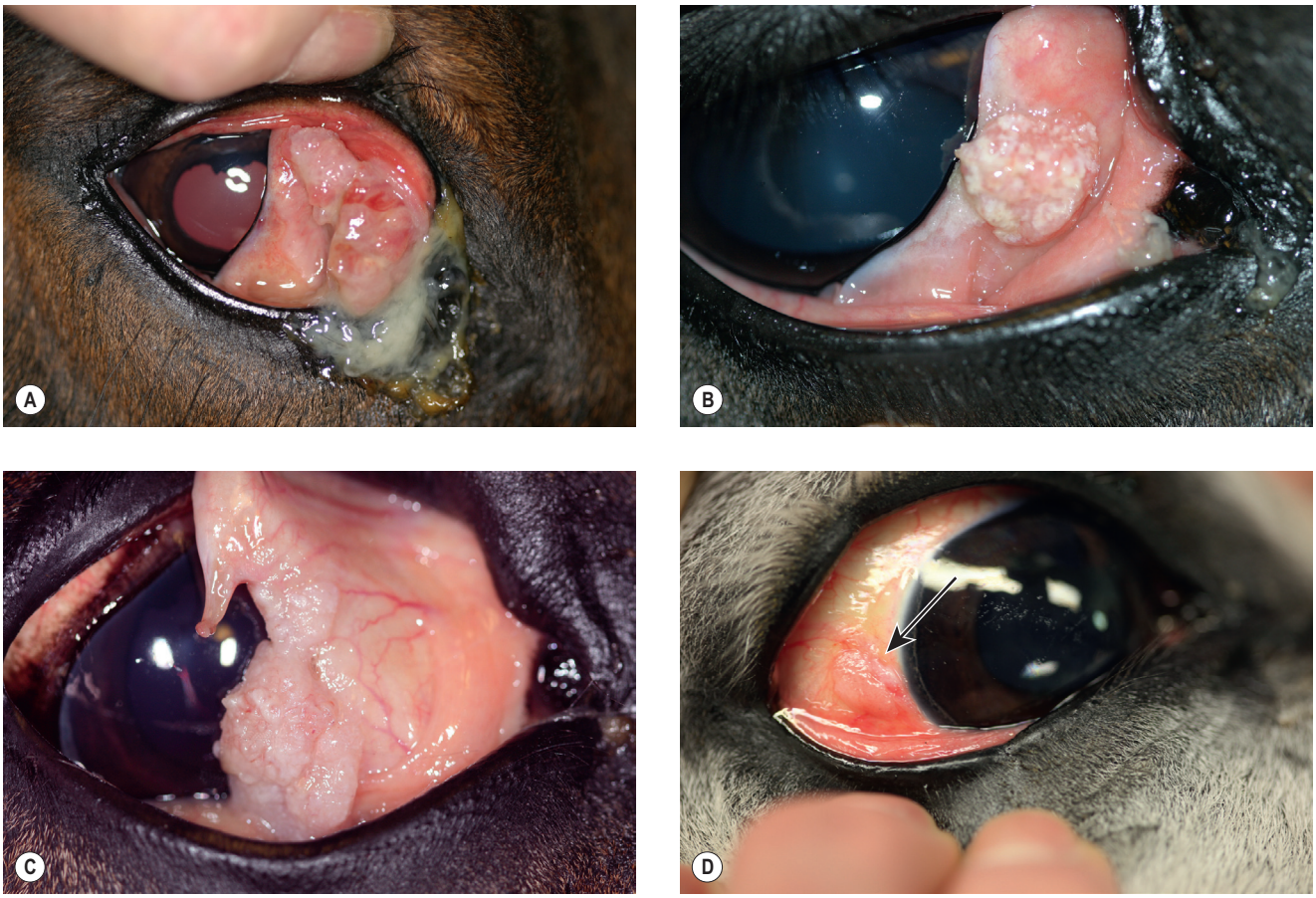


Figure 34.1 Conjunctival carcinoma. **(A)** A proliferative conjunctival carcinoma in a 9-year-old Arabian cross mare. Notice the mucopurulent discharge. **(B)** This papillomatous carcinoma grew slowly over 2 years in a 14-year-old Warmblood mare. Notice the 'frond-like' extensions and the characteristic grey/cream adherent material on the surface of the mass ('cake frosting'). This usually occurs on well-differentiated carcinoma lesions and may be keratin material, partially at least. **(C)** Conjunctival carcinoma may be highly destructive also, as shown in this picture. Usually, this equates with a less well-differentiated tumour. **(D)** A typical well-differentiated localized carcinoma of the lateral limbus (arrow) in an Appaloosa cross gelding. Notice the prominent blood supply.

- Intermittent blepharospasm and affected eyes often have associated conjunctivitis and a characteristic mucopurulent ocular discharge (see Fig. 34.1A).
- Some appear at the lateral limbal region, starting in the bulbar conjunctiva, and then may extend into the cornea. However, they may appear at any limbal location (see p. 21, Fig. 3.13)
  - Lesions occurring at the upper limbus or at the limbus following nictitans removal are in the authors' experience more dangerous
  - Less commonly, non-raised infiltrative corneal stromal lesions occur (corneal stromal-invasive SCC, CSI-SCC) (see Fig. 34.2B).
- A prominent vascular supply is a common feature, although this is only visible in some circumstances.
- Eyelid carcinoma can extend into the conjunctiva and conjunctival and palpebral forms can seed onto the cornea (see p. 60 and Fig. 4.33).
- Extensive destruction of the third eyelid and involvement of the palpebral or bulbar conjunctiva can result in significant tissue distortion and deformity (Fig. 34.1C).

The clinical signs associated with carcinoma of the cornea are more subtle in the early stages.

- Corneal opacity – usually grey in colour but sometimes more aggressively haemorrhagic and ulcerated
  - Early cases can be much more difficult to diagnose clinically
  - Later cases are often complicated by inclusion of volumes of keratin under the epithelium (Fig. 34.2A).
- Prominent superficial neovascularization
  - The co-existence of deep neovascularization is usually regarded as evidence of corneal invasion
- Concurrent dense granulation tissue-like proliferation can reflect proliferative carcinoma or concurrent granulation tissue (Figs 34.2B,C).

Differential diagnoses

Differential diagnoses for corneal/conjunctival/nictitating membrane SCC include:

- Other neoplasms
  - Haemangioma/sarcoma
  - Angiosarcoma
  - Lymphoma
  - Melanoma
  - Mast cell tumour
  - Basal cell tumour

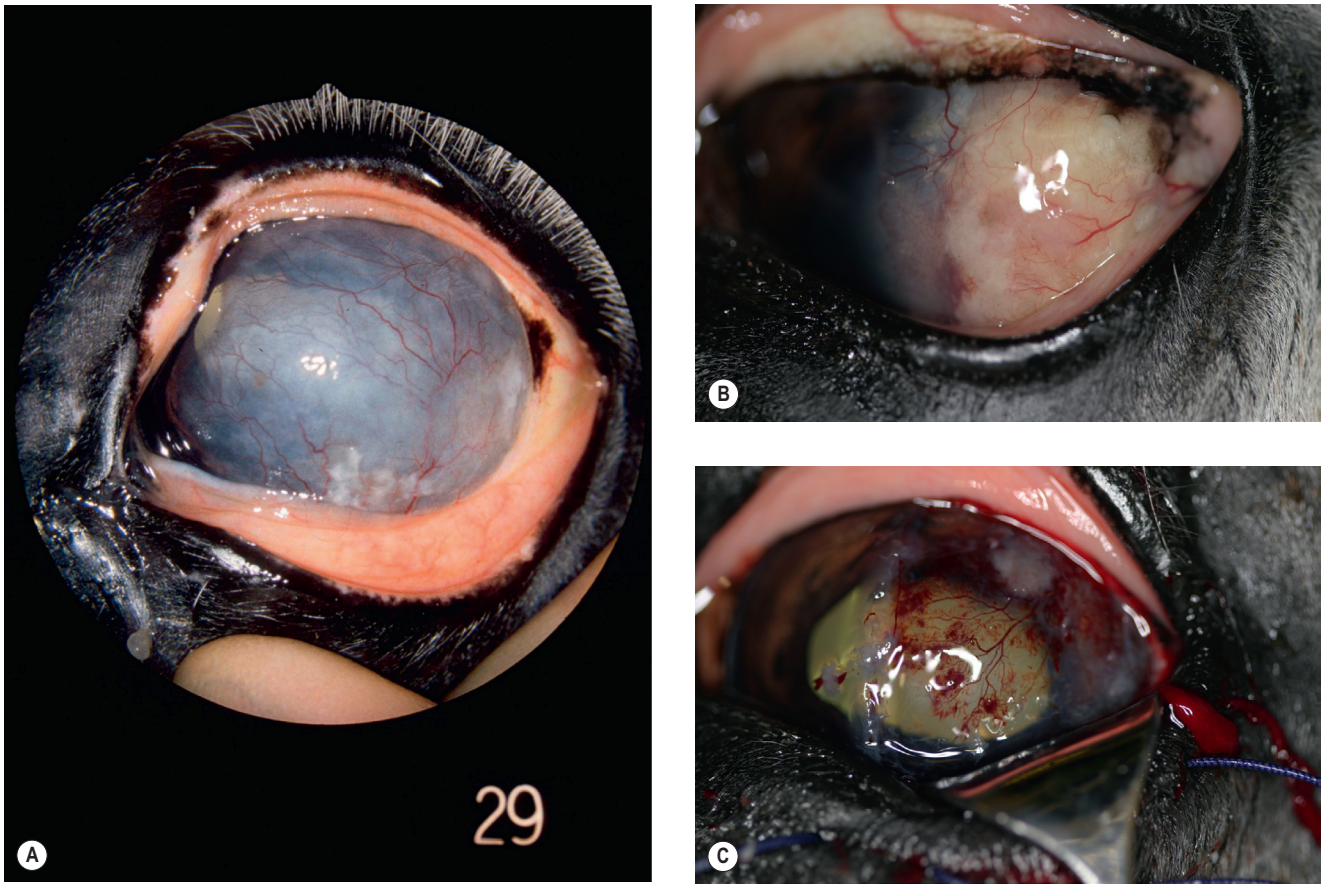


Figure 34.2 Corneal carcinoma (in situ carcinoma). **(A)** A superficial intraepithelial carcinoma occupying almost the entire surface of the eye. This was removed relatively simply by superficial keratectomy followed by radiation plesiotherapy using a strontium-90 wand and topical mitomycin C. **(B)** This well-differentiated carcinoma presented in a 9-year-old grey mare. Notice the prominent superficial neovascularization. The bulk of the mass was composed of keratin-like material. **(C)** Once the tumour was removed by lamellar keratectomy, prominent deep neovascularization was obvious. The site was treated with strontium-90 plesiotherapy and, apart from a limited scar on the cornea, there was no further problem.

  - Neurofibrosarcoma
  - Papilloma
  - Adenocarcinoma
  - Lipoma.
- Parasites
  - Habronemiasis
  - *Onchocerca cervicalis*.
- Corneal oedema/infiltrative corneal disease such as eosinophilic keratitis.
- Dermoid.
- Conjunctival pseudotumour.

Note

Unilateral or bilateral non-ulcerated conjunctival nodular masses with histological features characteristic of inflammatory lesions. Conjunctival pseudotumour is suspected to have an immune-mediated pathogenesis, because of a positive response to corticosteroids or other immunosuppressive agents.[41,42]

Diagnostic confirmation

- The location, appearance, age and breed of the animal, in most cases, is sufficient to make a clinical diagnosis of squamous cell carcinoma.
- Carcinoma sites on the conjunctiva stain very strongly with Rose Bengal stain
  - A lacrimal occult blood test can be carried out in very early cases – this is done by touching a urine haemoglobin dipstick onto the tear film – a positive outcome is a non-specific indicator of bleeding.
- Histological examination of a biopsy sample is the most accurate way to confirm the diagnosis
  - If this is not possible because of the location of the tumour (corneal lesions, for example), other means of diagnosis may be employed, including smears, scrapings or impression cytology.

Management

Treatment options are wide and should take account of the location, size and depth of the tumour, economics, history or known recurrences, previous treatment modalities and suitability of the patient for general anaesthesia.

- Treatment of any early dysplastic or neoplastic corneo-limbal or nictitating membrane lesions should be carried out as soon as possible because dysplastic lesions usually progress to overt carcinoma.

The options include:

1. Surgical methods:
   - Surgical excision (conjunctivectomy)
   - Keratectomy (with or without bulbar conjunctival grafts or amniotic membrane transplantation) and enucleation.[28,37,43–46]

Note

Conjunctivectomy and keratectomy should be performed with appropriate surgical instrumentation and magnification to ensure complete removal of abnormal tissue. Conjunctival lesions that require removal of >1.0 cm of tissue may benefit from conjunctival suturing to prevent excessive granulation tissue from arising postoperatively from the scleral and episcleral tissue. This may be easily confused with tumour regrowth, but usually occurs more quickly (<3 weeks).

2. Third eyelid resection is a standard approach to carcinoma of the nictitans. The method is described in current surgical and ophthalmic texts. This carries a good overall prognosis and can be performed in the standing sedated horse[47,48]
   - Compromised pre-corneal tear film due to the loss of mucus and lacrimal production from the excised third eyelid gland is a concern but has not resulted in any noticeable short- or long-term complications in horses[47]
   - Higher rates of recurrence have been reported with the use of surgical excision as the sole form of therapy because it is often not possible to achieve satisfactory excisional margins.[37] Lamellar keratectomy and conjunctivectomy are usually sufficient to remove all macroscopically abnormal tissue. However, macroscopic removal can leave residual and viable microscopic neoplastic cells.[49] For this reason, surgery is commonly combined with adjunctive therapies to reduce recurrence.[34,50]
3. Radiotherapy, including strontium-90, cobalt-60, gold-198, iridium-192, caesium-137, iodine-125 and radon-222, with or without preceding surgery (see p. 183, Fig. 9.46).[50–54] Success rates are reported to be very good.
4. Chemotherapy using mitomycin C:
   - A study to assess the efficacy of topical mitomycin C as an alternative adjunctive therapy to CO_2 laser ablation resulted in 3 of 10 affected eyes. Two of these were re-treated successfully.[33] The intraoperative application of 0.4 mg/mL mitomycin C for 5 min achieved a success rate of 86%
   - Localized corneal oedema was noted in 2 of 10 cases; however, this resolved over several days. No other side-effects were noted
   - Topical application of 0.2 mL of 0.04% mitomycin C every 6 h for a course of 7 days, either as sole therapy or as adjunct to surgical removal 48 h previously, has been described.[39] The course was repeated at 7-day intervals up to a maximum of 4 courses, or until resolution of the tumour was achieved. Recurrence rates after mitomycin C therapy alone were 25% and 23% when mitomycin C was used following surgery. The week-on/week-off regimen prevents damage to more slowly dividing epithelial cells and limbal stem cells[55]
   - Therapy with topical mitomycin C resulted in a non-recurrence rate comparable with that achieved with CO_2 photoablation.[56] Delaying topical mitomycin C treatment following epithelialization of the surgical site for a mean of 15 days postoperatively did not result in increased recurrence rates relative to treatment in the immediate postoperative period. The suggested ideal course of treatment is two to three 7-day on/off cycles, initiated following epithelialization of the surgical site.



- Mitomycin C has cytotoxic effects; it should be used and handled with caution.
- It should be prepared in a negative-pressure pharmaceutical isolator.
- Protective clothing, including mask, gloves, gown and protective goggles, should be worn at all times.
- Horses should be appropriately restrained.
- There are no specific guidelines on safe handling and disposal of waste following mitomycin C treatment in horses.
- The reader is referred to the ECVIM-CA guidelines on the safe use of cytotoxic drugs available at: http://www.ecvim-ca.org/guidelines (see p. 163).

5. Cryotherapy is frequently used in general practice.[57–59] It can be useful for small lesions and as an adjunct therapy
   - Proper instrumentation and probes are useful to prevent permanent corneal damage[2]
   - A double freeze thaw-freeze cycle is recommended
   - Cryotherapy, as adjunct therapy to surgical excision, has been reported to improve success rates to as high as 97%. However, in one study, 50% of cases treated with adjunct cryotherapy after surgical debulking showed local recurrence and 16.7% developed metastases.[37]
6. Radiofrequency hyperthermia has been used for small lesions with a minimal depth. Treatment consists of applications that deliver tumour temperatures of 50°C for 30 s.[35,37,60]
7. Carbon dioxide laser photoablation has been reported as both the primary and adjunctive therapy following the removal of corneo-limbal SCC in the horse.[49] Application of an unfocussed low-energy beam results in superficial tissue ablation (0.1 mm) and can be used to remove the tumour one cell layer at a time or as an adjunctive therapy[33,61]
   - A granulation tissue response mimicking tumour regrowth following photoablation of corneo-limbal SCC is common. In one report, 30% of cases had a documented occurrence of a mass arising at the keratectomy site that clinically appeared to be tumour regrowth. Repeat biopsy and histopathology can confirm the presence of granulation tissue and, in all cases, resolution of granulation tissue was seen with topical steroid therapy application.
8. A single case of successful treatment of metastatic SCC with oral piroxicam (80 mg orally once daily) has been reported.[62]

Prognosis

The prognosis for conjunctival carcinoma is generally good for lesions <1 cm in diameter and <2 mm deep. The prognosis worsens as the extent and depth of tumour increases, when tumours appear at multiple sites or when recurrence or metastases are detected. Tumour recurrence rates vary from 11.9% to 66.7%, depending on the treatment method.[34,37,46,50,63] A variety of treatment modalities for equine SCC have been reported in case reports and case series with variable success.

Multiple (at least) biannual examinations are recommended for all horses treated for SCC in case of recurrence. Recurrence has been noted to occur from several months to years after the initial therapy.[46]

Untreated SCC shows a tendency for local invasion of the soft tissues, the bony rim of the orbit, sinuses, brain and metastases to regional lymph nodes, salivary glands and thorax.[8,12,38] Involvement of local lymph nodes is a poor prognostic sign, then lateral, then medial retropharyngeal lymph nodes.

Metastasis is more likely from lesions of the eyelids and nictitating membrane than those of the limbus and cornea. Rates for metastasis reportedly range from 0 to 18.6%.[8,27,37,38,50,63] However, the likelihood of metastasis is significantly higher when diagnosis is made late in the course of disease. Orbital SCC usually originates from extension of ocular or adnexal carcinoma and is then more likely to have associated metastases (see Fig. 29.13 and p. 497).[2]

Delayed local extension or local metastasis in horses after ocular SCC without recurrence in the eye itself has recently been reported. Metastases may become clinically obvious between 1 and 3.5 years after initial treatment. In some cases invasion of blood or lymphatic vessels by neoplastic cells can be identified in the excisional biopsies of the primary tumour. It is therefore important to monitor cases following treatment of ocular carcinoma for at least 5 years, even in the absence of obvious local recurrence.[2] In one large retrospective study of ocular SCC, a main key to long-term success of the management of this disease was found to be the owner's willingness to return horses for re-examination.[34]

Melanoma (conjunctival and ocular)

See also page 239.

Overview

Melanoma is a very common tumour of grey horses and can sometimes affect horses other colours, including cremello and darker-skinned horses (pp. 570 and 573).[64,65] It occurs with some frequency in the eyelids, more rarely in the conjunctiva and caruncular tissues, and even less commonly in the eye itself, either as a episcleral mass or within the iris/ciliary body.[66]

Typically, the range of malignancy and the rate of growth and pathological progression are very variable but there are some highly malignant conjunctival masses.[67]

Intraocular melanoma appears to be a very benign state, but it can cause secondary pathology, including contact deep keratopathy (oedema as a result of endothelial contact), uveitis (as a component of tumour necrosis), functional compromise of the iris and lens position and blindness as a result of a space-occupying mass (Table 34.2).

Disease summary

Notes

Rare but significant tumour mainly affecting grey (or cream) horses within the conjunctiva (caruncular) and episcleral structures and within the eye associated with the iris or the ciliary body. Low malignancy but space-occupying compromises can occur. Younger grey or cremello horses are more commonly affected.

Clinical features

Dark invariably black (but occasionally pink or cream) tumours with well-defined margins – possibly causing local tissue distortion. Seldom clinically significant until late stages occur.

Diagnostic confirmation

Clinical and ultrasonographic features are usually typical and easily recognized.

Management

Advanced surgical options can be considered but usually they are best left alone. Enucleation is indicated for ocular melanoma having significant clinical implication.

Prognosis

The prognosis is reasonably good in the short term, since most are slow growing and usually benign or at least non-metastatic and non-invasive beyond the eye.

Secondary melanoma in the conjunctiva or within the eye is not reported but is a possible outcome of metastatic tumours.

Clinical features

- The clinical signs of melanoma are quite distinctive but can be masked by overlying conjunctiva (Fig. 34.3A), or they may occur in sites where examination is not easy (Fig. 34.3B).
- Highly malignant tumours will usually have a prominent blood supply and an ill-defined margin that may significantly complicate surgical removal.
- Intraocular melanoma is rarely detected, although it is fairly common in some forms.
- Signs are usually not obvious until the tumour impacts the corneal endothelium, when corneal opacity over the impact area (and possibly longer-term keratopathy with some pigmentation) does occur (Fig. 34.4D).[79]
- The presence of melanoma originating from the iris epithelium is more obvious in cremello or wall-eyed horses and can be bilateral (Figs 34.4B,C).
- They are slow growing and tend to have no overt pathological consequences in most cases.
- Melanoma arising from the ciliary body or the episcleral tissues tends to cause eyeball distortion and possibly lens displacement (Fig. 34.4A).
- Some melanoma tumours are not darkly pigmented.
- Blindness can follow if the tumour extends into the posterior segment or obliterates the anterior segment.
- Orbital melanoma results in exophthalmos.

Differential diagnoses

- Hyperplastic granulae iridicae
- Iris cyst
- Melanotic naevus.

Table 34.2 Clinical details of reported intraocular melanomas in horses

Ref. No.	Age (years)	Sex	Breed	Colour	Site	Description	Management/Prognosis
68	16	F	–	–	Choroid	Tumour pierced cornea and invaded brain	–
69	–	–	–	–	Iris	–	–
70	–	–	–	–	Iris	–	–
71	8	–	–	–	Ciliary body	Spindle cell sarcoma with many pigmented cells	–
72	9	F	–	Grey	–	'Sarcoma melanique' primary in left eye	–
73	–	–	Polo pony	–	Choroid	'Melanosarcoma'	–
19	–	–	–	–	–	Intraocular melanoma	–
74	2	F	–	Brown, mottled grey	–	Primary melanoma invading anterior chamber and extraorbital muscles	Enucleation; no recurrence at 12 months
75	7	G	QH	Grey	Ciliary body	Primary malignant intraocular melanoma	Exenteration; no recurrence at 6 months
76	7	G	TB-X Appaloosa	Grey	Iris	Benign melanoma	Sector iridectomy
77	7	S	Arab	Grey	Ciliary body	Primary malignant melanoma	
23	7	G	Part TB	Grey	Iris	Primary melanomas, bilateral arising simultaneously	Euthanasia; PM no other melanoma
20	11	F	Part Arab	Grey	Iris	Melanoma from anterior surface iris	–
	14	F	Connemara-X	Grey	Iris	Melanoma from anterior surface iris	–
	13	G	Welsh-X	Grey	Iris	Melanoma affecting upper iris	–
	7	G	Pony	Grey	Iris	Amelanotic melanoma	–
	6	F	Hack	Blue Roan	Iris	Melanoma	–
	16	M	Hack	Palomino	Iris	Melanoma	–
78	7	G	Mustang	Grey	Iris	Melanocytoma	Sector iridectomy; no recurrence at 15 months

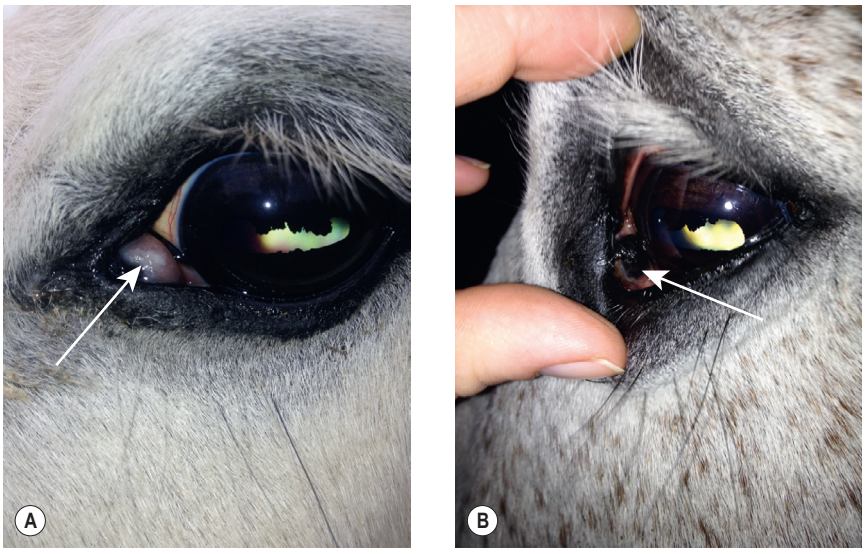


Figure 34.3 Conjunctival melanoma. **(A)** A darkly coloured mass developed in the medial canthal conjunctiva of this 4-year-old grey gelding. A diagnosis of benign melanoma was made after surgical removal of the mess. **(B)** Not all melanoma masses are obvious and it is important to examine horses thoroughly. This malignant conjunctival melanoma was only noticed incidentally. It was removed with a safe margin and was found to be malignant. *(Figure B courtesy of Pauline Gaven.)*

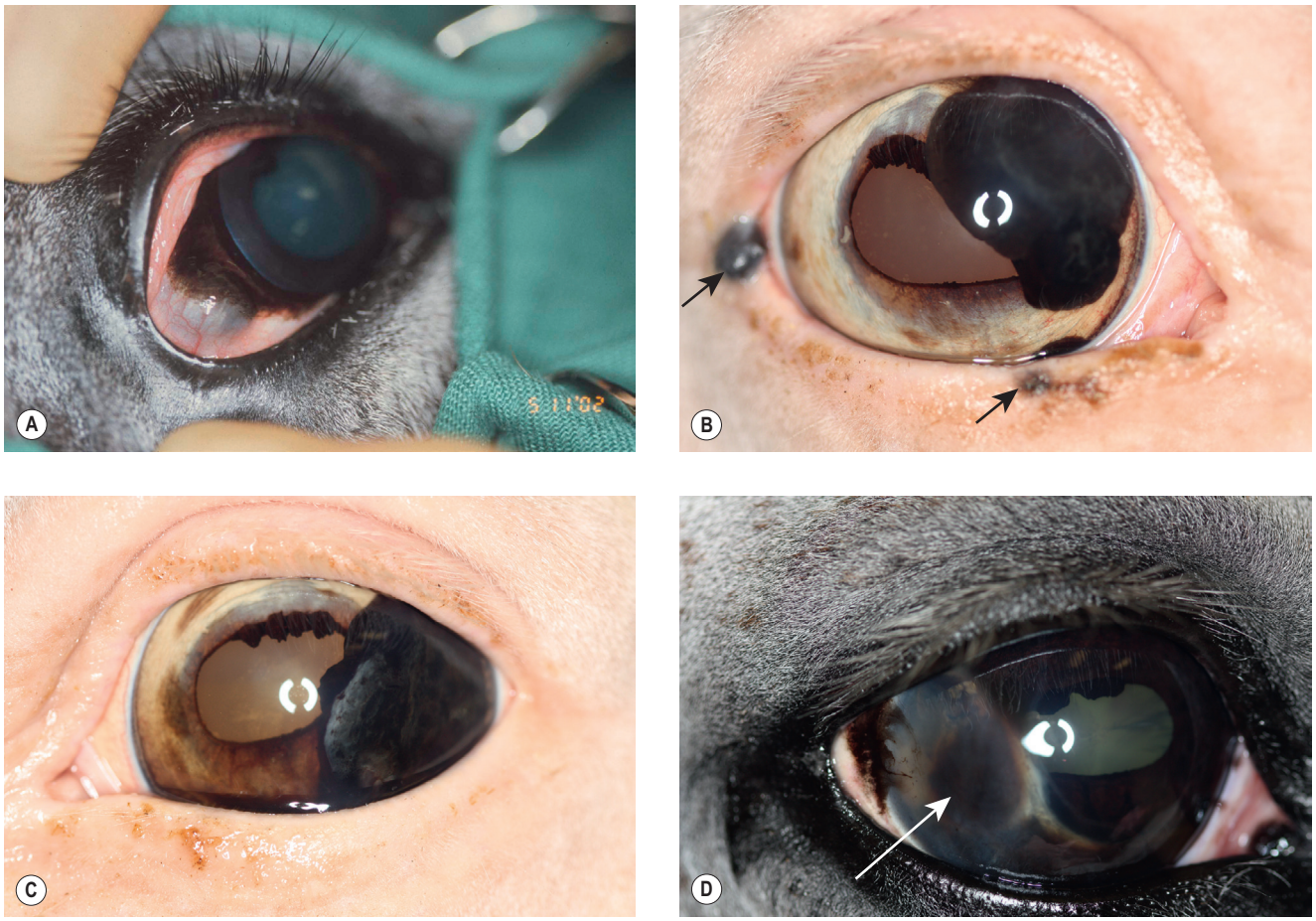


Figure 34.4 Ocular melanoma. (A) This episcleral melanoma was identified incidentally in a pony. It progressed slowly over 2 years and the eye was removed when the pony developed an intraocular haemorrhage and pain. **(B,C)** Bilateral iridal melanomas in a cremello mare. The masses caused no obvious pathology and remained static. Notice the palpebral melanomas also (arrows). **(D)** An iridal melanoma developed in this 14-year-old grey mare. It progressed over 5 years without clinical signs and then caused a contact keratopathy – notice the degenerative pigmented and fibrosing changes in the cornea (arrow) that result from chronic corneal compromise. *(Figure A courtesy of Andrew Melling.)*

Diagnostic confirmation

- Ultrasonographic features are distinctive and can be used to identify the extent and nature of the tumour. The ultrasonographic appearance of melanoma is easily recognized.
- Biopsy is feasible in most sites – fine-needle aspiration is usually enough to confirm the diagnosis but larger biopsies can bleed a great deal!

Management

- Surgical removal of conjunctival melanomas is entirely feasible and should probably be undertaken as early as possible. Adjunctive chemotherapy may help, e.g. carboplatin.[64]
- Sector iridectomy is described for removal of iris melanoma.
- Surgical neodymium:yttrium–aluminium–garnet (Nd:YAG) laser ablation treatment is also described.[80]
- Removal of episcleral and ciliary melanoma is extremely difficult.
- Medical therapy with cimetidine (see p. 146) has no material benefit but can be attempted in case of a responding tumour. There are no reports of intraocular tumour reduction from this approach. Vaccine technology may become significant in due course.
- Most advanced cases or those with symptoms, associated with the tumour, are subject to enucleation.

Prognosis

The prognosis is generally good in the short term for early tumours but almost all cases are progressive and will ultimately start to cause some clinical signs and/or some functional problem.

Lymphoma (orbital, conjunctival and corneal)

See also page 352.

Overview

Ocular structures are rarely the primary or exclusive site of lymphoma, with limited reports of ophthalmic or orbital involvement. More often, ocular lymphoma is the first indication of multicentric or more disseminated peripheral disease.[81,82]

Horses of all ages can be affected, but younger or young-mature horses are most often presented.

Ocular lymphoma usually involves the adnexa, but may also occur in the conjunctiva, uvea, cornea/sclera or as a retrobulbar mass. Infiltration of the eyelids and the conjunctival structures (including the nictitans) are the commonest forms affecting the eyes and the immediate surrounding tissues. Orbital forms are encountered but are usually part of a wider multicentric issue.[83,84] In one study, 27% of horses diagnosed with multicentric lymphoma also had ocular lesions.[84] Of all equine third eyelid neoplasms, 5% are diagnosed as lymphoma.[2]

Equine conjunctival, corneo-scleral and third eyelid lymphoma appear to present in two forms: diffuse and nodular.

- The diffuse form takes on the appearance of severe conjunctivitis. Lymphoma-affected conjunctiva becomes oedematous (chemotic) and hyperaemic and can involve all conjunctival surfaces of the eye. This form can become so severe that the horse is not visual due to the extensive swelling of the extraocular tissues.
- The nodular form has a unique and characteristic appearance. The nodules start small and progress, possibly involving multiple nodules that are usually pink, smooth to semi-smooth and well vascularized.
- Corneo-scleral/limbal lymphoma is very rare and may affect one or both eyes; it is seldom a primary state.

Immunohistology suggests that most ophthalmic forms are T-cell-rich B-cell lymphoma; T-cell lymphoma is less common.[85]

Disease summary

Notes

Rare but important conjunctival and corneal tumour. Can be primary lesions (single or few well-defined masses) or part of generalized lymphoma stages.

Clinical features

Most primary lesions are very focal and firm. They can be multiple.

Diagnostic confirmation

Clinical features are usually typical and easily recognized. Biopsy (usually excisional for conjunctival forms) is essential.

Management

A variety of surgical and chemotherapeutic options are available. Some are highly effective and others are less so in individual animals.

Prognosis

The prognosis is variable and depends on the specific form and cell type of the tumour. Corneal forms are usually devastating.

Clinical features

See also Figure 34.5.

- Conjunctival swelling, hyperaemia and, occasionally, palpable/visible nodules in the conjunctiva or the eyelid margin are the commonest presentation. Ocular pain or discharge is not common unless there is a concurrent exposure keratitis.
- Corneo-scleral/corneo-limbal forms are more often located in the temporal or infero-temporal regions. The

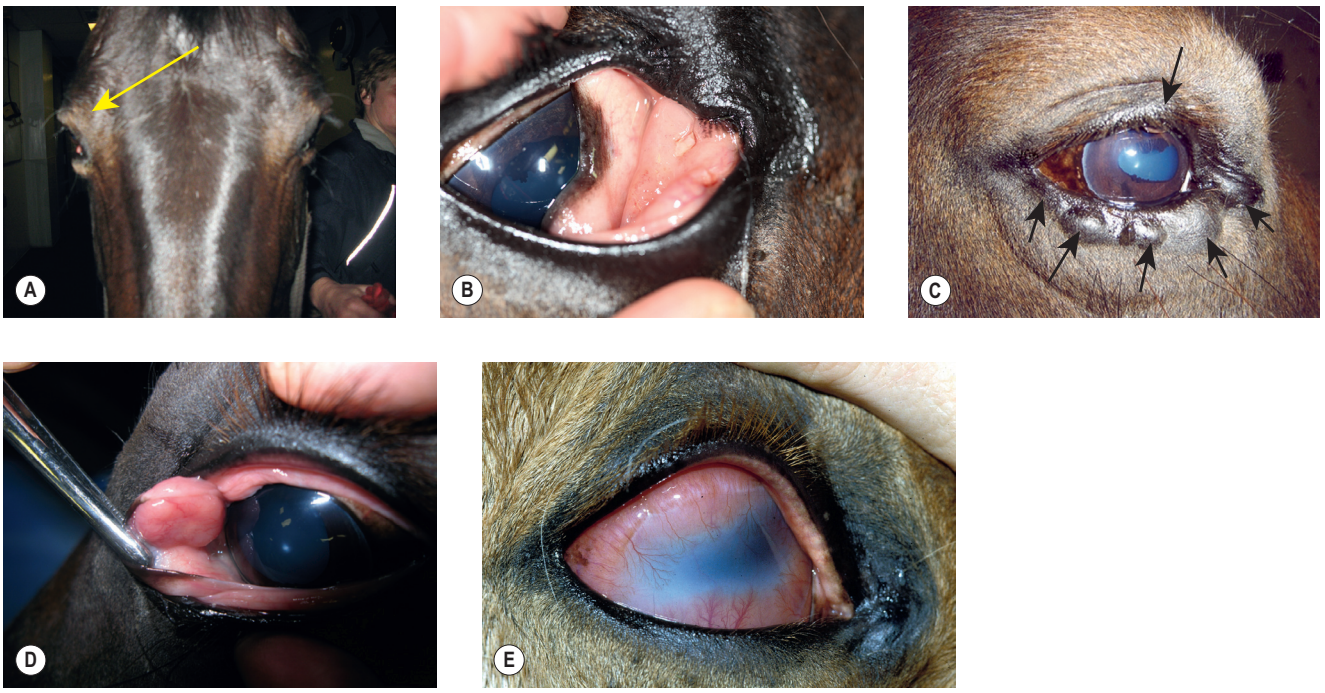


Figure 34.5 Conjunctival, orbital and ocular lymphoma. (A) This horse was presented with a unilateral (right) exophthalmos (arrow) but had bilateral orbital and conjunctival lymphoma. The right globe could not be repulsed normally. **(B)** In both eyes, the major lesions were in the inferonasal quadrant of the orbit and displaced the nictitans obviously. The horse had multicentric lymphoma (see p. 352). **(C)** Multiple focal conjunctival/eyelid lymphoma masses in the lower and upper (arrow) eyelids. **(D)** A slight distortion in the medial canthus was noticed by an observant owner and, when this was explored, focal lymphoma nodules were identified. Five such nodules were identified and removed. No further problem developed over at least 6 years. **(E)** Corneal lymphoma presented as part of a multicentric lymphoma. *(Figure E courtesy of David Wilkie.)*

infiltration crosses the limbus as an ill-defined, raised, white-yellow, vascularized mass. Pain is not a feature, but this is more often part of a multicentric disease.
- Orbital forms may be unilateral or bilateral but inevitably cause exophthalmos and supraorbital filling. Where the eye is significantly exophthalmic, there may be concurrent exposure keratitis and interference of drainage into the nasolacrimal duct with consequent epiphora. Blindness as a result of optic nerve distraction and/or strabismus can be present as a direct effect on the nerves.
- Intraocular lymphoma may present as uveal inflammation that may be unilateral or bilateral. In a case series of 21 horses with ocular lesions of lymphoma, four cases had evidence of uveitis. The clinical course is therefore one of uveitis that responds poorly or incompletely to appropriate anti-inflammatory and cycloplegic therapy.[84]

Differential diagnoses

- Squamous cell carcinoma
- Mast cell tumour
- Orbital fat pad prolapse
- Conjunctival pseudotumour
- Granuloma
- Eosinophilic keratitis
- Iris staphyloma.

Diagnostic confirmation

- Biopsy is definitive.
- Ultrasonography is indicated in all suspected orbital and conjunctival tumours.

Management

- Surgical removal of focal lesions is feasible but, since many cases are part of a wider multicentric problem, this is often not helpful overall apart from a palliative measure where there are direct and uncomfortable/painful consequences.
- Chemotherapy is feasible in some cases (see p. 129).

Prognosis

Overall, the outlook for lymphoma is poor – usually this is because of late presentation or delayed diagnosis. A high proportion of lymphoma cases that involve the eyelids, conjunctiva and intraocular disease end fatally.[84]

The nodular conjunctival form may have an overall better prognosis than the diffuse form; this may relate to its suitability for complete excision. The two forms also differ histologically, with the diffuse form of extraocular lymphoma being more malignant in nature than the nodular form.[86] Of 26 horses diagnosed with extraocular lymphoma, 14 survived longer than 1 year post-diagnosis and remained tumour-free for a mean of 3.7±2.6 years.[86]

Lymphoma confined solely to the third eyelid, cornea, sclera and conjunctiva has a fair to good prognosis with complete excision of the affected tissue.[86] However, it is obviously imperative that multicentric lymphoma is ruled out first.

The prognosis for orbital lymphoma is more dependent on the prognosis of the underlying multicentric disease but, in any case, is usually grave.

Haemangiosarcoma

See also pages 334 and 514.

Disease summary

Notes

Benign or aggressive/malignant tumour of blood vessels. Occurs in conjunctival or, more rarely, the cornea of middle-aged horses.

Clinical features

Highly vascular (often haemorrhagic) focal or diffuse masses with a prominent chaotic blood supply in the surrounding conjunctiva. Liable to heavy bleeding if traumatized. Serosanguineous ocular discharge is usually the earliest sign.

Diagnostic confirmation

Diagnosis is based on clinical appearance and biopsy.

Management

Early/benign forms can be removed surgically but most cases require exenteration.

Prognosis

Prognosis is generally very poor due to high malignancy rate.

Overview

Both the benign and malignant types of haemangioma/haemangiosarcoma are reported in the conjunctiva and cornea. Middle-aged/mature horses are more often affected, but any breed and sex can be involved.[87–89]

The pathological nature of these tumours has been described.[90]

Clinical features

(Fig. 34.6)

- Variable presentation, ranging from enlarged, chaotic limbal blood vessels, to focal haemorrhagic masses with a fleshy highly fragile vasculature.
- Lacrimal haemorrhage is common.
- Corneal and corneo-conjunctival tumours may be very invasive into the corneal stroma.

Differential diagnoses

- Traumatic injury
- Habronemiasis
- Chronic conjunctivitis
- Squamous cell carcinoma
- Conjunctival lymphoma.

Diagnostic confirmation

Biopsy is obligatory and the characteristics of the tumour have been described.[90]

Management

- Surgical removal of all affected tissue might be feasible, but presentation is usually late and most have a malignant nature.



Figure 34.6 Ocular and conjunctival (haem)angiosarcoma. (A) This 12-year-old gelding presented with a 'swollen eye' attributed to a traumatic event; a detailed examination revealed an extensive angiosarcoma in the lower conjunctiva. **(B)** This 14-year-old grey mare presented with a 4-month history of haemo-lacrimation and progressive swelling of the lower lid. An extensive haemangiosarcoma was present (arrow). **(C)** An extensive corneo-limbal haemangiosarcoma affecting the eye of a 9-year-old Thoroughbred mare. This was histologically highly malignant.

- Successful treatment using a combination of surgical tumour reduction and adjunctive beta irradiation and, possibly, cryosurgery has been reported.[88,91]
- Early enucleation/exenteration is required in most cases of corneo-limbal haemangiosarcoma. Delays are likely to be disastrous.

Prognosis

The prognosis will depend heavily on the nature of the tumour and its extent.[87] The outlook is reasonable for focal, early lesions that are accessible, but treatment has to be aggressive. Where the tumour is part of a disseminated haemangiosarcoma, the outlook is hopeless.

Conjunctival mast cell tumour

See also pages 357 and 564.

Disease summary

Notes

Rare but important eyelid, conjunctival and corneal tumour. Generally, very benign and localized but can become larger and more aggressive.

Clinical features

Most primary lesions are very focal and firm. They can be multiple. Easily mistaken for collagen granuloma, lymphoma and gland impaction/cysts.

Diagnostic confirmation

Clinical features are usually typical and easily recognized. Biopsy (usually excisional for conjunctival forms) is essential.

Management

Surgical excision is the best approach.

Prognosis

The prognosis is generally good.

Overview

Mast cell tumours of the eyelids, conjunctiva and cornea are very rare but important tumours that affect horses of all ages from young to old.[92,93] Most are benign and slow growing.

Palpebral and periorbital skin are probably commoner than ocular and conjunctival forms.

Many of the tumours actually lie somewhere between a genuine tumour (termed 'mast cell tumour') and a reactive accumulation of mast cells and eosinophils (termed 'mastocytosis').

Clinical features

See Figure 34.7.

- Non-painful greyish white mass – often ill-defined but some are more definite. The surface may be rough or smooth.
- Ocular discharge is usually minimal.
- Palpebral forms are usually firm nodules within the eyelid (see p. 564).

Differential diagnoses

- Lymphoma
- Melanoma
- Squamous papilloma/carcinoma
- Eosinophilic keratitis
- Granulation tissue
- Parasitic granuloma/habronemiasis
- Prolapse of the orbital fat pad.

Diagnostic confirmation

The diagnosis is relatively easy when the 'kunkers' are visible but biopsy is essential. The biopsy can be confused easily with eosinophilic granuloma, since mast cells attract eosinophils and vice versa.

Management

- Surgical removal is the best approach (Fig. 7.3, p. 89).[59,92–94]
- Chemotherapy or radiation (strontium plesiotherapy) can be useful adjunctive measures.
- Intralesional corticosteroids can also be useful.

Prognosis

The prognosis is good in most cases, although some do recur and require second or subsequent procedures.

Medulloepithelioma/retinoblastoma

See also page 372.

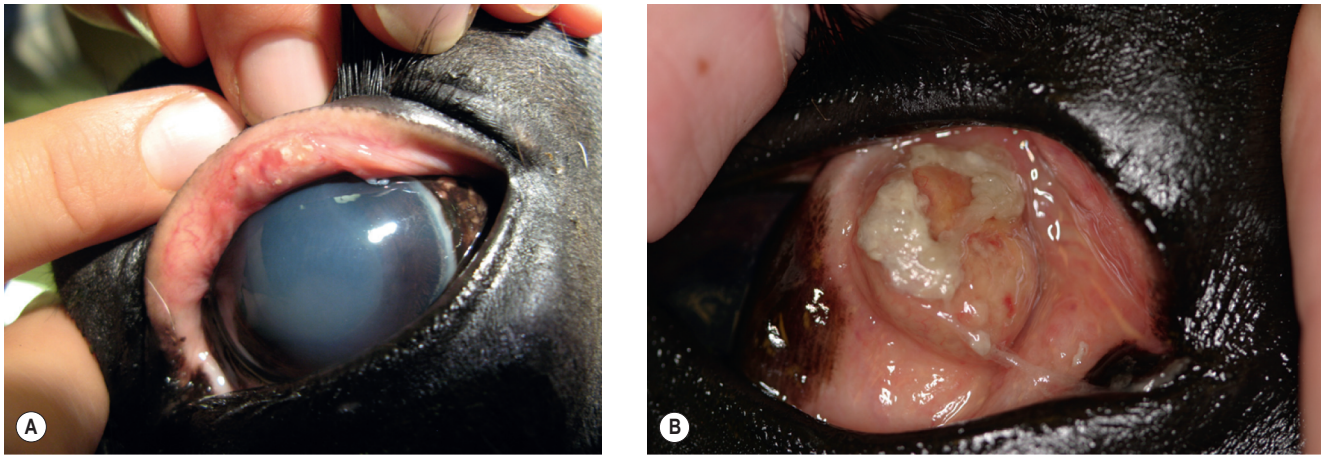


Figure 34.7 Mast cell tumour. (A) A diffuse conjunctival mast cell tumour under the upper eyelid. Notice the characteristic firm, gritty 'kunkers' that have caused corneal abrasion and ulceration. **(B)** A nodular conjunctival mast cell tumour on the outer aspect of the nictitans. The tumour was removed without removal of the nictitans itself without complication (see page 89 Fig. 7.3).

Disease summary

Notes

Extremely rare intraocular tumour deriving from the ciliary body.

Clinical features

Most primary lesions are very focal and firm. They can be multiple. Clinical features are usually typical and easily recognized.

Diagnostic confirmation

Biopsy (usually excisional for conjunctival forms) is essential.

Management

A variety of surgical and chemotherapeutic options are available. Some are highly effective and others are less so in individual animals.

Prognosis

The prognosis is variable, depending on the specific form and cell type of the tumour. Corneal forms are usually devastating.

Overview

The true nature of primitive neuroectodermal primary intraocular tumour (retinoblastoma) in animals is controversial (see p. 115, Fig. 8.5 and p. 116, Fig. 8.6). Only one report has been made of a primitive neuroectodermal tumour (PNET) with characteristics of retinoblastoma.[24] The controversy surrounding the existence of retinoblastoma in animals continues because the distinction between medulloepithelioma and retinoblastoma can be very difficult (see p. 115). In the one reported case, immunohistology and electron microscopy satisfied the requirements for a diagnosis of retinoblastoma.

Retinoblastoma is conventionally restricted to younger (often neonatal) animals. However, it be may be that the few previously described cases of medulloepithelioma were indeed retinoblastoma, as the diagnosis relies upon immunohistochemistry and electron microscopy. It may be that retinoblastoma can occur later in life in horses or it may simply be a very slow-growing mass.

Medulloepithelioma is a very rare potentially malignant intraocular tumour affecting younger adult horses (Table 34.3).[24,95] In contrast to the same tumour type in other species, which most often affects younger animals, in the horse it may arise in older animals within the ciliary body because its medullary epithelium appears to remain incompletely differentiated for longer than in other sites.[24]

From the few available literature reports, it seems there may be two subtypes of medulloepithelioma in the horse. The first is the more typical mass derived from the ciliary body, which has a more benign nature. Tumours derived from the retina or optic nerve tissue are possibly more aggressive.[14] This is relevant, as without a pre-surgical confirmed diagnosis, it is very difficult for the practitioner to provide an accurate prognosis.

Clinical features

See Figure 34.8.

- Slow-growing, fleshy, vascular mass within the pupil or anterior chamber[24,97]
  - The insidious and largely symptomless nature of the condition may mean that it is presented late or detected incidentally.
- Anterior chamber haemorrhage is likely.
- Secondary changes, including uveitis, pain, corneal oedema/fibrosis and corneal vascularization, may develop. Glaucoma has also been found in affected horses.[101]
- Advanced cases may result in corneal opacification, fibrosis and vascularization with buphthalmos.[102]

Differential diagnoses

- Melanoma (amelanotic)
- Iris cysts.

Diagnostic confirmation

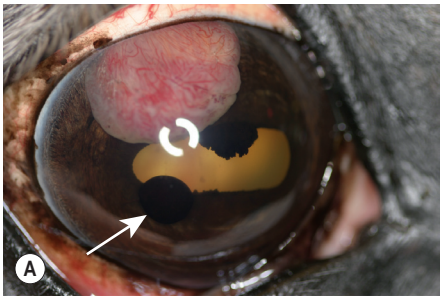
- *Ultrasonography* helps considerably because most cases also extend into the posterior segment.
- *Biopsy* is an attractive option, but these tumours are extremely fragile and liable to severe haemorrhage.

Management

- Exenteration is essential – some tumours are malignant and invasive and early intervention is essential.

Table 34.3 Reported cases of intraocular medulloepithelioma

Ref. No.	Age (years)	Sex	Diagnosis	Location	Management	Follow-up	Recurrence
96	2	M	Malignant non-teratoid medulloepithelioma	Optic nerve	Enucleation	No data	No data
19			Malignant non-teratoid medulloepithelioma	Optic nerve			No data
97	11	M	Non-teratoid medulloepithelioma	Anterior uvea	Enucleation	No data	No data
98	1.5	F	Malignant non-teratoid medulloepithelioma	Optic nerve	Exenteration	No data	No data
14	9	M	Malignant non-teratoid neuroepithelioma	Optic nerve	Enucleation	2 months	Spread into calvarium
99	5	F	Malignant teratoid medulloepithelioma	Ciliary body	Enucleation	2 years	No
95	4	M	Non-teratoid medulloepithelioma	Ciliary body	Exenteration	No data	No data
100	4 months	M	Malignant non-teratoid medulloepithelioma	Optic nerve	Euthanasia	No	–
95	3	F	Medulloepithelioma	No data	Enucleation	No data	No data
101	11	F	Benign teratoid medulloepithelioma	Ciliary body	Enucleation	8 years	No



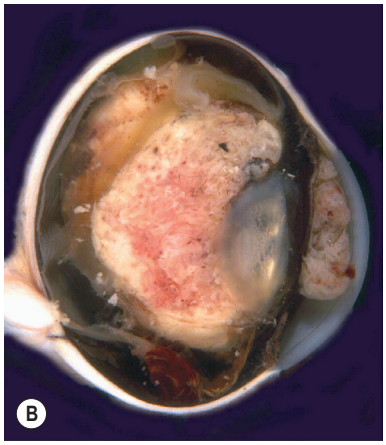


Figure 34.8 Medulloepithelioma/retinoblastoma. (A) A 'typical' medulloepithelioma/retinoblastoma that occurred in a mature grey mare. Notice the lack of fundic clarity but a responsive pupil. Also notice the incidental iris cyst (arrow). **(B)** The tumour bled profusely on induction of anaesthesia. Surgical pathology confirmed the extent of the tumour with massive expansion in the posterior segment. This case remained normal for some months and then a secondary tumour developed in the orbital rim and nasal cavity (see pp. 115 and 116).

- Aggressiveness is related mainly to extraocular extension, but distant metastases to lymph nodes, parotid gland, lungs and mediastinum have also been described.[98]

Prognosis

Because long-term follow-up of horses with medulloepithelioma has not been documented, biological behaviour of these tumours is unknown. Evidence of metastasis has not been reported in the horse, but tumoral extension has been reported in one case.[14]

Astrocytoma and proliferative optic neuropathy

See also page 363.

Overview

This is a very benign, slow-growing tumour of astrocyte nerve cells. Characteristically, it is noted incidentally because it has no known pathological effects. It is very easily mistaken for the relatively commoner proliferative optic neuropathy.

'Proliferative optic neuropathies' is a descriptive term identifying a range of proliferative tumour-like lesions of the optic papilla. Histologically, these comprise extruded glial cells containing lipid-filled cytoplasmic vesicles. In one case, Schwann cell-derived granular cells were described. The cause of the lesions is unknown, but they may represent a reactive glial cell response to a range of insults.[103]

Both astrocytoma and proliferative neuropathy are normally non-progressive, although slow enlargement has been described in older animals.[103]

Disease summary

Notes

Rare, very benign, usually static, retinal tumour. Most often found incidentally. Appearance is very similar to proliferative optic neuropathy.

Clinical features

Usually single grey or cream-coloured exophytic raised mass in the retina or associated with the margin of the optic papilla.

Diagnostic confirmation

Diagnosis is simply by observation. Biopsy is probably impossible and, in any case, is probably contraindicated.

Management

There is no treatment.

Prognosis

The prognosis is generally very good – most remain static and a few expand slowly.

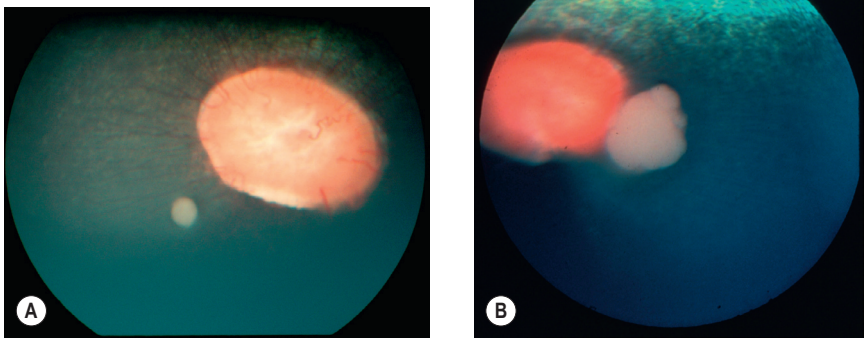


Figure 34.9 Astrocytoma/proliferative optic neuropathy. (A) A focal, static astrocytoma in the non-tapetal fundus. This lesion remained static for many years and was finally diagnosed histologically around 12 years after it had been seen incidentally. **(B)** Proliferative optic neuropathy has a very similar appearance but is usually attached to or associated with the optic papilla.



Figure 34.10 Undifferentiated myxoma of the conjunctiva. (A,B) This 19-year-old Irish cross mare was presented with a history of haemo-lacrimation. Investigation behind the lower eyelid revealed a highly invasive, haemorrhagic tumour that had invaded the orbital rim. A diagnosis of undifferentiated myxoma was made on histology. The tumour extended widely into the adjacent tissues but the horse had been remarkably unconcerned and showed no material clinical consequences.

Clinical features

- Small, grey, raised, rougly circular masses in the retinal or peripapillary regions of the eye
  - Astrocytoma can occur at any site in the retina but is only obvious in the non-tapetal fundus (Fig. 34.9A).
- A unilateral incidental finding with no apparent effect on vision.
- No clinical effects are reported.
- Superficial vascularization or haemorrhage may be present. The optic disc is otherwise normal.
- Focal proliferative optic neuropathy is an incidental almost indistinguishable tumour-like condition.
- Generalized proliferative optic neuropathy involves the entire disc surface and blindness in the affected eye. It typically follows orbital trauma or acute massive systemic haemorrhage. The affected disc shows whitish, raised, nodular masses across the surface, and in some cases, a generalized retinopathy may be present (Fig. 34.9B).[103]

Diagnostic confirmation

Direct examination using a direct or indirect ophthalmoscope.

Management

No treatment is either required or justified.

Prognosis

The prognosis is good for both conditions. A few cases of proliferative optic neuropathy are more generalized and can then be associated with visual compromises.

Other corneal, conjunctival and ocular tumours

Overview

Other tumours that have been reported to occur in conjunctiva and the globe of horses include:

- Basal cell tumour of the third eyelid.[34,104]
- Neurofibrosarcoma.[34,105]
- Corneal sarcoma resembling a malignant peripheral nerve sheath tumour.[106]
- Papilloma.[8,32]
- Sebaceous adenocarcinoma of the third eyelid.[107]
- Lacrimal gland adenocarcinoma of the third eyelid[108]
  - Clinical presentation of a large, fleshy, pink-red, ulcerated mass involving the entire third eyelid, present for approximately 3 weeks, consistent with SCC
  - Ocular ultrasound revealed the mass extended into the ventral orbit

- Treatment by exenteration; diagnosis was confirmed by histopathology
- No recurrence or metastasis at 12 months' post-surgery
- Some may be locally and systemically malignant.

- Solid carcinoma of the third eyelid.[109]
- Lipoma of the third eyelid.[31]
- Undifferentiated myxoma (Fig. 34.10).

References

1. Basher AW, Severin GA, Chavkin MJ, et al. Orbital neuroendocrine tumors in three horses. J Am Vet Med Assoc 1997; 210:668–671.
2. Rebhun WC. Tumours of the eye and ocular adnexal tissues. Vet Clin North Am Equine Pract 1998; 14:579–606.
3. Miesner T, Wilkie D, Gemensky-Metzler A, et al. Extra-adrenal paraganglioma of the equine orbit: six cases. Vet Ophthalmol 2009; 12: 263–268.
4. Goodhead AD, Venter IJ, Nesbit JW. Retrobulbar extra-adrenal paraganglioma in a horse and its surgical removal by orbitotomy. Vet Comp Ophthalmol 1997; 7:96–100.
5. Hong CB, Van Meter PW, Latimer CL. Malignant rhabdoid tumour in the orbit of a horse. J Comp Pathol 1999; 121:197–201.
6. Colitz CMH, Gilger BC, Davidson MG. Orbital fibroma in a horse. Vet Ophthalmol 2000; 3:213–216.
7. Sweeney CR, Beech J. Retrobulbar melanoma in a horse. Equine Vet J 1983; 15:123–124.
8. Lavach JD, Severin GA. Neoplasia of the equine eye, adnexa and orbit: a review of 68 cases. J Am Vet Med Assoc 1977; 170:202–203.
9. Hill FW, Moulton JE, Schiff PH. Exophthalmos in a horse resulting from an adenocarcinoma of the frontal sinus. J S Afr Vet Assoc 1989; 60: 104–105.
10. van Maanen C, Klein WR, Dik KJ, et al. Three cases of carcinoid in the equine nasal cavity and maxillary sinuses: histologic and immunohistochemical features. Vet Pathol 1996; 33:92–95.
11. Davis JL, Gilger BC, Spaulding K, et al. Nasal adenocarcinoma with diffuse metastases involving the orbit, cerebrum, and multiple cranial nerves in a horse. J Am Vet Med Assoc 2002; 221:1460–1463.
12. Eversole TG, Lavach JD. Primary ocular squamous cell carcinoma with metastasis in a horse. Vet Med Small Anim Clin 1978; 73:287–290.
13. Richardson DW, Acland HM. Multilobular osteoma (chondroma rodens) in a horse. J Am Vet Med Assoc 1983; 182:289–291.
14. Bistner S, Campbell RJ, Shaw D, et al. Neuroepithelial tumour of the optic nerve in a horse. Cornell Vet 1983; 73:30–40.
15. Freestone JF, Glaze MB, Pechman R, et al. Ultrasonic identification of an orbital tumour in a horse. Equine Vet J 1989; 21:135–136.
16. Koch DB, Leitch M, Beech J. Orbital surgery in two horses. Vet Surg 1980; 9:61–65.
17. Muñoz E, Leiva M, Naranjo C, et al. Retrobulbar dermoid cyst in a horse: a case report. Vet Ophthalmol 2007; 10:394–397.
18. Matiasek K, Cronau M, Schmahl W, et al. Imaging features and decision making in retrobulbar neuroendocrine tumours in horses – case report and review of literature. J Vet Med A Physiol Pathol Clin Med 2007; 54: 302–306.
19. Blodi FC, Ramsey FK. Ocular tumours in domestic animals. Am J Ophthalmol 1967; 64:627–633.
20. Barnett KC, Platt H. Intraocular melanomata in the horse. Equine Vet J Suppl 1990; 10:76–82.
21. Davidson HJ, Blanchard GL, Wheeler CA, et al. Anterior uveal melanoma, with secondary keratitis, cataract, and glaucoma, in a horse. J Am Vet Med Assoc 1991; 199:1049–1050.
22. Brooks DE, Matthews AG. Equine ophthalmology. In: Gelatt KN, ed. Veterinary ophthalmology, Vol. 2, 4th edn. Ames: Blackwell; 2007: 1165–1274.
23. Matthews AG, Barry DR. Bilateral melanoma of the iris in a horse. Equine Vet J 1987; 19:358–360.
24. Knottenbelt DC, Hetzel U, Roberts V. Primary intraocular primitive neuroectodermal tumour causing unilateral blindness in a gelding. Vet Ophthalmol 2007; 10:348–359.
25. Barnett KC, Crispin SM, Lavach JD, et al. Equine ophthalmology, 2nd edn. London: WB Saunders; 2004: 197–198.
26. Baptiste KE, Grahn BH. Equine orbital neoplasia: A review of 10 cases. Can Vet J 2000; 41:291–295.
27. Runnells RA, Benbrook EA. Epithelial tumours of horses. Am J Vet Res 1942; 3:176–179.
28. Koch SA, Cowles RRJ. Surgical removal of squamous cell carcinoma of the equine eye. Vet Med Small Anim Clin 1971; 66:327–329.
29. Strafuss A. Squamous cell carcinomas in horses. J Am Vet Med Assoc 1976; 168:61–62.
30. Cotchin E. A general survey of tumours in the horse. Equine Vet J 1977; 9:16–21.
31. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
32. Junge RE, Sundberg JP, Lancaster WD. Papillomas and squamous cell carcinomas of horses. J Am Vet Med Assoc 1984; 185:656–659.
33. Rayner SG, van Zyl N. The use of mitomycin C as an adjunctive treatment for equine ocular squamous cell carcinoma. Aust Vet J 2006; 84:43–46.
34. Dugan SJ. Ocular neoplasia. Vet Clin North Am Equine Pract 1992; 8: 609–626.
35. Dugan SJ, Roberts SM, Curtis CR, et al. Prognostic factors and survival of horses with ocular/adnexal squamous cell carcinoma: 147 cases (1978–1988). J Am Vet Med Assoc 1991; 198:298–303.
36. Dugan SJ, Curtis CR, Roberts SM, et al. Epidemiologic study of ocular/adnexal squamous cell carcinoma in horses. J Am Vet Med Assoc 1991; 198:251–256.
37. King TC, Priehs DR, Gum GG, et al. Therapeutic management of ocular squamous cell carcinoma in the horse: 43 cases (1979–1989). Equine Vet J 1991; 23:449–452.
38. Gelatt KN, Myers VSJ, Perman V, et al. Conjunctival squamous cell carcinoma in the horse. J Am Vet Med Assoc 1974; 165:617–620.
39. Malalana F, Knottenbelt DC, McKane SA. Mitomycin C, with or without surgery, for the treatment of ocular squamous cell carcinoma in horses. Vet Rec 2010; 167:373–376.
40. Sironi G, Riccaboni P, Mertel L, et al. p53 protein expression in conjunctival squamous cell carcinomas of domestic animals. Vet Ophthalmol 1999; 2:227–231.
41. Moore CP, Grevan VL, Champagne ES, et al. Equine conjunctival pseudotumours. Vet Ophthalmol 2000; 3:57–63.
42. Stoppini R, Gilger BC, Malarkey DE, et al. Bilateral nodular lymphocytic conjunctivitis in a horse. Vet Ophthalmol 2005; 8:129–134.
43. Gelatt KN. Corneolimbal squamous cell carcinoma in a horse. Vet Med Small Anim Clin 1975; 70:53.
44. Rebhun WC. Treatment of advanced squamous cell carcinomas involving the equine cornea. Vet Surg 1990; 19:297–302.
45. Ollivier FJ, Kallberg ME, Plummer CE, et al. Amniotic membrane transplantation for corneal surface reconstruction after excision of corneo-limbal squamous cell carcinomas in nine horses. Vet Ophthalmol 2006; 9:404–413.
46. Plummer CE, Smith S, Andrew SE, et al. Combined keratectomy, strontium-90 irradiation and permanent bulbar conjunctival grafts for corneolimbal squamous cell carcinomas in horses (1990–2002): 38 horses. Vet Ophthalmol 2007; 10:37–42.
47. Payne RJ, Lean MS, Greet TRC. Third eyelid resection as a treatment for suspected squamous cell carcinoma in 24 horses. Vet Rec 2009; 165: 740–743.
48. Labelle AL, Metzler AG, Wilkie DA. Nictitating membrane resection in the horse: a comparison of long-term outcomes using local vs. general anaesthesia. Equine Vet J 2011; 40(Suppl):42–45.
49. Michau TM, Davidson MG, Gilger BC. Carbon dioxide laser photoablation adjunctive therapy following superficial lamellar keratectomy and bulbar conjunctivectomy for the treatment of corneo-limbal squamous cell carcinoma in horses: a review of 24 cases. Vet Ophthalmol 2012; 15: 245–253.
50. Mosunic CB, Moore PA, Carmicheal KP, et al. Effects of treatment with and without adjuvant radiation therapy on recurrence of ocular and adnexal squamous cell carcinoma in horses: 157 cases (1985–2002). J Am Vet Med Assoc 2004; 225:1733–1738.
51. Frauenfelder HC, Blevins WE, Page EH. 90Sr for treatment of periocular squamous cell carcinoma in the horse. J Am Vet Med Assoc 1982; 180: 307–309.
52. Wilkie DA, Burt JK. Combined treatment of ocular squamous cell carcinoma in a horse, using radiofrequency hyperthermia and interstitial 198Au implants. J Am Vet Med Assoc 1990; 196:1831–1833.
53. Théon AP, Pascoe JR. Iridium-192 interstitial brachytherapy for equine periocular tumours: treatment results and prognostic factors in 115 horses. Equine Vet J 1995; 27:117–121.
54. Chahory S, Clerc B, Devauchelle P, et al. Treatment of a recurrent ocular squamous cell carcinoma in a horse with iridium-192 implantation. J Equine Vet Sci 2002; 22:503–506.
55. Chen Y-Y, Shen CJ. Preoperative mitomycin-C subconjunctival injection for needling revision of failed filtering blebs. Invest Ophthalmol Vis Sci 2004; 45:925.
56. Clode AB, Miller C, McMullen RJJ, et al. A retrospective comparison of surgical removal and subsequent CO_2 laser ablation versus topical administration of mitomycin C as therapy for equine corneo-limbal squamous cell carcinoma. Vet Ophthalmol 2012; 15:254–262.
57. Hilbert BJ, Farrell RK, Grant BD. Cryotherapy of periocular squamous cell carcinoma in the horse. J Am Vet Med Assoc 1977; 170:1305–1308.
58. Joyce JR. Cryosurgical treatment of tumors of horses and cattle. J Am Vet Med Assoc 1976; 168:226–229.
59. Bosch G, Klein WR. Superficial keratectomy and cryosurgery as therapy for limbal neoplasms in 13 horses. Vet Ophthalmol 2005; 8:241–246.
60. Grier RL, Brewer WGJ, Paul SR, et al. Treatment of bovine and equine ocular squamous cell carcinoma by radiofrequency hyperthermia. J Am Vet Med Assoc 1980; 177:55–61.
61. English RV, Nasisse MP, Davidson MG. Carbon dioxide laser ablation for treatment of limbal squamous cell carcinoma in horses. J Am Vet Med Assoc 1990; 196:439–442.
62. Moore AS, Beam SL, Rassnick KM, et al. Long-term control of mucocutaneous squamous cell carcinoma and metastases in a horse using piroxicam. Equine Vet J 2003; 35:715–718.
63. Schwink K. Factors influencing morbidity and outcome of equine ocular squamous cell carcinoma. Equine Vet J 1987; 19:198–200.
64. Hirst LW, Jabs DA, Stoskopf M, et al. Benign epibulbar melanocytoma in a horse. J Am Vet Med Assoc 1983; 183:333–334.
65. Valentine BA. Equine melanocytic tumours: a retrospective study of 53 horses (1988 to 1991). J Vet Intern Med 1995; 9:291–297.

66. Hamor RE, Ramsey DT, Wiedmeyer CE, et al. Melanoma of the conjunctiva and cornea in a horse. Vet Comp Ophthalmol 1997; 7:52–55.
67. Albanese V, Newton JC, Waguespack RW. Malignant melanoma of the third eyelid in a horse. Equine Vet Educ 2013: doi: 10.1111/eve.12012.
68. Bayer J. Small cell sarcoma of the eye, the caries profunda bones and the base of the skull [German]. Ztschr F verfl Augenh 1887; 5:45–55.
69. Kitt T. Lehrbuch der pathologisch – anatomischen diagnostik fur thierarzte und studierende der thiermedizin 2. Stuttgart: F Enke; 1895: 647.
70. Eberlein. Bericht über die Königliche Tierärztliche Hochschule, Berlin. 1900–1901. Poliklinik f. grossere Hausthiere. Arch Wissench Prakt Tierh 1902; 28:219–228.
71. Houdemer, Guyonnet. Tumeur de la choroïde. Rev Gen de Med Vet 1907; 10:474–476.
72. Darrespen E, Florio R, Meymandi MH. Des modifications humorales dans certaines varieties de tumeurs oculaire, cerebrales et viscerales, chez les equidaes, et les carnivores domestiques. Rev Med Vet Toulouse 1939; 91:65–92.
73. Kelly AJ. Melanosarcoma in the horse. J Royal Army vet Corps 1940; 12:31.
74. Ramadan RO. Primary ocular melanoma in a young horse. Equine Vet J 1975; 7:49–50.
75. Murphy J, Young S. Intraocular melanoma in a horse. Vet Pathol 1979; 16:539–542.
76. Latimer CA, Wyman M. Sector iridectomy in the management of iris melanoma in a horse. Equine Vet J 1983; 2:101–104.
77. Neumann S. Intraocular melanoma in a horse. Mod Vet Pract 1985; 66:559–560.
78. Scotty NC, Barrie KB, Brooks DE, et al. Surgical management of a progressive iris melanocytoma in a Mustang. Vet Ophthalmol 2008; 11:75–80.
79. McMullen RJ, Clode AB, Pandiri AKR, et al. Epibulbar melanoma in a foal. Vet Ophthalmol 2008; 11:44–50.
80. Gilger B. Diseases of the uvea. Equine ophthalmology, 2nd edn. St Louis: Saunders; 2011: 277–279.
81. Germann SE, Richter M, Schwarzwald CC, et al. Ocular and multicentric lymphoma in a young racehorse. Vet Ophthalmol 2008; 11:51–56.
82. Neufeld JL. Lymphosarcoma in the horse: a review. Can Vet J 1973; 14:129–135.
83. Rebhun WC, Bertone, A. Equine lymphosarcoma. J Am Vet Med Assoc 1984; 184:720–721.
84. Rebhun WC, Del Piero F. Ocular lesions in horses with lymphosarcoma: 21 cases (1977–1997). J Am Vet Med Assoc 1998; 212:852–854.
85. Kelley LC, Mahaffey EA. Equine malignant lymphomas: morphologic and immunohistochemical classification. Vet Pathol 1998; 35:241–252.
86. Schnoke AT, Brooks DE, Wilkie DA, et al. Extraocular lymphoma in the horse. Vet Ophthalmol 2013; 16:35–42.
87. Hacker DV, Moore PF, Buyukmihci NC. Ocular angiosarcoma in four horses. J Am Vet Med Assoc 1986; 189:200–203.
88. Bolton JR, Lees MJ, Robinson WF, et al. Ocular neoplasms of vascular origin in the horse. Equine Vet J Suppl 1990; 10:73–75.
89. Crawley GR, Bryan GM, Gogolewski RP. Ocular haemangioma in a horse. Equine Pract 1987; 9:11–14.
90. Moore PA, Hacker D, Buyukmihci N. Ocular angiosarcoma in the horse: morphological and immunohistochemical studies. Vet Pathol 1986; 23: 240–244.
91. Vestre WA, Turner TA, Carlton WW. Conjunctival haemangioma in a horse. J Am Vet Med Assoc 1982; 180:1481–1482.
92. Hum S, Bowers JR. Ocular mastocytosis in a horse. Aust Vet J 1989; 66:32.
93. Martin CL, Leipold HW. Mastocytoma of the globe in a horse. J Am Anim Hosp Assoc 1972; 8:32–34.
94. Ward DA, Lakritz J, Bauer RW. Scleral mastocytosis in a horse. Equine Vet J 1993; 25:79–80.
95. Riis RC, Scherlie PH, Rebhun WC. Intraocular medulloepithelioma in a horse. Equine Vet J Suppl 1990; 10:66–68.
96. Folger AF. To Tilfaelde af retinagliom hos hesten. Den Konelige Veterinaer-og Land Bohojskole. Aarskrift 1919: 257–282.
97. Bistner SI. Medullo-epithelioma of the iris and ciliary body in a horse. Cornell Vet 1974; 64:588–595.
98. Eagle RC, Font KL, Swerczek TW. Malignant medulloepithelioma of the optic nerve in a horse. Vet Pathol 1978; 15:488–494.
99. Szymanski CM. Malignant teratoid medulloepithelioma in a horse. J Am Vet Med Assoc 1987; 190:301–302.
100. Ueda Y, Senba H, Nishimura T, et al. Ocular medulloepithelioma in a Thoroughbred. Equine Vet J 1993; 25:558–561.
101. Leiva M, Felici F, Carvalho A, et al. Benign intraocular teratoid medulloepithelioma causing glaucoma in an 11 year old Arabian mare. Vet Ophthalmol 2013; 16:297–302.
102. Gilger BC. Medulloepithelioma. Equine ophthalmology, 2nd edn. Missouri: Elsevier; 2011: 274.
103. Matthews AG. Fundus. In: Barnett K, Crispin S, Lavach SD, et al., eds. Equine ophthalmology: an atlas & text, 2nd edn. Oxford: Elsevier Ltd; 2004: 244.
104. Baril C. Basal cell tumour of third eyelid in a horse. Can Vet J 1973; 14:66–67.
105. Strubbe DT. Periocular neurofibrosarcoma in a horse. Vet Ophthalmol 2001; 4:237–241.
106. Kappe EC, Köhler K, Felbert IV, et al. Pleomorphic corneal sarcoma resembling malignant peripheral nerve sheath tumour in a horse. Vet Pathol 2009; 46:444–448.
107. Kunze DJ, Schmidt GM, Tvedten HW. Sebaceous adenocarcinoma of the third eyelid of a horse. J Equine Med Surg 1979; 3:452–455.
108. Mathes RL, Carmichael KP, Peroni J, et al. Primary lacrimal gland adenocarcinoma of the third eyelid in a horse. Vet Ophthalmol 2011; 14: 48–54.
109. van der Linde-Sipman JS, van der Gaag I, van der Velden MA. Solid carcinoma of the glandula superficialis palpebrae tertiae in a horse. J Vet Med A 1986; 33:208–211.

35

Tumours of the male and female reproductive systems and mammary gland

Overview
Neoplasms of the male reproductive organs
Penis and prepuce 629
Tumours of the testicle 634
Neoplastic disorders of the tubular genital tract of mares
Overview 638
Ovarian tumours 641
Other tumours affecting the ovary 647
Neoplastic disease of the mammary gland
Overview 647

OVERVIEW

Neoplastic disease of the reproductive tract is conveniently divisible into tumours affecting the male reproductive organs and tumours affecting the female reproductive organs.

Tumours affecting the male reproductive organs

- Prepuce and penis
  - These form the large majority of reproductive organ tumours and a few tumour types are relatively common.
- Accessory glands
  - Primary tumours of the male accessory glands are extremely rare or possibly even non-existent, with no publications relating to them in the horse; only the canine prostate gland has any significant veterinary implication in neoplastic disease.[1]
- Testicle
  - Testicular tumours are very rare, but once the proportion of geldings is taken into account they are best considered to be uncommon rather than rare.
- Scrotum
  - The scrotal skin is subject to the range of skin tumours described above (see p. 544), but sarcoid is by far the most common neoplasm of this region.

Tumours affecting the female reproductive organs

- Vulva, vestibule, vagina and clitoris
  - Tumours of the vulva, vestibule and vagina occur with some frequency, but again they are very limited in type to a few recognized conditions.
- Cervix, uterus and fallopian tube
  - Tumours of the cervix are not reported in horses.
- Ovary
  - The ovary is subject to primary and secondary tumours of several types – each with its own characteristic clinical and pathological nature.
- Mammary gland.

NEOPLASMS OF THE MALE REPRODUCTIVE ORGANS

Penis and prepuce

Overview

Penile and preputial tumours occur with some frequency, but the large majority of these cases are sarcoid, squamous cell carcinoma and, in grey horses, melanoma. There are a few other types that occur very rarely, such as lymphoma and neurofibroma and mast cell tumour.

Clinical features

The penis and prepuce should be examined carefully in detail in the extended position, so that the whole length of the free part of the penis and the preputial reflection can be examined; some tumours are hard to identify in their early stages. The prepuce is examined again following retraction of the penis.

A presumptive diagnosis of neoplasia of the penis and prepuce can usually be made by direct observation and palpation of these structures in their entirety. The scrotum should be evaluated at the same time, because dermatological neoplasia (such as sarcoid) may extend to this structure as well (see p. 545).

No significant tumours are reported to affect the accessory sex glands of the horse.

Diagnostic confirmation

- *Rectal examination* is usually obligatory when there is neoplasia of the penis,

- The prepuce or the surrounding skin is suspected or confirmed because the draining lymph nodes are inguinal and subiliac; several neoplastic conditions can result in local lymph node involvement or secondary inflammatory lymphadenopathy.

Management

Treatment for the various neoplastic lesions will vary depending on the extent, character and location of the tumour. The therapeutic options include:

- Surgical excision
- Cryotherapy/cryonecrosis
- Chemotherapeutic agents (topical and/or systemic)
- Laser resection
- Radiation.

Penile squamous cell carcinoma

See also pages 203 and 575.

Disease summary

Notes

Relatively common potentially malignant tumour affecting geldings more than stallions.

Clinical features

Tumours range from early slow-growing squamous papilloma and squamous dysplasia (leukoplakia) to active, proliferative and or ulcerative/destructive tumours.

Diagnostic confirmation

Clinical and histological features are usually typical and easily recognized.

Management

A variety of surgical and chemotherapeutic options are available. Some are highly effective and others are less so in individual animal.

Prognosis

The prognosis is rather better for late (old age) onset carcinoma than earlier (young age) onset carcinoma.

Description

This is the most common neoplasia of the penis. Smegma (sebaceous secretion of the penile epithelium and epithelial cells shed from the prepuce) is suggested as being the most likely carcinogen, but this is a debatable relevance.[2] Non-pigmented skin surfaces of the prepuce and penis are recognizably more susceptible and are far more commonly presented.

Geldings are far more often affected than stallions, possibly because geldings produce more smegma than do stallions and the penis of geldings is less likely to be cleaned. Where the condition occurs in stallions, it is usually extremely aggressive and very dangerous in every sense.

The severity ranges from a mild (but sometimes extensive) precancerous, mildly ulcerative, dermatitis-like condition to highly aggressive malignant tumours. The condition has a lower malignancy in late-onset (older) horses.

Typically, penile carcinoma follows an almost predictable course from squamous dysplasia and squamous papilloma to a highly destructive, malignant carcinoma. Proliferative tumours produce cauliflower-like lesions; sometimes these are also ulcerated. There may be extensive proliferation over wide areas of the penile skin and the glans. The destructive form results in extensive distortion of the penis/glans.

As a rule, involvement of the preputial rings and surrounding skin is a serious complication and carcinoma can occur here in its own right without any penile involvement. Generally, this form has a higher malignancy rate.

Clinical features

Squamous cell carcinoma is typically found on the penile shaft, urethral orifice, the glans penis or the internal preputial skin.[3] Single or multiple lesions occur and tumours can vary in their clinical behaviour – some can remain very static and localized, whilst others can become highly aggressive (Figs 35.1, 35.2). Although most tumours remain localized, some are rapidly progressive and malignancy is more likely when destructive forms occur in younger horses (<10–12 years of age).

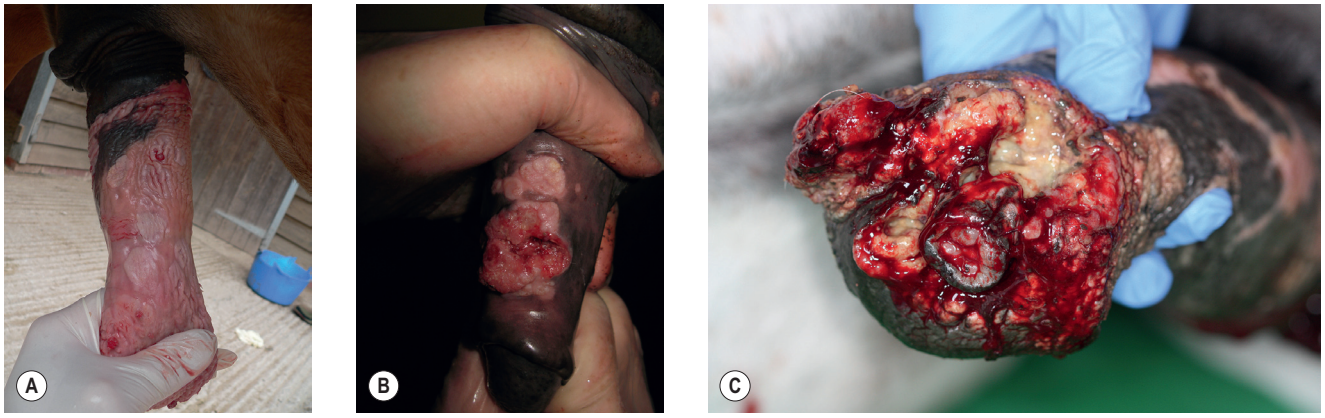


Figure 35.1 Penile carcinoma. **(A)** Typical squamous dysplastic areas showing as pale whitish often circular areas with an adherent surface; the surface may bleed after the sites are cleaned. **(B)** A focal highly destructive and invasive carcinoma of the shaft of the penis – notice that the skin in this case is pigmented – the relationship to non-pigmented skin is not a reason to exclude the diagnosis in pigmented skin. **(C)** A very destructive and highly malignant carcinoma of the glans penis. This 8-year-old horse had secondary tumours in the lungs and other organs.







Figure 35.2 Penile squamous cell carcinoma. (A) This very aggressive penile carcinoma developed in the glans penis of a 15-year-old Thoroughbred breeding stallion. The tumour was particularly aggressive and advanced very quickly over a few weeks. Tumours were found in the inguinal and iliac lymph nodes and myriad small tumour foci were found in the lungs. **(B)** Carcinoma of the sheath and preputial reflection is extremely serious in most cases with a high tendency to malignancy. **(C)** This 13-year-old gelding developed a sheath swelling with ventral edema over a period of 2 months. A small ulcerated focus was recognized in the preputial reflection and, within 2 weeks, a massive carcinoma had developed on the side of the prepuce, necessitating *en bloc* resection.

- Early evidence may be limited to a fetid or haemorrhagic preputial discharge. Blood may be observed in the ejaculate or in the urine.
- Early lesions appear as small, heavily keratinized plaques (<5 mm to 2 cm) (leukoplakia) (see Figs 35.1AB and pp. 221 and 576).
- Pain and swelling may be a feature, resulting in reluctance to prolapse the penis during urination, grunting during urination or pain on palpation.
- The tumour may infiltrate the surrounding tissue and form crusted, ulcerative lesions that bleed freely.
- The lesions may take on a cauliflower-like appearance and have a necrotic centre (see p. 576 and Fig. 31.32).
- This tumour may spread by local infiltration over the entire penis and prepuce if left unchecked. Oedema of the surrounding tissues and ventral oedema anterior to the umbilicus are bad signs.
- The aggressive (often malignant) forms may cause a wooden feel to the shaft of the penis (this is more common in younger horses).
- Secondary metastases in the pelvic organs, lumbar vertebrae and other major organs may cause signs apparently unrelated to the tumour, including hind quarter paralysis.[4]
- Extensively ulcerated tumours usually have a fetid odour, a heavy, haemorrhagic preputial discharge and can become infested with fly maggots.

Differential diagnoses

- Sarcoid (nodular or fibroblastic)
- Adenocarcinoma/adenoma
- Neurofibroma
- Posthitis/traumatic balanoposthitis
- Habronemiasis
- Foreign body reactions.

Diagnostic confirmation

Since the prognosis is highly dependent of the type and pathological behaviour of the tumour, a full investigation of the case is compulsory. This should include:

- Rectal examination
- Full metabolic assessment can be useful
- Thoracic ultrasonography and radiography should be considered in malignant cases
- Biopsy (focal or excisional) and histopathology are definitive.

Management

Depending on the precise location extent, pathological and clinical behaviour, the full range of therapeutic options can be considered including:

- *Surgery* (whether by conventional sharp surgery or laser excision)
- *Cryosurgery*
- *Chemotherapy* (topical and local intralesional methods) (see pp. 129 and 140).

Early treatment of the precancerous stage is based upon removal of all possible carcinogens and ensuring that the penis, penile skin and preputial lining are healthy and clean.

Surgery

Surgical treatment of squamous cell carcinoma includes any of the following alone or in combination:

- Laser excision of focal lesions[5]
- Cryosurgery (with or without concurrent local chemotherapy)
- Radical excision
- Reefing procedures (stripping of the penile and preputial skin)
- Penile amputation (partial phallectomy) or even *en bloc* resection with or without penile retroversion are viable options when there is extensive change and local malignancy but is of course a palliative procedure when metastatic tumours have already developed
- The various techniques are described fully in surgical texts.

Medical treatment

Medical treatment may include:

- Local infiltration with chemotherapeutic agents, such as 5-fluorouracil or cisplatin, either alone if the lesions are small or following surgical debulking therapy.
- Some chemotherapeutic creams are also now available for topical application.
- Radiation treatment using interstitial gamma brachytherapy or teletherapy.

Prognosis

The prognosis remains guarded in all but the earliest cases, since recurrences and new lesions are common. Metastasis to local lymph nodes may occur. Spread to other organs is uncommon but is clearly devastating when it occurs.

Melanoma

See also pages 237 and 568.

Description

Melanoma affecting the genitalia is largely restricted to the preputial reflection but can affect other sites. Typically, the full range of pathological behaviour that occurs at other sites can be seen (see p. 568). They rarely affect the skin of the free penis or the scrotum, but no site is completely excluded from the diagnosis.

The masses are round, smooth, hairless and generally small (<2 cm). At this site there can be very extensive tumours but they do seem to remain benign for longer than at other sites. This tumour is slow to spread to other sites or organs and treatment is usually not required unless the tumour interferes with mating or urination.

Most melanomas are benign but most will eventually take on a much more malignant behaviour.[6] Some melanomas can be aggressive, so biopsy of the tumour and microscopic assessment is recommended. In cases where melanoma is diagnosed on a non-grey horse, spread to other organs is more common.

If the tumour is found to be aggressive on microscopic examination of a biopsy specimen, surgical removal is recommended. In these cases, surgical excision or cryotherapy is generally effective. If the tumour is not aggressive, but growing actively, or in cases where the number of tumours is excessive, cimetidine administration is suggested as being an effective option to decrease the size of the tumour(s).[7] There is controversy over the effect of this approach.

Clinical features

See Figure 35.3.

- Well-defined, black, isolated or coalescent nodules of varying sizes
- Most often found on the preputial reflection and internal lamina of the sheath
- Ulcerated masses produce a black haemorrhagic discharge
- It can involve extensive areas
- Secondary infection and infestation with maggots can occur.

Differential diagnosis

- Sarcoid

Diagnostic confirmation

The clinical appearance is pathognomonic and easily confirmed by biopsy of any type, including fine-needle aspiration.

Disease summary

Notes

Relatively common, usually benign tumour found most often in the preputial reflection of middle-aged or older grey horses.

Clinical features

Few or large numbers of interlinking black nodules in the skin of the preputial reflection. Possibly some ulcerated and bleeding causing preputial discharge.

Diagnostic confirmation

Clinical features are usually typical and easily recognized. Histological examination may guide prognosis.

Management

A variety of surgical options are available. Chemotherapy is less effective.

Prognosis

The prognosis for the horse is seldom affected by melanomas at this site but they can be very extensive.

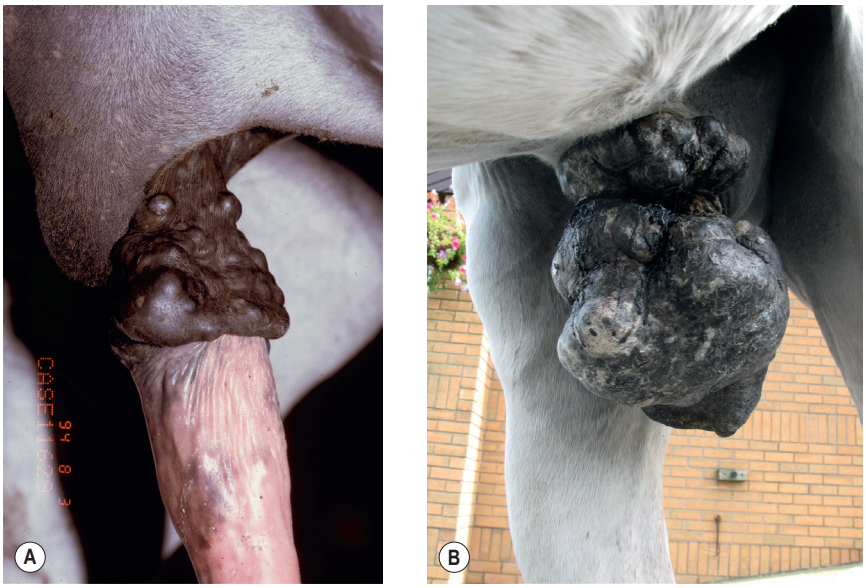


Figure 35.3 Penile/preputial melanoma. **(A)** These melanoma tumours were identified incidentally. They remained static for many years without significant problem. **(B)** This 20-year-old grey pony developed extensive preputial and penile melanoma over many years. Repeated infestations with fly maggots occurred annually. An *en bloc* resection was offered but declined.

Management

- *Surgical removal* is the best approach – this should probably be carried out early to avoid extensive procedures later. It is likely that repeated procedures will be required.
- *Oral cimetidine* has been suggested as an option for effective treatment, but in the authors' experience there is no material benefit.[7]
- *DNA plasmid vaccines and immunotherapy* options may be effective but, so far, little evidence for them has been found.[8]
  - There is no reported benefit of autogenous X-irradiated melanoma tumour cells in horses with melanoma
  - It is suggested that a DNA vaccine developed for use in dogs with melanoma that targets tyrosinase may be considered for use in other affected species, such as horses.[9]

Sarcoid

See also pages 203 and 545.

Description

These fibroblastic skin tumours are the most common tumour of the horse (all locations included) and affect horses of all ages. They occur with relatively high frequency in the penile skin and preputial skin of geldings, stallions and donkeys.

Six distinct types of sarcoid are recognized but only the nodular and fibroblastic forms occur with any degree of frequency on the penis and inner lamina of the prepuce.[10] Sarcoids are occasionally found on the scrotum, where all types can occur.

Donkeys are commonly severely affected with a highly invasive fibroblastic sarcoid in the sheath and penile skin.

The tumours tend to grow quickly but metastasis has not been reported with this neoplasm.

Disease summary

Notes

Relatively common benign tumour of fibroblasts, with a locally aggressive behaviour in some cases. All ages of horse and stallions, as well as geldings, can be affected. Donkeys have a particularly aggressive fibroblastic form. No metastatic tendency.

Clinical features

Tumours range from small single nodules (types A and B) to very aggressive and extensive involvement of the penile skin, prepuce or scrotum.

Diagnostic confirmation

Clinical and histological features are usually typical and easily recognized.

Management

A variety of surgical and limited chemotherapeutic options are available. Surgery is usually the preferred option, especially using SMART surgery.

Prognosis

The prognosis is good, provided that the tumour can be removed entirely. Repeated procedures may be required.

Clinical features

Individual lesions can be small or large, and multiple lesions are common (Fig. 35.4). Sarcoid tumours are more common on the prepuce than on the penis. They can also occur on the scrotal skin. Scrotal sarcoids take one of the six recognized forms of sarcoid tumour.[11]

The clinical features of sarcoid are typical (see p. 546); most cases are either nodular (often with multiple nodules) or fibroblastic.

Differential diagnoses

- Squamous cell carcinoma
- Neurofibroma
- Lymphoma



Figure 35.4 Penile and preputial sarcoid. (A) A multinodular and a pedunculated fibroblastic sarcoid on the penis of a 6-year-old gelding. Notice the presence of other tumours on the skin in the inguinal region. These tumours were successfully removed using SMART surgery and a diode laser. **(B)** This large fibroblastic sarcoid developed on the prepuce of a 12-month-old colt, intended for breeding. Again it was removed successfully with SMART surgery. No other lesions were present and no more developed subsequently. **(C)** A complex of verrucose and nodular sarcoids (Types A and B) affected the entire circumference of the preputial reflection and extended onto the free portion of the penis. A standard 'reefing procedure' using SMART surgical techniques gave a good outcome, although a second procedure was required some 4 months later for a small focal recurrence. **(D)** A focal fibroblastic sarcoid was removed from the penile skin of a working Welsh Section A stallion, but recurred – note the scar of the previous surgical procedure. A second procedure resolved the lesion without recurrence for at least 8 years.

- Habronemiasis
- Penile trauma with granulation/scarring.

Diagnostic confirmation

Clinical signs are usually sufficient but biopsy (punch or excisional) is probably the only definitive way of identifying the lesions. However, biopsy is regarded as potentially dangerous.

The presence of other lesions typical of sarcoid at other sites is a supportive evidence but of course can be misleading.

Management

The location of the tumours and their clinical and pathological behaviour largely preclude local chemotherapy.

Surgical excision using SMART (minimal cell contamination) procedure (see pages 122 and 556) is the preferred option in most cases. Recurrence is common and repeated procedures may be required. The full range of therapeutic options is applicable.

Prognosis

The prognosis is always guarded. There is a high rate of recurrence with most therapies and recurrences are likely to be more aggressive and infiltrative.

Lymphoma

See also page 349.

Tumours of the testicle

Overview

Tumours of the equine testicle are rarely encountered, although this may reflect the high numbers of geldings in most equine populations; therefore, in entire horses, they are probably best regarded as uncommon rather than very rare. The relationship between testicular tumours and cryptorchidism is well established.

Equine testicular cancers can be divided broadly into two categories:

1. *Germinal tumours*, including:
   - Teratoma and teratocarcinoma, seminoma and embryonic carcinoma
2. *Non-germinal tumours*:
   - Tumours of Leydig cells, Sertoli cell tumour, mast cell tumour and lipoma.

Clinical features

The clinical features of the various types of tumour are relatively easy to define and the ultrasonographic appearance also helps to differentiate them. Few of the tumours that have significant endocrinological affects in others species have any implications in horses.

Management

The standard approach to any testicular tumour is orchidectomy; of course, where the tumour is not directly accessible, laparotomy or laparoscopic methods need to be applied.

Teratoma/teratocarcinoma

See also pages 401 and 644.

Disease summary

Notes

Relatively common potentially testicular tumour affecting younger male horses. Many develop in cryptorchid testes. Most affected testes are endocrinologically active, so stallion-like behaviour can be exhibited. Usually unilateral but both sides can be affected.

Clinical features

Signs are usually incidental when castration is being performed.

Diagnostic confirmation

Ultrasonography of the inguinal region in a cryptorchid may identify an atypical enlarged testicle with a non-testicular sonogram.

Management

Surgical removal is the only solution.

Prognosis

The prognosis is good.

Description

Teratoma is a benign, progressive tumour that arises directly from the pluripotent stem cells of the seminiferous epithelium and therefore can transform into endoderm, mesoderm or ectoderm. For this reason, on cut surface, these tumours will have many different types of tissue, including differentiated hair, fat, teeth and bone.[12] Teratoma is usually multicystic. Teratoma with cyst formation was reported in three horses with abdominally retained testicles. Bone development in the head of the epididymis, near the vascular supply of the tumour, was a consistent finding.

These are relatively common findings in young horses (<3 years of age) and even in newborn foals.[13] There is a well-established relationship to cryptorchidism, but a significant number of teratoma of varying size and type have been found incidentally during routine castration procedures.[14] Bilateral cases can be found, and often the only indication of a problem is a difference in testicular size.

Teratocarcinoma and embryonal carcinoma are extremely rare. A single case of a testicular teratocarcinoma has been reported in the horse with metastatic tumours.[15] This tumour comprises both mature and primitive germ cell tissue and is highly malignant.[16]

Although germinal carcinoma cells have been suggested as the cause of teratomas, evidence of malignancy is singularly uncommon.

Clinical features

See Figures 35.5 and 35.6.

- A grossly enlarged (usually retained/non-descended) testicle is usually identified
- Most are non-painful and relatively slow growing
- There may be some endocrinological effects relating to the retained testicle, but the tumour itself has no significant metabolic effects
- Some cases present signs of abdominal discomfort or reduced performance.

Differential diagnoses

- Cryptorchidism
- Seminoma
- Interstitial cell tumour
- Sertoli cell tumour
- Abdominal abscess.

Diagnostic procedures

- Rectal examination with or without transrectal or percutaneous (via the inguinal region) ultrasonography is helpful
  - Some are recognizably cystic in nature and may require aspiration prior to removal.
- There are endocrine tests to establish the presence of a retained testicle (described in standard texts) but these do not predict the presence of a teratoma.

Management

- Removal of the affected testicle is highly advised, even when there are no immediate clinical effects, because of the risk of tumour exacerbation and enlargement.
- Aspiration of the cystic portion of the tumour was necessary for surgical removal in two cases.
- Laparoscopic techniques are increasingly being used to minimize the extent of surgical trauma.[17]

Seminoma

See also page 399.

Description

This is the most common tumour of the equine testicle. Seminomas can affect cryptorchid or descended testes.[18]

They derive from basal spermatogonia cells within the seminiferous epithelium; they do not have any endocrinological function or implication.[1] Bilateral cases

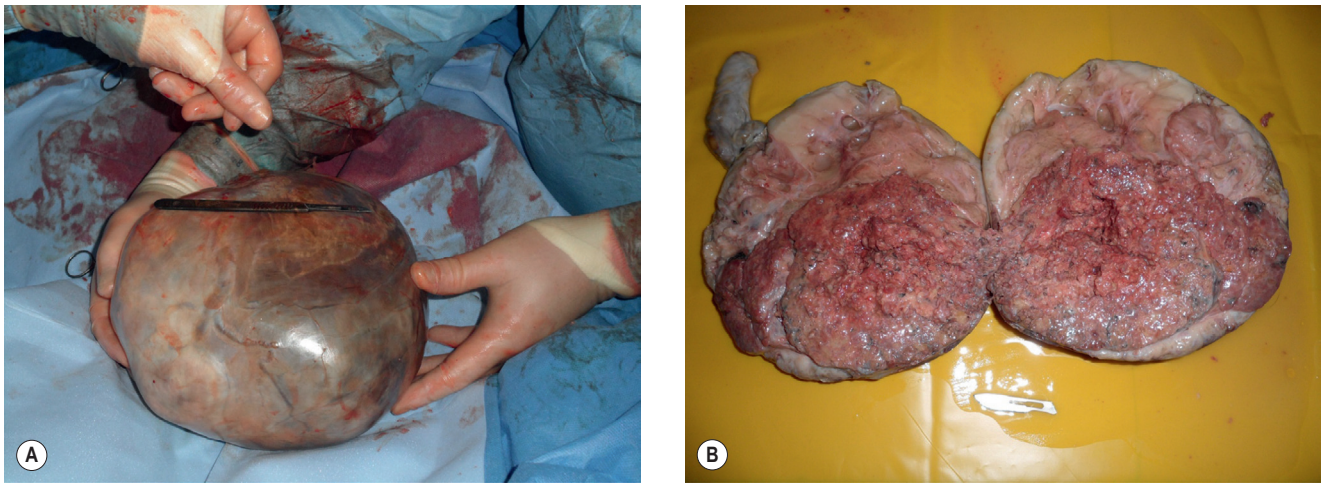


Figure 35.5 Testicular teratoma. **(A)** This massive testicular teratoma was identified in a cryptorchid 4-year-old horse that had been subjected to unilateral orchidectomy some 3 years previously and had shown recurrent episodes of vague abdominal discomfort. He had shown stallion-like behaviour and was positive to the endocrinological tests for cryptorchidism. **(B)** Multiple tissues, including hair, cartilage, nervous tissue and bone, were identifiable within the disorganized mass. Some testicular tissue was present also. *(Figure B courtesy of Neil Townsend.)*

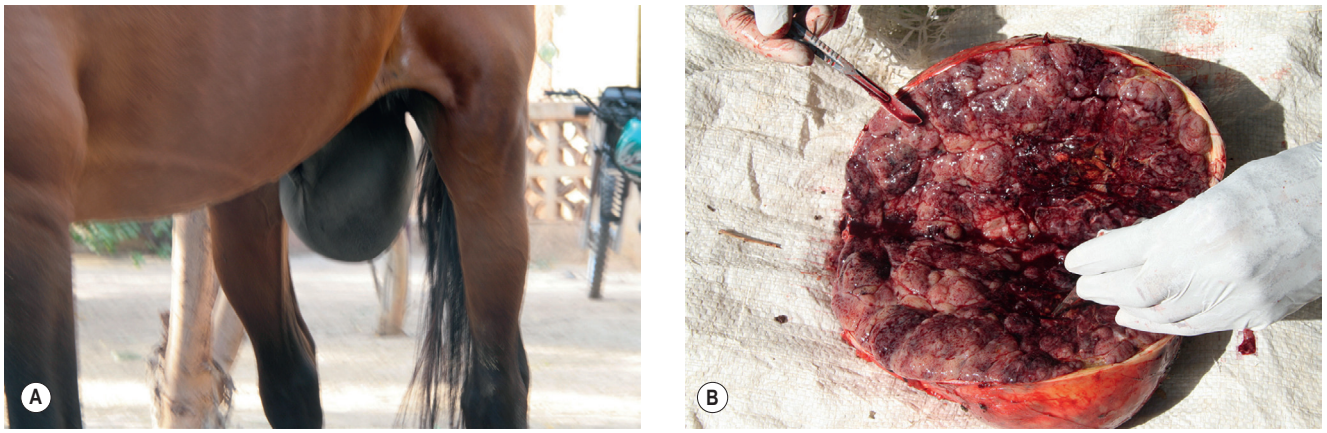


Figure 35.6 Teratocarcinoma. **(A)** This 4-year-old stallion developed a huge firm swelling in the scrotum. The large tumour was removed by a standard local approach without significant or unexpected complications. **(B)** The tumour was firm and contained a variety of tissues types with histological evidence of malignancy. The horse, however, recovered without any problem and was still alive and free of any obvious disease 2 years later. *(Figures courtesy of Adele Williams and Amadou Doumbia.)*

Disease summary

Notes

Seminoma, the most common testicular tumour of horses, is derived from seminiferous epithelium. There is a strong tendency to malignancy and metastasis.

Clinical features

Slow progressive, non-painful, almost innocuous testicular enlargement sometimes with a palpably nodular nature. Bilateral cases also exist.

Diagnostic confirmation

Clinical and ultrasonography features are diagnostic but histology is definitive.

Management

Urgent removal of the affected testicle(s) is required, but even then this is usually too late.

Prognosis

The prognosis is very guarded – all reported cases have died within 2–3 years in spite of castration/hemicastration.

are recorded, although most are unilateral, and most are multifocal within the affected testis.[19]

Mature or aged stallions over 10 years of age are most often affected.

Clinical features

- Slow but progressive testicular enlargement of one or both testes (Fig. 35.7A).
- Pain is not a feature; palpation may reveal a multinodular firm texture.
- There is profound effect on the surrounding testicular tissue (and, consequently, on fertility) that gradually disappears to be replaced by a large diffuse mass of moderately dense tumour tissue.
- The tumours are usually round or oval in shape, with irregular surfaces, but usually expand into diffuse tumour with a homogeneous echogenicity (Fig. 35.7B).
- Per rectum palpation of the subiliac lymph nodes is essential in all cases, as is careful palpation and ultrasonography of the spermatic cord.

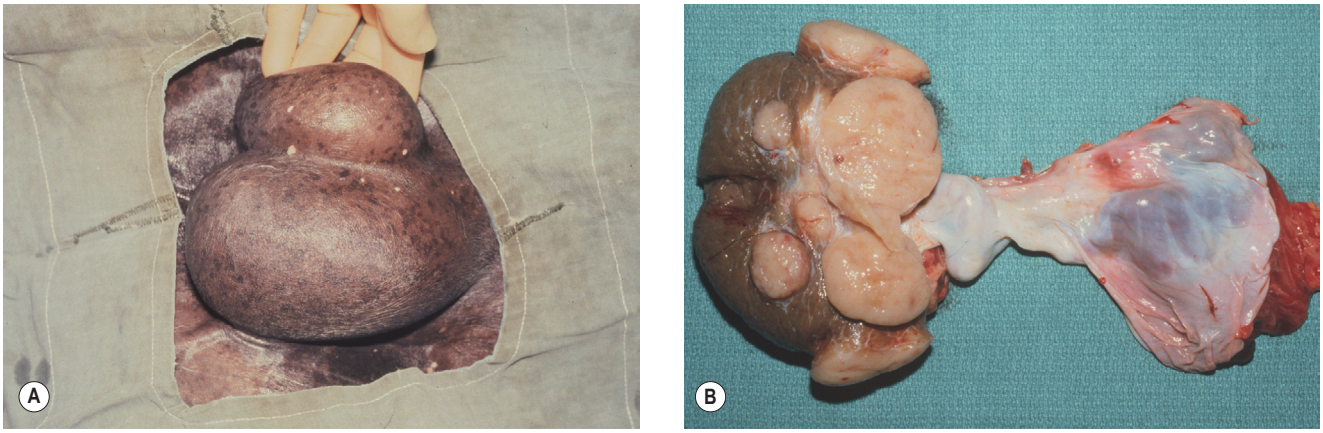


Figure 35.7 Testicular seminoma. (A) A 14-year-old Welsh Section D breeding stallion with two normally descended testicles was presented for investigation of a unilateral testicular enlargement. Following ultrasonographic examination, a presumptive diagnosis of unilateral seminoma was made. **(B)** Hemicastration was performed and this confirmed the multifocal nature of the tumour, with obliteration of a large proportion of the testicular tissue. The horse bred normally for 2 years and was presented with a similar seminoma on the contralateral testis. The horse showed signs of disseminated tumours and, at necropsy, a malignant seminoma was identified; it is not certain whether the secondary tumours backdated the second tumour development, i.e. were derived from the original tumour, or whether the second testis was a secondary tumour. *(Figure B reprinted from Knottenbelt DC, Pascoe R, Lopate C, et al. Equine Stud Farm Medicine and Surgery. Edinburgh: WB Saunders; 2003: 105 (Fig. 4.62B), copyright 2003, reprinted with permission from Elsevier.)*

Differential diagnoses

- Orchitis (infection or trauma)
- Testicular torsion
- Interstitial cell tumour
- Sertoli cell tumour.

Diagnostic confirmation

- *Ultrasonographic* findings are distinctive and enable a diagnosis to be made with reasonable certainty.[20] The affected testicle may reveal a diffusely heterogeneous parenchyma. The testicle is usually diffusely hypoechoic, with ill-defined regions of hyperechogenicity giving the appearance of hypoechoic nodules throughout the testicular parenchyma. Normal testicular tissue may or may not be seen, since the tumour gradually obliterates the normal structures. An echogenic band, representing a pseudocapsule, may be seen surrounding the testicle.
- *Biopsy* by hollow-needle methods is definitive but, since most affected tests are noticeably enlarged, removal is the best diagnostic approach.

Management

- The affected testicle should be removed as soon as possible and submitted for histological examination.
- In theory, intravenous 5-fluorouracil should be helpful but it is extremely poorly tolerated in horses.

Prognosis

Seminoma in horses is probably more aggressive than in other species, with a well-recognized tendency to malignancy and metastasis, in particular to thoracic and abdominal organs within 2 years of removal of the affected testis (see Fig. 35.7).[21–23] Metastatic spread is clearly an early process. All equine seminoma tumours should be regarded as potentially malignant and the prognosis should reflect that.

Interstitial (Leydig) cell tumour (interstitial cell adenoma)

Disease summary

Notes

Benign, slow-growing but functional tumour of androgen-producing interstitial cells. No known tendency to malignancy and metastasis.

Clinical features

Almost imperceptible testicular enlargement; possible secondary effects include acute colic. Behavioural changes (aggression) can occur.

Diagnostic confirmation

Diagnosis is difficult, but ultrasonographic examination may help. Histology is definitive.

Management

Removal of the affected testicle(s) is required but, even then, this is usually too late.

Prognosis

The prognosis is good: no cases are reported to have died directly from this tumour. Fertility is profoundly affected both physically and endocrinologically.

Description

This is a very rarely diagnosed benign functional tumour of horses that derives from the interstitial cells of Leydig. It is unilateral or, less often, bilaterally affected.[24]

Mature or aged stallions over 10 years of age are most often affected.

A series of nine cases have been reported – all but one occurred in undescended testes. Five of the cases had bilateral tumours (being bilateral cryptorchids). However, cases have also been reported on descended testicles.[25]

Clinical features

- Slow but progressive mild, most often unnoticeable testicular enlargement of one or both testes.
- Pain is not a feature; palpation may reveal a multinodular firm texture.
- There is a profound effect on fertility.
- Some animals show increased aggression, which is assumed to be endocrinologically based because it is said to resolve after hemicastration.

Differential diagnoses

- Orchitis (infection or trauma)
- Testicular torsion
- Seminoma
- Sertoli cell tumour.

Diagnostic confirmation

- *Ultrasonography* may confirm localized or multiple tumours with a homogeneous echogenicity and a thin but well-defined capsule.
- *Endocrinologic assays* may be helpful but there are no reports of the likely findings.
- *Biopsy* by hollow-needle methods is definitive but, since most affected tests are noticeably enlarged, removal is the best diagnostic approach.

Management

The affected testicle should be removed as soon as possible and submitted for histological examination.

Prognosis

The prognosis is good, although fertility may be affected.

Sertoli (sustentacular) cell tumour

See also page 398 and Fig. 25.2.

Disease summary

Notes

A rare tumour of cells from the germinal supporting (sustentacular) cells of the seminiferous tubules. Commoner in undescended testes, but also occurs in the descended testicle of a unilateral cryptorchid.

Clinical features

Little evidence of any significant clinical significance, with no endocrinological effects recognized in horses.

Diagnostic confirmation

Histology is definitive.

Management

Removal of the affected testicle(s) is sensible since they can become malignant.

Prognosis

The prognosis is good with castration/hemicastration. Fertility implications may be significant.

Description

These rare tumours derive from the supporting/sustentacular cells of the seminiferous tubules. The tumours may be found in undescended and descended testicles.

In one reported case of a 13-year-old Morgan [presumed] gelding, a mass was found in the caudal region of the abdomen at necropsy; a retained testis in the right retroperitoneal space was identified histologically as a malignant Sertoli cell tumour.[26] The retained testis contained neoplastic cells and metastases were identified in the liver, spleen, lungs, and sublumbar lymph nodes. Immunohistochemical examination of the testis and metastatic tissues confirmed the diagnosis.

There is no report of any behavioural or other clinical implication of this tumour type. They have no endocrinological implication in horses but may affect fertility.

Only mature or aged stallions are reported to be affected.

Clinical features

- Infertility is the likely only early sign.
- Weight loss has been part of the presentation history.
- Colic has been seen occasionally.
- Malignant cases may have a variety of secondary clinical evidence.

Differential diagnoses

- Orchitis (infection or trauma)
- Interstitial cell tumour
- Haematocoele/varicocoele/hydrocoele
- Sperm granuloma
- Testicular torsion
- Seminoma
- Haematoma
- Hernia.

Diagnostic confirmation

Biopsy by hollow-needle methods is definitive; most affected testes are not noticeably enlarged.

Management

The affected testicle should be removed as soon as possible and submitted for histological examination.

NEOPLASTIC DISORDERS OF THE TUBULAR GENITAL TRACT OF MARES

Overview

The female genital tract suffers from few neoplastic conditions. Older mares are more often affected. The ovary and the external genitalia are the most significant sites for neoplastic disease. Over 85% of reproductive tumours of the mare were attributable to a single tumour type (granulosa cell tumour) in a study of 35 cases.

Tumours affecting the tubular tract (vestibule, vagina, cervix, uterus and fallopian tubes) are extremely rare and probably insignificant; most often they are identified incidentally during reproductive examinations and so they may pass undetected in the general (non-breeding) population.

The external genitalia are affected by some significant tumour conditions, including:

- Squamous cell carcinoma (see also p. 575)
- Sarcoid (see p. 544)
- Melanoma (see p. 568).

The commonest problems affect the ovary and here, again, only a few neoplastic conditions have been recognized. These include:

- Epithelial tumours, which in horses is only the cystadenoma.
- Germ cell tumours, including dysgerminoma and teratoma.
- Sex cord-stromal tumours, including the most common ovarian tumour, the granulosa (theca) cell tumour and ovarian adenocarcinoma.
- Fibroleiomyoma.
- Lymphoma.

There does appear to be some difference in the overall incidence of ovarian tumours between horses and donkeys. In the latter, ovarian granulosa (theca) cell tumour does occur but it would seem that cavernous haemangioma is a major feature of the donkey population.[27] Additionally, the same study found that, in donkeys, tubular tract neoplasms occurred with some frequency; these included endometrial/cervical polyp, fibroleiomyoma/leiomyoma and cavernous hemangioma. The latter formed the biggest proportion again. There are no reports of cavernous hemangioma affecting the reproductive tract of the horse.

Vulvar and clitoral squamous cell carcinoma

See also pages 220 and 575.

Description

This is the most common tumour of the external genitalia of the mare.

The average age of affected mares is around 12 years.[28] Draft breeds, Appaloosa and other breeds lacking pigment in the skin are probably more likely to be affected, but this is by no means as clear as it is for other sites where carcinoma develops.

Many causes have been suggested, but none is universally convincing. These include virus papilloma, trauma and chronic exposure to smegma and other discharges. Sunlight is not convincing!

Characteristically, carcinoma is recognized in proliferative or ulcerative/destructive forms, but both can present at the same time. They have an aggressive pathological behaviour and can rapidly invade local tissues with extension to local (iliac) lymph nodes. Malignancy with metastasis is recognized with some frequency.

Clinical features

See Figure 35.8.

- Early cases may present with squamous papilloma.
- Proliferative or ulcerative or combined tumour in the vulvar lips/vestibule and clitoral area are characteristic.
- Early carcinoma may produce very little by way of indication of the severity of the problem; a slight haemorrhagic discharge may be all that is seen initially
  - Note that lack of pigment is not a common feature of these tumours.
- Some carcinoma tumours can be very destructive (Fig. 31.33)
  - The tumour gradually obliterates all normal structures.

Disease summary

Notes

The most common tumour affecting the vulvar and clitoris of older mares. A range of malignancy are common, with some being highly destructive and potentially metastatic.

Clinical features

Proliferative or ulcerative/destructive tumours with a fleshy/haemorrhagic or ulcerative nature. Often secondarily infected.

Diagnostic confirmation

Clinical features are usually recognizable. Biopsy is definitive.

Management

The full range of surgical, cryosurgical, chemotherapeutic and radiation options are available.

Prognosis

Early cases carry a good prognosis; late cases are a serious problem.





Figure 35.8 Vulvar and clitoral carcinoma. **(A)** A papillomatous form of carcinoma affecting the clitoral fossa and clitoris of a 19-year-old grey mare. **(B)** A destructive ill-defined carcinoma of the vulvar lip; note the depigmented skin.

- Metastatic spread is relatively common, with extension to the iliac lymph nodes and then to the lungs and other organs
  - Pseudohyperthyroidism and other paraneoplastic syndromes can develop.[29]

Differential diagnoses

- Viral infection (particularly coital exanthema – EHV3, and viral papilloma)
- Bacterial and parasitic infection
- Postpartum perineal lacerations and other vulvar trauma
- Melanoma
- Sarcoid.

Diagnostic confirmation

- The clinical appearance
- Histology of biopsy samples.

Management

The full range of options is available, from surgical resection to radiation (see p. 176). However, combinations of surgical debulking (surgical tumour reduction) (or cryosurgical necrosis) and concurrent chemotherapy (either topically or intralesionally or both) can be effective in early localized lesions

- Intralesional slow-release cisplatin (in emulsion or biodegradable bead form) and 5-fluorouracil (in aqueous or emulsion forms) are very effective measures when the tumour is confined or has been reduced surgically but are less effective for large and widespread tumours
- Topical 5-fluorouracil (5%) is also helpful, but needs to be applied frequently (every 8 hours).

Prognosis

The prognosis remains guarded since malignancy is a relatively common outcome. Recurrence is also common. Prevention through maintaining hygiene is theoretically possible, but the overall incidence is low enough to suggest this might not be a helpful measure. Horses with pale/depigmented perineal skin are possibly those where regular hygiene is helpful.

Leiomyoma/fibroleiomyoma

See Figure 35.9.

Description

This is a totally benign isolated tumour of smooth muscle. It can be found on the wall of the vestibule, vagina or uterus. A single case report described a leiomyoma of the ovary in a pregnant mare. Older mares are probably more liable to have these tumours. There is no known metastatic or malignant variation.

Clinical features

- Incidental finding during clinical examination of a fibrous firm single or multiple nodules within the wall of the uterus (between 2.5 and 15 cm in diameter).

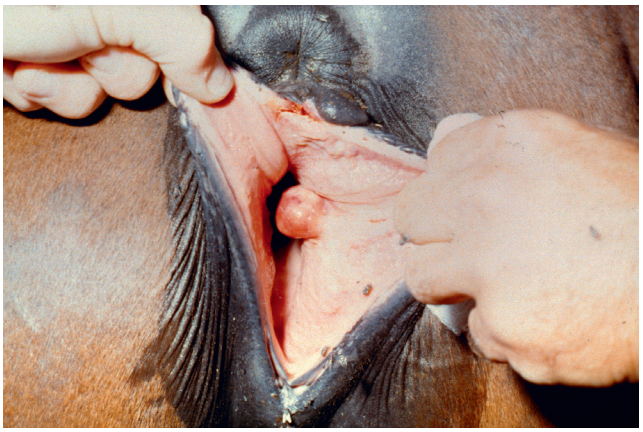


Figure 35.9 Leiomyoma. This fibroleiomyoma was identified during a routine reproductive examination. It was removed using a diathermy loop and did not recur. Although these tumours are not reported to become malignant, some of them can have an invasive behaviour and regular follow-up checks are advisable.

Disease summary

Notes

Small, benign (incidental) tumours of smooth muscle.

Clinical features

Slow progressive, non-painful, innocuous, usually single mass on the uterine, vaginal or vestibular wall. Occasionally ulcerating with possible haemorrhagic discharge.

Diagnostic confirmation

Clinical and ultrasonography features are diagnostic but histology is definitive.

Management

Surgical removal is effective – some can be performed using electrocautery or laser.

Prognosis

The prognosis is excellent, although those with a broadly rooted base can affect fertility.

- A few have an ulcerated surface (although this is unusual and in any case transient) and this may be evidenced as a slightly haemorrhagic vaginal discharge.
- Uterine leiomyoma may be associated with chronic infertility.[30]

Differential diagnoses

- Carcinoma
- Polyp
- Uterine cyst.

Diagnostic confirmation

- *Direct examination of video-hysteroscopy* can identify lesions incidentally and biopsy of suspect lesions can be taken transendoscopically.[31]
- *Ultrasonographically,* they are solid, highly echogenic structures with a distinct spherical shape.
- *Biopsy/excisional biopsy* by hollow-needle methods is definitive but, since most affected tests are noticeably enlarged, removal is the best diagnostic approach.

Management

- Surgical removal by any means is curative. Diathermy or laser ablation is effective and simple.[32]
- Recurrence is most unlikely.

Prognosis

The prognosis is excellent. Fertility may be adversely affected when the tumours form in the wall of the uterus or fallopian tubes; some tumours can be locally invasive.[32]

Ovarian tumours

Granulosa (theca) cell tumour

See also page 393.

Disease summary

Notes

The most common ovarian tumour of horses derived from theca cells. Tumour is usually functional. Some (rare) tendency to malignancy is reported.

Clinical features

Abrupt or insidious onset of masculine behaviour or persistent anoestrus. Palpably enlarged ovary (usually unilateral). Bilateral cases also exist.

Diagnostic confirmation

Clinical and ultrasonographic features are diagnostic but histology is definitive.

Management

Surgical removal of the affected ovary is required.

Prognosis

The prognosis is generally good both for fertility and survival.

Description

This is the most common tumour of the equine ovary.[33] This is a tumour that arises from granulosa–theca cells, and it therefore falls into the non-epithelial group of tumours.

Mares of any age can be affected, even foals and young pubertal mares.[34,35]

Although most cases are unilateral (with a normal or, at least, potentially normally functional contralateral ovary) some cases can be bilateral.[36–38] The tumour destroys the remaining normal ovarian tissue in the affected ovary and the functional nature results in a typical (diagnostic) hormone profile that is responsible for the (almost) complete atrophy of the contralateral ovary.

Most are functional and secrete abnormal hormonal profiles (including abnormal concentrations of inhibin and testosterone) that result in profound behavioural changes (virilism/nymphomania) and fertility issues (acyclicity). Mares can develop the tumour during pregnancy and the pregnancy may proceed normally to term or the ovary can be removed during the pregnancy without significant danger.[39]

Mares can develop a second tumour after one has been removed.

A few can be malignant and metastatic, with wide tissue dissemination.[40]

Clinical features

See Figure 35.10.

- Abnormal behaviour (whether during pregnancy or not) is the most common presenting sign. Virilism, aggression and nymphomania are common but, equally, some mares may have silent behaviour with a lack of cyclicity.
- Constant or irregular anoestrus.
- Stallion-like behaviour, including mounting mares in oestrus, aggressiveness, squealing and striking, is a relatively common sign
  - Changes in muscle distribution to a stallion-like physique may be seen if the condition is prolonged (even in mares who show no stallion-like activity).
- Anoestrous behaviour with no detectable cyclicity occurs in about 25% of cases.
- Rarely, a mare may have a granulosa cell tumour and continue to exhibit normal oestrous cycles and ovulate from the other ovary.
- Per-rectum palpation usually identifies a single (occasionally bilateral) ovarian enlargement with no palpable ovulation fossa with an abnormally small, firm and inactive contralateral (unaffected) ovary
  - The affected ovary is not very large in all cases – indeed many are only slightly bigger than the largest normal stage of ovarian function.
- Concurrent occasional signs include abdominal discomfort, reduced athletic performance and weight loss.
- Mares may develop the tumour during pregnancy and may not have any problem with the pregnancy; they will, of course, have considerable abnormalities (including postpartum anoestrus) after foaling
  - Pregnant mares do sometimes behave badly but the possibility of a granulosa–theca cell tumour should be considered whenever this occurs; endocrinological and ultrasonographic tests should be applied together.

Note

Secondary signs such as colic can occur when the tumour adheres to other abdominal structures.[41] Rupture of the tumour may cause (possibly severe) intra-abdominal blood loss.[42]

Differential diagnoses

- Ovarian cystadenoma
- Ovarian lymphoma
- Dysgerminoma
- Ovarian haematoma.

Diagnostic confirmation

Ultrasonographic findings are distinctive and enable a diagnosis to be made with reasonable certainty.[20] Ultrasonography usually reveals a multicystic or honeycomb structure (Fig. 35.11A). A few cases appear as dense,

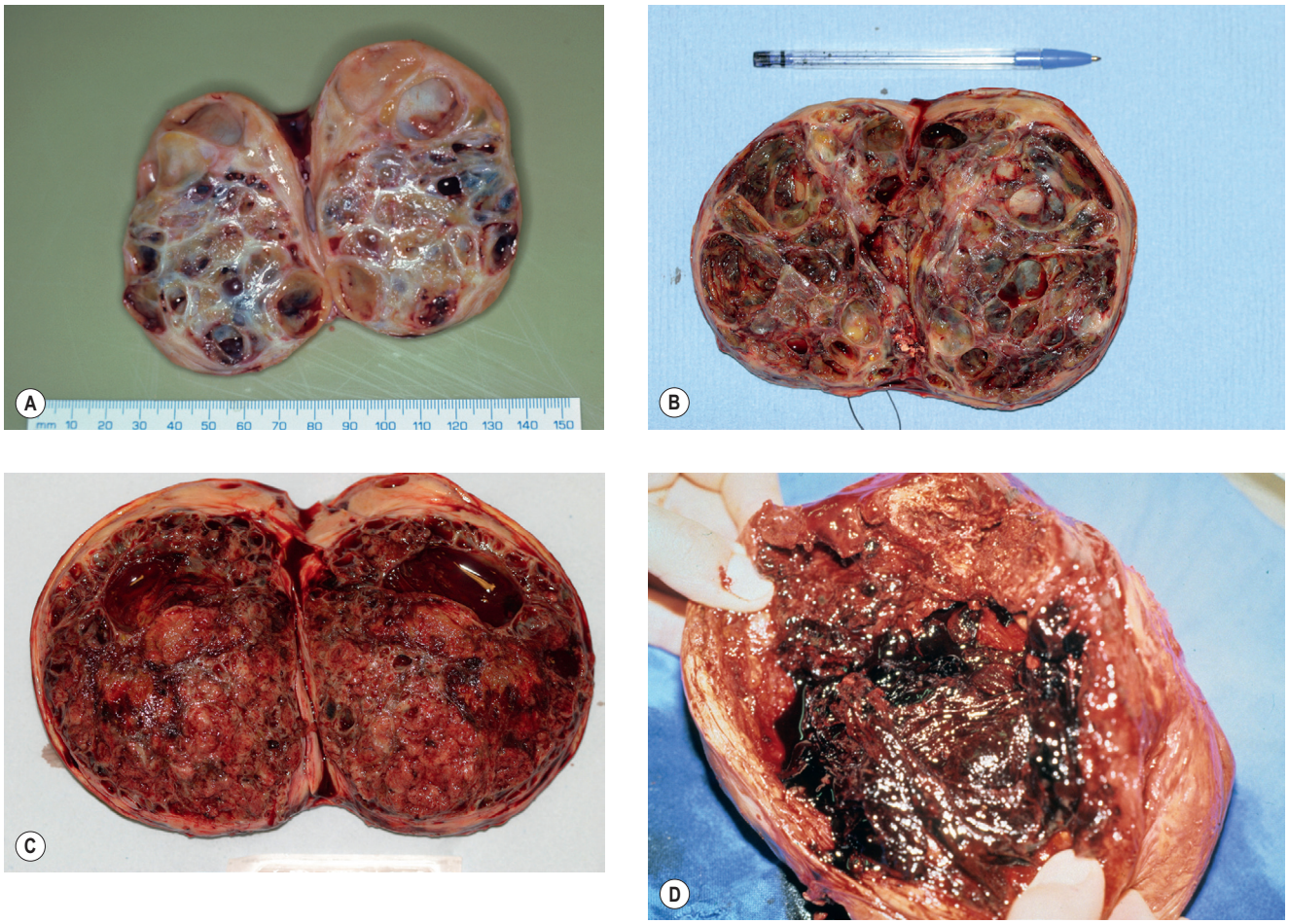


Figure 35.10 Granulosa cell tumour. The gross appearance of granulosa cell tumours can vary markedly and so the ultrasonographic features will vary accordingly. Most are multiloculated and confined **(A,B)**, some are more solid **(C)** and some contain a large amount of blood clot in a single or few cystic structures **(D)**. The one constant feature is the pathognomonic hormone profile.

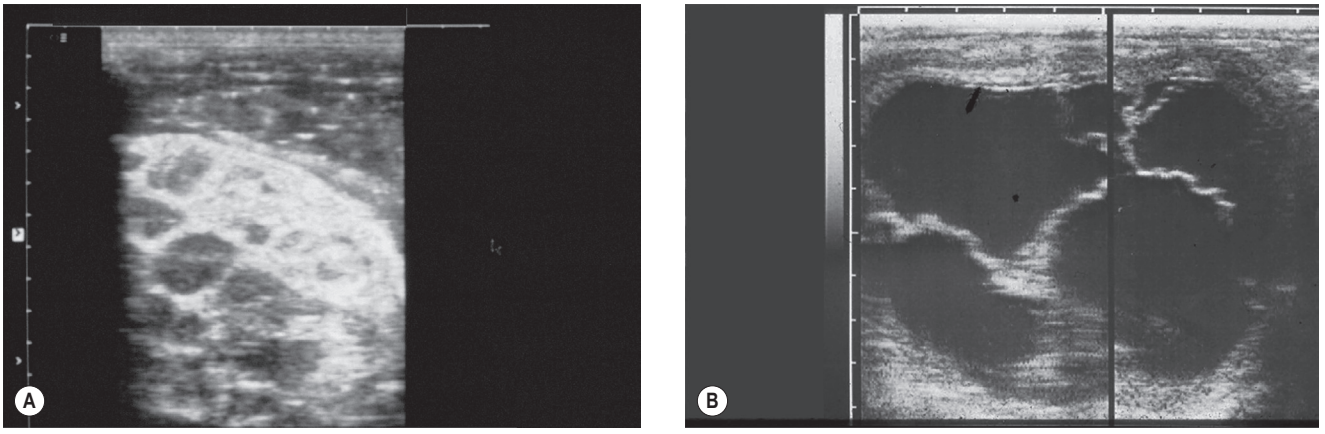


Figure 35.11 Granulosa–theca cell tumour. The ultrasonographic features are pathognomonic of the tumour. **(A)** The classical multiloculated, enlarged ovary makes the diagnosis simple. The pattern is entirely understandable from the gross nature of the tumours (see Fig. 35.10). **(B)** Where there are fewer cystic trabeculae and where there is solid tissue or blood clot present (or both), the diagnosis can be a little more equivocal, but the features are so typical there should be no mistake.

lobulated, smooth masses or appear as a solid ovarian mass with a single (or few), large fluid-filled cyst.

- Some tumours may contain one or more haematomas within the stroma; the homogeneous ultrasonographic appearance is distinctive (Fig. 35.11B).[43]
- Endocrinological assay, in particular abnormally high concentrations of inhibin and testosterone, are pathognomonic (Table 35.1).[44]
- Inhibin is elevated in approximately 90% of mares with a granulosa cell tumour. It has been suggested that

Table 35.1 The plasma concentrations of the major hormone parameters that can be used to investigate and diagnose equine granulosa–theca cell tumour

	Oestrone (pg/mL)	Progesterone (ng/mL)	Testosterone (nmol/L)	Inhibin (ng/mL)	Anti-Müllerian hormone ng/mL
Granulosa cell tumour	<1	<1	0.5 (>50 pg/mL)	>0.7	>4
[Reference plasma]	–	–	<4.5	<0.7	<4

inhibin produced by the tumour is responsible for the inactivity of the contralateral ovary through the suppression of pituitary follicle-stimulating hormone release.

- Serum testosterone levels may be elevated if a significant theca cell component is present in the tumour. Testosterone is elevated in approximately 50–60% of affected mares and is usually associated with stallion-like behaviour.
- Progesterone concentrations in mares with a granulosa cell tumour are almost always <1 ng/mL, since normal follicular development, ovulation and corpus luteum formation do not occur.

A diagnosis of granulosa cell tumour in a non-pregnant mare can be assured if[39]:

- Inhibin concentration is >0.7 ng/mL
- Testosterone concentration is >50–100 pg/mL
- Progesterone concentration is <1 ng/mL.

Anti-Müllerian hormone (Müllerian inhibiting substance) is expressed by granulosa cells, and assay of this hormone can be used to support a diagnosis.[45,46] The assay has a high specificity and high sensitivity since this hormone does not vary through the oestrous cycle and pregnancy.

Management

- *Surgical approaches* for tumour removal include colpotomy, flank and ventral midline laparotomy and laparoscopy (see below). These are described in detail in standard and advanced surgical textbooks.
- *Laparoscopy methods* are entirely feasible unless the ovary is very large (in which case the ovarian pedicle will be large enough to facilitate midline removal)
  - Most cases can be reduced in size by aspiration of the contents and this will facilitate flank removal in a laparotomy organ bag
  - Vessel ligation is most reliably achieved using the cautery systems (LigaSure™, Covidien, Ireland).

Prognosis

The prognosis for mares with a granulosa (theca) cell tumour is good. Fertility rates that approach normal are achieved in mares with a single ovary.

Removal of the affected ovary will usually result in a return to normal behaviour within 8–10 weeks and a resumption of normal ovarian cyclicity within 9 months of surgery.[36,47]

Note

An interdependence between hormonally dependent tumours of other structures and the granulosa cell tumour has been identified in horses in respect of cutaneous lymphoma (see p. 349).[48] A 9-year-old Arabian mare that had been diagnosed with histiolymphocytic (T-cell-rich B-cell lymphoma) lymphoma was also found to have a granulosa cell tumour. Removal of the affected ovary resulted in remission of the lymphoma. It is therefore probably always wise to carry out a full clinical investigation in all cases of neoplastic disease.

Cystadenoma/cystadenocarcinoma/adenocarcinoma

See also page 274.

Disease summary

Notes

Unilateral, usually benign, tumour of epithelial cells of the ovary. Malignant adenocarcinoma may also occur with a tendency to transcoelomic metastasis.

Clinical features

Usually identified incidentally as a unilateral ovarian enlargement. Malignant forms will usually have concurrent secondary signs such as colic or anaemia.

Diagnostic confirmation

Clinical and ultrasonographic features are diagnostic but histology is definitive.

Management

Surgical removal of the affected ovary is possible in benign forms.

Prognosis

The prognosis is good for unilateral serous cystadenoma but very poor for the malignant carcinoma variations.

Description

This is a rare tumour of the equine ovary. Equine ovarian adenoma is of epithelial origin and is usually formed from the surface of the ovulatory fossa or oviductal fimbriae. If they are cystic, these tumours are referred to as cystadenomas, which are non-secretory and are not considered to be hormonally active.[49] Hormonally active cystadenoma with production of testosterone over normal oestrus cyclicity has been reported.[50] The condition appears to affect mature mares over 10–12 years of age.

Cystadenomas occur unilaterally and the contralateral ovary is invariably normal. They are usually unilobular or multilobular.

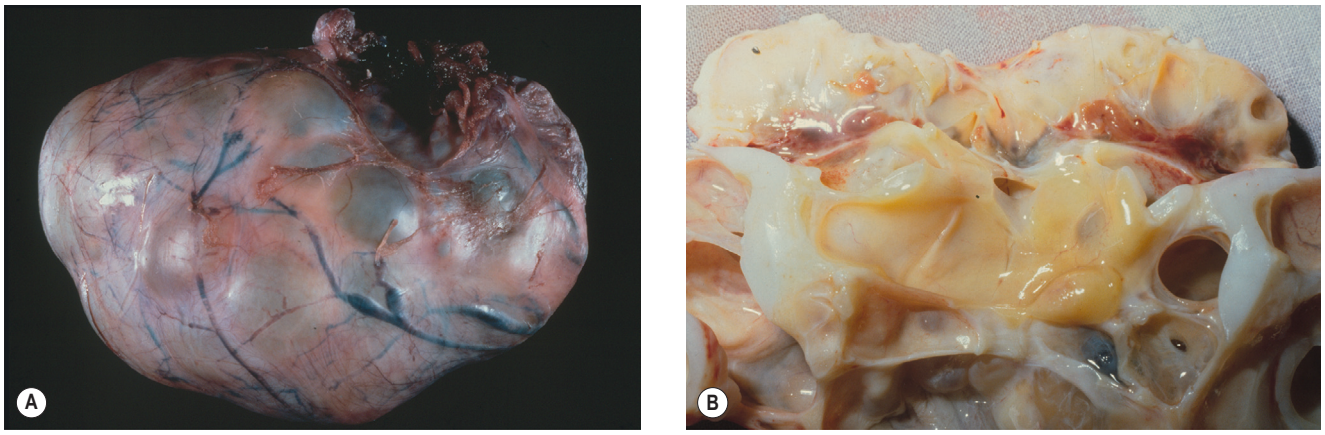


Figure 35.12 Ovarian cystadenoma. (A) A 14-year-old mare presented for routine reproductive examination and a polycystic left ovary was identified by palpation and ultrasonographically. The ovary was removed laparoscopically. **(B)** The polycystic nature of the tumour is distinctive in cross-section.

On rare occasions, an adenoma metastasizes and is then classified as an adenocarcinoma.[51] This may also be bilateral.[52] Malignant cystadenocarcinoma or adenocarcinoma is aggressive and may metastasize transcoelomically or haematogeneously to the chest.[52,53]

Clinical features

See Figure 35.12.

- Most cases are detected incidentally during routine examinations
  - An enlarged ovary with an excessive number of follicles detected on ultrasonographic examination is typical of the benign form (cystadenoma)[50]
  - The ovulation fossa is a palpable ovary, and the contralateral ovary is usually normal, with normal activity.
- Malignant adenocarcinoma/cystadenocarcinoma will probably present with other concurrent signs of apparently more serious disease such as colic, haemoperitoneum, weight loss, ventral oedema and anaemia. Some of these signs will be physical consequences of the tumour or its metastases but concurrent paraneoplastic signs may also be present.
- Secondary signs, such as constriction of the rectum, may be presented when the malignant form extends into the pelvic organs.

Differential diagnoses

- Granulosa–theca cell tumour
- Polycystic/transitional ovary
- Ovarian haematoma
- Dysgerminoma
- Ovarian lymphoma.

Diagnostic confirmation

- Rectal examination.
- Ultrasonographically, they are solid, highly echogenic structures with a distinct spherical shape.
- Plasma testosterone concentrations may be high (0.15 ng/mL), but then decrease to reference concentration (0.09 ng/mL) after removal of the affected ovary cystadenoma.
- Surgical pathology will be definitive in both benign and malignant forms (see p. 274).

Management

- Surgical removal of an ovary affected by benign cystadenoma is curative; this is best carried out using laparoscopic techniques.
- Recurrence is most unlikely.

Prognosis

The prognosis is good for the benign forms but very poor for the malignant ones. Fertility may be adversely affected.

Ovarian teratoma/germ cell tumour

See page 401.

Disease summary

Notes

Ovarian teratoma is relatively common and found in younger mares (<8 years of age). They are benign, non-active tumours that arise from germ cells. Teratocarcinoma is a malignant variant.

Clinical features

Enlarged abnormally-shaped ovary detected by palpation. Most are detected incidentally.

Diagnostic confirmation

Ultrasonographic examination reveals bizarre variable echo patterns dependent on the tissues present.

Management

Removal of the affected ovary is curative.

Prognosis

The prognosis is good for unilateral benign cases.

Overview

This is a benign, unilateral germ cell tumour that is relatively common – it is the second most common ovarian tumour. Teratomas contain misplaced embryonic structures, such as bone, skin, teeth, cartilage, nerves, blood vessels and hair.

The tumours are therefore composed of variable cell types, including hair, cartilage, bone and other tissues. They are solid or contain large cystic spaces, occasionally lined with squamous epithelium.

They are usually identified in younger mares – often at the first pre-breeding examination. There is usually no endocrinological activity associated with any form of the tumour.

A malignant form (teratoadenocarcinoma) has been described, which showed cartilage and hair-like material in the primary tumour and resulted in direct extension to the uterus and metastatic masses in the abdominal cavity and lungs.

Clinical features

See Figure 35.13.

- Incidental finding during rectal examination: variably nodular enlarged (or normal) ovary without normal structures. The ovary feels firm and enlarged, with rough, irregular surfaces.
- Mares with ovarian teratoma continue to cycle and ovulate from the contralateral unaffected ovary.

Differential diagnoses

- Cystic adenoma/adenocarcinoma
- Granulosa–theca cell tumour
- Ovarian lymphoma
- Ovarian abscess.

Diagnostic confirmation

- Ultrasonographically, this tumour is of very variable size and echogenicity, with an absence of any normal ovarian structures.
- Differentiation from other non-secretory ovarian tumours is difficult without excision.

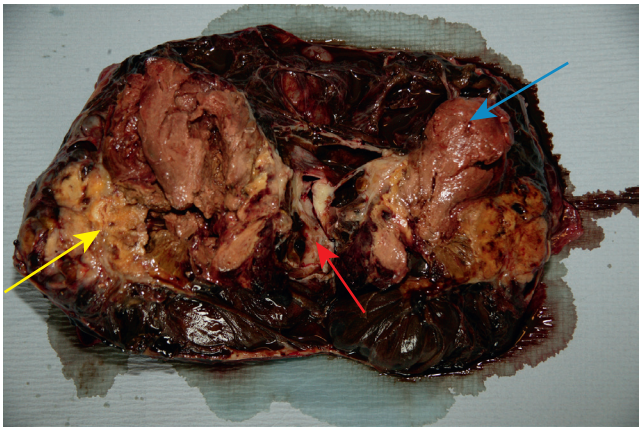


Figure 35.13 Ovarian teratoma. A 5-year-old mare was presented with a long history of ill thrift from weaning, poor athletic performance, anaemia and recurrent episodes of colic over the previous 4 months. Rectal palpation identified a massively enlarged and irregular left ovary with a very mixed echogenicity. No normal ovarian structures were identifiable. Peritoneocentesis produced significant amounts of haemorrhagic fluid. At exploratory laparotomy, the affected ovary was heavy and could not be exteriorized at all. The horse was euthanized. Necropsy showed a massive ovarian teratoma with hair (red arrow), cartilage/bone (yellow arrow) and liver-like tissue (blue arrow). The ovarian capsule was torn and the structure enclosed an extensive blood clot.

Management

- Surgical removal by any means is curative.
- Recurrence is most unlikely.

Prognosis

The prognosis is excellent for the benign form but some are malignant and these carry a far worse prognosis of course.[54,55] It is unlikely that teratomas will interfere with fertility unless they are large enough to cause the reproductive tract to become dependent in the abdomen.

Dysgerminoma

See also page 400.

Disease summary

Notes

Malignant tumour of germ cells of the ovary; most occur in young horses (<4–5 years of age).

Clinical features

Clinical signs are nonspecific – usually detected as part of an investigation for weight loss, abdominal pain and reduced performance. Acute signs associated with rupture of tumour or metastatic development.

Diagnostic confirmation

Clinical and ultrasonographic features are nonspecific. Surgical pathology is definitive.

Management

Urgent removal of the affected ovary is required, but even then this is usually too late.

Prognosis

The prognosis is very guarded. Some horses do survive if surgery is performed early.

Overview

Dysgerminoma is a tumour of the ovary that is composed of primitive, undifferentiated germ cells. It is an extremely rare potentially highly malignant tumour composed of a uniform population of cells that resemble primordial germ cells. Younger horses are more likely to be presented with this tumour, but older horses can be affected.[56]

The tumours have a variable rate of growth and some may be detected incidentally at an early (treatable stage).[57]

They are generally considered to be malignant, rapidly metastasizing via lymphatic and haematogenous routes, as well as by direct transcoelomic means, to major organs and to both the abdominal and thoracic cavities.

There are few reports of dysgerminoma in horses.

Clinical features

- The signs of dysgerminoma are characteristically nonspecific. It is usually identified incidentally during clinical or reproductive examination.
- Rectal palpation may identify a variably-sized (usually very large), fibrous/firm single or multiple nodular mass affected ovary (Fig. 35.14). The outline may be smooth and relatively soft, or lobulated with multiple cysts containing gelatinous fluid (identifiable ultrasonographically).

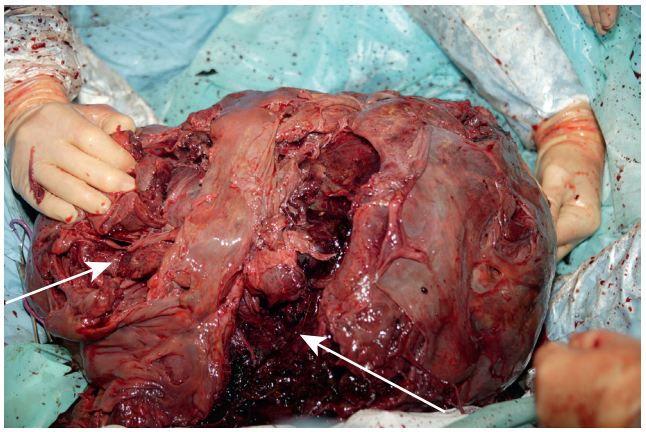


Figure 35.14 Dysgerminoma. (A) This massive tumour was identified during investigation for colic in a 4-year-old Arabian mare with a long history of repeated mild colic episodes and poor body condition. The mass had been identified during rectal palpation. Ultrasonographic examination identified the mass and its approximate size, but no diagnostically useful information could be defined. The peritoneal fluid was haemorrhagic and the horse was profoundly anaemic. The tumour measured over 40 cm in diameter and was composed of soft, mottled, tan and red neoplastic tissue. There was a very large tear in the tumour (white arrow), with an adherent blood clot (yellow arrow). The tumour contained a large smooth-lined cyst in addition to the more obviously neoplastic areas. At necropsy, further tumours were identified in the wall of the posterior vena cava, the mesentery, the diaphragm, both kidneys and widely throughout the peritoneal cavity. It was assumed that metastasis had taken place via the lymphatic and blood vessels and transcoelomically.

- Early cases present no distinctive clinical signs at all and the tumour may be detected either incidentally or as a result of apparent unrelated clinical problems, including colic, weight loss and profound anaemia and peritoneal effusion.
- Abdominal discomfort/colic and weight loss with failure to thrive and to perform normally are nonspecific signs of this tumour.
- A wide range of paraneoplastic signs and even hypertrophic osteopathy (Marie's disease) (see p. 81) may develop associated with this tumour[58]
  - Hypertrophic pulmonary osteopathy (Marie's disease) has been found in conjunction with this malignant neoplasm, causing subperiosteal new bone formation (with pain on palpation), weight loss, stiffness and oedema of the extremities.[58]
- Reproductive hormone assays and reproductive cyclicity are typically unaffected.

Differential diagnoses

- Ovarian abscess
- Granulosa–theca cell tumour
- Malignant [cyst]adenocarcinoma
- Secondary (metastatic) lymphoma or carcinoma.

Diagnostic confirmation

- *Rectal examination* will detect a large solid mass associated with one ovary.
- *Ultrasonography* will identify a poorly-defined, solid mass with a homogeneous echo-density, possibly with one or more large fluid-filled cysts within it
  - Neither rectal palpation nor ultrasonography shows any characteristic features.
- *Histological and ultrastructural examinations* allow the diagnosis to be made.[59] However, there are few cases reported.

Management

Where the diagnosis can be made early, i.e. before the tumour becomes inoperable and has metastasized, surgical removal can be effective.[57] In that event, more-or-less normal reproductive function can be maintained.

Prognosis

The prognosis is very poor for advanced cases – metastatic tumours will clearly make the prognosis hopeless.

(Primary) ovarian lymphoma

Disease summary

Notes

Very rare primary B-cell tumour of the ovary (secondary ovarian lymphoma as part of a wider syndrome is also very rare). Only unilateral cases have been reported. No endocrinological or reproductive cyclicity implication.

Clinical features

Slow progressive, non-painful, single mass within the ovary. Occasionally secondary signs of abdominal pain. Usually identified incidentally.

Diagnostic confirmation

Ultrasonographic features are suggestive but surgical pathology is definitive.

Management

Removal of the affected ovary may be curative.

Prognosis

The prognosis is very guarded – there are too few cases reported to allow useful evidence.

Overview

Isolated B-cell lymphoma in the ovary is a very rare event; few reports exist.[60] Anecdotal reports of more cases do exist. The condition is likely to be unilateral.

The tumour has a variable rate of growth and some may be detected early enough to be removed effectively.

There are too few reports to give guidance on the implications of an isolated ovarian lymphoma.

Clinical features

- The signs of ovarian lymphomas are characteristically vague – most are detected incidentally during routine clinical or reproductive examination
  - Early cases present no distinctive clinical signs at all and the tumour may be detected either incidentally or as a result of apparent unrelated clinical problems, including colic, weight loss and anaemia and peritoneal effusion
  - Abdominal discomfort/colic and weight loss with failure to thrive and to perform normally are nonspecific signs of this tumour.

- Rectal palpation may identify a variably-sized (usually large), firm, roughly spherical ovary. The surface is likely to be may be smooth.
- A wide range of paraneoplastic signs may develop.
- Reproductive hormone assays and reproductive cyclicity are typically unaffected.

Differential diagnoses

- Ovarian abscess
- Granulosa–theca cell tumour
- Malignant [cyst]adenocarcinoma
- Melanoma
- Secondary (metastatic) lymphoma or carcinoma.

Diagnostic confirmation

- *Rectal examination* may identify an enlarged (possibly spherical) firm ovary.
- *Ultrasonography* may identify a well-defined, solid mass of varying size with a homogeneous echo-density.
  - Neither rectal palpation nor ultrasonography shows any characteristic features.
- *Histological and ultrastructural examination* allow the diagnosis to be made.[59]

Management

Where the diagnosis can be made early, i.e. before the tumour becomes inoperable and has metastasized, surgical removal can be effective.[57] In that event, more-or-less normal reproductive function could be maintained.

Prognosis

The prognosis is very poor for advanced cases – metastatic tumours will clearly make the prognosis hopeless.

Other tumours affecting the ovary

Other tumours that can affect the ovary as a result of metastatic spread from other sites include:

- Melanoma (see p. 237)
- Haemangiosarcoma (see p. 334).

NEOPLASTIC DISEASE OF THE MAMMARY GLAND

Overview

See also page 260.

Tumours of the mammary gland of horses are very rare; most cases of mammary neoplasia involve secondary tumours such as sarcoid or melanoma. An incidence of 0.1–1% has been identified in slaughter house studies.[61]

Mammary adenocarcinoma

See page 260 and Fig. 14.4.

Description

These are rare, highly malignant tumours arising from mammary glandular tissue in mature horses between 12 and 25 years of age.[62–65] It is clear that there are cases of a more benign adenoma nature also and it is possible that this is a stage of progression.

Diagnosis is often delayed because of the similarity of the early stages to infectious mastitis.

Disease summary

Notes

Very rare, highly malignant tumour of mammary gland tissue of mature mares. Adenocarcinoma can be ulcerated and faster growing, with some local destruction. High tendency to metastasis.

Clinical features

Rapidly developing solid, hot tumour with a prominent blood supply. Possibly ulcerated.

Diagnostic confirmation

Biopsy is definitive.

Management

Early surgical removal may be effective, but margins may not be easy to define. Late presentation gives less chance of success.

Prognosis

Prognosis is very poor – the tumour commonly recurs and is often metastatic.

Clinical features

- Usually unilateral, rapidly enlarging mammary gland with palpable poorly-demarcated solid tissue (Fig. 35.15A,B)
  - Extension to the contralateral mammary gland is common at an early stage[66,67]
  - Early adenocarcinoma or adenoma lesions are often overlooked because of the protected site of the mammary glands in mares and because they are often misdiagnosed as cysts or mastitis.
- Usually hot and well-vascularized.
- Painful on palpation.
- Ulceration and extension to local lymph nodes (inguinal and iliac) are common and rapid.
- Secretions are bloodstained and highly cellular.
- Inguinal and iliac lymphadenopathy.
- Secondary signs, including thoracic and abdominal fluid accumulations, reflect metastatic spread.[68]
- Paraneoplastic signs are expected, including cachexia, pyrexia and anaemia.

Differential diagnoses

- Mastitis and idiopathic mammary enlargement/ mammary abscess
- Sarcoid (nodular or fibroblastic)
- Squamous cell carcinoma.

Diagnostic confirmation

- *Mammary secretion* is bloodstained and contains abnormal cells along with inflammatory cells.[65,69]
- *Ultrasonography* can be helpful in determining the extent of the mass and its blood supply.
- *Biopsy* is definitive (wedge or hollow-needle procedures are far better than fine-needle aspirates).





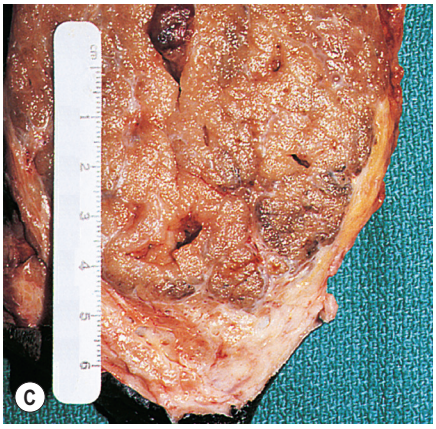


Figure 35.15 Mammary adenocarcinoma. (A,B) This 13-year-old Warmblood mare was presented with a rapidly expanding, painful, hot mammary gland. A diagnosis of mammary adenocarcinoma was made by biopsy. **(C)** A cross-section through a mammary gland with an early adenocarcinoma. Note the total loss of lactiferous sinuses and normal mammary architecture. *(Figures A and B courtesy of Christoph Koch, VetSuisse Bern; Figure C courtesy of Dr RR Pascoe, reprinted from Knottenbelt DC, Pascoe R, Lopate C, et al. Equine Stud Farm Medicine and Surgery. Edinburgh: WB Saunders; 2003: 350 (Fig. 10.8), copyright 2003, reprinted with permission from Elsevier.)*

Management

- *Surgical removal* of the entire affected tissue is essential, but usually metastatic spread has taken place prior to presentation. Removal of regional lymph nodes is essential[70]
  - The best chance is when an early lesion diagnosed as a benign adenoma is removed and, in this case, a total mastectomy should be performed.
- *Concurrent chemotherapy*, either locally or systemically, is probably wise but will not help much if the condition is widespread.

Prognosis

The prognosis is poor or hopeless.

Mammary squamous cell carcinoma

See also page 220.

Description

Mammary squamous cell carcinoma is best regarded as an extension of a cutaneous carcinoma, with invasion of the mammary gland.[70]

Clinical features

- Papillomatous or, more commonly ulcerated fleshy and invasive tumour of the skin of the mammary gland – more often on the teat than the body of the gland in the early stages at last.
- Concurrent carcinoma at other sites (especially the vulva) is common but the relationship between the tumours occurring at the two sites is not clear.

Disease summary

Notes

Very rare, benign, usually solitary tumour of cutaneous sebaceous glands. Adenocarcinoma can be ulcerated and faster growing, with some local destruction. No recognized metastatic tendency.

Clinical features

Focal nodular (possibly multinodular) mass in the skin itself.

Diagnostic confirmation

Biopsy (excisional) is definitive.

Management

Surgical removal is usually effective, but margins may not be easy to define.

Prognosis

Prognosis is good, provided it is excised fully – recurrence may occur, but this remains local.

Differential diagnoses

- Sarcoid (nodular or fibroblastic)
- Adenocarcinoma/adenoma
- Neurofibroma
- Mastitis
- Insect bite reactions
- Foreign body reactions.

Diagnostic confirmation

- Biopsy
- Surgical excision
- Histopathology.

Management

- Surgical excision with concurrent chemotherapy or radiation is effective if the case is presented early enough.
- Once the tumour invades the mammary gland itself, the outlook is poor.

Mammary melanoma

See also page 237.

Disease summary

Notes

Relatively common site for melanoma development.

Clinical features

Focal nodular (possibly multinodular) mass in the skin or mammary tissue.

Diagnostic confirmation

Biopsy (excisional) is definitive.

Management

Surgical removal is usually effective but margins may not be easy to define; mastectomy can be curative but sadly there are other lesions also.

Prognosis

Prognosis is good, provided it is excised fully – recurrence may occur, but this remains local.

Description

These are relatively common tumours in the mammary gland of grey horses (possibly exclusively).

Clinical features

See Figure 35.16.

- Solitary masses that vary in form from nodules to multilobulated growths.
- They are usually slow-growing and benign in nature, but may ulcerate early and discharge a sticky, black, haemorrhagic material.

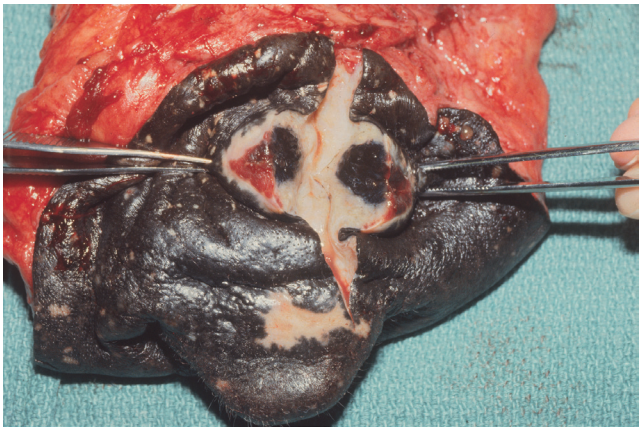


Figure 35.16 Mammary melanoma. This nodule was identified on palpation and was diagnosed as a malignant melanoma by hollow-needle biopsy under ultrasonographic guidance. A mastectomy was performed and healed without complication. It was impossible to guess whether this improved the long-term prognosis for the mare, since there were plentiful other melanomas at other sites. *(Figure courtesy of Reg Pascoe.)*

- Haemorrhage and a non-healing margin are major problems.

Differential diagnoses

- Sarcoid (nodular or fibroblastic)
- Squamous cell carcinoma
- Neurofibroma
- Mastitis
- Mammary cyst.

Diagnostic confirmation

- Biopsy
- Surgical excision
- Histopathology.

Management

Surgical excision is effective, with little tendency to recurrence.

Prognosis

The prognosis is good, provided that the tumour is benign or at least non-metastatic.

Mammary sarcoid

See also pages 203 and 544.

Disease summary

Notes

The mammary gland is a common site for sarcoid development.

Clinical features

Focal nodular (possibly multinodular) mass in the skin itself but some do invade the mammary tissue.

Diagnostic confirmation

Biopsy (excisional) is definitive.

Management

Surgical removal is usually effective, but margins may not be easy to define and recurrence is common.

Prognosis

Prognosis is good, provided it is excised fully – recurrence may occur.

Description

These are common tumours and the mammary gland is subject to the full range of sarcoid types (see p. 545) rare tumours arising from sebaceous gland cells in adult to aged horses. They may occur at any cutaneous site and the causative factors are unknown.

Donkeys seem to be predisposed to the development of invasive nodular and fibroblastic sarcoids on the skin of the mammary gland and teat.

There is no known age, sex or breed predilection and no metastatic tendency.

Clinical features

- Solitary masses, which vary in form from nodules to alopecic lobulated growths. Some also have verrucose components.

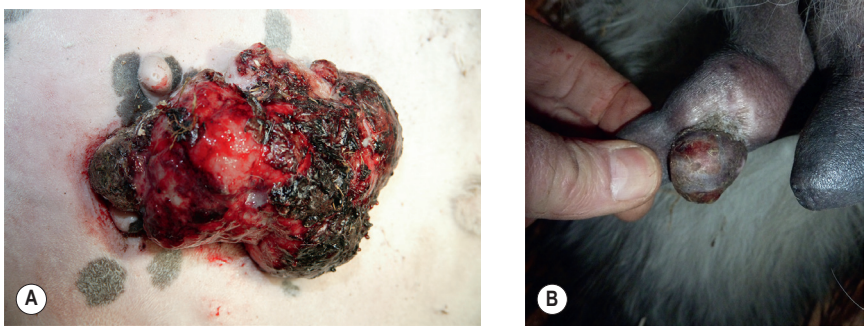


Figure 35.17 Mammary sarcoid. All sarcoid types can occur on the mammary skin. **(A)** This large fibroblastic sarcoid on a 9-year-old donkey was attached to the mammary skin but did not penetrate into the gland itself. It was removed successfully using SMART (minimal cell contamination) surgery (see p. 120). **(B)** A small nodular sarcoid developed on the teat of a 4-year-old donkey. Within a period of 6 weeks, the teat became extensively involved with an invasive fibroblastic sarcoid that also penetrated into the mammary tissue. A hemi-mastectomy was performed successfully.

- They are usually slow-growing and benign in nature, but ulcerate early and become an exophytic tumour mass (Fig. 35.17).
- Some invade the mammary tissue very quickly and become much more aggressive.

Differential diagnoses

- Sarcoid (nodular or fibroblastic)
- Squamous cell carcinoma
- Neurofibroma
- Dermoid cyst
- Nodular collagenolytic granuloma/eosinophilic collagen granuloma
- Insect and insect bite reactions
- Foreign body reactions.

Diagnostic confirmation

- Biopsy (or surgical excision)
- Histopathology (see p. 203).

Management

There are many suggested treatments for the equine sarcoid (see p. 555).

Prognosis

The prognosis is generally good if the tumours are recognized and treated early, but far worse if the lesions are neglected or interfered with ill-advisedly.

References

1. Brinsko SP. Neoplasia of the male reproductive tract. Vet Clin North Am Equine Pract 1998; 14:517–533.
2. Plaut A, Kohn-Speyer AC. The carcinogenic action of smegma. Science 1947; 105:391–392.
3. MacFadden KE, Pace LW. Clinical manifestations of squamous cell carcinoma in horses. Comp Cont Ed Pract Vet 1991; 13:669–676.
4. Patterson LJ, May SA, Baker JR. Skeletal metastasis of a penile squamous cell carcinoma. Vet Rec 1990; 126:579–580.
5. Rosemberg SK. Lasers and squamous cell carcinoma of external genitalia. Urology 1986; 27:430–433.
6. Phillips JC, Lembcke LM. Equine melanocytic tumors. Vet Clin North Am Equine Pract 2013; 29:673–687.
7. Goetz TE, Ogilvie GK, Keegan KG, et al. Cimetidine for the treatment of melanoma in 3 horses. J Am Vet Med Assoc 1990; 196:449–452.
8. Heinzerling LM, Feige K, Rieder S, et al. Tumor regression induced by intratumoral injection of DNA coding for human interleukin 12 into melanoma metastases in gray horses. J Mol Med 2001; 78:692–702.
9. Phillips JC, Lembcke LM, Noltenius CE, et al. Evaluation of tyrosinase expression in canine and equine melanocytic tumors. Am J Vet Res 2012; 73:272–278.
10. Taylor S, Haldorson G. A review of the equine sarcoid. Equine Vet Educ 2013; 25:210–216.
11. Knottenbelt DC. A Clinical classification of the equine sarcoid. Clin Tech Equine Pract 2005; 4:278–295.
12. Stick JA. Teratoma and cyst formation of the equine cryptorchid testicle. J Am Vet Med Assoc 1980; 176:211–214.
13. Pollock PJ, Prendergast M, Callanan JJ, et al. Testicular teratoma in a three-day-old thoroughbred foal. Vet Rec 2002; 150:348–350.
14. Willis RA, Rudduck HB. Testicular teratomas in horses. J Pathol Bacteriol 1943; 55:165–171.
15. Shaw DP, Roth JE. Testicular teratocarcinoma in a horse. Vet Pathol 1986; 23:327–328.
16. Martin GR. Teratocarcinoma and mammalian embryogenesis. Science 1980; 209:768–775.
17. Cribb NC, Bouré LP. Laparoscopic removal of a large abdominal testicular teratoma in a standing horse. Vet Surg 2010; 39:131–135.
18. Schönbauer M, Schönbauer-Längle A. Seminomas in the horse. A retrospective study. [Article in German]. Zentralbl Veterinarmed A 1983; 30:189–198.
19. Govaere J, Ducatelle R, Hoogewijs M, et al. Case of bilateral seminoma in a trotter stallion. Reprod Domest Anim 2010; 45:537–539.
20. Beck C, Charles JA, Maclean AA. Ultrasound appearance of an equine testicular seminoma. Vet Radiol Ultrasound 2001; 42:355–357.
21. Trigo FJ, Miller RA, Torbeck RL. Metastatic equine seminoma: report of two cases. Vet Pathol 1984; 21:259–260.
22. Becht JL, Thacker HL, Page EH. Malignant seminoma in a stallion. J Am Vet Med Assoc 1979; 175:292–293.
23. Smith BL, Morton LD, Watkins JP, et al. Malignant seminoma in a cryptorchid stallion. J Am Vet Med Assoc 1989; 195:775–776.
24. Gelberg HB, McEntee K. Equine testicular interstitial cell tumours. Vet Pathol 1987; 24:231–234.
25. May KA, Moll HD, Duncan RB, et al. Unilateral Leydig cell tumour resulting in acute colic and scrotal swelling in a stallion with descended testes. Equine Vet J 1999; 31:343–345.
26. Pratt SM, Stacy BA, Whitcomb MB, et al. Malignant Sertoli cell tumour in the retained abdominal testis of a unilaterally cryptorchid horse. J Am Vet Med Assoc 2003; 222:486–490.
27. Sokkar SM, Hamouda MA, Abdel-Rahman SM. Histopathological studies on neoplasms in the genital tract of female donkeys in Egypt. Berl Munch Tierarztl Wochenschr 2001; 114:166–168.
28. McCue PM. Neoplasia of the female reproductive tract. Vet Clin North Am Equine Pract 1998; 14:505–515.
29. Karcher LF, Le Net J, Turner BF, et al. Pseudohyperparathyroidism in a mare associated with squamous cell carcinoma of the vulva. Cornell Vet 1990; 80:153–162.
30. Berezowski C. Diagnosis of a uterine leiomyoma using hysteroscopy and a partial ovariohysterectomy in a mare. Can Vet J 2002; 43:968–970.
31. Bracher V, Mathias S, Allen WR. Videoendoscopic evaluation of the mare's uterus: II. Findings in subfertile mares. Equine Vet J 1992; 24: 279–284.
32. Bartmann CP, Stief B, Schoon HA. Thermal injury and wound healing of the endometrium subsequent to minimally invasive transendoscopic use of Nd:YAG-laser-and electrosurgery in horses. [Article in German]. Deutsche Tierartztl Wochenschr 2003; 110:271–280.
33. McCue PM, Roser JF, Munro CJ, et al. Granulosa cell tumours of the equine ovary. Vet Clin North Am Equine Pract 2006; 22:799–817.
34. Hultgren BD, Zack PM, Pearson EG, et al. Juvenile granulosa cell tumour in an equine weanling. J Comp Pathol 1987; 97:137–142.
35. Charman RE, McKinnon AO. A granulosa-theca cell tumour in a 15-month-old Thoroughbred filly. Aust Vet J 2007; 85:124–125.
36. Crabtree J. Review of seven cases of granulosa cell tumour of the equine ovary. Vet Rec 2011; 169:251–252.

37. Frederico LM, Gerard MP, Pinto CRF, et al. Bilateral occurrence of granulosa-theca cell tumours in an Arabian mare. Can Vet J 2007; 48:502–505.
38. Turner TA, Manno M. Bilateral granulosa cell tumour in a mare. J Am Vet Med Assoc 1983; 182:713–714.
39. Gee EK, Dicken M, Archer RM, et al. Granulosa theca cell tumour in a pregnant mare: concentrations of inhibin and testosterone in serum before and after surgery. N Z Vet J 2012; 60:160–163.
40. Gift LJ, Gaughan EM, Schoning P. Metastatic granulosa cell tumour in a mare. J Am Vet Med Assoc 1992; 200:1525–1526.
41. Rambags BP, Stout TA, Rijkenhuizen AB. Ovarian granulosa cell tumours adherent to other abdominal organs; surgical removal from 2 Warmblood mares. Equine Vet J 2003; 35:627–632.
42. Alexander GR, Tweedie MA, Lescun TB, et al. Haemoperitoneum secondary to granulosa cell tumour in two mares. Aust Vet J 2004; 82:481–484.
43. Hinrichs K, Hunt PR. Ultrasound as an aid to diagnosis of granulosa cell tumour in the mare. Equine Vet J 1990; 22:99–102.
44. Stabenfeldt GH, Hughes JP, Kennedy PC, et al. Clinical findings, pathological changes and endocrinological secretory patterns in mares with ovarian tumours. J Reprod Fertil Suppl 1979; 27:277–285.
45. Ball BA, Almeida J, Conley AJ. Determination of serum anti-Müllerian hormone concentrations for the diagnosis of granulosa-cell tumours in mares. Equine Vet J 2013; 45:199–203.
46. Ball BA, Conley AJ, MacLaughlin DT, et al. Expression of anti-Müllerian hormone (AMH) in equine granulosa-cell tumours and in normal equine ovaries. Theriogenology 2008; 70:968–977.
47. Maurice KT. Diagnosis and surgical removal of a granulosa-theca cell tumour in a mare. Can Vet J 2005; 46:644–646.
48. Henson KL, Alleman AR, Cutler TJ, et al. Regression of subcutaneous lymphoma following removal of an ovarian granulosa-theca cell tumour in a horse. J Am Vet Med Assoc 1998; 212:1419–1422.
49. Held JP, Buergelt C, Colahan P. Serous cystadenoma in a mare. J Am Vet Med Assoc 1982; 181:496–498.
50. Hinrichs K, Frazer GS, deGannes RV, et al. Serous cystadenoma in a normally cyclic mare with high plasma testosterone values. J Am Vet Med Assoc 1989; 194:381–382.
51. Son Y, Lee C, Jeong W, et al. Cystadenocarcinoma in the ovary of a Thoroughbred mare. Aust Vet J 2005; 83:283–284.
52. Pauwels FE, Wigley SJ, Munday JS, et al. Bilateral ovarian adenocarcinoma in a mare causing haemoperitoneum and colic. N Z Vet J 2012; 60:198–202.
53. Morris DD, Acland HM, Hodge TG. Pleural effusion secondary to metastasis of an ovarian adenocarcinoma in a horse. J Am Vet Med Assoc 1985; 187:272–274.
54. Frazer GS, Robertson JT, Boyce RW. Teratocarcinoma of the ovary in a mare. J Am Vet Med Assoc 1988; 193:953–955.
55. Lefebvre R, Theoret C, Doré M, et al. Ovarian teratoma and endometritis in a mare. Can Vet J 2005; 46:1029–1033.
56. Gehlen H, Haist V, Baumgärtner W, et al. Malignant dysgerminoma in an 18-year-old Warmblood mare. J Equine Vet Sci 2006; 26:23–26.
57. Harland S, Smith CS, Mogg TD, et al. Surgical resection of a dysgerminoma in a mare. Aust Vet J 2009; 87:110–112.
58. McLennan MW, Kelly WR. Hypertrophic osteopathy and dysgerminoma in a mare. Aust Vet J 1977; 53:144–146.
59. Chandra AMS, Woodard JC, Merritt AM. Dysgerminoma in an Arabian filly. Vet Pathol 1998; 35:308–311.
60. Lock TF, Macy DW. Equine ovarian lymphosarcoma. J Am Vet Med Assoc 1979; 175:72–73.
61. Schmahl VW. Solides Karzinom der Mamma bei einem Pferd. Berl Munch Tierarztl Wochenschr 1972; 85:141–142.
62. Reppas GP, McClintock SA, Canfield PJ, et al. Papillary ductal adenocarcinoma in the mammary glands of two horses. Vet Rec 1996; 138:518–519.
63. Spadari A, Valentini S, Sarli G, et al. Mammary adenoma in a mare: clinical, histopathological and immunohistochemical findings. Equine Vet Educ 2008; 20:4–7.
64. Seahorn TL, Hall G, Brumbaugh GW, et al. Mammary adenocarcinoma in four mares. J Am Vet Med Assoc 1992; 200:1675–1677.
65. Prendergast M, Basett H, Larkin HA. Mammary carcinoma in three mares. Vet Rec 1999; 144:731–732.
66. Munson L. Carcinoma of the mammary gland in a mare. J Am Vet Med Assoc 1987; 191:71–72.
67. Hirayama K, Honda Y, Sako T, et al. Invasive ductal carcinoma of the mammary gland in a mare. Vet Pathol 2003; 40:86–91.
68. Foreman JH, Weidner JP, Parry BW, et al. Pleural effusion secondary to thoracic metastatic mammary adenocarcinoma in a mare. J Am Vet Med Assoc 1990; 197:1193–1195.
69. Freeman KP. Cytological evaluation of the equine mammary gland. Equine Vet Educ 1993; 5:212–213.
70. Snyder JR, Maher O. Mammary neoplasia In: McKinnin AO, Squires EL, Vaala WE, et al., eds. Equine reproduction. Oxford: Wiley Blackwell; 2011: 2472–2743.

36 Tumours of the urinary tract

Overview	652	Bladder carcinoma	658
Renal carcinoma/adenocarcinoma	652	Secondary tumours of the urinary tract	661
Ureteral neoplasia	657		

Overview

Primary neoplasia of the urinary tract is very rare in horses but those that do occur have a high tendency to create serious problems. The most prevalent primary conditions affect the lower urinary tract, but secondary tumours of the kidney are probably more frequent than secondary tumours of the lower urinary tract. Even in secondary tumour involvement, both kidneys are seldom equally involved and most renal tumours involve one kidney only. The ureters themselves have not been reported to have any tumour involvement – either primary or secondary.

Horses that present with renal neoplasia show nonspecific clinical signs and clinicopathological findings. Diagnosis is most often based on rectal palpation, abdominal ultrasound examination, investigation of haematuria and biopsy. Most cases are identified late in the course of disease and survival is poor. However, early diagnosis may confer a less grave prognosis and allow exploration of treatment options, such as laparoscopic nephrectomy, allowing renal neoplasia to be more manageable.

Ureteral tumours are singularly rare in all species, with only one reported case in the horse.[1] For the most part, the ureters can probably be regarded as 'unaffected' by neoplasia.

Bladder tumours are very rare – most cases that are diagnosed with bladder tumour in primary practice on a clinical basis have reactive inflammatory changes rather than overt tumour. However, epithelial tumours (bladder carcinoma) do occur with some frequency; these can be divided into squamous and transitional cell carcinoma (the latter are very rare in fact and most tumours are squamous cell carcinoma). Rarely, primary non-epithelial tumours of other cell types can be identified; these can include leiomyoma (/sarcoma) and rhabdomyoma (/sarcoma), vascular tumours such as haemangiosarcoma and tumours of fibrous tissue including polyps and fibrosarcoma. These are even less common in horses. However, there have been single reports in the literature of leiomyosarcoma, rhabdomyosarcoma and lymphosarcoma.[2–4]

Note

Fibromatous polyp, rhabdomyosarcoma and urachal cystadenoma are the only reported bladder neoplasms in horses <3 years old.[4–6]

Tumours of the urethra are again very rare, with no reports of any occurring in the main part of the structure. Anecdotally, however, from time to time, tumours do develop – mainly these seem to be leiomyoma or polypoid tumours of the epithelium. The main urethral tumour that is significant in both male and female horses is squamous cell carcinoma that develops at the distal end of the urethra (see pp. 630 and 639).

The reported urinary tract tumours are shown in Table 36.1 and the reported cases are shown in Table 36.2.

Renal carcinoma/adenocarcinoma

See also page 271.

Description

Renal carcinomas arise from the tubular epithelium and most are localized in the pole of one kidney. They are usually large and unilateral, and so renal function is often maintained normally.[16] Tumour cells may vary greatly in shape, size and cytoplasmic staining; they may be arranged with a solid, tubular, acinar or papillary pattern, and the appearance may

Disease summary

Notes

Very rare malignant tumour of tubular epithelial cells (carcinoma) and renal glandular cells (adenocarcinoma) affecting middle-aged horses (mean age 13 years).

Clinical features

Chronic but accelerating weight loss, anorexia, colic and haematuria; possible multiple organ involvement with rapidly developing metastatic tumours to liver and lungs.

Diagnostic confirmation

Rectal palpation, ultrasonography and percutaneous biopsy.

Management

Unilateral nephrectomy (possibly by laparoscopy) if unilateral disease is confirmed and there is no evidence of metastatic disease.

Prognosis

Prognosis is very poor – possibly the most malignant tumour of horses.

Table 36.1 Equine urinary Tract tumours reported in the literature

	Primary	Secondary
Kidney	1. Carcinoma 2. Adenoma 3. Papilloma 4. Nephroblastoma[7,8] 5. Renal mucous gland cystadenoma[9] 6. Papillary adenoma of distal nephron differentiation[10] 7. Renal clear cell tumour (hypernephroma)	1. Lymphoma 2. Haemangiosarcoma 3. Melanoma 4. Carcinoma
Bladder	1. Transitional cell carcinoma 2. Squamous cell carcinoma 3. Polyp (fibromatous)[6,11] 4. Lymphosarcoma[3,6] 5. Rhabdomyosarcoma[4,12] 6. Leiomyosarcoma[2]	1. Carcinoma 2. Lymphosarcoma 3. Haemangiosarcoma 4. Melanoma

Table 36.2 Cases of renal neoplasia reported in the horse after 1980

Ref. No.	Presenting signs	Tumour type and location	Management/prognosis	Age (years)	Breed	Sex
13	Gross haematuria – 3 weeks	Papillary adenoma	Nephrectomy by hand-assisted laparoscopic technique, no abnormalities at 18 months' follow-up	20	TB	G
14	Chronic haematuria – 3 months and acute lameness at repeat presentation	Adenocarcinoma	Euthanasia	19	WB	F
15	Collapse, anorexia, colic and diarrhoea	Anaplastic carcinoma	Euthanasia	14	Mustang	G
16	Depression, weight loss, collapse	Renal cell carcinoma	Euthanasia	6	TB	G
9	Neurological deficits and hindlimb weakness	Renal mucous gland cystadenoma	Euthanasia	35	Unknown	F
17	Haematuria, colic, weight loss	Renal adenocarcinoma	Euthanasia	4	Shire	F
18	Poor performance and chronic weight loss	Renal carcinoma	Euthanasia	9	TB	F
19	Ulcerated mass on premaxilla	Renal cell carcinoma	Euthanasia	14	Hunter	G
7	Poor performance and intermittent haematuria	Triphasic nephroblastoma	Euthanasia	3	TB	F
20	Shoulder lameness	Perirenal carcinoma	Euthanasia	18	TB	G
8	Post-exercise haematuria	Nephroblastoma	Hand-assisted laparoscopic removal; in race training and raced successfully multiple times at 18 months post-surgery	3	TB	S
10	Colic – not related	Papillary renal adenoma	Euthanasia for LCT; incidental finding at PM	20	TB	F
21	Lameness, partial anorexia	Renal carcinoma	Euthanasia	21	Arab	G
22	Haematuria, intermittent pyrexia and decreased appetite	Renal carcinomatosis	Euthanasia	14	Hunter	F

Continued

Table 36.2 Cases of renal neoplasia reported in the horse after 1980 – cont'd

Ref. No.	Presenting signs	Tumour type and location	Management/prognosis	Age (years)	Breed	Sex
23	Intermittent colic, recurrent fever and weight loss	Renal carcinoma	Euthanasia	7	Anglo-Arab	G
24	Haematuria, weight loss, partial anorexia	Renal cell carcinoma	Euthanasia	15	Pony	G
	Weight loss, back pain, partial anorexia, colic, polyuria/ polydipsia	Renal carcinoma	Died	10	Pony	G
	None	Renal carcinoma	Died in recovery after laryngeal surgery	4	TB	G
	Intermittent haematuria, colic, weight loss and partial anorexia	Renal carcinoma	Euthanasia	7	TBX	G
25	Weight loss	Renal adenocarcinoma	Euthanasia	6	TB	F
26	Haematuria	Renal cell carcinoma	Hand-assisted laparoscopic nephrectomy; metastatic carcinoma at 7 months' follow-up	18	QH	G
27	Acute-onset lameness	Papillary renal carcinoma	Euthanasia	14	Pony	G
28	Colic	Renal carcinoma	Died	23	TBX	G
29	Chronic weight loss, inappetence and intermittent diarrhoea	Renal cell carcinoma	Euthanasia	16	TB	F
30	Depression, anorexia, weight loss, colic	Renal adenocarcinoma	Euthanasia	15	American Saddle horse	G
31	Presented due to abortion at 7 months' gestation, severe ascites and shock	Renal cell carcinoma	Died	10	Albino	F
	2 weeks' weight loss and haematuria	Renal cell carcinoma	Euthanized at ex lap. due to extensive nature of mass	16	SB	F
32	Right-sided abdominal mass, weight loss, inappetence and PD	Renal adenocarcinoma	Unilateral nephrectomy Outcome – alive at 12 months post-surgery No mets No PNS	16	QH	F
33	Mass in sublumbar region and PU/PD	Renal tubular cell carcinoma	Euthanasia	15	Ten Walk	F

G, gelding; F, mare; S, stallion.

vary markedly between adjacent areas of the same tumour.[24] Renal adenocarcinoma derives from glandular cells in the kidney.

Several surveys reviewing the occurrence of tumours in the horse failed to mention the occurrence of any renal neoplasia.[34–36] Renal carcinoma, also known as renal cell carcinoma and renal adenocarcinoma, is the most common form of renal neoplasia in humans and accounts for approximately 3% of all malignant neoplasms in human adults. Renal carcinoma is the most common form of primary renal neoplasia in horses.[37] In a survey of 3633 horses examined at post mortem in New York State University from 1953 to 1976, only four cases of renal neoplasia were identified: an incidence of 0.11%.[31] One study of slaughtered animals reported a case in a horse.[38] Primary renal carcinomas are most commonly unilateral and exhibit locally aggressive behaviour and metastasis to regional lymph nodes, lungs and liver, but it has been reported bilaterally.[17,22,24,29,30] In one retrospective study, 100% cases were unilateral, and 64% affected the right kidney.[17]

In an analysis of nine different reports of renal carcinoma from 1934 to 1986, information from 15 horses showed an age range of 4–20 years, with 7/15 being ≤10 years, a nearly equal percentage of geldings and mares, with several breeds

being represented.[17] In a retrospective study of 27 cases of renal carcinoma, there was a wide range of ages (4–25 years, mean 13 years, median 14 years) with no sex predilection. Breeds significantly associated with the presence of renal carcinoma included Thoroughbreds and Arabs, whilst Quarter Horses were under-represented; however, small numbers of published reports makes conclusions difficult.[39]

Genetic predisposition to forms of renal carcinoma has been described in humans and dogs, and the possibility of similar genetic factors in horses cannot be discounted. However, in humans, renal cell carcinoma has been implicated to result from exposure to fumonisin B1. Clear evidence for carcinogenic potential has been demonstrated in rats and mice and may be considered a component of the aetiology in horses.[40]

Clinical features

Horses with renal neoplasia present with a variety of nonspecific signs. The lack of specific signs is stated in many reports, making diagnosis of renal neoplasia, especially early in the course of the disease, extremely challenging.

The main presenting signs include[39]:

- Weight loss
- Fever
- Haematuria (Fig. 36.1)
- Ascites/haemoperitoneum
- Abortion
- Haemothorax/haemabdomen
- Anorexia (partial or complete)/depression
- Colic signs/back pain
- Diarrhoea
- Ventral oedema

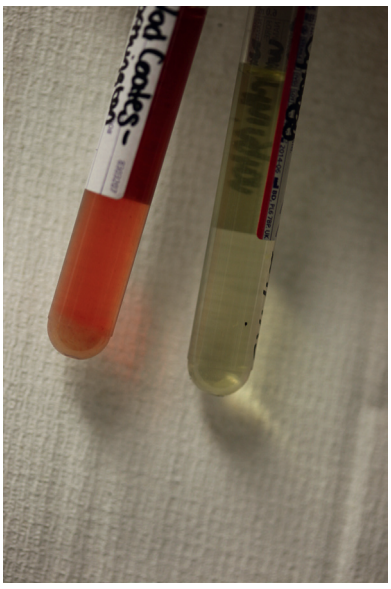


Figure 36.1 Large mass with variable echogenicity.
A 12-year-old gelding was presented with a 2-week history of haematuria, weight loss and dullness associated with recurrent fever. Urine was sampled from each renal pelvis via ureteroscopy; blood was only present in urine from the left kidney. Ultrasonography revealed a very large mass with variable echogenicity and very prominent blood supply in the left kidney.

- Polyuria/polydipsia
- Anaesthetic-related death.[18,30]

Since the tumour is invariably unilateral, signs of renal failure are unusual.[14,24,28,41] A few cases may have palpable swellings or masses in the flank area that are painful and sensitive to palpation. Other physical examination findings are generally unremarkable.

There is a high rate of metastatic spread and so the signs can be very diverse, depending on which structures/organs are most affected (Fig. 36.2).[19]

Differential diagnoses

- Haematuria arising from other uses including cystitis, pyelonephritis or cystic or ureteral calculus
- Haemorrhagic diathesis
- Haemoglobinuria and other causes of pigmenturia
- Other causes of weight loss, colic or depression
- Mesothelioma
- Renal secondary tumours such as lymphoma.

Diagnostic confirmation

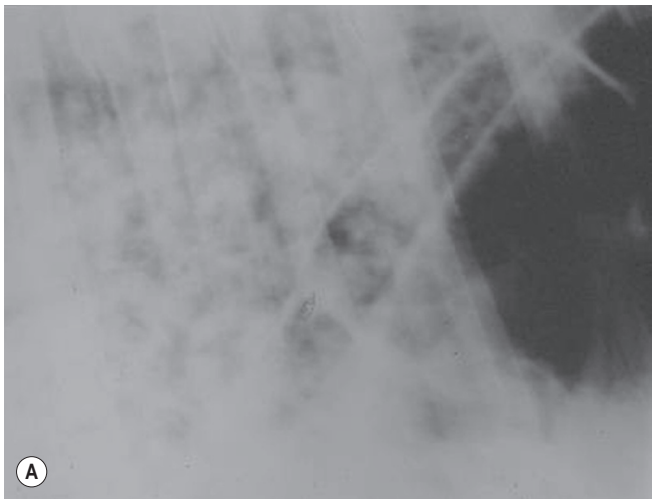
Note

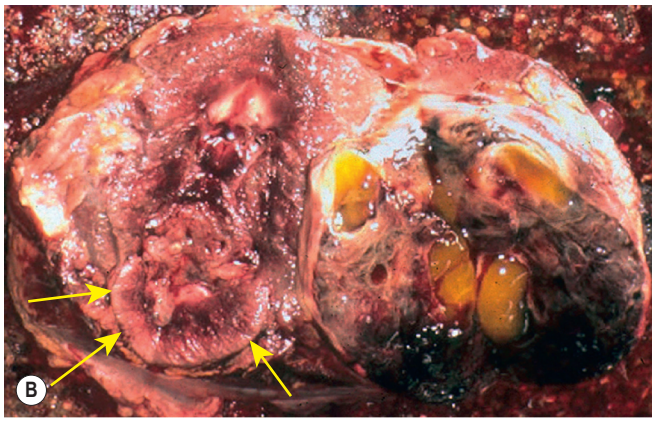
The diagnosis of renal neoplasia can easily be overlooked if it is not included in the differential diagnoses of horses with the nonspecific clinical signs listed above, no matter how rare it actually is.

- Rectal detection of a painful dorsal abdominal mass in the region of the kidney, especially if a normal kidney cannot be palpated in that area, is suggestive of renal neoplasia.[25,32,39]
- Haematology, serum biochemistry and urinalysis results are variable and are not definitive indications of renal neoplasia.[37,39]
- Reported haematological abnormalities have included:
  - Anaemia
  - Neutrophilia
  - Leukocytosis
  - Lymphocytosis
  - Hyperfibrinogenaemia
  - Thrombocytopaenia
  - Hypercupraemia
  - Hypoglycaemia and mild azotaemia may be found.[15,16,42]

Interestingly, clinically insignificant paraneoplastic hypoglycaemia has been identified frequently in cases of equine renal carcinoma, indicating that it may be an important feature of this disease.[18,22,30] Where metastatic tumour has developed, other signs including liver enzyme elevations can be present. One report described hypercupraemia as a possible paraneoplastic syndrome associated with renal adenocarcinoma.[17]

- Urinalysis may reveal haematuria (micro or overt) but this can be intermittent. However, gross or microscopic haematuria is present in nearly all horses with renal carcinoma.[39] Although neoplastic cells could





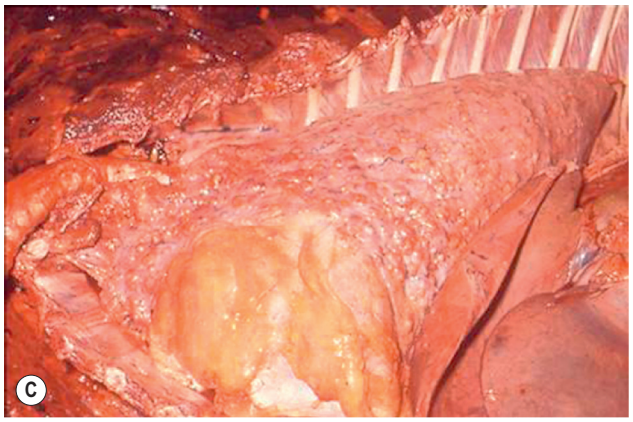


Figure 36.2 Metastatic tumours. A middle-aged mare was presented with chronic haematuria, weight loss and fever. Ultrasonography and haematology suggested renal neoplasia. Renal biopsy confirmed renal carcinoma in the right kidney. **(A)** A lateral radiograph of the thorax showed extensive metastatic tumours, emphasizing the malignant nature of the condition. **(B)** At necropsy, the extent of the tumour and its severity was obvious with only a very small amount of recognizable renal tissue (arrow). **(C)** Metastatic tumours were found throughout the lungs and, in addition, further metastatic tumours were found in the liver, spleen, thorax and abdomen. *(Figures courtesy of Tim Mair.)*

theoretically be detected in the urine, this has not been reported.

- Neoplastic cells have been detected in abdominal fluid from horses with renal carcinoma.[22,33] Around 70% of cases of renal carcinoma have abnormal peritoneal fluid samples, including haemabdomen and exfoliated neoplastic cells.[39] Immunohistochemistry on cells derived from peritoneal fluid may be diagnostically beneficial.[16]
- Cystoscopy is relatively easy to perform and is essential to evaluate the source of haematuria (Fig. 36.3).[39]
- Transcutaneous ultrasonography provides a non-invasive method of examining both kidneys[33]; a grossly enlarged kidney with abnormal architecture is likely to be identified (see Fig. 36.3). Differentiation between acute and chronic renal disease can usually be made because of the advanced degree of morphological change in chronic conditions.[41] It is useful for confirming the unilateral nature of the disease.
- Although renal biopsies are rarely performed in horses, the procedure is extremely useful for confirming the diagnosis.[39] Immunohistochemistry may be diagnostically beneficial.[16]
- Renal scintigraphy might prove useful for better evaluation of glomerular filtration rate and evaluation of split renal function. However, availability and cost of the equipment required limit its use.

Notes

Metastasis of renal carcinoma is common. The most common sites identified at post mortem include liver and lung, but many other metastatic sites have been identified.[27,37,39] Whilst metastasis to the liver and lung is most common (see Fig. 36.3), osseous metastasis, although extremely rare, should be considered as a differential diagnosis for progressive unexplained lameness. Osseous metastasis has been reported in the maxilla, olecranon and third phalanx.[14,19,21] Thoracic radiographs should probably always be performed and may be helpful in confirming the presence of metastatic lung disease (see Fig. 36.2A).[24,29]

Management

- In both carcinoma and adenocarcinoma, early surgical nephrectomy (either via direct conventional surgery following rib resection or laparoscopic nephrectomy) can be curative, provided that no metastatic spread has occurred, but in the large majority of cases the tumour is too invasive for resection.[39] It is important to realize that even if nephrectomy can be performed successfully, a proportion of the cases will already have undergone metastatic spread to the lungs and liver, in particular, and so signs of organ involvement may appear some months or years later.[26] Bony metaplasia of a renal tumour (tubule-papillary transitional cell carcinoma of the renal pelvis) has been described in a horse.[23]

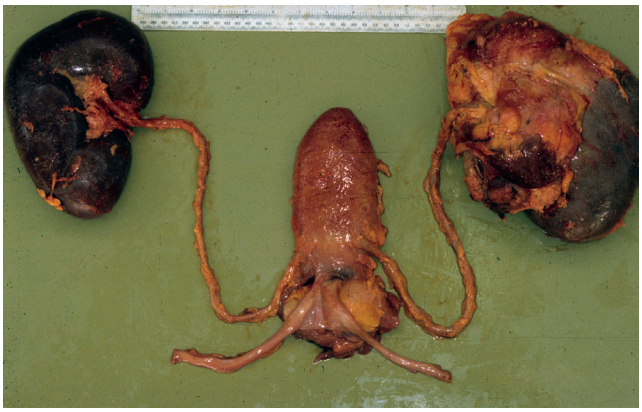


Figure 36.3 Renal adenocarcinoma. A 16-year-old Thoroughbred mare was presented with a 4-month history of unattended haematuria. She developed abdominal pain and anaemia and was then referred. Endoscopy of her urinary tract confirmed the presence of blood in the urethra and the bladder. Unilateral ureteral (right) haematuria was noted. Ultrasonography of her urinary tract revealed a large disorganized mass with little recognizable renal tissue in the right kidney. A percutaneous biopsy was taken and this confirmed renal adenocarcinoma. At necropsy, the extent of the pathology was obvious. Metastatic micro-tumours were found in the lungs, pericardium and spleen.

- Whilst there are no reports of successful surgical removal of renal carcinoma, two reports have described hand-assisted laparoscopic removal of other renal neoplasms:
  - A hand-assisted laparoscopic nephrectomy of a renal papillary adenoma was carried out in a 20-year-old TB gelding without metastatic spread[13]
    - No complications were reported by the owner at 18 months postoperatively
  - A hand-assisted laparoscopic removal of a nephroblastoma in a 3-year-old TB stallion was performed successfully.[8]

Surgical removal of an equine kidney is not a commonly performed procedure. The procedure has previously been described while the horse is anaesthetized and using either a rib resection technique or intercostal technique. Complications with these approaches include poor exposure, postoperative haemorrhage, increased morbidity, risks of general anaesthesia and intraoperative pneumothorax while under general anaesthetic. Both traditional and hand-assisted laparoscopic surgery techniques have been described for nephrectomy.

If nephrectomy is to be considered as a treatment option, early diagnosis, confirmation of unilateral disease and absence of metastatic disease (including thoracic radiography and transabdominal ultrasonography) are essential. Preoperative evaluation of the contralateral kidney must of course be performed.

The surgical procedure is described in standard surgical texts but it is one of the most challenging surgeries in equine practice.

Prognosis

In general, the prognosis for renal carcinoma or adenocarcinoma cases is grave.[39] Most affected horses are euthanized due either to deleterious systemic effects of the neoplasm, inability to pursue treatment or poor prognosis for survival despite treatment. The median survival time for 24 horses with recorded renal carcinoma is 11 days (range 0 days to 1 year). Without the opportunity to make an early diagnosis and implement surgical and potentially chemotherapeutic therapy, the prognosis remains grave.[43]

Ureteral neoplasia

Overview

There has been one report of two horses with transitional cell carcinoma suspected to originate from the ureter.[1] Tumours of the equine ureters have also been reported in horses as a consequence of invasion from the renal pelvis.

Case reviews

A 20-year-old Warmblood mare[1]

Presentation

- Weight loss
- Partial anorexia
- Ventral oedema of 5 weeks' duration.

Differential diagnoses

- Transabdominal ultrasonography identified the presence of large volumes of free fluid within the abdomen and cytology of this fluid confirmed the presence of atypical cells. Multiple masses were found post mortem along the abdominal aorta and a large mass surrounded the proximal ureter. There was no connection between the kidney and the mass. Metastases were present in lung parenchyma. The second case presented with very similar signs but also had numerous radio-opacities in the dorsal lung fields.
- In both cases, histopathology and immunohistochemistry confirmed a diagnosis of transitional cell carcinoma with intra-abdominal dissemination, pulmonary metastases in both cases, and liver metastases in one case. Although no direct proof of ureteral origin was found, primary ureteral origin was considered most likely.

Management

- This tumour is aggressive and undergoes early metastatic spread via lymphatic vessels; this might explain multiple masses encircling the abdominal aorta. Haematogenous spread can occur later in the disease, explaining the lung and liver metastasis.

An 18-year-old Crossbreed mare

One case of a primary ureteral papilloma has been encountered by the author (KS) in an 18-year-old Crossbreed mare.

Presentation

- Haemorrhagic vaginal discharge
- Intermittent haematuria.

Differential diagnoses

- Vaginal examination revealed a multilobulated mass on the floor of the vagina, originating from the urethra. Rectal palpation was unremarkable.
- Transrectal ultrasonography revealed an area of thickening along the dorsal urethra, bladder neck and ureteral opening.
- Endoscopy of the bladder revealed a smooth coiled mass exiting the right ureter, extending along the bladder neck and urethra, contiguous with the lobulated mass in the vagina.
- Histological examination of a biopsy specimen of the mass revealed a ureteral papilloma.

Management

The mare was treated with a combination of surgical debulking, intralesional 5-fluorouracil and transendoscopic laser ablation and had no signs of recurrence for at least 36 months.

Bladder carcinoma

See also page 273.

Disease summary

Notes

Very rare highly malignant, slow-growing tumour of epithelial cells (squamous cell carcinoma more often identified than transitional cell carcinoma) and more prevalent in older female horses. Commonest metastasis to peritoneum (by direct spread), liver and lungs.

Clinical features

Haematuria is usually the only major sign until the tumour has spread. Free-flowing urine is usually pigmented but more obvious blood is usually seen at end of urination.

Diagnostic confirmation

Rectal examination, transrectal ultrasonography, cystoscopy and biopsy.

Management

Combined direct laser or diathermy ablation and (possibly) local chemotherapy using piroxicam or mitomycin C.

Prognosis

Prognosis is very poor for carcinoma and possibly better for transitional cell carcinoma. Treatment must be started very early for any hope of success, but most cases are presented late.

Description

Neoplasia of the equine urinary bladder is very rare. It has frequently been reported as a post-mortem finding and more recently as a clinical finding.[2–4,6,11,12,44–49] The most common bladder neoplasm in equines, especially those in the older age range, is squamous cell carcinoma (SCC) followed by transitional cell carcinoma (TCC).[6,47–49] The presence of squamous cell carcinoma is explained by the islands of squamous epithelium in the bladder mucosa; these seem more prone to tumour transformation.[1] The published clinical evidence on the carcinoma group of tumours is shown in Table 36.3.

Carcinoma is further classified into four types[11,49–51]:

1. Transitional cell carcinoma
2. Squamous cell carcinoma
3. Adenocarcinoma
4. Undifferentiated carcinoma.

Carcinoma may be further described as:

- *Non-papillary or non-infiltrating*: when the tumour is confined to the bladder surface.
- *Papillary*: The neoplasm grows into the lumen with a relatively broad base and may have a cauliflower-like appearance.
- *Papillary and infiltrating*: This resembles papillary carcinoma and invades the stroma of its own stalk and lamina propria of the bladder wall.
- *Infiltrating*: The tumour grows into the wall of the bladder and usually appears as a flat plaque-like lesion, or as an ulcerated and infiltrated mucosal patch overlying a nodular growth.[11]

The cause of the malignant transformation of both squamous and transitional cells is unknown. Potentially, chronic inflammation or infection could play a role in transition of mucosa from a normal healing processes to a neoplastic process. SCC and TCC are liable to metastatic spread via the bloodstream and lymphatic system. Additionally, transcoelomic spread can occur if the tumours invade the full depth of the bladder wall.

Nearly all primary neoplasms of the urinary bladder occur in horses over 10 years of age, and more commonly in females than in males.[11] Moulton (1978) reported no apparent breed predisposition.[50] In human beings, bladder cancer occurs more frequently in men than women.[52] In horses, mares have a higher occurrence of bladder neoplasia for unknown reasons. However, this apparently higher incidence could be attributed in substantial part to more frequent rectal examinations in the mare, allowing earlier recognition of the tumour.[4,6,48] Exposure to certain carcinogenic agents and circumstances that result in exposure to these may be significant.[52] Lithiasis or chronic infection of the urinary tract may predispose to squamous metaplasia, which is a precancerous lesion.[37] The role of bracken fern (*Pteridium aquilinum*) ingestion in horses is uncertain, as is the role of bovine papilloma virus.

Note

Aside from the histological differences between the transitional and squamous cell carcinoma of the bladder, there are few significant differences in the clinical signs but the outlook for early diagnosed transitional cell carcinoma is probably marginally better than for squamous cell carcinoma.

The two tumours are grouped together here and, where differences are reported, they are identified.

Clinical features

Clinical signs associated with bladder neoplasia are similar to those associated with cystic calculi:

- *Gross chronic and persistent haematuria* is the most common clinical sign of bladder neoplasia and is due

Table 36.3 Case reports/series of bladder neoplasia in the horse

Ref. No.	Presenting signs	Tumour type and location	Management/prognosis	Age (years)	Breed	Sex
49	Haematuria 2 months	SCC – dorsocranial aspect of bladder	Resection cystoplasty + piroxicam p.o. No recurrence at 6 months, still on piroxicam	22	Arabian	F
2	Haematuria 5 days + vulval haemorrhage	Leiomyosarcoma – multilobulated mass on floor of vagina extending from bladder	Surgical debulking + chemo therapy: doxorubicin/ Diphenhydramine/ dexamethasone: poor response	2	TB	F
48	Unknown	SCC	Monthly debulking + intracystic 5-fluorouracil – prolonged survival for 9 months	17	U	F
46	Acute-onset haematuria	TCC – ventral bladder + intra-abdominal dissemination	Euthanasia	14	TB	G
5	Pollakiuria	Cystadenoma – urachal		2.5	TB	F
47	Stranguria, pollakiuria + haematuria 4 weeks	SCC – ventro-cranial bladder	Attempted surgical excision but too extensive. Euthanasia	10	Appaloosa	F
12		TCC		8	Anglo-Norman	S
4	Recent-onset stranguria + haematuria	Rhabdomyosarcoma – large multilobulated mass in vagina from urethral orifice	Surgical debulking 3 months; follow-up stranguria recurred and intra-abdominal mass – euthanasia	2	Appaloosa	F
3		Lymphosarcoma		9	TB	F
6	Stranguria, pollakiuria, haematuria + weight loss	4/6 SCC 1/6 TCC 1/6 Fibromatous polyp	1 SCC tx intracystic 5-FU s.i.d. 4×, e.o.d. 4×, bladder mass ↓ abdo mass ↑ Euthanasia	19	QH	F
				23	Arabian	F
				3	Morgan	G
				13	TB	S
				20	Arabian	F
				14	Morgan	F
44	Abdominal pain, stranguria + urinary incontinence	Fibroepithelial polyp	Euthanasia	11	Pony	G
45		TCC			Percheron	F
11		37 bladder neoplasms reported to date in the literature: 13/35 SCC (no other information disclosed)		>10	U	U

G, gelding; F, mare; S, stallion; U, unknown/not reported; TB, Thoroughbred.

to ulceration of the bladder mucosa over the tumour mass[6]

- However, micro-haematuria may have been present for some time prior to the more obvious clinical presentation.

- The mass is usually a *fleshy consistency* in horses, i.e. papillary and infiltrating (rectal examination, cystoscopy and ultrasonography) (Fig. 36.4).
- *Pollakiuria* is frequently noticed and may be related to decreased bladder capacity or secondary cystitis.[37]
- *Pyelonephritis* may occur in up to half of the cases – probably as a result of ascending infection from secondary cystitis.[6]
- *Hydronephrosis can also occur* where tumour mass has obstructed urine outflow, but there may be no clinical evidence of this.[6]

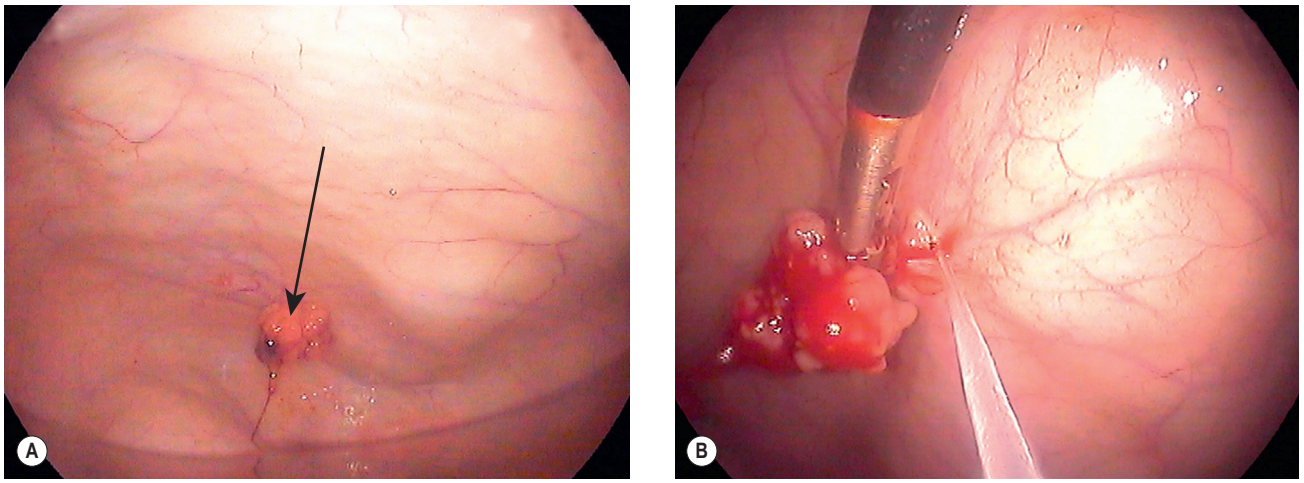


Figure 36.4 Papillary and infiltrating carcinoma. This 15-year-old pony mare presented with a history of increasingly noticeable haematuria. **(A)** A haemorrhagic, fragile mass was noticed on the mucosa of the urinary bladder (arrow). This was papillomatous in nature but broadly based and, following biopsy, was classified as a papillary and infiltrating carcinoma. **(B)** The tumour was treated with a combination of laser surgical ablation and intralesional mitomycin C with piroxicam flushing. No follow-up was available. *(Figures courtesy of Veronica Roberts.)*

- *Mild non-regenerative anaemia is common* and is probably related to chronic inflammation, but could also be attributed to chronic blood loss from ulceration of the tumour and associated haematuria and to paraneoplastic bone marrow suppression. Polycythaemia may also be encountered.

Notes

Urinary bladder carcinoma in horses tends to spread by local invasion to abdominal organs and via lymphatic vessels to the internal iliac and sublumbar lymph nodes. Haematogenous spread generally occurs much later in the course of the disease, with involvement of lungs and other organs. Involvement of lymph nodes may not occur at all, but extension of the tumour appeared to be by direct invasion and involvement of adjacent structures throughout the abdomen by transcoelomic spread.[6,37]

Differential diagnoses

- Cystic or urethral calculus
- Trauma
- Cystic haematoma[53]
- Drug toxicity[54]
- Cystitis[55,56]
- Pyelonephritis[56]
- Renal neoplasia[37,39,48]
- Cantharidin toxicosis[56]
- Idiopathic renal haematuria
- Urethral defects[57]
- Pigmenturia, including myoglobinuria from muscle disease
- Primary/secondary coagulopathies.[2]

Diagnostic confirmation

- *Rectal palpation*: A mass may be palpable, or more often a generalized or localized thickening of the bladder wall can be felt. Cystic calculi can be distinguished from masses based on their firmer, hard, rock-like texture, compared with the fleshy consistency of a mass.

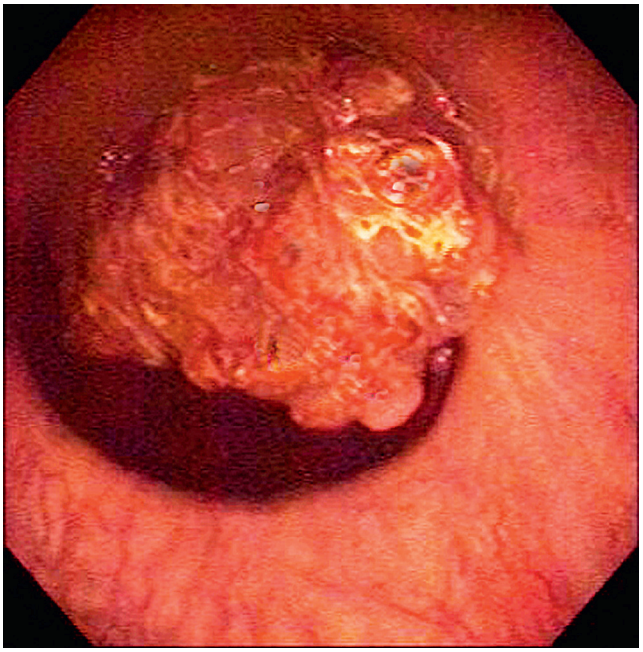


Figure 36.5 Transitional cell carcinoma. A 12-year-old Belgian Warmblood gelding was presented with a 24 h history of patent haematuria and dysuria. Cystoscopy identified this exophytic mass lying at entrance to the bladder. A biopsy confirmed transitional cell carcinoma – this is rarer than squamous cell carcinoma, in spite of the higher cell prevalence of transitional cells in the bladder mucosa. The bladder mass was surgically debulked via a temporary perineal urethrotomy and a course of oral piroxicam was administered. Follow-up examination 18 months postoperatively revealed no evidence of tumour recurrence. It is important to use every available diagnostic aid to determine if the tumour is superficial or infiltrating, because this property has a profound influence on prognosis and treatment options. *(Figure courtesy of Tim Mair.)*

- *Transrectal ultrasonography* may help differentiate between an echogenic freely mobile calculus within the bladder, and a solid soft tissue echogenicity mass, perhaps attached and infiltrated within the bladder wall.
- *Cystoscopy* via the urethra allows direct visualization of the mass and subsequent biopsy (Fig. 36.5).

- *Biopsy*: Histopathology of the biopsy specimen collected via endoscopy enables definite identification of the neoplasm.

Notes

Since bladder carcinoma (of both squamous and transitional types) is a very serious threat to the horse, every possible means should be used to establish the extent and pathological behaviour of the tumours. An early diagnosis is key to a satisfactory outcome, so micro-haematuria should always be viewed with suspicion and a full investigation, including cystoscopy and ultrasonography, should be completed.

Management

There are a few case reviews describing attempted treatments, including surgical debulking or excision, systemic and intracystic chemotherapeutics and oral piroxicam.[58–60]

Case review

A squamous cell carcinoma in a pregnant mare, with the sole objective of salvage of the foal[6]

Management

- Daily topical intracystic irrigation with 5-fluorouracil (100 mg in 50 mL saline solution) for 5 days.
- Followed by alternate day therapy for 4 treatments resulted in decreased bleeding, decreased size of bladder mass and a more fibrous appearance to the mass.

Prognosis

- During the following 2 weeks, the mare developed signs of abdominal pain and was euthanized. Increase in size of an associated abdominal mass was the likely cause of abdominal pain. Had the neoplasm been identified earlier, treatment by surgery and intracystic 5-fluorouracil may have been successful.[6]

Surgical debulking has prolonged short-term survival where this has been possible.[4,47] For early cases of transitional carcinoma, a combination of debulking surgery (with or without laser assistance) followed by prolonged oral piroxicam can be successful.[60]

- Monthly debulking and intracystic 5-fluorouracil instillation lead to prolonged survival (9 months).[48]
- Successful resection cystoplasty, in combination with oral piroxicam, for treatment of an SCC at the dorsocranial aspect of the bladder has been reported.[49] There had been no recurrence at 6 months' post-treatment. The location of the tumour within the bladder facilitated surgical resection.

Prognosis

Bladder carcinoma in the horse is clinically challenging and often fatal. Late detection of the tumours, together with the challenges of equine bladder surgery, contribute to a very poor prognosis. Earlier detection, successful surgical excision and adjunct treatment with cytotoxic and other chemotherapeutic agents may increase survival time in affected horses. The outlook for transitional cell carcinoma appears to be better than that for squamous cell carcinoma.

Secondary tumours of the urinary tract

Overview

The high blood flow to the kidneys makes it a potential target for metastatic development from tumours at other sites. For the most part, secondary tumours are limited to the kidney, but there are reports of secondary tumours in the bladder wall.

The commonest secondary tumours occurring in the kidney include:

1. Lymphoma (Fig. 36.6)
2. Melanoma
3. Haemangiosarcoma.

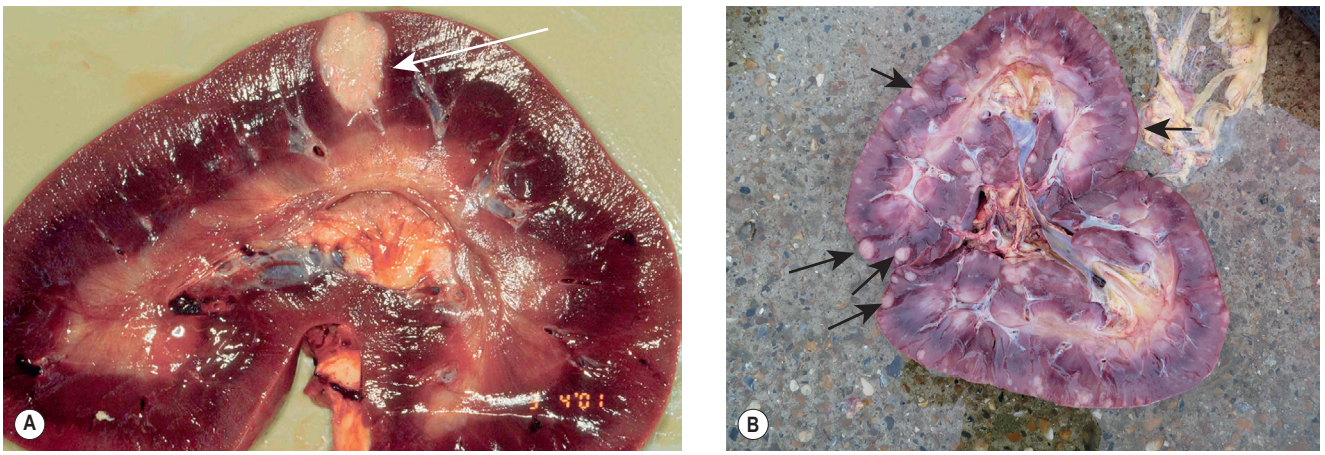


Figure 36.6 Splenic primary tumour. A 7-year-old Welsh Section B gelding was presented with signs of generalized lymphoma, which was confirmed at biopsy from multiple sites and necropsy. A splenic primary tumour was identified **(A)** and secondary tumours were found in the renal cortex of both kidneys (arrow). **(B)** Multiple tumours, usually within the renal cortex (arrows), can be present without any evidence of renal compromise. *(Figure B courtesy of Tim Mair.)*



Figure 36.7 Renal metastatic melanoma. Metastatic melanoma is commonly found in cases of widespread malignant melanoma – the presence of the tumours is usually incidental to the wider issue of metastatic tumour spread. These are usually found incidentally and seldom have any clinical implications. A 16-year-old grey mare was presented with a history of weight loss and behavioural problems. Her urine was noted to be very dark in colour with a black sediment. This urine was collected from the right ureter under endoscopic guidance. A presumptive diagnosis of melanoma was made with renal secondary tumours. Renal function was unremarkable. A renal biopsy was performed percutaneously under ultrasonographic guidance and a black, rather amorphous sample containing malignant melanocytes was harvested from one of the focal areas of abnormal tissue. At necropsy, disseminated malignant melanoma was confirmed; both kidneys were extensively infiltrated with many secondary melanomas.

The large majority of the tumours have no material implication for renal function, since there is an effective functional reserve but, in some cases, significant diagnostic information can be gleaned from the use of further tests, such as rectal palpation, percutaneous and transrectal ultrasound examination, urinalysis (Fig. 36.7), peritoneocentesis and haematology. Usually, however, the secondary tumours are discovered post mortem.

The proximity of the kidneys to the adrenal glands and the liver in the case of the right kidney, means that the kidney may become involved in a variety of perirenal tumours. All these are rare, but haemangiosarcoma and rhabdomyosarcoma may be the most common. Additionally, an undifferentiated/unclassified sarcoma has been identified (Fig. 36.8).

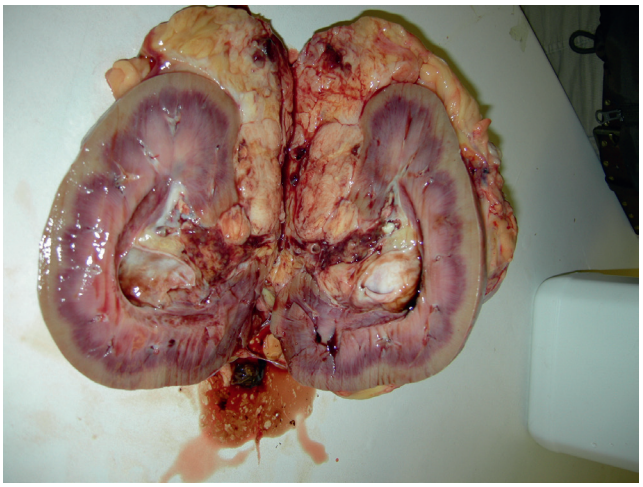


Figure 36.8 Perirenal sarcoma. A unilateral (left) perirenal sarcoma was identified ultrasonographically and confirmed by ultrasound-guided biopsy and at necropsy. The 16-year-old horse had shown nonspecific signs of weight loss and back/lumbar pain. No paraneoplastic signs were identified. *(Figure courtesy of Tim Mair.)*

References

1. Maes S, De Clercq D, Saey V, et al. Transitional cell carcinoma of suspected ureteral origin, with intra-abdominal metastases in two horses. Vlaams Diergen Tijds 2011; 80:281–286.
2. Hurcombe SD, Slovis NM, Kohn CW, et al. Poorly differentiated leiomyosarcoma of the urogenital tract in a horse. J Am Vet Med Assoc 2008; 233:1908–1912.
3. Sweeney RW, Hamir AN, Fisher RR. Lymphosarcoma with urinary bladder infiltration in a horse. J Am Vet Med Assoc 1991; 199:1177–1178.
4. Turnquist SE, Pace LW, Keegan K, et al. Botryoid rhabdomyosarcoma of the urinary bladder in a filly. J Vet Diagn Invest 1993; 5:451–453.
5. Gibson KT, Cantley CE, Donald JJ, et al. Urachal cystadenoma in a filly. Aust Vet J 1999; 77:638–640.
6. Fischer AT, Spier S, Carlson GP, et al. Neoplasia of the equine urinary bladder as a cause of hematuria. J Am Vet Med Assoc 1985; 186:1294–1296.
7. Jardine JE, Nesbit JW. Triphasic nephroblastoma in a horse. J Comp Pathol 1996; 114:193–198.
8. Romero A, Rodgerson DH, Fontaine GL. Hand-assisted laparoscopic removal of a nephroblastoma in a horse. Can Vet J 2010; 51:637–639.
9. Loynachan AT, Bryant UK, Williams NM. Renal mucus gland cystadenomas in a horse. J Vet Diagn Invest 2008; 20:520–522.
10. Matsuda K, Kousaka Y, Nagamine N, et al. Papillary renal adenoma of distal nephron differentiation in a horse. J Vet Med Sci 2007; 69:763–765.
11. Pamukcu AM. Tumours of the urinary bladder. Bull World Health Organ 1974; 50:43–52.
12. Turner RM, Love CC, McDonnell SM, et al. Use of imipramine hydrochloride for treatment of urospermia in a stallion with a dysfunctional bladder. J Am Vet Med Assoc 1995; 207:1602–1606.
13. Ferguson N, Couetil L, Hawkins J, et al. Unilateral nephrectomy in two aged horses. Equine Vet Educ 2007; 19:300–305.
14. Oosterlinck M, Raes E, Verbraecken S, et al. Severe lameness caused by metastatic renal adenocarcinoma of 3rd phalanx in a Warmblood mare. Equine Vet Educ 2011; 23:512–516.
15. Baker JL, Aleman M, Madigan J. Intermittent hypoglycemia in a horse with anaplastic carcinoma of the kidney. J Am Vet Med Assoc 2001; 218: 235–237.
16. Swain JM, Pirie RS, Hudson NP, et al. Insulin-like growth factors and recurrent hypoglycemia associated with renal cell carcinoma in a horse. J Vet Intern Med 2005; 19:613–616.
17. Owen RA, Haywood S, Kelly DF. Clinical course of renal adenocarcinoma associated with hypercupraemia in a horse. Vet Rec 1986; 119:291–294.
18. Van Mol KA, Fransen JL. Renal carcinoma in a horse. Vet Rec 1986; 119:238–239.
19. Rhind SM, Hawe C, Dixon PM, et al. Oral metastasis of renal cell carcinoma in a horse. J Comp Pathol 1999; 120:97–103.
20. Young AC, Hoffmann KL, Begg AP, et al. Acute lameness associated with osseous metastasis of a peri-renal carcinoma in a horse. Aust Vet J 2010; 88:346–350.
21. Rumbaugh ML, Latimer FG, Porthouse KR, et al. Renal carcinoma with osseous and pulmonary metastases in an Arabian gelding. Equine Vet J 2003; 35:107–109.
22. West HJ, Kelly DF, Ritchie HE. Renal carcinomatosis in a horse. Equine Vet J 1987; 19:548–551.
23. Servantie J, Magnol JP, Regnier A, et al. Carcinoma of the renal pelvis with bony metaplasia in a horse. Equine Vet J 1986; 18:236–238.
24. Brown PJ, Holt PE. Primary renal cell carcinoma in four horses. Equine Vet J 1985; 17:473–477.
25. Pomroy W. Renal adenocarcinoma in a horse. Equine Vet J 1981; 13: 198–200.
26. Hilton HG, Aleman M, Maher O, et al. Hand-assisted laparoscopic nephrectomy in a standing horse for the management of renal cell carcinoma. Equine Vet Educ 2008; 20:239–244.
27. Rhind SM, Sturgeon B. Papillary renal carcinoma with an unusual clinical presentation in a horse. Equine Vet Educ 1999; 11:171–173.
28. Knowles EJ, Withers JM, Day J, et al. Renal carcinoma as a cause of sudden death in an aged horse. Equine Vet Educ 2008; 20:452–455.
29. Van Amstel SR, Huchzermeyer D, Reyers F. Primary renal cell carcinoma in a horse. J S Afr Vet Assoc 1984; 55:35–38.
30. Berggren PC. Renal adenocarcinoma in a horse. J Am Vet Med Assoc 1980; 176:1252–1253.

31. Haschek WM, King JM, Tennant BC. Primary renal cell carcinoma in two horses. J Am Vet Med Assoc 1981; 179:992–994.
32. East LM, Savage CJ, Traub-Dargatz JL. Weight loss in the horse: a focus on abdominal neoplasia. Equine Vet Educ 1999; 11:174–178.
33. Ramirez S, Seahorn TL. Ultrasonography as an aid in the diagnosis of renal cell carcinoma in a horse. Vet Radiol Ultrasound 1996; 37:383–386.
34. Nielsen SW, Mackey LJ, Misdorp W. XVIII. Tumours of the kidney. Bull World Health Organ 1976; 53:237–246.
35. Cotchin E. A general survey of tumours in the horse. Equine Vet J 1977; 9:16–21.
36. Sundberg JP, Burnstein T, Page EH, et al. Neoplasms of Equidae. J Am Vet Med Assoc 1977; 170:150–152.
37. Traub-Dargatz JL. Urinary tract neoplasia. Vet Clin North Am Equine Pract 1998; 14:495–504.
38. Vítovec J. Carcinomas of the renal pelvis in slaughter animals. J Comp Pathol 1977; 87:129–134.
39. Wise LN, Bryan JN, Sellon DC, et al. A retrospective analysis of renal carcinoma in the horse. J Vet Intern Med 2009; 23:913–918.
40. Newberne PM, Connor M. Effects of sequential exposure to aflatoxin B1 and diethylnitrosamine on vascular and stomach tissue and additional target organs in rats. Cancer Res 1980; 40:4037–4042.
41. Rantanen NW. Diseases of the kidneys. Vet Clin North Am Equine Pract 1986; 2:89–103.
42. Roby KA, Beech JC, Black M. Hepatocellular carcinoma associated with erythrocytosis and hypoglycaemia in a yearling filly. J Am Vet Med Assoc 1990; 196:465–467.
43. Davis E. Diagnostic considerations for acute death in horses: How common is acute death associated with renal cell carcinoma and other neoplasms in horses? Equine Vet Educ 2008; 20:457–458.
44. Ricketts SW, Frauenfelder H, Button CJ, et al. Urinary retention in a pony gelding associated with a fibroepithelial polyp in the bladder. Equine Vet J 1983; 15:170–172.
45. Traub JL, Bayly WM, Reed SM, et al. Intra-abdominal neoplasia as a cause of chronic weight loss in the horse. Compend Contin Educ Pract Vet 1983; 5(suppl):S526–S534.
46. Patterson-Kane JC, Tramontin RR, Giles RC, et al. Transitional cell carcinoma of the urinary bladder in a Thoroughbred, with intra-abdominal dissemination. Vet Pathol 2000; 37:692–695.
47. Gandini G, Pietra M, Cinotti S, et al. Squamous cell carcinoma of the urinary bladder in a mare. Equine Pract 1998; 20:18–20.
48. Cornelisse CJ. Urinary tract neoplasia. In: Robinson NE, ed. Current therapy in equine medicine, 5th edn. Philadelphia: WB Saunders; 2003: 835–837.
49. Serena A, Naranjo C, Kock C, et al. Resection cystoplasty of a squamous cell carcinoma in a mare. Equine Vet Educ 2009; 21:263–266.
50. Moulton JE. Tumours of domestic animals. Berkeley: University of California Press; 1978.
51. Maxie MG, Newman SJ. Renal dysplasia. Jubb, Kennedy and Palmer's pathology of domestic animals, 5th edn. Philadelphia: Elsevier Saunders; 2007: 439–442.
52. Wynder EL, Onderdonk J, Mantel N. An epidemiological investigation of cancer of the bladder. Cancer 1963; 16:1388–1407.
53. Arnold CE, Chaffin MK, Rush BR. Hematuria associated with cystic hematomas in three neonatal foals. J Am Vet Med Assoc 2005; 227:778–780.
54. Gunson DE, Soma, L.R. Renal papillary necrosis in horses after phenylbutazone and water deprivation. Vet Pathol 1983; 20:603–610.
55. Saulez MN, Cebra CK, Snyder SP. Small colon polyp with peritonitis in an Arabian yearling filly. Equine Vet Educ 2004; 16:184–187.
56. Helman RG, Edwards WC. Clinical features of blister beetle poisoning in equids: 70 cases (1983–1996). J Am Vet Med Assoc 1997; 211:1018–1021.
57. Schumacher J, Schumacher J, Schmitz, D. Macroscopic haematuria of horses. Equine Vet Educ 2002; 14:201–210.
58. Zantingh AJ, Gaughan EM, Bain FT. Case report: squamous cell carcinoma of the urinary bladder in a horse. Compend Contin Educ Pract Vet 2012; 34:E1–E5.
59. Barrell E, Hendrickson DA. Tumours of the equine bladder: what makes treating these cases so difficult? Equine Vet Educ 2009; 21:267–268.
60. Lisowski ZM, Mair TS, Fews D. Transitional cell carcinoma of the urinary bladder in a 12-year-old Belgian Warmblood gelding. Equine Vet Educ 2013.

37

Tumours of the musculoskeletal system

Overview 664
Neoplastic bone masses 664
Non-neoplastic bone masses 672
Non-aneurysmal cystic lesions of bone 674
Tumours of skeletal muscle 674
Metastatic tumours of the musculoskeletal system 676

Overview

Neoplasia of the musculoskeletal system in the horse is remarkably rare and therefore tends to behave unpredictably; these tumours do not feature in the broad studies of post-mortem cases and histology submissions in major referral centres.

Tumours of the axial skeleton are more common than those of the appendicular skeleton, and metastasis of malignant tumour from other body tissues to bone is uncommon. Tumours that affect the musculoskeletal system are listed in Box 37.1.

Tumours associated with joints of the horse are extremely uncommon, with very few reports of synovial sarcoma being published.[1]

Osteogenic tumours are very rare in the horse, but there have been several reports involving the head, mostly the jaws and the mandible in particular, and this may be a predilection site.[2] The histological characteristics of bone-derived tumours have been described and the classification of this group of tumours is based upon these features.[3]

Neoplastic bone masses

Osteoma

See also page 321.

Description

Osteoma is an extremely rare, bone-forming tumour of various species, mainly horses, cattle, sheep, dogs and cats.[4] Osteoma has been reported in all ages of horses, from 3 weeks to adult, with most being in the head region and in the mandible, maxilla and paranasal sinuses.[5] Of approximately 25 osteomas reported in the horse to date, all affected the head, except one found on the proximal tibia.[6] They are slow-growing, solitary, well-differentiated masses of bone enclosing marrow and fat. The term 'hamartoma' has been used to describe them: i.e. a benign, tumour-like nodule composed of an overgrowth of mature cells and tissues normally present in the affected part. However, they have also been described as 'fibro-osseous tumours', in a category including osteoma, ossifying fibroma and fibrous dysplasia. All such lesions display varying degrees of differentiation and ossification, which may represent different phases of the same process, with osteoma as the end stage.[4] The osteoma may reach a large size and has a distinctive discrete radiodense outline. The cause of osteoma remains unknown.

Disease summary

Notes

Rare, benign, slow-growing tumour of bone that affects the facial bones (mandible or maxilla) most often.

Clinical features

Painful, hot, progressive swelling of mandible or maxilla – other locations reported to involve appendicular skeleton (tibia, shoulder, tarsus, pedal bone, middle phalanx).

Diagnostic confirmation

Radiographical appearance characterized by sunburst pattern; biopsy.

Management

Surgery alone is *not* effective. Adjunctive chemotherapy with cisplatin bead implants and/or radiotherapy may provide palliation.

Prognosis

Prognosis is poor to hopeless.

Clinical features

Osteoma is benign, but may cause some local functional difficulty because the growth compromises adjacent soft tissues. Clinical signs include:

- Facial deformity/distortion
  - May cause disfigurement, obstruct the nasal passages or interfere with mastication and swallowing (Fig. 37.1)
- Exophthalmos
- Unilateral or bilateral nasal discharge
  - Unilateral epistaxis at exercise is occasionally present
- Abnormal respiratory noise
- Headshaking at exercise; one reported case resolved with surgical removal of the mass.[7]

Differential diagnoses

- Ossifying fibroma
- Dystrophic mineralization

Box 37.1 Tumours that affect the musculoskeletal system

Bone		
Osteoma	Osteosarcoma	Osteochondroma
Osteochondromatosis	Osteoclastoma (giant cell tumour)	Osteoblastoma
Chondroma/chondrosarcoma	Plasma cell myeloma	Fibroma
Fibrosarcoma/myofibroblastic fibrosarcoma	Myxoma/myxofibroma/myxosarcoma	Metastatic tumours
Joints		
Synovial sarcoma	Chondrosarcoma	
Tendons and ligaments		
Haemangiosarcoma	Melanosarcoma	
Skeletal muscle		
Rhabdomyoma	Metastatic tumours	Rhabdomyosarcoma
Tumour-like conditions		
Hygroma	Ganglion	Calcinosis cutis
Villonodular synovial sarcoma		



Figure 37.1 Osteoma/fibro-osseous tumour. This 14-year-old pony gelding developed a slowly expanding solid (warm) mass on the left mandible. A biopsy collected from the mass confirmed osteoma. Ultimately, the tumour became painful and obliterated the mandible, necessitating euthanasia. The majority of these tumours occur in the maxillary region (see p. 314).

- Tooth root abscess
- Foreign body sequestration
- Osteomyelitis
- Other neoplasia
  - Differentiation between an osteoma and an ossifying fibroma prior to treatment is important because ossifying fibromas tend to be more aggressive tumours requiring more radical surgical treatment such as rostral mandibulectomy.

Diagnostic confirmation

- Clinical and oral examination
- Endoscopy
- Radiography
  - Computer tomography may be more useful: in particular, for identifying the extent of the lesion and surgical planning[8]
- Scintigraphy
- Biopsy.

Management

- *En bloc* excision with wide non-affected margins is the standard approach.
- Recurrence is common, with incomplete removal.[9]

Prognosis

The prognosis is good, provided that complete excision is possible, but must actually remain guarded as many will present a significant surgical challenge by the time a diagnosis is established (Table 37.1).

Osteosarcoma

See also page 316.

Disease summary

Notes

Very rare, malignant tumour of bone.

Clinical features

Painful, hot, progressive swelling of the affected bone – most often in the mandible or maxilla but also may involve the appendicular skeleton (tibia, shoulder, tarsus, pedal bone, middle phalanx) or the vertebrae. Radiographical appearance has a characteristic sunburst pattern.

Diagnostic confirmation

Biopsy is essential.

Management

A single report of successful surgical treatment with adjunctive chemotherapy using cisplatin bead implants. Radiotherapy may provide palliation.

Prognosis

Prognosis is best regarded as hopeless.

Description

Osteosarcoma is a malignant mesenchymal tumour of bone affecting horses of any age, in which the neoplastic cells produce modified or distinctive osteoid or bone matrix in a haphazard arrangement. Osteosarcomas are the most common bone tumours in humans, dogs and cats, comprising 80% of malignant bone tumours in dogs and 70% in cats.[15] In horses, osteosarcoma is an extremely rare tumour. Over 80% of reported osteosarcomas involve the head, and the majority are reported in the mandible.[16,17] The remaining 9.4% involve the axial skeleton, 3.1% ribs and 6.3% the bones of the forelimb. The mean age incidence of 12 cases of equine osteosarcoma was 5.6 years, with a range from 4 months to 15 years.[18] Two cases were reported at 6 months old and 6 weeks old.[2] Age ranges from 6 months to 20 years, with a median age of 7 years, have also been reported.[19] The aetiology and pathogenesis of osteosarcoma are unknown. However, trauma, viral infection, exposure to radiation and genetic factors have been hypothesized as predisposing factors.[2,20] Trauma as a predisposing factor is supported by the fact that osteosarcomas in humans and small animals are predominantly found in weight-bearing bones, such as the proximal humerus, distal radius, femur and proximal tibia. It has been postulated that osteosarcomas occur in the mandible of large animal species because of the trauma associated with persistent chewing.[2,19]

Clinical features

- The condition is usually presented as a painful, hot, progressive swelling of the affected bone – the commonest sites include the mandible or maxilla, but limb bones have also been reported (Fig. 37.2).
- There are also rare reports of painful tumours on the appendicular skeleton, causing lameness (see Fig. 19.3).[21]
- Fever and other paraneoplastic changes are rarely detected in spite of the severity of some of these tumours.
- Pathological fractures can occur.

Differential diagnoses

- Osteoma
- Chondroma, chondrosarcoma, osteochondroma
- Fibroma, fibrosarcoma
- Abscess
- Severe degenerative joint disease
- Osteomyelitis, and infection resulting in osteitis or osteomyelitis (particularly with *Actinobacillus* spp.) can be very destructive and appear in a similar clinical and radiographical fashion.

Various cystic structures, such as ameloblastoma, ossifying fibroma and fibrous dysplasia can be similar but usually have characteristic radiographical features.

Table 37.1 Case reports/series of osteoma in the horse

Ref. No.	Age (years)	Sex	Breed	Presenting complaint	Diagnosis	Treatment	Outcome
8	2	M	QH	Left facial deformity of 2 months' duration, unilateral nasal discharge of 7 months' duration	Osteoma (PNS)	Surgery, complicated by pneumocephalus	Survived, no recurrence 2.5 years post-surgery
10	various (4 cases)				3 × osteoma 1 × ossifying fibroma	4 All surgery × sx.	2 × euthanasia 2 survived
11	6	G	Arab	Purulent nasal discharge, facial distortion and exophthalmus	Osteoma of frontal and maxillary sinuses	Surgery	Survived, no recurrence at 5 years post-surgery
4	0.5	M	WB	Facial distortion and abnormal respiratory noise of 2 weeks' duration	Mucinous osteoma with features of ossifying fibroma in nasal cavity	None	Euthanasia
9	5	M	Paint	Mass on ventral left mandible of 2 years' duration	Osteoma	Surgery	No recurrence at 6 months
12	11	F	QH	Exophthalmia	Osteoma (PNS)	None	Euthanasia
13	2	G	QH	Torticollis, facial protuberance, persistent nasal discharge	Osteoma (PNS)	Surgery	No complication 23 months post-surgery
14	12	F	TB	2-month history of pale firm palpable orbital mass	Multilobular osteoma (chondroma rodens)	Surgery	Recovered – no further complications
7	6	G	XB	3 months' headshaking at exercise	Osteoma	Surgery	Stopped headshaking 5 months post-surgery, some wound discharge

G, gelding; F, mare; S, stallion.

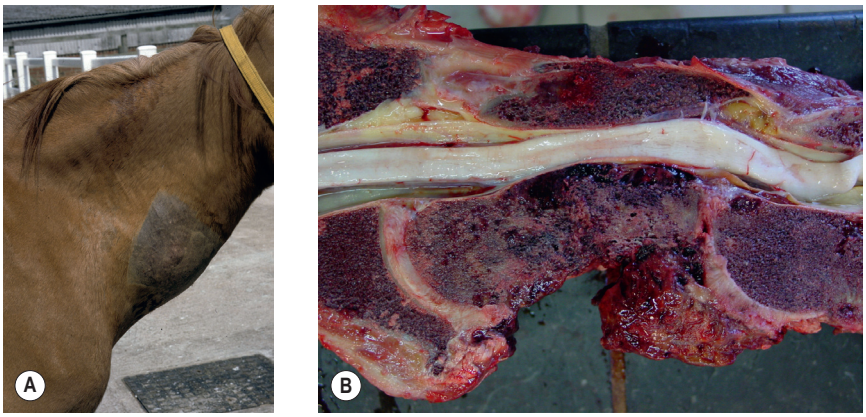


Figure 37.2 Osteosarcoma. (A,B) This 5-year-old Irish mare was presented with a 4-week history of a warm, bilateral cervical swelling, painful neck movement and progressive hindlimb ataxia. Lateral radiographs suggested a neoplastic bone lesion. A bone biopsy was taken from several sites and the horse was diagnosed with osteosarcoma. **(B)** The destructive sarcoma in the vertebral body of C5 was obvious and had destabilized the vertebra with consequent cord compression.

Diagnostic confirmation

Radiographical appearance is highly suggestive of the condition.

- *Radiographical* evaluation of osteosarcoma reveals destruction of the cortex and irregular formation of periosteal new bone. Consequently, margins are not smooth, and a 'sunburst' pattern may be present.
- Grossly, at *surgery* or post mortem, there is distortion of the bone's normal shape and thinning or destruction of the cortical wall.
- *Biopsy* provides the only definitive diagnosis. Bone biopsies can usually be performed in the standing horse. They are easier to obtain since the bone is usually softer than normal and easier to penetrate. In one case series, 5/8 osteosarcoma cases were categorized histologically as fibroblastic, with 7/8 containing chondromucinous matrix.[19] The medullary cavity is filled with a friable pink–white material containing variable amounts of cancellous bone (see Fig. 37.2B). It is easy to overlook tumour tissue in small bone biopsies and florid, non-neoplastic reactive bone or fracture callus can easily be mistaken histologically for neoplasia. Multiple biopsies should therefore be collected from sites identified by radiography or CT or MR imaging methods, but this is not an easy procedure. The tumour tissue may also be found penetrating the cortex and forming tumours in the soft tissue around the affected bone. Cysts and haemorrhages are typically present, and necrosis may be prevalent in some tumours.[22]

Management

Treatment options for osteosarcoma in the horse are limited. In the largest series of eight cases, four were euthanized because of progressive disease after incomplete excision; one died from presumed respiratory obstruction; one horse survived and two were lost to follow-up.[19] The most common reasons for euthanasia were impaired respiratory and masticatory function.

- *Surgery* on its own is not effective.
- *Radiation* may offer some prospect of success or palliation, but tumours are likely to be locally malignant and treatment is usually not contemplated.
- *Surgery + adjunct chemotherapy*
  - There is one report of the successful treatment of an appendicular osteosarcoma with surgical excision and cisplatin bead implants.[23]

Prognosis

There is insufficient evidence to provide a reliable prognosis. The majority of affected horses are euthanized at the time of diagnosis, so no correlation can be made between histological subtype and prognosis (Table 37.2). Although metastasis is seldom reported in osteosarcoma at any site in the horse, it is impossible to make any sensible predictions on the course of the condition. Metastatic disease has not been reported at post mortem or clinically in any horse, suggesting that equine osteosarcoma has a relatively low rate of metastasis.[19] Some cases may progress relatively slowly and are therefore at least tolerable for limited periods. However, the highly aggressive nature and rapid course in most cases justify an extremely poor prognosis.

Osteochondroma

See also page 315.

Disease summary

Notes

Rare, benign, solitary, cartilage-capped tumour usually attached to bone (usually long bones) by a bony stalk.

Clinical features

Carpal sheath distension, bomy protuberance on caudo-lateral aspect of radius when limb held in flexed position, painful on firm palpation, moderate swinging limb lameness and decreased range of motion and ability to flex carpus.

Diagnostic confirmation

Radiography and ultrasonography are the main diagnostic aids.

Management

Surgical removal is curative – this can sometimes be undertaken endoscopically.

Prognosis

Prognosis is good.

Table 37.2 Case reports/series of osteosarcoma in the horse

Ref. No.	Age (years)	Sex	Breed	Presenting sign	Diagnosis	Treatment	Outcome
23	14	G	Arab	Mass on lateral aspect of left tarsus and proximal lateral metatarsus of 10 months' duration	Telangiectatic osteosarcoma	Surgical excision + cisplatin bead implants	Performing 8.5 years post surgery
24	11	G	TB	Acute-onset hindlimb lameness with swelling over dorsolateral aspect of pastern, painful on palpation	Osteoblastic osteosarcoma	None	Euthanasia
19	7	G	TB	Caudal maxillary sinus	Fibroblastic osteosarcoma	Surgery	Euthanasia
	20	G	Grade	Soft tissues caudal to shoulder	Osteoblastic osteosarcoma	Surgery	Alive 14 months later
	6 months	M	Unknown	Mandible	Fibroblastic osteosarcoma	None	Euthanasia
	3	G	WB	Maxilla	Fibroblastic osteosarcoma	None	Unknown
	19	G	Arab	Mandible	Osteoblastic osteosarcoma	None	Euthanasia
	15	F	QH	Nasal cavity	Osteoblastic osteosarcoma	Medical treatment	Died 2 months later
	5	G	Appaloosa	Tibia	Fibroblastic	None	Unknown
	?	?	Unknown	Mandible	Fibroblastic osteosarcoma	None	Unknown
25	5	G	WB	Zygomatic arch	Osteosarcoma	None	Euthanasia
20				Tarsus	Osteosarcoma		
26			Donkey	Pedal bone	Osteosarcoma		
27	8	G	Arab	Left forelimb lameness of unspecified duration; painful to palpation of shoulder joint with soft tissue enlargement of shoulder joint and bicipital bursa	Periosteal osteosarcoma of scapula	None	Euthanasia
2	6 months	M	QH	Mandibular symphysis – displaced incisor teeth and halitosis	Osteosarcoma	None	Euthanasia
	7 weeks	F	SB	RH lameness, difficulty to rise, bilateral posterior paresis, extensor rigidity to FLs, recumbency	Multifocal tumours of skeleton – L maxilla, L4, L7, T8, 11th rib, lung	None	Died

G, gelding; F, mare; S, stallion

Description

Osteochondroma formation is a rarely reported condition causing lameness in the horse. Osteochondroma is a solitary (monostotic) lesion, separate and distinct from 'osteochondromatosis', a term used when numerous (polyostotic) lesions exist (see below). These are said to be histologically and radiologically identical but differ aetiologically and pathogenetically, as osteochondromatosis is an inherited condition.[28–32] No hereditary or breed predisposition has been identified or proposed for osteochondromata.[32] The distal caudal radius is considered the most common site for osteochondromata in the horse, but they have also been reported on the middle phalanx, calcaneus and caudal distal tibia.[32–41]

Osteochondroma is a benign cartilage-capped exostosis arising from the surfaces of bones, formed by endochondral ossification adjacent to the physis or subarticular growth plate.[42,43] It may be considered to be a manifestation of dysplastic physeal growth rather than a true neoplasm.[42,43] It may result from separation of a portion of the metaphyseal growth plate margin, creating an island of chondrogenic tissue, capable of endochondral ossification, which is carried into the metaphysis during growth of the bone. This results in a cartilage-capped mushroom or sessile exostosis that projects from the metaphyseal surface. Growth is thought to stop at skeletal maturity.[42]

A histopathological study of osteochondromata in man suggested that they were derived from aberrant metaphyseal growth plate tissue, which proliferates autonomously and

separates from the normal growth cartilage near its edge.[44] As growth progresses, the aberrant tissue remains in a subperiosteal location, where it may either disappear through remodelling or proliferate as an osteochondroma, perpendicular to the orientation of the growth plate from which it was derived.[44]

The explanation for the most common site of osteochondromata in horses being the caudal distal radius is unknown. In man, it has been suggested that they may represent an abortive expression of inherited multiple osteochondromata. However, no heritability has been recognized.[45] The most accepted explanation is displacement of a fragment of growth cartilage that subsequently undergoes endochondral ossification perpendicular to the diaphysis of the bone.[36,45,46] The possibility of an aberrant nest of subperiosteal growth cartilage or herniation of growth cartilage through a perichondral defect has also been suggested.[46] This does not, however, explain the occurrence of osteochondromata on the (intramembranous) nasal bones of horses, suggesting that an alternative mechanism may apply in this location.[47–49]

Clinical features

The majority of the clinical signs of osteochondromata are a result of their impingement on the carpal sheath and, more specifically, on the deep digital flexor tendon (DDFT). They usually present with:

- An obvious swelling of the carpal canal sheath cranial to the *ulnaris lateralis* muscle
- Palpation of the affected limb may reveal a bony protuberance on the caudo-medial aspect of the radius when the limb is held in a flexed position
- Firm palpation may be painful
- Moderate swinging limb lameness is usually seen and carpal flexion may exacerbate this
- The range of motion and ability to flex the carpus may be reduced.[32]

Differential diagnoses

- Traumatic injury to bone with callus formation
- Osteosarcoma/osteoma
- Tendon sheath ganglion
- Skin tumours with invasion (e.g. sarcoid)
- Carpal tunnel or other chronic cause of tendon sheath distension.

Diagnostic confirmation

Investigation of a suspected osteochondroma should involve radiography of the distal radius and carpus and ultrasonographic evaluation of the carpal sheath in particular.

- *Radiographically* the tumours appear as conically-shaped bony protuberances with an outer cortex and inner medullary cavity. In most cases, lesions are located on the caudo-medial aspect of the distal radius, although lesions have also been identified on the caudo-lateral aspect of the distal radius.[32]
- *Ultrasonographic* evaluation of the carpal sheath using a 10 MHz linear probe with the limb under full weight-bearing will demonstrate distension of the carpal sheath. Most recently, assessment of the carpal sheath with the carpus semi-flexed, using a curved array probe in a medial position, enabled assessment of the extent of impingement on the DDFT and accompanying defects in the DDFT.[49]

Management

- Prolonged rest may help
- Administration of systemic, topical or intrathecal anti-inflammatory agents
  - As might be expected, intrathecal corticosteroids are likely to only give temporary relief[32,46]
- Resection/division of the carpal retinaculum[36]
  - This can also be used to facilitate the removal of osteochondromata.[50]

Surgery

- Open surgery in dorsal recumbency has been described but endoscopic removal is recommended[30,32,34–37,51,52]
  - The importance of evaluation and treatment of lesions of the DDFT are emphasized[52]
- Release of the carpal flexor retinaculum can be performed if chronic distension of the carpal sheath is a complicating problem, and a tenoscopic technique has been described.[46,53] However, very few cases exhibit clinical features of true carpal canal syndrome and this may therefore be considered unnecessary.[49]

Prognosis

The prognosis, previously based on relatively few cases in the literature, is good.[32,46,49,54]

Osteochondromatosis (multiple cartilaginous exostoses/hereditary multiple exostoses)

See also page 315.

Disease summary

Notes

Uncommon benign disorder of endochondral bone, only reported in North American horses.

Clinical features

Multiple firm bony enlargements or irregular protuberances, most often around costochondral junctions of ribs. May cause shuffling gait, muscle wasting, reluctance to move, difficulty rising and poor performance. As a horse ages, lesions become more externally obvious.

Diagnostic confirmation

Radiography and biopsy are required.

Management

There is no effective treatment.

Prognosis

Prognosis is fair for survival but poor for athletic function.

Description

Osteochondromatosis is a skeletal disorder, which primarily affects endochondral bones during skeletal development and is characterized by the abnormal development of bones preformed in cartilage. The condition has been

designated several descriptive terms, including multiple cartilaginous exostoses, diaphysial aclasia, hereditary deforming chondrodysplasia, dyschondrodysplasia, hereditary multiple exostoses, osteogenic disease, chondroma, osteochondroma, enchondromatosis and hereditary enchondromatosis.

Multiple benign bone neoplasms are featured, most commonly at metaphyseal regions of long bones as well as in ribs, scapula, pelvis and vertebrae. The affected sites coincide with body areas in which bone growth is most active and in which stress and strain are most severe.[55] The condition is uncommon in horses and has only been reported in North American horses.

The gross and microscopic appearance of lesions in horses simulates that of osteochondromatosis in man. Therefore, comparative studies of horse and man have provided information on aetiology, genetics and pathogenesis of the disease. The genetic pattern displayed by an affected stallion and his progeny group studied is that of dominant inheritance through a single gene. Second-generation progeny involving horses that expressed the trait further demonstrates dominant inheritance of the gene and heterozygous genotypes of all showing the trait. Therefore, horses that do not clinically exhibit the trait are not known to transmit osteochondromatosis to offspring. There is no difference in occurrence or severity of clinical signs between males and females. The genealogical records from affected human families also consistently show a pattern of inheritance controlled by a single dominant autosomal gene.[56–59]

Osteochondroma may be derived from aberrant cartilaginous physeal growth plate tissue, which proliferates autonomously and separates from the normal growth plate near its edge. As growth progresses, the aberrant tissue remains in a subperiosteal location, where it may either disappear through remodelling or proliferate as an early osteochondroma perpendicular to the orientation of the growth plate from which it was derived.[44]

Clinical features

The developmental changes must begin early during fetal osteogenesis because lesions, particularly in limbs and ribs, are often detectable at birth.

- Grossly, the tumours are multiple firm bomy enlargements or irregular protuberances under the skin that may be conical, rounded, pedunculated, multilobulated or spur-like in shape. They have been found in most bones of the body except the skull.
- They vary in size, shape and texture. Some are not well-delineated but tend to be bilaterally symmetrical.
- Most often seen near costochondral junctions of ribs and metaphyseal areas of the radioulnar, tibiofibular, metacarpal and metatarsal bones. They are firmly attached to the bone:
  - May also occur at other sites. Occasionally they have been located adjacent to intervertebral foramina and in vertebral foramina in the horse
  - Lesions in such locations could induce neuromuscular or locomotor disorders.
- The tumours are usually associated with zones of most active growth and greatest stress and strain. Mature affected animals often have extensive rib lesions on both medial and lateral rib surfaces, with medial aspect being especially prominent. The largest lesions usually occur on the lower half of the caudal ribs and lower third of the sternal ribs; more caudal ribs tend to be worse affected, with a gradual decrease in severity and size towards the cranial ones.
- Some lesions have been associated with the tendinous insertion of the diaphragm[57]
  - Lesions do not enlarge with age but lesions on ribs and scapulae may become much more externally obvious during periods of most active skeletal maturation, primarily up to 4 years old. Clinically, some lesions (particularly on limbs) appear to decrease in size
  - In humans, 80% of diagnoses are made in the first 10 years of life and lesions are usually discovered by 2–5 years old.[29] The state of skeletal development at birth may be a factor relating to differences between age of first appearance in horses and man.
- Clinical signs may also include:
  - Shuffling gait
  - Muscle wastage
  - Reluctance to move
  - Difficulty rising
  - Poor performance.

Differential diagnoses

- Neoplasia, particularly osteosarcoma, ossifying fibromas, chondromas, multiple osteomas
- Bone cysts
- Hypertrophic osteopathy
- Osteodystrophia fibrosa
- Zinc toxicity.

Diagnostic confirmation

Evaluation of the medical history of the patient and detailed clinical, radiographical and histopathological examinations are sufficient to definitively diagnose osteochondromatosis.[29,57]

- *Radiographically*, the tumours lack uniformity in size, shape, texture and degree of mineralization. They occasionally appear as poorly-delineated diffuse lesions.[57]
- *Histological examination* of affected bones shows a pathognomonic orderly endochondral ossification beneath superficial cartilage caps.[29]

Management

No treatment has been described in the literature. Owners should be made aware of the genetic background of the disease.[32]

Sarcomatous transformation has been reported in some osteochondromatosis-affected people and in the dog and cat.[55] In humans, up to 25% of osteochondromatoses develop into either osteosarcoma or chondrosarcoma.[29] There are no similar reports of this in horses.[57]

Osteoblastoma

Disease summary

Notes

Extremely rare tumour of bone.

Clinical features

Painful, hot, progressive, chronic swelling of a long bone.

Diagnostic confirmation

Radiographical appearance is suggestive; biopsy is definitive.

Management

Surgery may be successful.

Prognosis

Prognosis is unknown, but one case was successfully treated.

Description

Osteoblastoma has clinical and histological manifestations similar to those of osteoid osteoma; the two tumours may be variants of the same disease, with osteoblastoma representing a giant osteoid osteoma. The aetiology of osteoblastoma is unknown.

Histologically, osteoblastoma is similar to osteoid osteoma, producing both osteoid and primitive woven bone within fibrovascular connective tissue. Although the tumour is usually considered benign, a controversial aggressive variant has been described in the literature, with histological features similar to those of malignant tumours, such as an osteosarcoma. In contrast to the pain associated with osteoid osteoma, the pain of osteoblastoma is less severe. There is a single reported case in horses.

Clinical features

- Osteoid osteoma are small (<1 cm) lesions in cortical bone, and have an extensive surrounding zone of sclerotic bone.
- It is extremely painful; an osteoblastoma of the distal radial metaphysis was reported in a 5-year-old pony mare, with a 4-month history of moderate left forelimb lameness[1]
  - Clinical signs included a painful warm swelling in the region of the disto-medial radius.

Differential diagnoses

- Osteoma
- Ossifying fibroma
- Osteosarcoma
- Fibrous dysplasia.

Diagnostic confirmation

- In the one reported case, the clinical, radiographical and histological appearance was similar to a benign osteoblastoma described in man
  - *Radiography* revealed a large, well-defined, expansive, osteolytic lesion at the medial distal metaphysis of the radius, ballooning out and bordered by a thin uninterrupted layer of bone[1]
  - *Biopsy* is definitive.

Management

The lesion in the one reported case was successfully resected surgically.

Osteoclastoma (giant cell tumour of bone)

See also page 319.

Disease summary

Notes

Extremely rare tumour of bone.

Clinical features

Painful, hot, progressive, chronic swelling of a long bone.

Diagnostic confirmation

Radiographical appearance is suggestive; biopsy is definitive.

Management

Surgery may be successful.

Prognosis

Prognosis is unknown, but one case was successfully treated.

Description

Giant cell tumours of bone (osteoclastoma) are extremely rare in domestic animals, most case reports involving the cat and dog. Giant cell tumour of soft parts is reported in the horse, and discussed elsewhere (see p. 290). There are only two reported cases of giant cell tumour of bone in the horse.[60,61]

Clinical features

- Nonspecific signs include progressive lameness over a short course, with a rapid onset of an acute severe lameness; the acute lameness was likely associated with a pathological fracture involving the femoro-tibial joint.

Differential diagnoses

- Aneurysmal bone cyst
  - Osteoblastoma may show some radiographical similarity[62]
- Soft tissue tumours affecting bone, e.g. fibrosarcoma and haemangiosarcoma.

Diagnostic confirmation

- *Radiography* may reveal a large, well-defined lucent area in the proximal metaphysis and epiphysis of the affected long bone (case reports involve the tibia) with fracture fragments identifiable. The lesion has a lacy pattern or 'soap-bubble' appearance.
- Definitive diagnosis relies on post-mortem histopathology.

Management

No treatment is reported – the prognosis seems to be poor.

Chondroma/chondrosarcoma

See also page 319.

Disease summary

Notes

Very rare, primary tumour of cartilage.

Clinical features

Signs are nonspecific and depend on site/location of tumour. Skeletal tumours present with progressive lameness, swelling and pain on palpation; lesions affecting the tongue present with dysphagia and ptyalism; cases affecting the larynx present with respiratory distress.

Diagnostic confirmation

Radiography, CT, biopsy.

Management

Surgical removal is the treatment of choice.

Prognosis

Short-term prognosis is fair as result of slow metastatic progression.

Description

Primary cartilaginous tumours are extremely rare.[63] Few cases of chondroma/chondrosarcoma are reported in the horse. Chondrosarcoma is considered rare in horses and most involve the flat bones, ribs, larynx or cartilage of the ear or nasal cavity.[64] Chondroma is slow growing but not locally invasive, but the size may cause clinical problems. Chondroma shares many histological characteristics with chondrosarcoma. Chondrosarcoma tends to grow expansively and infiltrate surrounding tissue. In man, and dogs, chondrosarcomas have been shown to be slower and less likely to metastasize than osteosarcomas.

Clinical features

Clinical presentation is dependent on the site/location of the tumour.

- Chondrosarcoma is found most commonly on flat bones, followed by the appendicular skeleton
  - Progressive lameness, swelling and pain on palpation are associated with skeletal lesions.[64,65]
- At extra-skeletal sites, it will induce relevant signs; in the tongue it can cause severe dysphagia and ptyalism and laryngeal chondroma causes decreased size of the rima glottidis, leading to respiratory distress and upper respiratory tract obstruction.[66]

Differential diagnoses

Differential diagnoses for skeletal lesions include:

- Osteochondroma
- Osteosarcoma
- Chondroma rodens
- Giant cell tumour of bone.

For extra-skeletal lesions, differential diagnoses are more varied and depend on the location of the tumour. In the tongue, the following conditions should be considered:

- Rhabdomyosarcoma
- Mast cell tumour
- Perineuroma
  - Lymphoma
- Tumours suspected to originate in lingual taste buds
- All soft tissue tumours should be considered
- Non-neoplastic lesions, including foreign body granuloma, abscessation, etc.

In the larynx, the condition may be confused with:

- Neuroendocrine tumours
- Arytenoid chondritis and abscess.

Diagnostic confirmation

- *Radiography*
- *Biopsy* and histopathological examination.

Management

Treatment recommendations for chondroma/chondrosarcoma depend on the location/extent of the tumour.

Surgery

Surgical excision has been reported in a case of laryngeal chondroma and a case of chondrosarcoma of the tongue. There was no recurrence at 1 year and 11 months, respectively.[66,67]

There have been no successful reports of treatment involving chondrosarcoma of the appendicular skeleton.[64,65] However, in one case of chondrosarcoma affecting the metatarsophalangeal joint of a pregnant mare, there was no evidence of metastases for 1.5 years after an initial diagnosis and the affected mare foaled normally and was re-bred.

Local infiltration into adjacent cortical bone and recurrence following incomplete excision is likely. It is impossible to speculate on best treatment options, based on a few single case reports.

Prognosis

There are too few case reports for a reliable prognosis. Metastatic disease is not reported, either at post mortem or clinically in any horse thus far, apart from a single case of metastasis to lungs and lymph node in a chondrosarcoma of a rib. This suggests that the biological behaviour of equine chondrosarcoma is similar to that in humans and dogs, with a relatively slow rate of metastasis. However, this is based on a small number of cases. Some may progress relatively slowly and are therefore at least tolerable for limited periods.[65]

Non-neoplastic bone masses

Mandibular aneurysmal bone cyst

Description

Although localized (usually very small), bone cysts are relatively common in long bones and in particular in their epiphyseal regions, mandibular bone cysts are very rare in horses. In man, they probably arise from circulatory disturbances within the bone structure or traumatic alteration of the blood supply to a small area of bone.[68,69] While such structures might be expected in young horses,

they may also occur in older horses, possibly as a result of trauma.[70] There is no evidence to suggest that these lesions are truly neoplastic, but diagnosis based on radiographical examination alone is probably unwise. While there are no reports of concurrent neoplasia in the horse, complexes of tumours and cysts are reported in other species.

Clinical features

These present as a sterile, firm, expanding swelling, usually on the horizontal ramus of the mandible.

- The mandible becomes thickened from progressive destruction of cortical bone accompanied by reactive periosteal new bone formation. The region may be warmer than the normal contralateral mandibular ramus (Fig. 37.3A).
- Some pain associated with mastication may develop.
- Teeth may be shed abnormally as the alveoli are destroyed.
- Aspiration reveals small volumes of yellow or red-orange fluid.
- The rate of expansion may be sufficient to cause disruption and bleeding into the surrounding tissues and may easily suggest a neoplastic lesion.
- Pathological fractures may occur
  - In advanced cases, the extent of bone destruction can be considerable (Fig. 37.3B,C) and then pathological fractures are likely
  - Although parotid duct obstruction can occur, this is an insignificant clinical event
  - One report of a case of congenital aneurysmal bone cyst occurred in the mandible of a foal and resulted in a swelling large enough to prevent delivery.[70]

Disease summary

Notes

Very rare, benign tumour-like condition of bone; mandible most often.

Clinical features

Firm, slowly expanding swelling on horizontal ramus of mandible, heat and pain with mastication. Pathological fractures and premature shedding of teeth.

Diagnostic confirmation

Radiography. Aspiration is usually unrewarding but may reveal serous yellowish fluid.

Management

Surgery: deep and aggressive curettage of all abnormal tissue but danger of pathological fracture.

Prognosis

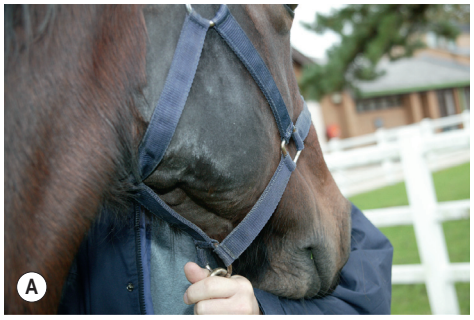
Prognosis is poor; repair is slow and may be cosmetically and functionally compromised with continued risk of pathological fracture.

Differential diagnoses

- Congenital cysts of dental and sinus origin
- Tumours of dental origin:
  - Ameloblastoma
  - Odontoma
- Tumours of soft tissue origin:
  - Ossifying fibroma
- Nutritional secondary hyperparathyroidism (brain disease/big head)
- Fibrous dysplasia
- Paranasal sinus cysts have a similar radiographical appearance, but will be in a very different location.

Diagnostic confirmation

- Radiographical appearance reveals a complex, loculated cyst-like structure containing bone fragments, cartilage and soft tissue, usually with a fine rim of thin bone around the periphery (Fig. 37.3B)





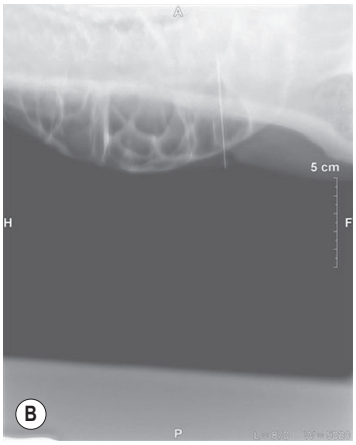


Figure 37.3 Mandibular aneurysmal bone cyst. **(A)** This 19-year-old gelding had a 9-month history of a slowly expanding swelling affecting the right mandible. The swelling was warm and a dental technician had easily removed several loose cheek teeth. **(B)** Radiographs revealed a multiloculated mass that had almost destroyed the mandible itself. The pony was pain-free and managed reasonably for a further 4 months before pain, dysmasesis and weight loss necessitated euthanasia. **(C)** At necropsy, the extent of the aneurysmal bone cyst was quite dramatic, but of course accurately reflected the radiography and ultrasonographic findings.

- The structure closely resembles the complex of paranasal sinus cysts that may also arise congenitally or at later ages.

Management

The only effective treatment is deep and aggressive curettage of all abnormal tissue:

- The defect may be filled with cancellous bone grafts collected from a remote site
- Repair may be slow and the site may be cosmetically compromised but cases can be cured
- In most cases, however, treatment is not really justified and palliative care should be provided until euthanasia can be justified.

Prognosis

The prognosis is poor unless the lesions are detected early and treated with aggressive surgical ablation and suitable reconstructive measures. However, the chances of an early diagnosis are low, so the outlook is generally poor. Complications (including dental shedding and pathological fractures) will reduce the prognosis considerably.

Non-aneurysmal cystic lesions of bone

Overview

Cystic lesions of the jaws present as bony swellings, and may affect mastication. Radiographically, the cysts differ from the multiloculated destructive aneurysmal cysts in being rounded with a smooth bony lining and radiolucent centre. The generic term 'odontogenic cyst' is appropriate for these non-inflammatory cysts lined by epithelium.[71] Radicular cysts occur adjacent to tooth roots. They are reactive lesions associated with oral inflammatory disease. Histologically, they are lined by stratified squamous epithelium with associated inflammatory cells.

Fibrous dysplasia

See also page 321.

Description

Fibrous dysplasia is a very rare non-cancerous abnormal bone growth, where the medullary cavity of bones is filled with fibrous tissue, causing the expansion of the areas of bone involved and consequent thinning of the bone itself. The bone trabeculae are abnormally thin and irregular. Most lesions are single/solitary (monostotic) and asymptomatic and are usually identified incidentally. Fibrous dysplasia can occur in any part of the skeleton, but the mandible is the most common site in horses.

Clinical features

- The condition is recognized as a smooth-contoured bone deformity arising from loss of bone structure with extensive formation of fibro-osseous matrix (Fig. 37.4; see also Fig. 28.23).[18]
- The lesion is probably not a true neoplasm and its major effects in the jaw/face region are due to the slowly expansile space-occupying nature of the mass.



Figure 37.4 Fibrous dysplasia. This 6-year-old pony gelding developed a single slowly expanding asymptomatic swelling of the left rostral mandible. A biopsy of the site showed no evidence of neoplastic change. A radiograph (see Fig. 28.23) showed the lesion as an indistinct intraosseous mass with loss of bone density, which is replaced by a fibrous radiodensity.

Differential diagnoses

- The changes are easily recognized histologically but may be confused with neoplastic lesions both radiographically and clinically.

Diagnostic confirmation

- Radiography and, where feasible, computed tomography
- Gamma scintigraphy
- Biopsy.

Management

Surgical removal may be undertaken, but many remain static and do not affect the horse; there is no evidence to suggest it may be a precursor to neoplastic transformation.

Tumours of skeletal muscle

Rhabdomyoma/rhabdomyosarcoma

Description

The definition is 'a malignant neoplasm that differentiates to form striated muscle'. Rhabdomyosarcoma is a neoplasm derived from primitive mesenchyme with characteristics of myogenesis. They are invasive with metastatic potential.[72]

Tumours of striated (skeletal and cardiac) muscle are extremely rare in man and domestic animals.[73] In the UK, a 15-year survey of 244 equine tumours revealed one rhabdomyosarcoma, and in the USA a 10-year survey did not show any tumours of striated muscle.[74,75] Single case reports and one case series of rhabdomyosarcoma have been published. To-date, there are three reports of equine rhabdomyoma and less than 20 reports of equine rhabdomyosarcoma.[72,74,76–84]

Equine rhabdomyoma is histologically similar to human adult-type rhabdomyoma.[78] In the human, rhabdomyosarcoma has a predilection for the head and neck, genitourinary tract, retroperitoneum, and to a lesser

extent, the extremities (in adults).[83] In the horse, the age range is from newborn to 21 years (median 5 years, mean 6.4 years), but it appears to be more common in younger animals.

No sex or breed predisposition is apparent and various breeds have been described, predominantly Thoroughbreds and Quarter Horses, but this may reflect hospital populations.

Clinical features

See Figure 37.5.

The location of tumours reported is varied and includes:

- Tongue
- Buccal mucosa
- Masseter muscle
- Abdominal wall
- Limb and epaxial muscles
- Heart
- Bladder
- Uterus.

Clinical signs of striated muscle tumours depend on the muscle group affected, but most commonly include:

- Presence of a slow-growing, externally visible swelling/mass within a muscle mass
- Lameness
- Colic/respiratory distress
- Stranguria and haematuria/haemorrhagic vaginal discharge
- Dysphagia and nasal discharge of feed material.

Differential diagnoses

Tumour conditions presenting with lameness, such as:

- Osteosarcoma
- Malignant melanoma
- Melanosarcoma
- Chondrosarcoma
- Osteoclastoma
- Haemangiosarcoma
- Anaplastic sarcoma
- Fibrosarcoma.

For lesions involving the tongue, all soft tissue neoplasms must be considered as potential differential diagnoses.

Non-neoplastic differential diagnoses include:

- Bone cysts
- Abscess
- Severe degenerative joint disease
- Osteomyelitis
- Osteochondroma
- Fibro-osseous tumours
- Dystrophic mineralization
- Tooth root abscess
- Foreign body sequestration/granuloma
- Osteomyelitis.

Disease summary

Notes

Extremely rare group of muscle tumours, with rhabdomyosarcoma being the most often reported.

Clinical features

Variable signs, depending on affected muscle group, including slow-growing visible mass with corresponding muscle-related clinical signs.

Diagnostic confirmation

Ultrasonography and biopsy; histopathology with immunohistochemistry and ultrastructural studies to confirm rhabdomyoma/rhabdomyosarcoma.

Management

Surgery, adjunctive chemotherapy and, possibly, radiotherapy.

Prognosis

Prognosis is very guarded; it depends on the site and extent at the time of diagnosis.

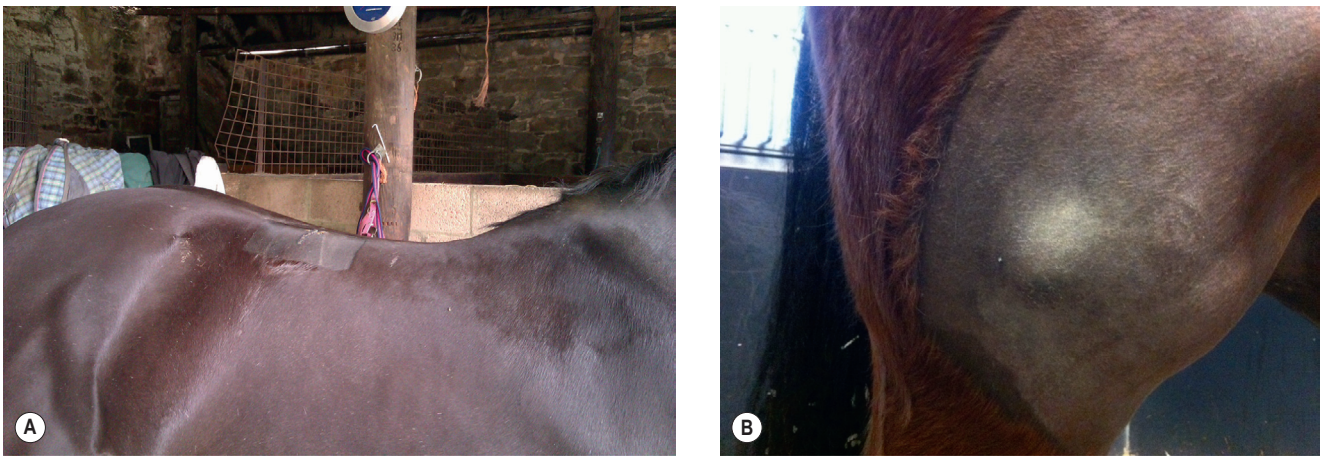


Figure 37.5 Rhabdomyosarcoma. (A) This 10-year-old Hunter-type gelding developed a rapidly expanding, hot, painful swelling in the epaxial muscles of the back. Ultrasonography and biopsy were used to confirm a diagnosis of rhabdomyosarcoma. The lesion was managed with a combination of surgical tumour reduction and intralesional chemotherapy. **(B)** This warm progressive mass developed over some weeks. Ultrasound-guided biopsy confirmed a rhabdomyosarcoma. It was removed surgically but recurred. *(Figure A courtesy of Edward Chin; Figure B courtesy of Dylan Gorvy.)*

Diagnostic confirmation

Diagnosis may be confirmed by a combination of clinical examination and oral, dermatological or orthopaedic assessment, depending, respectively, on clinical presentation of dysphagia, externally visible mass or lameness.

Diagnostic imaging includes radiography, ultrasonography, endoscopy and CT:

- *Radiography* has been used in the evaluation of a mass on the proximo-medial hock, causing lameness.[72] No radiographical abnormalities were identified, ruling out several osseous pathologies. There may also be radiographical evidence of pleural effusion in cases of rhabdomyoma and rhabdomyosarcoma.[77]
- *Ultrasonography* is valuable for identification of location, extent and any secondary effects.[81]
- *Oral and nasal endoscopy* can be useful in cases involving the tongue; the soft palate may be displaced dorsally; any mass on the dorsal aspect of the base of the tongue can be easily visualized.
- *Computed tomography (CT) or magnetic resonance imaging (MRI)* may be useful for identifying the extent of tongue or head and neck lesions and surgical planning.

Biopsy and histopathology is required for confirmatory diagnosis, and immunohistochemistry and ultrastructural investigations are helpful in confirming a diagnosis of rhabdomyoma/rhabdomyosarcoma. Immunohistochemistry may detect early gene activation, as well as neoplastic cells that express actin and myosin filaments, and this may be used in combination with demonstration of striations ultrastructurally to identify less advanced cases that may be more responsive to treatment.

Management

Treatment options reported for rhabdomyoma/rhabdomyosarcoma include surgery and radiotherapy.

Surgery

- Of three cases of rhabdomyoma, one involving the inguinal canal causing strangulating hernia was treated surgically with a successful outcome. Another case presenting with a ventral cervical mass was also resected surgically with success. The third case involved a 30×20×30 cm mass in the caudal ventral mediastinum, believed to originate via a stalk from the diaphragm, and surgery was unsuccessful. This space-occupying lesion caused a pleural effusion and respiratory distress.[76–78]
- Of 17 cases of rhabdomyosarcoma, seven underwent surgery; of the latter, four were treated successfully with follow-up times from 7 months to 3 years.

Radiotherapy

One case of rhabdomyosarcoma was treated with radiotherapy and was free of recurrence at 4 years.

Reasons for treatment failure include:

- Tumour size >10 cm diameter
- Incomplete resection
- Surgical complications causing death or necessitating euthanasia
- All successful surgically treated tumours were <10 cm in diameter; the successful treatment of these cases is probably associated with early diagnosis and intervention prior to the neoplasm exceeding 10 cm diameter.[80]

Criteria for grading equine rhabdomyosarcoma have not been developed and there is no meaningful evidence to provide sensible advice on prognosis. However, based on tumour behaviour of previously published reports, 4 of 17 cases had evidence of metastasis at post mortem, two from alveolar rhabdomyosarcoma in the hindlimbs, one botryoid rhabdomyosarcoma in the bladder and one pleomorphic rhabdomyosarcoma of the abdominal wall. Alveolar type and tumour size >10 cm diameter were strongly associated with metastasis. A high mitotic index may be associated with infiltrative and metastatic behaviour, whereas cellular pleomorphism does not appear to be a useful indicator of biological behaviour.

Metastatic tumours of the musculoskeletal system

Disease summary

Notes

Metastasize to muscle and bone are singularly rare. Most common include squamous cell carcinoma, haemangiosarcoma, lymphoma and melanoma.

Clinical features

A wide variety of signs can be expected, depending on the location, extent and pathological behaviour of the tumour type. Metastatic tumours in the muscles or bones or joints would be expected to cause vague chronic lameness unresponsive to conventional treatments.

Diagnostic confirmation

Radiography, ultrasonography, scintigraphy, biopsy and histopathology.

Management

Metastatic tumours of all types are probably best regarded as untreatable.

Prognosis

The prognosis for any metastatic tumour in horses is poor to hopeless.

Description

In the horse, there have been a small number of case reports and series of neoplasms that have metastasized to the musculoskeletal system. These include:

- Renal carcinoma[85,86]
- Haemangiosarcoma[87–92]
- Leiomyosarcoma[93]
- Colonic adenocarcinoma[94,95]
- Squamous cell carcinoma[96]
- Lymphoma[97]
- Melanoma[98]
- Mast cell tumour.[99]

In other species, the skeleton is an important target of metastatic carcinoma, which most commonly affects the

axial skeleton and proximal long bones.[100] In many cases, skeletal metastasis is the first indication of neoplastic disease, since some types of carcinoma may not lead to clinical abnormalities associated with the primary tumour until late in the course of disease.[100] In cats, metastatic neoplasia secondary to injection-site sarcoma is the most common form of musculoskeletal neoplasia.[101]

In the horse, the most common form of equine neoplasia is dermatological neoplasia and none of these tumours has a predilection to metastasize to bones. Therefore, metastatic bone neoplasia is not a clinically significant problem.

Metastatic bone neoplasia should always be considered as a potential differential diagnosis of vague chronic lameness in the horse, particularly if primary tumours have been diagnosed.[102]

- Haemangiosarcoma is a malignant neoplasm originating from vascular endothelium. Cutaneous, locally invasive and disseminated forms have been reported in the horse
  - Skeletal muscle was the second most common site, affecting 46% of cases, in which musculoskeletal problems were the second most common presenting complaint.[91] These included intramuscular swelling, haematoma formation and lameness
  - In a case series of 11 young horses with haemangiosarcoma, all horses presented with cutaneous or leg swellings or joint effusion[88]
  - A primary haemangiosarcoma in the proximal humerus of a Clydesdale gelding that presented with left forelimb lameness of 2 weeks' duration[87] also had an 8×10 cm diameter red/black mass in the proximal metaphysis of the humerus with no other body organ involvement[87]
  - A further case of a 14-year-old Paint gelding identified an intrapelvic haemangiosarcoma causing clinical signs of lethargy, abdominal pain, haemorrhagic wound and marked limb oedema[90]
  - A horse presenting with ataxia of all four limbs, low head carriage and reluctance to flex the neck was found at necropsy to have a tumour involving the second cervical vertebrae and associated hypaxial musculature with secondary intravertebral extradural infiltration and focal compressive myelopathy. Histopathology confirmed haemangiosarcoma.[92]
- Lymphoma (Fig. 37.6) has also been reported to be associated with neurological signs. However, only one case of true axial skeletal involvement has been reported[97]:
  - A 23-month-old Quarter Horse mare presented with hindlimb paresis and recumbency. A subperiosteal mass at the level of the first lumbar vertebrae was identified. On cross-section, there was destruction of the vertebral body. Focal destruction of the cortex of the vertebral body had allowed formation of the subperiosteal mass, which protruded into the vertebral canal, causing neurological signs.
- Metastatic melanomas (Fig. 37.7) involving skeletal muscle, including epimysial fascia, were found in 57% of horses in a case series[98]:

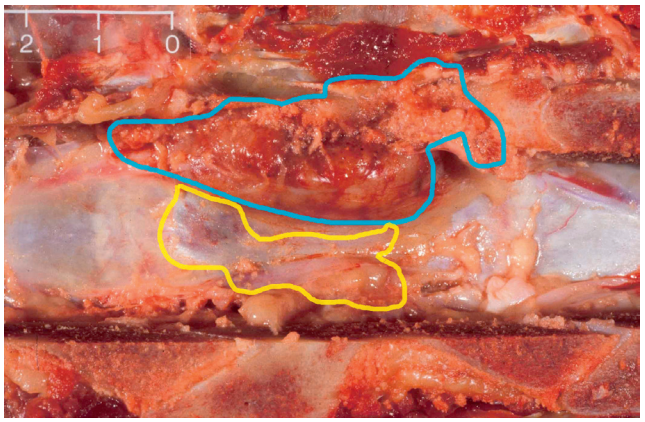


Figure 37.6 Spinal lymphoma. A 4-year-old mare had a 4-month history of weight loss that was attributed at first to dental and dietary problems. However, she became anaemic and dull and over a 10-day period developed progressive hindlimb ataxia and strong spinal pain over L5 during ventro- and dorsoflexion. A neurological examination was carried out and a spinal lesion was diagnosed clinically. During the investigation it became clear that the horse had a multicentric lymphoma. At necropsy, the diagnosis was confirmed and this focal lymphoma was identified in the vertebral body and spinal cord of L5. The tumour virtually obliterated the vertebral body and impinged into the spinal canal with the expected consequences.



Figure 37.7 Metastatic melanoma. A 14-year-old grey mare developed a progressive weight loss and marked muscle wasting of the right pelvic musculature. Extensive muscular infiltration with melanoma and invasion into and around the sacral plexus was identified post mortem. Melanoma can involve any muscle organ or indeed any organ at all. *(Figure courtesy of Wendy Talbot.)*

  - Under half (6/14) of the cases had masses associated with bone or bone marrow and vertebrae were infiltrated in 21% (3/14) of the cases. Of those, two had neurological deficits. One horse developed hindlimb ataxia secondary to spinal cord compression caused by an epidural mass and had two additional infiltrated vertebrae not causing spinal cord damage. The other horse developed cauda equina syndrome and severe gluteal muscle

atrophy because of a large mass that occluded the cauda equina and infiltrated the sacral bone. Other sites of bony involvement in this case series included the maxilla and rib.

Case reviews

Two cases of bone metastasis secondary to colonic adenocarcinoma have been reported.

A 19-year-old Quarter Horse mare[94]

Presentation

- Lameness of the left forelimb
- Swelling of the left shoulder region.

Findings

- Post-mortem examination revealed a primary colonic carcinoma with metastases to mesenteric lymph nodes, spleen and humerus.

A 5-year-old Arab horse[95]

Presentation

- Inappetence
- Acute collapse.

Diagnosis

- Colonic adenocarcinoma.

Diagnostic confirmation

- *Neurological examination* has been used to anatomically localize the lesion to the thoracolumbar spine.
- *Radiography* was used in a case to reveal lysis and exuberant new bone formation and sequestrum formation in the region of the proximal humerus.
- *Needle aspiration and core biopsy* was used to give definitive diagnosis of a malignant neoplasm.[94]
- *Leukocyte-labelled scintigraphy* has been used effectively to identify polyostotic disease and biopsy of an affected rib identified as disseminated adenocarcinoma.[95]

A combination of scintigraphy, ultrasonography and ultrasound-guided biopsy did not confirm a diagnosis, highlighting the difficulty of ante-mortem diagnosis of bone lesions.[87]

The prognosis for any metastatic tumour in horses is poor to hopeless, although juvenile haemangiosarcomas have been reported to resolve spontaneously.[4]

References

1. Cheli R, Zaraga L. Synovioma della grande sesamoideanelcavallo. Clin Vet 1977; 100:280.
2. Livesey MA, Wilkie IW. Focal and multifocal osteosarcoma in two foals. Equine Vet J 1986; 18:407–410.
3. Slayter MV, Boosinger TR, Pool RR, et al. Histological classification of bone and joint tumours of domestic animals. Washington, DC: Armed Forces Institute of Pathology; 1994: 9–45.
4. Puff C, Ohnesorge B, Wagels R, et al. An unusual mucinous osteoma with features of an ossifying fibroma in the nasal cavity of a horse. J Comp Pathol 2006; 135:52–55.
5. Head KW, Dixon PM. Equine nasal and paranasal sinus tumours. Part 2: A contribution of 28 case reports. Vet J 1999; 157:279–294.
6. Collins JA. Ossifying fibroma/osteoma in the proximal tibia of a mature gelding. Vet Rec 1998; 143:367–368.
7. Kold SE, Østblom LC. Headshaking caused by a maxillary osteoma in a horse. Equine Vet J 1982; 14:167–169.
8. Ragle CA, de Mira MC, Pearson LK, et al. Pneumocephalus secondary to removal of an osteoma from the paranasal sinuses of a horse. J Am Vet Med Assoc 2009; 235:184–188.
9. Olds AM, Stewart AA, Grimm JB. What is your diagnosis? A pedunculated heterogeneous mineral opacity structure is evident ventral to the third premolar on the left mandible. J Am Vet Med Assoc 2004; 224:1073–1074.
10. Cilliers I, Williams J, Carstens A, et al. Three cases of osteoma and an osseous fibroma of the paranasal sinuses of horses in South Africa. J S Afr Vet Assoc 2008; 79:185–193.
11. Schaaf KL, Kannegieter NJ, Lovell DK. Calcified tumours of the paranasal sinuses in three horses. Aust Vet J 2007; 85:454–458.
12. Scotty NC, Ford M, Williams FR, et al. Exophthalmia associated with paranasal sinus osteoma in a Quarterhorse mare. J Vet Diagn Invest 2004; 16:155–160.
13. Schumacher J, Smith BL, Morgan SJ. Osteoma of paranasal sinuses of a horse. J Am Vet Med Assoc 1988; 192:1449–1450.
14. Richardson DW, Acland HM. Multilobular osteoma (chondroma rodens) in a horse. J Am Vet Med Assoc 1983; 182:289–291.
15. Meuten DJ. Tumors of domestic animals, 4th edn. Ames: Iowa State Press; 2002: 266–267.
16. Thorpe F, Graham R. A large osteosarcoma of the mandible. J Am Vet Med Assoc 1934; 84:118–119.
17. Jacobson SA. Parosteal osteoma (juxtacortical osteogenic sarcoma) in animals. Am J Pathol 1969; 58:85a.
18. Jacobson SA. Comparative pathology of the tumors of bone. Springfield: CC Thomas; 1971: 164–211.
19. Bush JM, Frederickson RL, Ehrhart EJ. Equine osteosarcoma: A series of 8 cases. Vet Pathol 2007; 44:247–249.
20. Jenner F, Solano M, Gliatto J, et al. Osteosarcoma of the tarsus in a horse. Equine Vet J 2003; 35:214–216.
21. Gorlin RJ, Meskin LH, Brodey RS. Odontogenic tumours in man and animals: Pathological classification and clinical behaviour – a review. Ann N Y Acad Sci 1969; 108:722–771.
22. Schooley EK, Hendrickson DA. Musculoskeletal system neoplasia. Vet Clin North Am Equine Pract 1998; 14:535–542.
23. Gutierrez-Nibeyro SD, Sullins KE, Powers BE. Treatment of appendicular osteosarcoma in a horse. Equine Vet Educ 2010; 22:540–544.
24. Cillan-Garcia E, Kearns LJ, Hetzel U, et al. Osteosarcoma of the middle phalanx in a horse. Equine Vet Educ 2010; 22:535–539.
25. Snalune KL. Exercise induced epistaxis secondary to a benign osteoma of the nasal turbinate, unpublished data; 2009.
26. Nelson AM, Baker DC. Pedal osteosarcoma in a donkey. Vet Pathol 1998; 35:407–409.
27. Zaruby JF, Williams JW, Lovering SL. Periosteal osteosarcoma of the scapula in a horse. Can Vet J 1993; 34:742–744.
28. Morgan JP, Carlson WD, Adams OR. Hereditary multiple exostosis in the horse. J Am Vet Med Assoc 1962; 140:1320–1322.
29. Wilson RG, Auer DE, Kelly WR. Multiple cartilaginous exostoses in a horse. Equine Vet J 1985; 17:462–465.
30. Jansson N. Osteochondroma at the distal radius metaphysis in a horse. Pferdeheilkunde 1998; 14:151–154.
31. Green EM, Adams WM, Steinberg H. Malignant transformation of solitary spinal osteochondroma in two mature dogs. Vet Radiol Ultrasound 1999; 40:634–637.
32. Stashak TS, ed. The forearm (antebrachium). Adams' lameness in horses, 5th edn. Philadelphia: Lippincott, Williams & Wilkins; 2002: 864–879.
33. Lundvall RL, Jackson LL. Periosteal new bone formation of the radius as a cause of lameness in two horses. J Am Vet Med Assoc 1976; 168: 612–613.
34. Lee HA, Grant BD, Gallina AM. Solitary osteochondroma in a horse: a case report. J Equine Med Surg 1979; 3:113–114.
35. Held JP, Patton CS, Shires M. Solitary osteochondroma of the radius in three horses. J Am Vet Med Assoc 1988; 193:563–564.
36. Squire KR, Adams SB, Widmer WR, et al. Arthroscopic removal of a palmar radial osteochondroma causing carpal canal syndrome in a horse. J Am Vet Med Assoc 1992; 201:1216–1218.
37. Southwood LL, Stashak TS, Fehr JE, et al. Lateral approach for endoscopic removal of solitary osteochondromas. J Am Vet Med Assoc 1997; 210: 1166–1168.
38. Easter JL, Watkins JP, Berridge B, et al. A digital osteochondroma as the cause of lameness in a foal. Vet Comp Orthop Traumatol 1998; 11:44–46.
39. Chan CC-H, Munroe GA, Callanan JJ. Congenital solitary osteochondroma affecting the tarsus in a filly foal. Equine Vet Educ 1996; 8:153–156.
40. Kenzora KT, Wagner von Matthiessen P, Sheehan RM. A uniquely located solitary plantar tibial osteochondroma in a Thoroughbred racehorse. Equine Pract 1995; 17:23–25.
41. Secombe CJ, Anderson BH. Diagnosis and treatment of an osteochondroma of the distal tibia in a 3-year-old horse. Aust Vet J 2000; 78:16–18.
42. Thompson KG, Pool RR. Tumors of bones. In: Meuten DJ, ed. Tumors in domestic animals, 4th edn. Ames: Iowa State Press; 2002: 245–317.
43. Thompson K. Tumors and tumor-like lesions of bones. In: Maxie MG, ed. Jubb, Kennedy and Palmer's pathology of domestic animals, 5th edn. Edinburgh: Elsevier; 2007: 110–130.
44. Milgram JW. The origin of osteochondromas and enchondromas: a histopathologic study. Clin Orthop Relat Res 1983; 174:264–284.
45. Athanasou NA, Woods C. Bone tumours and tumour like conditions of bone. In: McGee JO, Isaacson PG, Wright NA, eds. Oxford textbook of pathology: pathology of systems, Vol. 2B. Oxford: Oxford University Press; 1992: 2047–2072.
46. Watkins JP. Radius and ulna. In: Auer JA, Stick JA, eds. Equine surgery, 3rd edn. St Louis: Elsevier; 2006: 1267–1279.
47. Adair HS, Duncan RB, Toal RL. Solitary osteochondroma of the nasal bone in a horse. Cornell Vet 1994; 84:25–31.
48. Pasolini MP, Greco M, Trapani F, et al. Nasal bone osteochondroma in a horse. Vet Rec 2009; 164:534–535.

49. Wright IM, Minshall GJ. Clinical, radiological and ultrasonographic features, treatment and outcome in 22 horses with caudal distal radial osteochondromata. Equine Vet J 2012; 44:319–324.
50. Nixon AJ. Carpal canal syndrome. In: White NA, Moore JN, eds. Current practice of equine surgery. Philadelphia: Lippincott Co; 1990: 461–464.
51. Honnas CM. Surgical treatment of selected musculoskeletal disorders of the forelimb. In: Auer JA, ed. Equine surgery. Philadelphia: WB Saunders; 1992: 985–1054.
52. McIlwraith CW, Nixon AJ, Wright IM, et al. Tenoscopy. Diagnostic and surgical arthroscopy in the horse, 3rd edn. Edinburgh: Elsevier; 2005: 365–408.
53. Textor JA, Nixon AJ, Fortier LA. Tenoscopic release of the equine carpal canal. Vet Surg 2003; 32:278–284.
54. Dyson SJ. The deep digital flexor tendon. In: Ross MW, Dyson SJ, eds. Diagnosis and management of lameness in the horse. Philadelphia: WB Saunders; 2003: 644–650.
55. Li JK, Moloney BK, Shupe JL, et al. DNA polymorphism analysis of hereditary multiple exostoses in horses. Am J Vet Res 1989; 50: 978–983.
56. Hanselka DV, Roberts RE, Thompson RB. Equine multiple cartilaginous exostoses. Vet Med Small Anim Clin 1974; 69:979–986.
57. Shupe JL, Leone NC, Olson AE, et al. Hereditary multiple exostoses: clinicopathologic features of a comparative study in horses and man. Am J Vet Res 1979; 40:751–757.
58. Shupe JL, Leone NC, Gardner EJ, et al. Hereditary multiple exostoses. Hereditary multiple exostoses in horses. Am J Pathol 1981; 104:285–288.
59. Leone NC, Shupe JL, Gardner EJ, et al. Hereditary multiple exostosis. A comparative human-equine-epidemiologic study. J Hered 1987; 78: 171–177.
60. Gordon GE. Osteoclastoma in a mare. Mod Vet Pract 1974; 55:540–541.
61. May SA, Baker JR. A giant cell tumour (osteoclastoma) of the tibia in a horse. Equine Vet J 1985; 17:477–479.
62. Goedegebuure SA, Firth EC, Dik KJ. Osteoblastoma in the radius of a pony. Vet Pathol 1983; 20:650–652.
63. Sullivan DJ. Cartilaginous tumours (chondroma and chondrosarcoma) in animals. Am J Vet Res 1960; 21:531–535.
64. Bertone AL, Powers BE, Turner AS. Chondrosarcoma in the radius of a horse. J Am Vet Med Assoc 1984; 185:534–537.
65. Riddle WE, Wheat JD. Chondrosarcoma in a horse. J Am Vet Med Assoc 1971; 158:1674–1677.
66. Trotter GW, Aanes WA, Synder SP. Laryngeal chondroma in a horse. J Am Vet Med Assoc 1981; 178:829–830.
67. Wilson GJ, Anthony ND. Chondrosarcoma of the tongue of a horse. Aust Vet J 2007; 85:163–165.
68. Biesecker JL, Marcove RC, Huvos AG, et al. Aneurysmal bone cysts; a clinicopathological study of 66 cases. Cancer 1970; 26:616–625.
69. Dabezies EJ, D'Ambrosia RD, Chuinard RG, et al. Aneurysmal bone cyst after fracture. J Bone Joint Surg Am 1982; 64:617–621.
70. Lamb CR, Schelling SH. Congenital aneurysmal bone cyst in the mandible of a foal. Equine Vet J 1989; 21:130–132.
71. Dubielzig RR. Odontogenic tumors and cysts. In: Meuten DJ, ed. Tumors in domestic animals, 4th edn. Ames: Iowa State Press; 2002: 402–410.
72. Clegg PD, Coumbe A. Alveolar rhabdomyosarcoma: an unusual cause of lameness in a pony. Equine Vet J 1993; 25:547–549.
73. Willis RA. Pathology of tumors, 4th edn. London: Butterworth and Co; 1967.
74. Baker JR, Leyland A. Histological survey of tumours of the horse with particular reference to those of the skin. Vet Rec 1975; 96:419–422.
75. Alden CL, Kerr KM. Equine neoplasia. A ten-year survey. Proc Am Assoc Vet Lab Diag 1974; 17:183–187.
76. Sohrabi Haghdoost I, Zakaran B. Neoplasms of equidae in Iran. Equine Vet J 1985; 18:237–239.
77. Hamir AN. Striated muscle tumours in horses. Vet Rec 1982; 111:367–368.
78. Meyerholz DK, Caston SS, Haynes JS. Congenital foetal rhabdomyoma in a foal. Vet Pathol 2004; 41:518–520.
79. Turnquist SE, Pace LW, Keegan K, et al. Botryoid rhabdomyosarcoma of the urinary bladder in a filly. J Vet Diagn Invest 1993; 5:451–453.
80. Castleman WL, Toplon DE, Clark CK, et al. Rhabdomyosarcoma in 8 horses. Vet Pathol 2011; 48:1144–1150.
81. Aupperle H, Börgel C, Raila G, et al. Morphological, immunohistochemical, and ultrastructural findings in an embryonal rhabdomyosarcoma of a newborn Thoroughbred foal. J Equine Vet Sci 2004; 24:159–164.
82. Torbeck RL, Kittleson SL, Leathers CW. Botryoid rhabdomyosarcoma of the uterus of a filly. J Am Vet Med Assoc 1980; 176:914–916.
83. Hanson PD, Frisbie DD, Dubielzig RR, et al. Rhabdomyosarcoma of the tongue in a horse. J Am Vet Med Assoc 1993; 202:1281–1284.
84. Finnochio EJ, Coffman JR, Strafuss AC. Rhabdomyosarcoma in a horse. Vet Med Small Anim Clin 1969; 64:494–496.
85. Young AC, Hoffmann KL, Begg AP, et al. Acute lameness associated with osseous metastasis of a peri-renal carcinoma in a horse. Aust Vet J 2010; 88:346–350.
86. Rumbaugh ML, Latimer FG, Porthouse KR, et al. Renal carcinoma with osseous and pulmonary metastases in an Arabian gelding. Equine Vet J 2003; 35:107–109.
87. Cottle HJ, Hughes KJ, Philbey AW, et al. Primary haemangiosarcoma in the proximal humerus of a Clydesdale gelding. Equine Vet Educ 2008; 20: 575–579.
88. Johns I, Stephen JO, Del Piero F, et al. Haemangiosarcoma in 11 young horses. J Vet Intern Med 2005; 19:564–570.
89. Dunkel BM, Del Piero F, Kraus BM, et al. Congenital cutaneous, oral, and periarticular haemangiosarcoma in a 9-day-old Rocky Mountain horse. J Vet Intern Med 2004; 18:252–255.
90. Kiupel M, Frank N, Stevenson GW, et al. Intrapelvic haemangiosarcoma in a horse. J Vet Diagn Invest 2000; 12:91–95.
91. Southwood LL, Schott HC, Henry CJ, et al. Disseminated haemangiosarcoma in the horse: 35 cases. J Vet Intern Med 2000; 14:105–109.
92. Newton-Clarke MJ, Guffoy MR, Dykes NL, et al. Ataxia due to vertebral haemangiosarcoma in a horse. Vet Rec 1994; 135:182–184.
93. MacGillivray KC, Graham TD, Parente EJ. Multicentric leiomyosarcoma in a young male horse. J Am Vet Med Assoc 2003; 223:1017–1021.
94. Jann HW, Breshears MA, Allison RW, et al. Occult metastatic intestinal adenocarcinoma resulting in pathological fracture of the proximal humerus. Equine Vet J 2009; 41:915–917.
95. East LM, Steyn PF, Dickinson CE, et al. Occult osseous metastasis of a colonic adenocarcinoma visualized with technetium tc 99m hydroxymethylene diphosphate scintigraphy in a horse. J Am Vet Med Assoc 1998; 213:1132–1133,1167–1170.
96. Patterson LJ, May SA, Baker JR. Skeletal metastasis of a penile squamous cell carcinoma. Vet Rec 1990; 126:579–580.
97. Zeman DH, Snider TG 3rd, McClure JJ. Vertebral lymphosarcoma as the cause of hind limb paresis in a horse. J Vet Diagn Invest 1989; 1:187–188.
98. MacGillivray KC, Sweeney RW, Del Piero F. Metastatic melanoma in horses. J Vet Intern Med 2002; 16:452–456.
99. Ritmeester AM, Denicola DB, Blevins WE, et al. Primary intraosseous mast cell tumour of the third phalanx in a Quarter Horse. Equine Vet J 1997; 29:151–152.
100. Cooley DM, Waters DJ. Skeletal metastasis as the initial clinical manifestation of metastatic carcinoma in 19 dogs. J Vet Intern Med 1998; 12:288–293.
101. Chun R. Common malignant musculoskeletal neoplasms of dogs and cats. Vet Clin North Am Small Anim Pract 2005; 35:1155–1167.
102. Henson F. Skeletal neoplasia in the horse – a review. Equine Vet Educ 2007; 19:569–570.

Glossary

Anaplastic/anaplasia: characterized by, composed of, or being cells which have reverted to a relatively undifferentiated state representing a potentially dangerous tumour type.

Angiogenesis: the physiological process involving the growth of new *blood vessels* from pre-existing vessels.

Antigen presenting cell: a cell that is specialized in activating a T-cell mediated immune response by presenting antigen to naive T cells.

Apoptosis: a cell suicide process resulting in cell death that requires active gene transcription and translation. Planned/natural cell death that occurs in a controlled fashion (planned dismantling) without any deleterious effects locally or systemically.

Autocrine: relating to, promoted by or being a substance secreted by a cell and acting on surface receptors of the same cell.

Autophagy: a normal process in which a cell destroys proteins and other substances in its cytoplasm (the fluid inside the cell membrane but outside the nucleus), which may lead to cell death. Autophagy may prevent normal cells from developing into cancer cells, but it may also protect cancer cells by destroying anticancer drugs or substances taken up by them.

Benign (in respect of cancer): of a mild type or character that does not threaten health or life; a mass that remains local and has no remote implication. Having a good prognosis: responding favourably to treatment.

Cachexia: the loss of body mass that cannot be reversed nutritionally.

Cancer: a term for malignant neoplasm/tumour.

Carcinogen: a substance that causes or promotes cancer.

Cell-mediated immunity: immunity that can be transferred by the cellular fraction of blood but not by serum/plasma. The specificity of a cell-mediated response is determined by T-cell receptor of T cells.

Chemokine: a group of chemotactic bioactive substances that are produced by various cells (such as at sites of inflammation), that are thought to provide directional cues for the movement of white blood cells (as T cells, monocytes and neutrophils).

Chemotherapy: treatment with drugs that kill cancer cells.

Cytokine: a group of immunoregulatory proteins (including interleukin, tumour necrosis factor and interferon) that are secreted by cells, especially of the immune system.

Cytomorphosis: the processes that a cell passes through over its life-cycle.

Cytotoxicity: the ability of a compound to kill cells.

Doubling time: the amount of time it takes for one cell to divide or for a group of cells (such as a tumour) to double in size. The doubling time is different for different kinds of cancer cells or tumours.

Drug resistance: the ability of cells to withstand/resist challenges by compounds which in previous generations of the cells were lethal.

Dysplasia: abnormal growth or development (as of organs or cells); abnormal anatomical structure due to such growth.

Endocrine: cells or organs producing secretions that influence the function of tissues and cells remotely through being distributed in the body by the bloodstream.

Epigenetics: the study of inherited changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence.

Genotoxicity: the ability of a chemical compound or substance to damage DNA.

Grading: a process that sets out to provide an abbreviated index of how abnormal tumour cells look under a microscope and how quickly the tumour is likely to grow and spread.

Growth: increase in the number of macromolecules within a cell; enlargement of individual cells.

Hormone: a product of living cells that circulates in body fluids, including the blood, to induce a specific often stimulatory effect on the activity of cells usually remote from its source.

Immune surveillance: the concept that the immune system recognizes and destroys incipient neoplastic cells. Hosts with impaired immunity will likely be more susceptible to cancer, and cancers in immunocompetent hosts must develop strategies to evade the natural protective immune responses.

Interstrand cross-link: a covalent linking of DNA bases from opposite strands of the DNA double helix.

Intrastrand cross-link: a covalent linking of DNA bases from the same strand of the DNA double helix.

Malignant (in respect of cancer): tending to infiltrate, metastasize and terminate fatally; can be locally invasive or locally malignant.

Metastasis: the spread of a disease-producing agency (as cancer cells or bacteria) from the initial or primary site of disease to another part of the body; secondary malignant tumour resulting from metastasis.

MHC (major histocompatibility) molecules: molecules on the surface of cells that present antigen in the form of peptide epitopes so that it can be recognized by host T cells. MHC class I molecules typically present cytoplasmic proteins. MHC class II molecules present antigens present in endosomal and lysosomal compartments.

Mitotic Index: the fraction of cells in a sample that are in mitosis. It is a measure of the relative length of the mitotic phase of the cell-cycle.

Neoplasia: 'new growth' – a new growth is termed 'a neoplasm'.

Oncogene: a gene having the potential to cause a normal cell to become cancerous.

Oncology: the study of tumours or neoplasms.

Palliative chemotherapy/radiotherapy: chemotherapy/radiotherapy given without curative intent, but simply to decrease tumour load and increase life expectancy and patient welfare.

Paracrine: relating to, promoted by or being a substance secreted by a cell and acting on adjacent cells, e.g. paracrine stimulation of tumour growth.

Proliferation: increase in the number of (cells); specifically, increases in the total biomass of a structure or mass.

Staging: staging of cancer is a method of tumour classification that provides abbreviated clinically useful information relating to the size, site and spread of the tumour.

Telomere: a protective cap at each end of a chromosome that stabilizes chromosomal ends and prevents them from being recognized as double strand breaks by the cellular surveillance system that monitors intracellular damage.

Telomerase: a ribonuclear reverse transcriptase that maintains telomere length.

T-cell receptors: molecules on the surface of T cells capable of recognizing antigens complexed with MHC. Each T cell has one specific set of T-cell receptors.

Tumour: the term was classically used to describe a 'swelling' caused by inflammation but is now widely taken to be synonymous with neoplasm or cancer.

Tumour antigens: antigens on tumours that the immune system is capable of recognizing and responding to. They may be exclusive to tumours or may be shared with normal non-cancerous cells.

Vaccination: the strategy of actively inducing immunity by administration of an antigen.

Specialist terms used in radiotherapy

Radiotherapy: the practice of treating disease (mainly malignancy) with ionizing radiation.

Plesiotherapy: the process in which radioactive sources are applied directly onto the tumour surface.

Brachytherapy: radiation therapy in which radioactive material sealed in needles, seeds, wires or catheters is placed directly into or near a tumour. Also called implant radiation therapy, internal radiation therapy and radiation brachytherapy.

Teletherapy: the process in which externally generated ionizing radiation is beamed into a tissue from a distance (usually around 80–100 cm).

Dosimeter: an instrument used to measure the dose of radiation – usually applied to the instrument or device worn by the operator to determine the dose of radiation that has been delivered from the source and is a measure of operator exposure.

Dosimetry: the specialized physics calculating the amount of radiation that is delivered to a tumour using the information regarding the tumour type and its location and the source and type of radiation (especially in respect of X- or gamma-radiation). Measurement of therapeutic radiation exposure; the calculation of radiation dose from internally administered radionuclides.

Index

Page numbers followed by 'f' indicate figures, 't' indicate tables, and 'b' indicate boxes.

A

Abdominal cavity, tumours of, 429–479
Abdominocentesis, 97–98, 98f
  of gastric squamous cell carcinoma, 459
  of haemangiosarcoma, 516
  of intestinal neoplasia, 461
Ablative biopsy, 89
Ablative therapy, 120–129
  surgical methods of, 120–125
    cryotherapy/cryonecrosis/cryoablation, 126–127
    diathermy ('electrosurgery'), 125–126
    hyperthermia, 127
    laser surgical excision, 124–125
    sharp excision, 120–122, 121f
    smart surgery, 122–124
    vascular or tumour ligation, 127–129, 128f
Abnormal circulating cells, 100t
Abnormal respiratory noise, paranasal sinus cysts and, 494
Acanthosis, definition of, 248–249
'Accelerated repopulation', 168
'Accessibility' tissue, 87
Accuracy, of laser surgical excision, 124
Acetone, for cryotherapy/cryonecrosis/cryoablation, 127
Aciclovir, in equine chemotherapy, 144–145
Acquired bone cysts, of tarsus, 322
ACTH. *see* Adrenocorticotrophic hormone (ACTH)
Actinic keratosis (AK), squamous cell carcinoma in situ and, 220–221
Actinomycosis, 323
Active (specific) immunotherapy, 187–191, 188f
Active tumour cell migration, 50–51
Acute myeloblastic (M1 and M2) leukaemia, 541
Acutely-transforming viruses, 46
Adamantinoma. *see* Ameloblastoma
Adenocarcinoma, 464–465, 464b, 465f
  colon, 266
  endometrial. *see* Endometrial adenocarcinoma
  exocrine pancreatic. *see* Pancreatic adenocarcinoma, exocrine
  extensive nasal, 63f
  gastric, 460–461, 460b
  intestinal. *see* Intestinal adenocarcinoma
  mammary, 647–648, 647b, 648f
  ovarian. *see* Ovarian adenocarcinoma
  pulmonary. *see* Pulmonary adenocarcinoma
  renal. *see* Renal adenocarcinoma
  salivary, 448–449, 449b, 449f
  sinonasal. *see* Sinonasal adenocarcinoma
  thyroid, 590–591, 590b, 591f
  of upper and lower respiratory tract, 483–485, 483b
    clinical features of, 484, 484f
    description of, 484
    diagnostic confirmation of, 484
    management and prognosis of, 485, 485b
Adenofibroma, biliary. *see* Biliary adenofibroma
Adenoma-carcinoma sequence, molecular model for evolution of colorectal cancers through, 40f
Adenoma(s), 15–16
  adrenal cortical. *see* Adrenal cortical adenomas
  C-cell, 591–592
  hepatocellular. *see* Hepatocellular adenoma
  intestinal. *see* Intestinal adenoma
Adenoma(s) (*Continued*)
  oviductal. *see* Oviductal adenoma
  pituitary. *see* Pituitary adenoma
  pulmonary. *see* Pulmonary adenoma
  renal. *see* Renal adenoma
  sinonasal. *see* Sinonasal adenoma
  thyroid. *see* Thyroid adenoma
  ultimobranchial, 592
Adjunctive chemotherapy, 178–185
  method of, 179, 179f
  principles of, 178–184
  safety aspects of, 178
Adjuvant chemotherapy, 141
  intraoperative or postoperative, 133
Adrenal cortical adenomas, 386
  and carcinoma, 384–385
    biological behaviour of, 384–385
    cellular origin of, 384
    differential diagnoses for, 385b
    electron microscopy in, 385
    gross pathology of, 385
    histopathology of, 385
    immunohistochemical labelling for, 385
    profile of, 384
Adrenal glands, neoplasia of, 592–593
Adrenal medulla, neoplasia of, 594–599
Adrenocortical neoplasia, 593
Adrenocorticotrophic hormone (ACTH), 95t
Aetiopathogenesis, of various syndromes, 71
Aggressive melanosarcoma, 63f
AK. *see* Actinic keratosis (AK)
ALA. *see* 5-Aminolevulinic acid (ALA)
ALARA principle, 163
Alimentary lymphoma, 462
  of cardiovascular system, 528–531, 528b
    clinical features of, 528–529, 529f
    description of, 528
    diagnostic confirmation of, 529–530, 530f
    management of, 531, 531f
    prognosis of, 531
Alimentary lymphosarcoma, 346–348
  biological behaviour of, 347
  gross pathology of, 347–348, 347f
  histopathology of, 348
  profile of, 346–347
Alimentary syndrome, 72t
Alimentary tract
  squamous cell carcinoma of, 230–232
  tumours of, 429–479
Alkaline phosphatase (ALP), 95t
Alkylating agents, 137
Alopecia, 129
Alpha-fetoprotein, hepatocellular carcinoma/adenoma and, 268–269
Alpha (α) particles, 166
Ameloblastic carcinoma
  biological behaviour of, 325
  cellular origin of, 325
  differential diagnoses of, 326b
  gross pathology of, 325
  histopathology of, 325–326
  immunohistochemical labelling of, 326
  profile of, 325
Ameloblastic fibro-odontoma
  biological behaviour of, 326
  cellular origin of, 326
  differential diagnoses of, 326b
  gross pathology of, 326
Ameloblastic fibro-odontoma (*Continued*)
  histopathology of, 326
  profile of, 326
Ameloblastic odontoma, 431t
Ameloblastoma, 431t, 432–433, 432b
  biological behaviour of, 323–324
  cellular origin of, 323
  clinical features of, 432, 433f
  description of, 432
  diagnostic confirmation of, 432–433
  differential diagnoses of, 325b, 432
  gross pathology of, 324, 324f
  histopathology of, 324–325
  immunohistochemical labelling of, 325
  management and prognosis of, 433
  profile of, 323
American Joint Commission on Cancer, 18
American Quarter Horse, 419
5-Aminolevulinic acid (ALA), 162
Amniotic teratocarcinoma, 406–407
  histopathology of, 407
Amyloid, 230
Amyloidosis, 81
  cutaneous, 230, 231f
  multiple myeloma and, 356
  'tumour-like' nasal, profile of, 260
Anaemia, 75–76, 100t
  in gastric squamous cell carcinoma, 231
  haemolytic, 76
  non-regenerative, in bladder carcinoma, 660
  progressive, 91
Anaplastic malignant melanoma, 569, 569f
Anaplastic sarcoma
  biological behaviour of, 292
  cellular origin of, 292
  differential diagnoses of, 292b
  gross pathology of, 292
  histopathology of, 292, 292f
  profile of, 292
Aneurysmal bone cysts, 322
Angiogenesis, 48–50, 49f
  continued, 52
  tumour, 49
Angiosarcoma
  biological behaviour of, 339
  of cardiovascular system, 519–521, 519b
    clinical features of, 519–520, 520f
    description of, 519
    diagnostic confirmation of, 520
    differential diagnoses of, 520
    management of, 521
    prognosis of, 521
  cellular origin of, 339
  differential diagnoses of, 339b
  profile of, 339
Anisocytosis, 213
Anisokaryosis, 213
Ann Arbor tumour staging, 21–22
Anorexia-cachexia syndromes, 73–74
Antibody(ies)
  goat anti-rabbit, 114
  HMB45, 243–245
  monoclonal, availability of specific, 113
  peroxidase enzyme, 114
Anticancer drugs, 163
Anti-diuretic hormone (ADH), 73
Antimetabolites, 135
Antimitotic drugs, 163

Anti-mitotic/cytotoxic chemicals
  for equine sarcoids, 558–559
  for mastocytoma, 566
  for squamous cell carcinoma, 579
Anti-T-cell factors, production/over expression of, 35
Antoni A pattern, definition of, 300
Antoni B pattern, definition of, 300
Aortico-sympathetic paraganglioma, 598
  biological behaviour of, 390
  cellular origin of, 390
  gross pathology of, 390
  histopathology of, 390
  immunohistochemical labelling of, 390
  profile of, 390
APC gene, 26t
Apoptosis, 29–31, 32f, 144
  altered pathways for, 144
  cellular evasion of, 31–32
  control of, 24–25
  in radiation therapy, 166
Arachnoid diverticulum, 370
Arrhenoblastoma. *see* Sertoli-Leydig cell tumour of ovary
Arsenic compounds, 138–139
Arsenic trioxide, topical, 139
Aseptic surgery, preparation of, 122
Aspartate dehydrogenase (AST), 95t
Aspiration
  of alimentary lymphoma, 530
  bone marrow, 99
    indications for, 100t
    technique, 100–101
AST. *see* Aspartate dehydrogenase (AST)
Astrocytoma, 363–364, 601–602, 601b
  biological behaviour of, 363
  cellular origin of, 363
  differential diagnoses for, 364b
  of eye, 625–626, 625b, 626f
  gross pathology of, 363, 364f
  high-grade, 363–364
  histopathology in, 363–364
  immunohistochemical labelling of, 364
  low-grade, 363–364
  medium-grade, 363–364
  profile of, 363
Atheroma. *see* False nostril epidermal inclusion cyst
Aural plaques, 248
Autoimmunity, 72
Autologous grafting, 191–192, 193f
Autophagy, 32–33
  as lysosome-mediated destruction, 34f
AW4-LUDES, 139

B

Bacillus Calmette-Guérin (BCG), 188
  immunostimulation/immunomodulation
    in dermal melanoma, 574
    in equine sarcoids, 559–560
  immunotherapy in practice, 189–191, 189b–190b, 190f
    advantages of, 191
    disadvantages of, 191
    indications of, 189
    method, 189–190, 190f
    responses observed, 190–191
    treatment of anaphylaxis, 191, 191b, 192f
Basal cell carcinoma, 17, 34f, 563–564, 563b, 564f
Basal cell tumour
  biological behaviour of, 252
  cellular origin of, 252
  differential diagnoses of, 252b
  gross pathology of, 252, 253f
  histopathology of, 252
  immunohistochemical labelling of, 252
  oncogenesis of, 252
  profile of, 252
BCG. *see* Bacillus Calmette-Guérin (BCG)
ben Maimon, Moses, 3
Bence-Jones proteins, 356
Benign neglect
  in dermal melanoma, 574
  in incidental tumour-like dental masses, 436
  in sarcoids, 441, 555–556, 556f
Benign proliferative fibro-osseous lesions, 445
Beta (β) electrons, 166
Bilateral rostral mandibulectomy, for ameloblastoma, 433
Biliary adenofibroma
  biological behaviour of, 271
  cellular origin of, 271
  differential diagnoses of, 271, 271b
  gross pathology of, 271
  histopathology of, 271
  immunohistochemical labelling of, 271
  profile of, 271
Biliary cholangioma. *see* Biliary adenofibroma
Biliary cystadenoma. *see* Biliary adenofibroma
Biochemical syndrome, 72t
Biochemistry, 90–93, 94t
  as diagnostic aid, 425
Biodegradable beads, 141
  for sarcoid, 442
Biopsy, 87–90
  in alimentary lymphoma, 530
  in angiosarcoma, 520
  in basal cell carcinoma, 564
  in bladder carcinoma, 661
  bone marrow, 100, 100f
  in cutaneous lymphoma, 534
  as diagnostic aid, 426
  diagnostic value of, improving, 108
  in epulis, 453
  excisional/ablative, 89
  fine-needle aspiration, 89, 90f
  in guttural pouch neoplasia, 496
  in haemangiosarcoma, 518
  handling, and processing, 108
  in hepatosplenic/splenic lymphoma, 536
  hollow-needle, 89–90
  information supplied to pathologist in, 109–110, 109f, 111f
  information the clinician expected in, 110–112
  in interstitial cell tumour, 638
  in leiomyoma, 640
  in lymphangioma/lymphangiosarcoma, 522
  in lymphoma, 505
  in malignant histiocytoma, 567
  in mediastinal/thoracic/thymic lymphoma, 533
  in melanoma, 443
  in metastatic thoracic tumours, 507
  methods, 88–90, 88f
  in nasal polyp, 489
  in neurofibroma, 563
  oncology and, 108–112
  in oral fibroma/fibrosarcoma, 445
  in oral papilloma, 452
  in osteosarcoma, 667
  portional, 89
  in pulmonary granular cell tumour, 500
  punch, 88
  rectal, 89
  in rhabdomyoma, 676
  in sarcoids, 210–211, 554
  selecting site and maximizing the return, 108–109
  in seminoma, 637
  in squamous cell carcinoma, 438–439
  technique, correct and appropriate selection of, 87
  wedge, 88–89
Bladder carcinoma, 658–661, 658b
  case reports of, 659t
  case review on, 661
  classification of, 658, 658b
  clinical features of, 658–660, 660b, 660f
  description of, 658
  diagnostic confirmation of, 660–661, 661b
  differential diagnoses of, 660
  infiltrating, 658
  management of, 661
  prognosis of, 661
Bleeding, reduced, as laser surgical excision advantage, 124
Bleomycin
  in equine chemotherapy, 145
  for equine sarcoids, 559
Body cavities, fluid aspirated from, differential features of, 99t
Body surface area (BSA), dosing based on, 133–134
Bone
  giant cell tumour of, 671
  multilobular tumour of. *see* Multilobular tumour, of bone
  neoplastic masses in, 664–672
  non-aneurysmal cystic lesions of, 455–457, 674
  non-neoplastic masses in, 672–674
Bone cysts
  acquired, of tarsus, 322
  aneurysmal, 322
  juxtacortical, 322
  mandibular aneurysmal. *see* Mandibular aneurysmal bone cyst
  subchondral, 322
  unicameral, 322
Bone lesions, multiple myeloma and, 356
Bone marrow
  biopsy, 100, 100f
    indications for, 100t
  leukaemia and, 353–354
  obliteration, 76
  suppression, 76
Bone masses, non-neoplastic, 321–323
Boveri, Theodor, 4
Bovine papillomavirus (BPV), 45, 203–205, 205b
  cattle *versus* horses, 207
  DNA, dogma-breaking detection of, in epidermis of sarcoids, 201
  experimentally infected with, 206–207
  exposure to, 421–422, 422f
  as latent infections, 208–209
  in sarcoids, 204
  transmission to horses, 208
Bovine papillomavirus-1, 209
BPV. *see* Bovine papillomavirus (BPV)
Brachytherapy, 165, 179–182
  fractionation with, 171
  gamma radiation, using iridium-192, for neurofibroma, 563
  hazards/precautions of, 181
  low-dose iridium, 170f
  manual implantation in, 181
  outcomes of, involving isotopes, 184t
  radionuclides used in, physical characteristics of, 180t
  remote afterloading, 181–182, 182f–183f
  sources of, 182–184
  surface, 184–185
BRCA1 gene, 26t
BRCA2 gene, 26t
BSA. *see* Body surface area (BSA)
Bullous stomatitis, paraneoplastic, 80
  haemangiosarcoma with, 335

C

'Cachexin', 74
Caesium-137, in brachytherapy, 180t
Calcinosis, tumoral, 323
Calcitonin, 95t
Call-Exner bodies, in granulosa cell tumours, 396
Calreticulin, 36f
  role of, in tumour development, 36–37
Calretinin, 283
Cancer, 3
  age of, 46–47
  clinical effects of, 62–69
  colorectal, 40f
  development of, and sex of animal, 10
  diagnosis of, 7–8
  as disease of abnormal cell differentiation, 5
  immunotherapy for, 186–192
  incidence of, 7
  in medical and veterinary professions, 6
  molecular and genetic (cellular) basis of, 23–39
    carcinogenesis, 39–47
    cell interactions, 37–39
    cellular senescence, 37
    chemical carcinogenesis, 42–44
    DNA repair genes, 28–29
    guardian of genome, 26–28
    immune evasion, 34–36
    microbiological/infectious agents of carcinogenesis, 45–46
    radiation carcinogenesis, 44–45

Cancer (*Continued*)
role of calreticulin in tumour development, 36–37
tumour development, 46–47
multistep origin of, 41f
results from mutation, 5
stress, 47
types of, effect of radiation on, 172–174
vaccination against, 188
viral aetiology of, 5
Cancer case, approach to, 415–428
client counselling in, 418
client management in
expectations/complications, 428
risks and benefits of, 428
clinical examination in, 424–426, 425f
of body systems, 424, 424f
diagnostic aids in, 425–426
problem list in, 425, 425f
regional, 424f
vital signs in, 424
clinical investigation in, 418–419, 419f
clinical reporting, 418
clinician, objectives of, 415, 416f
epidemiology of tumours, 416–418
evidence-based medicine in, 416–418, 417f
follow-up in, 418
future of, in equine practice, 428
history/anamnesis in, 419–424, 423f
age in, 420
breed in, 419
colour of patient in, 420–421, 420f
contact horses and, 421–422, 422f
duration of ownership in, 421
medications and, 422–423
peer groups in, 421–422
previous disease, accident, and injury and, 422, 423f
routine procedures in, 422
sex in, 419–420, 420f
short-term, 423–424, 424f
use/management in, 421
prognosis, factors influencing, 426–428
duration, 427
extent, 426, 426f
facility, 427
financial constraints in, 427
horse, relative value of, cost of treatment and, 427
location, 427
owner, compliance of, 427
patient compliance, 427
treatment, availability of, 427
tumour, type of, 426
publication, 418
screening, 418
trials design, 418
Cancer stem cells (CSCs), 406
Cancerous growth, appearance of, 13f
Cancerous tumours, 13–14
Capsule, benign tumours, 14–15
Carbohydrate absorption tests, for alimentary lymphoma, 530
Carbon dioxide (CO_2)
for cryotherapy/cryonecrosis/cryoablation, 127
machines, use of, constraints to, 125
Carbon dioxide laser photoablation, for squamous cell carcinoma of eye, 617
Carboplatin, in equine chemotherapy, 145, 148b
Carcinogenesis, 10, 39–47
chemical, 42–44
multistep nature of, 43f
Knudson hypothesis, 39–42
microbiological/infectious agents of, 45–46
multistep proposal, 40–42
radiation, 44–45
Carcinogenicity, of radiation, 44
Carcinogens
chemical, 43t
genotoxic, 41
non-genotoxic, 41
putative, 437
'Carcinoids', 390
'Carcinoma associated fibroblasts', 38, 39f
Carcinoma in situ, 400
Carcinoma(s)
carcinoma-associated fibroblasts within, 39f
of eye, 44f
immunohistochemical profile of, 115
immunohistochemical staining of, 115t
of nictitans, 60f
in situ intraepithelial, 21f
Cardiac neoplasia, 522–523
Cardiovascular system, tumours of, 512–543, 512b
cardiac neoplasia, 522–523
leukaemia, 539–541
neoplasia of the haematopoietic system, 523–539
vascular neoplasia, 512–522
Carmustine, in equine chemotherapy, 146
Cartilaginous exostoses. *see* Osteochondroma
'Caspases', 31
Cavernous haemangioma. *see* Haemangioma, of cardiovascular system
CBN. *see* Cellular blue naevus (CBN)
CCBN. *see* Combined cellular blue naevus (CCBN)
C-cell adenoma, 591–592
C-cell carcinoma, 591–592
C-cell medullary microfollicular carcinoma, mixed, 592
CD31, 334, 337
CD117 , for congenital mast cell tumours, 359
Cell contamination, reduced, as laser surgical excision advantage, 124
Cell culture, in vitro, assessment of, 107
Cell destruction, 29–34
apoptosis, 29–31, 32f
autophagy, 32–33
necrosis, 33–34
Cell-cycle, 23, 23f
Cell(s)
death, 31f
division, unregulated, 29
growth, normal, 31
interactions, 37–39
for mitosis, 23f
morphological characteristics of, 30f
normal, neoplastic cells and, 38f
replication, fundamental method of, 23f
selective evolution of cloned, 34
suicide, 29
survival, after exposure to radiation therapy, 166, 167f
Cellular blue naevus (CBN), 242, 243f
Cellular homeostasis, 36
Cellular senescence, 37
Cementifying fibroma
biological behaviour of, 328
cellular origin of, 328
histopathology of, 328
profile of, 328
Cementoblasts, cementoma from, 433–434
Cementoma, 431t, 433–435, 434b
biological behaviour of, 328
cellular origin of, 327
clinical features of, 434, 434f
description of, 433–434
differential diagnoses of, 328, 328b, 328f
gross pathology of, 328
histopathology of, 328
management and prognosis of, 435
oncogenesis of, 328
profile of, 327
Central nervous system (CNS)
neoplasms of
haematopoietic, 368
meningeal, 367–368
in neuroepithelial tissue, 363–366
neuronal and mixed neuronal tumours, 366–367
pineal, 368
secondary tumours affecting, 609–610
cErb-2 oncogene, overexpression of, 117
Cerebrospinal fluid, sampling, 99, 99f
Cervix, fibroleiomyoma of, 305
'Chaotic' destruction, 29
Chaperone-mediated autophagy, 34f
Chemical carcinogenesis, 42–44
multistep nature of, 43f
Chemical carcinogens, 43t
Chemical cautery, 160, 161f
Chemodectoma(s), 389–390, 598
biological behaviour of, 390
cellular origin of, 389
gross pathology of, 390
histopathology of, 390
immunohistochemical labelling of, 390
profile of, 389
Chemoreceptor paraganglia, 387
Chemotherapy, 129–144
adjuvant, 141
intraoperative or postoperative, 133
advantages and disadvantages of, 136f
alternative classifications of, 137
associated/adjunctive, 178–185
cellular mechanisms of drug resistance, 142–144, 143f
combined modality, 131–134, 132f
control of exposure of, 163–164
corticosteroids in, 138
cytological targets for, 135
dose calculations for, 133–134, 134f
drug sanctuary sites (protected by blood-tissue barriers), 142
functions of, 136f
fundamental premise of, 129f
for haemangiosarcoma, 519
inadequate drug dosage, 142
intralesional/intratumoral, 140–141
intravenous (systemic), 137–138
local, 139–140, 139f
for melanoma, 444
mode of action of, 135–137
palliative, 133
pharmacological and physiological mechanisms of, 142
poor/impaired drug diffusion into cancer tissues, 142
of progressive ethmoidal haematoma, 492–493, 493f
protocols of, 133b
restrictive chemotherapy support, 134–137, 135f
safety aspects for use of, 163–165
safety issues in, 163–165
for sarcoids, 442, 558–559
selection of, 131
sites of action of, 132f
slow-release biodegradable beads of, 151–152, 151f
for squamous cell carcinoma, 440, 579
of eye, 617
strategies for use of, 130
suboptimal administration schedules of, 142
systemic/local, causes of failure of, 144f
topical (surface), 139–140, 140b
toxicity in, fundamental rules for, 133
use of, 129
Children, pleuropulmonary blastomas in, 409
Chlorambucil, 137b, 146
for multicentric lymphoma, 527t
Cholangiocellular carcinoma, 469–470, 469b
biological behaviour of, 270
cellular origin of, 270
clinical features of, 469–470
description of, 469
diagnostic confirmation of, 470
differential diagnoses of, 271b
gross pathology of, 270–271
histopathology of, 271
immunohistochemical labelling of, 271
management and prognosis of, 470
oncogenesis of, 270
profile of, 270
Cholesterol granuloma(s), 370, 609–610, 609f
Chondroma, 672, 672b
biological behaviour of, 320
cellular origin of, 320
differential diagnoses of, 320b
gross pathology of, 320
histopathology of, 320
laryngeal, 498f
profile of, 320
Chondroma rodens. *see* Multilobular tumour, of bone
Chondrosarcoma, 672, 672b
biological behaviour of, 320
cellular origin of, 320

Chondrosarcoma (*Continued*)
differential diagnoses of, 321b
gross pathology of, 320
histopathology of, 320–321
profile of, 320
CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), 137
chemotherapy protocol, 138b
Choroid plexus tumour, 366
biological behaviour of, 366
cellular origin of, 366
differential diagnoses, 366b
gross pathology of, 366
histopathology in, 366
immunohistochemical labelling, 366
profile of, 366
Chromaffin cells, 387
Chromaffin reaction, phaeochromocytoma and, 387
Chromosome 17, short arm of, 26
Chronic myeloid leukaemias, 353
monocytic, 353
neutrophilic or eosinophilic, 353
polycythaemia vera, 353
Ciliary body cysts, squamous cell carcinoma and, 228
Cimetidine, 131
for dermal melanoma, 574
in equine chemotherapy, 146
Circulatory syndrome, 72t
Cisplatin, 133, 141
effects of, 147f
in equine chemotherapy, 146–151
injection method, 149f
intralesional
for dermal melanoma, 574
for neurofibroma, 563
for sarcoids, 442, 559
intralesional emulsion of, 147–151, 150f
practical applications of, 147–151
repeated injection of aqueous solution, 147
resistance mechanisms of, 147t
stable emulsion of, protocol for preparation of, 148b
theoretical calculated total dose of, 159t
Client counselling, 418
Client management
expectations/complications, 428
risks and benefits of, 428
Clinical oncology facility, aims of, 8
Clinical tumour volume (CTV), 177
Clinicians
information expected by, 110–112
responsibility of, 416f
Clonal evolution model, 53–54
Clonal expansion, tumour formed by, 25
Cloned cells, selective evolution of, 34
Clonorchis sinensis, 46
Closure of site, in smart surgery, 122–123
Clotting abnormalities difficulties, 92
CMN. *see* Common melanocytic naevus (CMN)
CNS. *see* Central nervous system (CNS)
CO_2. *see* Carbon dioxide (CO_2)
Coagulation dysfunction, 76
Cobalt-60, for brachytherapy, 180t
Coeliotomy, exploratory, of intestinal neoplasia, 461
Colon adenocarcinoma, 266
Colorectal cancers, 40f
'Combination chemotherapy', 131, 137, 141–142
Combined cellular blue naevus (CCBN), 243, 243f
Common melanocytic naevus (CMN), intradermal, 242, 242f
Comorbidity, 422–423
Complete transabdominal ultrasonography, of intestinal neoplasia, 461
Complex odontoma, 431t, 435–436, 435b
biological behaviour of, 327
cellular origin of, 327
clinical features of, 435–436
description of, 435
diagnostic confirmation of, 436
differential diagnoses of, 327b, 435–436
gross pathology of, 327
histopathology of, 327
Complex odontoma (*Continued*)
management and prognosis of, 436
occurrence of, 435
profile of, 327
Compound odontoma, 431t, 435–436, 435b
biological behaviour of, 327
cellular origin of, 327
clinical features of, 435–436, 435f
description of, 435
diagnostic confirmation of, 436
differential diagnoses of, 435–436
gross pathology of, 327
histopathology of, 327
management and prognosis of, 436
occurrence of, 435
profile of, 327
Computed tomography (CT), 102f
in cholesterol granuloma, 610
as diagnostic aid, 426
full spiral, 103f
in nasopharyngeal/laryngeal neoplasia, 498
in orbital paraganglioma, 597
standing, 102f
x-ray, 101–103
Concurrent disease, in oncogenesis, 47
Congenital equine cutaneous mastocytosis, 565
Congenital papillomas, 247
Conjunctiva
angiosarcoma of, 520f
tumours of, 613–626
Conjunctival carcinoma, 615f
Conjunctival pseudotumours, 616b
squamous cell carcinoma and, 228
Conjunctivectomy, 617b
Continuous hyperfractionated accelerated radiation therapy (CHART), 170
Contrast radiography, of gastric squamous cell carcinoma, 459
Cornea, angiosarcoma of, 520f
Corneal carcinoma, 616f
'Corneal stromal-invasive SCC' (CDI-SCC), 227
Cortical folds, adrenal cortical adenomas and, 386
Corticosteroids
in equine chemotherapy, 138
use of, 138
'Crab-like' appearance, of tumours, 3, 4f
Creatine kinase (CK), 95t
Cryoablation, 126–127
methods of application of, 126–127
precautions and hazards of, 127
Cryonecrosis, 126–127
methods of application of, 126–127
precautions and hazards of, 127
'Cryoprobes', 126
Cryosurgery, 126–127
for dermal melanoma, 574
for haemangioma/vascular hamartoma/cavernous haemangioma, 513
for progressive ethmoidal haematoma, 493
for sarcoids, 441, 557
for squamous cell carcinoma, 579
Cryotherapy, 126–127
chemotherapy and, combination of, 131
methods of application of, 126–127
precautions and hazards of, 127
for squamous cell carcinoma of eye, 617
Cryptorchid testes, seminoma and, 399
Cryptorchid testicles, 420
CSCs. *see* Cancer stem cells (CSCs)
CT. *see* Computed tomography (CT)
Curie, Marie, 44
Cushing's disease, 63, 585–586
Cutaneous lymphoma, of cardiovascular system, 533–535
clinical features of, 533–534, 533f
description of, 533
diagnostic confirmation of, 534
differential diagnoses of, 534
management of, 534–535
prognosis of, 535
Cutaneous lymphosarcoma
biological behaviour of, 349
gross pathology of, 349–350
histopathology of, 350
profile of, 349
Cutaneous mastocytosis, 564–566
Cutaneous neoplasia, 544
Cutaneous nodular mastocytosis/mast cell tumour
biological behaviour of, 357
profile of, 357
'Cyclin dependent kinases' (CDKs), 24–25
inhibitors, 24f
Cyclins, 24
role of, 24f
Cyclooxygenase (COX)-2, expression, 222, 222f
Cyclophosphamide, 137–138
in equine chemotherapy, 152, 152t
for multicentric lymphoma, 527t
Cyst epithelium, 259
Cystadenocarcinoma
ovarian. *see* Ovarian cystadenocarcinoma
papillary, 276
Cystadenoma(s), 15–16
ovarian. *see* Ovarian cystadenoma
renal, 272–273
renal mucous gland, 273
Cystoscopy, in bladder carcinoma, 660, 660f
Cysts, 431t
see also Bone cysts
dermoid, 230
epidermal inclusion (atheroma), 487–488
epidermoid, 370
false nostril epidermal inclusion, 260
fimbrial, ovarian cystadenoma and, 275
follicular, 230
germinal inclusion, ovarian cystadenoma and, 275
intraosseous epidermoid, 321, 322f
odontogenic, 455
paranasal sinus, 494–495
paraovarian, ovarian cystadenoma and, 275
radicular, 436, 455
uveal, anterior, squamous cell carcinoma and, 228
Cytology, of pleural fluid, in thymic tumours, 502–503
Cytopaenia, lymphosarcoma and, 342
Cytosine arabinoside, 137b
for multicentric lymphoma, 527t
Cytotoxic drugs, 163
Cytotoxic therapy, 129–144

D

Dehiscence, as laser surgical excision disadvantage, 125
Densitometer, of plasma from multiple myeloma, 93f
'Denticles', 435
Dermal melanoma(s), 239, 243, 244f, 569, 569f
clinical features of, 570, 571f–572f
management of, 574
Dermal melanomatosis, 569, 569f
Dermatological paraneoplastic signs, 79–80
Dermatological syndrome, 72t
Dermoid cysts, 230
Desmoid 'tumours,' intramuscular. *see* Fibromatosis
Desmoids, 294
Dexamethasone, 138
Diagnosis, principles of, 85–107
abdominocentesis/thoracocentesis, 97–98, 98f
clinical investigations and specialized tests/imaging methods, 86–87, 86f
cytological assessment, 99–101
haematology and biochemistry, 90–93, 94t
laparoscopy/pleuroscopy/endoscopy, 104
radiography, 101–103, 101f
scintigraphy, 104
tissue sampling, 87–93
total protein assay, 98–99
tumour markers, 104–107
ultrasonography, 93–97
Diagnostic aids, 425–426
Diagnostic tests, 86
from practice and client-relationship perspective, 86
Diathermy
for oral fibroma/fibrosarcoma, 445
surgical, 125–126
methods of, 126
precautions and hazards of, 126
use of, 125

Diffuse large B-cell lymphosarcoma (non-cleaved or cleaved), 345
Diffuse large-cell lymphosarcoma of B-cell origin, 343–345
Diffuse small-cell lymphosarcoma, 343
Diffuse verrucose sarcoid, topical treatment for, 155f
Dimethyl ether with propane, for cryotherapy/cryonecrosis/cryoablation, 127
Direct haemorrhage, 75–76
Direct immunosuppressive effects, 35
Direct method, of immunohistochemistry, 114
Discharge, chronic low-grade unilateral, non-odorous sero-haemorrhagic, progressive ethmoidal haematoma and, 490
Disorders of mouth, jaws and teeth
  epulis, 453–454
  mandibular aneurysmal bone cyst, 454–455
  oral papilloma, 452
  resembling neoplasms, 452–455
Disseminated haemangiosarcoma, 334, 335f, 515
  laboratory abnormalities in, 335
Diverticulum, arachnoid, 370
DNA, bovine papillomavirus, dogma-breaking detection of, in epidermis of sarcoids, 201
DNA alkylating drug, 47
DNA helicases, 152
'DNA provirus' hypothesis, of cancer, 4
DNA repair genes, 26f–27f, 28–29
DNA-dependent protein kinase (DNA-PKcs) allele, 206
Dopamine, POMC and, 377
Dopaminergic neurodegeneration hypothesis, 377
Doxorubicin
  in equine chemotherapy, 152–153
    guidelines of administering, 153, 153f–154f
    outcome of, 153
    practical applications of, 153
    precautions of, 153
  for multicentric lymphoma, 527t
Drug resistance
  acquired and inherent/intrinsic, 142
  cellular mechanisms of, 142–144, 143f
Drugs
  see also Chemotherapy
  active metabolites of, 143
  for chemotherapy, 135–137
    in equine, 144–158
    impaired uptake of, 143
    molecular target alteration/mutation, 143
    resistance and failure of expected efficacy, 141–144
    risk classification of, 164–165
    selection of, 131
    use of, 144–158
  efflux transporters, 142–143
  enhanced DNA repair mechanisms, 143
  metabolism of, 143
Dysgerminoma, 400–401, 645–646, 645b, 646f
  biological behaviour of, 400–401
  cellular origin of, 400
  gross pathology of, 401, 401f
  histopathology of, 401
  immunohistochemical labelling of, 401
  profile of, 400
Dyskeratotic cells, 223
Dysphagia, progressive ethmoidal haematoma and, 490
'Dysplasia', 15

E

E2 protein, 205
E5 protein, 204
  localization of, in cytoplasm, 216
E6 protein, 204–205
E7 protein, 205
Ecchondromas, 320
Echocardiography, of metastatic melanoma, 523
Electrocautery, 125
  for equine sarcoids, 557–558
Electrochemotherapy (ECT), 158–160
  for equine sarcoids, 559
  method of, 159, 159f–160f
  precautions and hazards of, 159–160
Electromagnetic ionizing radiations, 44
Electron microscopy
  in adrenal cortical adenomas and carcinoma, 385
  in embryonal carcinoma, 403
  in ependymoma, 365
  in fibrosarcomas, 288
  in ganglioneuroma and peripheral ganglioneuroblastoma, 369
  in gastrointestinal stromal tumours (GISTs), 370
  in granular cell tumours, 303
  in lymphangioma, 338
  in lymphangiosarcoma, 339
  in medulloepithelioma, 374
  in melanocytic neoplasms, 245
  in mesothelioma, 283
  in myofibroblastic tumours, 289
  in myxomatous neoplasms of jaw, 315
  in nerve sheath tumours, benign and malignant peripheral, 302
  in olfactory neuroblastoma, 367
  in phaeochromocytomas, 388
  in pituitary adenoma, 380
  in rhabdomyosarcoma, 310
  in sarcoids, 217
  in thyroid C-cell adenoma and carcinoma, 383
  in viral squamous papilloma, 249
Electrophoresis, of plasma from multiple myeloma, 93f
'Electrosurgery', 125–126
  methods of, 126
  precautions and hazards of, 126
  use of, 125
Elevated total white cell counts, 91–92
Embryonal carcinoma, 403
  biological behaviour of, 403
  cellular origin of, 403
  differential diagnoses for, 403b
  electron microscopy in, 403
  gross pathology of, 403
  histopathology of, 403
  immunohistochemical labelling of, 403
  profile of, 403
EMPF. *see* Equine multinodular pulmonary fibrosis (EMPF)
Emulsions
  of chemotherapeutic drug, 141
  intralesional, of cisplatin, 147–151, 150f
Encephalopathy, hepatic, 266
Enchondromas, 320
Endocrine neoplasms, 376–387
  adrenal cortical adenomas, 386 and carcinoma, 384–385
  cellular origin of, 376
  metastatic, 385–386
  pancreatic islet cell neoplasm, 386
  parathyroid adenoma, and carcinoma, 384
  pituitary adenoma, 376–380
  thyroid adenoma and carcinoma, 380–382
  thyroid C-cell adenoma and carcinoma, 382–383
  thyroid ultimobranchial remnant neoplasms, 383–384
Endocrine syndromes, 71
Endocrine system, tumours of, 585–600, 586t
  in adrenal glands, 592–593
  adrenocortical neoplasia, 593
  in endocrine pancreas, 593
  multiple endocrine neoplasia, 593
  in parathyroid glands, 592
  in pituitary gland, 585–586, 585b
  in thyroid gland, 586–591, 588b
Endocrine tumour, benign functional, 13–14
Endocrinologic assays, in interstitial cell tumour, 638
Endocrinological syndrome, 72t
Endocrinological variations, 93
Endocrinology tests, in neoplastic disease, 95t
Endometrial adenocarcinoma
  biological behaviour of, 276
  cellular origin of, 276
  differential diagnoses of, 277, 277b
  gross pathology of, 276
  histopathology of, 277
  profile of, 276
Endometrial polyps, endometrial adenocarcinoma and, 277
Endoscopic biopsy, of gastrointestinal neoplasia, 459
Endoscopy, 104, 106f
  as diagnostic aid, 426
  in guttural pouch neoplasia, 496
  in haemangiosarcoma, 517
  in nasal polyp, 489
  in rhabdomyoma, 676
Enzymology, as diagnostic aid, 425
Ependymoma, 365–366, 602–603, 602b
  biological behaviour of, 365
  cellular origin of, 365
  differential diagnoses for, 366b
  electron microscopy in, 365
  gross pathology of, 365
  histopathology in, 365
  immunohistochemical labelling in, 365
  profile of, 365
Epidermal hyperplasia, in sarcoids, 213, 215f
Epidermal inclusion cyst (atheroma), 487–488, 487b
  clinical features of, 487, 488f
  description of, 487
  diagnostic confirmation of, 487
  differential diagnoses of, 487
  management of, 487–488
  prognosis of, 488
Epidermis, papillated hyperplasia of, 249
Epidermoid cysts, 370
Epiphora, progressive ethmoidal haematoma and, 490
Epithelial basement membrane, invasion of, 51f
Epithelial neoplasms, 247–280
Epithelioid haemangiosarcoma, 519
Epithelioid mesothelioma cells, 282
Epitheliotropic lymphosarcoma, 349
  patch stage of, 350, 350f
  plaque stage of, 350
  tumour stage of, 350
Epitrichial (apocrine) sweat gland, adenoma and carcinoma of
  biological behaviour of, 254
  cellular origin of, 254
  gross pathology of, 254
  histopathology of, 254
  immunohistochemical labelling of, 254
Epulis, 453–454, 453b, 453f
Equine leukocyte antigen (ELA) haplotypes, 205–206
Equine multinodular pulmonary fibrosis (EMPF), associated with herpesvirus-5 (EHV-5) infection, 264–265
Equine oncological practice, challenges and problems of, 7–10
Equipment, modern ultrasonographic, 93
Equus caballus papillomavirus 2 (EcPV2), 221
  in papillomas, 201
Erythrocytosis, 76–77
  absolute secondary, hepatocellular carcinoma/adenoma and, 268–269
  differential diagnoses for elevation of, 77b
  lymphosarcoma and, 342
  secondary inappropriate, 407
Erythroleukaemic (M6) leukaemia, 541
Erythropoietin, 76
European College of Veterinary Internal Medicine – Companion Animals (ECVIM-CA), in chemotherapeutic drug exposure, 163–164
Euthanasia, 427
Evidence-based medicine, 416–418, 417f
Excision, surgical, 122
Excisional biopsy, 89
  for sarcoid diagnosis, 554
Exostoses, hereditary multiple, 669–670
Exploratory coeliotomy, of intestinal neoplasia, 461
Exploratory laparoscopy, of intestinal neoplasia, 461
Extensive nasal adenocarcinoma, 63f
External beam radiotherapy, 178, 180t
External beam therapy, 166
External genitalia, squamous cell carcinoma of, 228–229
Extra-adrenal paragangliomas, 389–390
Extracellular matrix, 47
Eye
  carcinoma of, 44f
  squamous cell carcinoma of, 225–228, 226f–227f

Eye tumours, 613–628, 614t
  in conjunctiva, globe and orbit, 613–626
    astrocytoma, and proliferative optic neuropathy, 625–626, 625b, 626f
    haemangiosarcoma, 622–623, 622b, 623f
    lymphoma, 620–622, 621b, 621f
    mast cell tumour, 623, 623b, 624f
    medulloepithelioma/retinoblastoma, 623–625, 624b, 625f
    melanoma, 618–620, 618b
    squamous cell carcinoma, 614–618, 614b, 615f–616f
  corneal, conjunctival and ocular, 626–627
Eyelids, neurofibromas of, 299

F

Facial swelling
  paranasal sinus cysts and, 494
  progressive ethmoidal haematoma and, 490
False nostril epidermal inclusion cyst
  biological behaviour of, 260
  gross pathology of, 260
  histopathology of, 260
Fever, in gastrointestinal neoplasia, 458
Fibroblastic cells, forming sarcoids, 213
Fibroblastic sarcoid(s), 212, 550–552
  clinical and pathological features of, 550–552, 550t
  differential diagnoses of, 552
  pedunculated, 550, 551f
  sessile, 550, 551f–552f
  University of Liverpool protocol for, 190b
Fibroblasts, carcinoma associated, 38, 39f
Fibroepithelial polyps, 274
Fibroleiomyoma
  biological behaviour of, 305–306
  cellular origin of, 305
  differential diagnoses of, 306b
  of female genital tract, 640–641, 640b, 640f
  gross pathology of, 306
  histopathology of, 306, 306f
  immunohistochemical labelling of, 306
  oncogenesis of, 305
  profile of, 305
Fibroma, 561, 561b
  bilateral non-ossifying, 285
  biological behaviour of, 285
  cellular origin of, 285
  cementifying. *see* Cementifying fibroma
  differential diagnoses of, 286b
  gross pathology of, 285–286
  histopathology of, 286
  juvenile mandibular ossifying. *see* Juvenile mandibular ossifying fibroma
  ossifying. *see* Ossifying fibroma
  profile of, 285
  sarcoids *versus*, 286
Fibromatosis
  differential diagnoses of, 294
  gross pathology of, 294
  histopathology of, 294
  profile of, 294
Fibromatous epulis, of periodontal ligament origin
  biological behaviour of, 329
  cellular origin of, 329
  differential diagnoses of, 329b
  gross pathology of, 329
  histopathology of, 329, 329f
  profile of, 329
Fibromatous polyps, 274
Fibro-osseous tumours, 321
Fibropapilloma, 249–251
Fibrosarcoma(s), 17, 561, 561b, 562f
  biological behaviour of, 287
  cellular origin of, 287
  differential diagnoses of, 288b
  electron microscopy of, 288
  gross pathology of, 287–288
  histopathology of, 288
  immunohistochemical labelling of, 288
  in musculoskeletal system, 287
  nasomaxillary, 288, 487
  profile of, 287
  in sinonasal region, 487
Fibrotic myopathy, fibromatosis and, 294
Fibrous dysplasia, 455, 456f, 674, 674f
  classification of, 321
  histopathology of, 321, 321f
  profile of, 321
Fibrous hamartoma
  histopathology of, 294
  profile of, 293
Fibrous sheath, benign tumours, 14–15
Fibrous tumours, 285–289
  fibroma, 285–286
  fibrosarcomas, 287–288
  myxoma (myxofibroma), 286
  myxosarcoma, 288–289
Fimbrial cysts, ovarian cystadenoma and, 275
Fine-needle aspiration, 89, 90f
Flexner-Wintersteiner rosettes, in medulloepitheliomas, 373
Fluorescein, 114
Fluorescent immunohistochemistry, 115, 115f
5-Fluorouracil, 153–154, 154b, 154f
  cream, 139
    for squamous cell carcinoma, 440
  drops, 131
  in equine sarcoids, 558
  intratumoral injection of, 153–154
  in neurofibroma, 563
  practical use of, 153–154
  in squamous cell carcinoma, 579
  topical applications of, 154
Focal cutaneous angiosarcoma, 520f
Focal haemangiosarcoma, 517f
Focal intestinal lymphoma, 464f
Follicle stimulating hormone, inhibin and, 394
Follicular cysts, 230
Follicular oocytes, dysgerminoma from, 400
'Follow-up,' concept of, 112, 113f
Formalin, 90
  -based gels, in equine sarcoids, 559
Fractionation, in radiotherapy, 170–171
Fractures, pathological, osteosarcoma and, 318
Fragile Histidine Triad (FHIT), study of tumour suppressor gene in sarcoids, 205
'Functional tumour', 66

G

Galen, 3
Gamma (γ) ray photons, 166
Gamma scintigraphy, 104, 105f
  using 99mTc-MDP, of plasma cell myeloma, 538
Gangliocytoma, 366–367
  biological behaviour of, 366
  gross pathology of, 366
  histopathology of, 366–367
  immunohistochemical labelling in, 367
  profile of, 366
Ganglioneuroma, peripheral ganglioneuroblastoma and, 369
  biological behaviour of, 369
  cellular origin of, 369
  electron microscopy in, 369
  gross pathology of, 369
  histopathology of, 369
  immunohistochemical labelling in, 369
  profile of, 369
Gastric adenocarcinoma, 460–461, 460b
  see also Intestinal adenocarcinoma
Gastric carcinoma, *Habronema/Draschia* infestations and, 422
Gastric leiomyoma, 460
Gastric leiomyosarcoma, 460
Gastric squamous cell carcinoma, 459–460, 459b, 460f
Gastrointestinal neoplasia, 457–461
  case reports/series of, 458t
  diagnostic confirmation of, 458–459, 458b
  gastric adenocarcinoma, 460–461
  gastric squamous cell carcinoma, 459–460
  leiomyoma/sarcoma, 460
  management and prognosis of, 459
Gastrointestinal stromal tumours (GISTs), 117, 369–370
  biological behaviour of, 369–370
  cellular origin of, 369
  electron microscopy in, 370
  gross pathology of, 370
Gastrointestinal stromal tumours (GISTs) (*Continued*)
  histopathology in, 370
  immunohistochemical labelling in, 370
  profile of, 369
Gastroscopy
  of gastric squamous cell carcinoma, 459
  of gastrointestinal neoplasia, 459
GCTs. *see* Granular cell tumours (GCTs)
GD2 antigen, 186
Gene therapy, 192–196, 194f
Genetics, role of, in cancer, 5
Genital papilloma, 248
Genital tract, of mares, neoplastic disorders of, 638–647
  leiomyoma/fibroleiomyoma, 640–641, 640b, 640f
  vulvar and clitoral squamous cell carcinoma, 639–640, 639b, 639f
Genome, guardian of, 26–28
Genotoxic carcinogens, 41
Germ cell tumour, ovarian, 644–645, 644b
Germinal inclusion cysts, ovarian cystadenoma and, 275
Germinal tumours, of testicle, 635
Giant cell tumour, 52f
  of bone, 671
    biological behaviour of, 319
    cellular origin of, 319
    differential diagnoses of, 319b
    gross pathology of, 319
    histopathology of, 319
    profile of, 319
  extra-skeletal, 566–567, 567f
  of soft parts, 290–292
    biological behaviour of, 291
    cellular origin of, 290
    differential diagnoses of, 292b
    gross pathology of, 291
    histopathology of, 291–292, 291f
    immunohistochemical labelling of, 292
    profile of, 290
    recurrence of, 291
Gingivae, myxomatous neoplasms of, 447–448, 447b
Gingival hyperplasia, benign, 453f
GISTs. *see* Gastrointestinal stromal tumours (GISTs)
GLDH. *see* Glutamate dehydrogenase (GLDH)
Glioblastoma, 364f
Globe, tumours of, 613–626
Glutamate dehydrogenase (GLDH), 95t
Glutaraldehyde, 90
Gold-198, 180t, 183–184, 184f, 184t
Gompertzian model, 60, 60f
Gonadal neoplasms, 393–405
  germ cell tumours, 399–403
    dysgerminoma, 400–401
    embryonal carcinoma, 403
    profile of, 399
    seminoma, 399–400
    teratocarcinoma, 402–403
    teratoma, 401–402
  sex cord-stromal, 393–399
    granulosa cell tumour, 393–396
    interstitial (Leydig) cell tumours, 396–397
    rete testis, adenoma and carcinoma of, 398–399
    Sertoli cell tumour, 397–398
    Sertoli-Leydig cell tumour of ovary (arrhenoblastoma), 398
Goodman , Louis, 4
Grading of tumours, 18–19, 19b, 19f
  objective of, 18
Grafting, autologous, 191–192, 193f
Granular cell tumours (GCTs)
  biological behaviour of, 302
  bronchial, 502f
  cellular origin of, 302
  differential diagnoses of, 303b
  electron microscopy of, 303
  gross pathology of, 302
  histopathology of, 302–303, 303f
  immunohistochemical labelling of, 303
  profile of, 302
  pulmonary, 302
  single bronchogenic, 65

Granulosa (theca) cell tumours, 66, 96f, 117, 393–396, 641–643, 641b
  biological behaviour of, 393–395
  cellular origin of, 393
  clinical features of, 641, 641b, 642f
  description of, 641
  diagnostic confirmation of, 641–643, 642f, 643t
  differential diagnoses for, 396, 396b
  gross pathology of, 395
  histopathology of, 395–396, 395f
  immunohistochemical labelling of, 396
  management of, 643
  metastasis of, 393
  profile of, 393
  prognosis of, 643, 643b
Gray (Gy), 174
Gross tumour volume (GTV), 177
Guttural pouch neoplasia, 496, 496b

H

Habronemiasis, cutaneous, squamous cell carcinoma and, 227
Haemangioma
  biological behaviour of, 332–333
  of cardiovascular system, 512–514
    clinical features of, 512–513, 513f–514f
    description of, 512
    diagnostic confirmation of, 513
    differential diagnoses of, 513
    management of, 513–514
    prognosis of, 514
  cellular origin of, 332
  classical, 333
  differential diagnoses of, 334b
  epithelioid variant of, 333–334
  gross pathology of, 333, 333f
  histopathology of, 333–334, 333f
  immunohistochemical labelling of, 334
  oncogenesis of, 332
  profile of, 332
Haemangiomatosis, 340
Haemangiopericytoma
  biological behaviour of, 290
  cellular origin of, 290
  differential diagnoses of, 290b
  gross pathology of, 290
  histopathology of, 290
  profile of, 290
Haemangiosarcoma, 472–473, 472b, 607–609, 609f, 622–623, 622b, 623f
  biological behaviour of, 335
  of cardiovascular system, 514–519, 515b
    clinical features of, 515–516, 516f–518f
    description of, 514–515, 514b
    diagnostic confirmation of, 516–518
    differential diagnoses of, 515–516
    management of, 518–519
    prognosis of, 519
  cellular origin of, 334
  clinical features of, 472–473
  cutaneous, 334–335
  description of, 472
  diagnostic confirmation of, 473
  differential diagnoses of, 337b
  disseminated, 334
  epithelioid variant of, 336–337, 336f
  gross pathology of, 335–336, 335f
  histopathology of, 336–337, 336f
  immunohistochemical labelling of, 337
  management and prognosis of, 473
  metastatic, 677
  ocular, 335
  oncogenesis of, 334
  profile of, 334
  in sinonasal region, 487
  of upper and lower respiratory tract, 507, 507b, 508f
Haematocrit, differential diagnoses for elevation of, 77b
Haematogenous spread, metastasis, 59
Haematological syndromes, 71, 72t
Haematology, 90–93, 94t
  as diagnostic aid, 425
  of haemangiosarcoma, 516
  of pulmonary granular cell tumour, 500
Haematoma(s)
  progressive ethmoidal. *see* Progressive ethmoidal haematoma (PEH)
  uterine, endometrial adenocarcinoma and, 277
Haematopoietic neoplasms, 368
  immunohistochemical profile of, 115
Haematopoietic (round cell) neoplasms, 342–362
  congenital mast cell tumours, 357–359
  cutaneous nodular mastocytosis/mast cell tumour, 357
  histiocytic sarcoma, 359–360
  leukaemia, 352–355
  lymphosarcoma, 342–352
    alimentary, 346–348
    hepatosplenic and splenic, 350–351
    mediastinal, thymic and thoracic, 348–349
    multicentric, 346
    nasal, paranasal, and nasopharyngeal, 351
    nervous system, 352
    ocular, 352
    subcutaneous and cutaneous, 349–350
  malignant mast cell tumours, 357
  mast cell tumour, 357
  plasma cell neoplasms, 355–357
Haematopoietic system, neoplasia of, 523–539
  alimentary lymphoma, 528–531
  clinical features of, 524
  cutaneous lymphoma, 533–535
  description of, 523
  diagnostic confirmation of, 524
  hepatosplenic/splenic lymphoma, 535–536
  management of, 524
  mediastinal/thoracic/thymic lymphoma, 531–533
  multicentric lymphoma, 524–528
  plasma cell myeloma, 536–539
  prognosis of, 524
Haematuria
  in bladder carcinoma, 658–659
  in renal carcinoma, 655f
  renal carcinoma/adenoma and, 272
Haemolytic anaemia, severe, alimentary lymphosarcoma and, 347
Hamartoma(s), 431t
  definition of, 332, 337
  fibrous. *see* Fibrous hamartoma
  osseous, 322
  polypoid, 267
  pulmonary, 265
  subcutaneous, of limbs, 333
  vascular. *see* Vascular hamartoma
Hamartomatous polyp, 232
Handling, of tissue samples, 87
Hard palate, carcinoma of, 438f–439f
'Hayflick limit', 37
'Hayflick phenomenon', 37
HB. *see* Hepatoblastoma (HB)
Heavy metal compounds, in equine sarcoids, 558, 558f
Heavy metal therapy, 138–139
Helicobacter pylori, 45
Helium atoms, 166
Hepatic encephalopathy, gastric adenocarcinoma and, 266
Hepatic neoplasia, 467–470
  cholangiocellular carcinoma, 469–470
  hepatoblastoma, 467–468
  hepatocellular carcinoma, 468–469
Hepatoblastoma (HB), 407–408, 467–468, 467b
  biological behaviour of, 407
  cellular origin of, 407
  clinical features of, 468
  description of, 467–468
  diagnostic confirmation of, 468
  differential diagnoses for, 408
  embryonal-type tumour cells in, 408
  epithelial cell types in, 408
  fetal-type tumour cells in, 408
  gross pathology of, 407
  histopathology of, 407–408
  immunohistochemical labelling of, 408
  management and prognosis of, 468
  profile of, 407
  summary of findings of, 468t
Hepatocellular adenoma
  biological behaviour of, 268–269
  cellular origin of, 268
Hepatocellular adenoma (*Continued*)
  differential diagnoses of, 270, 270b
  gross pathology of, 269
  histopathology of, 269–270
  immunohistochemical labelling of, 270
  profile of, 268, 269f
Hepatocellular carcinoma, 408, 468–469, 468b
  biological behaviour of, 268–269
  cellular origin of, 268
  clinical features of, 469, 469f
  description of, 468–469
  diagnostic confirmation of, 469
  differential diagnoses of, 270, 270b
  gross pathology of, 269
  histopathology of, 269–270
  immunohistochemical labelling of, 270
  management and prognosis of, 469
  profile of, 268, 269f
Hepatosplenic lymphosarcoma, 349–351
  biological behaviour of, 350–351
  gross pathology of, 351
  histopathology of, 351, 351f
  profile of, 350
Hepatosplenic/splenic lymphoma, of cardiovascular system, 535–536
  clinical features of, 535, 535b, 535f
  diagnostic confirmation of, 535–536
  management of, 536
  prognosis of, 536
Hereditary multiple exostoses, 669–670
  see also Osteochondroma
High-grade melanoma, 22f
Hippocrates, 3
Hirsutism, in pituitary adenoma, 377
Histiocytic sarcoma
  biological behaviour of, 359
  cellular origin of, 359
  gross pathology of, 359
  histopathology of, 359–360
  immunohistochemical labelling for, 360
  profile of, 359
Histiocytoma
  malignant, 52f
  malignant fibrous, 566–567, 566b, 567f
HMB45 antibody, 243–245
Hodgkin, Thomas, 11
Hodgkin's disease, 11
Hollow-needle biopsy, 89–90
  ultrasound guided, 91f
Homeopathy, 195, 417
Homeostasis, cellular, 36
Homer-Wright rosettes
  in medulloepitheliomas, 373
  in olfactory neuroblastoma, 367
Hope Score, 114
Horizontal ramus, of mandible, 454f
Huggins, Charles, 4
Humoral hypercalcaemia of malignancy, and ameloblastoma, 323–324
Hydronephrosis, in bladder carcinoma, 659
Hypercalcaemia, 75, 100t
  differential diagnoses for, 75b
  lymphosarcoma and, 343
  multiple myeloma and, 356
Hypercementosis, 328
Hypercortisolaemia, 72
Hypercupraemia, 77
Hypereosinophilia, alimentary lymphosarcoma and, 347
Hyperfibrinogenaemia, 77–78
  differential diagnoses for, 78b
Hyperfractionated radiotherapy, 168
Hyperfractionated regimens, 170
Hyper-gammaglobulinaemia, 100t
Hyperglobulinaemia, 77–78
  effects of extreme, 78
  monoclonal gammopathy with, lymphosarcoma and, 343
Hyperglycaemia, 92
Hypericin, 162
Hyperparathyroidism, 592
Hypersalivation, in gastrointestinal neoplasia, 458
Hyperthermia, 127
  in equine sarcoids, 557
  safety measures during, 127

Hypertrophic (pulmonary) osteopathy, 81–83, 82f
Hypoalbuminaemia, lymphosarcoma and, 342–343
Hypocalcaemia, 75
Hypogammaglobulinaemia, lymphosarcoma and, 343
Hypoglycaemia, 77, 92
  differential diagnoses for, 77b
  hyperinsulinaemic, islet cell neoplasms and, 386
  and mesothelioma, 281
  paraneoplastic, renal carcinoma/adenoma and, 272
Hypoproteinaemia, 100t

I

'Idiopathic' synchronous diaphragmatic flutter, 75
IL-2. *see* Interleukin-2 (IL-2)
Imatinib mesylate, 117
Imiquimod, 139
  in equine chemotherapy, 154–156
  for equine sarcoids, 558
  practical use of, 156, 156f
Immune evasion, 34–36
Immune suppression, 72–73
Immune system
  'hiding' from, 35
  mechanisms by which tumours evade, 35f
Immune-complex production, 72
Immunohistochemical labelling, 202
Immunohistochemical staining, 112
  tumour differentiation by, 115t
Immunohistochemistry, 112–117
  advantages of, 115–117, 117t
  definition of, 112–113
  direct method of, 114
  fluorescent, 115, 115f
  of hepatoblastoma, 468
  indirect method of, 114–115, 114f
Immunomodulation
  for sarcoids, 442, 559–560
  for squamous cell carcinoma, 579
Immunophenotyping, for alimentary lymphoma, 530
Immunostaining, 112–117
Immunostimulation, in equine sarcoids, 560
Immunosuppression, 129
Immunotherapy
  active (specific), 186–191, 188f
  Bacillus Calmette-Guérin, in practice, 189–191
  cancer, 186–192
  cell-based, 187
  passive/adoptive, 187
'Implantation'
  manual, in brachytherapy, 181
  of radioactive sources, 181
Impression smears, 90
IMRT. *see* Intensity-modulated radiotherapy (IMRT)
In vitro cell culture, assessment of, 107
Inappetence, in gastrointestinal neoplasia, 457–458
Incidental tumour-like dental masses, 436
Indirect method, of immunohistochemistry, 114–115, 114f
Infection(s)
  cross-species, bovine papillomavirus, 203–205
  latent, bovine papillomavirus as, 208–209
  persistent, cancer and, 45
  reduced risk of, as laser surgical excision advantage, 124
  in squamous cell carcinoma, 221
  tumours and, 67–68
Infectious agent(s)
  of carcinogenesis, 45–46
  direct transformation induced by, 45
  persistence of, 45
  secondary effects of, 45
Infiltrating bladder carcinoma, 658, 660f
Infiltrative lipoma
  biological behaviour of, 295
  cellular origin of, 295
  gross pathology of, 296
  histopathology of, 296, 296f
  myocardial, 296
  profile of, 295
Inhibin, 95t
  granulosa cell tumour and, 394
Insulin, 95t
Insulinoma, 115–117
Intensity-modulated radiotherapy (IMRT), 167
Interferon, for equine sarcoids, 560
Interleukin, for equine sarcoids, 560
Interleukin-2 (IL-2), 187
Internal lymphosarcoma, 80f
Internal ocular neoplasms, 372–375
  neoplastic masses in, 372–374
    iridociliary epithelial tumour, 372
    medulloepithelioma, 372–374
    optic disc astrocytoma, 374
    retinoblastoma, 374
  non-neoplastic masses in, 374
    proliferative optic neuropathy in, 374
  other conditions, 374
Internal radiotherapy, 179–180
Interstitial brachytherapy, 171
Interstitial cell adenoma. *see* Interstitial (Leydig) cell tumours
Interstitial cells of Cajal, 369
Interstitial (Leydig) cell tumours, 396–397, 637–638, 637b
  biological behaviour of, 397
  cellular origin of, 396
  gross pathology of, 397
  histopathology in, 397
  immunohistochemical labelling, 397
  oncogenesis of, 397
  profile of, 396–397
Intestinal adenocarcinoma
  biological behaviour of, 266
  cellular origin of, 265
  differential diagnoses of, 267b
  gross pathology of, 266–267
  histopathology of, 267
  immunohistochemical labelling of, 267
  profile of, 266
Intestinal adenoma
  biological behaviour of, 265, 266f
  cellular origin of, 265
  gross pathology of, 265
  histopathology of, 265
  immunohistochemical labelling of, 265
  profile of, 265
Intestinal ALP, 95t
Intestinal leiomyosarcoma, 465f
Intestinal lymphoma, 462–464, 462b
  clinical features of, 462, 463f
  description of, 462
  diagnostic confirmation of, 462–463
  differential diagnoses of, 462
  management of, 463, 464f
  prognosis of, 463–464
Intestinal neoplasia, 461–465
  adenocarcinoma, 464–465
  intestinal lymphoma, 462–464
Intestinal submucosal haematoma, 232
Intestinal tract, leiomyomas in, 306
Intraepithelial carcinoma, in situ, 21f
Intralesional chemotherapy, 140–141
Intralesional formalin injection
  for epidermal inclusion cyst, 488
  technique of, in progressive ethmoidal haematoma, 492–493
Intramembranous ossification, of osteoma, 314–315
Intraocular melanoma, 618, 619t
Intraocular tumour, 117
Intraoperative haemorrhage, progressive ethmoidal hematoma and, 492
Intraosseous epidermoid cyst, 321, 322f
Intratumoral chemotherapy, 140–141
Intravagal paraganglia, 387
Intravenous chemotherapy, 137–138
Iodine-125, 180t, 183
Iodine-128, 184t
Ionizing radiation, 165
  causing DNA damage, 44
Iridal body cysts, squamous cell carcinoma and, 228
Iridal melanoma, 65f
Iridium-192, 180t, 182–183, 184t
Iridociliary epithelial tumour, 372
  biological behaviour of, 372
  cellular origin of, 372
  gross pathology of, 372
  histopathology in, 372
  immunohistochemical labelling in, 372
  profile of, 372
Iron profiles, 100t
Irradiation, cytological effects of, 168
Isoenzyme-1, 95t
Isoenzyme-2, 95t
Isoenzyme-3, 95t
Isoenzyme-4, 95t
Isoenzyme-5, 95t

J

Jaw
  myxomatous neoplasms of, 315, 447–448, 447b
  non-neoplastic (cystic) lesions of, 329–330
Jejunal ganglioneuroma, 369
Juvenile mandibular ossifying fibroma, 312–313, 445–447, 445b
  clinical features of, 445–446
  description of, 445
  diagnostic confirmation of, 446
  differential diagnoses of, 446
  management of, 446
  occurrence of, 445
  prognosis of, 447
Juxtacortical bone cysts, 322

K

Karkinos, 3
Keratectomy, 617b
Keratinocytes, in epithelial neoplasms, 249
Keratoma, 582–583, 582f, 583b
  biological behaviour of, 256
  cellular origin of, 256
  differential diagnoses of, 257b
  gross pathology of, 256
  histopathology of, 256
  oncogenesis of, 256
  profile of, 256
Keratosis, actinic, squamous cell carcinoma in situ and, 220–221
Knudson hypothesis, 39–42
Koilocytes, in epithelial neoplasms, 249

L

LA. *see* Levulinic acid (LA)
Lactate dehydrogenase (LDH), 95t
Laminitis, pituitary adenoma and, 378
Langerhans' cells (LCs), epidermal, 249
Laparoscopy, 104
  exploratory, of intestinal neoplasia, 461
  in granulosa cell tumour, 643
  of hepatosplenic/splenic lymphoma, 536
  limitations of, 104
  technique in, 104
Large B-cell lymphosarcomas. *see* Diffuse large-cell lymphosarcoma of B-cell origin
Large cell immunoblastic lymphosarcoma, 344f, 345
Laryngeal chondroma, 498f
Laser ablation, of haemangioma/vascular hamartoma/cavernous haemangioma, 513
Laser beams, accessibility of, 125
Laser photoablation, carbon dioxide, for squamous cell carcinoma of eye, 617
Laser surgery, for equine sarcoids, 558
Laser surgical excision, 124–125
  advantages of, 124
  disadvantages of, 125
  methods of, 125
  for oral fibroma/fibrosarcoma, 445
  precautions and hazards of, 125
Lasers, accessibility of, 124
L-asparaginase, 138b
  for multicentric lymphoma, 527t
LDH. *see* Lactate dehydrogenase (LDH)
Leiomyoma, 460, 460b
  biological behaviour of, 305–306
  cellular origin of, 305
  differential diagnoses of, 306b
  of female genital tract, 640–641, 640b, 640f
  gross pathology of, 306
  histopathology of, 306, 306f
  immunohistochemical labelling of, 306
  oncogenesis of, 305
  profile of, 305
  uterine, 306
Leiomyomatosis
  biological behaviour of, 307
  cellular origin of, 307

Leiomyomatosis (*Continued*)
gross pathology of, 307
histopathology of, 307
immunohistochemical labelling of, 307
profile of, 307
Leiomyosarcoma
biological behaviour of, 307
cellular origin of, 307
differential diagnoses of, 308b
gross pathology of, 307–308
histopathology of, 308
immunohistochemical labelling of, 308
profile of, 307
Lesions
leukaemia and, 354
papillomatous, 17f
of sarcoid, 212
Leukaemia, 17–18, 352–355, 523, 525f, 539–541, 539b
accepted classification of, 539t
associated lesions with, 354
cellular origin of, 352
chronic myeloid, 353
classification and profile of, 352
clinical features of, 539–540
diagnostic confirmation of, 540
differential diagnoses for, 355, 540
gross pathology of, 353–354
histopathology of, 354–355
immunohistochemical labelling of, 354–355
lymphoid, 353, 540
lymphosarcoma and, 342
management of, 540
myeloid, 352–353, 540–541
prognosis of, 540
Leukaemic (B-cell) lymphoma, 92f
Leukaemic lymphoma, 525f
Leukocytosis, 91–92
Leukopaenia, 100t
Leukoplakia, 221, 232, 421, 421f
Levulinic acid (LA), 162
Leydig cell tumour. *see* Interstitial (Leydig) cell tumours
Ligation
in dermal melanoma, 574
in equine sarcoids, 556
tumour, 127–129, 128f
Limitless replicative potential, sequence of events in development of, 33f
Linear accelerators, in radiotherapy, 166, 167f
Lip melanoma, surgical excision for, 444
Lipizzaner horse, 419
Lipocytic (adipose) tumours, 294–296
infiltrative lipoma, 295–296
lipoma, 294–295
liposarcoma, 296
Lipoma, 465–467, 466b, 567–568, 567b, 568f
biological behaviour of, 294–295
cellular origin of, 294
clinical features of, 466
description of, 465–466
diagnostic confirmation of, 466
differential diagnoses of, 466
gross pathology of, 295
histopathology of, 295, 295f
infiltrative. *see* Infiltrative lipoma
management and prognosis of, 466–467, 467b
profile of, 294
Lipomatosis, colonic, 296
Liposarcoma
see also Lipoma
biological behaviour of, 296
cellular origin of, 296
differential diagnoses of, 296b
gross pathology of, 296
histopathology of, 296
mediastinal, 296
profile of, 296
Liquid nitrogen, 126, 127f
Liver, hepatoblastoma and, 407
Local chemotherapy, 139–140, 139f
Local sarcoid, 62
Low-grade melanoma, 22f
Lymphangioma
biological behaviour of, 337
of cardiovascular system, 521–522, 521b
Lymphangioma (*Continued*)
clinical features of, 521–522, 521f
description of, 521
diagnostic confirmation of, 522
differential diagnoses of, 522
management of, 522
prognosis of, 522
cellular origin of, 337
differential diagnoses of, 338b
electron microscopy of, 338
gross pathology of, 337
histopathology of, 337–338, 338f
immunohistochemical labelling of, 338
multinodular, 337
profile of, 337
Lymphangiosarcoma
biological behaviour of, 338–339
of cardiovascular system, 521–522, 521b
clinical features of, 521–522, 521f
description of, 521
diagnostic confirmation of, 522
differential diagnoses of, 522
management of, 522
prognosis of, 522
cellular origin of, 338
electron microscopy of, 339
gross pathology of, 339
histopathology of, 339
immunohistochemical labelling of, 339
profile of, 338
Lymphatic vessels, invasion of, 59
Lymphoblasts, 504f
Lymphoid leukaemia(s), 353, 540
Lymphoma(s), 17–18, 523
alimentary, 462, 528–531, 528b
CNS, 605–606, 606t, 607f
immunohistochemical profile of, 115
in immunohistochemical staining, 115t
leukaemic (B-cell), 92f
metastatic, 677, 677f
multicentric, 73f
leukaemic, 80f
orbital, conjunctival and corneal, 620–622, 621b
clinical features of, 621–622, 621f
diagnostic confirmation of, 622
management of, 622
prognosis of, 622
ovarian, 646–647, 646b
protein variations and, 92–93
renal, 67
T-cell, formalin preserved of, 114f
of upper and lower respiratory tract, 503–506, 503b
clinical features of, 504–505
description of, 503–504
diagnostic confirmation of, 505, 506f
differential diagnoses of, 505
management and prognosis of, 505–506, 506b
in urinary tract, 661f
Lymphomatoid granulomatosis, 344f, 345
Lymphosarcoma, 9–10, 342–352
biological behaviour of, 342–343
cellular origin of, 342
classifications of, 343–346
gross pathology of, 343
histopathology of, 343–346, 344f
immunohistochemical labelling of, 344f, 346
internal, 80f
oncogenesis of, 342
pathology of, general and site-specific, 343
profile of, 342
Lysosome-mediated destruction, autophagy as, 34f

M

Magnetic resonance imaging (MRI), 103
in angiosarcoma, 520
in cholesterol granuloma, 610
as diagnostic aid, 426
in nasopharyngeal/laryngeal neoplasia, 498
in orbital paraganglioma, 597
in plasma cell myeloma, 538
Major histocompatibility complex (MHC), reduction in, 35
MAL. *see* Methyl aminolevulinate (MAL)
Malignancy, development of, 54f
Malignant equine mastocytosis, 565
Malignant fibrous histiocytoma. *see* Giant cell tumour, of soft parts
Malignant histiocytoma, 52f
'Malignant lymphomas', 17–18
Malignant mast cell tumours
biological behaviour, 357
profile of, 357
Malignant rhabdoid tumour, 410
biological behaviour of, 410
cellular origin of, 410
gross pathology of, 410
histopathology of, 410
immunohistochemical labelling for, 410
profile of, 410
Malignant sarcoid, 62, 212, 553–561, 553f–554f
Mammary adenocarcinoma, 647–648, 647b, 648f
Mammary carcinoma, 34f
Mammary gland(s)
adenocarcinoma, carcinoma, and adenoma of
biological behaviour of, 261
differential diagnoses of, 263b
gross pathology of, 261, 262f
histopathology of, 261–263
immunohistochemical labelling of, 261–263
profile of, 260
neoplastic disease of, 647–650
adenocarcinoma in, 647–648, 647b, 648f
melanoma in, 649, 649b, 649f
sarcoid in, 649–650, 649b, 650f
squamous cell carcinoma in, 648–649, 648b
Mandibular aneurysmal bone cyst, 454–455, 454b, 672–674, 673b
clinical features of, 454, 673, 673f
description of, 454, 672–673
diagnostic confirmation of, 454–455, 673–674
differential diagnoses of, 454, 673
management of, 455, 674
prognosis of, 455, 674
Mares, with granulosa cell tumour, 420
Marie's disease, 81–83
Mast cell tumour(s), 89f, 94t–95t, 357
see also Mastocytoma
cellular origin of, 357
congenital, 357–359
biological behaviour of, 358
differential diagnoses for, 359, 359b
gross pathology of, 358
histopathology of, 358–359, 358f
immunohistochemical labelling of, 359
malignancy in, indications of, 359
profile of, 357–358
conjunctival, 623, 623b, 624f
intranasal, 485, 485b
malignant. *see* Malignant mast cell tumours
profile of, 357
Mastocytoma, 357, 564–566, 565b
clinical features of, 565–566
diagnostic confirmation of, 566
management of, 566
prognosis of, 566
Mastocytosis, 357
equine cutaneous, 564–566
Matrix metalloproteinases (MMPs), 39
Maximum tolerated dose (MTD), 133
Mediastinal lymphosarcoma, 348–349
biological behaviour of, 348–349, 348f
gross pathology of, 349
histopathology of, 349
profile of, 348
Mediastinal/thoracic/thymic lymphoma, of cardiovascular system, 531–533, 531b
clinical features of, 531–532, 532f
description of, 531
diagnostic confirmation of, 532–533
management and prognosis of, 533
Mediator therapy, 187
Medical therapy, 129–144
Medulloblastoma, 605
Medulloepithelioma, 372–374, 623–625, 624b, 625t
biological behaviour of, 373
cellular origin of, 372
clinical features of, 624, 625f
diagnostic confirmation of, 624
differential diagnoses of, 374, 374b
electron microscopy in, 374

Medulloepithelioma (*Continued*)
gross pathology of, 373
histopathology in, 373–374
immunohistochemical labelling, 373
management of, 624–625
profile of, 372–373
prognosis of, 625
Megakaryocytic (M7) leukaemia, 541
Melanin, metabolism of, melanocytic neoplasm and, 238
Melanocytes, 237, 240–241
Melanocytic naevus, 20f, 241–242, 569, 569f
clinical features of, 570, 570f
management of, 573–574
Melanocytic neoplasms, 237–246
affected sites of
internal, 238–239
ocular, 239
skin, 238
biological behaviour of, 239–240
cellular origin of, 237
classification of, 237
cutaneous, 239
differential diagnoses of, 245b
electron microscopy of, 245
general features of, 240–241, 241f
gross pathology of, 240
histopathology of, 240–243
immunohistochemical labelling of, 243–245, 245f
metastasis of, 239–240, 240f
ocular, 239
oncogenesis of, 238
profile of, 237–238
Melanocytoma, 237, 569
Melanocytosis. *see* Dermal melanoma(s)
Melanoma cells, 240–241
Melanoma(s), 9, 20f, 45, 62, 424–425, 442–444, 442b, 568–575, 568b, 572b, 606–607, 608t
affecting peripheral nerves, 607f
anaplastic malignant, 239, 243
ciliary, 239
classification of, 569f
clinical features of, 443, 443f, 570–573, 572f
conjunctival and ocular, 618–620, 618b, 619t
clinical features of, 618, 619f–620f
diagnostic confirmation of, 620
differential diagnoses of, 618
management of, 620
prognosis of, 620
dermal, 239, 243, 244f
description of, 443
diagnostic confirmation of, 443, 573
differential diagnoses of, 443
disseminated malignant, 238–239
immunohistochemical profile of, 115
in immunohistochemical staining, 115t
iridal, 65f
limbal (epibulbar), 239
low-grade and high-grade, 22f
mammary, 649, 649b, 649f
management of, 443–444, 573–574
metastatic, 677–678, 677f
milder forms of, 497f
in non-grey horses, 573f
penile and preputial, 632–633, 632b, 633f
prognosis of, 444, 575
renal metastatic, 662f
secondary, 607f
within spinal canal, 63f
Melanomatosis, dermal, 239, 243
Melanosarcoma, 568–575, 568b, 572f
aggressive, 63f
malignant, 151f
Melanosis, milder forms of, 497f
Melphalan, in equine chemotherapy, 156–157
Membrane nictitans, 10
MEN. *see* Multiple endocrine neoplasia (MEN)
Meningeal neoplasms, 367–368
Meningioma, 367–368, 605
biological behaviour of, 368
cellular origin of, 367
gross pathology of, 368
histopathology in, 368
immunohistochemical labelling, 368
profile of, 368
Mesenchymal masses, non-neoplastic, 293–294
fibromatosis, 294
fibrous hamartoma, 293–294
Mesenchymal neoplasms, 285–298
Mesenchymoma, malignant
abdominal, 293
biological behaviour of, 293
cellular origin of, 292
differential diagnoses of, 293b
gross pathology of, 293
histopathology of, 293
profile of, 293
Mesenteric lipoma, 16, 16f, 466f
Mesothelial cells, 281
Mesothelioma, 281–284, 474–475, 474b
biological behaviour of, 281
versus carcinoma, 283, 283f
cases of, 475t
cellular origin of, 281
clinical features of, 474, 476f
description of, 474
diagnostic confirmation of, 474–475
differential diagnoses of, 283b, 474
electron microscopy of, 283
gross pathology of, 281
histopathology of, 281–283, 282f–283f
immunohistochemical labelling of, 283, 283f
management and prognosis of, 475
oncogenesis of, 281
profile of, 281
of upper and lower respiratory tract, 503, 503b
Metabolic derangements, 71
Metabolic syndromes, 71
Metastasis, 53–59
development of, 53f
by direct seeding, 59
genetic theory of, 53–58
local, presence of, 57
of melanocytic neoplasms, 239–240, 240f
morphological diagnosis of, 52f
routes of, 58–59, 59f
'Metastasis signature' theory, 53f, 54
Metastatic gastric carcinoma, 55–56
Metastatic hepatic carcinoma, secondary, 76f
Metastatic melanoma, in cardiovascular system, 523, 523f
Metastatic thoracic tumours, 506–507
clinical features of, 507
diagnostic confirmation of, 507
haemangiosarcoma, 507
Metastatic tumours, 55
type of, determination of original tissue, 115–117, 116f, 117t
Methyl aminolevulinate (MAL), 162
MHC. *see* Major histocompatibility complex (MHC)
Microadenomas, pituitary adenoma and, 378, 380f
Microbial agents, of carcinogenesis, 45–46
Mitomycin-C, 141, 157
intralesional injection of, 157, 157f
ophthalmic drops of, 131, 157
for squamous cell carcinoma, 579
of eye, 617
Mitotic phase (M), 23f
Mixed neuronal tumours, 366–367
Mixed sarcoids, 552–553, 553f
verrucose, nodular and fibroblastic, 212, 212b
Mixed-cell lymphosarcoma, 345
in small intestine, 344f
MMPs. *see* Matrix metalloproteinases (MMPs)
Monoclonal antibody(ies)
availability of specific, 113
systems, 35
therapy, 187
Monoclonal gammopathy, 77–78
differential diagnoses for, 78b
Monocytic (M5) leukaemia, 541
Mononuclear cells, blood, peripheral, 201
MRI. *see* Magnetic resonance imaging (MRI)
MTD. *see* Maximum tolerated dose (MTD)
Mucocutaneous syndromes, 71
Mucocutaneous tumours, 9
Mucopurulent nasal discharge, paranasal sinus cysts and, 494
Muller, Johannes, 4
Multicentric (generalized) lymphosarcoma
biological behaviour, 346
gross pathology of, 346
Multicentric lymphoma, 73f, 462
of cardiovascular system, 524–528, 524b
clinical features of, 524, 525f
description of, 524
diagnostic confirmation of, 524–526, 525f
management of, 526–528
prognosis of, 528
World Health Organization clinical staging system of, 526t
leukaemic, 80f
Multilobular tumour, of bone, 319
biological behaviour of, 319
cellular origin of, 319
differential diagnoses of, 319b
gross pathology of, 319
histopathology of, 319
profile of, 319
Multinodular hyperplasia, thyroid adenoma and, 381
Multiple cartilaginous exostoses, 669–670
Multiple endocrine neoplasia (MEN), 593
cellular origin of, 386
profile of, 386–387
Multiple leiomyoma. *see* Leiomyomatosis
Multiple melanomas, 443f
Multiple myeloma, 78
biological behaviour of, 356
cellular origin of, 356
electron microscopy in, 357
electrophoresis and densitometer scan of plasma from, 93f
gross pathology, 356
histopathology of, 356–357
immunohistochemical labelling, 357
profile of, 356
Multistep carcinogenesis proposal, 40–42
Musculoaponeurotic fibromatosis. *see* Fibromatosis
Musculoskeletal syndrome, 72t
Musculoskeletal system, tumours of, 664–679, 665b
metastatic, 676–678, 676b
case reviews on, 678
description of, 676–678
diagnostic confirmation of, 678
neoplastic bone masses in, 664–672
chondroma/chondrosarcoma, 672, 672b
osteoblastoma, 671, 671b
osteochondroma, 667–669, 667b
osteochondromatosis, 669–670, 669b
osteoclastoma, 671, 671b
osteoma, 664–665, 664b, 665f, 666t
osteosarcoma, 665–667, 665b, 667f
non-aneurysmal cystic lesions of bone, 674
non-neoplastic bone masses in, 672–674
skeletal muscle tumours, 674–676
Mutation-selection theory, of tumour progression, 48f
Mycosis fungoides, clinical features of, 533–534, 534f
Myeloid blast cells, in leukaemia, 354
Myeloid leukaemia(s), 352–353, 540–541
acute, 352–353
chronic, 353
Myeloma
multiple, 93f
plasma cell, 92f
Myelomonocytic (M4) leukaemia, 541
Myelophthisis, importance of, 353
Myeloproliferative disease, 76
Myofibroblastic sarcoma, mesenteric, 289
Myofibroblastic tumours
anaplastic sarcoma, 292
biological behaviour of, 289
cellular origin of, 289
differential diagnoses of, 290b
electron microscopy of, 289
giant cell tumour of soft parts, 290–292
gross pathology of, 289
haemangiopericytoma, 290
histopathology of, 289
immunohistochemical labelling of, 289

Myofibroblastic tumours (*Continued*)
intra-abdominal, 289
malignant mesenchymoma, 292–293
primary retroperitoneal tumour, 293
profile of, 289
Myofibroblastoma, mesenteric, 289
Myopathy, fibrotic, 294
Myxofibroma, 561
see also Myxoma
Myxoma
biological behaviour of, 286
in cardiovascular system, 523f
cellular origin of, 286
of conjunctiva, undifferentiated, 626f
differential diagnoses of, 286, 286b
gross pathology of, 286
histopathology of, 286, 287f
nasal, 286
profile of, 286
of upper and lower respiratory tract, 485–486, 485b
clinical features of, 485–486, 486f
diagnostic confirmation of, 486
differential diagnoses of, 486
management of, 486
prognosis of, 486
Myxomatous neoplasms
of jaw, 315
biological behaviour of, 315
cellular origin of, 315
electron microscopy of, 315
and gingivae, 447–448, 447b
gross pathology of, 315
histopathology of, 315
immunohistochemical labelling of, 315
profile of, 315
of premaxilla, 447f
Myxosarcoma
biological behaviour of, 288
cellular origin of, 288
differential diagnoses of, 289b
gross pathology of, 288
histopathology of, 288
malignant, 448f
profile of, 288

N

Naevus (naevi), 237, 241–243
cellular blue, 242, 243f
combined cellular blue, 243, 243f
cutaneous, 239
intradermal common melanocytic, 242, 242f
melanocytic, 241–242
Nasal adenocarcinoma, extensive, 63f
Nasal airflow obstruction, progressive ethmoidal haematoma and, 490
Nasal amyloidosis, 'tumour-like,' profile of, 260
Nasal lymphosarcoma, 351
differential diagnoses for, 351
gross pathology of, 351
histopathology of, 351
profile of, 351
Nasal masses, non-neoplastic, 258–260
Nasal myxoma, 286
Nasal polyp, 488–496, 488b
clinical features of, 488, 489f
description of, 488
diagnostic confirmation of, 489
gross pathology of, 259
guttural pouch neoplasia, 496
histopathology of, 259
management of, 489
paranasal sinus (PNS) cysts, 494–495
profile and biological behaviour of, 259
prognosis of, 489
progressive ethmoidal haematoma, 489–494
Nasomaxillary fibrosarcoma(s), 288, 487
Nasopharyngeal lymphosarcoma, 351
differential diagnoses for, 351
gross pathology of, 351
histopathology of, 351
profile of, 351
Nasopharyngeal/laryngeal neoplasia, 496–498, 496b
clinical features of, 497–498
description of, 496–497
diagnostic confirmation of, 498
Nasopharyngeal/laryngeal neoplasia (*Continued*)
management of, 498
prognosis of, 498
Natural planned cell death, 29
Nd:YAG laser machines, use of, constraints to, 125
Necropsy, of haemangiosarcoma, 518
Necrosis, 29
cell destruction, 33–34
central, in chondrosarcomas, 321
Neoplasms (neoplasia), 201
benign, 11–12
bone and dental region, 312–331
cardiac, 522–523
of central nervous system, 363–366
composed primarily of odontogenic ectomesenchyme, 327–328
derived from tissues of periodontal ligament, 329
endocrine, 376–387
epithelial, 247–280
gastrointestinal, 457–461
gonadal, 393–405
guttural pouch, 496
haematopoietic (round cell), 342–362
of haematopoietic system, 523–539
hepatic, 467–470
internal ocular, 372–375
internal surface-based, 281–284
intestinal, 461–465
malignant, 12
melanocytic, 237–246
mesenchymal, 285–298
nasopharyngeal/laryngeal, 496–498
nerve sheath, 299–304
neuroendocrine, 387–391
odontogenic, 430–436
of oral cavity, 429–430
pancreatic, 473–474
of peripheral nervous system, 369–370
of peritoneum/omentum, 474–475
skeletal, 312–321
smooth muscle and skeletal muscle, 305–311
of soft-tissue origin, 436–449
of spleen, 470–473
stem or progenitor cell, 406–411
of thoracic cavity, 499
of tongue, 449–452
tracheal, 498–499
upper airway, 480–486
vascular, 332–341, 512–522
Neoplastic disease, 7–8
as differential diagnoses, 415–416, 416b
Neoplastic pleural effusion, of metastatic thoracic tumours, 507
Neovascularization, to tumour development, 50
Nephrectomy, for renal carcinoma, 657
Nephroblastoma, 409–410
biological behaviour of, 409
cellular origin of, 409
differential diagnoses for, 410
gross pathology of, 409–410
histopathology of, 410
immunohistochemical labelling of, 410
profile of, 409
triphasic, 410
Nerve sheath neoplasms, 299–304
Nerve sheath tumour, 562–563
Nerves, tumours of, 601–612, 601b
Nervous system lymphosarcoma, 352
profile of, 352
Nervous tissue, tumours of, 601–612, 601b
primary, 601–605
astrocytoma in, 601–602, 601b
choroid plexus tumour in, 603, 603b
ependymoma in, 602–603, 602b
medulloblastoma in, 605
meningioma in, 605
olfactory neuroblastoma in, 604, 604b, 604f
oligodendroglioma in, 602, 602b
pineoblastoma in, 605
secondary, 605–609
haemangiosarcoma in, 607–609, 609f
lymphoma in, 605–606, 606t, 607f
melanoma in, 606–607, 607f, 608t
Nesidioblastosis, 386
Neural crest cells, primitive neuroectodermal tumour and, 410
Neurilemmoma, 562–563
Neurinoma, 562–563
Neuroendocrine carcinoma, 367
Neuroendocrine neoplasms, 387–391
aortico-sympathetic paraganglioma, 390
cellular origin of, 376, 387
chemodectomas, 389–390
equine orbital paraganglioma, 389
extra-adrenal paragangliomas, 389–390
phaeochromocytoma, 387–388
Neuroendocrine system
dispersed, neuroendocrine neoplasms of, 390–391
biological behaviour of, 391
cellular origin of, 390
gross pathology of, 391
histopathology of, 391
immunohistochemical labelling of, 391
profile of, 390–391
neoplasia of dispersed, 598–599
Neuroendocrine tumour/neuroblastoma/extra-adrenal paraganglioma, in sinonasal region, 486–487
Neuroendocrine tumours, 593–599
in adrenal medulla, 594–599
neoplasia of dispersed neuroendocrine system, 598–599
Neuroepithelial tissue, neoplasms in, 363–366
Neurofibroma(s), 299, 301, 562–563, 562b, 563f, 610–611
of eyelid, 299
Neurological syndromes, 71, 72t
Neuroma, 610
traumatic, 302
Neuromuscular syndrome, 72t
Neuronal tumours, 366–367
Neuron-specific enolase (NSE), 243–245
Neuropathy, proliferative optic, 625–626, 625b, 626f
Neutrophilia, lymphosarcoma and, 342
Nictitans, carcinoma of, 60f
Nictitating membrane gland, adenocarcinoma and carcinoma of
biological behaviour of, 255
cellular origin of, 255
differential diagnoses of, 256b
gross pathology of, 255
histopathology of, 255
profile of, 255
Nodular dermatofibrosis, 80
Nodular equine cutaneous mastocytosis, 564–565
Nodular hyperplasia , adrenal cortical adenomas and, 386
Nodular sarcoid(s), 211–212, 548–549
clinical and pathological features of, 548t
type A, 548–549, 549f
type B, 549, 550f
University of Liverpool protocol for, 190b
Non-aneurysmal cystic lesions, of bone, 455–457
fibrous dysplasia, 455
oesophageal carcinoma, 455–457
Non-cancerous mass, appearance of, 13f
Non-genotoxic carcinogens, 41
Non-germinal tumours, of testicle, 635
Non-healing oral wounds, squamous cell carcinoma and, 438
Non-lethal genetic damage, of cancer, 25
Non-neoplastic mass lesions, 370
arachnoid diverticulum, 370
cholesterol granulomas, 370
epidermoid cysts, 370
Non-neoplastic masses, within nervous system, 609–610
cholesterol granuloma in, 609–610, 609f
Non-papillary bladder carcinoma, 658
Non-pigmented ciliary body epithelium (NPE), immunohistology profile of, 117t
Non-teratoid medulloepitheliomas, 373
Non-viral squamous papilloma. *see* Squamous papilloma, non-viral
'Nowell Hypothesis', 47
NPE. *see* Non-pigmented ciliary body epithelium (NPE)
NR4A3, 238
NSE. *see* Neuron-specific enolase (NSE)

Nuclear scintigraphy
as diagnostic aid, 426
of haemangiosarcoma, 517–518

O

Obstructive dyspnoea, paranasal sinus cysts and, 494–495
Occult sarcoid(s), 211, 211b, 213, 215f, 546–547, 547b, 547f
Ocular adnexal tissues, squamous cell carcinoma of, 225–228, 226f–227f
Ocular dermoids, squamous cell carcinoma and, 228
Ocular haemangiosarcoma, 518f
Ocular lymphosarcoma
profile of, 352
unusual sites of, 352
'Odontogenic cyst', 455
Odontogenic epithelium
arrangement and morphology of, 324
neoplasms of
with odontogenic mesenchyme, 326–327
without odontogenic mesenchyme, 323–326
Odontogenic neoplasia, 430–436, 430f
ameloblastoma, 432–433
case reports/series of, 431t–432t
cementoma, 433–435
complex/compound odontoma, 435–436
summary of features of, 431t
Odontogenic neoplasms, 323–330
classification of, 323
Odontoma(s), 64f, 326
complex. *see* Complex odontoma
compound. *see* Compound odontoma
Oedema, 73
ventral, leukaemia and, 353
Oesophageal carcinoma, 455–457, 456b
clinical features of, 456, 457f
description of, 456
diagnostic confirmation of, 456
differential diagnoses of, 456
management and prognosis of, 456–457
Oestradiol, 95t
Oestrogens, granulosa cell tumour and, 395
Oestrus, persistent, dysgerminoma and, 400–401
Olfactory neuroblastoma, 367, 604, 604b, 604f
biological behaviour of, 367
differential diagnoses for, 367, 367b
electron microscopy in, 367
gross pathology of, 367
histopathology in, 367
immunohistochemical labelling in, 367
profile of, 367
Oligodendrocytes, 602
Oligodendroglioma, 364–365, 602, 602b
biological behaviour of, 364
cellular origin of, 364
differential diagnoses for, 365b
gross pathology of, 364
histopathology in, 364–365
immunohistochemical labelling in, 365
profile of, 364
Oncogenes, 25
Oncogenesis
of basal cell tumour, 252
of cementoma, 328
of cholangiocellular carcinoma, 270
of fibroleiomyoma, 305
of haemangioma, 332
of haemangiosarcoma, 334
of keratoma, 256
of melanocytic neoplasms, 238
of mesothelioma, 281
of nerve sheath tumours, benign and malignant peripheral, 299
of non-viral squamous papilloma, 250
of ossifying fibroma, 313
of osteochondroma, 316
of osteoma, 314
of osteosarcoma, 317
of placental teratoma and teratocarcinoma, 406
of sarcoids, 203–209
of squamous cell carcinoma, 220–222
of urinary bladder transitional carcinoma and adenoma, 273–274
of viral squamous papilloma, 247–248
Oncological biopsy, 89
Oncological therapy
see also Chemotherapy
ablative therapy, 120–129
cancer immunotherapy, 186–192
cytotoxic/medical therapies, 129–144
drugs used in, 144–158
safety issues in, 163–165
electrochemotherapy, 158–160
gene therapy, 192–196, 194f
principles of, 118–197, 119f, 119t
radiation therapy/radiotherapy, 165–185
Oncology, science of, 11
Oncoproteins, 205
Oocytes, follicular, dysgerminoma from, 400
Oral cavity, neoplasia of, 429–430
clinical features of, 429–430
Oral fibroma/fibrosarcoma, 444–445, 444b
clinical features of, 444–445, 445f
description of, 444
diagnostic confirmation of, 445
management and prognosis of, 445
occurrence of, 444
Oral haemangiosarcoma, 448, 448b
Oral papilloma, 452, 452b
Oral/gingival carcinoma, 451f
Orbit, tumours of, 613–626, 614t
Orbital extra-adrenal paraganglioma, 595–598, 596t–597t
clinical features of, 595–597, 597f
diagnostic confirmation of, 597–598
differential diagnoses of, 597
management of, 598, 598b
prognosis of, 598
Orbital paraganglioma, 389
biological behaviour of, 389, 389f
cellular origin, 389
gross pathology of, 389
histochemistry of, 389
histopathology of, 389
immunohistochemical labelling of, 389
profile of, 389
Orodental masses, in horse, 430f
Oro-facial sarcoid, 441f
Osseous hamartoma, 322
Osseous metastasis, of renal carcinoma, 656b
Ossifying fibroma
cellular origin of, 312
clinical features of, 313
differential diagnoses of, 314
gross pathology of, 313
histopathology of, 313
juvenile mandibular. *see* Juvenile mandibular ossifying fibroma
in mandible, 313
oncogenesis of, 313
profile of, 312–313, 313f
Osteitis, suture line, 322–323
Osteoblastoma, 671, 671b
biological behaviour of, 318
cellular origin of, 318
differential diagnoses of, 318, 318b
gross pathology of, 318
histopathology of, 318
profile of, 318
Osteochondroma, 667–669, 667b
biological behaviour of, 316
cellular origin of, 315
clinical features of, 669
description of, 668–669
diagnostic confirmation of, 669
differential diagnoses of, 669
gross pathology of, 316
histopathology of, 316
management of, 669
multiple, 316
oncogenesis of, 316
profile of, 315–316
prognosis of, 669
Osteochondromatosis, 315, 669–670, 669b
see also Osteochondroma
clinical features of, 670
description of, 669–670
diagnostic confirmation of, 670
differential diagnoses of, 670
Osteochondromatosis (*Continued*)
management of, 670
synovial, 323
Osteoclastoma, 671, 671b
see also Giant cell tumour, of bone
'Osteodystrophia fibrosa', 592
Osteoid osteoma, 671
Osteoma, 664–665
biological behaviour of, 314
case reports of, 666t
cellular origin of, 314
clinical features of, 664–665, 665f
description of, 664
diagnostic confirmation of, 665
differential diagnoses of, 315
gross pathology of, 314
histopathology of, 314–315
management of, 665
oncogenesis of, 314
ossifying fibroma and, 314
paranasal sinus or nasal, 314
profile of, 314, 314f
prognosis of, 665
well-structured, 315
Osteopathy, hypertrophic (pulmonary), 81–83, 82f
Osteosarcoma, 665–667, 665b
biological behaviour of, 317
case reports of, 668t
cellular origin of, 316
clinical features of, 666, 667f
description of, 666
diagnostic confirmation of, 667
differential diagnoses of, 318, 318b
giant cell, 319
gross pathology of, 317, 317f
histopathology of, 317–318
management of, 667
oncogenesis of, 317
profile of, 316–317
prognosis of, 667
Ovarian adenocarcinoma, 643–644, 643b, 644f
biological behaviour of, 275
cellular origin of, 275
gross pathology of, 275–276
histopathology of, 276
profile of, 275
Ovarian cystadenocarcinoma, 643–644, 643b, 644f
biological behaviour of, 275
cellular origin of, 275
gross pathology of, 275–276
histopathology of, 276
profile of, 275
Ovarian cystadenoma, 643–644, 643b, 644f
biological behaviour of, 275
cellular origin of, 274
differential diagnoses of, 275, 275b
gross pathology of, 275
histopathology of, 275
profile of, 274
Ovarian teratoma, 644–645, 644b, 645f
Ovarian tumours, 641–647
cystadenoma, cystadenocarcinoma, adenocarcinoma, 643–644, 643b, 644f
dysgerminoma, 645–646, 645b, 646f
granulosa cell tumour, 641–643, 641b, 642f
lymphoma, 646–647, 646b
teratoma, 644–645, 644b, 645f
Oviductal adenoma
biological behaviour of, 276
cellular origin of, 276
differential diagnoses of, 276b
gross pathology of, 276
histopathology of, 276
profile of, 276

P

p53
genes, 144
mutation, in squamous cell carcinoma, 222
protein, 204–205
P161NK4 gene, 26t
Pain
colic, in gastrointestinal neoplasia, 458
less, as laser surgical excision advantage, 124

Palliation
  for ameloblastoma, 433
  in cancer therapy, 195–196
Palliative chemotherapy, 133
Palliative radiotherapy, 174
Palpebral carcinoma, 578f
Palpebral nodules, 13f
Pancreas, endocrine, neoplasia of, 593
Pancreatic adenocarcinoma, exocrine
  biological behaviour of, 268
  cellular origin of, 267
  gross pathology of, 268
  histopathology of, 268
  immunohistochemical labelling of, 268
  profile of, 267–268
Pancreatic carcinoma, 473–474, 473b
  clinical features of, 473–474
  description of, 473
  diagnostic confirmation of, 474
  management and prognosis of, 474
Pancreatic islet cell neoplasm, 386
  biological behaviour of, 386
  cellular origin of, 386
  differential diagnoses for, 386, 386b
  gross pathology of, 386
  histopathology of, 386
  profile of, 386
Pancreatic neoplasia, 473–474
Papillary bladder carcinoma, 658, 660f
Papillary cystadenocarcinoma, 276
Papillary endothelial hyperplasia, intravascular, 340
Papilloma(s), 17
  congenital, 247
  development of, 248
  genital, 248
  squamous. *see* Squamous papilloma
  viral, 452
  viral squamous. *see* Viral squamous papilloma
Papillomatous carcinoma, 576f
Papillomatous lesions, 17f
Papillomavirus
  bovine, 203–205
  equine, squamous cell carcinoma and, 221–222
Papyrus, Edwin Smith, 3
Paraganglia
  chemoreceptor, 387
  intravagal, 387
  neuroendocrine neoplasms and, 387
  sympathetic, 387
  visceral-autonomic, 387
Paraganglioma
  aortico-sympathetic, 390, 598
  equine orbital extra-adrenal, 595–598, 596t–597t, 597f, 598b
  extra-adrenal, 389–390
  orbital, equine, 389, 389f
Paranasal lymphosarcoma
  differential diagnoses for, 351
  gross pathology of, 351
  histopathology of, 351
  profile of, 351
Paranasal sinus cyst
  biological behaviour of, 259
  gross pathology of, 259
  histopathology of, 259
  profile of, 259
  recurrence of, 259
Paranasal sinus cysts, 494–495, 494b
  clinical features of, 494–495, 495f
  description of, 494
  diagnostic confirmation of, 495
  management of, 495
  prognosis of, 495
Paraneoplastic erythrocytosis, 76
Paraneoplastic hypoglycaemia, renal carcinoma/adenoma and, 272
Paraneoplastic pemphigus, 79–80, 79f
Paraneoplastic syndromes, 66, 70–84, 72t
  amyloidosis, 81
  anaemia, 75–76
  anorexia-cachexia and wasting syndromes, 73–74
  bullous stomatitis, 80
  erythrocytosis (polycythaemia), 76–77
  hypercalcaemia/hypocalcaemia, 75
  hypercupraemia, 77
Paraneoplastic syndromes (*Continued*)
  hyperfibrinogenaemia, hyperglobulinaemia, and monoclonal gammopathy, 77–78
  hypertrophic (pulmonary) osteopathy, 81–83
  hypoglycaemia, 77
  importance of, 70–71
  pemphigus and other dermatological paraneoplastic signs, 79–80, 79f
  protein-losing enteropathy, 80–81
  pruritus, 78–79
  pyrexia, 75
  renal failure, 81
  thrombocytosis/thrombocytopaenia, 77
  tumour lysis syndrome, 74–75
  ulcerative coronitis, 80
Paraovarian cysts, ovarian cystadenoma and, 275
Parathormone, 95t
Parathyroid (chief cell) adenoma and carcinoma, 384
  biological behaviour of, 384
  cellular origin of, 384
  differential diagnoses for, 384b
  gross pathology of, 384
  histopathology of, 384
  immunohistochemistry for, 384
  profile of, 384
Parathyroid glands, neoplasia of, 592
Parathyroid hormone related peptide, 72
Parathyroid-hormone related protein (PtHRP), 75, 356
Parenchyma, 18
'Parent cell', 23f
Pars intermedia, pituitary adenoma and, 376, 379f
Passive/adoptive immunotherapy, 187
Pathological methods, in equine ecology, 108–117
  biopsy, 108–112
  'follow-up' concept, 112
  immunostaining/immunohistochemistry, 112–117
  'review' concept, 112
Pathologist
  information supplied to, in biopsy, 109–110, 109f
  report, 111f
Pathology, introduction to, 201–202
PDT. *see* Photodynamic therapy (PDT)
Pedunculated lipomas, 465–466
PEH. *see* Progressive ethmoidal haematoma (PEH)
Pemphigus, paraneoplastic, 79–80, 79f
Penile carcinoma(s), 9, 121f
Penile precancerous plaque, 221
Penile squamous cell carcinoma, 630–632, 630b
  clinical features of, 630–631, 630f–631f
  description of, 630
  diagnostic confirmation of, 631
  management of, 632
  prognosis of, 632
Penis and prepuce, neoplasms of, 629–634
  melanoma, 632–633, 632b, 633f
  penile squamous cell carcinoma, 630–632, 630b, 630f–631f
  sarcoid, 633–634, 633b, 634f
Perineural fibroblastoma, 562–563
Perineurioma(s), 299, 301
Periocular sarcoid, University of Liverpool protocol for, 190b
Peripheral blood mononuclear cells, 201
Peripheral nerve sheath tumours (PNSTs), 202
  benign and malignant
    biological behaviour of, 300
    cellular origin of, 299
    differential diagnoses of, 302b
    electron microscopy of, 302
    gross pathology of, 300
    histopathology of, 300–302, 300f–301f
    immunohistochemical labelling of, 301–302, 301f
    oncogenesis of, 299
    profile of, 299
Peripheral nervous system
  neoplasms of, 369–370
    ganglioneuroma, peripheral ganglioneuroblastoma and, 369
    gastrointestinal stromal tumours (GISTs), 369–370
    peripheral nerve sheath tumours, 369
  tumours of, 610–611
Perirenal sarcoma, 662f
Peritoneal mesothelioma, 282
Peritoneocentesis, 98f
Peritoneum/omentum, neoplasia of, 474–475
  mesothelioma, 474–475
Peroxidase enzyme antibody, 114
Personnel, precautions for, in chemotherapeutic drugs, 164
P-glycoprotein, 142–143
Phaeochromocytoma(s), 387–388, 594–595, 594b
  biological behaviour of, 387
  cellular origin of, 387
  clinical features of, 594
  diagnostic confirmation of, 594–595, 594f
  differential diagnosis of, 594
  electron microscopy of, 388
  gross pathology of, 387–388, 388f
  histopathology of, 388, 388f
  immunohistochemical labelling of, 388
  malignant, 388
  management and prognosis of, 595, 595t
  profile of, 387
Pharyngeal carcinoma, 498f
Pharyngeal melanoma, 443f
Phenylbutazone, in thyroid adenoma, 590b
Photoablation, carbon dioxide laser, for squamous cell carcinoma of eye, 617
Photodynamic agents, 162
Photodynamic therapy (PDT), 160–163
  for equine sarcoids, 559
  improvement of, 162
  technique of, 162–163
'Photoradiation therapy' (PRT), with porphyrins, 160–161
Photosensitizer, 161
Phytotherapy, 194–195, 559
Pineal neoplasms, 368
Pineoblastoma, 368, 605
  biological behaviour of, 368
  cellular origin of, 368
  differential diagnosis for, 368
    neoplastic, 368
  gross pathology of, 368
  histopathology of, 368
  profile of, 368
Piroxicam, in equine chemotherapy, 158
Pituitary adenoma, 64, 376–380, 588f
  biological behaviour of, 376–377
  cellular origin of, 376
  electron microscopy in, 380
  extra-pituitary lesions in, 378–380
  grading of, 378, 379f
  gross pathology of, 377–378
  histopathology of, 378–380
  immunohistochemical labelling in, 380
  profile of, 376
  types of cells in, 378
Pituitary gland, neoplasia of, 585–586, 585b
Pituitary pars intermedia dysfunction (PPID), 376, 585–586, 587f
  alimentary lymphosarcoma and, 347
  diagnostic tests for, 588t
Plant alkaloids, 137
Plasma cell myeloma, 92f
  of cardiovascular system, 536–539, 536b
    clinical features of, 536–537, 537f
    description of, 536
    diagnostic confirmation of, 538
    differential diagnoses of, 537, 537b
    management of, 538
    prognosis of, 538–539
Plasma cell neoplasms, 355–357
  multiple myeloma, 356–357
  plasmacytoma, 355
Plasmacytoma
  biological behaviour of, 355
  cellular origin of, 355
  differential diagnoses for, 355, 355b
  gross pathology of, 355
  histopathology of, 355
  immunohistochemical labelling in, 355
  profile of, 355
Plesiotherapy, 184–185
Pleuropulmonary blastoma, 408–409
  biological behaviour of, 408–409
  cellular origin of, 408

Pleuropulmonary blastoma (*Continued*)
differential diagnoses for, 409b
gross pathology of, 409
histopathology of, 409
immunohistochemical labelling of, 409
profile of, 408
Pleuroscopy, 104
PNSTs. *see* Peripheral nerve sheath tumours (PNSTs)
Podophyllum, for equine sarcoids, 558
Pollakiuria, in bladder carcinoma, 659
Polycystic kidney disease, renal carcinoma/adenoma and, 273
Polycythaemia, 76–77
Polymerase chain reaction (PCR)
to detect BPV DNA, 210–211
in EHV-5 DNA detection, 264–265
techniques, 201
'Polypoid cancer', 16
Polyps, 16, 64f
endometrial, endometrial adenocarcinoma and, 277
fibroepithelial, 274
fibromatous, 274
hamartomatous, 232
nasal, 488–496
rectal, 17f
small, 62–63
Portional biopsy, 89
Positive chromogenic change, for antigen, 114
Positron emission tomography (PET), 104
Pott, Percivall, 3–4, 42
Prednisolone, 137b
for multicentric lymphoma, 527t
Premaxilla, myxomatous tumour of, 447f
Primary cardiac lymphoma, 522f
Primary epithelial neoplasms
intrathoracic, 264
pulmonary, 264
Primary meningeal lymphosarcoma, 352
Primary retroperitoneal tumour
biological behaviour of, 293
cellular origin of, 293
differential diagnoses of, 293b
gross pathology of, 293
histopathology of, 293
immunohistochemical labelling of, 293
profile of, 293
Primary thoracic tumours, 499–501
pulmonary granular cell tumour, 500–501
Primary tumour, development of metastasis from, 53f
Primitive neuroectodermal tumour (PNET), 410–411
biological behaviour of, 410–411
cellular origin of, 410
gross pathology of, 411
histopathology of, 411
immunohistochemical labelling for, 411
profile of, 410
Pro-carcinogens, indirect, 43
Progesterone, 95t
granulosa cell tumour and, 395
'Programmed cell death.' *see* Apoptosis
Progressive ethmoidal haematoma (PEH), 489–494, 489b
biological behaviour of, 258
clinical features of, 490–491, 490f–491f
description of, 489–490
diagnostic confirmation of, 491, 492f
differential diagnoses of, 490–491
gross pathology of, 258
histopathology of, 258–259
immunohistochemical labelling of, 258–259
management of, 491–494
profile of, 258
prognosis of, 494
Proliferative optic neuropathy, 625–626, 625b, 626f
Promyelocytic (M3) leukaemia, 541
Pro-opiomelanocortin (POMC), 376–377
dopamine and, 377
processing pathway of, 377f
Propionibacterium acnes, in equine sarcoids, 560
Proprionibacterium cell-wall extracts, 188
Protective genes, multiple families of, 26
Protein-losing enteropathy, 80–81
Protein(s)
Bence-Jones, 356
E2, 205
E5, 204
E6, 204–205
E7, 205
p53, 204–205
total assay, 98–99
variations, 92–93
'Proto-oncogenes', 25
mechanism for conversion from, 25
PROX-1, 338–339
PRT. *see* 'Photoradiation therapy' (PRT)
Pruritus, 78f
paraneoplastic, 78–79
Pseudo-diverticula, alimentary lymphosarcoma and, 347–348
Pseudohyperparathyroidism, 592
'Pseudoneuroma', 302
PtHRP. *see* Parathyroid-hormone related protein (PtHRP)
Pulmonary adenocarcinoma
biological behaviour of, 264
cellular origin of, 263
differential diagnoses of, 264–265, 265b
gross pathology of, 264
histopathology of, 264
immunohistochemical labelling of, 264
profile of, 264
Pulmonary adenoma
biological behaviour of, 264
cellular origin of, 263
differential diagnoses of, 264–265, 265b
gross pathology of, 264
histopathology of, 264
immunohistochemical labelling of, 264
profile of, 264
Pulmonary blastoma (biphasic), 408–409
biological behaviour of, 408–409
cellular origin of, 408
differential diagnoses for, 409b
gross pathology of, 409
histopathology of, 409
immunohistochemical labelling of, 409
profile of, 408
Pulmonary carcinoma
biological behaviour of, 264
cellular origin of, 263
differential diagnoses of, 264–265, 265b
gross pathology of, 264, 264f
histopathology of, 264
immunohistochemical labelling of, 264
profile of, 264
Pulmonary granular cell tumour, 500–501, 500b, 501f
Punch biopsy, 88
PUO. *see* Pyrexia of unknown origin (PUO)
Pyelonephritis
in bladder carcinoma, 659
urinary bladder transitional carcinoma and adenoma and, 274
Pyrexia, 75, 425
Pyrexia of unknown origin (PUO), 75
differential diagnoses for, 75b

R

Radiation, 184b
for ameloblastoma, 433
application of, general principles of, 170f, 171–176
dose and tolerance of, 174–175
effect on cancer, 5, 172–174
for equine sarcoids, 560, 560f
for myxomatous neoplasms of jaw and gingivae, 447
for squamous cell carcinoma, 579–580
therapeutic ratio of, 172–174, 172f–174f
Radiation carcinogenesis, 44–45
Radiation fields, planning of, 177–178, 178f
'Radiation oncology', 165
Radiation therapy, 165–185
acute effects of, 169
chronic effects of, 169
clinical basis of, 175–176
Radiation therapy (*Continued*)
of cutaneous lymphoma, 535
molecular basis of, 166–168
objective of, 176
physics of, 165–166, 166f
prognostic factors of, 176–177
Radicular cysts, 436, 455
Radioactive isotopes, 166
physical characteristics of, in medical therapy, 166t
Radiofrequency hyperthermia
for equine sarcoids, 557
for squamous cell carcinoma of eye, 617
Radiography, 101–103, 101f
as diagnostic aid, 426
of haemangiosarcoma, 517
of mediastinal/thoracic/thymic lymphoma, 532
of nasal polyp, 489
of nasopharyngeal/laryngeal neoplasia, 498
of orbital paraganglioma, 597
in osteoblastoma, 671
in osteochondroma, 669
in osteochondromatosis, 670
in osteoclastoma, 671
in osteosarcoma, 667
in rhabdomyoma, 676
Radionuclides, used in brachytherapy, 180t
'Radio-resistant', 172
Radio-sensitivity, 175, 175f
Radiotherapy, 165–185
for equine juvenile mandibular ossifying fibroma, 446
external beam, 178, 180t
four Rs of, 168–170
for haemangioma/vascular hamartoma/cavernous haemangioma, 514
for haemangiosarcoma, 519
internal, 179–180
for melanoma, 444
for nasopharyngeal/laryngeal neoplasia, 498
palliative, 174
planning stages of, 176
for progressive ethmoidal haematoma, 494
for rhabdomyoma, 676
for sarcoid, 441–442
for squamous cell carcinoma, 440, 483
for squamous cell carcinoma of eye, 617
for thyroid adenoma, 590
Radium-226, for brachytherapy, 180t
Ramazzini, Bernardino, 3
'Random genetic fragility' theory, 48
Recamier, Joseph, 4
Recovery time, and laser surgical excision, 124, 125f
Rectal biopsy, 89
for intestinal neoplasia, 461
Rectal examination
for gastric squamous cell carcinoma, 459
for gastrointestinal neoplasia, 458
for intestinal neoplasia, 461
Rectal palpation, in bladder carcinoma, 660–661
Rectal polyp, 17f
Redistribution, in radiotherapy, 168
Regression, of sarcoids, 210
Remote afterloading, 181–182, 182f–183f
Renal adenocarcinoma, 652–657, 652b
clinical features of, 655, 656f
description of, 652–655
diagnostic confirmation of, 655–656, 655b, 657f
differential diagnosis of, 655
haematuria in, 655f
management of, 656–657
metastasis of, 656b
prognosis of, 657
Renal adenoma
biological behaviour of, 272
cellular origin of, 271
differential diagnoses of, 273, 273b
gross pathology of, 272–273
histopathology of, 273
immunohistochemical labelling of, 273
profile of, 272
Renal carcinoma, 67, 79, 652–657, 652b
biological behaviour of, 272
cellular origin of, 271
clinical features of, 655, 656f

Renal carcinoma (*Continued*)
description of, 652–655
diagnostic confirmation of, 655–656, 655b, 657f
differential diagnoses of, 273, 273b, 655
gross pathology of, 272–273
haematuria in, 655f
histopathology of, 273
immunohistochemical labelling of, 273
management of, 656–657
metastasis of, 656b
profile of, 272
prognosis of, 657
Renal cystadenomas, 272–273
Renal failure, 81
Renal lesions, multiple myeloma and, 356–357
Renal lymphoma, 67
Renal metastatic melanoma, 662f
Renal mucous gland cystadenomas, 273
Renal neoplasia, 272
Reoxygenation, in radiotherapy, 168
Repair, in radiotherapy, 168
'Replicative senescence', 37
Repopulation, in radiotherapy, 167f, 168–170, 169f
Reproductive systems, tumours of, 629–651
female
in genital tract, 638–647
in mammary gland, 647–650
in ovary, 641–647
male
in penis and prepuce, 629–634
in testicle, 634–638
Respiratory tract
squamous cell carcinoma of, 232–233
upper and lower, tumours of, 480–511
metastatic thoracic tumours, 506–507
nasal polyp, 488–496
nasopharyngeal/laryngeal neoplasia, 496–498
neoplasia of the thoracic cavity, 499
primary thoracic tumours, 499–501
in sinonasal region, 486–487
thymic tumours, 501–506
tracheal neoplasia, 498–499
tumour-like lesions, 487–488
upper airway neoplasia, 480–486
Resting energy expenditure, anorexia, 73
Rete testis, adenoma and carcinoma of
biological behaviour of, 399
cellular origin of, 398
gross pathology of, 399
histopathology of, 399
profile of, 399
Retina, immunohistology profile of, 117t
Retinoblastoma, 26t, 374, 623–625, 624b, 625t
biological behaviour of, 374
cellular origin of, 374
clinical features of, 624, 625f
diagnostic confirmation of, 624
gross pathology of, 374
management of, 624–625
profile of, 374
prognosis of, 625
Retinoblastoma gene (Rb), 5
Retinoids, for squamous cell carcinoma, 579
'Review,' concept of, 112
R-Gel systems, stable, 141
Rhabdomyoma, 674–676, 675b
biological behaviour of, 308
cellular origin of, 308
clinical features of, 675
description of, 674–675
diagnostic confirmation of, 676
gross pathology of, 308
histopathology of, 308–309
immunohistochemical labelling of, 308–309
management of, 676
profile of, 308
Rhabdomyosarcoma, 674–676, 675b
alveolar, 309
biological behaviour of, 309
botryoid ('grape-like'), 309
cellular origin of, 309
clinical features of, 675, 675f
description of, 674–675
diagnostic confirmation of, 676
differential diagnoses of, 310b
Rhabdomyosarcoma (*Continued*)
electron microscopy of, 310
embryonal, 309
gross pathology of, 309
histopathology of, 309–310
immunohistochemical labelling of, 309–310
management of, 676
pleomorphic, 309
profile of, 309
Rhodamine, 114
Röntgen, Wilhelm Conrad, 4–5
Rostral mandibulectomy, for equine juvenile mandibular ossifying fibroma, 446
Rous, Francis, 4
'Rous sarcoma', 4
Routine haematological analyses, of gastrointestinal neoplasia, 458–459
Ruthenium-106, for brachytherapy, 180t

S

Safety issues, in chemotherapy, 163–165
Salivary adenocarcinoma, 448–449, 449b, 449f
Salivary gland(s)
adenoma and adenocarcinoma of
biological behaviour of, 260
cellular origin of, 260
gross pathology of, 260
histopathology of, 260
profile of, 260
neoplasia of, 448
Sanguinaria canadensis, extracts of, 195
Sarcoid(s), 4f, 86, 203–219, 288, 440–442, 440b, 545–546, 545b, 545f
associated lesions of, 212
biological behaviour of, 210–211
biopsy and, 210–211
bovine papillomavirus in, 203–205, 205b
cellular origin of, 203
clinical features of, 440–441, 441f, 546
clinical implications of, 546
commonly affected sites, 209–210
contagion of, 421–422, 422f
description of, 440
diagnostic confirmation of, 441, 554–555
differential diagnoses of, 217b, 441
diffuse verrucose, topical treatment for, 155f
electron microscopy of, 217
experimentally infected with, 206–207
fibroblastic, 212, 550–552, 550t, 551f–552f
general comments on, 560
genetic risk factors of, 205–206
gross pathology of, 211–213
histopathology of, 213–217, 214f–216f
immunohistochemical labelling of, 216
in immunohistochemical staining, 115t
immunological treatment of, 188
likelihood and nature of recurrence of, 210
local, 62
malignant, 212, 553–561, 553f–554f
mammary, 649–650, 649b, 650f
management of, 441–442, 442b, 555–560
benign neglect in, 555–556, 556f
chemotherapy in, 558–559
electrochemotherapy in, 559
immunological methods in, 559–560
intralesional anti-mitotic/cytotoxic chemicals in, 559
palliative treatment in, 556
photodynamic therapy in, 559
phytotherapy in, 559
radiation methods in, 560, 560f
surgical methods in, 556–558
treatment considerations in, 555, 555b, 555f
treatment methods in, 555–560
mixed, 552–553, 553f
verrucose, nodular and fibroblastic, 212, 212b
molecular diagnostics of, 217
nature of recurrence of, 210f
nodular, 211–212, 548–549, 548t
type A, 549f
type B, 550f
occult, 211, 211b, 213, 215f, 546–547, 547b, 547f
oncogenesis of, 203–209
oral papilloma and, 452
penile and preputial, 633–634, 633b, 634f
Sarcoid(s) (*Continued*)
periocular, nodular, and fibroblastic, University of Liverpool protocol for, 190b
profile of, 203
prognosis of, 442, 561
regression of, 210
trauma and, 206, 206f
types of
variations in proportions of, 212
viral activity of, relationship of, 212–213
verrucose, 211, 211b, 547–548, 547f
Sarcoma(s), 460, 460b
anaplastic. *see* Anaplastic sarcoma
immunohistochemical profile of, 115
perirenal, 662f
Scarring, in sarcoid, 442
SCC. *see* Squamous cell carcinoma (SCC)
SCCIS. *see* Squamous cell carcinoma in situ (SCCIS)
Schistosoma spp., 46
Schwann cell tumours. *see* Granular cell tumours
Schwannoma(s), 202, 299–300, 562–563, 610–611
Scintigraphy, 104
gamma. *see* Gamma scintigraphy
Sebaceous gland
adenoma and carcinoma of
biological behaviour of, 255
cellular origin of, 254
gross pathology of, 255
histopathology of, 255
immunohistochemical labelling of, 255
profile of, 254–255
tumour/carcinoma, 580–581, 580b, 580f
Second growth phase (G2), 23f
Secondary hepatic neoplasms, 470, 471t
'Secondary necrosis', 33–34
'Seed and soil' theory, 4
Seminoma, 18, 399–400, 635–637, 636b, 637f
associated lesions, 400
biological behaviour of, 399
cellular origin of, 399
gross pathology of, 399–400
histopathology of, 400, 400f
immunohistochemical labelling of, 400
metastasis of, 399
profile of, 399
Senescence, 29, 37f
cellular, 37
replicative, 37
Sequential mutation, 25
Serology, as diagnostic aid, 425
Serous cystadenoma. *see* Ovarian cystadenoma
Sertoli cell tumour, 397–398, 638, 638b
biological behaviour, 397–398
cellular origin of, 397
gross pathology of, 398, 398f
histology of, 398
immunohistochemical labelling of, 398
profile of, 397
Sertoli-Leydig cell tumour of ovary, 398
biological behaviour of, 398
cellular origin of, 398
histopathology of, 398
profile of, 398
Serum biochemistry, of haemangiosarcoma, 516
Serum enzyme variations, 93
Sézary syndrome, 350
Silver nitrate, for equine sarcoids, 559
Silver staining, of orbital paragangliomas, 389
Simpler 192-iridium interstitial brachytherapy, for squamous cell carcinoma, 440
Single bronchogenic granular cell tumour, 65
Single mutation, 25
Single photon emission computed tomography (SPECT), 104
Sinonasal adenocarcinoma
biological behaviour of, 257
cellular origin of, 257
differential diagnoses of, 258b
gross pathology of, 257
histopathology of, 258
immunohistochemical labelling of, 258
profile of, 257
Sinonasal adenoma
biological behaviour of, 257
cellular origin of, 257

Sinonasal adenoma (*Continued*)
gross pathology of, 257
histopathology of, 257
immunohistochemical labelling of, 257
profile of, 257
Sinonasal region
fibrosarcoma, 487
haemangiosarcoma, 487
neuroendocrine tumour/neuroblastoma/extra-adrenal paraganglioma, 486–487
tumours in, 486–487
Sinus adenocarcinoma, 484f
Skeletal muscle
atrophy of, pituitary adenoma and, 377
neoplasms, 305–311
of tumours, 674–676
Skeletal neoplasms, 312–321
Skin
melanocytic neoplasms in, 238
pituitary adenoma and, 380
squamous cell carcinoma of, 229–230
tumours of, 9, 544–584
basal cell carcinoma, 563–564, 563b, 564f
fibroma and fibrosarcoma, 561, 561b, 562f
keratoma, 582–583, 582f, 583b
lipoma, 567–568, 567b, 568f
malignant fibrous histiocytoma, 566–567, 566b, 567f
mastocytoma, 564–566, 565f
melanoma and melanosarcoma, 568–575, 568b
neurofibroma, 562–563, 562b, 563f
sarcoid, 545–546, 545b, 545f
sebaceous gland tumour/carcinoma, 580–581, 580b, 580f
squamous cell carcinoma, 575–580, 575b
sweat gland tumour, 581, 581b
trichoepithelioma, 581–582, 581b, 581f
Skin syndromes, 71
'Skin tags,' oral papilloma and, 452
Slowly-transforming viruses, 46
Smart surgery, 122–124
advantages and disadvantages of, 124
method of, 122–124, 123f
precautions and hazards of, 124
for sarcoid, 441
Smegma
in penile squamous cell carcinoma, 630
in squamous cell carcinoma of male genitalia, 221
Smooth muscle
neoplasms, 305–311
tumours, 465–467
lipoma, 465–467
Soft-tissue origin, neoplasia of, 436–449
equine juvenile mandibular ossifying fibroma, 445–447
melanoma, 442–444
myxomatous neoplasms of the jaw and gingivae, 447–448
oral fibroma/fibrosarcoma, 444–445
oral haemangiosarcoma, 448
salivary adenocarcinoma, 448–449
sarcoid, 440–442
squamous cell carcinoma, 437–440
'Soil and seed' hypothesis, 55, 58f
Solar elastosis, 223
Somatic cells, replication of, 33f
Space-occupying effects, of benign tumours, 65
Specialist radiologist, 175
S-phase (synthesis), during DNA replication, 23–24, 23f
Spinal canal, melanoma within, 63f
Spleen, neoplasia of, 470–473
haemangiosarcoma, 472–473
lymphoma, 470–472
Splenic lymphoma, 470–472, 470b
case reports of, 471t
clinical features of, 471, 472f
description of, 470
diagnostic confirmation of, 471–472
management and prognosis of, 472
Splenic lymphosarcoma, 349–350
biological behaviour of, 350–351
gross pathology of, 351
histopathology of, 351, 351f
profile of, 350
Splenic primary tumour, 661f
Spread/run-off, topical treatments, in chemotherapy, 139–140
Squamous cell carcinoma (SCC), 9, 66, 67f, 220–236, 419–420, 420f, 437–440, 437b, 575–580, 575b
aetiological factors of, 221–222
of alimentary tract, 230–232
biological behaviour of, 231
differential diagnoses of, 232b
gross pathology of, 231–232
histopathology of, 232
ameloblastoma and, 325
cellular origin of, 220
cellular pathways of, 222
clinical features of, 437–438, 576–579, 576f–578f
description of, 437
destructive, 577f
diagnostic confirmation of, 438–439, 579
differential diagnoses of, 438
of external genitalia, 228–229
biological behaviour of, 228–229
differential diagnoses of, 229b
gross pathology of, 229
histopathology of, 229
metastasis of, 229
of eye, 614–618, 614b
clinical features of, 614–616, 615f–616f
diagnostic confirmation of, 616
differential diagnosis of, 615–616, 616b
management of, 616–617, 617b
prognosis of, 618
of eye and ocular adnexal tissues, 225–228, 226f–227f
biological behaviour of, 225–227
differential diagnoses of, 227–228, 228b
gross pathology of, 227
histopathology of, 227, 228f
metastatic rate of, 226–227
recurrence rates of, 226
survival time in, 226
gastric, 459–460
grading of, 223–225
gross pathology of, 223
highly invasive, 227
histopathology of, 223–225, 224f
immunohistochemical labelling of, 225
mammary, 648–649, 648b
management of, 439–440, 579–580
metastasis of, 223
occurrence of, 437, 437f
oncogenesis of, 220–222
pathology of, general and site-specific, 222–234
penile, 630–632, 630b
clinical features of, 630–631, 630f–631f
description of, 630
diagnostic confirmation of, 631
management of, 632
prognosis of, 632
'precursor lesions' of, 220–221, 223
prevention of, 580
profile of, 220
prognosis of, 440, 580
rare sites of, 234
of respiratory tract, 232–233
biological behaviour of, 233
differential diagnoses of, 234b
gross pathology of, 233
histopathology of, 233
secondary lesions of, 225, 225f
of skin, 229–230
biological behaviour of, 230
differential diagnoses of, 230b
histopathology of, 230
solar-associated lesions of, 223
of tongue, 450–452, 450b
clinical features of, 450–452, 451f
description of, 450
diagnostic confirmation of, 452
differential diagnoses of, 450–452
management and prognosis of, 452
of upper and lower respiratory tract, 482–483, 482b
clinical features of, 482, 483f
diagnostic confirmation of, 482–483
Squamous cell carcinoma (SCC) (*Continued*)
differential diagnoses of, 482
management of, 483
prognosis of, 483
of urinary bladder, 233–234
biological behaviour of, 234
differential diagnoses of, 234b
gross pathology of, 234
histopathology of, 234
vulvar and clitoral, 639–640, 639b, 639f
Squamous cell carcinoma in situ (SCCIS), definition of, 220–221
Squamous dysplasia, pre-carcinomatous, 576f
Squamous papilloma
non-viral
biological behaviour of, 250–251
cellular origin of, 249
gross pathology of, 251
histopathology of, 251, 251f
oncogenesis of, 250
profile of, 250
viral. *see* Viral squamous papilloma
Staging, of tumours, 19–22
Ann Arbor, 21–22
TNM, 19–21
Stem cells, 406
tumour, in chemotherapy, 130
Stem or progenitor cell neoplasms, 406–411
hepatoblastoma, 407–408
malignant rhabdoid tumour, 410
medulloepithelioma, 411
nephroblastoma, 409–410
olfactory neuroblastoma, 411
pineoblastoma, 411
pleuropulmonary blastoma, 408–409
primitive neuroectodermal tumour, 410–411
pulmonary blastoma (biphasic), 408–409
teratoma and teratocarcinoma (placental), 406–407
Steroids, use of, in equine, 137
Stroma, 18
Stromal micro-environment of a tumour, 52–53
Strontium-90, 185, 185f
for brachytherapy, 180t
hazards and safety of, 185
Subchondral bone cysts, 322
Subcutaneous lymphosarcoma
biological behaviour of, 349
gross pathology of, 349–350
histopathology of, 350
profile of, 349
'Summer sores', 227
Surface brachytherapy, 184–185
Surgery
for cutaneous lymphoma, 534
for equine juvenile mandibular ossifying fibroma, 446
for haemangioma/vascular hamartoma/cavernous haemangioma, 513
for melanoma, 444
for multicentric lymphoma, 526
for oral haemangiosarcoma, 448
for osteochondroma, 669
for penile squamous cell carcinoma, 632
for progressive ethmoidal haematoma, 492
for rhabdomyoma, 676
for sarcoid, 441
for squamous cell carcinoma, 439–440
for temporal teratoma, 436
for thyroid adenoma, 590
Surgical ablation, in squamous cell carcinoma, 579
Surgical debulking, of pulmonary granular cell tumour, 500–501
Surgical diathermy, 125–126
Surgical en bloc resection, for epidermal inclusion cyst, 488
Surgical excision
for equine juvenile mandibular ossifying fibroma, 446
for equine sarcoids, 556–557, 557f
for haemangiosarcoma, 518
for lip melanoma, 444
for myxomatous neoplasms of jaw and gingivae, 447
for salivary adenocarcinoma, 449

Surgical methods, for squamous cell carcinoma of eye, 617, 617b
Surgical resection, of pulmonary granular cell tumour, 501
Sustentacular cell tumour. *see* Sertoli cell tumour
Sustentacular (type 2) cells, orbital paragangliomas and, 389
Suture line osteitis, 322–323
Swabs, superficial, for sarcoid diagnosis, 555
Sweat gland tumour, 581, 581b
Swedish Halfbreds, sarcoid risk for, 206
Swiss Warmblood horses, sarcoid risk for, 206
Sympathetic paraganglia, 387
Syntaxin-17 gene, identification of genetic mutation in, 201
Syntaxins, 238
Systemic chemotherapy, 137–138
  for cutaneous lymphoma, 534–535
  for multicentric lymphoma, 526–528, 527b, 527t

T

Tachycardia, in gastrointestinal neoplasia, 458
Tasmanian devil *(Sarcophilus harrisii)*, 59
Tazarotene, 139
T-cell lymphoma, formalin preserved of, 114f
T-cell rich B-cell lymphosarcoma, 343
  of liver, 344f
T-cell therapy, 187
Teletherapy, 178–179, 180t
  for squamous cell carcinoma, 440
Telomerase, 205
Telomeres, 32
  cellular responses to, 32f
Temporal teratoma, 436, 436f
  biological behaviour of, 329–330
  classification of, 329
  histopathology of, 330
Teratocarcinoma, 402–403
  amniotic, 406–407
    histopathology of, 407
  biological behaviour of, 402–403
  cellular origin of, 402
  gross pathology of, 403
  histopathology of, 403
  placental, 406–407
    biological behaviour of, 406
    cellular origin of, 406
    differential diagnoses for, 407, 407b
    gross pathology of, 406–407
    histopathology of, 407
    nodules of, 407
    oncogenesis of, 406
    profile of, 406
  profile of, 402
  testicular, 635, 635b, 636f
Teratoma
  nephroblastoma and, 410
  ovarian or testicular, 401–402
    biological behaviour of, 402
    cellular origin of, 401
    differential diagnoses for, 402b
    gross pathology of, 402
    histopathology of, 402
    oncogenesis of, 402
    profile of, 401–402
  placental, 406–407
    biological behaviour of, 406
    cellular origin of, 406
    differential diagnoses for, 407, 407b
    gross pathology of, 406–407
    histopathology of, 407
    nodules of, 407
    oncogenesis of, 406
    profile of, 406
  temporal. *see* Temporal teratoma
  testicular, 635, 635b, 636f
Testicle, tumours of, 634–638
  interstitial (Leydig) cell tumour, 637–638, 637b
  seminoma, 635–637, 636b, 637f
  Sertoli (sustentacular) cell tumour, 638, 638b
  teratocarcinoma, 635, 635b, 636f
  teratoma, 635, 635b, 636f
Testicular leiomyosarcomas, bilateral, 307
Testosterone, 95t
  granulosa cell tumour and, 394–395
Therapeutic ratio, of radiation, 172–174, 172f–174f
Thermal therapy, 127
Thermotherapy, 127
Third eyelid resection, for squamous cell carcinoma of eye, 617
Thoracic cavity, neoplasia of, 499
Thoracic lymphosarcoma
  biological behaviour of, 348–349, 348f
  gross pathology of, 349
  histopathology of, 349
  profile of, 348
Thoracic radiography
  of lymphoma, 505
  of thymic tumours, 502–503
Thoracic ultrasonography
  of lymphoma, 505
  of thymic tumours, 502
Thoracocentesis, 97–98
  of haemangiosarcoma, 516
  of lymphoma, 505
  of mediastinal/thoracic/thymic lymphoma, 532
  of mesothelioma, 503
  of thymic tumours, 502–503
Thoracoscopy
  of lymphoma, 505
  of mediastinal/thoracic/thymic lymphoma, 532–533
Thorax, epithelial neoplasm of, 263–265
Thrombocytopaenia, 77, 91, 100t
Thrombocytosis, 77, 91
Thrombosis, 68
Thymic lymphosarcoma
  biological behaviour of, 348–349, 348f
  gross pathology of, 349
  histopathology of, 349
  profile of, 348
Thymic tumours, 501–506, 501b
  clinical features of, 502, 502f
  description of, 501–502
  diagnostic confirmation of, 502–503
  differential diagnoses of, 502
  lymphoma, 503–506
  management and prognosis of, 503
  mesothelioma, 503
Thymoma
  biological behaviour of, 263
  cellular origin of, 263
  differential diagnoses of, 263b
  gross pathology of, 263
  immunohistochemical labelling of, 263
  profile of, 263
Thyroid adenocarcinoma, 590–591, 590b, 591f
Thyroid adenoma, 587–590, 588b
  and carcinoma, 380–382
    biological behaviour of, 380
    cellular origin of, 380
    gross pathology of, 380, 381f
    histopathology of, 381–382, 381f
    immunohistochemical labelling of, 382
    profile of, 380
  clinical features of, 588–590, 589b, 589f
  diagnostic confirmation of, 590
  management of, 590, 590b
  prognosis of, 590
Thyroid carcinoma, 52f
Thyroid C-cell adenoma and carcinoma, 382–383
  biological behaviour, 382
  cellular origin of, 382
  differential diagnoses for, 383b
  electron microscopy in, 383
  gross pathology of, 382
  histopathology of, 382–383, 383f
  immunohistochemical labelling of, 383
  profile of, 382
Thyroid gland
  neoplasia of, 586–591
    adenocarcinoma in, 590–591, 590b, 591f
    adenoma in, 587–590, 588b, 589f
  tumours of, 591–593
  unilateral enlargement of, 15f
Thyroid storm, 591b
Thyroid transcription factor1 (TTF-1), 382
Thyroid ultimobranchial remnant neoplasms, 383–384
  biological behaviour of, 383
  cellular origin of, 383
  gross pathology of, 383
  histopathology of, 383–384
  immunohistochemical labelling for, 384
  profile of, 383
Tissue
  column of, 88
  fixatives, 90
  sampling of, 87–93
  type of, in tumours, 62
  wedge of, 88–89
TNM tumour staging, 19–21
  measured/assessed parameters, 20–21
Tongue, neoplasia of, 449–452
  case reports of, 450t
  squamous cell carcinoma of, 450–452
Topical chemotherapy, 139–140, 140b
  for ameloblastoma, 433
  poor cosmesis/functional outcome, 140
  shallow/limited absorption and poor or uncertain intralesional distribution within the tumour, 140
  spread/run-off, 139–140
Topical cytotoxic chemicals, for sarcoid, 442
Topoisomerase inhibitors, 135–137
Total protein assay, 98–99
Total white cell counts, elevated, 91–92
Toxic by-products, as laser surgical excision disadvantage, 125
(T)p53 gene, 26–28, 26f, 26t, 28f
  homozygous loss of, 27
  mutation of, complex, 30f
  role of, 27–28
Tracheal neoplasia, 498–499
Transabdominal/transrectal ultrasonography, of hepatosplenic/splenic lymphoma, 535–536
Transcoelomic spread, 59
Transitional cell carcinoma, in renal pelvis, 273
Transplantation, in metastasis, 59
Trauma, role in sarcoid development, 206, 206f
Trials design, cancer cases and, 418
Trichoblastoma. *see* Basal cell tumour
Trichoepithelioma, 581–582, 581b, 581f
  biological behaviour of, 253
  cellular origin of, 253
  differential diagnoses of, 254b
  gross pathology of, 253
  histopathology of, 253–254
  immunohistochemical labelling of, 254
  profile of, 253
Triglyceride concentration elevations, 93
True ameloblastoma, 432
TTF-1. *see* Thyroid transcription factor1 (TTF-1)
Tumoral calcinosis, 323
Tumour cells
  in ameloblastic carcinoma, 325
  in ameloblastoma, 325
  in anaplastic malignant melanomas, 243
  in anaplastic sarcoma, 292
  arrest in capillary bed site in remote organ/tissue, 56–57
  in basal cell tumour, 252
  in bronchioloalveolar carcinoma, 264
  in cellular blue naevus, 242
  in cholangiocellular carcinoma, 271
  in chondromas, 320
  in chondrosarcomas, 320–321
  in dermal melanomas and melanomatosis, 243
  in endometrial adenocarcinoma, 277
  epithelial, 324–325
  in epitrichial (apocrine) sweat gland, adenoma and carcinoma of, 254
  in exocrine pancreatic adenocarcinoma, 268
  in fibroblastic, and supporting stroma, arrangements of, 213, 214f
  in fibroma, 286
  in fibrosarcoma, 288
  in giant cell tumour of soft parts, 291
  in granular cell tumours, 302–303
  in haemangioma, 334
  in haemangiopericytoma, 290
  in haemangiosarcoma, 336
  in hepatocellular carcinoma, 270

Tumour cells (*Continued*)
immunohistology profile of, 117t
in intestinal adenocarcinoma, 267
in intradermal common melanocytic naevus, 242
in leiomyoma and fibroleiomyoma, 306
in leiomyomatosis, 307
in leiomyosarcoma, 308
in liposarcoma, 296
in lymphangioma, 337–338
in lymphangiosarcoma, 339
in mammary gland adenocarcinoma, carcinoma and adenoma, 261
in melanocytic naevi, 241–242
in mesothelioma, 282
migration, active, 50–51
in myofibroblastic tumours, 289
in myxomatous neoplasms of jaw, 315
in osteosarcomas, 318
in papillary cystadenocarcinoma, 276
in peripheral nerve sheath tumours, benign and malignant, 300
in primary retroperitoneal tumour, 293
proliferation rate, altered, 51–52
in renal carcinoma/adenoma, 273
in rhabdomyoma, 308
in rhabdomyosarcoma, pleomorphic, 309
in sinonasal adenocarcinoma, 258
in squamous cell carcinoma, 223, 224f
in urinary bladder transitional carcinoma and adenoma, 274
Tumour lysis syndrome, 74–75, 281
Tumour marker(s), 104–107
detection of, 93
immunochemistry, as diagnostic aid, 425
Tumour 'seeding', 123–124
Tumour stem cells, in chemotherapy, 130
Tumour suppressor gene, in sarcoids, Fragile Histidine Triad (FHIT) study of, 205
Tumour(s)
of alimentary tract and abdominal cavity, 429–479
angiogenesis, 49
Ann Arbor staging of, 21–22
antigens, reduced expression of, 35
assessment of, 122–124
activity and behaviour in vitro and in vivo, 18–22
basal cell. *see* Basal cell tumour
benign, 12t, 13–18, 14f
functional endocrine, 13–14
bronchial granular cell, 502f
cancerous and benign, 8
of cardiovascular system, 512–543
clinical effects of, 67f
clinical examination of, 85
clinical features of, 68f
clinical signs and consequences, 62–65
crab-like appearance of, 4f
defined, 11–12
detection of molecules, for targeted therapy, 117
development
factors that promote, 46–47
role of calreticulin in, 36–37
differential diagnoses of, 66–68
differentiation by, in immunohistochemical staining, 115t
duration of, 66
of endocrine system. *see* Endocrine system, tumours of
epidemiology of, 416–418
of eye, 613–628, 614t
fibro-osseous, 321
fibrous, 285–289
functionality of, 66
gastrointestinal stromal, 117
genetic/clonal origin of, 11
giant cell. *see* Giant cell tumour
grading, 18–19, 19f
granular cell. *see* Granular cell tumours (GCTs)
growth of, 60
biology of, 23–61
identification of most representative, 87
interstitial (Leydig) cell. *see* Interstitial (Leydig) cell tumours
Tumour(s) (*Continued*)
intraocular, 117
invasion, 50–53
iridociliary epithelial. *see* Iridociliary epithelial tumour
isolation of base of, 122
ligation of, 127–129, 128f
lipocytic (adipose), 294–296
location of, 64–65, 177
malignant, 11, 12t, 13–18, 14f
mast cell, 89f, 94t–95t, 485
metastatic, 115–117, 116f, 117t
spread of, major steps in, 56f
thoracic, 506–507
minor expansion of, 63
of musculoskeletal system, 664–679, 665b
mutation-selection theory of progression, 48f
myofibroblastic. *see* Myofibroblastic tumours
of nervous tissue. *see* Nervous tissue, tumours of
of neuroendocrine system. *see* Neuroendocrine tumours
nomenclature, 11–22
number of, 65
open/ulcerated, 122
ovarian. *see* Ovarian tumours
parameter of, 15f
physical appearance of, 68–69
pre-carcinomatous/dysplastic, 16f
prevalence of, 9t
primary, development of metastasis from, 53f
primary thoracic, 499–501
prognosis of, 12, 14f
progression and proliferation of, 47–53
angiogenesis, 48–50, 49f
pulmonary granular cell, 500–501
radio-sensitive, 173, 173f
range of, 85
rate of progression of, 423–424
sharp excision of, 120–122, 121f
advantages in, 120–121
disadvantages in, 121
in sinonasal region, 486–487
size/extent of, 62–63
of skin. *see* Skin, tumours of
smooth muscle, 465–467
specific nature and pathological behaviour of, 65–66
staging, 19–22
suppressor genes, 25
role of, 26t
surgical reduction of, 131–133
surveys of, 86
thecal cell, 117
thymic, 501–506
tissue type and, 62
treatment of, 12
type of, 176–177
ulceration and infections in, 67
of upper and lower respiratory tract, 480–511
of urinary tract, 652–663
uveal melanocytic, anterior, 239
volume of, 177
Wilms', 409
'Two-hit hypothesis', 39f
see also Knudson hypothesis
Type 1 fibroblastic sarcoids, 212
Type 1a fibroblastic sarcoids, 212
Type 1b fibroblastic sarcoid, 212
Type 2 fibroblastic sarcoids, 212
Type A nodular sarcoids, 211
Type A1 nodules, 211
Type A2 nodules, 211
Type B nodular sarcoids, 211
Type B1 nodules, 211
Type B2 nodules, 211
Tyrosine kinase (KIT) inhibitor, 117

U

Ulcerated mass, on rostral mandible, 446f
Ulceration, tumours and, 67–68
Ulcerative coronitis, 80
Ultimobranchial adenoma, 592
Ultrasonography, 93–97, 97f
of abdomen, 530
advantages of, 96f
in angiosarcoma, 520
Ultrasonography (*Continued*)
in cutaneous lymphoma, 534
in dysgerminoma, 646
in granulosa cell tumour, 641–643, 642f
in granulosa theca cell tumours, 96f
in interstitial cell tumour, 638
in leiomyoma, 640
in mediastinal/thoracic/thymic lymphoma, 532
in nasopharyngeal/laryngeal neoplasia, 498
in orbital paraganglioma, 597
in osteochondroma, 669
in ovarian lymphoma, 647
in renal carcinoma, 656
in rhabdomyoma, 676
in seminoma, 637
in thyroid adenocarcinoma, 591, 591f
transrectal, in bladder carcinoma, 660
Ultrasound guided biopsy, of thymic tumours, 503
Ultraviolet light radiation, 221
Unicameral bone cysts, 322
'Unicorn syndrome', 322–323
University of Liverpool, protocol for periocular, nodular, and fibroblastic sarcoids, 190b
Unusual 'tumour' of odontogenic epithelial origin, 455f
Upper airway neoplasia, 480–486
adenocarcinoma, 483–485
clinical features of, 480–481
diagnostic confirmation of, 481
management of, 481–482
mast cell tumour (intranasal), 485
myxoma, 485–486
prognosis of, 482
squamous cell carcinoma, 482–483
Ureteral neoplasia, 657–658
Urinalysis, for renal carcinoma, 655–656
Urinary bladder
squamous cell carcinoma of, 233–234
transitional carcinoma and adenoma of
biological behaviour of, 274
cellular origin of, 273
differential diagnoses of, 274, 274b
gross pathology of, 274
histopathology of, 274
immunohistochemical labelling of, 274
oncogenesis of, 273–274
profile of, 273
Urinary tract, tumours of, 652–663, 652b, 653t–654t
bladder carcinoma, 658–661, 658b
renal carcinoma/adenocarcinoma, 652–657, 652b, 657f
secondary, 661–662
ureteral neoplasia, 657–658
Uterine haematomas, endometrial adenocarcinoma and, 277
Uterine leiomyoma, 306
UV-B light, as carcinogen, 44–45
Uveal cyst, anterior, squamous cell carcinoma and, 228
Uveal melanocytic tumours, anterior, 239

V

Vaccination, against cancer, 188
Vaccines (autogenous)
for dermal melanoma, 574
for equine sarcoids, 559
Vascular endothelial growth factors (VEGFs), 52
Vascular hamartoma, 340
see also Haemangioma
Vascular ligation, 127–129, 128f
Vascular masses
neoplastic, 332–339
angiosarcoma, 339
haemangioma, 332–334
haemangiosarcoma, 334–337
lymphangioma, 337–338
lymphangiosarcoma, 338–339
non-neoplastic, 340
haemangiomatosis, 340
hamartoma, 340
intravascular papillary endothelial hyperplasia, 340

Vascular naevus. *see* Haemangioma
Vascular neoplasia, 512–522
  angiosarcoma, 519–521
  haemangioma/vascular hamartoma/cavernous haemangioma, 512–514
  haemangiosarcoma, 514–519
  lymphangioma/lymphangiosarcoma, 521–522
Vascular neoplasms, 332–341
Ventricular arrhythmia, 523
Verrucose sarcoids, 211, 211b, 547–548, 547f
Vinblastine, in equine chemotherapy, 158
Vincristine, 137–138
  in equine chemotherapy, 158
  for multicentric lymphoma, 527t
Viral papilloma, 452
Viral squamous papilloma
  biological behaviour of, 248
  cellular origin of, 247
  differential diagnoses of, 250b
  electron microscopy of, 249
  gross pathology of, 248
  histopathology of
Viral squamous papilloma (*Continued*)
    development phase, 249
    growth phase, 248–249
    regression phase, 249, 250f
  immunohistochemical labelling of, 249
  oncogenesis of, 247–248
  profile of, 247
Viruses
  acutely-transforming, 46
  slowly-transforming, 46
Visceral-autonomic paraganglia, 387
Viscum album austriacus, 194
  extract of, protocol for use of, 195t
  remote injection of, 195f

W

Warts, 248
Wasting syndromes, 73–74
Wedge biopsy, 88–89
Weight loss, 421
  in gastrointestinal neoplasia, 458
Western blot, 113–114
White cell counts, elevated total, 91–92
Wilms' tumour, 409
World Health Organization (WHO), clinical staging system for multicentric lymphoma, 526t
Wound(s)
  breakdown, as laser surgical excision disadvantage, 125
  healing, delayed, in radiation therapy, 170
  in squamous cell carcinoma, 221
WT-1 gene, 26t

X

X-ray computed tomography, 101–103
X-rays, 166

Z

Zona fasciculate, 593
Zona glomerulosa, 592
Zona reticularis, 593