Henderson's Orbital Tumors

FOURTH EDITION

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This volume is dedicated to my daughter Holly and in the memory
of my wife Nadine and eldest daughter Sally

JWH

Contents

Preface to the First Edition

Although orbital tumors often are briefly discussed among the tumors affecting the ocular appendages (the eyelids, lacrimal gland, epibulbar structures, caruncle, and lacrimal excretory passages), no publication of textbook size in the English language has been exclusively devoted to this subject for some years. The infrequency of tumors, primary in the orbit, secondarily invading this space, or metastasizing to this area, makes difficult the assembly of meaningful data on the subject and contributes to the dearth of statistical, clinical, and pathologic data on a large series of consecutive cases.

It has, however, been my privilege to be associated with a large group practice for several decades, and this has provided an opportunity to observe a larger number of patients with orbital tumors than is possible in an average private practice of ophthalmology. To record this diagnostic experience, to compare and contrast the behavior patterns of individual tumors to each other and to the clinical symptomatology of the group as a whole, to update the pathologic classification and nomenclature of these tumors, and to detail my own and my colleagues' experience in the treatment of tumors are the purposes of this text. Such data, assembled in one volume, should be useful to graduate students of ophthalmology who seek information about the subject when they first encounter a case of ocular proptosis, and to practicing physicians who may wish to pursue the clinical and pathologic ramifications of any given tumor but find it difficult to locate the widely scattered literature on the subject quickly.

The core of this monograph is a consecutive series of orbital tumors treated and pathologically verified at the Mayo Clinic during a 19-year period, 1948 through 1966. This time interval was chosen for several reasons. First, it corresponded to the period in which I had the most personal contact with patients having orbital tumors. Second, clinical data and pathologic material were better preserved and more complete than for earlier periods. Third, follow-up information was more easily obtained than would have been possible for many of the patients observed at the Mayo Clinic prior to 1948. The last feature, follow-up information, is more peculiar to this survey than to other reported studies of orbital tumors (both larger and smaller numerically than our own). The longer periods of observation have confirmed the expected course of some tumors but have also suggested revision in the assumed clinical course and prognosis based on the more incomplete protocols of other surveys.

My initial plan was to include the orbital manifestations of endocrine exophthalmos and orbital infectious disease as part of the study, but the voluminous research and clinical data associated with endocrine exophthalmos and the time-consuming search for isolated reports of infectious disease were beyond the time limits available to me for the efficient completion of the writing project.

It was also deemed advisable not to include a complete bibliography at the conclusion of each subchapter and to avoid duplication of bibliographic lists already published. Instead, only key references pertinent to the subject under discussion are used throughout the text and these are supplemented with a list of selected references in the Appendix. The Appendix contains data basic to the overall subject and should be useful to both students and graduates who wish to pursue in depth the study of orbital tumors. The selected references are identified by a numerical designation throughout the text.

A venture of this scope, of course, would not be possible without the contributions of many of the personnel and departments ancillary to ophthalmology. Among my professional associates, my chief collaborator, Dr. George Farrow, should first be noted. With dogged determination he traced down the gross and microscopic specimens of many of the tumors in the earlier periods of our survey, carefully reviewed and revised where necessary the histopathologic diagnosis of all tumors described in the text, assembled representative photographs of the various tumors, and gave helpful advice concerning the application of current classifications and nomenclature used in general surgical pathology to the problem of orbital tumors. Also, the text is more comprehensive because of the individual chapters by Dr. Kenneth Devine and Dr. Ross Miller, who graciously tried to adapt their formats to the style of the remainder of the manuscript.

Another close collaborator in the final manuscript was the editor, Dr. David Shephard, who counseled caution on statements in the text that seemed too broad, who buoyed up passages that seemed redundant, who reorganized the format for easier perusal by the reader, and who rephrased many sentences to make their meaning more clear and correct. Dr. Martin Van Herik rewrote some of the discussion on the radiotherapy of infantile hemangiomas to make it more technically compatible with the current concepts of radiotherapeutic physics. Dr. Omer Burgert, Jr., and Dr. Stephen Mills, of the Department of Pediatrics, and Dr. Harry Bisel, of the Division of Clinical Oncology

and Internal Medicine, willingly kept me informed on the practical application of recent advances in the field of chemotherapy relative to many of the malignant tumors of infancy and childhood. Unsolicited and collective collaboration also should be noted from my associates in the Department of Ophthalmology, particularly that of Dr. Roger Neault and Dr. Fenwick Riley, who allowed me to see their patients and shared with me the dilemmas, as well as the discoveries, of orbital diagnosis.

In the earlier stages of this endeavor, Ruth Alexander and Myrna DeWitz, of the Department of Medical Statistics and Epidemiology, were instrumental in the retrieval of case histories and records so necessary for a complete and consecutive study of orbital tumors. Through their intricate search of cross references, all cases with but a remote relation to the problem were assembled in an effort to negate any chance that significant data were overlooked. Mr. Gerald Dreblow, of the Business Office of the Department of Administration, was the successful sleuth in tracking down former patients who would otherwise have been lost for follow-up study. Many of the patients were infants or children when first seen with orbital tumors but, as they passed into adulthood, were lost to further contact through routine channels because of change of name or address. All members of the Mayo Clinic Library, particularly Ruth Mann, helped to trace elusive and rare references.

The team of Kathleen Grutzmacher, Karen Otis, and Bonnie Ronken performed the tedious chore of typing the initial manuscript drafts, keeping an alert eye for mistakes in spelling and syntax. In addition, Miss Grutzmacher, with her usual secretarial efficiency, tended to countless, forgotten details and errands necessary to the preparation of the text. Mr. John Hutcheson and Mr. Robert Benassi, of the Section of Medical Graphics, prepared the several illustrations so appropriate to the subject matter, and almost all members of the Section of Photography, at one time or another, contributed time and effort to the reproduction of photographs and preparation of numerous prints. When the task of writing and editing was completed, Deanna Servick, of the Section of Publications, supervised production of the manuscript and, with the aid of Roberta Flood who typed the copy and verified the references and Nancy Nelson who handled the proofreading, deftly prepared the completed manuscript. The publisher, the W. B. Saunders Company, completed the collaborative teamwork, so necessary for an endeavor of this type, with their usual patience and courteous cooperation.

The text is dedicated to my wife (Nadine) and daughters (Sally and Holly), whose quiet forbearing during evenings and weekends encouraged my work on the manuscript in time that might otherwise have been devoted to family affairs.

In retrospective perusal of the text, I note several shortcomings. Discussions of the diagnostic features and clinical course of other orbital disturbances—such as endocrine exophthalmos and infectious diseases of the orbit (as already noted)—would have been ideal but time was of the essence. As with other physicians who become enmeshed in the writing of texts, the project must be subordinate to the economics of patient care and the myriad administrative affairs of either a private or institutional practice. In this vortex, spare time is a precious commodity.

The first compilation of clinical and biographic data commenced in 1964 and, at that time, a completion data seemed but a few years away; however, this goal soon became almost a mirage. Obsolescence of material during the last year devoted to editing, proofreading, printing, and assembly is a scourge common to this as well as other texts of this scope. Here, it is particularly noticeable in the application to orbital tumors of the rapidly changing field of chemotherapy.

Should I ever again be seized with a restless desire to write a text on any other subject, I vow I will recline on a cushioned chaise longue until the feeling goes away.

J. W. Henderson

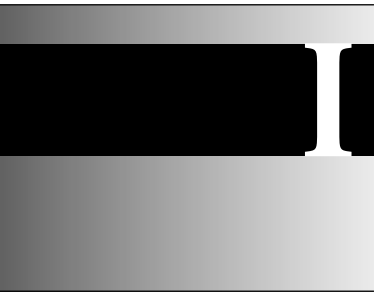
Preface

Dr. John Henderson (JWH) is 93 years old, very much alive, very much alert although only recently starting to slow down. This author (JAG) has had the distinct privilege of working closely with JWH for the past 20 years. This fourth edition of *Orbital Tumors* collates the Mayo Clinic experience in dealing with pathologically verified tumefactions or angiographically proven arteriovenous communications involving the orbit over a 50-year period. While preparing this edition, there were ongoing discussions with JWH concerning various orbital problems, which always incorporated the historical perspective and have been incorporated into the text as appropriate. While diagnostic tools are more robust in the JAG era, this author has been reeducated in the art and craft of a detailed history and a careful examination, a skill set seemingly displaced by the ready availability of neuroimaging. As JWH often mentions, "the patient is telling you the answer to their problem, we just have to hear the answer." This from a clinician who did not have access to the modern neuroimaging we take for granted. We have attempted to resolve this dilemma, as appropriate.

In many instances, a final answer does involve surgery, many aspects of which are surprisingly unchanged over the 50-year period. The fourth edition details some new approaches not described in the earlier editions. We also give patient profiles, treatment recommendations, and an ultimate prognosis for the busy clinician with orbital questions. Our intended target audience includes ophthalmologists, neurosurgeons, plastic surgeons, otorhinolaryngologists, along with interested neurologists and internists. This edition also represents the last effort for JWH. I, for one, will be forever grateful for JWH's wisdom, insight, and advice.

This is also a perfect opportunity to acknowledge the tireless efforts of many whose contributions are vitally important but perhaps not as visible as others. From the Mayo Foundation staff: Marlene Messenger, James Wentz, LeAnn Stee, Roberta Schwartz, Susan Miller, and Jane Wiggs. From the Lippincott staff: Joanthan Pine, Jean McGough, Fran Gunning, and from Laserwords Ann Mary Francis. This book would not have been possible without their help.

Diagnosis of Orbital Tumors



1 Evaluation of the Patient

When the first two editions of this book were written, considerable emphasis was placed on the physical aspects of orbital diagnosis. In particular, the overall appearance of the eye and ocular adnexa, careful palpation of the orbit, and precise exophthalmometry were believed to be important in the initial evaluation of the patient. These features, when combined with the analysis of subjective symptoms and other objective findings, enabled an educated guess of the position and size of an assumed orbital mass. This was the first step in an orderly progression leading to a logical decision about the surgical or nonsurgical management of the problem.

When the third edition was written, the discovery, refinement, and sophistication of radiographic imaging shifted orbital diagnosis toward the realm of technology and away from almost sole reliance on ophthalmologic assessment. The wizardry of imaging makes possible such a positive display of most tumors that even the patient can see the putative orbital mass. The latter has been a tremendous help in establishing an effective communication between the physician and patient, a contrast to former times when dialogue was so frequently based on assumption. Orbital imaging is now so refined that either computed tomography scan or magnetic resonance imaging is an absolute necessity in the patient's workup. However, the clinician should not let these diagnostic tools replace or overshadow the importance of the patient's anamnesis.

THE STORY

Allowing the patient to verbalize the reasons for seeking ocular consultation is the first priority. The ophthalmologist should set aside time to be an attentive and patient listener. Usually, the first sentence or initial paragraph of the anamnesis highlights the symptom or sign of disease most important to the patient. This chief complaint should definitely be kept in mind when all the preliminaries of diagnosis are completed and the physician is ready to propose treatment. Is the patient's main concern a protrusion or displacement of the eye? If so, an "exploratory" orbitotomy, combined with incisional biopsy, may not meet the patient's expectations of relief because the proptosis may still be noticeable postoperatively. Does the patient seek help principally because of loss of vision or diplopia? Here, the necessary surgical management of the orbital problem is likely to worsen the symptoms temporarily. The patient should be advised of these eventualities. Later, this sort of discussion may help maintain a smooth rapport with the patient if recovery is slow. Is the patient's problem fundamentally aesthetic, such as marked edema or discoloration of the eyelids or a disturbing redness of the eye? Such features may forewarn a complex set of events requiring a treatment approach that meets the patient's cosmetic expectations. Finally, the patient may frame the problem as one of pain or headache, as contrasted to the frequent expression of pressure. The latter is but a common manifestation of increased orbital bulk. Relief from pain and headache may require more than one mode of therapy and a greater commitment of time and expense on the part of the patient.

At some point in the evaluation, a discreet inquiry is made about any earlier event that might have a bearing on the current complaint. The patient is usually willing to talk about prior treatment but is often reticent about previous diagnoses. This may enhance the patient's opinion of the objectivity of the physician's forthcoming recommendations.

More direct questioning is reasonable if the current complaint is related to previous surgical procedures. Women should be asked about previous breast surgery, although the interval between the surgery and the current orbital disorder may seem too long to be relevant. The possibility of metastasis is always present in such situations. The

same possibility of metastatic disease also exists in elderly men who have undergone surgery of the prostate gland. In either sex, nasal surgery may presage an unsuspected mucocele or carcinoma that first becomes manifest by secondary invasion of the orbit. A prior thyroidectomy should alert the ophthalmologist either to possible orbital sequelae of Graves orbitopathy with asymmetric features or to occult thyroid carcinoma. Finally, previous biopsy findings from small lymph nodes or lumps might be compatible with orbital spread of lymphoma, neurofibroma, melanoma, squamous cell carcinoma, and adenocarcinoma of various origins. Considering the anatomic size of the orbital cavity, the variety of lesions and tumors that select this small space for a second residence is amazing.

Sometimes, in adults, the story is told by a spouse or a close relative of the patient. Here, the descriptive events may reflect only the opinion of the observer and, therefore, lack the subjective input of the patient. Such patients are often less concerned about their orbital problem than the narrator is and may be less responsive to treatment options. If the outcome of treatment is unsatisfactory, these patients may avoid any responsibility for the event with the statement, "I only did what the doctor told me to do." It may be prudent to defer orbitotomy for a while, unless absolutely necessary, in an adult patient who is mentally competent but does not take an active role in the discussion.

In children, of course, the parent or guardian develops the story. Parents tend to relate the orbital ailment to some previous trauma or minor respiratory illness and to understate the severity and progression of the symptoms. Even direct recall by older children and adolescents may be colored by what they have heard their parents say.

As the interview winds down, keep in mind the patient's age and the pantheon of tumors for the patient's age-group. These tumors are listed in Chapter 3.

Pressure, Headache, and Pain

These subjective manifestations of disease are difficult to assess, whatever their cause and wherever their anatomic location. Fortunately, in a very severe form, they are not a common accompaniment of orbital tumors. The pressure sensation and uncomfortable feeling described by some patients are probably caused by increasing orbital bulk secondary to slowly expanding tumors and cysts. A more severe form of pressure sensation is encountered in patients with progressive exophthalmos of Graves orbitopathy, in which edematous extraocular muscles and retrobulbar tissues shove the eye forward against the constraint of retracted eyelids and the tethering effect of the extraocular muscle. These patients usually say the affected eye "feels as though it will pop." We have seen the most severe forms of this symptom in a few patients whose ocular apparatus ultimately decompensates after a long-standing end-stage bout with an inflammatory tumor. In such patients, the eye of the affected orbit is blind and phthisic, the fibrotic orbital contents are hard and stony, and the pressure sensation is unremitting.

Pain, rather than pressure, from an orbital disorder may also be severe. It tends to be more localized and more or less constant, may have a nocturnal phase, and is not easily alleviated by over-the-counter remedies. If the patient describes the pain as localized to the deep orbit, consider the likelihood of an orbital apex lesion, particularly if there is an associated ocular motility disturbance or dysesthesia in the distribution of the second division of the trigeminal nerve on the side of the affected orbit. Orbital angiitis, an invasive fungal infection, or thrombotic sequelae of an arteriovenous malformation deep in the orbit may mimic this type of pain. A sudden extravasation of blood into the cystic space of a lymphangioma in a child or hemorrhage from a varicocele also fits into this category of pain.

If the pain seems most severe in the nasal or inferior portion of the orbit, think of a possible carcinoma of the ethmoid or maxillary sinus. Numbness of the forehead may accompany infiltration of the supraorbital nerve by a squamous cell carcinoma of the adjacent forehead skin. If the pain is referred to the lateral orbit, be wary of a malignant neoplasm of the lacrimal gland, although such localized pain sometimes accompanies an acute inflammatory process of this structure.

Headache lies somewhere between pressure and pain in intensity, more bothersome than pressure but less severe than pain. It is not easily described by the patient ("the eye just hurts"), is poorly localized, variable in duration and frequency, and often soothed by over-the-counter analgesics. Headache may accompany inflammatory and vasculitic disorders of the orbit sometime during their course. Headache also is a nuisance in patients with orbitocranial meningioma and secondary orbital invasion by a malignant tumor of a paranasal sinus.

Another subjective manifestation that may be the compelling reason for the patient to seek early consultation is "head noise." The patient is startled by the precipitous onset of noise, most commonly described as swishing or pulsating in type or as being synchronous with the heartbeat. Less frequently, the noise is buzzing, blowing, rushing, pumping, or throbbing in type. The noise may be constant, intermittent, or postural (i.e., when standing, sitting, or lying down). Often, the sound is lateralized to the ipsilateral ear.

This noise is a telltale symptom of vascular malformation in the orbit or the intracranial vault just posterior to the orbit. It tends to be more frequent and intense in traumatic arteriovenous fistulas than in the spontaneous type. Surprisingly, the noise may not be audible on auscultation, particularly in spontaneous arteriovenous fistulas. Patients with a dural arteriovenous shunt seldom note head noise, unless the shunt is large or bilateral in extent. A bruit is heard best by auscultation directly over the front of the eye of the affected orbit with the eyelid closed.

Chronology

The rate of progression and overall duration of the patient's presentation are of equal importance in diagnosis. In general, the more rapid the progression, the shorter the interval since onset. The literature that addresses these features usually postulates that lesions with a long interval of presentation are benign, whereas orbital disorders of short duration are more likely to be malignant or inflammatory. This overlooks the fact that, among adults, some patients really do not know how long their disorder has been present. Here, prior photographs may be the only proof of an overlooked proptosis of many years' duration. Such photographs, in some patients, have suggested a duration of 15 to 30 years; but, instead of being benign, such lesions on excision prove to be a malignant degeneration of a long-standing benign process (see Fig. 1.1). A sudden spurt in the amount of proptosis of an otherwise indolent course may also signify the onset of malignancy.

More acute presentations of short duration may also behave contrary to conventional dicta, particularly in children. The child with a bulging eye and red, edematous eyelids of orbital rhabdomyosarcoma of a few days' duration may look strikingly similar to the child with an inflammatory tumor of similar duration. Both lesions can be equally alarming to the parent. The former lesion is malignant, whereas the latter is benign, although potentially aggressive. The inflammatory lesion is associated with pain, but the malignant lesion creates little, if any, discomfort (see Fig. 1.2). A tissue diagnosis should be obtained quickly in these situations and appropriate treatment started, rather than dithering over whether the lesion is benign or malignant on the basis of its dynamics.

In other cases, the presentation may not be acute, subacute, or chronic but instead may wax and wane—sometimes better, sometimes worse. In adults, this behavior suggests one of the inflammatory tumors. A tumor commonly associated with an episodic course in infants and children may also show episodic features, but the triggering mechanism is often an upper respiratory tract infection. The presentation of a mucocele of frontal or ethmoid sinus origin may also undergo transient changes induced by respiratory-like illness. Overall, the literature tends to overstate the importance of the duration of disease in orbital diagnosis.

Figure 1.1 Malignant mixed tumor in a 49-year-old man whose prior photographs indicated a slowly progressive displacement of the left eye of 30 years' duration. The slow progression suggested benignity, but the tumor proved to be a benign mixed tumor that had undergone malignant degeneration. The downward and inward displacement of the eye is usually the result of some lesion of the lacrimal gland fossa.

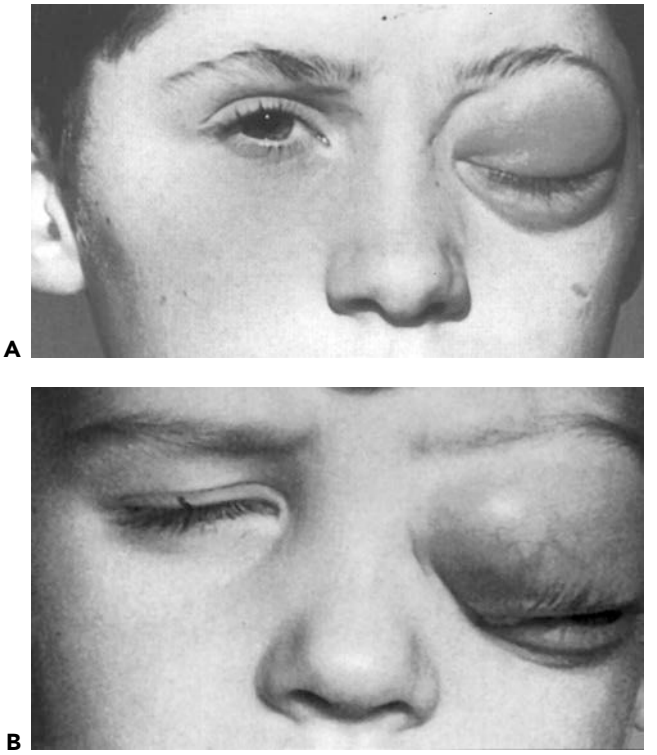


Figure 1.2 Two adolescent males of the same age decade with reddish discoloration, proptosis, and edema of one eyelid of several weeks' duration. The presence of pain in one patient **(A)** (vasculitides, left upper eyelid) but the absence of pain in the other patient **(B)** (rhabdomyosarcoma, left lower eyelid) was a differential point in the presentation of these tumors.

INSPECTION OF THE EYE AND ADNEXA

When discussion with the patient is completed and a written summary recorded, an objective assessment of the orbital ailment is next in importance. Inspection of the eye and adnexal structures should include an assessment of the color and texture of the adnexal tissue and the surface of the eye, measurement of the degree of proptosis, a notation of any disparity in the anatomic relationship of the eye and covering eyelids, and palpation of the orbital rim and soft tissue components of the anterior orbit. These examinations, along with a subsequent analysis of ocular function and motility, were once avenues leading to an educated guess about the position and size of an orbital mass and the nature of the putative disorder. Now, principally because of orbital imaging techniques, determination of size, position, and configuration of a

tumor is no longer a guess; it is a reality. Therefore, the once-important alterations of the external eye and adnexa are now more documentary rather than diagnostic in the overall assessment plan.

Assessment of Proptosis

Exophthalmometry is essential in the initial evaluation of any orbital disorder, although proptosis (forward protrusion) may either not be present or is masked by a droopy or swollen eyelid. In addition, exophthalmometry is important to the patient's record as a baseline for judging the patient's course or response to therapy and is a universal standard of reference for any future correspondence pertaining to the orbital problem.

Some combination of proptosis and displacement of the eye was present in approximately 80% of the cases in a 50-year case series. Exophthalmometry was impractical in some cases because of the removal of the eye on the side of the affected orbit, an ulcerating carcinoma of the periorbital area, an orbital deformity secondary to surgery for recurrent sinus carcinoma, or an orbital deformity associated with fibrous dysplasia or massive neurofibromatosis. Enophthalmos, such as occurs with metastatic scirrhous carcinoma of the breast, is present in $<1\%$ of cases.

Initially, we used the Hertel exophthalmometer to measure the degree of proptosis. For the last 30 years or so, we have used the Krahn modification of the Hertel instrument. The normal values derived with the Krahn device range from 14 to 21 mm in adults. Any value <14 mm can usually be considered diagnostic of enophthalmos. Values >21 mm are encountered occasionally in individuals with a hereditary tendency for prominent eyes or a moderate degree of myopia. A difference of 2 mm or more in the position of one eye relative to the other is noteworthy. All measurements are subject to variables such as asymmetry of the patient's face, shifting position of the exophthalmometer, or strabismus of one eye. The physician may use any exophthalmometer that is practical as long as the method of measurement and positioning of the physician in relation to the patient's eyes are kept constant. In children, the use of an exophthalmometer may not be possible. In such cases, unilateral proptosis may be determined by looking downward over the brow and noting the relative position of the eyes (see Fig. 1.3).

Bilaterality of an orbital tumor at the time of the patient's visit is not common. The tumors most apt to behave in this manner, excluding Graves orbitopathy, are malignant lymphoma, Wegener granulomatosis, metastatic carcinoma, and dural arteriovenous communications in adults. In children, keep in mind the possibility of nonvasculitic inflammatory tumor, Langerhans histiocytosis, leukemic infiltrates, and metastatic neuroblastoma. More often, bilaterality occurs later in the course of what initially was a unilateral orbital tumor. External extension across the midline is not uncommon in long-standing sinus carcinoma, esthesioneuroblastoma, orbitocranial meningioma, chondrosarcoma, and fibrous dysplasia. In the systemic neoplasias, multifocal deposits of malignant lymphoma and multiple myeloma may eventually lodge in both orbits.

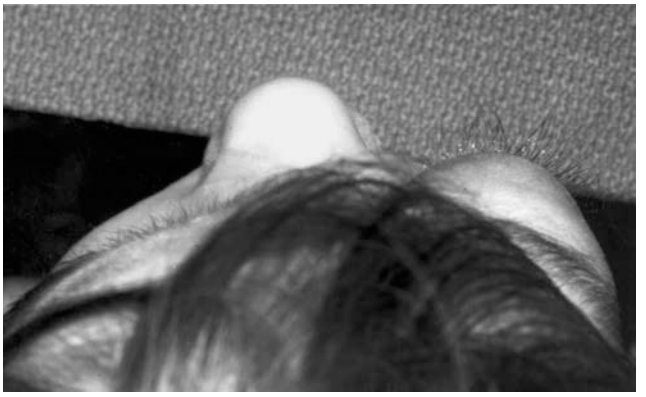


Figure 1.3 Unilateral proptosis in a 22-month-old girl as viewed from above the eyebrow. This is a practical method for the clinical assessment of proptosis in children. The subtle subcutaneous spread of orbital lymphangioma and neurofibromatosis into the tissues of the eyelid and eyebrow may be more clearly documented with a brow view than with a front face photograph.

Displacement of the eye, a shift along a plane other than the normal visual axis, accompanies proptosis. Almost without exception, the direction of displacement is opposite the mass effect of an enlarging tumor. Orbital imaging has relegated assessment of displacement to a documentary rather than a diagnostic role.

There are, however, some infrequent exceptions to the tenet that protrusion of the eye is invariably associated with progression of an orbital tumor. Enophthalmos is one of these. Most often, enophthalmos is secondary to the tractive effect of an infiltrative, sclerosing, metastatic carcinoma of orbital soft tissue (see Fig. 1.4). Other tumors with a

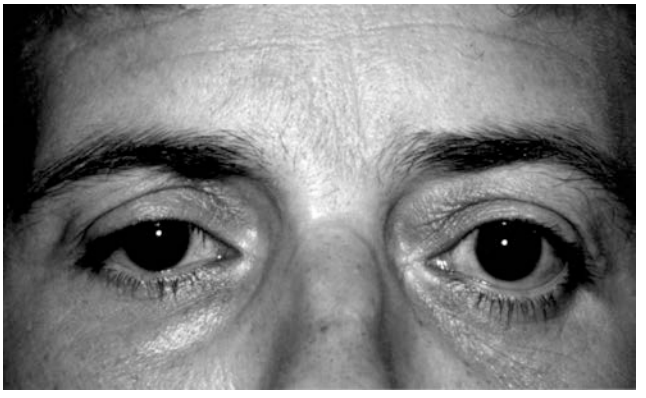


Figure 1.4 Metastatic adenocarcinoma in a 45-year-old woman with blepharoptosis, deepening of the upper lid sulcus, and enophthalmos (5 mm) of the right eye of 3 months' duration. These were first manifestations of metastasis from carcinoma of the breast removed 4 years previously.

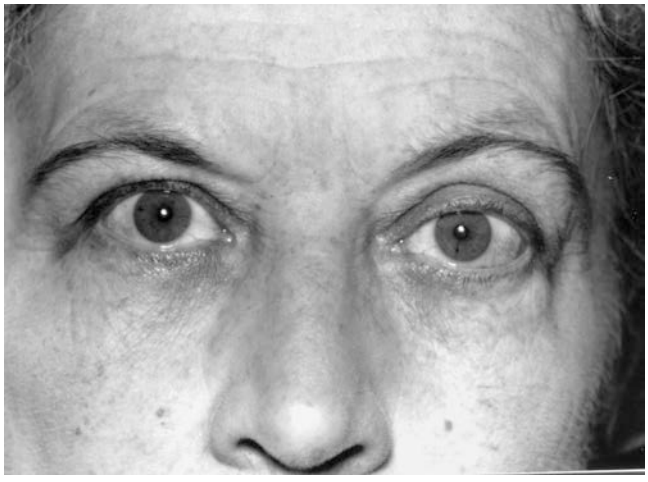


Figure 1.5 A 53-year-old woman with slowly progressive prominence of the left eye since birth had visual acuity of counting fingers, Krahn exophthalmometer readings of R 17 mm and L 20 mm, and high myopia of 20 diopters.

similar effect are squamous cell carcinoma of adnexal origin and Wegener granulomatosis. Enophthalmos may also be secondary to fat atrophy associated with orbital varix or long-standing firm tumors such as cavernous hemangioma and neurofibroma. In these situations, the vertical width of the palpebral fissure may appear normal, but the upper eyelid sulcus is deep and sunken posteriorly.

Rarely, enophthalmos can be overlooked because the patient's complaint and the clinician's attention are focused on the prominence (pseudoproptosis) of the normal eye. In such cases, the enophthalmic eye is usually an orbital manifestation of an unsuspected metastatic carcinoma. Conversely, unilateral pseudoproptosis may be nothing more serious than a slowly enlarging, highly myopic eye (see Fig. 1.5). Finally, there is the example of a tumor pushing out of the orbit rather than dislocating the eye. This is a characteristic mannerism of infantile capillary hemangioma. The tumor's rapid and exuberant growth may even conceal the eye (see Fig. 1.6).

Another exception to the association of displacement and proptosis as a cardinal manifestation of an orbital tumor is the mass that displaces the eye without proptosis. An example is a dermoid cyst attached to the superior bony rim of the orbit just posterior to the orbital septum. To a lesser extent, the exceptions are the carcinomas and lymphomas primary in the eyelid, which finally penetrate the orbital septum into the anterior orbit. Here, the eye is definitely displaced, but proptosis measures only 1 or 2 mm.

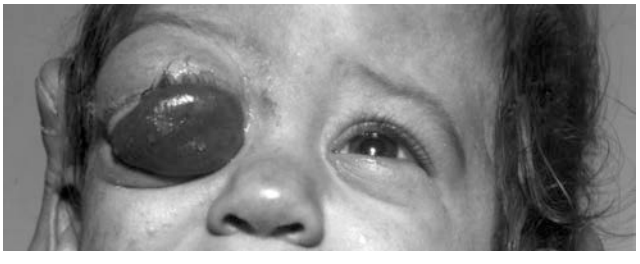


Figure 1.6 A 5-month-old child had rapidly enlarging capillary hemangioma that completely obscured the right eye.

Some proptosed eyes may show abnormal motion. If the movement of the eye is rhythmic and synchronous with the arterial pulse, it is usually called *pulsating exophthalmos*. Most of these cases are associated with traumatic carotid-cavernous fistulas, bony erosion of the orbit associated with neurofibromatosis, fronto-orbital mucoceles, meningoencephalopathy, and postoperative removal of the orbital bony roof. Pulsation may also occur rarely with highly vascular tumors such as capillary hemangiomas, malignant hemangiopericytomas, and metastatic adenocarcinomas. In these disorders, the pulsation is the result of a hemodynamic force transmitted to the eye directly from the orbital mass or indirectly through intervening soft tissue from pulsation of the brain. A nonpulsatile orbital varix may show some pulsation when induced by a Valsalva maneuver.

Bullock and Bartley (1986) reviewed this subject in depth and included an extensive bibliography. They proposed the term *dynamic proptosis* to encompass all these entities.

Finally, there is the type of pulsation associated with a dermoid cyst arising from the synostosis along the lateral orbital wall. The intra- and extraorbital lobes (dumbbell shape) of the cyst erode the lateral orbital wall. Contraction of the temporalis muscle during mastication is transmitted to the eye through the cyst. Knight et al. (1984) named this *chewing oscillopsias*, and Rootman (1988a) called it *bobbing* of the eye.

Tenderness elicited by palpation is an uncommon and unpredictable feature of orbital tumor. The frequent administration of systemic corticosteroids for the treatment of anything that "hurts" has lessened the frequency and diagnostic importance of tenderness. We have encountered it occasionally when palpating a mucocele. This probably indicates a conversion to a pyocele and the need for preoperative antibiotics. Tenderness along the inferior orbital rim may herald an infiltration of the infraorbital nerve by an expanding carcinoma of the maxillary antrum. The association of tenderness with inflammatory tumor is inconsistent. More constant and, perhaps, more noteworthy is the tenderness encountered in some lacrimal gland tumors. This may indicate either an invasion of the periorbita and underlying bone by a malignant process or a compression of nerves by an acute inflammatory process expanding the capsule of the lacrimal gland.

Eyelids

Whether an apparent prominence of one eye is due to asymmetric widening of the palpebral aperture (Graves orbitopathy) or a protrusion secondary to a slow-growing

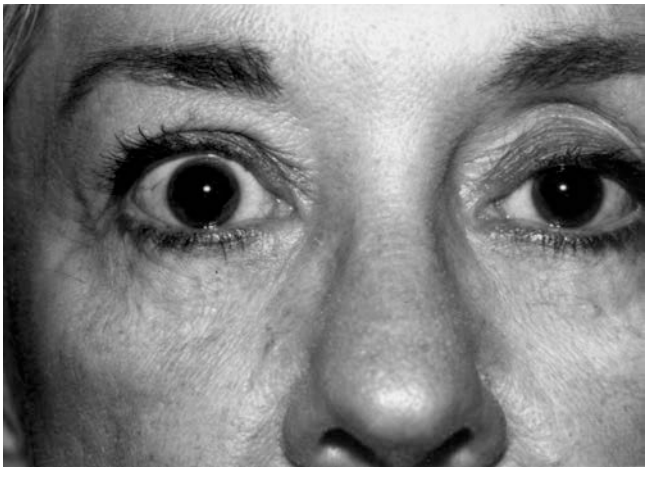


Figure 1.7 Retraction of right upper eyelid, an early sign of Graves orbitopathy. Palpebral fissure width of R 4 mm greater than that of L. The patient had no proptosis.

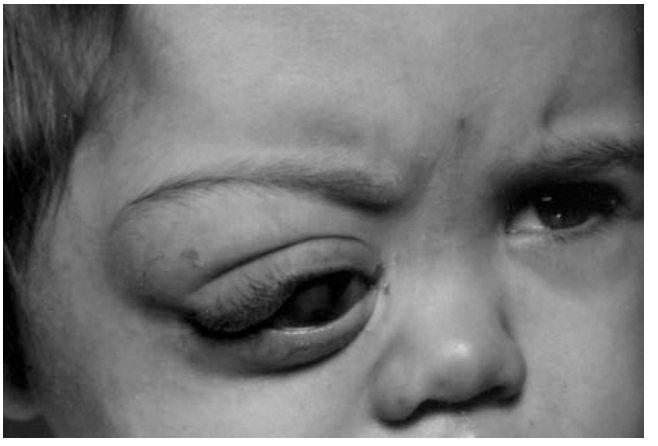


Figure 1.8 Neurofibromatosis with drooping and hypertrophy of the lateral half of the right upper eyelid in a 1-year-old girl was present since birth. The eyelid margin has a sinuous curve.

tumor is of initial concern. The so-called eyelid retraction of Graves orbitopathy may affect both upper and lower eyelids but most frequently affects only the upper. The retraction may be so marked and the baring of sclera so striking that a false impression of proptosis is conveyed to the observer (see Fig. 1.7). The most accurate means to detect eyelid retraction is measurement of the distance between the margin of the upper eyelid and the superior palpebral fold. In adults, this distance is reasonably constant and equal bilaterally. When eyelid retraction occurs, the superior palpebral fold deepens, the tissues overlying the tarsus are pulled upward, and the interval between the palpebral fold and the lid margin is shortened. This fold–lid margin ratio is a more dependable marker of eyelid retraction than long-used tests such as Graefe sign or Stellwag sign.

The picture of eyelid retraction—baring of the sclera and widening of the palpebral fissure—may be mimicked by rapidly expanding neoplasms. In such situations, the increase of orbital pressure is so intense the eye is pushed out of the protective cover of the eyelids. However, in such an eventuality, the upper eyelid is not necessarily foreshortened.

In general, most neoplasms expand at a steady rate, so the eyelids maintain a nearly normal anatomic relationship to the affected eye, although the eye may be greatly displaced from its normal position. Rarely, the palpebral fold–lid margin ratio may be widened because of the stretching of lid tissue attendant to proptosis of many years' duration or long-standing unilateral myopia.

Mild edema of the eyelid (usually the upper eyelid) may accompany tumors that are lodged in the superior areas of the orbit. The patient usually calls this a *puffy eye*. This edema is not associated with rubor and is relatively unimportant, except in the following circumstances. If localized to the temporal portion of the upper eyelids in adults, the edema may portend the early stage of a lacrimal gland tumor, particularly if the patient notes some discomfort or pain in this area. Such edema is more evident in the morning hours and is of sufficient degree to produce a slight peripheral contraction in the visual field corresponding to this area. If the drooped eyelid is elevated manually, the visual field defect disappears. It is easy to misconstrue this edema as a localized contact allergy or the result of an insect bite. In children, edema localized to this area may be a manifestation of occult neurofibromatosis. On closer inspection, a ropy, ill-defined mass is palpable in the subcutaneous tissue (see Fig. 1.8). Boggy edema localized to the nasal portion of the upper eyelid, particularly if episodic, suggests an underlying mucocele of the frontal sinus that is slowly eroding the bony roof of the orbit.

Edema of all four eyelids (see Fig. 1.9) is one of the frequent presenting symptoms of lymphoma. These neoplasms are usually associated with the foci of tumors in

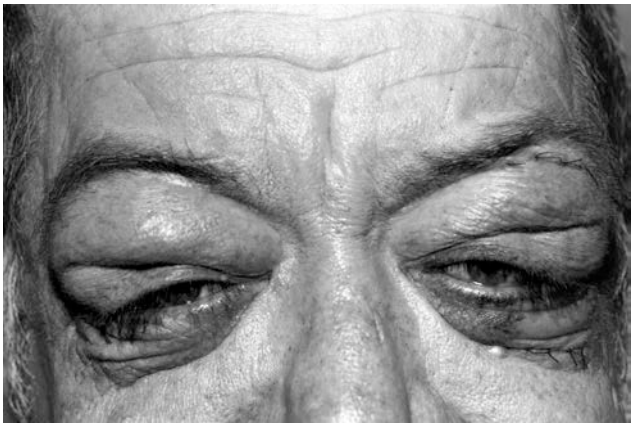


Figure 1.9 Malignant lymphoma of 3 years' duration with bilateral progressive edema of the eyelids in a 53-year-old man.

other areas of the patient's anatomy. Unilateral edema of one or both eyelids is more likely associated with lymphoma limited to one orbit without the systemic foci of tumors. The edema of lymphoma is painless, and there is no discoloration of the skin of the eyelid. However, if the subcutaneous tissue of the eyelid is unduly distended by edema, the overlying skin has a dusky hue. Edema with a similar texture may be observed with orbitocranial meningioma that either has been partially removed or has existed in the rear of the orbit for several years. This edema differs slightly from the one seen in lymphoma in that the former affects the lower eyelid (dependent edema) more than the upper eyelid (see Fig. 1.10). Infiltrating secondary neoplasms of the posterior orbit that are of lesser size, such as sinus carcinoma, esthesioneuroblastoma, and bony tumors, may mimic the eyelid edema of orbital meningioma.

Some degree of edema of the eyelids is also associated with hard, infiltrating basal cell, squamous cell, and sebaceous carcinomas, and eyelashes are frequently absent in the indurated area. In addition, pagetoid spread of sebaceous carcinoma may induce a symblepharon.

Rubor of the eyelids (with or without edema) suggests a more urgent orbital problem. Rubor and edema are most intense in infants with orbital cellulitis. In this case, the eyelids may be so swollen that they cover the proptosed eye. An increase in local heat and a systemic, febrile illness differentiate this acute inflammatory process from an eyelid or orbital tumor. Rubor and edema, without an increase in local heat, may also accompany fast-growing neoplasms or acute inflammatory tumors located in the more anterior areas of the orbit. Neoplasms with similar presentations in children and adolescents are rhabdomyosarcoma (Fig. 1.2B) and leukemia (see Fig. 1.11). In general, if rubor is present, the patient's examination should be expedited so that treatment can be initiated as quickly as possible. The varying types of rubor should not be confused with ecchymosis of the eyelids, which is associated with hematoma, metastatic neuroblastoma (see Fig. 1.12), amyloid deposit, and focal Langerhans histiocytosis.

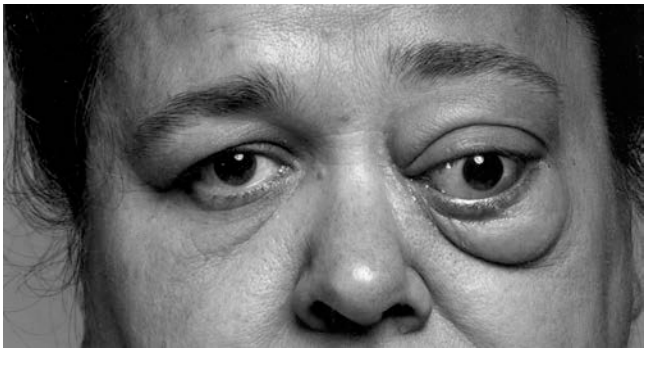


Figure 1.10 Meningioma with proptosis, loss of vision, and displacement of the left eye of 14 years' duration associated with edema of the left lower eyelid in a 49-year-old woman.

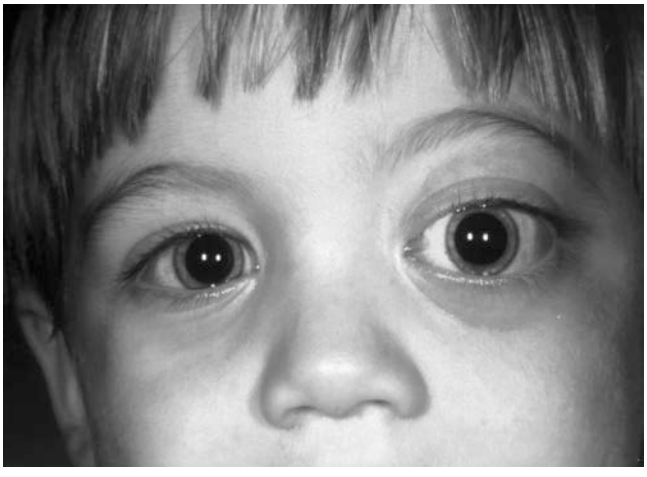


Figure 1.11 Granulocytic sarcoma with proptosis and displacement of the left eye with discoloration of the eyelid of 3 weeks' duration in a 22-month-old boy. The initial clinical impression was rhabdomyosarcoma. (Courtesy of J D Bullock, MD, Dayton, Ohio)

Surface of the Eye

Alterations in the pattern, color, and caliber of the epibulbar vascular plexus are visible clues for the diagnosis of several tumor families, which will be discussed in more depth later. Dilated, tortuous, reddish purple, corkscrew-like vessels extending across the surface of the eye are particularly diagnostic of vascular malformations and shunts in the posterior orbit and cavernous sinus. The singular color reflects the mixing of arterial and venous blood; the tortuosity results from elevated venous pressure. These vascular arcades usually terminate at the limbus, a feature rarely observed in other types of orbital disorders (see Fig. 1.13). Chemosis

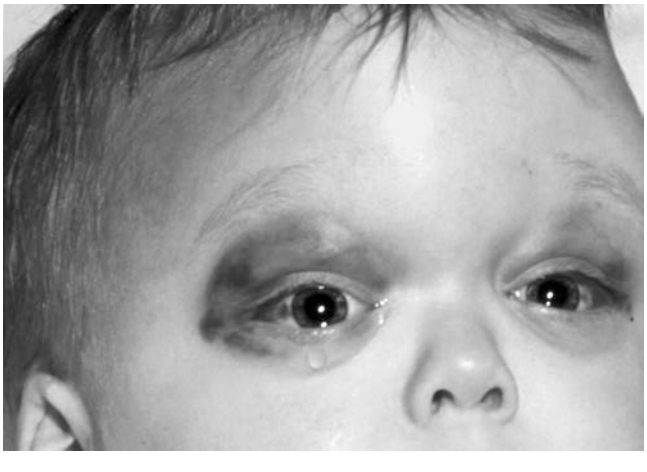


Figure 1.12 Metastatic neuroblastoma of 1 months' duration with ''black eye,'' easy bruising, bilateral ecchymosis of eyelids, and protrusion of the right eye in a 2-month-old boy.

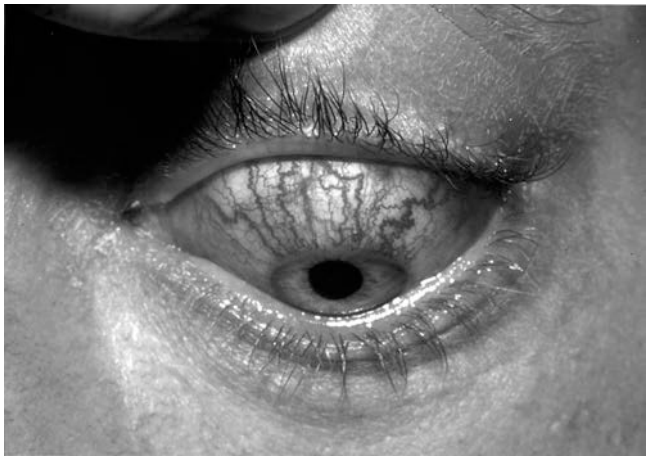


Figure 1.13 Carotid-cavernous fistula (high flow) with severe left frontal headache, prominent epibulbar vascular arcade, proptosis, and elevated intraocular pressure in the left eye, and bruit in the left orbit of 5 months' duration in a 44-year-old woman.

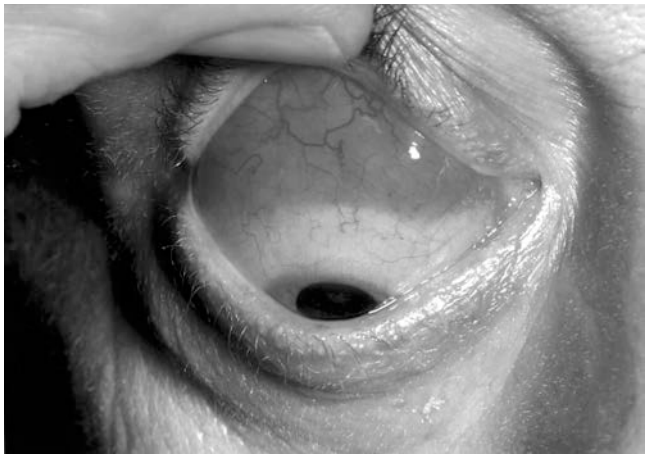


Figure 1.14 Non-Hodgkin lymphoma in a 52-year-old woman with a flesh-colored mass occupying the superior *cul-de-sac* of the right eye of 5 months' duration. The mass was a forward extension of an orbital focus.

is usually not associated with this pattern of dilated vessels unless some inflammatory or thrombotic component has supervened.

The pattern of vascular dilatation in early Graves orbitopathy is different. At the canthal area, more often the lateral than the nasal canthus, is an arcade of dilated, slightly tortuous, purplish vessels that tend to fade away as they approach the limbus. Some degree of chemosis also accompanies this vascular flush. This pattern represents simple, passive venous congestion and is quite distinctive of Graves orbitopathy, even in the absence of lid retraction. However, the more severe form of Graves orbitopathy is an acute process associated with intense chemosis and a more diffuse and intense discoloration.

Even the common subconjunctival hemorrhage may be a presenting facet of an orbital tumor. By history, these hemorrhages are episodic. We have rarely seen them with large cavernous hemangiomas, which, anatomically, are closely positioned to the eye or an extraocular muscle. Sudden movement of such an eye or pressure on the affected orbit during sleep seems to be the triggering mechanism for the hemorrhage. Similar episodic subconjunctival hemorrhage is also seen in some children who have a slowly evolving cystic lymphangioma that has pushed forward into the conjunctival fornix. A parent may say that such a child has *bloody tears*.

Another epibulbar discoloration of diagnostic import is the tumor of lymphoma. This salmon-hued lesion stealthily creeps along the surface of the eye beneath the conjunctiva, extending from the conjunctival fornix toward the limbus (see Fig. 1.14). It is painless and slow growing and may reach considerable size, particularly in a superior location, before being discovered by the patient. A few fine dilated vessels may arch over the surface of the mass. Such a fornix tumor is usually a forward extension of an occult mass deeper in the orbit. Proptosis or displacement of the eye may not be present in such a patient because the tumor is soft.

A similar-colored lump pushing externally from the conjunctival fornix is the friable excrescence of amyloid. This mass may also extend into the orbit. Eversion of the eyelid to inspect the mass may trigger a conjunctival hemorrhage.

Finally, the epibulbar melanotic spot of sudden onset may bring the patient for consultation. If the pigmented spot is ringed by prominent capillaries, be wary of an extrascleral extension of an intraocular melanoma, a metastatic focus of occult melanoma of the skin, a satellite deposit of orbital melanoma, or a primary melanoma of the conjunctiva.

FUNCTIONAL EVALUATION OF THE EYE

After listening to the patient's story and assessing the mechanical and dynamic features of the orbital presentation, the next step is determining ocular function and its role in both diagnosis and management of the putative orbital tumor. Although the eye itself is only a passive participant in most derangements resulting from an orbital tumor, preservation of its function is usually the patient's uppermost concern when debating the potential benefits of the physician's proposed management. Therefore, thorough baseline documentation of ocular function is helpful in diagnosis and essential in judging the "before and after" scenarios of therapy. Ocular function may be affected in several ways by an orbital mass, such as malposition of the eye secondary to increased orbital pressure, anatomic contact of tumor and eye, infiltration of nerves and muscles attached to the eye, and direct or indirect compromise of

the blood supply to the eye and appendages. Will the plan of treatment eliminate one or several of these factors and still preserve good ocular function? If not, will the whys and outcomes of therapy be discussed with the patient?

Visual Acuity

The discovery of visual loss in small children is worrisome. Optic nerve glioma, infantile hemangioma, and lymphangioma are the usual tumors in this category. A child with optic nerve glioma has visual loss disproportionate to the degree of proptosis. For example, the visual acuity may be no better than 20/80 although proptosis is <3 mm, the intrinsic destructive effect of the tumor being greater than its extrinsic bulk effect. Neither refraction nor surgery can reverse visual loss in such cases.

In infantile hemangioma, visual loss is not as severe, and the tumor is discovered earlier than the glioma noted earlier. If the hemangioma extends into the upper eyelid, as is often the case, the eye's visual axis is quickly compromised, resulting in eccentric fixation and amblyopia. Prompt therapeutic intervention, with either corticosteroids or surgical excision, is necessary to have any hope of reversing the decrease in vision.

Lymphangioma behaves in a similar manner, except eventual visual loss is more severe because of the tumor's relentless growth and resistance to treatment.

Visual Field

Orbital imaging techniques, particularly computed tomography and magnetic resonance imaging, have replaced visual field examination in the clinical diagnosis of orbital tumors that interfere with the function of the optic nerve. The role of perimetry is to record the degree of pretreatment visual loss. For example, the decision to remove a putative optic nerve glioma may be based on this test. Also, the visual field defect is a baseline with which the effect of subsequent treatment may be compared. Finally, it may be important in any future medicolegal entanglement where it takes precedence over orbital imaging in the patient's record.

In these lesions, the visual evoked potential procedure may also be useful intraoperatively to determine the degree of success of decompression of the orbital mass on the visual system (Miller, 1982).

Ocular Motility

Orbital imaging techniques have not lessened the practical value of the assessment of ocular motility. The abnormal pattern of ocular rotation may reflect the nature of the invasive orbital disease. One pattern is the result of the mechanical effect of two firm masses (eyeball and tumor) competing for space in the limited area of the bony orbit. The expanding tumor, either primary or secondary, is usually confined to one sector or quadrant of the orbit, and in such cases, ocular rotation is not impaired until the last phase of ocular excursion into the area occupied by the tumor. Diplopia, only in the sector of the mass, is the subjective clue of this type of motility impairment.

A more startling manifestation of this sequence is the blurring or obfuscation of vision that also occurs when the impaired extraocular muscle reaches the limits of its excursion. This gaze-evoked amaurosis is transient, and vision recovers as the eye is redirected to primary gaze. This phenomenon probably foretells either a bulky mass in the medial orbit or a tumor in the apex of the orbit. Such lesions are thought to impinge on the vascular supply of the orbital portion of the optic nerve in the course of the eye's excursion. An afferent pupillary defect may also be observed, indicating an additional impingement of the tumor on an adjacent nerve. Optic nerve sheath meningioma, cavernous hemangioma, and osteoma are tumors that are usually implicated in this gaze-evoked mischief.

Quite opposite is the paretic pattern associated with lesions in the apical region of the orbit. Here, diplopia is noted early in movement of the eye from its primary position and increases as the affected muscle struggles to complete its excursion. This indicates functional impairment of the nerve supply to affected muscles in the region of the superior orbital fissure.

The third pattern is more restrictive in degree and is secondary to edema, inflammation, or infiltration of the affected muscle. Graves orbitopathy, in its early stage, is an example of a rotational deficit caused by edema. The inferior rectus and medial rectus are the two muscles most severely impaired, causing diplopia in the patient's reading range. If edema subsides quickly, the diplopia usually resolves. If edema persists, a restrictive fibrosis occurs. A restricted forced duction test is the hallmark of this derangement.

So-called orbital myositis is an example of inflammatory impairment of ocular motility. A distinctive clue to this disease is pain on rotation of the eye into the field of restricted motility. In addition, there may be redness of the ocular surface overlying the site of insertion of the inflamed muscle or even a scleritis in the affected sector of the globe.

Lastly, there are the infiltrative processes involving extraocular muscles. The chief culprit in this category is metastatic adenocarcinoma from any source. These muscles, probably because of their rich blood supply, are the principal target of these neoplasms. The onset is sudden, unexpected, and painless. The patient may notice sudden diplopia while driving or on awakening in the morning. The muscles respond to this insult by initiating fibrosis, which quickly compounds the severity of the ensuing muscle paralysis. The end result is muscle contracture with either deviation of the eye or limitation of rotation in the area of infiltration.

Scirrhous carcinoma from the breast is the neoplasm that incites the severest form of such desmoplasia. Several muscles, rather than a single muscle, are usually stricken. The result is a droopy eyelid, and the eye, its rotation severely paralyzed, is "frozen" in the primary position of gaze. Gradually, the progressive contracture of the muscle produces enophthalmos. Bilateral orbital metastasis is not uncommon, and in such patients, diplopia is not a bothersome problem because the rotation of both eyes is equally restricted. Amyloid deposition in an extraocular muscle is another infiltrative disorder that presents in a similar pattern (Erie et al., 1989).

Finally, there is a pattern of restrictive motility involving an extraocular muscle that produces retraction of the globe on attempted gaze opposite the field of action of the involved muscle. It has been described with such orbital lesions as Graves orbitopathy, inflammatory tumors, and localized liposarcoma (Osher et al., 1980). The tethering effect of the involved muscles produces a clinical picture akin to Duane retraction syndrome. The forced duction test confirms the site of the restrictive process.

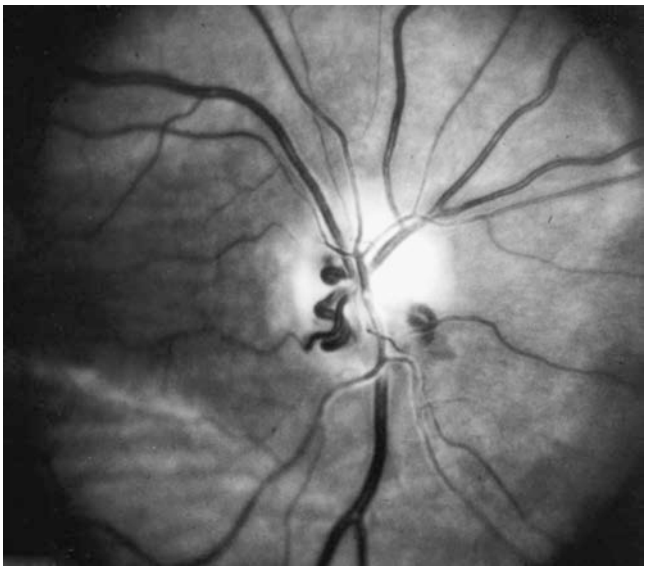


Figure 1.15 Optociliary veins associated with marked pallor of optic disk from long-standing optic nerve sheath meningioma. (From Hollenhorst RW Jr, Hollenhorst RW Sr, MacCarty CS. Visual prognosis of optic nerve sheath meningioma producing shunt vessels on the optic disk: The Hoyt-Spencer syndrome. *Trans Am Ophthalmol Soc.* 1977;75:141–163, with permission.)

Ophthalmoscopy

Although ophthalmoscopy is an integral part of a routine ophthalmologic examination, its role in the evaluation of a patient suspected of having an orbital tumor is only confirmatory. The most common discovery is indentation of the wall of the eye, which reflects the pressure from an expanding orbital mass. Other findings may be radial lines of stress in the retina resembling fine wrinkles and large, undulating choroidal folds. These signs have no importance other than to indicate the contour of the tumor, and they occur more commonly with expanding tumors in the anterior portion of the orbit. In this zone, the space for expansion is more limited. The choroidal folds are not always on the same side of the globe as the tumor and therefore are of limited value in the localization of the tumor. Although choroidal folds tend to regress after removal of the orbital mass, we have observed a few cases in which the folds persist for several years postoperatively.

A marked indentation at the posterior pole of the globe, when associated with hyperemia, edema, or elevation of the optic disk, indicates a tumor in which the optic nerve joins the eye. A meningioma of the optic nerve sheath may localize in this manner. In children, a similar picture may portend the forward extension of an optic nerve glioma or a retinoblastoma that has made its escape from the interior of the eye.

Pallor of the optic disk is associated more often with orbital tumor than with either edema or hyperemia of the disk. Such pallor, as a rule, is not characterized by either loss of nerve substance or increase in size and contour of the optic cup, such as occurs with primary optic atrophy and glaucoma. Pallor proportionate to the degree of proptosis in an adult suggests meningioma; pallor associated with little or no proptosis in a child suggests optic nerve glioma.

A less common, but more important, ophthalmoscopic finding is the combination of pallor with optociliary shunt veins of the optic disk (see Fig. 1.15). Fluorescein angiography demonstrates the intercommunication between retinal and choroidal venous plexus. Inasmuch as no arterial flow is involved, "shunt" is not an appropriate designation unless its venous nature is emphasized. Simply stated, a shunt is the dilatation of a preexisting venous channel occurring in response to the compression of venous blood flow by a mass along the intraorbital portion of the optic nerve.

Among orbital tumors, this venous dilatation most often manifests an optic nerve sheath meningioma. Less often, this vascular pattern is seen with compressive orbital lesions such as cavernous hemangioma, neurofibroma, and meningocele. If, on the basis of the assessment of the patient up to this point, there is some question whether an orbital mass is responsible for the patient's symptoms, the prominent optociliary veins may be a manifestation of some nonorbital disorder such as central retinal vein occlusion, branch retinal vein occlusion, chronic papilledema, phakomatosis, drusen of the optic disk, intracranial arteriovenous malformation, colloid cyst of the third ventricle, and congenital anomaly.

A final feature of possible importance is the color and configuration of the retinal venous tree. Dilatation and tortuosity of the vessels may accompany some alteration in the vascular dynamics of the orbit. Such vessels usually tend to be more purplish in color.

Applanation Tonometry

A rise in intraocular pressure may occur in some types of arteriovenous intercommunication or malformation in the posterior orbit. The carotid-cavernous fistula, aneurysm, and dural vascular shunt are in this category. All these types cause backflow rise in orbital venous pressure that produces the dilated, tortuous, limbic vascular arcades described in an earlier paragraph. The elevation of intraocular pressure in such cases is usually constant, steady, and resistant to medical therapy. In most cases, the eye seems to adapt to this secondary glaucoma and does not seem to suffer a degree of visual impairment compared with the primary glaucoma of comparable degree and duration.

Auscultation

Auscultation is not routine in the assessment of a patient suspected of having an orbital tumor. However, it is useful in the differential diagnosis of pulsation exophthalmos and in patients whose anamnesis includes a ''noise'' in the head. In either of these situations, the discovery of a bruit indicates a vascular malformation either in the orbit or in the retro-orbital portion of the intracranial vault, although the absence of a bruit does not necessarily exclude the presence of a vascular malformation.

A bruit is almost always present in arteriovenous fistulas of traumatic origin (high-flow, high-pressure vascular intercommunications). It is less common in arteriovenous fistulas of a spontaneous type and is seldom heard in the low-flow, low-pressure dural shunt, unless the latter is quite diffuse or bilateral in extent. A bruit usually is not present in patients with a purely venous malformation such as orbital varix. This suggests that an arterial component is always necessary to create a bruit in the orbital area.

The magnitude and character of the bruit are usually clues to the severity, size, and extent of the arteriovenous intercommunication. The bruit is loud, coarse, and synchronous with the radial pulse in a high-flow, high-pressure intervascular fistula. In a low-flow, low-pressure fistula and the extensive dural shunt, it is soft, faint, and only a ''murmur.''

A bruit is usually ipsilateral to the side of the affected orbit and is heard best when the stethoscope is placed over the temple, the inner canthus or the eyelid, the closed eye, or the frontal bone.

Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy was first noted in the third edition of this text, published in 1994 (pages 30 to 32), as an up-and-coming modality for diagnosis of orbital tumors. We discussed its inception, evolution in clinical practice, instrumentation, contraindications, complications, and references spanning 1980 to 1989.

In the ensuing years, no reports appeared to have equaled or surpassed the series of 242 cases summarized in 1989 by Kennerdell (1989). Zajdela et al. (1990) reported fine-needle cytology of 292 palpable masses of the orbit and eyelid with a diagnostic accuracy of approximately 75%.

Other authors continue to report computer-assisted fine-needle aspiration biopsy to be useful in orbital hematoceles, abscesses, suspected metastasis from any source, masses that appear unresectable, lymphoproliferative disorders, recurrent tumors, and mentally impaired elderly individuals in whom orbitotomy and attendant anesthesia is risky.

Complications of computer-assisted fine-needle aspiration include retrobulbar hemorrhage, transient visual disturbance, seeding of tumor along the exit tract of the needle, ocular motility disturbance, blepharoptosis, an epithelial implantation cyst, and inadvertent needle puncture of the eye. In the earlier edition of this text, we advised against fine-needle aspiration of solid tumors of the lacrimal gland fossa that are encapsulated or well circumscribed on ocular imaging. The benign mixed tumor of the lacrimal gland is prone to perpetual recurrence once seeding has occurred through a torn pseudocapsule, although the surgeon subsequently believes the tumor is grossly removed through orbitotomy.

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2 Orbital Imaging and Radiography

Nothing in the field of orbital diagnostics has so increased in importance during the editions of this text as the refinements in orbital imaging. The use of the computer and its assistance in processing the orbital scan, by whatever method, have played a chief role in the study of orbital bones and soft tissue contents. The computer is responsible for the evolution of imaging modalities such as computed tomography (CT) scanning, magnetic resonance imaging (MRI), radionuclide imaging, reconstructive tomography, angiography, and MRI-guided fine-needle aspiration (FNA) biopsy. These modalities, including ultrasonography, and their application to the diagnosis of orbital tumors are discussed in this chapter. Pertinent references to the subjects are cited from 1988 to the present, updating the references cited in the previous edition. More specific application of these modalities to the diagnosis of the individual tumors and tumor groups is noted in Section II.

COMPUTED TOMOGRAPHY

In the 1980s and early 1990s, CT scanning was the principal modality for imaging orbital tumors. It remains an effective, cost-efficient clinical tool, and many CT scan applications have become routine (Rootman, 1988; Garrity and Gilbertson, 2002). Since the third edition was published in 1994, helical CT scanning with slip-ring technology and rapid-contrast injections has evolved and is readily available on most state-of-the-art CT scanners. The most recent technology has advanced to 64-slice architecture CT scanners, which offer dramatic new levels of speed, resolution, and processing. In orbital imaging, direct axial and coronal scans were the standard of care and involved a fair amount of scanner time and radiation dose. Now, a single helical acquisition of the head in the axial plane can take as little as 4 seconds and provides 0.6-mm minimum slice thickness with 0.4-mm resolution in any plane. Indeed, the direct imaging plane is no longer dramatically better in quality than the reconstructed planes (e.g., coronal, sagittal, or even off-axis). Reconstructed images in the plane of the optic nerve or even curved reformatted images of the nonlinear superior oblique muscle can be obtained with little loss of image quality. Perhaps of even greater importance is the fact that the radiation dose can be cut nearly in half because examination in a second acquisition plane need not be performed.

Because of these characteristics, CT scan remains the screening examination of choice for patients with orbital tumors. Most lesions are adequately visualized, which is helpful with differential diagnosis or surgical planning. The effects of lysis or erosion on the adjacent bone are better appreciated with CT scan, although dense bone may compromise visualization of the orbital apex. Although CT scan may suggest certain characteristics of tissue type, MRI is better. In certain instances, CT scan and MRI are complementary, for example, in a patient with an ethmoid sinus tumor who also has an opacified frontal sinus. Bony changes around the ethmoid sinus are visualized on CT scan, but MRI can differentiate tumor from benign mucous accumulations.

Suojanen et al. (1992) noted in 21 patients that high-quality diagnostic scans were possible with excellent anatomic resolution, minimal motion artifacts, and scanning time of 24 to 36 seconds. Also, vascular opacification was optimized with substantially less contrast medium than in conventional studies.

Rubin and Remulla (1997) found in three patients with orbital venous anomalies resulting in retrobulbar hemorrhage that the pathologic vessel filled with blood can be imaged during a single breath hold using a scanning time of 24 seconds in conjunction with the Valsalva maneuver.

We have previously noted (in Chapter 2 of the third edition) a fascination for ophthalmologists to report calcification in an extraocular orbital tumor. Numerous single case reports were published soon after CT scan became the standard modality for the imaging of orbital masses.

Initially, each author thought that he or she was the first to report an important advance in CT scan observations. By the time the third edition was published in 1994, 19 individual tumors or tumor families with calcification were listed. Subsequently, the numerical list has expanded.

Froula et al. (1993) studied the differential diagnosis of orbital calcification as detected on CT scans. They stated that calcification of soft tissues may be either metastatic or dystrophic. The metastatic type includes precipitation of calcium phosphate salts secondary to hypercalcemia, and a systemic disease is usually present. The dystrophic type is associated with cellular injury secondary to trauma, tissue hypoxia, tumor growth that exceeds vascular supply, or vascular stasis. In a detailed search of the literature, Froula et al. (1993) found approximately 21 metastatic entities attributable to congenital, endocrine, infectious, idiopathic, toxic, traumatic, and neoplastic etiologies. The differential diagnosis of the group of lesions with dystrophic deposition of calcium included 13 entities with intraocular calcium, 6 within the lacrimal gland fossa, and 23 extrinsic to the lacrimal gland fossa.

Froula et al. (1993) also surveyed 171 CT scans that fulfilled their study criteria. Thirty-seven (22%) scans showed calcific densities. Calcium deposition was intraocular in 20 cases and extraocular in 17. Among the extraocular tumors, calcium deposition was noted in the family of vascular malformations and neoplasms, benign lesions, and malignant neoplasms. In view of the profusion of human disorders associated with calcium deposition in the orbital space, calcium can no longer be specific for a probable diagnosis, except for the large, smooth-surfaced, round or elliptical phlebolith that is pathognomic of a vascular tumor. Some malignant neoplasms, regardless of their orbital location, may show a small, poorly defined clump of calcium. Scrutinize the scan carefully to detect calcium adjacent to or within a cystic-like space void of contrast enhancement to identify the area of necrosis.

MAGNETIC RESONANCE IMAGING

When this section was written for the 1994 edition of this text, we had viewed MRI as being roughly comparable in its state of development to the stage of refinement reached by CT scan 10 years previously. We posited that in time we would know whether MRI would reach the level of importance in orbital diagnosis that CT scan had occupied.

Subsequently, the literature on MRI has been voluminous. Between 1990 and 2000, we estimate that publications pertaining to MRI probably equaled in number to all the publications written about the other subjects in this chapter.

Initially, many publications described ongoing advances in technology that refined the MRI display (Atlas et al., 1988; Roden et al., 1988; Runge, 1990; Barakos et al., 1991; Higgins et al., 1992; Breslau et al., 1995; Herrick et al., 1997; Sutton, 1998; Jackson et al., 1999; Stark and Bradley, 1999). The opinions and recommendations of these authors, roughly in chronology of publication, were as follows:

- More information is obtained with standard spin-echo sequences than with short-time inversion recovery sequences.
- Advances have made the technology more cost-effective.
- Gadolinium–pentetic (diethylenetriaminepentaacetic) acid (Gd-DTPA) has had a major impact on the use of MRI.
- The high signal intensity of fat on T_1-weighted MRI has limited the utility of gadolinium pentetate dimeglumine in the imaging of extracranial head and neck areas.
- Fat-suppression techniques in combination with gadolinium enhancement should replace postcontrast T_1-weighted spin-echo imaging.
- The flexibility of MRI is derived from the signal's dependence on not one but at least seven physical characteristics.
- Imaging of the orbit and orbital apex is clearly superior with dual-phased array coil, resulting in a higher resolution than can be obtained with a head probe.
- Tissue interface artifacts can be minimized with the use of spin-echo rather than gradient-echo sequences.
- The use of fat suppression combined with postcontrast sequences has markedly improved visualization of orbital masses and lesions of the optic nerves.
- Selective partial inversion recovery combined with fluid-attenuated inversion recovery sequences is an appropriate screening technique that has advantages over currently used fat-suppression sequences.
- Small, unilateral or bilateral surface coils have proved critical for the success of MRI in the orbit.

As physicians became aware of these refinements, a series of articles appeared in the literature citing the merits of MRI in a clinical setting. However, there are only a few publications pertaining to the orbit and visual pathways (Dorfman and Spickler, 1990; Bond et al., 1992; Bilaniuk and Rapoport, 1994; Davis and Newman, 1996). Their combined conclusions are as follows:

- MRI provides more information about orbital apex lesions compared to CT scan.
- MRI is the modality of choice for optic nerve glioma, optic neuritis, optic nerve sheath meningioma, perioptic hemangiomas, and sarcoidosis.
- Orbital pseudotumor can be differentiated from metastatic disease and reactive lymphoid hyperplasia on the basis of differences in signal intensity.
- The signal void of MRI is useful in visualizing the septal lobulations and patency of the vascular supply to vascular malformations.

- Thrombosis in a vascular malformation can be identified without the use of intravenous contrast.

In general, the publications comparing and contrasting MRI and CT scanning were laudatory of the former. One article suggested that refinements in MRI make it the procedure of choice for the initial screening of patients with orbital tumors, thereby eliminating the cost of CT scan unless it is needed for a suspected tumor involving the bone. According to Stark and Bradley (1999), the endorsement of MRI of the orbit must be qualified because CT scan shows excellent contrast between retrobulbar fat and disease and MRI is sensitive to globe and eyelid motion.

Because the paramagnetic qualities of hemoglobin are better characterized by MRI, it may be ideally suited for evaluating a lymphangioma or a hematocele.

MRI of individual tumors is discussed in more detail in Section II.

RADIOISOTOPE (RADIONUCLIDE) IMAGING

The use of gallium scanning has increased to assess the pathophysiology of the target tumor. The cellular content of some tumors has an affinity to bind with the gallium ion, which intensifies the image display. Some lymphomas belong to this category.

For example, if a patient presents with an orbital mass that, on further workup, proves to be an initial manifestation of a multifocal lymphoma, he or she is usually treated with chemotherapy. In the follow-up period, the effect of the treatment can be monitored by interval gallium scans. If treatment is successful, the contrast enhancement of tumor masses disappears. At this point, the patient may have achieved remission without the need for further interventional procedures.

Therefore, interval scans should continue. If, at some time in the later months or years, a lymphomatous mass again shows positive enhancement, the malignancy probably has recurred. This recurrence may not yet be visible by conventional scanning methods (Warwar and Bullock, 1999) but would be evident with radioisotope scan.

Other radioisotopes, such as thallium 201 and technetium 99m, have been in use for several decades to assist in the functional study of many human organs, but their use in the study of orbital tumors is limited (Gdal-On et al., 1999). These radioisotopes are thallium 201 and technetium 99m.

Thallium and technetium were used initially in the 1970s to study myocardial perfusion. Later preliminary studies indicated that both isotopes may be used for tumor imaging. The limited application of these radioisotopes to specific tumors is discussed in Section II. The study by Lambre et al. (1996) summarizes all information available on these isotopes up to the year of its publication.

MAGNETIC RESONANCE IMAGING–GUIDED FINE-NEEDLE ASPIRATION BIOPSY

The paramagnetic compound Gd-DTPA was approved for clinical use in 1988. Since then, it has been widely used by ophthalmologists and radiologists as the agent of choice for contrast enhancement of MRI displays. This contrast supplement delineates the size, contour, composition, vascularity, location, and proximity of the orbital mass. A patient viewing the tumor display can better comprehend the surgeon's approach and proposed manipulation of the tumor, biopsy, or removal.

MRI-guided intervention also has the potential as a delivery system for treatment, which might be utilized at the time of diagnosis or later. Lambre et al. (1996) envisioned interventional probes that could be modified for chemoablation, cryoablation, thermal tissue destruction, laser ablation, and radiofrequency ablation of the target tumor.

COLOR DOPPLER IMAGING

In the 1960s and early 1970s, ultrasonography (both A and B modes) was one of the first means of recognizing the soft tissues of the orbit that, until then, were never visible by angiography or plain-film radiography. The visibility of the structural matrix of these tissues was based on the differing acoustic impedance of the tissue traversed by the ultrasound waves.

In the early 1970s, the first CT scan machines were adapted for orbital scanning. Initially, ultrasonography and CT scan produced complementary scan displays. However, refinements in CT scanning were so rapid that by 1980 this was the preferred method of orbital imaging in most clinical settings. Concomitantly, interest in ultrasonography for orbital tumor display gradually diminished.

This interest was however revived in the 1980s with the introduction of color Doppler imaging (CDI) (Erickson et al., 1989). In this technique, the ultrasonographic signal is analyzed for alterations in echo amplitude, frequency, and phase shift Cennamo et al. (1994) also studied the utility of an echographic contrast agent. This provides color-coded data of the hemodynamics of a vascular structure, which can be superimposed on a conventional B-mode display. The composite display is easy to analyze. Blood flow traveling toward the transducer is coded red, and blood flow away from the transducer is coded blue.

Although CT scan and MRI have undergone many refinements over the last decade, CDI has remained a useful supplement to orbital scanning. Its present use is in the diagnosis and monitoring of the components and the extent of the blood flow in the vascular malformation of the orbit. This modality is also used with orbital varices to demonstrate the reversal of blood flow associated with the Valsalva maneuver (Wildenhain et al., 1991). CDI can

outline the complex of blood vessels affected by a high-flow carotid-cavernous fistula that drains through the superior orbital vein (Flaharty et al. 1991). Also, in low-flow dural vascular shunts, it images the tiny-caliber vessels of the shunt that are poorly seen on MRI and not seen on CT scan. Should any of these vascular malfunctions be treated with interventional surgery (cryoablation, embolization, etc.), CDI can be used to show the effectiveness of treatment and to monitor the follow-up course for recurrence. CDI eliminates the need for repeated angiography (Berrocal et al., 1996; Costa et al., 1997).

CDI also has been used to study orbital entities other than the vascular lesions listed in the preceding text. Mendivil and Cuartero (1999) were interested in the effect of solid orbital masses on blood flow through the central retinal artery. They found that a proved cavernous hemangioma and a presumed optic nerve glioma could produce enough pressure to impair blood flow through the central retinal artery. In turn, this impaired blood flow probably accounts for the transient or diminished visual acuity encountered with some orbital masses. Ivekovic et al. (2000) analyzed the use of CDI in the differentiation of benign and malignant tumors. They studied 20 patients with intraocular malignant melanoma and 19 patients with orbital cavernous hemangioma. The internal blood flow of the hemangiomas was slower and the resistance index was lower than those in the malignant melanomas.

ANGIOGRAPHY

Angiography is an imaging modality that was once the mainstay of the detection of vascular malformations and fistulas affecting the orbit and the adjacent intracranial vascular space. Its role was first usurped by CT scan in the 1970s, and in turn, CT scan was replaced by MRI in the 1980s. MRI was particularly useful for the study of intracranial vascular abnormalities. In the 1990s, the role of MRI in the study of orbital vascular anomalies was partially eclipsed by the advent of CDI. The latter could identify small feeder vessels to a low-flow dural arteriovenous fistula, which were not imaged on MRI. This further reduced the diagnostic role of angiography relative to the orbit.

In the 1990s, digital subtraction angiography (DSA) was usually reserved for imaging a vascular anomaly, particularly fistulas involving the orbit or orbitocranial interface, where a therapeutic interventional procedure was planned, such as recanalization of a secluded vessel or embolization of the vascular anomaly. DSA was the procedure of choice because it could show ramifications of the fistulas that extended beyond the imaging frame of CT scan, MRI, or CDI (Duvoisin et al., 1998). The goal of most embolization procedures was to occlude the fistula through the internal carotid artery on the side of the vascular abnormality.

In the early 1990s, there was interest in selective angiography of the ophthalmic artery (Tsai et al., 1990). This had been attempted rarely because of the technical difficulties in performing the procedure and the fear that the retinal artery would inadvertently be occluded, resulting in blindness. The authors recommended a change in the tip of the catheter to make the procedure easier and safer.

The breakthrough in the safe therapeutic use of selective angiography of the ophthalmic artery was reported by Lefkowitz et al. (1998). They described embolization of the ophthalmic artery in four patients with orbital arteriovenous malformations, four with dural arteriovenous fistulas, two with orbital meningiomas, one with planum sphenoidal meningioma, and one with juvenile nasal angiofibroma.

A Tracker 18 microcatheter (Boston Scientific, Natick, MA) is navigated into the ophthalmic artery using a steerable guidewire plus digital roadmapping. After lidocaine and amobarbital (Amytal) provocative tests are negative for any visual disturbances, embolic agents are injected, including polyvinyl alcohol particles ranging from 350 to 1,500 nm in diameter, 2-mm platinum microcoils, and *n*-butyl cyanoacrylic. A single transient decrease in visual acuity lasting 4 days was the only embolization-related complication.

THREE-DIMENSIONAL IMAGING

Three-dimensional (3D) imaging is a computerized post-processing technique that provides a comprehensive topographic overview of an abnormality or pathologic defect of the anatomic area that is imaged. This technique, first introduced in the 1970s, has had rather limited use in reference to orbital tumor. At present, it is useful in defining the shape and extent of cranio-orbital, orbitofacial, or orbital deformities of the bone that compromise the orbital space. Zonneveld et al. (1998) considered it a unique tool to assess congenital disorders of the orbit.

An exuberant fibrous dysplasia of the zygoma may produce a massive deformity of the upper face and orbit, resulting in the displacement of the eye and visual impairment in childhood. Likewise, congenital neurofibromatosis may produce a similar distortion of the orbital contour. Fukuta and Jackson (1993) reported two patients assessed by 3D CT imaging who had such an increase in the size of the orbit that orbital fat herniated into the infratemporal fossa through a gap in the inferior orbital fissure, thereby causing enophthalmos. An expanding retrobulbar dermoid cyst in early childhood and an enlarging naso-orbital meningoencephalocele are also candidates for 3D CT imaging to diagnose the full extent of the disruptive gap in a bone. In most of these situations, a surgery must eventually be performed to correct the abnormality. Postoperative 3D CT scans are helpful in mapping the extent of replacement of the bone or the

replacement of soft tissue volume necessary for satisfactory visual function and an acceptable cosmetic result.

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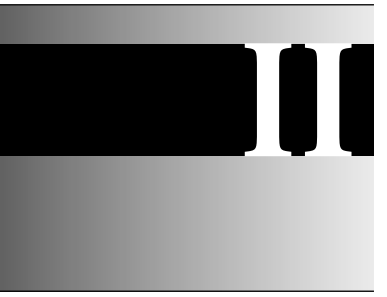
The Individual Tumors



The Tumor Survey

3

By precedent, the present tumor survey does not include most of the orbital conditions associated with infectious agents, disruptions related to trauma, and Graves orbitopathy. In keeping with the format of prior editions, this chapter tabulates and updates the number, type, frequency, and age distribution of a series of consecutive, histologically verified tumors seen at Mayo Clinic between 1948 and 1997. A detailed analysis of individual tumor groups is undertaken in other chapters of this section.

OVERVIEW OF PAST MAYO CLINIC SURVEYS, 1948 TO 1987

In our 50-year collection of literature on orbital tumors (1948 to 1997), many clinicopathologic correlations, lists, and classifications pertaining to the frequency, prevalence, and incidence of these disorders have appeared. Some of these surveys from earlier years are now out of date because of the small size of the sample, the type of tumor selected for study, changes in nomenclature, and the like. Lists, however, can be considered ''dynamic'' and subject to change simply because of pathologic revisions and reclassifications.

We have reprinted the summary table from the third edition (see Table 3.1) and noted the variables that evolved in the tumor mix during the 40-year period 1948 to 1987. These variations from the expected norm may interest readers who want to compare and contrast their experiences with ours.

The survey tabulated in our third edition (1975 to 1987) added 612 consecutive cases to a cohort of 764 surveyed from 1948, bringing the total to 1,376 consecutive orbital tumors. The 612 cases seen over the 13-year period represent an average of 47 patients per year, 10 more per year than in the second series. A striking aspect of the second and third series is the consistency of percentages of primary, secondary, and metastatic lesions from 1948. The proportion of primary tumors declined from 45.0% to 41.7% with the addition of data from the third case series. In the secondary tumors, the change was a decline of only 0.9%, from 45.0% to 44.1%. The proportion of metastatic tumors increased from 7.0% to 8.1%. These minimal shifts in distribution underline the pathoanatomic stability of our tumor cohort.

A similar consistency prevailed among the major histologic tumor groups as cases were added to the series. Also, the five most common primary tumors remained the same from the first to the second series (i.e., hemangioma, non-Hodgkin lymphoma, inflammatory pseudotumor, meningioma, and optic nerve glioma).

In the third series, basal cell carcinoma replaced malignant melanoma as the fifth most frequent tumor among the secondary orbital tumors. The radiopaque therapy for ocular malignant melanoma probably is the contributing factor for this shift in incidence. On a further analysis of the third series, we found 1,036 neoplasms (1,036 out of 1,376), increasing the incidence to 75%. Of the 1,036 neoplasms, 659 were malignant and 377 were benign, a ratio of 1.7:1.

By 1987, several changes in terminology had occurred. *Organizing hematoma, esthesioneuroblastoma, non-Hodgkin lymphoma, Langerhans histiocytosis*, and *angiomyoma* replaced the terms *hematic cyst, olfactory neuroblastoma, malignant lymphoma, histiocytosis X*, and *vascular leiomyoma*, respectively. *Acquired meningocele* is a new addition, and we replaced the word *generalized* (second edition) with the more appropriate term *multifocal*.

About the time of the third edition, many physicians were interested in counting orbital tumors in pediatric patients. Four of the larger reviews of this type were by Eldrup-Jorgenson and Fledelius (1975), Iliff and Green (1978), Shields et al. (1986), and Bullock et al. (1989). Collectively they reported 809 cases. Our own tabulation totaled 212 cases, a 15% (212 out of 1,376) share of total patients.

Compilations of cases in the literature confirm the wide spectrum of tumor types in pediatric patients. Prominent in all these surveys is vascular hamartoma (capillary hemangioma), developmental cyst, rhabdomyosarcoma, optic nerve glioma, and plexiform neurofibroma. However, our series differs from other surveys because of the lower incidence of dermoid cyst. This lesion usually is said to be the most common orbital tumor of childhood. This

TABLE 3.1
SUMMARY OF 1,376 CONSECUTIVE ORBITAL TUMORS, MAYO CLINIC, 1948 TO 1987

Histologic Type	Primary	Secondary	Metastatic	Multifocal	Totals
Carcinoid			2		2 (0.1%)
Carcinomas					311 (22.6%)
Adenocarcinoma	5	15	74		94
Adenoid cystic	22	26	1		49
Basal cell		40			40
Mucoepidermoid	2	3			5
Sebaceous		4			4
Squamous cell	2	102	6		110
Transitional		6			6
Undifferentiated		1	2		3
Cysts					166 (12.1%)
Cephalocele		4			4
Dermoid	30				30
Conjunctival	2				2
Mucocele		114			114
Optic nerve sheath meningocele	2				2
Organizing hematoma	10				10
Respiratory tract		1			1
Teratoma	3				3
Fibrous connective tissue					20 (1.5%)
Fibromatosis	2	2			4
Fibrosarcoma	4	6			10
Fibrous histiocytoma	1	5			6
Granulation tissue		1			1 (0.1%)
Granuloma (unclassified)	3				3 (0.2%)
Hematopoietic					129 (9.4%)
Amyloid	3				3
Granulocytic sarcoma	1			1	2
Leukemic infiltrate				2	2
Lymphoid hyperplasia	2				2
Multiple myeloma				6	6
Non-Hodgkin lymphoma	61	6		45	112
Plasmacytoma	2				2
Histiocytic					20 (1.5%)
Langerhans cell	1	4		6	11
Sarcoid and sarcoidosis	7			2	9
Indeterminate	1				1 (0.1%)
Inflammatory					98 (7.1%)
Nonvasculitic	58				58
Vasculitic, nongranulomatous	23				23
Wegener granulomatosis	6	9		2	17
Malignant melanoma	4	35	4		43 (3.1%)
Meningioma	42	97			139 (10.1%)
Mesodermal and adipose					45 (3.3%)
Lipoma	3				3
Liposarcoma	3	1			4
Rhabdomyosarcoma	17	21			38
Mixed					41 (3.0%)
Benign	25	1			26
Malignant	10	5			15
Nerve sheath					54 (3.9%)
Malignant		1		2	3
Neurilemmoma	15	1			16
Neurofibroma (plexiform)	9			18	27
Neurofibroma (solitary)	8				8
Neuroepithelial					73 (5.3%)
Esthesioneuroblastoma		12			12
Glioblastoma multiforme		1			1
Medulloblastoma			1		1
Neuroblastoma			19		19

TABLE 3.1
(*continued*)

Histologic Type	Primary	Secondary	Metastatic	Multifocal	Totals
Optic nerve glioma	34				34
Retinoblastoma		5	1		6
Osseous and cartilaginous					42 (3.0%)
Adamantinoma		1			1
Ameloblastoma		2			2
Aneurysmal bone cyst	2				2
Chondroma	1				1
Chondrosarcoma	1	5			6
Chordoma		1			1
Fibrous dysplasia	5	1			6
Osteogenic sarcoma	2	11			13
Osteoma	3	7			10
Papilloma (epithelial)		3			3 (0.2%)
Vascular					131 (9.5%)
Angiomyoma	1				1
Capillary hemangioma	30				30
Cavernous hemangioma	60				60
Hamartoma	1				1
Hemangiopericytoma	16	4	1		21
Lymphangioma	18				18
Vascular malformations					54 (3.9%)
Aneurysm	2	1			3
Arteriovenous	5	42			47
Varix	4				4
Total	574 (41.7%)	607 (44.1%)	111 (8.1%)	84 (6.1%)	1,376 (100.0%)

discrepancy probably is attributable to the inclusion of cysts in adnexal locations (eyebrow and eyelid) in many other series, whereas the cysts in our list were all retroseptal. The lower incidence of dermoid cyst in our series also may alter the ratio of benign to malignant lesions. In our pediatric cases, 70% (149 out of 212) were benign tumors and 30% (63 out of 212) were malignant. This is a considerably higher ratio of malignant tumors in children than that reported in the literature.

Also in the third edition, we referenced some 27 publications pertaining to the classification and frequency of orbital tumors. These were a heterogeneous collection of facts and figures. No two of these studies were identical in the coverage of the various parameters of an incidence survey. In an earlier year, 1979, after reviewing several surveys of such types, Jones and Jakobiec (1979) noted that there probably is no unbiased, parametrically complete tumor series, and efforts to blend and compare the data of one series with another still leave the goal of a true and perfect survey unrealized.

MAYO CLINIC SURVEY, 1988 TO 1997

Since the tabulation of orbital tumors in the 1948 to 1987 series (third edition), an additional 419 consecutive orbital tumors were surgically confirmed between 1988 and 1997 (see Table 3.2). The composite total is now 1,795 cases (see Table 3.3).

The course of a glioma of the orbital portion of the optic nerve is now monitored by imaging, and surgical removal is postponed until the glioma progresses into the intracranial portion of the nerve or the eye is blind. Surgical removal of the 19 gliomas in the Mayo survey before 1975 was necessary because it was not known whether tumor extension toward the optic chiasm was present. Also, the expected number of meningiomas with secondary involvement of the orbit decreased compared with tabulations in previous editions of this book. Many presumed meningiomas near the cavernous sinus are now managed with the Gamma Knife. These tumors were not pathologically verified and have not been included in the present series.

This lower tumor count is partially offset by a surprising increase in the number of non-Hodgkin lymphoma cases in the current series, which (Table 3.2) includes 64 new cases of this lymphoma, whereas the entire series before 1987 included only 112 cases. We and other physicians were aware of this emerging trend in the late 1980s and early 1990s. Most physicians attributed the increased number of cases to earlier staging of lymphomas owing to improved imaging techniques and bone marrow

TABLE 3.2
SUMMARY OF 419 CONSECUTIVE ORBITAL TUMORS, MAYO CLINIC, 1988 TO 1997

Histologic Type	M/F	P	S	MS	U	MF	No.	Totals
Carcinomas								100
Adenocarcinoma	15/22	3	3	31			37	
Adenoid cystic	7/8	7	8				15	
Basal cell	7/5		12				12	
Carcinoid	1/1	2					2	
Carcinosarcoma	0/1		1				1	
Mucoepidermoid	0/1	1					1	
Sebaceous	2/4		6				6	
Squamous cell	15/8		20	3			23	
Undifferentiated	3/0		3				3	
Cysts and celes								31
Dermoid	4/7	11					11	
Hematocele	1/3	4					4	
Inclusion	1/2		3				3	
Microphthalmos with cyst	2/0	2					2	
Mucocele	5/6		11				11	
Fibrous tissue								9
Fibrosarcoma	2/3	1	4				5	
Fibrous histiocytoma	1/0	1					1	
Solitary fibrous tumor	0/3	3					3	
Hematopoietic								74
Hodgkin disease	0/1	1					1	
Lymphoid hyperplasia	3/5	8					8	
Multiple myeloma	1/0					1	1	
Non-Hodgkin lymphoma	35/29				22	42	64	
Histiocytic								7
Eosinophilic granuloma	1/0				1		1	
Sarcoidosis	0/6				3	3	6	
Inflammatory								34
Pseudotumor	10/15	25					25	
Vasculitis (nongranulomatous)	1/3	4					4	
Wegener granulomatosis	2/3				2	3	5	
Mesodermal and adipose								20
Lipoma	0/1	1					1	
Liposarcoma	2/0	2					2	
Rhabdomyosarcoma	10/6	9	6	1			16	
Xanthomatosis	0/1	1					1	
Mixed								1
Malignant	1/0	1					1	
Nerve sheath								9
Neurilemmoma	2/2	4					4	
Neurofibroma (plexiform)	3/1	4					4	
Neurofibroma (solitary)	0/1	1					1	
Neuroepithelial								5
Esthesioneuroblastoma	3/0		3				3	
Optic nerve glioma	1/0	1					1	
Retinoblastoma	1/0		1				1	
Osseous and cartilaginous								17
Aneurysmal bone cyst	1/0	1					1	
Brown tumor	0/1	1					1	
Chondrosarcoma	2/0	1	1				2	
Fibrous dysplasia	4/2	6					6	
Osteoma	2/0	1	1				2	
Osteosarcoma	2/3	2	3				5	
Vascular								39
Capillary hemangioma	0/4	4					4	
Cavernous hemangioma	9/12	21					21	
Fibroangioma	1/0		1				1	
Hemangioma of bone	0/1	1					1	

TABLE 3.2
(*continued*)

Histologic Type	M/F	P	S	MS	U	MF	No.	Totals
Hemangiopericytoma	1/2	3					3	
Lymphangioma	5/4	9					9	
Vascular malformation								19
Carotid-cavernous fistula (high-flow)	1/1		2				2	
Carotid-cavernous fistula (low-flow)	0/12		12				12	
Varix	1/4	5					5	
Miscellaneous								54
Malignant melanoma	8/7		7	8			15	
Meningioma	17/22	22	17				39	
Total	196/223	174	125	43	28	49		419

F, female; M, male; P, primary; S, secondary; MS, metastatic; U, unifocal; MF, multifocal.

TABLE 3.3
SUMMARY OF 1,795 CONSECUTIVE ORBITAL TUMORS, MAYO CLINIC, 1948 TO 1997

Histologic Type	M/F	P	S	MS	U	MF	No.	Totals
Carcinomas								414
Adenocarcinoma	54/77	8	19	104			131	
Adenoid cystic	32/33	30	34	1			65	
Basal cell	34/18		52				52	
Carcinoid	2/2			4			4	
Carcinosarcoma	1/0		1				1	
Mucoepidermoid	0/6	3	3				6	
Sebaceous	5/5		10				10	
Squamous cell	96/37	2	122	9			133	
Transitional cell	4/2		6				6	
Undifferentiated	4/2		4	2			6	
Cysts and celes								193
Cephalocele	1/3		4				4	
Dermoid	19/22	41					41	
Hematocele	10/3	13					13	
Inclusion	2/1		3				3	
Microphthalmos with cyst	2/0	2					2	
Mucocele	65/60		125				125	
Optic nerve sheath meningocele	1/1	2					2	
Respiratory	1/1		2				2	
Retention	1/0		1				1	
Fibrous tissue								29
Fibromatosis	4/0	2	2				4	
Fibrosarcoma	7/8	5	10				15	
Fibrous histiocytoma	5/2	2	5				7	
Solitary fibrous tumor	0/3	3					3	
Hematopoietic								203
Amyloid	1/2	3					3	
Hodgkin lymphoma	0/1					1	1	
Leukemic infiltrate	1/1					2	2	
Lymphoid hyperplasia	5/6	11					11	
Multiple myeloma	4/3					7	7	
Myeloid sarcoma	1/1	1				1	2	
Non-Hodgkin lymphoma	94/81		6		82	87	175	
Plasmacytoma	1/1	2					2	
Histiocytic								27
Eosinophilic granuloma	1/0				1		1	

(*continued*)

TABLE 3.3
(*continued*)

Histologic Type	M/F	P	S	MS	U	MF	No.	Totals
Langerhans cell	8/3	1	4			6	11	
Sarcoidosis	3/12				10	5	15	
Inflammatory								135
Granuloma (unspecified)	0/3	2	1				3	
Pseudotumor	40/43	83					83	
Vasculitis	12/15	27					27	
Wegener granulomatosis	9/13		9		8	5	22	
Mesodermal and adipose								66
Angiomyoma	0/1	1					1	
Lipoma	3/1	4					4	
Liposarcoma	5/1	5	1				6	
Rhabdomyosarcoma	35/19	26	27	1			54	
Xanthomatosis	0/1	1					1	
Mixed								42
Benign	15/11	25	1				26	
Malignant	11/5	11	5				16	
Nerve sheath								63
Malignant schwannoma	3/0		1			2	3	
Neurilemmoma	10/10	19	1				20	
Neurofibroma (plexiform)	17/14	13				18	31	
Neurofibroma (solitary)	4/5	9					9	
Neuroepithelial								78
Esthesioneuroblastoma	7/8		15				15	
Glioblastoma multiforme	1/0		1				1	
Medulloblastoma	1/0			1			1	
Neuroblastoma	12/7			19			19	
Optic nerve glioma	15/20	35					35	
Retinoblastoma	5/2		6	1			7	
Osseous and cartilaginous								59
Adamantinoma	1/0	1					1	
Ameloblastoma	2/0		2				2	
Aneurysmal bone cyst	1/2	3					3	
Brown tumor	0/1	1					1	
Chondroma	1/0	1					1	
Chondrosarcoma	5/3	2	6				8	
Chordoma	0/1		1				1	
Fibrous dysplasia	6/6	11	1				12	
Osteoma	9/3	4	8				12	
Osteosarcoma	8/10	4	14				18	
Vascular malformation								73
Aneurysm	1/2	2	1				3	
Arteriovenous	7/7	3	11				14	
Carotid-cavernous fistula	6/42	1	47				48	
Varix	1/7	8					8	
Vascular								170
Capillary hemangioma	15/19	34					34	
Cavernous hemangioma	37/45	82					82	
Fibroangioma	1/0		1				1	
Hamartoma	0/1	1					1	
Hemangioma of bone	0/1	1					1	
Hemangiopericytoma	13/11	19	4	1			24	
Lymphangioma	13/14	27					27	
Miscellaneous								243
Malignant melanoma	35/24	4	43	12			59	
Meningioma	49/129	64	114				178	
Teratoma	3/0	3					3	
Papilloma (epithelial)	3/0		3				3	
Total	891/904	668	737	155	101	134		1,795

F, female; M, male; P, primary; S, secondary; MS, metastatic; U, unifocal; MF, multifocal.

biopsy. Greater occupational exposure to toxins and chemicals may also contribute to the increased number of cases.

Although the total number of patients increased during the initial 40 years of the survey, the distribution of tumors among the groups remained uniform. The 1997 series showed slight changes in the pathoanatomic consistency of the total tumor cohort. In the following analysis, cavernous hemangioma (82 cases) and capillary hemangioma (34 cases) were considered as one tumor type to facilitate comparison with the 1987 tabulation. Overall, the five most common primary tumors were hemangioma, 116; pseudotumor, 83; unifocal non-Hodgkin lymphoma, 82; meningioma, 64; and dermoid cyst, 41.

The dermoid cyst replaced the optic nerve glioma as the fifth most common primary tumor. If non-Hodgkin lymphoma continues its present rapid increase, it will replace pseudotumor in second place.

The five most common secondary tumors remained the same. In the 1997 survey, their totals were mucocele, 125; squamous cell carcinoma, 122; meningioma, 114; carotid-cavernous shunt, 47; and basal cell carcinoma, 52. In prior tabulations, carotid-cavernous shunt was listed as an arteriovenous malformation.

The adenocarcinomas of various origins are the most frequent metastatic tumors (104 cases). Likewise, non-Hodgkin lymphoma is the predominant tumor of the multifocal type (87 patients). Of further interest are 1,369 neoplasms in the total series of 1,795 cases, an incidence of 76%. Of the 1,369 neoplasms, 869 were malignant and 500 were benign, a ratio of 1.7:1.

The tendency to classify tumors according to patient age categories, such as childhood, adolescence, and middle age, is subject to defining a minimum or maximum for each age-group. A classification based on age decade at diagnosis is more accurate. Total tumors in successive decades are shown in Table 3.4.

Overall, the age distribution of tumors is bimodal, with an initial peak in the first decade, a lesser number in second, third, and fourth decades, followed by a gradual increase in the fifth, sixth, and seventh decades, where the numbers plateau and decline again after 70 years of age.

Our 50-year survey (Table 3.3) includes more than 66 tumor types. Is there any other anatomic area as small as the orbit that attracts such a profusion of tumefactions?

Some change in terminology should be noted in the current tumor classification. We consider *hematocele* (a pocket of blood either in the orbital soft tissue or orbital bone) a better term than *organizing hematoma*. The latter is only a stage in the resolution of the hemorrhage. Likewise, the term *inflammatory pseudotumor* should replace *nonvasculitic inflammatory tumor*. *Vasculitic inflammatory tumor* can be shortened to *vasculitis*. The term *fibrous tumor* is a new addition to our tumor vocabulary.

REVIEW OF THE LITERATURE

In the preceding editions, we reviewed surveys that included 100 or more cases. These reports were more numerous in past years than they are now. Here, we summarize a similar case series published since 1988.

Bullock et al. (1989) analyzed 141 cases of orbital tumor in children from Bullock's private practice. Their clinically based service included all childhood tumors, irrespective of whether a biopsy was performed. However, they did not state the percentage of cases that were not pathologically verified. Cystic lesions accounted for the largest number of orbital tumors (59 cases, 41.8%), followed by vasculogenic tumors (23 cases, 16.3%) and adipose-containing lesions (11 cases, 7.8%).

Bullock et al. (1989) reviewed nine other series comprising 1,229 cases, all of which had been published before 1989, one as early as 1964. Seven of them dealt with patients in the United States, one reviewed orbital tumors in African children, and one included children in Denmark. Gunalp and Gunduz (1995) also reviewed 376 pediatric tumors in Turkey. All diagnoses were based on histopathologic study. The most frequent lesion to invade the orbit in their study was secondary retinoblastoma.

Kodsi et al. (1994) reviewed 340 patients aged 18 years or younger from the tumor registry of Mayo Clinic spanning the 60-year period from 1932 through 1991. The patients in their group who were analyzed between 1948 and 1987 were also included in our preceding survey (third edition) of patients of all age-groups. The same pathologist, R. J. Campbell, was responsible for the histopathologic diagnoses in both surveys. The most common tumors in the pediatric series reported by Kodsi et al. (1994) were cysts, 23.2% (79/340); vascular lesions, 17.6% (60/340); and optic nerve and meningeal neoplasms, 16.5% (56/340), followed by inflammatory masses, osseous and fibrocystic lesions, and rhabdomyosarcoma. The overall frequency of malignancies was 18.2% (62/340), and of this total, 11.5% (39/340) were primary in the orbit and 6.8% (23/340) were secondary and metastatic types. The percentage of primary orbital malignancies in the first 30-year period and the second 30-year period were almost identical, 12.0% (17/142) and 11.1% (22/198), respectively. However, secondary and metastatic orbital neoplasms occurred in 13.4% (19/142) during the first 30-year period but only in 2% (4/198) in the second 30-year period. This marked difference was attributed to refinements in the surgical management of the primary tumor and the use of combined chemotherapy and radiotherapy in the second 30-year period of their series.

Purgason and Hornblass (1992) published a retrospective review of all orbital tumors treated during a 7-year period, January 1983 through December 1989. All tumors managed by orbitotomy, including inflammatory

TABLE 3.4
OCCURRENCE OF TUMORS BY AGE-GROUP

	Decade															
	≤10 (*n* = 202)		11–20 (*n* = 114)		21–30 (*n* = 131)		31–40 (*n* = 181)		41–50 (*n* = 276)		51–60 (*n* = 321)		61–70 (*n* = 361)		≥71 (*n* = 209)	
Tumor	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Adamantinoma															*	
Adenocarcinoma			*		*		10	5	18	6	32	9	51	14	17	8
Adenoid cystic carcinoma					8	6	10	5	9	3	18	5	11	3	6	2
Amyloid									*				*			
Aneurysmal bone cyst	*		*								*					
Angioblastoma													*			
Angioma	*															
Basal cell carcinoma					*		*		4	1	13	4	14	3	16	7
Capillary hemangioma	29	14	4	3							*					
Carcinoid											*		*			
Carcinosarcoma							*									
Carotid-cavernous fistula													13	3	17	8
Cavernous hemangioma	*		*		4	3	21	11	33	11	13	4	6	1	*	
Cephalocele	*		*													
Chondroma											*					
Chondrosarcoma							*		*		*		*			
Chordoma									*							
Dermoid cyst	16	7	11	9	5	3	6	2	*		*					
Esthesioneuroblastoma					*		*		*		*		4	1		*
Fibromatosis	*		*						*							
Fibrosarcoma									*		4	1	5	1		
Fibrous dysplasia	*		5	4	4	3							*			
Fibrous histiocytoma			*						*				*		*	
Fibrous tumor									*		*				*	
Glioblastoma multiforme											*					
Granulocytic sarcoma	*		*													
Granuloma (unclassified)							*				*					
Hamartoma									*							
Hemangiopericytoma			*		*		4	2	8	2	*		*		*	
Hematocele					*		4	2	*		*				*	
Hodgkin's lymphoma							*									
Hyperparathyroid adenoma					*											

Inclusion cyst	*				*										*	
Langerhans histiocytosis	9	4	*													
Leukemic infiltrate													*			
Lipoma			*		*		*				*					
Liposarcoma			*		*								*			
Lymphangioma	14	6	6	5	*				*							
Lymphoid hyperplasia							*		*		*		*		*	
Malignant melanoma			*		*		*		10	3	6	1	28	6	10	4
Malignant schwannoma	*								*						*	
Medulloblastoma					*											
Meningioma	4	1	6	5	7	5	38	20	43	15	41	12	31	8	8	3
Meningocele													*			
Microphthalmos with cyst	*															
Mixed tumor					11	8	5	2	9	3	7	2	*		4	1
Mucocele			8	7	16	12	9	4	27	9	29	9	22	6	11	6
Mucoepidermoid carcinoma											*		*		*	
Multiple myeloma									*				4	1	*	
Neuroblastoma	19	9														
Neurofibroma (plexiform)	13	6	7	6	5	3			*		*					
Neurofibroma (solitary)									*		4	1	*			
Neurilemmoma			*		5	3			4	1	*		*		*	
Non-Hodgkin lymphoma			*		*		7	3	20	6	43	13	55	15	42	20
Optic nerve glioma	24	11	7	6	*				*							
Optic nerve sheath meningocele							*									
Osteoma	*				*		*		*		*		*			
Osteosarcoma	*		*		*		*		*		*		*			
Papilloma											*		*			
Plasmacytoma															*	
Pseudotumor	6	2			10	7	10	5	18	6	12	3	14	3	10	4
Retinoblastoma	7	3														
Rhabdomyosarcoma	31	15	14	12	6	4	*									
Sarcoidosis									*		6	1	6	1	*	
Sebaceous carcinoma											*		*		5	2
Squamous cell carcinoma			*		4	3	6	2	18	6	28	8	59	16	28	13
Teratoma	*				*											
Transitional cell carcinoma					*				*		*		*		*	
Undifferentiated carcinoma							*		*		*		*			
Vascular malformation	*		*		5	3	6	2	8	2	19	5				
Vasculitis	*		5	4	6	4	*		4	1	*		*		5	2
Wegener granulomatosis			*		*		*		4	1	4	1	*		4	1
Xanthomatosis													*			

* ≤3 Tumors of this type in the age-group.
Blanks indicate no tumors of this type occurred in the age-group.

lesions simulating tumors, and secondary orbital tumors, were included in their studies. The total series consisted of 137 cases comprising 15 different tumor types. The four most common types that required surgery (and their frequency) were lymphoid tumors (22%), lacrimal gland tumors (20.5%), cystic lesions (20.5%), and vasculogenic tumors (12.5%). These four types made up 75.5% of the total sample. They were chiefly concerned with the surgical complications encountered among the total 137 cases.

Seregard and Sahlin (1999) conducted a histopathologic review of specimens from 300 consecutive patients with space-occupying orbital lesions, requiring incisional or excisional biopsy, over a 24-year period at a tertiary referral center, St. Erik's Eye Hospital and Karolinska Institute in Stockholm, Sweden. This series included secondary and metastatic tumors in addition to primary orbital tumors. The series was similar to the study of Purgason and Hornblass (1992); the four most common tumors, in order of frequency, were lacrimal fossa lesions (17.7%), lymphoproliferative lesions (12.7%), cystic lesions (12.3%), and vasculogenic lesions (12.0%)—54.7% of the 300 cases. More than half the total cases were neoplastic tumors.

Margo and Mulla (1998) studied only primary malignant tumors of the orbit on the basis of the Florida Cancer Data System from 1981 through 1993. They noted that the average annual incidence of lymphoma increased 166% in the last 6 years of the study period compared with the first 6 years.

Finally, the survey of Lee et al. (2000), based on their experience at the National University of Singapore, included 125 patients with intraocular and conjunctival tumors in addition to orbital tumors. For comparison purposes, this study is not compatible with surveys limited to orbital lesions. The purpose of the study of Wilson et al. (1996) was to review 312 histopathologic specimens from the L. F. Montgomery Laboratory of Ophthalmic Pathology at Emory University, between May 1942 and December 1993, to determine whether there was any geographic difference in the distribution of the orbital lesions from prior surveys in the northeastern United States (Kennedy, 1984; Shields et al., 1984), the midwestern states (our second edition, 1980), and northwestern North America (Rootman, 1988). Wilson et al. (1996) concluded there was no apparent difference in their series of tumors from the southeastern United States compared with reviews from other regions of North America.

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Cysts and Celes

4

DEVELOPMENTAL CYSTS

Dermoid Cysts

This benign tumor runs the gamut from a small, superficial, surgically accessible, easily eradicable lesion to a large, deeply recessed, relentlessly expanding, bone-contouring mass. Because of these frequent extraorbital ramifications, this tumor may defy intact removal. The age range of affected patients is wide, extending from infancy through middle adult life.

Terminology and Classification

The exact pathogenesis of the orbital cyst is not known, but its origin is probably a nidus of embryonic ectoderm entrapped by the juxtaposition of membranous bones and epithelial fusion lines. In this regard, the cyst is a choristoma.

The small, anterior orbital cyst is usually adjacent to the frontolacrimal, frontoethmoidal, or frontozygomatic suture. The larger, more posterior cyst is usually associated with the sphenozygomatic suture and less often with the sphenoethmoidal suture. The origin of the deeper cyst may be obscure, because its base is masked by the large size of the mass, the cyst ruptures during the course of surgical manipulation, or the pedicle of the lesion has atrophied during the long course of development.

At the time of our first edition (1973), this tumor was usually classified on the basis of histologic characteristics into dermoid and epidermoid types. This classification might have been artificial because a tissue specimen from a deeply positioned cyst would be so small or so fragmented that a definitive histologic differentiation was not possible. In addition, some clinicians have argued that histologic classification is academic, inasmuch as complete removal of tumor is the goal of management regardless of histology. In the 1980s, Grove (1981) and several other authors suggested that because the histology of epidermoid and dermoid cysts is so similar, they should be considered as one tumor type, classified on the basis of their anatomic location, superficial or deep. Accordingly, in our third edition, the two histologic types were tabulated as dermoid cysts.

The evolution of high-resolution computed tomography (CT) scan and magnetic resonance imaging (MRI) in the 1990s provided more precise indications about the location of the dermoid cyst in relation to the bone as well as the origin from orbital soft tissue. This is the basis for expanded anatomic classification (Shields et al., 1997) that should improve the management of these cysts. Shields et al. (1997) broadly divided the cysts into juxtasutural, sutural, and soft tissue types.

The juxtasutural type is attached to the bone by dense fibrous bands but does not affect the bone unless unchecked tumor growth causes fossa formation. The cysts presenting along the orbital rim are usually of this type. The nidus of the sutural type is within the synostosis of the orbital bone (intradiploic). The cyst may expand within the cancellous tissue of the bone but more often extends into the soft tissues. The sutural type is associated with bony defects, draining sinuses of the orbital bone (Honig, 1998), and extension into the intracranial cavity (Niederhagen et al., 1998; Meyer et al., 1999). Giant dermoid cysts reported in the literature often are of this type. The soft tissue type includes rarer cysts arising from soft tissues of the orbit (Howard et al., 1994; Atilla et al., 2000; Coevoet et al., 2000). The surgical management related to this classification is discussed later in this section.

Bonavolonta et al. (1995) classified their 145 patients, studied over 16 years, as exophytic and endophytic, according to the site of attachment to the orbital rims. This explains their different presentation. The exophytic cysts are discovered earlier in childhood, whereas the endophytic ones are discovered later in life and are associated with bone damage and invasion of orbital space. Many authors discuss the dermoid cysts without regard to their location, anterior or posterior, relative to orbital septum, lumping them together as orbital in origin. The cyst anterior to the orbital septum should be correctly classified as periorbital, extraorbital, or adnexal in location. Also, these cysts are sometimes referred to incorrectly as "dermoids." This designation is inappropriate because of the confusion with the solid dermoid (dermolipoma) on the surface of the eye. The older term *cholesteatoma* should not be used in place of the correct name, *dermoid cyst*.

Incidence

Forty-one dermoid cysts are tabulated in Table 3.3, an incidence of 2.3% (41/1,795) of total tumors. These 41 cysts include both the histologic types and exclude cysts located anterior to the orbital septum. Many authors who write on the subject of dermoid cysts combine preseptal and postseptal cysts as orbital in location. If we had included the preseptal cysts that we encountered surgically since the beginning of our survey (1948), our present total would be approximately 70 cysts.

The popular, anatomically broad (both preseptal and postseptal types) concept is the basis for an oft-repeated statement that the dermoid cyst is the most common orbital tumor of childhood. In our strictly orbital categorization, dermoid cyst was fifth in frequency in the list of childhood (first decade) tumors (Table 3.4). In the second decade, dermoid cyst was second in frequency. Two thirds of all dermoid cysts in our survey occurred in the first two decades of life. The cysts located in the retrobulbar space occurred more often in the later decades and were usually of the epidermoid types.

Our oldest patient was a 75-year-old woman who presented with a history of "fullness" in the right temporal fossa (see Fig. 4.1) and protrusion of the eye, of 4 years' duration. The eye had a 3-mm proptosis with inward and downward displacement of 2 mm. The cyst was intradiploic in the orbital portion of the sphenoid bone, causing expansion of bone in both the orbital space and temporal fossa. The sex incidence of our series was 19 men and 22 women. All cysts were unilateral.

The largest series of orbital dermoid cysts published since our last edition is that of Shields et al. (1997). They compiled 195 consecutive, histopathologically proved cases over a 32-year period. They included ten cases of conjunctival cysts and an unspecified number of periorbital cysts. Their incidence data would be more valid had they excluded these conjunctival and periorbital cysts. The value of their article is the anatomic classification they proposed for the management of cysts lined by keratinizing stratified squamous epithelium and containing adnexal elements of hair, sebaceous glands, and sweat glands.

Bonavolonta et al. (1995) reported 145 patients observed between 1976 and 1992. They carefully classified their cases, in relation to the orbital septum, as exophytic (76 patients) and endophytic (69 patients). The median age was 7 years, and the oldest patient was 53 years.

Clinical Features

We follow the current trend of addressing the clinical aspects of these cysts according to their clinical and anatomic location—superficial, palpable, and nonpalpable deep cysts.

The palpable type (see Fig. 4.2) is a smooth, firm, nontender, oval mass usually located along the superior orbital rim and attached by a pedicle of fibrous tissue to the zygomatic frontal synostosis or maxillofrontal synostosis. In this location, the mass is easily palpable and can be rolled between the thumb and forefinger. The mass is not attached to the skin. Seldom is it larger than 2 cm in length. The tumor is usually diagnosed before the patient reaches 5 years of age.

The other superficial cyst (see Fig. 4.3), postseptal in location, requires a longer period of growth before breaching the septum and becoming palpable in the subcutaneous space of the eyelid. This cyst usually pops through a hiatus that develops between the orbital septum and its attachment to the bone, which may not occur until adolescence. In two of our patients, such a cyst was located in the lower orbit, one in the medial quadrant and the other in the lateral quadrant. Proptosis or displacement of the eye, bone

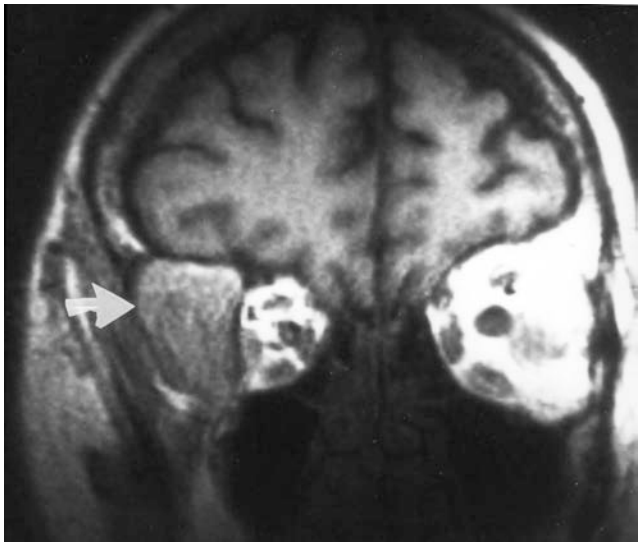

Figure 4.1 Magnetic resonance imaging showing large extension of a cyst into the right temporal fossa (*arrow*).

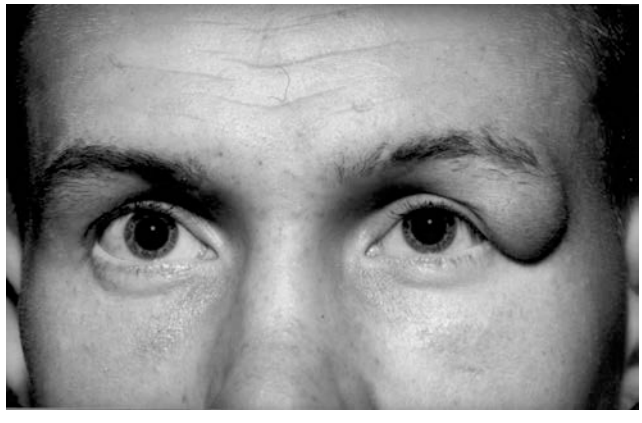

Figure 4.2 A superficial, juxtasutural, exophytic dermoid cyst with a small, nontender mass in the superolateral area of the left upper eyelid just beneath the orbital rim. During the subsequent 17 years, the tumor slowly increased in size. When the tumor was surgically removed intact, it measured 2.5 cm in diameter.

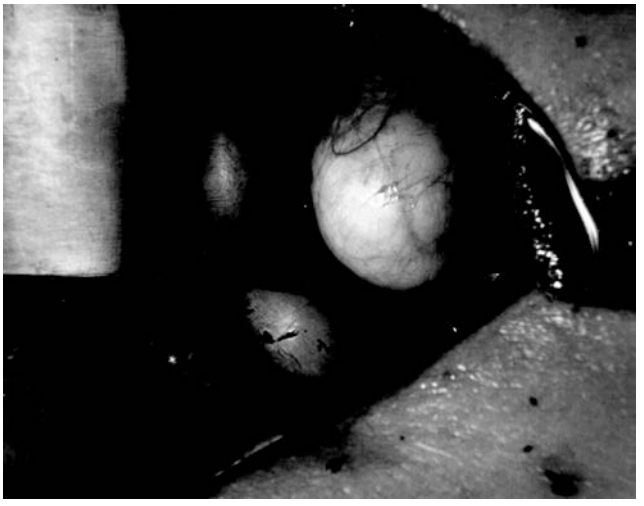

Figure 4.3 An *in situ* superficial, juxtasutural, endophytic dermoid cyst (3 × 2 × 1 cm) attached to the superolateral wall of the left orbit in a 17-year-old man. Two metal retractors are positioned to the right of the mass.

remodeling, (Sathananthan et al., 1993) and diplopia are seldom features of these superficial cysts.

Clinical features of deep (retrobulbar and peribulbar) cysts are another story. Their behavior is contrary to the predictable behavior of superficial cysts. The origin of the deep cyst is either some unseen or unknown embryonic rest attached to a soft tissue structure, usually muscles in the orbital space, or, more often, the diploic space of the frontal, sphenoid, or zygomatic bone. If the cyst selects the frontal or sphenoid bone, a round hiatus eventually develops in the outer table of the affected bone, allowing access to anterior or middle cranial fossa. Less often, the cyst expands into the temporal fossa.

The "giant," "dumbbell," and "hourglass" dermoid cysts are usually intradiploic in origin. These cysts have expanding orbital and extraorbital components. If the extraorbital component presents in the infratemporal fossa, the pressure of the temporalis muscle on the cyst may induce proptosis of the eye during mastication (Whitney et al., 1986), "chewing oscillopsia" (Knight et al., 1984), and "bobbing" of the eye (Rootman and Lapointe, 1988). Emerick et al. (1997) reported chewing-induced transient visual impairment in a 29-year-old woman.

An intradiploic cyst rarely presents as a discharging sinus tract. Honig (1998) reported such a case involving the frontozygomatic synostosis. More likely, a chronic draining sinus was associated with recurrent cysts that resisted complete excision.

The origin of a long-standing deep cyst in the medial confines of the orbit is usually obscure. It probably arises from an epithelial nidus attached to some soft tissue structure. This cyst can easily penetrate the thin ethmoid plate, but we are not aware of any report where it blossomed into an ethmoid sinus. Instead, it may expand superiorly, remodel the frontal bone, and ultimately evacuate dirty tan–colored contents with a slightly musky odor through a sinus tract opening under the superior nasal rim near the trochlea. In the years before present imaging technology, the draining sinus was easily mistaken for a tract from a mucocele of the frontal sinus. These cysts may reach a considerable size because of their insidious expansion, with proptosis of 5 to 8 mm. Diplopia and impairment of extraocular muscle motility are common accompaniments, but severe reduction of visual acuity is uncommon.

Imaging Aspects

While discussing this subject, it is important to keep in mind the multiple tissue variables of a dermoid cyst, because relative homogeneity or heterogeneity of the mass influences the ultimate imaging display. The cyst may include all or a few of the following: Keratinizing squamous epithelium, fat, cholesterol clefts, old hemorrhage, hairs, keratin, sebaceous gland, macrophages, lipid globules, multinucleated giant cells, chronic inflammatory cells, and calcium.

MRI of the small superficial cyst located along the orbital rim is rather consistent. Usually, the cyst is a smooth, oval, well-outlined mass with a homogeneous center of low attenuation (see Fig. 4.4). The rim of the mass may show enhancement with contrast injection, but the cyst's contents show no enhancement. A slight faceting or pressure thinning of adjacent orbital rim is present in some cases.

In the posterior orbit, the cyst is larger and associated with bone erosion that allows many cysts to egress into

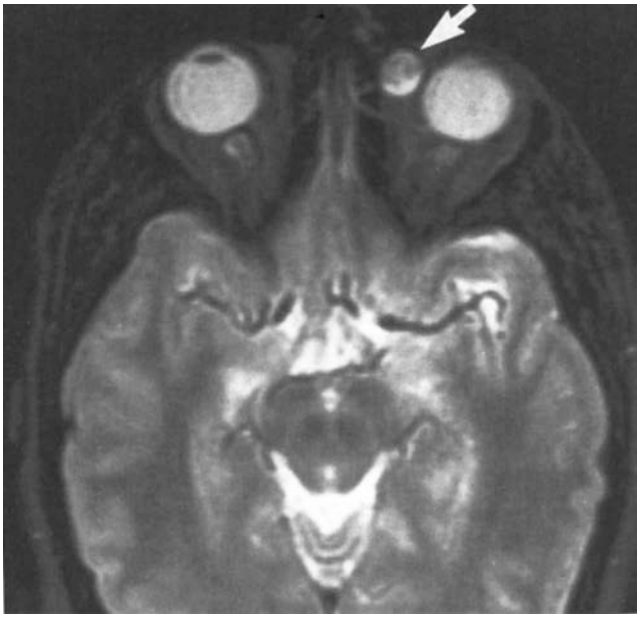

Figure 4.4 T_2-weighted magnetic resonance imaging of an oval mass (*arrow*) in the superonasal quadrant of the left orbit of an 18-year-old woman. The mass shows mixed signal characteristics compatible with both fat and fluid components.

the intracranial vault or temporal fossa. The contents show a heterogeneous signal, reflecting different densities of fat, fluid, keratin, and epithelial debris.

Chawda and Moseley (1999) reviewed CT scan images of 160 patients with histologically proved orbital dermoid cysts over a 20-year period. Eighty-five percent (136/160) had adjacent bone changes, 46% (73/160) showed lower signal attenuation than water in the vitreous body, 14% (22/160) had calcification, and 5% (8/160) had fluid levels. They concluded that the range of appearance was wide.

MRI is also useful because of the high signal intensity of fat that provides excellent contrast between the cyst and its environs (see Fig. 4.5A). In large posterior-positioned cysts, the signal may show differing intensities dependent on the content of the tumor. This may vary from one cyst to another. Some tumors emit a T_1/T_2 signal similar to vitreous or only the T_2-weighted signal that shows hyperintensity. The tumor may also be hyperintense on T_1-weighted images (Newton and Bilaniuk, 1990). Finally, the image may indicate a fluid level within the cyst that shifts when the patient changes from a supine to decubitus position (Fig. 4.5B).

Plain film radiography is seldom used now for diagnosis of an orbital mass unless the tumor invades the bone. Such is the case with a large dermoid cyst in the posterior orbit that erodes the bone and enters the intracranial vault. To a lesser extent, this applies to the intradiploic cyst in the lateral portion of the sphenoid bone that reaches the intracranial vault through the marrow space. Both of these situations require surgical intervention. The size and location of the bony aperture are well outlined in a standard Caldwell or Water projection (see Fig. 4.6). The diagnostic feature, almost unique to the dermoid cyst, is the polished appearance of the bone rim surrounding the protruding cyst wall. A skull film is superior to CT scan in delineating this feature. This sclerosis is the result of long-time, persistent pressure from the expanding mass. Bone sclerosis of such a degree is not seen in other tumors that enter or exit through an unwanted hole in the bone partition between the orbital space and the intracranial vault, such as encephaloceles, meningoceles, various cranial heterotopias, plasmacytoma, hematoceles, Langerhans

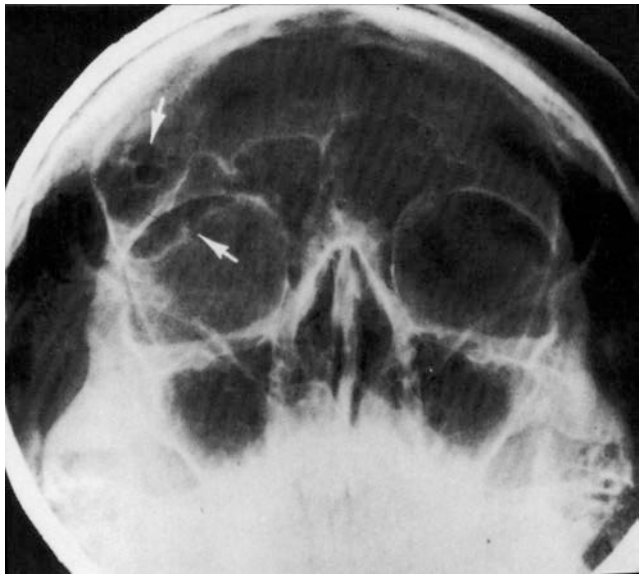

Figure 4.6 Large epidermoid cyst eroding the roof of the right orbit (*lower arrow*) with a small hiatus (*upper arrow*) through the inner table of bone into the intracranial vault (Water view).

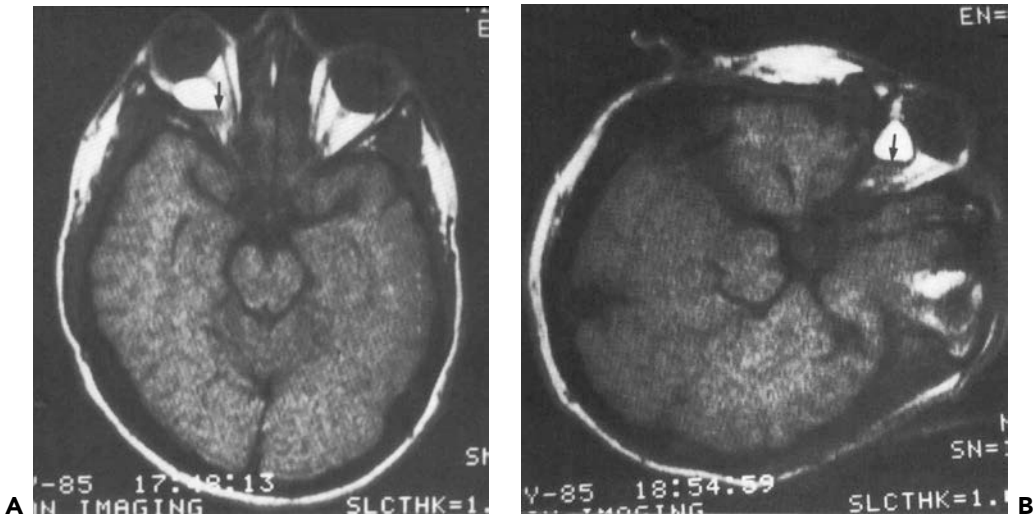

Figure 4.5 Magnetic resonance imaging of a 27-year-old man with a sharply outlined mass directly posterior to the right eye showing high signal intensity of fat. **A:** Supine position showing a narrow lucent zone (*arrow tip*) of fluid along the posterior rim of the mass. **B:** Left decubitus position showing a change in the contour of the mass and a shift of the fluid level (*arrow tip*) to the dependent position. (Courtesy of Byrd WA, Shreveport, Louisiana.)

histiocytosis, mucoceles of the frontal sinus, malignant neoplasms, and aneurysmal bone cyst.

Ultrasonography is a practical method for office diagnoses of a superficial dermoid cyst in a small child.

Pathology

Histopathologically, this cyst is divided into dermoid and epidermoid types. In the initial pages of this chapter, we stated our intent based on diagnosis, clinical features, and management, to regard it as one tumor. Both types have a lining of stratified squamous epithelium, but the epidermoid type does not have epidermoid appendages in its wall, which are characteristic of the dermoid type. Both types contain desquamated keratin.

This thick-walled dermoid type contains hair follicles, hair, sebaceous glands, and sweat glands (see Fig. 4.7). The smaller dermoid type has a whitish yellow color and may have shallow fat pads attached to its surface. Anatomically, it is usually located in the anterior orbit.

The larger, thin-walled epidermoid type is filled with a cheesy-textured material (see Fig. 4.8), flecks of calcium, and cholesterol clefts. The walls of these cysts have a lipogranulomatous reaction featuring macrophages, multinucleated giant cells, and hemosiderin deposition (see Fig. 4.9A and B).

In our third edition, two reports are referenced in which squamous cell carcinoma was found in an epidermoid cyst.

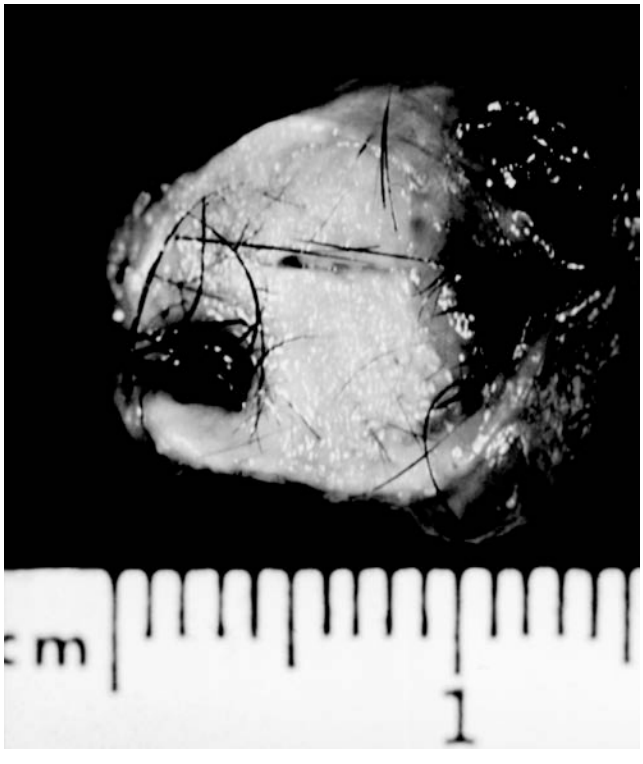

Figure 4.7 Dermoid cyst (opened) showing exuberant growth of hair.

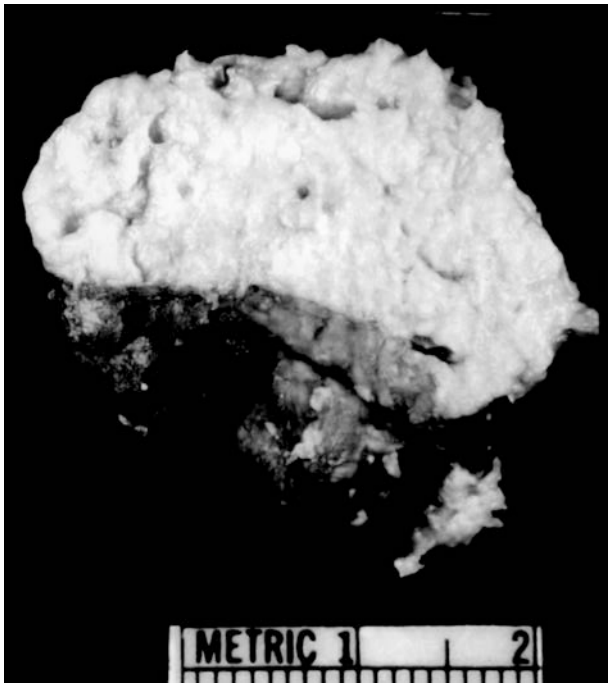

Figure 4.8 Epidermoid cyst (opened) showing copious cheesy material.

Both patients were 53 years old. Since then, Holds et al. (1993) reported two patients in whom the lining of their epidermoid cysts underwent malignant transformation into invasive squamous cell carcinomas. Each patient underwent orbital exenteration combined with craniofacial resection.

Treatment

We limit this discussion to the surgical management of cysts posterior to the orbital septum. This excludes superficial cysts located in the adnexal tissues of the upper eyelid. This cyst is usually juxtasutural, seldom larger than 5 mm, and usually removed before school-going age. It can be removed intact through an eyelid crease incision.

Our favorite approach to the common cyst attached to, or adjacent to, the zygomatic frontal suture is the superotemporal, anterior infrabrow incision. The incision can be made directly over the cyst, and the aim of further dissection is intact removal of the mass. Next, the orbicularis muscle and fascia of the eyelid are incised and retracted. At this point, the anterior face of the cyst may be seen through a hiatus in the orbital septum that has been eroded by the expanding tumor. The hiatal opening is enlarged superiorly and inferiorly to accommodate delivery of the cyst.

These cysts are large, probably have been present since birth, but are not accessible for surgical removal until the second decade of life. Figure 4.10 illustrates the surgical exposure necessary to remove a sizable dermoid cyst just before severing its attachment to the bone. To prevent

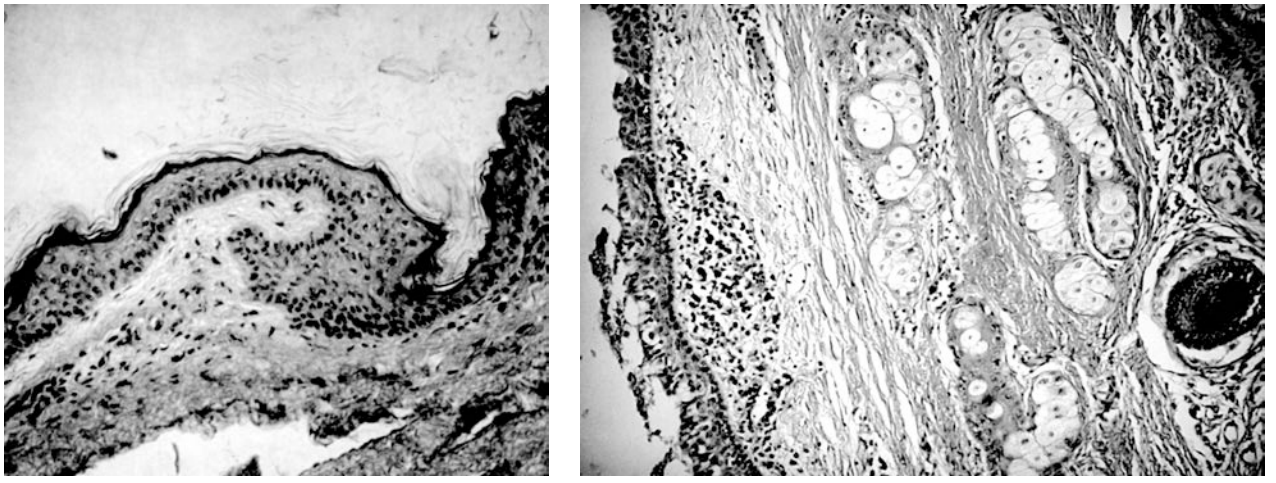

Figure 4.9 **A:** Section of epidermoid cyst. The lumen is shown at the top. The lining (*arrow*) is keratinizing squamous epithelium. Thin strands of keratin are shedding into the lumen from the epithelial surface (hematoxylin and eosin, original magnification ×160). **B:** This section of dermoid cyst wall shows squamous epithelial lining, hair shaft, sebaceous glands, and focal collections of chronic inflammatory cells (hematoxylin and eosin, original magnification ×70).

undue rupture of the cyst, a tag of periorbita is left attached to the bone at the time of excision.

In many cases, because of the size and long duration of growth, the cyst is adherent to the posterior surface of the orbital septum in addition to the adjacent soft tissue components of the anterior orbit. These cysts usually have a thick wall that permits freeing of adhesions to surrounding soft tissues once the mass is detached from the bone. Detaching the mass from the bone is accomplished by grasping the pedicle of the tumor and adjacent periorbita with a small forceps, excising the tumor from the bone, and bringing the specimen forward through the incision in the orbital septum. Thus mobilized, the back and sides of the tumor can be freed of adhesions, and with use of cotton-tipped applicators augmented by a cryoprobe as a traction lever, the mass is peeled away from the orbital septum. Whatever the method of dissection, there is usually immediate, profuse bleeding when the tumor's vascular pedicle is severed. Bleeding can be controlled by wet-field bipolar cautery. If, on inspection of the surgical field, an embryonic rest of epithelium remains within the bone, it can be reamed out by a small burr attached to a bone drill. A remnant of epithelium in a niche of bone is easily overlooked and may be a nidus for recurrence of the cyst. Recurrent cysts should be imaged radiographically or by CT scan to rule out this possibility.

After suturing the orbital septum to either the periorbita or periosteum, the soft tissue and skin are closed in layers. With present-day sutures, there is little worry about healing with a scar.

Occasionally, aberrant cysts occur somewhere along the inferior or lateral rim of the orbit just beneath the attachment of the lateral palpebral raphe. They are small and present at birth or soon after. A lump or a surface of the mass is frequently visible beneath the conjunctival fornix. A transconjunctival fornix incision is appropriate for removal of this cyst, and intact removal is the rule. The incision should be sutured to prevent symblepharon.

Before the use of CT scan and MRI, surgical removal of an epidermoid-type cyst from the retrobulbar space, without bone involvement, was a frustrating endeavor. The patient's symptoms suggested that the suspected cyst had been present for many months or several years and was probably quite large. The size of the cyst could be estimated by the amount of proptosis—the greater the numerical value of proptosis, the larger the cyst. The position of the cyst could be guessed by the direction of displacement of

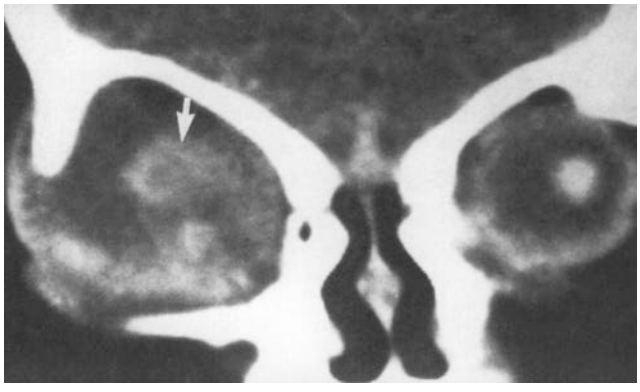

Figure 4.10 Coronal computed tomography scan of 25-day-old female infant with a congenital cystic eyeball in the right orbit. The orbit is enlarged and occupied by a partially cystic mass. On histopathologic study, the solid portion (*arrow*) showed nests of dysplastic retinal rosettes. (Reprinted from Wildon RD, Traverse L, Hall JG, et al. Oculocerebrocutaneous syndrome, *Am J Ophthalmol*. 1985;99(2):142–148, with permission from Elsevier.)

the eye. The size and position of the cyst are now part of the imaging mode display. The surgeon can select the best place to enter the orbit for direct access to the tumor. Once the appropriate approach has been made and the surface of the mass is visible, there remains the frustration of how to remove the tumor intact.

If the cyst has not become large enough or has not been present long enough to have fused with surrounding soft tissue, a cleavage plane is probably present. The surgeon may commence dissection using cotton-tipped applicators and blunt scissors or other dissecting tools. Dissection of tumor from surrounding soft tissue is similar to removal of a cavernous hemangioma. However, application of the cryoprobe to the surface of the cyst for its traction and leverage may not be a useful adjunct because the thin wall of the cyst may rupture, defeating the goal of intact removal.

Many large cysts of long duration in the retrobulbar space fuse to the surrounding soft tissue because of relentless pressure incurred in expansion. The wall of such a cyst is almost paper-thin and has a bluish color in contrast to the flesh color of a thick-walled dermoid-type cyst in the anterior orbit. Also, the cyst is quite firm and filled with cheesy-textured material and semifluid debris almost to the point of rupture. Removing such a cyst intact is impossible.

Instead, we prefer to open the mass widely and decompress it by sucking out the contents. Once the cyst is collapsed, the surgeon can see the important structures in the orbit—muscles, large blood vessels, and nerves—to which the cyst wall is attached. The periphery of the tumor likely is adherent to the dura of the optic nerve. Bits and pieces of the cyst wall can be nibbled away from the muscles, large peripheral nerves, and blood vessels with scissors. However, this dissection should not be attempted along the optic nerve because it inevitably results in some visual loss. It is best to observe the maxim, ''The less manipulation of the optic nerve, the better the visual outcome.'' At this point, the surgeon wraps several layers of gauze around his forefinger and scoops out, swabs, and scours the remaining lining epithelium. The surgeon may or may not wish to insert a removable drain into the orbital cavity at the time of closure.

Epidermoid cysts that have extension into the intracranial vault through erosion of the frontal or sphenoid bone and dumbbell cysts arising from an embryonic epithelial rest within the synostosis of the sphenoid and zygomatic bones should be approached through a coronal orbitocraniotomy for maximum exposure. This approach allows evacuation of the orbital portion of the cyst, relieving the possibility of any complications caused by penetration of the cyst into the intracranial space. Likewise, along the lateral orbital wall, both orbital and temporal fossa lobes of a dumbbell cyst are visible for removal. Bits of bone surrounding the bony aperture housing the sutural embryonic epithelial nidus can be easily removed, and the marrow passages of the sphenoid can be inspected for any epithelial extension.

Technically, these large epidermoid cysts are only partially or incompletely removed by all these surgical maneuvers, and the patient is subject to recurrence. However, such an excision is not invariably a factor in recurrence. If all the epithelial lining is peeled away, the cyst does not recur.

Conjunctival Cysts

Another congenital cyst closely related to the preceding dermoid cyst, but very rare, is the conjunctival cyst. In the older literature, it is called a *simple cyst*. Jakobiec et al. (1978) performed a retrospective study of all cystic adnexal lesions that had been classified as *epidermoid*, *dermoids*, or *cholesteatomas* on file in the ophthalmic pathology library at Columbia University's College of Physicians and Surgeons, accessioned from 1929 to 1977. A total of 128 specimens were reviewed.

Among them were seven cysts lined by stratified, nonkeratinized epithelium, and their walls contained adnexal structures. These cysts, therefore, were neither epidermoid nor dermoid. The name *conjunctival dermoid* was assigned to this group. Another five had a similar epithelium without adnexal structures in their walls. To this group, Jakobiec et al. (1978) assigned the designation *conjunctival cyst*. We believe this is the congenital cyst in our classification.

Since 1978, conjunctival dermoid cysts have been reported nearly three times as often as simple conjunctival cysts. The former are a hybrid lot; their pathogenesis is speculative. The congenital conjunctival cyst has a lining of stratified, nonkeratinizing cuboidal epithelium intermixed with mucous-producing goblet cells and containing either a clear or sticky serous fluid. The cyst is thin-walled, translucent, and soft, does not alter the orbital bone, and is usually not evident at birth. The cyst remains hidden in the deeper portions of the superior conjunctival fornix until it enlarges and presents as a puffiness of the adjacent upper eyelid or a palpable mass of indefinite contour. This does not occur until later in infancy, early childhood, or adolescence. If it is possible to evert the patient's upper eyelid, the cyst comes into view.

Since 1988, several cases of this type have been reported—one case by Tsai et al. (1996), two of four cases by West et al. (1997), two cases among 197 orbital cyst specimens by Shields et al. (1997), and one case by Boynton et al. (1992).

With the present orbital-imaging techniques, cases are now identified, which are attached to the superior oblique tendon (Boynton et al., 1992) and to the common sheath of superior rectus and levator palpebrae superioris muscles (Can et al., 1999; Rose and O'Donnell, 1995). These three references seem to be the first to authenticate the origin of the simple cysts from peribulbar extraocular muscles in the superior anterior orbit. We believe that, in the years

before the CT scan and MRI, the origin of these cysts was unknown.

In the report by Rose and O'Donnell (1995), the two female patients, aged 14 months and 23 years, and the two male patients, aged 3 1/2 and 39 years, all with unilateral cysts, are of particular interest. A bluish purple mass was visible in the upper conjunctival fornix and palpable through the upper eyelid. All patients had blepharoptosis but normal levator muscle function. The 23-year-old patient had ptosis since birth. The duration of signs and symptoms in the other three patients was shorter.

The authors approached the tumors through a transconjunctival incision along the upper border of the superior tarsal plate. With careful microdissection, the cyst was mobilized superiorly and posteriorly through the orbital septum to its terminus sandwiched between the levator palpebrae superioris and superior rectus muscles, within the sheath encompassing both muscles. In all four patients, the tumor was removed intact.

There is less information about the 37-year-old woman reported by Can et al. (1999). A transconjunctival approach was used, and the approximate dimensions of the cyst were 25 × 19 × 13 mm. The approximate measurement suggests that the tumor might have been decompressed or ruptured during removal. Acquired conjunctival cysts are a frequent postoperative complication of present-day scleral buckling procedures.

Congenital Cystic Eyeball

The present name of this developmental cyst was suggested by Ida Mann (1937) in her text. It is the same tumor described by earlier authors as an anophthalmos with a cyst. It is quite rare. Hayashi et al. (1999) found only 14 histopathologically proved cases, including their two cases, published in the English language literature since 1964. The stage for this tumor is set at about the fourth week of embryonic life, when the primitive optic vesicle should invaginate and form the secondary optic vesicle. Such development is aborted at this point and results in a slowly enlarging primary optic vesicle. Histopathology reflects the primitive nature of the tumor. It is composed of a dysplastic array of primitive neuroectodermal elements, immature mesenchyme, connective tissue, glial and neuroglial tissue, squamous and glandular epithelium, cartilage, bone, and calcium. The cyst may be unilocular or multilocular. A tiny white or yellow dot-like structure corresponding to the optic nerve head may be found along some of the mass. The fluid content is usually clear yellow; a more viscous purple fluid probably represents prior hemorrhage.

The sex incidence is equal. The cystic eye usually affects one orbit of an infant, with a normal eye in the other orbit. Cases of this type reported in the literature since the subject was reviewed in our third edition include those published by Gupta et al. (1990) and Mansour and Li (1996). Hayashi et al. (1999) also observed two infants, a 13-month-old boy and a 2-week-old girl, who were considered to be anophthalmic and developed a cystic lesion in the left orbit with protrusion of lower eyelid. Neonates with cystic eyes are also subject to myriad other congenital anomalies (Wilson et al., 1985; Pasquale et al., 1991).

The cystic eyeball differs from teratoma in the same age-group in its smaller size, it does not have a formed eye, and it is partially covered by an upper eyelid unless the elasticity of the eyelid is overcome by pressure of the expanding mass.

Both CT scan and MRI show a cystic mass containing an admixture of solid components and fluid. The orbit may be enlarged and an optic nerve track visible (Fig. 4.10).

The common management of a cystic eyeball is surgical removal. The conjunctiva is incised and dissected from the underlying cyst, creating flaps. Mansour and Li (1996) removed a 3 × 3.5-mm cyst intact in spite of adhesion of the cyst wall to periorbita. If the wall of a large cyst seems too thin to permit dissection, the fluid content can be aspirated and the cyst extirpated or exenterated by severing the optic nerve with a snare. Conjunctival flaps are used to cover the exposed bone. A noteworthy case reported by Awan (1986) was a 29-year-old woman with a translucent, multiloculated cyst in the left orbit, first noted at birth. After an initial period of slow enlargement in early childhood, the mass became stationary (see Fig. 4.11). No surgical excision was necessary.

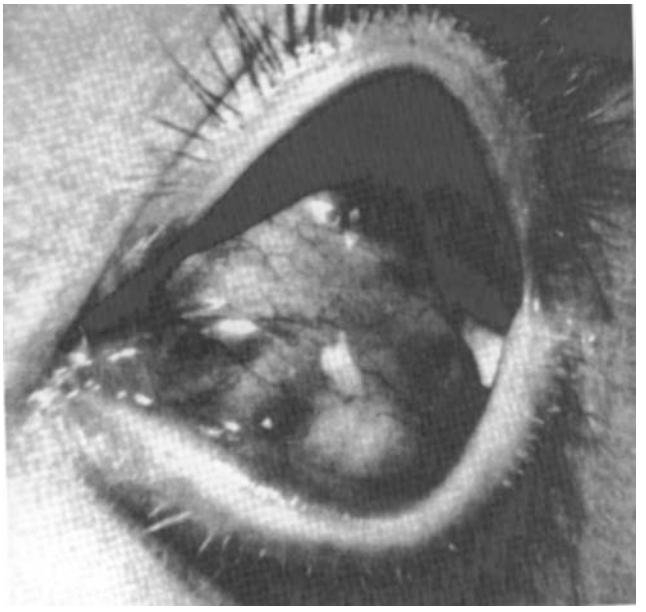

Figure 4.11 Congenital cystic eyeball in a 29-year-old woman that had not increased in size since early childhood. The pyramidal-shaped, multiloculated eyeball (*center*) has a poorly developed cornea at its apex. The eyelids and conjunctival vessels appear normal. (Reprinted from Awan KJ. Intraocular and extraocular colobomatous cysts in adults. *Ophthalmologica*. 1986;192:76–81, with permission.)

Microphthalmos with Cyst

This anomaly of the embryonic eye occurs at a stage immediately after a mishap during fetal development that results in the preceding tumor, the congenital cystic eyeball. The basic defect is improper fusion of margins of the fetal fissure, in essence, a coloboma. If prolapse of primitive ocular tissue into the imperfect cleft occurs soon after the fourth week of embryonic life, the 8-mm stage, the resulting cyst is present at birth. However, if closure of the fetal fissure is complete but defective, ectasia of thin sclera with a cyst-like expansion into the orbit may not occur until some time after birth. A noteworthy case of this type was a 27-year-old man reported by Nowinski et al. (1984). The patient was born with an enophthalmic eye and had worn a cosmetic shell for approximately 20 years. Then, progressive proptosis occurred owing to delayed enlargement of the cystic component.

The end result is a defective small eye to which is attached a herniated cyst-like mass. The cyst may be a small appendage of the larger eye or a large mass that greatly exceeds the size of the attached globe. In the latter, the microphthalmic eye may not be evident at the time of presentation because it is concealed by the oversized cyst. Size may vary between these large and small extremes. If the bilobed structure (eye and cyst) is small, an enophthalmic, strabismic eye with a cystic appendage is the presenting feature. When the cyst becomes larger than the eye, a soft, vascular pink mass occupying the palpebral fissure may be the presenting feature. Finally, a larger bluish, balloon-like mass may push out of the orbit, partially covered by a stretched lower eyelid (see Fig. 4.12). It is these larger cysts that require differential diagnosis from other orbital tumors in the neonatal period.

The incidence of microphthalmos with cyst is greater than that of either teratoma or congenital cystic eyeball but less than that of encephalocele. The laterality of the tumor and its sex incidence are equal. Most of the cases in the literature are unilateral, including two cases in our total series. Since our review of this subject in the third edition, single cases have been recorded by Guterman et al. (1990) and Kodama et al. (1998). Bilateral cases are not common. Mutations in the *PAX6* homeobox gene and chromosomal deletion in the 14q, g22g23 region of the genome may be responsible for the congenital defect (Bennett et al., 1991; Bardakjian et al., 1997).

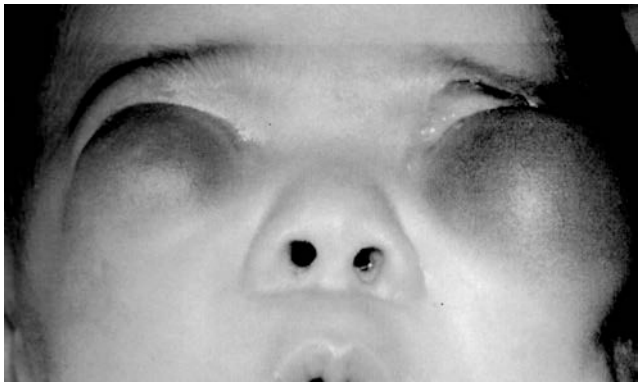

Figure 4.12 Microphthalmos with cyst in a 3-month-old female infant with bilateral orbital cysts that were attached to microphthalmic globes. The cysts were surgically verified. (Courtesy of Cameron JD, Rochester, Minnesota.)

Pathologically, the eye is markedly small and displaced superiorly by the inferior nasal colobomatous cyst. The eye may contain immature or dysplastic evidence of cornea, iris, ciliary body, lens, vitreous, choroid, and retina. The colobomatous defect allows protrusion of the cystic structure that is lined by highly vascularized glial tissue mixed with some dysplastic retinal tissue. This inner lining in the case described by Lieb et al. (1990) stained diffusely with glial fibrillary acidic protein. Deep to the glial tissue along the inner wall, some staining for neurofilaments was also noted. Attached to the outer scleral wall posteriorly, some skeletal muscle fibers may be identified.

CT scan outlines the position of the abnormal eye and the size of the cyst. If the cyst is very large, it encompasses the small eye and hides it from view. If the cystic structure is located superiorly, it is probably a congenital cystic eyeball, not a microphthalmic cystic eyeball. If the CT scan display shows specks of calcium, the lesion is probably a cystic teratoma. The colobomatous cyst appears hypotense on T_1-weighted MRI and hyperintense on T_2-weighted MRI (Kaufman et al., 1998).

In almost all cases, the microphthalmic eye and its appendage must be removed for cosmetic reasons because of continued expansion of the cystic component. After removal of the tumor, some hemifacial deformity may occur due to lack of stimulus for orbital bone growth. To ameliorate this, Gossman et al. (1999) used an orbital tissue expander in five children aged 10 months to 6 years. Gradual inflation of the expander to a diameter of 22 mm reduced the average preoperative orbital dimension deficit of the group from 14.6% to 3.8% after surgery. The average expansion period was 56.8 weeks (range, 20–100 weeks).

Cephaloceles

Cephalocele is a broad term that encompasses herniations into the orbit of the parenchymal brain tissue (encephalocele), membranous brain cover (meningocele), or a mixture of brain and meninges (meningoencephalocele). Technically, the cephaloceles retain some attachment to the brain by a cord or stalk of tissue. Usually, they are associated with a defect of orbital bone at the junction of the frontal and ethmoid bones, or at the lesser and greater wings of the sphenoid bone, or at the skull base.

Incidence

These tumors are not common but are more frequent than teratomas. They are mostly found in the young and

often are visible at birth. Their occurrence in adults is a curiosity. Mahapatra et al. (1994) reported 30 cases of anterior encephaloceles treated between 1973 and 1990. At the time of surgery, >60% of the patients were <2 years old. Only one child was older than 10 years. Twenty-six patients had frontoethmoidal defects. Later, Mahapatra (1997) retrospectively studied 65 children with anterior encephaloceles spanning a 22-year period (1973–1994). Six children were older than 10 years. Nasoethmoid type was the most frequent, encountered in 45 patients. In our 50-year survey, we observed only four cases, three females and one male. Three of these patients were <1 year of age. The fourth patient was 11 years old at the time of presentation.

Clinical Features

These lesions have been classified according to anatomic location, structural configuration, and presence or absence of external manifestations. Anatomically, in reference to the orbit, cephaloceles are either anterior or posterior. The anterior tumor is usually visible, but the posterior lesion may remain hidden for some months or years. Structurally, the herniations are either sincipital or basal in origin. The sincipital mass is almost always visible. The basal tumor may or may not be manifest in early life, depending on the size and location of the osseous dehiscence.

The anterior sincipital variant is the most common and is usually evident at birth as a paranasal mass located at the nasofrontal–orbital junction (Koopmann and Reynolds, 1981) (see Fig. 4.13). The mass in this illustration is smaller than most of the anterior cephaloceles depicted in the literature. The size of the mass determines the degree of displacement of the eye. The mass is painless and feels less firm than other developmental cysts because the content of soft neural tissue within the mass usually exceeds that of fluid. The mass slowly enlarges during a period of months or years because of an intrinsic cystic degeneration.

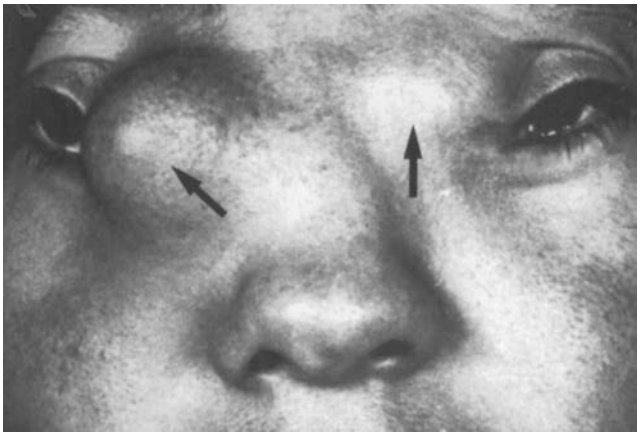

Figure 4.13 Bilateral nasoethmoidal encephalomeningocele in an 18-year-old woman that had enlarged slowly since birth. Note the paranasal sinus masses (*arrows*), broad nasal root, hypertelorism, and increased bitemporal diameter. At surgery, the herniations measured 4 × 4 × 5 cm on the right side and 1 × 1 × 1 cm on the left. (Reprinted from Koopmann CF, Reynolds AF, Combined neurosurgical-otolaryngologic. *Otolaryngol: Head Neck Surg.* 1981;89:545–549, with permission from American Academy of Otolaryngology: Head and Neck Surgery Foundation, Inc.)

If the dehiscence in bone is located posteriorly along the frontoethmoid suture, the herniation of tissue pushes the eye laterally. In this case, the paranasal mass may not become apparent until some months later. The cephalocele was of this type in the 11-year-old girl in our series of four patients. She presented with a protrusion of the left eye of 8 months' duration (see Fig. 4.14A). The left eye had a 4 mm proptosis, with 3-mm downward displacement and 7-mm lateral displacement. A bony mass was palpable in the superonasal orbit. CT scan imaging revealed an enlargement of the orbit and an intraorbital mass extending into the anterior cranial fossa (Fig. 4.14B). Anterior orbitotomy uncovered a bluish cyst-like mass covered by a thin shell of bone. The bone was removed, the cyst contents were evacuated, and the membrane-like wall of the cyst was stripped from the exposed dura. Bleeding was marked and difficult to control. Others who approach these tumors surgically have also commented on this bleeding tendency.

The spheno–orbital encephaloceles are oriented to the posterior orbit. Herniation occurs either through the superior orbital fissure, a defect in the bone along the lesser wing of the sphenoid bone, or an aplasia of the greater wing of the sphenoid bone. Most of these are caused by the mesodermal dysplasia associated with neurofibromatosis type 1 (Sugawara et al., 1996; Clauser et al., 1998; de Vries et al., 1998). These tumors, secondary to aplasia of the greater wing of the sphenoid bone, are large and result in a pulsating exophthalmos. A meningoencephalocele arising in the anterior skull base associated with neurofibromatosis and extending through an enlarged superior orbital fissure should also be included in this group (Chapman et al., 2000).

Several cephaloceles with unusual presentations have been recorded (see Fig. 4.15). Soyer et al. (1990) reported a case presenting with trigeminal neuralgia caused by a herniation through a congenital defect in the greater wing of the sphenoid bone associated with angioma of the soft palate. Terry et al. (1993) observed a neonate presenting with a soft mass in the superomedial conjunctival fornix that on surgical exploration was an ependymal cyst filled with cerebrospinal fluid and containing neuroglial and meningeal tissue. Gunduz and Gunalp (1997) reported an 18-year-old man with right congenital symblepharon (abortive cryptophthalmos), cleft palate, visual acuity of no light perception, and an absent right orbital roof. Bilateral cases associated with midline craniofacial abnormalities have been reported by Levy et al. (1989), Cataltepe and Ozcan (1990), and Hershewe et al. (1995). A white, excavated distorted optic disk is often associated with basal encephalocele, the "morning glory" disk (Goldhammer and Smith, 1975).

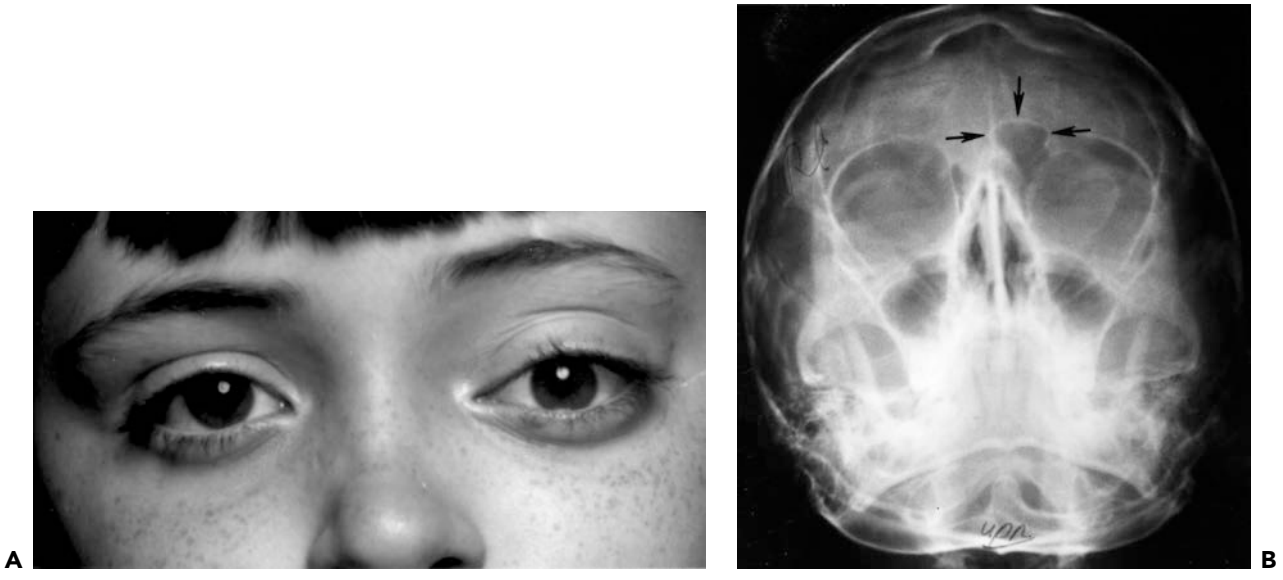

Figure 4.14 Meningoencephalocele. **A:** An 11-year-old girl with displacement of the left eye (forward 4 mm, down 3 mm, laterally 7 mm) of 8 months' duration. The bony hard mass, palpable in the superior nasal orbit, was surgically removed. **B:** Plain film radiograph shows a well-delineated defect (*arrows*) in the upper nasal orbital quadrant. The sharp, slightly polished margin of the defect suggested the diagnosis of dermoid cyst.

Imaging Aspects

Unless the bony dehiscence is tiny, CT scan images the defect and outlines the homogeneous appearance and cystic extension of the mass into the orbit. The solid content of the mass is isodense with the brain. MRI also shows features similar to that of the brain. The appearance of the cephalocele differs from that of dermoid cyst and teratoma, which have more fluid content.

Pathology

The basic element of these tumors is glial tissue with supporting connective tissue trabeculae. Occasionally, neurons, nerve fibers, and an ependymal lumen may be present. If the cyst is large, there may be a communication with the ventricular system (see Fig. 4.16). When a cephalocele is of long standing, as in adults, the meningeal layers may fuse and fibrose. The neural tissue also becomes edematous and degenerate, and calcium deposits may appear.

Treatment

The management of this developmental cyst is more complex than that of a posterior dermoid cyst of similar size located along the orbital–cranial interface. The best approach to the lesion is determined by the extent, size, and location of the congenital defect as revealed by imaging methods. The goal of the surgical team should be excision of the extracranial extension, resection of the

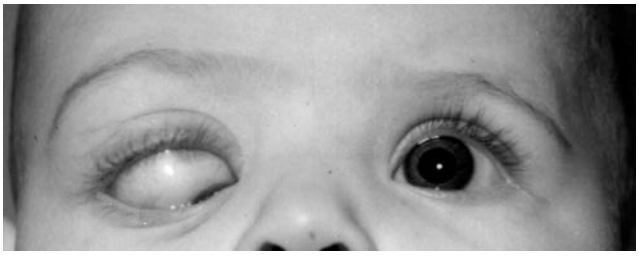

Figure 4.15 Downward and inward displacement of the right eye since birth in a 5-month-old female infant. The displacement was caused by a posterosuperotemporal meningoencephalocele. The cornea is almost covered by her lower eyelid.

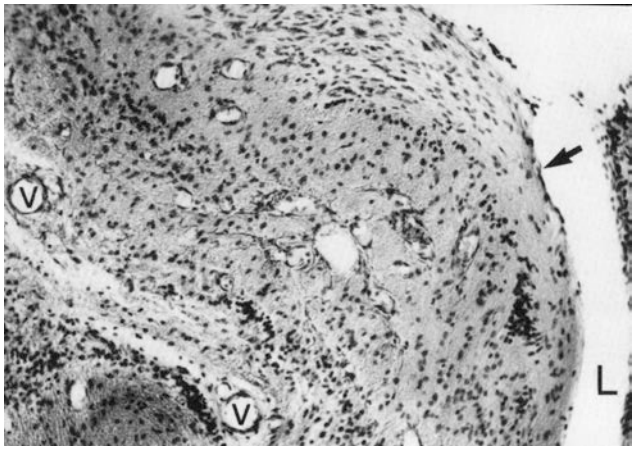

Figure 4.16 Cephalocele. The lumen (L) is lined by flattened ependymal cells (*arrow*) and communicates with the ventricular system (top). The mass of glial tissue contains many capillaries (V) (hematoxylin and eosin, original magnification ×120).

intercommunicating stalk, watertight repair of any dural tear, and repair of any remaining osseous defect, if it is large.

Surgical repair of frontoethmoidal and anterior fossa encephaloceles has been described by Forcada et al. (1993); Jacob et al. (1994); Mahapatra et al. (1994); Songur et al. (1999) and Holmes et al. (2001). Between 1986 and 1991, the Forcada group operated on six children and compared the advantages of the transcranial surgical approach versus a transfacial approach. They felt more comfortable using the transcranial approach to repair the defect. Macfarlane et al. (1995) treated 114 encephaloceles of the anterior cranial fossa in the 15 years preceding 1994. All were repaired transcranially. The craniofacial team of Songur et al. (1999) treated 21 patients. The team of Holmes et al. (2001) surgically treated 35 patients. They recommend a one-stage repair using both the transcranial and the external approach.

Repair of sphenoid orbital and frontotemporal encephaloceles is more complicated because of the frequent absence of a large portion of the greater wing of the sphenoid bones, a complication of an associated neurofibromatosis type 1. de Vries et al. (1998), comprising a team of surgeons from departments of neurosurgery, maxillofacial surgery, and ophthalmology, reported a 43-year-old woman with neurofibromatosis and complete absence of the superolateral wall of the right orbit. Intraoperatively, a new wall was constructed using the inner wall of the left frontal bone as a bone transplant. A free galeoperiosteum flap was used for watertight dural reconstruction. Neurosurgeons Clauser et al. (1998) reported a 25-year-old patient with neurofibromatosis localized in the cranio-orbital region. The defect in the greater wing of the sphenoid bone was closed by splitting part of the parietal bone flap. The bone graft had a concavity that fit perfectly and was fixed with wire to the margins of the anterior cranial bone defect.

The repair of basal encephalocele is even more complicated. Hershewe et al. (1995) reported a 35-year-old woman with bilateral absence of bony orbital roofs and a large defect in the floor of the anterior cranial fossa. Polyglycolic acid (Dexon) mesh filled with methacrylate was used to make a new floor for the anterior fossa and keep the frontal lobes of the brain out of the orbit. Chapman et al. (2000) described an unusual meningocele of the lateral wall of the cavernous sinus associated with neurofibromatosis. The defect consisted of a large space filled with cerebrospinal fluid that extended extracranially through an enlarged superior orbital fissure into the pterygopalatine fossa adjacent to the nasal cavity. It was obliterated through an intradural middle fossa approach, with fat packing and fenestration into the subarachnoid spaces.

Most encephaloceles affect the anatomic domain of more than one surgical specialty. In the past years, repair of this congenital defect was shifted from one surgical specialist to another, resulting in one, two, or three surgeries. In the past 10 years, surgeons from the fields of neurosurgery, ophthalmology, otorhinolaryngology, plastic and reconstructive surgery, maxillofacial surgery, and craniofacial surgery have shared their expertise to complete the necessary repair in one surgery.

ACQUIRED CYSTS

Hematocele

In the first two editions of this text, we titled this section of the chapter "Hematic Cyst." In the third edition, we changed the heading to "Organizing Hematoma." In retrospect, we do not believe either of these titles is proper for this hematogenous tumor. Technically, hematic cyst is not a true cyst because it lacks an epithelial lining. It is really a cele, a collection of blood in a tissue space. Hematoma also is a tumor containing effused blood and usually refers to a visible and localized collection of blood. In reference to the orbit, we seldom think of hematoma as a deeply placed cyst-like structure that remains unchanged and unidentified for long periods of time. *Hematocele* is a better term for an effusion either in the subperiorbital space or diploë of the orbital bone, which cannot escape, is not absorbed, and silently remains as an accumulation of hematogenous debris surrounded by a wall of fibrous tissue. Terms such as *cholesterol granuloma* and *organizing hematoma* designate the histologic features of the end-stage inflammatory response to an indolent hematocele.

The terms *blood cyst* and *orbital hemorrhage* are easily confused with hematocele. The former usually refers to extravasation of blood into the orbital reticulum and has no association with the bone. Hemorrhages of this type are associated with systemic disorders of leukemia, thrombocytopenia, hemophilia, familial hemorrhagic disease, advanced arterial disease, scurvy, orbital hemorrhage associated with effusion of blood into the retrobulbar space from lymphangiomas, dermoid cyst, extramedullary plasmacytoma (Rappaport et al., 1996), varix, arteriovenous malformation, and hemangioma. Foreign bodies and various implant materials used for injury repair also induce orbital hemorrhage.

Incidence

If use of the term *hematocele* is limited to a pocket of old blood that is either within or on the surface of an orbital bone covered by periorbita, then incidence data are scarce. Most reports in the literature, with titles that include the terms *cholesterol granuloma* and *hematic cyst of bone*, describe only one or two cases. Since 1988, only three publications have a more sizable number of cases on which incidence data may be based—McNab and Wright (1990), who observed 27 cases observed between 1967 and 1988; Eijpe et al. (1990), who reported 11 patients seen between 1979 and 1989; and Hill and Moseley (1992), who described 31 patients reviewed from 1974 to 1991. In Chapter 3, we added our 13 patients, accessioned

between 1948 and 1997. The reports of McNab and Wright (1990) and Hill and Moseley (1992) are from the same institution, Moorfields Eye Hospital, the Department of Ophthalmology and the Department of Radiology, respectively. Some of the data reported are duplicative, each report including patients from the other series.

Of the 27 patients reported by McNab and Wright (1990), three were women. At presentation, they ranged in age from 25 to 68 years (median, 43 years; mean, 43.7 years). Almost two thirds of the cases occurred in patients aged 35 and 55 years. Right and left orbits were similarly affected in 13 and 14 cases, respectively. Of the 31 patients reported by Hill and Moseley (1992), 28 were men; the mean age of presentation was 43 years (range, 25–68 years). The mean age of the three women was 44 years (range, 40–50 years). A clear history of blunt trauma to the affected orbit was given by seven patients (23%). This occurred between 1 month and 3 years before onset of symptoms. In the report of Eijpe et al. (1990), all patients were men between the age of 30 and 64 years (mean, 41.2 years). The right orbit was involved in eight patients and the left in three patients. There was no history of recent or remote orbital trauma in any of these patients.

Of the 13 patients in our series, three were women. At presentation, they ranged in age from 27 to 75 years (mean, 43 years; median, 41 years). Three fourths of the patients were between the ages of 31 and 50 years. Right and left orbits were equally affected.

The frontal bone was affected in all our patients with one exception, the intraosseous portion of the sphenoid bone. A definite history of trauma was noted in five patients (41%). The frontal bone in the region of the lacrimal fossa was affected in all except one of the 27 patients described by McNab and Wright (1990). Six of these patients (22%) gave a definite history of trauma. In the Hill and Moseley (1992) series, the hematoceles were in the frontotemporal margin of the orbit. Blunt trauma was a factor in seven patients (23%). The frontal bone likewise was affected in all 11 patients reported by Eijpe et al. (1990).

Several additional cases have been reported since 1990: A 46-year-old woman by Loeffler and Hornblass (1990); a 3-year-old boy by Tosaka et al. (1992); a 35-year-old man by Goldberg et al. (1992); a 31-year-old man by Heaton et al. (1993); a 44-year-old man by Ehlinger et al. (1993); and a 72-year-old man by Privat et al. (2000).

Clinical Features

The incidence data from the four preceding series of hematoceles are almost identical except for one feature—there was no history of recent or remote orbital trauma in any of the 11 patients recorded by Eijpe et al. (1990). The initial injury to the superior rim of the affected orbit may result in some visible hematoma, slight edema of the surrounding soft tissues, with or without a slight break in the overlying skin. These signs resolve in a few days; the patient regards the episode as trivial, and it is easily forgotten. This sequence occurred in a patient who had an intraosseous orbitofrontal hematocele and was unaware of any association with prior trauma. However, in the course of our conversation, an almost invisible, 5-mm, linear, smooth-surfaced white scar, partially covered by eyebrow overlying the superior bony rim of the affected orbit, became apparent. Looking at the scar in a mirror, he then recalled blunt trauma to his forehead 6 years or so previously (see Fig. 4.17). The interval between trauma and onset of symptoms is quite variable. In the series of Hill and Moseley (1992), it was 1 month to 3 years. In the series of McNab and Wright (1990), the interval was 1 month to 2 years.

Since the invention of CT scan and MRI, it is possible to know at the time of presentation whether the primary locus of the lesion is intraosseous bone or whether the pocket of blood is between the inner surface of the orbital bone and its covering periorbita. The presenting signs and symptoms common to both locations are forward

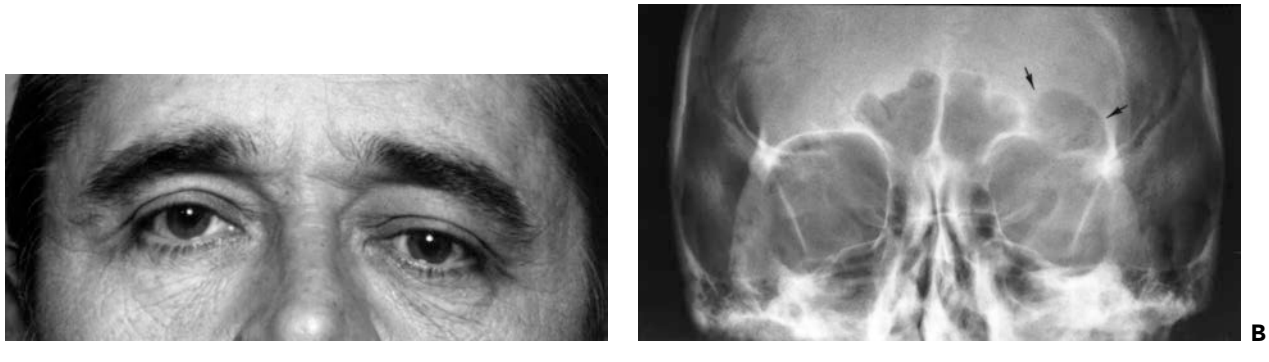

Figure 4.17 **A:** Orbitofrontal hematocele in a 50-year-old man who was unaware of downward and inward displacement of his left eye until the diagnosis was made by his family physician. Visual acuity was 20/20 in his left eye. An injury to his forehead several years previously caused ecchymosis that resolved spontaneously. He underwent surgical evacuation of the tumor and was without recurrence at 4 1/2 years' follow-up. **B:** Radiograph showing a well-defined, oval, bony defect, 3 cm in diameter, eroding the roof of the left orbit (*arrows*).

and downward displacement of the eye and a palpable firm mass underneath the orbital roof. The patient says vision is blurred, which, on examination, proves to be diplopia. If the tumor is the subperiorbital type, there is poorly localized discomfort, headache, or pain due to stretching of the periorbita by the expanding tumor. The intraosseous locus of tumor, however, is pain-free until the lytic granulomatous inflammatory reaction breeches the bone, and the heterogeneous debris is exteriorized beneath the periorbita.

Hemorrhage into retrobulbar tissue is a different matter. It is associated with preexisting, expanding orbital tumors, particularly lymphangioma, arteriovenous malformation, leukemic infiltrates, posttraumatic acrylic implants, and systemic hemorrhagic diathesis. These effusions of blood are usually quite large and exert marked pressure on the eye. Onset of unilateral proptosis is sudden and painful. Effusion of blood is rapid and associated with chemosis, restriction of ocular motility, blurring of vision, and a marked rise of intraorbital pressure. The patient is frightened and aware that something serious has happened. The pouch of blood contains a large quantity of fluid, more than a hematocele, which is responsible for the patient's pain. However, the alarming rise in intraorbital pressure tends to halt the bleeding.

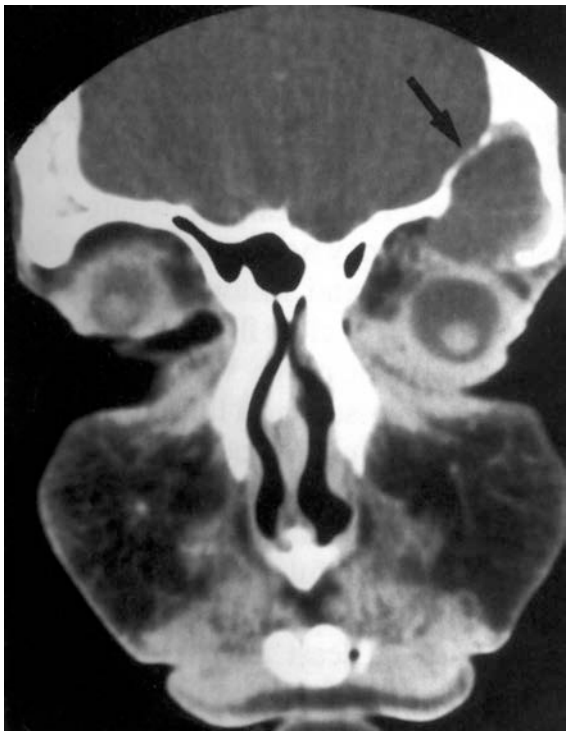

Figure 4.18 Orbitofrontal hematocele. Coronal computed tomography scan of a 43-year-old woman with an isodense, nonenhancing mass in the left superolateral orbital wall. Note thinning of the floor of the anterior cranial fossa (*arrow*), inferior extension of the mass into the orbit, and remodeling of the orbital wall adjacent to the mass. A scar over the left superolateral orbital rim supported a history of previous trauma. The tumor was evacuated through an orbitocranial approach.

Imaging Aspects

On CT scan, the hematocele is well defined, homogeneous, and nonenhancing. With MRI, the T_1 signal intensity is nearly equal to that of orbital fat but hyperintense on T_2-weighted images. Surgically, with a snip of the scissors, the cele is easily evacuated and, unless a hemorrhagic diathesis is ongoing, another episode of hemorrhage may not occur for some time.

CT scan of an intraosseous hematocele shows a well-delineated, nonenhancing mass with both bone expansion and bone erosion (see Fig. 4.18). The lytic effect of the blood degradation products causes slow resorption of the bone with resulting enlargement and expansion of the cavity. The margin of the defect in the bone is usually smooth. If the erosion has a moth-eaten appearance, this would suggest a malignant process. The bony margin is not sclerosed as it occurs with an epidermoid cyst. The lesions are homogeneous except fragments of bone or specks of calcium may be seen particularly in a cele of long duration (see Fig. 4.19). MRI shows the high signal intensity of blood and blood products. A T_1-weighted image is equal to orbital fat but is hyperintense on T_2-weighted images (Kersten et al., 1988) (see Fig. 4.20). On CT scan, the subperiorbital hematocele has an intermediate density, and the image shows the displaced periorbita. The MRI is essentially the same as for the intraosseous tumor (Dobben et al., 1998).

Pathology

Whether the color is red, red-brown, yellowish brown, muddy, or purple and whether the content is viscid, liquid, or semisolid with aggregates of golden crystals, the lesion is basically altered blood in various stages of degeneration and organization. The histopathologic makeup in any given case may depend on initial size of the hemorrhage, its location in either orbital soft tissue or bone, and the period of time that has elapsed while waiting for reabsorption of blood. The smaller celes of orbital soft tissue and peripheral orbital space may undergo resolution in a few weeks. Larger collections of blood of several weeks' or months' duration show, microscopically, granulation tissue rich in capillaries. As time passes without complete resolution, the degraded blood products, that is, cholesterol and hemosiderin, are phagocytosed by histiocytes that fuse to form giant cells (see Fig. 4.21).

In advanced stages, particularly evident in lesions of the orbital bone, the residue becomes increasingly hard and fibrotic, and fragments of bone, deposits of calcium, and hematoidin crystals appear. The hematoidin crystals are reddish brown and highly birefringent and represent breakdown product of bile pigment. Hemosiderin deposits also are brown, but they react to Prussian blue stain because of their iron content, whereas hematoidin, which is iron free, reacts positively to Gmelin test for bile pigments. The presence of hematoidin indicates a slow, indolent

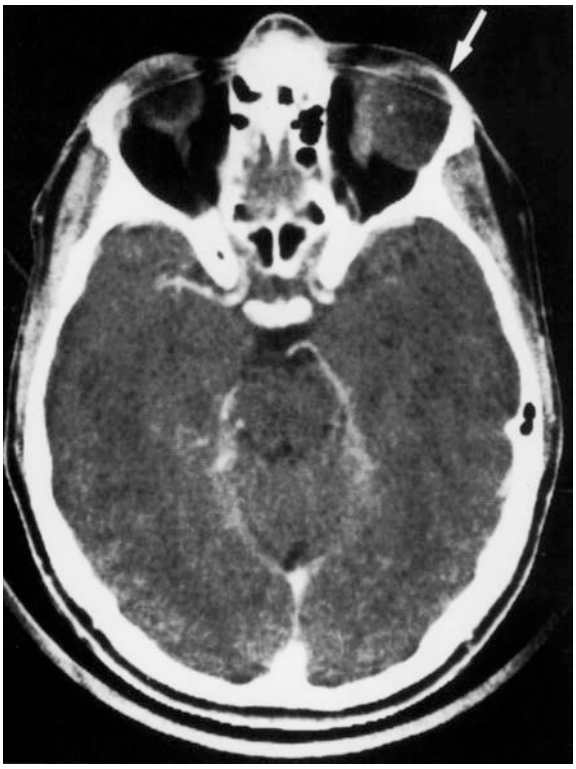

Figure 4.19 Subperiorbital hematocele. Axial computed tomography scan of a 27-year-old man with an expansile mass in the left superolateral orbit (*arrow*) that contains a fleck of calcium and has slightly eroded the orbital wall. Note the smooth contour of the lesion, which was removed by surgical excision through an anterolateral orbitotomy.

process of absorption. The lumen is surrounded by a fibrous capsule. There are no epithelial elements or keratin.

Treatment

Management of either a subperiorbital or intraosseous hematocele is straightforward: Evacuation of the liquid and the semisolid contents. Most of our patients with an intraosseous hematocele have been managed by either an anterior superotemporal orbitotomy or a standard lateral orbitotomy depending on CT scan localization of the lesion. The subperiorbital hematocele also may be managed by an anterosuperior nasal, medial, or temporal orbitotomy, depending on which orbitotomy best accesses the lesion. For the superolateral intraosseous cele that shows erosion of the outer table of either frontal or sphenoid bone, a craniotomy is prudent. However, if the erosion of either bone is located in the deep recess of the medial orbit near the optic nerve, an orbitocraniotomy with unroofing of the orbit probably provides the best access to the lesion. For a soft tissue hematocele in the retrobulbar orbital space, where aspiration of fresh blood may be the only necessary maneuver, a lateral orbitotomy or an anteromedial orbitotomy combined with lateral canthotomy may be sufficient.

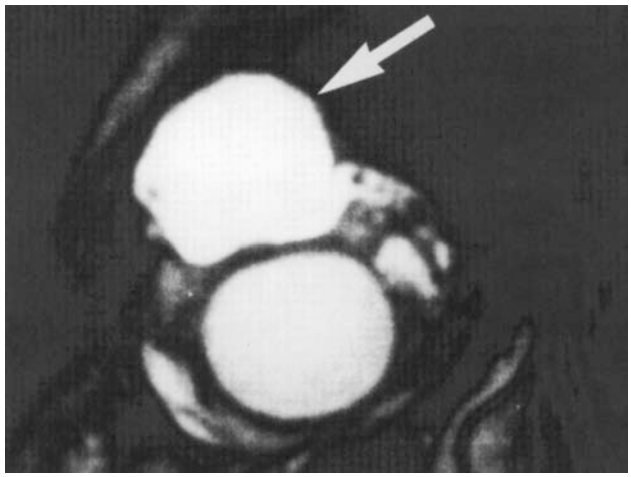

Figure 4.20 Intraorbital organizing hematocele. Coronal T_2-weighted magnetic resonance imaging showing marked hyperintensity of a mass (*arrow*) superotemporal to the right eye of a 37-year-old man. The mass was removed surgically through an eyelid crease incision. (Reprinted from Kersten RC, Kersten JL, Bloom HR, et al. Chronic hematic cyst. *Ophthalmology.* 1988;95(11):1549–1553, with permission from the American Academy of Ophthalmology.)

The bone, once the periorbita is stripped away, has a distinctive discoloration. In the area where bone dissolution is either threatened or complete, the bone is paper-thin, mushy, and bluish. This area of bone merges centrifugally into a wider area of yellowish discoloration, which finally fades peripherally into the ivory color of the normal bone. The zone of yellowish colored bone is also softer in consistency than the normal bone. No other abnormality of the bone associated with an orbital tumor has this unique variation in color.

Figure 4.21 Orbitofrontal organizing hematocele comprising a mixture of inflammatory cells, cholesterol, hemosiderin, and giant cells (hematoxylin and eosin, original magnification ×64).

The bluish bone is easily removed with hand forceps, and a narrow rim of yellowish bone is nibbled away with biting rongeurs only to the extent necessary to gain adequate access to the tumor's contents. The liquid content is easily aspirated, but the semisolid contents may need to be wiped out of the cavity with a pledget or removed with a curette spoon. There is no need to remove bone other than what is required for surgical exposure. In our experience, the oozing of blood from the surface of the exposed bone has been minimal and, if necessary, can be stopped with bone wax. Placement of a temporary drain is optional in cases where the lesions are evacuated through an orbital approach, but for those evacuated through a frontal craniotomy, a drain is advised.

Access to the subperiorbital cele does not require any bony removal. The lesion is reached by a simple dissection along the peripheral orbital space. It may be necessary to pick away or wipe away semisolid fragments attached to the roughened surface of the adjacent bone. Control of bleeding and recurrence of hemorrhage may be a greater problem than with intraosseous lesions. We are inclined to insert a drain in the subperiorbital cavity on completion of surgery and exercise standby alert for recurrence of hemorrhage in a 2-week postoperative period. Continuous suction is advised in handling a large, acute, soft tissue hematocele accompanied by marked hemorrhage.

Mucocele

This section is written with the ophthalmologist in mind who is the first to see a patient with a forward, outward, or inward displacement of one eye combined with two or more of the following: Restriction of upward gaze, vertical diplopia, swelling of the upper eyelid, blepharoptosis, reduced vision, orbital pain or headache, a palpable mass in a superior orbital quadrant, sinusitis, orbital pain with an upper respiratory infection, or a draining sinus just beneath the superior orbital rim (see Fig. 4.22). An imaging procedure shows either a mucocele or a pyocele in the frontoethmoid, frontal, or ethmoid sinus. In short, the patient has a disorder in the field of surgical rhinology that masquerades as an orbital tumor.

Incidence

Over the years of our survey of 1,376 orbital tumors (1948–1987), the incidence of mucoceles with orbital involvement remained essentially the same—8.5% of 765 tumors (second edition, 1980) and 8.3% of 1,376 tumors (third edition, 1994). When we add the 11 cases accumulated between 1988 and 1997, the overall incidence declines to 7.0%, that is, 125 mucoceles among 1,795 total tumors. We suspect this decrease is the result of improved imaging, earlier diagnosis, and improved surgical management with fewer recurrences. Mucocele remains the most common of the secondary tumors in our overall tabulation.

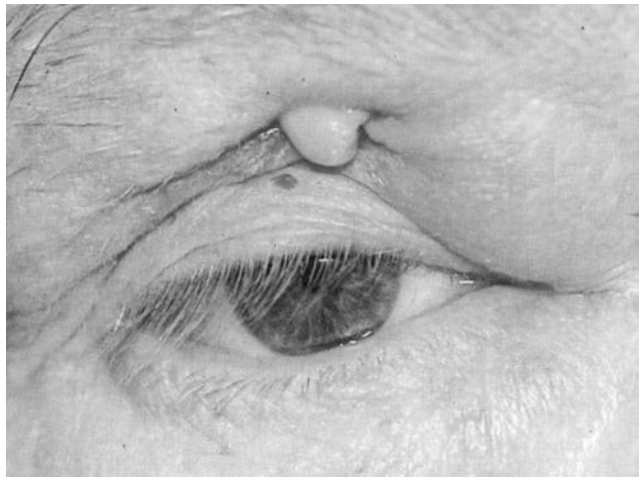

Figure 4.22 Intermittent drainage of pus from a fistulous tract in the right upper eyelid of 6 months' duration in a 61-year-old man was caused by a pyocele of the frontal sinus. Note the bulging mass in the superonasal orbit.

In our series, mucoceles with orbital involvement occurred in the frontal sinus in 63 patients, in the frontoethmoid sinus in 38, in the ethmoid sinus in 20, in the maxillary sinus in 1, in the sphenoid sinus in 1, and in more than two sinuses in 2. The right side was involved in 49 patients and the left side in 73 patients; involvement was bilateral in three patients. The tumor occurs in all decades of life but is most frequent in the fifth, sixth, and seventh decades. The sex ratio is nearly equal—65 men and 60 women. Ndiaye et al. (1994) discussed the incidence of this tumor. They reported 35 cases of frontal sinus mucocele treated from 1977 to 1991. The average age was 41 years with 74% men. Fronto–orbital involvement occurred in 40% of cases.

Clinical Features

Most of the symptoms and signs associated with this benign tumor, during its course or presentation, have been discussed in the first paragraph of this section. Several reports of less frequent patterns of presentation of orbital invasion have been published since the third edition. Isolated third nerve palsies were noted by Sethi et al. (1997) in two patients and by Ehrenpreis and Biedlingmaier (1995) in one case. The former were secondary to sphenoid sinus mucoceles, and the latter was secondary to a frontal mucocele. Sphenoid sinus mucoceles were responsible for retrobulbar pain and ipsilateral optic nerve atrophy (Fujimoto et al., 1999), painful ophthalmoplegia (Clarke et al., 1992), and monocular blindness (Elverland et al., 1991). Optic nerve atrophy was noted from a frontoethmoid mucocele (Desvaux et al., 1994), and optic nerve compression with temporal visual field loss was also reported (Chen et al., 1991).

Infrequent orbital invasion by maxillary sinus mucoceles was reported by Garber et al. (1995) and Hasegawa and

Kuroishikawa (1993). Even more rare is the orbital invasion by a mucocele originating in the nasal concha bulbosa (Armengot et al., 1999).

Publications in the literature have recorded one or two cases of orbital invasion by frontal mucocele (Smoot et al., 1995; Yap et al., 1998); by frontoethmoid tumors (Chen et al., 1997); by ethmoid lesions (Terris and Davidson, 1994; Luxenberger et al., 1999); and by a combination of three sinuses (Pop et al., 1994; Girard et al., 1999; Martin et al., 2000).

An association of secondary orbital mucoceles with both benign and malignant tumors has long been known. Since 1989, the following benign tumors have been reported: Osteoma (Nakajima et al., 2000); fibrous dysplasia (Weisman et al., 1990; Hirabayashi et al., 1998); and cystic fibrosis (Sharma et al., 1994). Valles et al. (1990) noted a primary orbital lymphoma develop as part of a sinus mucocele. Weaver and Bartley (1991), reviewing a series of patients who had undergone surgical treatment for paranasal mucocele, found four malignant neoplasms in mucoceles that had invaded the orbit. These were a grade 4 small cell undifferentiated carcinoma, a grade 3 squamous cell carcinoma, a grade 2 squamous cell carcinoma, and an adenoid cystic carcinoma. In these four patients, the malignant neoplasm was discovered incidentally during routine surgery for mucocele.

Imaging Aspects

In the past, plain film radiography was usually sufficient, particularly for the diagnosis of frontal mucocele, with or without invasion of the orbit. It showed expansion and clouding of the affected sinus secondary to accumulation of mucoid secretion and cellular debris. The increase in pressure caused thinning of the bone and a smooth oval erosion of the floor of the sinus (see Fig. 4.23).

CT scan better delineates the posterior wall of the frontal sinus in addition to imaging mucoceles of the ethmoid and sphenoid sinuses. The well-defined homogeneous mass in most cases is isodense with the brain. Some rim enhancement may occur if an inflammatory reaction converts the tumor to a pyocele stage.

MRI shows variable density of the tumor's content attributable to alterations in the fluid viscosity and the degree of desiccation of the solid components. The signal intensity is higher on T_2- than on T_1-weighted imaging.

Pathology

The principal histopathologic feature is a lining of pseudostratified, columnar, ciliated respiratory epithelium with occasional goblet cells. This epithelium secretes mucus, causing an increase in the mass of the cell. As the pressure of the content rises, the epithelium flattens and becomes atrophic in some areas with loss of cilia (see Fig. 4.24). With

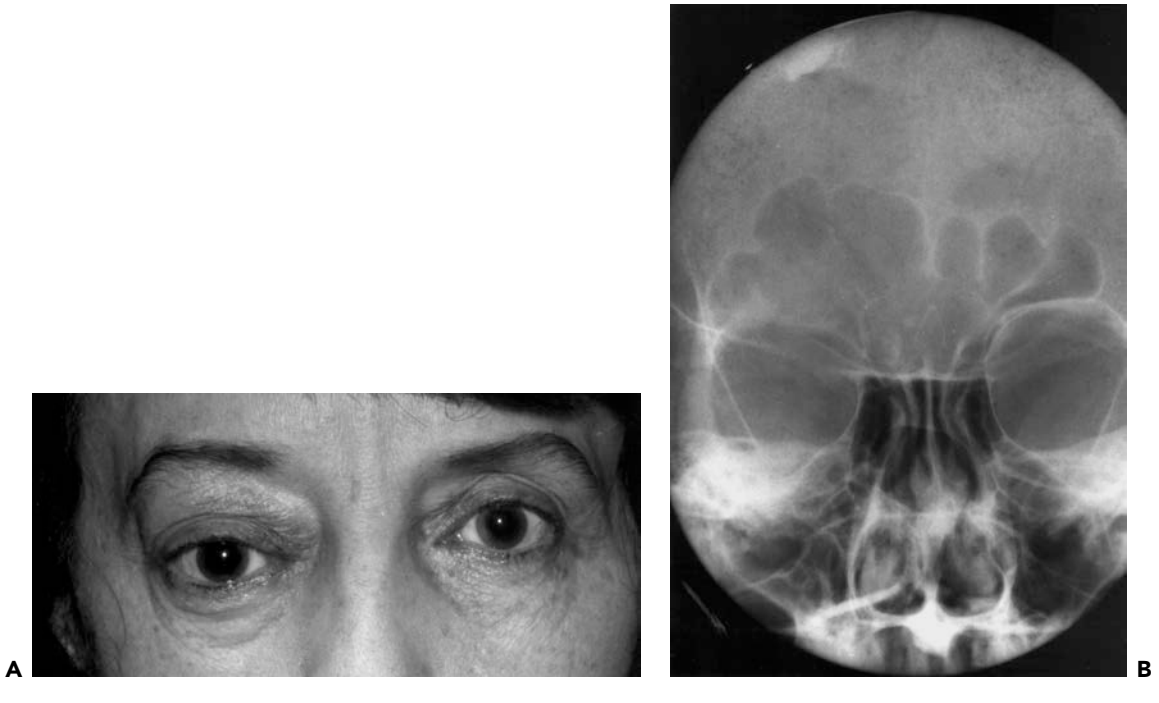

Figure 4.23 **A:** Mucocele of right frontal sinus of 6 years' duration with erosion into the right orbit causing signs common to frontal mucoceles: Downward displacement of eye with minimal proptosis, puffiness and drooping of the upper eyelid, narrowing of the palpebral fissure, a palpable mass in the upper nasal quadrant of the orbit, and flattening of the sulcus between the bridge of the nose and the bony orbital rim. **B:** Radiograph shows enlargement of the frontal sinus, erosion of the superior nasal wall of the orbit, and flattening of the intrasinus bony septa.

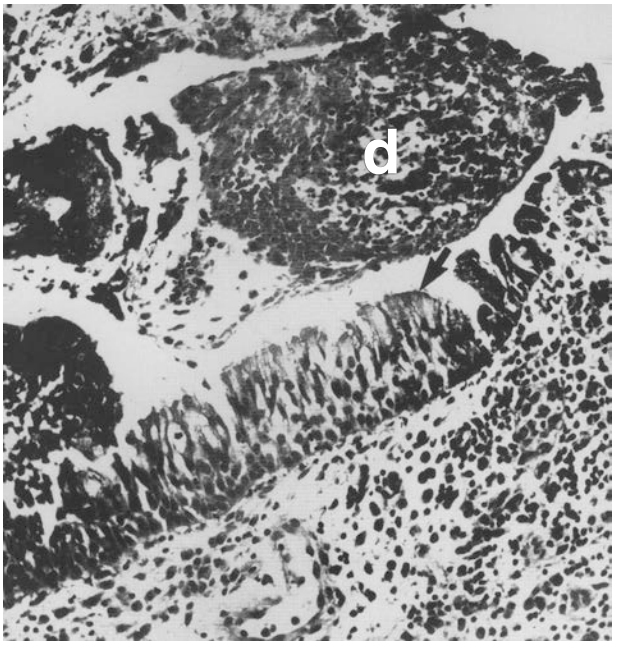

Figure 4.24 Mucocele. Cystic lesion lined with pseudostratified, columnar, ciliated respiratory epithelium (*arrow*). The lumen is filled with semisolid debris (d). The wall of the cyst may show a chronic inflammatory reaction with capillaries, macrophages, and mucus glands (original magnification ×250).

further expansion, the bony wall is attenuated and eventually eroded. The color of the content is dirty gray or brown. The viscosity of the fluid content varies in proportion to the amount of cellular debris.

The outer wall of the cele is a laminated layer of fibrous tissue beneath the epithelium. If an inflammatory phase supervenes, the wall shows a chronic inflammatory response (lymphocytes and plasma cells) with scattered bits of calcium. It is important to obtain an adequate sample of the wall for histopathologic study. Such a sample may disclose an unsuspected area of malignant degeneration. If a frontal mucocele converts to a pyocele that erodes the sinus floor, it may exteriorize as a yellow, pus-filled fistula in the upper eyelid beneath the eyebrow (Fig. 4.22).

Treatment

In the several decades covered by the previous three editions, we kept abreast of rhinologists' efforts to improve the surgical management of orbitofrontal and orbitofrontoethmoidal mucoceles and thereby decrease the frequency of recurrence. In those years, the surgical options were either simple intranasal drainage of the cyst or, more often, an "external frontal" approach through a naso–orbital incision similar to the superonasal orbitotomy familiar to ophthalmologists. The goal of these procedures was to evacuate the contents of the cyst into the peripheral orbital spaces or the nasal cavity, remove the diseased mucosa, and insert some type of temporary stent to promote a permanent nasosinus drainage tract.

With modifications, these surgical approaches gradually evolved into complex procedures such as those described by Rinehart et al. (1993). They described a 25-year-old man who had undergone nasal polypectomy at the age of 17 and presented with bilateral nasal obstruction, telecanthus, and bilateral proptosis. The diagnosis was multiple sinus polyposis with obliteration and complex osteolysis or osteogenesis in the frontal, ethmoid, and sphenoid sinus regions. In brief, after a coronal flap elevation, a frontal craniotomy and a nasoethmoid orbitotomy were performed, which included both supraorbital rims, orbital roofs, glabella, and nasal bones. The frontal and ethmoid sinuses were filled with exuberant polyps. The posterior wall of the frontal sinus was resected totally with complete removal of mucosa. The medial orbital wall, septum, and turbinates were removed. After the resection, the supraorbital and nasomaxillary osteotomy blocks were replaced. The right orbital roof and frontal bone were reconstructed with split-thickness skull grafts. The communication between the anterior cranial fossa and nasopharynx was closed by elevating and introducing a galeal frontalis myofascial flap. In conclusion, we believe that multiple-site, locally aggressive sinus disease is best treated by open surgical techniques rather than by endoscopic techniques, which are useful for less-aggressive sinus disease.

Later, Biedlingmaier and Lester (1995) recommended the free bone flap approach to frontal mucoceles with orbital extension in three patients. One patient was blind in one eye from retinal disease. On the side of the seeing eye, the patient had had three previous failed endoscopic sinus surgeries.

In all three patients, a bicoronal flap was elevated to the supraorbital rim, which included periosteum of the anterior wall of the frontal sinus and supraorbital nerves. Using an angular saw to connect burr holes, a free bone plate of the anterior wall was removed. The mucosa on the underside of the bone plate was burred away with continuous irrigation. The nasal frontal duct and the sinus were obliterated using either bone pâte or fat.

The contemporary literature also has an increasing collection of reports pertaining to endoscopic sinus surgery. This was briefly referenced in our prior edition as a relatively new surgical alternative for mucoceles (Kennedy et al., 1989). Kennedy, a strong proponent of functional endoscopic sinus surgery, brought attention to the potential for reestablishing sinus drainage and mucosal recovery by use of the endoscope. His proposal has increased the discussion on the merits of the procedure.

Benninger and Marks (1995) retrospectively reviewed 15 patients with primary mucoceles of sphenoid and ethmoid sinuses who underwent endoscopic decompression over the previous 3 years of their practices. In 11 patients, the mucocele extended outside the confines of the sinus. Among the latter were three patients with orbital extension and three patients with both orbital and intracranial involvement. All mucoceles were decompressed through

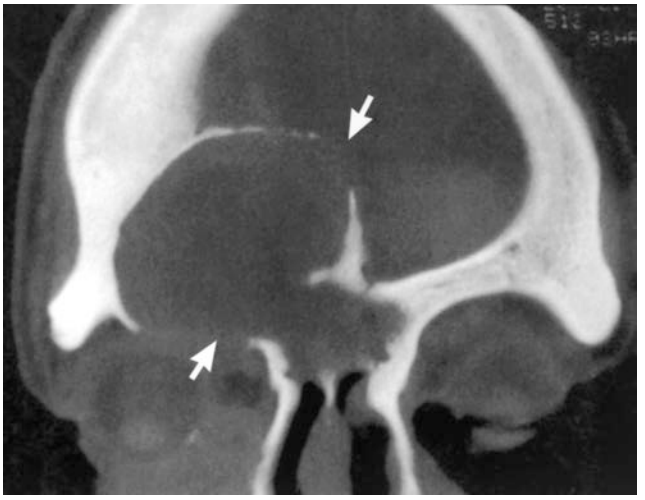

Figure 4.25 Large frontal mucocele with intracranial (*upper arrow*) and intraorbital (*lower arrow*) extension. The lesion was managed unsuccessfully by way of frontal sinusotomy and ultimately treated successfully by endoscopic removal of the frontal intersinus septum and floor and adjacent nasal septum. (Reprinted from Kennedy DW, Senior BA. Endoscopic sinus surgery: A review. *The Otolaryngol Clin N Am.* 1997;30:313–330, with permission from Elsevier.)

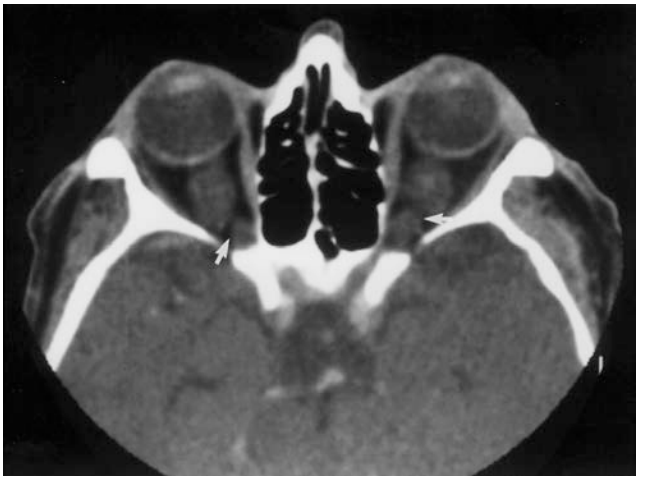

Figure 4.26 Bilateral optic nerve sheath meningoceles. Axial computed tomography scan with contrast reveals lobulated enlargement with some kinking (*arrows*) without pathologic contrast enhancement, enlargement of the optic foramina, or evidence of chiasmal involvement in a 61-year-old man.

endoscopic approach. Wide decompression or marsupialization of those with extension allowed drainage and aeration. No attempt was made to remove the mucosal lining as long as the mucocele was well opened. The dura or periorbita comprising the thick wall of the mucocele was also left intact, if possible.

Later, Kennedy and Senior (1997) published an extensive review of the history of endoscopic sinus surgery (57 references), advances in surgical techniques, and the usefulness of endoscopic sinus surgery in mucoceles with orbital and intracranial extension and in a previously obliterated frontal sinus (see Fig. 4.25). The most important change in technique resulting from endoscopic sinus surgery is mucosal preservation.

Optic Nerve Sheath Meningocele

Terminology

Optic nerve sheath meningocele is the name proposed by G. S. Forbes, a neuroradiologist at Mayo Clinic. He was hopeful this term would reduce the overlap in nomenclature and standardize future discussions of the subject, at least among neuroradiologists. This name was the title of the publication by Garrity et al. (1990) for which Forbes was a coauthor. They described an optic nerve sheath meningocele as a saccular dilation of the optic nerve sheaths containing cerebrospinal fluid (see Fig. 4.26).

Before this publication, the saccular dilation of the optic nerve sheath was favored with many other names, including "perioptic hygroma," "ascites of the optic nerve," "optic hydrops," "patulous subarachnoid space," "perioptic subdural hygroma," "cystic hygroma," "arachnoid cyst," and "optic nerve sheath cyst." Subsequently, we have found only one additional designation in the literature, "dural ectasia of the optic nerve sheath" (Lovblad et al., 1994). Standardization of the terminology seems to have been achieved. Whether these tumors are true cysts, possessing a lining layer of cells, or celes, localized collections of fluid, is not settled. We do not believe that the cells lining the sheath of the optic nerve have any secretory function. Therefore, these saccular dilations are celes.

Incidence

These entities are known to be associated with surgically proved neoplasms and malformations of the orbital optic nerve complex such as meningioma, glioma, vascular hamartoma, neurofibromatosis, hemangioendothelioma, von Hippel-Lindau disease, Hadju-Cheney syndrome, and Arnold-Chiari malformation. In a broad sense, all such nerve sheath dilations are secondary in type. If these were documented according to the lesion to which they are an accessory, particularly the neoplasm, the nomenclature would be simplified, and the clinical course of sundry primary *cysts* and *celes* might be better defined. There is also a definite association with trauma, but the relationship to putative inflammatory disease is less definite. We favor a more restrictive role for this new term and confine its use to the acquired entities of unknown or uncertain origin. This, of course, would exclude the congenital meningoceles in this area.

If this more restrictive approach is acceptable, the incidence of optic nerve sheath meningocele is narrowed to those few cases that have been surgically verified. However, such verification is not assurance that some explanation for this entity may develop. The report of Garrity et al. (1990)

contains 46 references on the subject of optic nerve sheath meningocele. In this list are a number of case reports that seem to fit the restrictive category. Lunardi et al. (1997) stated that approximately 31 cases have been reported in the literature. These cases occurred in both sexes and all age-groups. Their survey indicated a strong male prevalence. The two surgical cases in our summary are one of each sex.

Clinical Features

Headache and blurring of vision are two of the most common presenting symptoms. In the 31 cases in the series reported by Lunardi et al. (1997), headache was present in 13 patients. The visual deficit may be either a decrease in visual acuity or a visual field deficit of the optic nerve type. The decrease in visual acuity is caused by an acquired hyperopia shift. Such cases show choroidal folds on ophthalmoscopic examination. In the series of Lunardi et al. (1997), a pale optic disk or papilledema was present in 29 patients. Nine of the patients had proptosis. The absence of proptosis and lack of gadolinium enhancement differentiates optic nerve meningocele from optic nerve glioma and meningioma of optic nerve sheath.

Imaging Aspects

Garrity et al. (1990) consider MRI, with fat suppression techniques and off-axis sagittal views, the radiographic procedure of choice. Gadolinium contrast and short echo time and repetition time pulse sequences provide additional delineation (see Fig. 4.27). CT scan axial views with contrast show enlargement of the optic nerve, but no enlargement of the optic foramina or evidence of chiasmal involvement. Coronal views show normal-sized nerves within the dilated sheath.

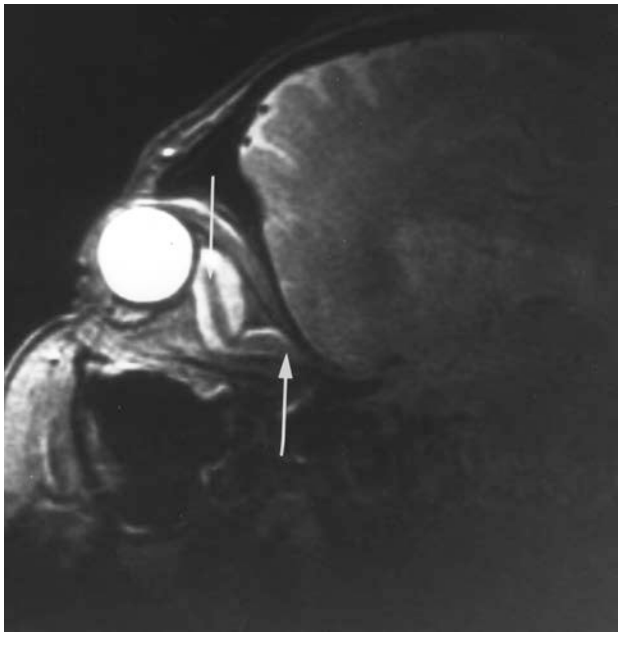

Figure 4.27 Optic nerve sheath meningocele. Off-axis, sagittal, T_2-weighted magnetic resonance imaging shows a normal-sized optic nerve (*upper arrow*) within dilated sheath. Note compression of the nerve at the kink (*lower arrow*) of the sheath near the orbital apex.

Management

One of our patients, a 61-year-old man, presented with unilateral reduced vision of 3 weeks' duration in the right eye. Visual acuity of 20/80 could be improved to 20/20 with sphere + 2.25 diopters, cylinder + 0.50 diopter, and axis of 167 degrees. This refraction represented an increase of 0.75 sphere in the correction he was wearing. Several choroidal folds were visible superior to the right macula. Visual acuity, visual field, and ophthalmoscopic evaluation of the left eye were normal. However, CT scan demonstrated enlargement of both optic nerve complexes without enhancement.

Optic nerve sheath decompression was performed only on the right side. An incision on the bluish colored mass released a crystal-clear fluid. An 8 × 8-mm segment of sheath was removed for histopathologic study. Two years after decompression, vision in the right eye was reduced to hand movements in a small, nasal isle of visual field. Moderate pallor of the optic disk was present. The unoperated left eye remained normal.

The other patient, a 32-year-old woman, likewise presented with reduced vision of 4 months' duration in one eye, but CT scan suggested bilateral meningoceles. Visual acuity was 20/50, 14/141 in the right eye, and 20/20, 14/21 in the left eye. There was no proptosis. A right afferent pupillary defect was present, and visual field examination showed a cecocentral scotoma. The optic disks of both eyes looked normal.

Because of apparent intracranial involvement, a right pterion craniotomy was performed. At surgery, the right optic nerve lay in the middle of a large evagination of subarachnoid space that had eroded the roof of the optic canal. The optic nerve sheath was opened, therefore decompressing the nerve. At 6-month follow-up, there was no change in either visual field or visual acuity. The right optic nerve meningocele did not appear as prominent compared with its appearance on initial CT scan. There was no appreciable subjective change as assessed by telephone follow-up 2 years later.

If the diagnosis of meningocele is suggested by the imaging display, but the visual acuity of the eye is not impaired, it is probably prudent not to propose surgical intervention.

Lacrimal Ductule Cyst

A lacrimal ductule cyst is usually a distention of a branch of an excretory duct of the lacrimal gland. However, cyst formation may occur in any location where lacrimal gland tissue is present. Bullock et al. (1986) proposed a useful clinical classification based on the cyst's anatomic location. They noted four types: In the palpebral lobe of the lacrimal

gland, in the orbital lobe, in the accessory lacrimal glands of Krause and Wolfring, and in ectopic lacrimal gland rests. The last named is a choristoma, whereas the others are acquired lesions. Our discussion is limited chiefly to the cysts of orbital lobe origin.

The orbital cyst is very rare. We believe it is the least common of the cysts and celes referenced in this chapter. Ikawa et al. (1994) found only five such cases in the literature. These are a 60-year-old man (McMullen, 1920); a 25-year-old man (Smith and Rootman, 1986); a 7-month-old girl (Bullock et al., 1986); a 26-month-old girl (von Domarus, 1987); and a 16-year-old boy (Conway, 1988).

Ikawa et al. (1994) added the case of a 16-year-old boy first seen in 1989 with progressive proptosis of the right eye of several years' duration. A diagnosis of orbital cyst was made on the basis of CT scan and MRI. The patient refused surgery. The patient returned 2 years later with inferomedial displacement of the eye and 4-mm proptosis. The cyst was aspirated. A postoperative MRI revealed collapse of the cyst and disappearance of proptosis. Two months later, MRI showed regrowth of the cyst. The cyst was then completely removed. There was no residual tumor or recurrence of tumor 6 months after surgery.

Presentation of the orbital cyst is similar to a benign, slowly growing neoplasm in the lacrimal gland fossa, that is, progressive, painless, inferonasal displacement of the eye with some forward proptosis but minimal disruption of visual function. If the mass is in the forward portion of the orbital lobe, there is some fullness of the superolateral portion of the upper eyelid, and the front surface of the firm mass may be palpable. CT scan shows the size and position of the nonenhancing cystic mass with some thinning and remodeling of the adjacent bone. The margin of the mass may show slight enhancement suggesting some prior inflammatory response. The MRI of the patient reported by Ikawa et al. (1994) revealed a low-intensity mass on T_1-weighted images and a high-intensity mass on T_2-weighted images.

The pathophysiology of the orbital cyst is not known, but the presence of lymphocytes and plasma cells in the tissue specimen suggests some prior inflammatory process or an immune reaction in the ductule of the gland provoked the forming of the cyst. The cyst wall is very thin, consisting of two layers of cuboidal, pseudocolumnar epithelium. In long-standing cases, the increasing pressure exerted by the contents of the cyst may attenuate the epithelial lining to one layer.

The goal of management is intact removal of the cyst. Because of this cyst's large size and delicate, thin-walled structure, intact removal is easier said than done. The surgical approach of choice is the lateral orbitotomy. When the bone flap is retracted or the bone is temporally removed, it is best to lay the scissors aside. Dissection of the cyst from its base along the surface of the lacrimal gland is best done with cotton-tipped applicators to minimize rupture of the cyst. Bullock et al. (1986) used this method to remove a $21 \times 19 \times 19$-mm cyst intact (see Fig. 4.28). If CT scan shows a cyst that extends posteriorly into the orbital apex and crowds the optic nerve, an orbitofrontal craniotomy may be necessary instead of lateral orbitotomy.

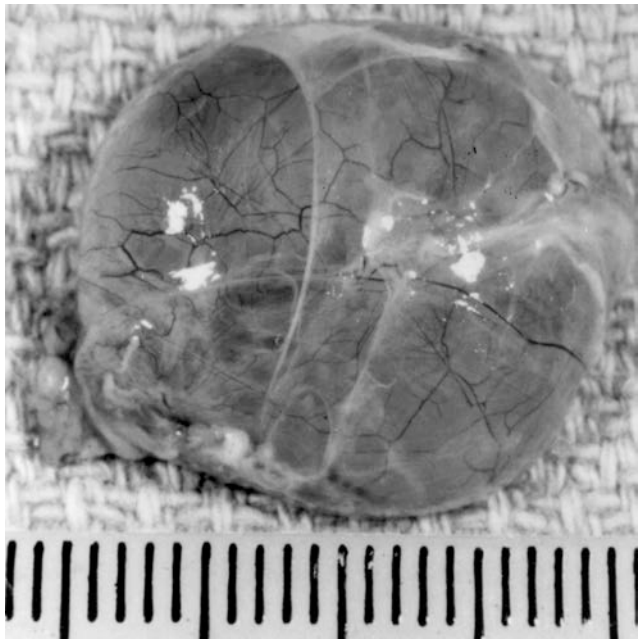

Figure 4.28 A $21 \times 19 \times 19$-mm cyst that was removed intact. (From Bullock JD, Fleishman JA, Rosset JS. Lacrimal ductal cysts. *Ophthalmology*. 1986;93:1355–1360, with permission.)

Before leaving this section, we should note an orbital cyst associated with an ectopic lacrimal gland reported by Kao et al. (2000). A 33-year-old man presented with a palpable mass above the inferior orbital rim. CT scan showed a lesion in the lower orbit of the right eye near the inferior rectus muscle, without bony erosion. A tense, thin-walled, clear fluid–filled cyst ($15 \times 12 \times 13$ mm) was removed intact. Pathologic examination disclosed a nest of normal gland tissue surrounded by a cystic lesion lined by two layers of ductule epithelial cells.

Dentigerous Cyst

The word *dentigerous* refers to a cyst surrounding the coronal portion of a tooth and originating after the crown is completely formed. They are found mainly in the mandibular third molar and maxillary canine areas. The cyst is lined by stratified squamous epithelium within a connective tissue wall and filled with fluid. The cyst contains the crown or some portion of the tooth. A long-standing cyst easily erodes into the maxillary sinus and, if large, may involve the inferior orbit.

The latter event prompted the report of Kaya and Bocutoglu (1994). A 40-year-old woman gave a history of swelling of the right cheek and the floor and lateral wall of the nose of 5 years' duration. The right globe was

slightly displaced superiorly. The cyst was removed by a Caldwell-Luc approach. Thirteen references on the subject, spanning 1965 to 1992, are included in their report.

PARASITIC CYSTS

Our contact with parasitic cysts of the orbit is limited except for a brief clinical stint one of us had many years ago in Nigeria. Therefore, in this section, we update the literature on the subject and point out some interesting events that have transpired since the previous edition of this text. Our discussion is limited to the orbital lodgment of the larvae of the tapeworms *Echinococcus granulosus* (hydatid cyst) and *Taenia solium* (a tapeworm formerly known as *Cysticercus cellulosus*). Among the tapeworms these are the most common orbital invaders.

Echinococcus Granulosus

Incidence

The mature form of this small tapeworm occupies the gastrointestinal tract of dogs and other carnivores. The worm has been known since the time of Hippocrates. The eggs of the worm are excreted in the feces of the animal. Humans ingest the eggs either from contaminated soil or by handling the animal. An egg opens, and the larvae may then travel to any anatomic site. Wherever the larva lodges, it is encased by a round, hollow, cyst-like hydatid. The word *cyst* has long been loosely applied to the hydatid. This cyst does not have an epithelial lining, in contrast to other cysts described in this chapter.

Over the decade 1990–2000, we are aware of 21 reports of single cases of hydatid cyst. No other tumor in this text has enamored or fascinated clinicians enough to warrant nearly two dozen reports of single cases. In the same period, eight reports described two cases per publication. Rather than individually detail these 29 publications, we reference only those that have some out-of-the-ordinary presentation, course, or complication.

An assessment of orbital incidence data is best obtained from publications surveying larger cohorts of cases of hydatid cysts. Three reviews included ten cases or more: Gomez Morales et al. (1988); Sami et al. (1995) and Xiao and Xueyi (1999). Gomez Morales et al. (1988) reviewed 35 cases over a 40-year period (1944–1985) in Argentina. All were histopathologically verified. The age range was 2 to 57 years, with a median age of 16 years. Sami et al. (1995) operated on ten cases between January 1985 and December 1991. The mean age was 25 years, with five women and five men. Progressive unilateral proptosis was noted in eight cases and acute onset of proptosis in one case. Visual acuity was reduced in six cases and blindness occurred in one case. Xiao and Xueyi (1999) reviewed the records of their hospital and issues of Chinese medical journals between 1956 and 1994 and found 18 cases of orbital hydatid cyst, including ten cases from their hospital. All cases were verified by surgery. Among the 18 cases, 7 were male, and 11 were female, with an age range of 3 to 55 years. The ten orbital cases from their own hospital were from a total of 3,736 cases from all anatomic sites, an incidence of 0.3%.

Clinical Features

Progressive, unilateral proptosis with or without off-axis displacement is probably seen in almost all cases of orbital hydatid cyst. Puffiness of one or more eyelids and restriction of gaze of the affected eye signal an enlarging mass. As the mass increases in size, an afferent pupillary defect, choroidal folds, edema of the optic disk, and visual impairment develop. The end stage is an exposure keratitis because the eye is pushed beyond the protective cover of its eyelids, resulting in visual loss. Pain, chemosis, and congestion of the eyeball also may herald an inflammatory response. Last, the tumor that initially was retrobulbar pushes forward and becomes palpable in one of the orbital quadrants (see Fig. 4.29). In a child, the course may be more rapid and suggest an orbital sarcoma.

More unusual presentations are the cases reported by Ozek et al. (1993) and Gelisken et al. (1994). Ozek et al. (1993) described a 52-year-old woman with a 6-month history of painless proptosis of the right eye and a 4-day history of total visual loss associated with severe orbital pain. A proptosis of 28 mm was present. Through a lateral orbitotomy they found three daughter cysts within a thick, ruptured capsule of a mother cyst. The three thin-walled daughter cysts were carefully removed intact along with gross removal of the remnants of the mother cyst. The orbital cavity was irrigated with 3% sodium chloride solution, and mebendazole was started postoperatively. There was no sign of recurrence at 7 months after surgery, but the eye remained blind.

The case described by Gelisken et al. (1994) was a 20-year-old Turkish woman who presented with a unilateral

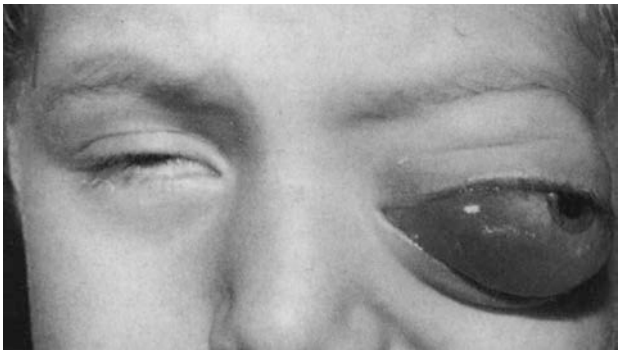

Figure 4.29 Hydatid cyst. Extensive proptosis and chemosis of the left eye in a 4-year-old Turkish boy. His visual acuity was light perception only in the affected eye. (Reprinted from Hanioglu S, Saygi S, Yazar Z, et al. Orbital hydatid cyst. *Can J Ophthalmol.* 1997;32:334–337, with permission.)

orbital hydatid cyst associated with an exudative retinal detachment. After *en toto* excision of the cyst, the retina reattached spontaneously.

Also unusual was the report of Diren et al. (1993) of a *triple header* case in a 10-year-old girl. A 30 mm diameter cyst was in the right orbit, a 20 mm diameter cyst was in the intracranial frontal area, and a 38 mm diameter cyst was present in the right frontal horn of the ventricle. All three pearly white cysts, removed in a single surgery, contained the characteristic ectocyst and scolices.

Imaging Aspects

The introduction of CT scan imaging made diagnosis of an orbital hydatid a reality. Before CT scan, serologic diagnosis of an orbital infestation based on antigen and antibody immunophoresis often was negative because of the self-contained, isolated location and the thick cover of the ectocyst. CT scan and MRI are now the foremost tests for diagnosis and management.

Sperryn and Corr (1994) discussed their experience with ten cases of histologically proved orbital hydatid disease. In seven cases, the content of the cyst was nonenhancing and hypodense with vitreous. Peripheral rim enhancement following contrast enhancement was present in all cases. In addition, CT scan was useful in detecting bony changes, particularly the orbital roof (see Fig. 4.30). The three hyperdense lesions in their study were initially considered to be soft tissue orbital tumors, but contrast enhancement of contents was not detected in any of the three cases. They could not demonstrate any histologic difference between the hyperdense and hypodense cysts. They conclude that the hyperdense appearance is caused by the high protein level of the cyst contents. If MRI is available, it shows a low-intensity signal on T_1-weighted images and a high-intensity signal on T_2-weighted images. Because of the cost, MRI may be limited to cases that have an uncertain diagnosis after history taking, ultrasonography, and CT scanning (Hanioglu et al., 1997).

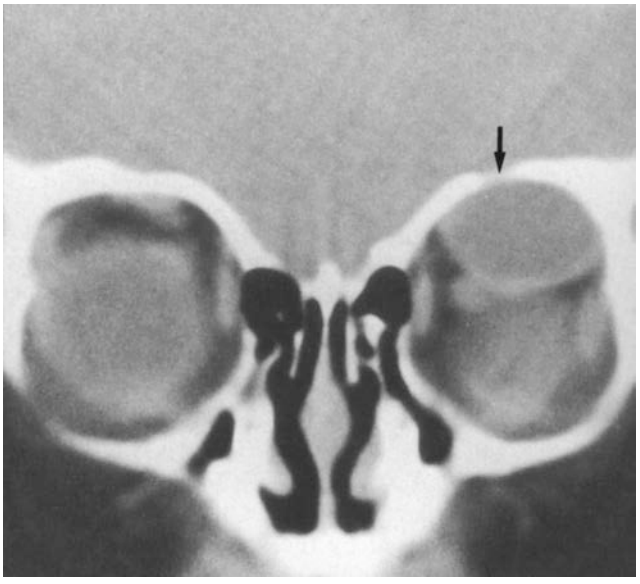

Figure 4.30 Hydatid cyst. Coronal computed tomography scan shows orbital roof thinning (*arrow*) due to a superolateral cyst. (Reprinted from Sperryn CW, Carr PD, CT evaluation of orbital hydatid disease: A review of 10 cases. *Clin Radiol*. 1994;49:703–704, with permission from Elsevier.)

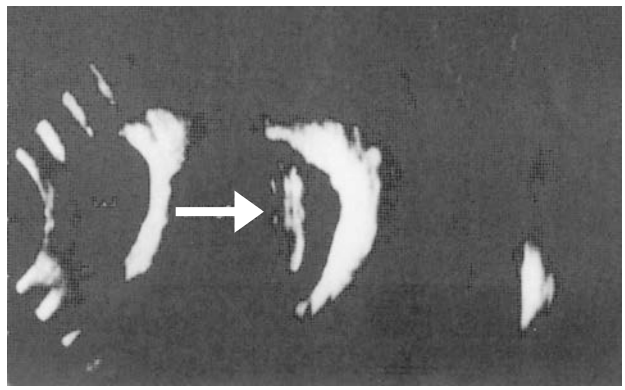

Figure 4.31 Orbital sonogram shows the water lily sign (*open arrow*) in a hydatid cyst. (Reprinted from Malde HM, Gadkari SS, Chadha D, et al. Water lily sign in an orbital hydatid cyst. *J Clin Ultrasound*. 1993;21:458–459 with permission from John Wiley & Sons, Inc.)

In impoverished endemic areas, ultrasonography remains the mainstay for both screening and diagnosis. The cyst is a well-circumscribed, thin-walled, anechoic lesion. In addition, several linear echo densities may be seen within the cyst, suggestive of floating membranes, the "water lily sign" (Malde et al., 1993) (see Fig. 4.31). By manipulating the patient's body position, it sometimes is possible to demonstrate floating hydatid sand on sonography.

We should mention the role of fine-needle biopsy in diagnosis. Saenz-Santamaria et al. (1995) used this technique in 17 cases. In 13 cases, the aspirated material was diagnostic. In four cases, only acellular laminated membranes were present in the aspirate, but this absence of cells in the membrane confirms the diagnosis.

If, by imaging, the diagnosis is indeterminate and aspiration biopsy is not feasible, serologic tests may be helpful. Enzyme-linked immunosorbent assay (ELISA) and the indirect hemagglutination test are highly sensitive procedures for screening of serum; sensitivity rates vary from 60% to 90%.

Pathology

The tumor is pearly white (see Figs. 4.32 and 4.33) and has a wall consisting of a three-layer, structureless, acellular, laminated, homogeneously basophilic material. This is the cuticular membrane of the cyst. The avascular fluid-filled cyst may show hooklets and scoleces if the cyst is intact (see Fig. 4.34). In cysts of long duration, specks of calcium may be present.

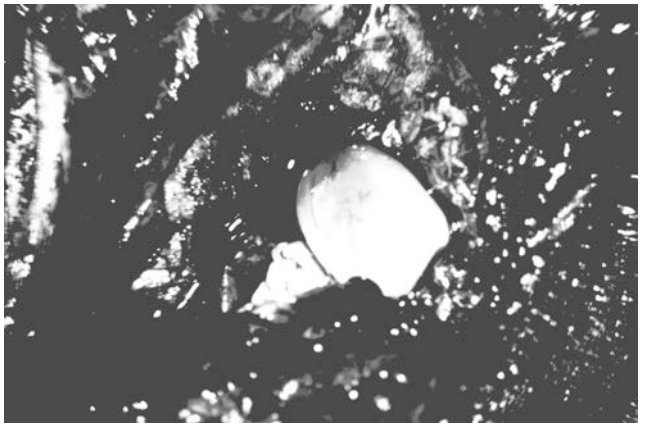

Figure 4.32 Echinococcus cyst. The pearly white tumor is nested in orbital tissue of an adult male. (Courtesy of Friesen H, Kabul, Afghanistan.)

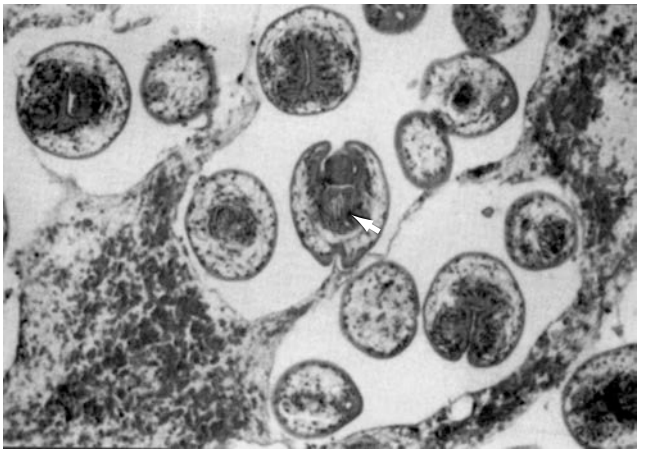

Figure 4.34 Orbital hydatid disease. The photomicrograph shows multiple protoscolices with hooklets (*arrow*) (original magnification ×400). (Reprinted from Sperryn CW, Carr PD, C T evaluation of orbital hydatid disease: A review of 10 cases. *Clin Radiol.* 1994;49:703–704, with permission from Elsevier.)

Treatment

Intact surgical removal of the cyst is the ideal outcome of therapy. A procedure used by many surgeons in the past has been, successively, aspiration of the cyst, establishment of the diagnosis, reinflation of the mass with some agent (e.g., hypertonic saline, alcohol, formalin) to detach the scolices from the inner germinal wall, a second aspiration to empty the cyst, and followed by extirpation of the endocyst with or without the overlying ectocyst (Chana et al., 1986). Most of the publications in the 1990s have proposed some modification of this fairly standard procedure.

Nahri (1991) introduced the use of the cataract cryoprobe in two cases. An initial aspiration causes the cyst to collapse so that the outer fibrous wall is easily tented and grasped with nontoothed forceps, and the needle puncture site is snipped open. The endocyst is bonded to the cryoprobe and completely extracted. The outer fibrous wall is left behind, thereby eliminating dissection from surrounding orbital structures. There were no recurrences during 18 and 24 months of follow-up.

Akhan et al. (1998) proposed percutaneous treatment as an alternative approach to conventional surgery. Under ultrasonographic guidance, the cyst was aspirated with 15% hypertonic saline and then reaspirated without complication. Twenty-one months later, imaging of the shrunken mass showed a volume of only 0.5 mL, and the patient was asymptomatic.

Gokcek et al. (1997) recommends total removal of the cyst by means of a microdissection technique.

Jimenenez-Mejias et al. (2000) described a case wherein the cyst ruptured during surgical removal. The surgical field was irrigated with hypertonic saline solution, and

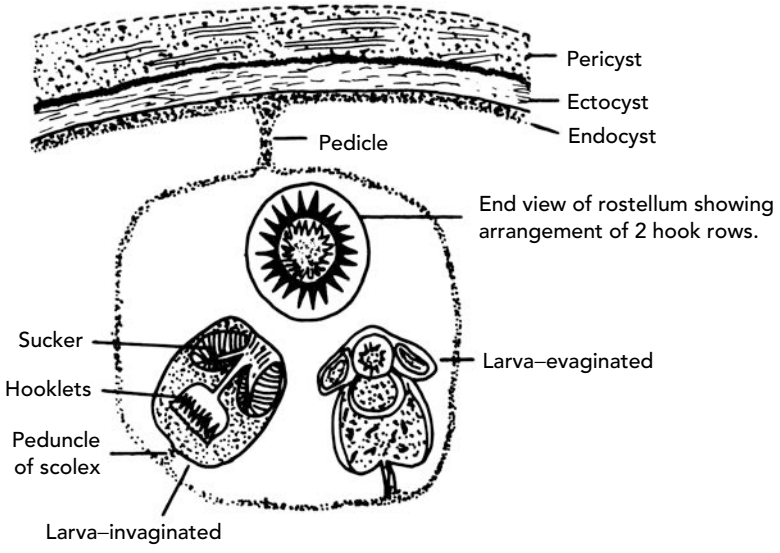

Figure 4.33 Diagram of a hydatid cyst section. (From Chana HS, Klauss V, Shah A. Orbital hydatid cyst disease in Kenya. *Am J Trop Med Hyg.* 1986;35:991–994, with permission.)

the remnants of the cyst were excised. Treatment with albendazole, 400 mg every 12 hours, plus praziquantel, 1,200 mg every 8 hours, was started. After surgery, both the eosinophil count and sedimentation rate were elevated. Treatment was maintained for 3 months. Praziquantel was then discontinued, but albendazole, 400 mg every 12 hours for 28 days, followed by a 2-week rest period, was continued in cycles for another 15 months. At the end of the sixth month of therapy, the eosinophil count, sedimentation rate, and serologic test results were normal. Another drug of this class, mebendazole, has also been used either alone or in combination with albendazole for antihelminth therapy.

Taenia Solium

This is the larval form of the pig tapeworm *Taenia solium* (formerly *Cysticercus cellulosae*). Humans are infected by ingestion of contaminated pork or fecal-contaminated vegetables and water. Once ingested, the eggs mature, and larvae penetrate the intestinal mucosa and are carried to other organs by a hematogenous route. Common sites of lodgment of interest to ophthalmologists are the ocular adnexa, the eye, the extraocular muscles (and orbit), and the brain.

The parasite is endemic in Mexico, Africa, southeast Asia, eastern Europe, central America, South America, and India. The parasite is rare in the United States. We list no cases of orbital involvement in our 50-year collection of orbital tumors.

Incidence

The literature on this subject usually is a statistical mix that includes the eye, the ocular adnexa, and even the brain, in addition to the orbit (Atul et al., 1995; Sekhar and Lemke, 1997; Pushker et al., 2001). The series reported by Atul et al. (1995) comprised 33 outpatients, from 1989 to 1993, in New Delhi, India. Seventy percent of patients had a lower socioeconomic status, were vegetarians, and were ignorant of the importance of washing their hands. There were 22 males and 11 females with an age range of 8 to 60 years; 45% were between 31 and 40 years of age. Six patients (18%) had orbital involvement. The most common location for the parasite was the vitreous (54%).

The study by Sekhar and Lemke (1997) analyzed 20 patients from an urban practice in southern India. There were 11 female and 9 male patients ranging in age from 5 to 25 years (mean, 12.5 years). Nine patients manifested subconjunctival cysts. The remaining 11 patients had a cyst in a single extraocular muscle with associated proptosis.

Pushker et al. (2001) also studied 20 patients from an outpatient service at a hospital in New Delhi, India. Twelve patients (60%) had orbital involvement. The other eight patients had cysts in either the ocular adnexa or the eye. The orbital group comprised seven males and five females ranging in age from 7 to 50 years (mean, 15 years).

Clinical Features

The extraocular muscles have the best blood supply among the tissues in the retrobulbar space. Therefore, it is logical that an extraocular muscle is the structure most frequently affected by larvae migrating to the orbit through its blood supply. This is responsible for the patient's presentation with proptosis or displacement of the eye, restricted ocular motility, and pain. Pain is the result of the inflammatory response to the lodgment of the larvae in the muscle. Pain differentiates the cyst from a benign neoplasm lodged in the muscle. If the cyst is lodged in the tissues near the apex of the orbit, vision may be disturbed because of the spread of the inflammatory response to the optic nerve sheath, causing papilledema. A more marked visual loss is probably caused by an additional intraocular cyst. Pandey et al. (2001) described a 20-year-old man who presented with acquired Brown syndrome secondary to infestation of the superior oblique muscle. The patient was started on systemic corticosteroids and albendazole in prescribed doses for a month, with resolution of the cystic lesion after completion of the regime. Ocular motility was restored in upgaze, but mild restriction of the right eye persisted in levoelevation.

None of the 33 patients of Atul et al. (1995) had notable eosinophilia, and stool specimens were negative for ova and cysts.

Imaging Aspects

Either ultrasonography or CT scan can confirm the diagnosis. With ultrasonography, the cyst with the scolex attached to the inner wall can be recognized by the hanging drop sign (Gulani, 1998). This sign was seen in all seven cases studied using simultaneous A- and B-scan modes. CT scan shows a nonenhancing circular area of low attenuation with a tiny area of increased attenuation within the cyst, which is pathognomic of scolex. It is also important to have CT scan of the head to rule out cysts in the brain.

Pathology

Microscopically, in the early (vesicular) stage, the cyst has a small, circular, white, opalescent spot surrounded by translucent, straw colored fluid and a high protein content (Rahalkar et al., 2000). The cyst has well-defined outer and inner walls. If the worm is partially decomposed, it is encompassed by an intense, zonal, granulomatous inflammatory infiltrate characterized by numerous epithelioid cells and multinucleated giant cells adjacent to the outer cyst, with dense lymphoid aggregates containing germinal centers (see Fig. 4.35). On higher-power magnification, the scolex shows numerous basophilic, calcareous corpuscles (Myles et al., 1994).

Management

Contrary to the initial management of *Echinococcus granulosus* by some type of surgical manipulation, *Taenia solium* seems responsive to initial medical therapy. In the 1990s,

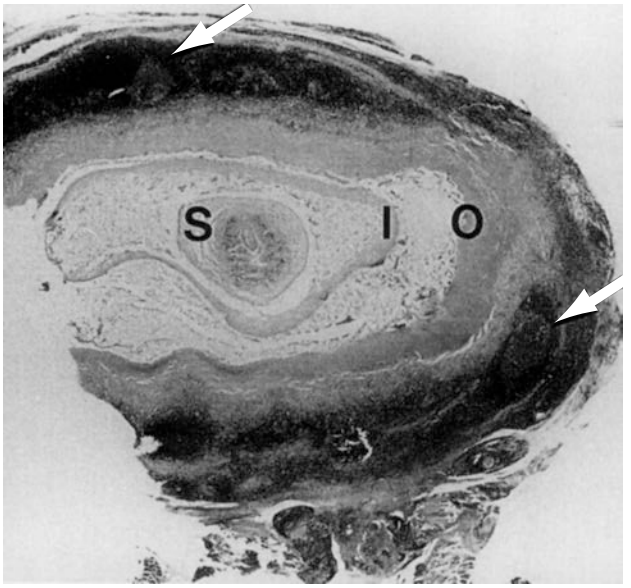

Figure 4.35 Cysticercosis. Low-power view of a specimen showing outer (O) and inner (I) cyst walls, scolex (S), and granulomatous inflammation with lymphoid follicles (*arrows*) (hematoxylin and eosin, original magnification ×14). (Reprinted from Myles WM, Antoszyk JH, Brownstein S, et al. Cysticercosis of the orbit. *Can J Ophthalmol*. 1994;29:291–294, with permission from The Canadian Ophthalmological Society.)

the standard drug was oral albendazole. Tandon et al. (1998) treated two patients, 26- and 33-year-old men. Diagnosis was made on the basis of ultrasonographic images and a positive serum ELISA test. In each case, vision was 20/20 in the affected eye. The patients were started on albendazole, 15 mg/kg/day, to be continued for 1 month. In 5 to 7 days, there was sudden loss of vision, declining to 20/200 in the affected eye. Ultrasonography revealed disorganization of the cyst structure with an inflammatory reaction involving the adjacent optic nerves. The patients were started on prednisolone, 1 mg/kg/day, in addition to albendazole. Vision was restored to 20/20 by 3 weeks. In the 30-year-old patient, proptosis subsided, and the patient was asymptomatic after 2 years' follow-up. MRI of the 26-year-old patient performed 6 weeks after therapy showed complete resolution of the cyst, and the patient was asymptomatic at 1 year of follow-up. They recommend that if the cyst is located near the optic nerve, a therapeutic regimen combining albendazole with oral steroids should be used.

Of the 20 patients with cysticercosis, 12 cysts were located in the orbit (Pushker et al., 2001). Nine of the 12 cysts were lodged in an extraocular muscle. Diagnosis was based on a combination of ultrasonography and CT scans. Medical therapy consisted of oral albendazole, 15 mg/kg/day in two divided doses, along with oral prednisolone, 1.5 mg/kg/day in a single dose, for 4 to 6 weeks. Once ultrasonography showed a static response, surgical removal and histopathologic examination followed.

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5 Fibrous and Connective Tissue Tumors and Proliferations

Fibrous tumors and tumor-like proliferations are a large and diverse group of entities, which differ greatly in behavior. Some are perfectly benign, remain localized, and usually do not recur even after simple excision. Others are poorly circumscribed, grow in an infiltrative manner, and tend to recur unless widely excised. Still others are frankly malignant, recur, and metastasize in a high percentage of cases. On the basis of age at incidence, Enzinger and Weiss (1995) divided them into four categories: (i) Benign fibrous proliferations, (ii) fibromatoses, (iii) fibrosarcomas, and (iv) fibrous proliferations of infancy and childhood.

MYOFIBROMA AND MYOFIBROMATOSIS (INFANTILE TYPE)

Stout (1954) described a group of abnormal fibrous proliferations in patients younger than 16 years. To the tumors in this age-group he applied the term *juvenile fibromatosis*. Later, Chung and Enzinger (1981) reviewed the clinical and pathologic characteristics of 61 cases and to this tumor group they applied the term *infantile myofibromatosis*. "Infantile" replaced "juvenile" because 89% of their cohort occurred within the first 2 years of life. The prefix "myo-" was added because the microscopic features of the tumor cells were intermediate between fibroblasts and smooth muscle cells. The authors also recognized solitary and multicentric forms of the tumor. We prefer the terms "myofibroma" for the solitary tumor and "myofibromatosis" for the multicentric lesions because the form may vary according to the age at presentation (infancy, childhood, or adulthood). The suffix "-tosis" may be reserved for a discussion of a spectrum of multiple causes of the fibrous tumor.

Incidence

Only one publication in the literature attempts an analysis of the incidence of orbital involvement. In an extensive review of 340 orbital tumors in children, Kodsi et al. (1994) found only one case (incidence 0.3%) of orbital myofibroma. Our survey of 1,795 orbital tumors (see Table 3.3) includes four cases of fibromatosis (0.0022%).

In Table 5.1, we list the seven myofibromas reported in the literature since 1988. There are five males and two females. All but one patient were <4 years old at the time of presentation. Not included in the list is a case of desmoid fibromatosis reported by Maillard and Kountakis (1996). This case probably was associated with trauma. Myofibromas also occur in adults, usually in the lower eyelid, although the literature contains only a smattering of adult cases.

Clinical Features

Myofibroma is a gray, benign, nonencapsulated, locally invasive tumor that usually presents as a painless proptosis of several weeks' to several months' duration. If located in the inferior orbit, there is swelling of the overlying eyelid and a hard mass is palpable. Because the development is painless, there may be undue delay before the child is brought to the attention of the ophthalmologist. In such cases, there may be chemosis and redness of the eye and a look of alarm on the patient's face.

Such patients may also have papilledema. All the neoplasms in Table 5.1 were solitary. Five of these seven patients had some degree of orbital bone erosion. In three of the five patients, erosion involved the bony interface between the orbit and the intracranial vault. The largest

TABLE 5.1
MYOFIBROMAS REPORTED SINCE 1988

Authors (date)	Patient's Age	Patient's Sex
Waeltermann et al. (1988)	Birth	Male
Campbell and Garrity (1991)	2½ y	Male
Stautz (1991)	Birth	Male
Linder et al. (1996)	11 d	Male
Duffy et al. (1997)	4 y	Female
Shields et al. (1998)	3 mo	Female
Tokano et al. (2001)	10 y	Male

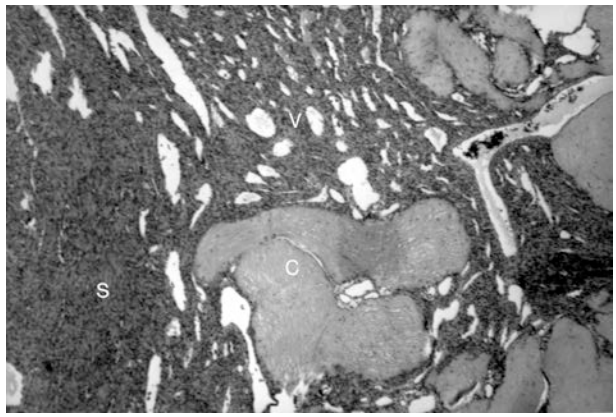


Figure 5.2 Cellularity of this myofibroma varies from area to area. Note solid spindle cells (S), vascular component (V), and dense collagen (C) (hematoxylin and eosin, original magnification ×160).

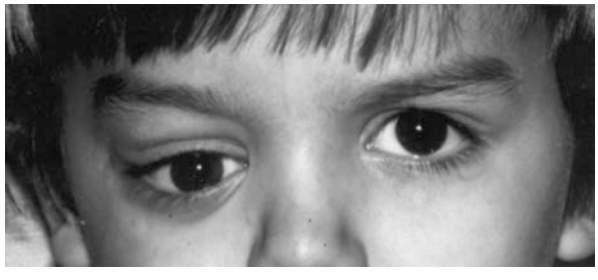
tumor, measuring 5.2 × 5.4 cm (Stautz, 1991), entered the anterior cranial fossa through the lamina papyracea and optic foramen and entered the middle fossa through the greater wing of the sphenoid bone. All patients underwent some type of surgical intervention. Incisional biopsy was performed in three patients, and another three patients had total excision, piecemeal removal, or extirpation. The patient described by Campbell and Garrity (1991) underwent two surgical procedures (see Fig. 5.1). An initial incisional biopsy was performed. However, clinical progression of the tumor continued. Nine months later the tumor was excised through a lateral orbitotomy. Tumor regression occurred in all cases.

Imaging Aspects

On computed tomography (CT) scan, because of the frequency of some degree of bone remodeling, the tumor probably appears circumscribed, with marginal sclerosis. Magnetic resonance imaging (MRI) shows isodense to high signal intensity on T_1-weighted images, and T_2-weighted and gadolinium-enhanced images demonstrate the high signal intensity of the tumor. The intensity of the enhancement may be useful in judging the degree of regression of the tumor in the follow-up period.

Pathology

Histologically, sections from a myofibroma show marked variation of cellularity from area to area within a given tumor and from one tumor to another. This display is called a *zoning pattern* (see Figs. 5.2 to 5.4). The center of the tumor usually has some type of a vascular component, slit-like cavities, capillary channels, or a hemangiopericytoma-like pattern. This area is surrounded by an admixture of spindle, fusiform, and oval cells arranged in ribbons, fascicles, or bundles that vary in density from area to area. Areas of marked density may have deposits of dense collagen. Areas of less cellularity may show patches of loose fibromyxomatous stroma. Long-standing tumors show patches of necrosis and calcium deposition. Mitoses are either rare or absent.



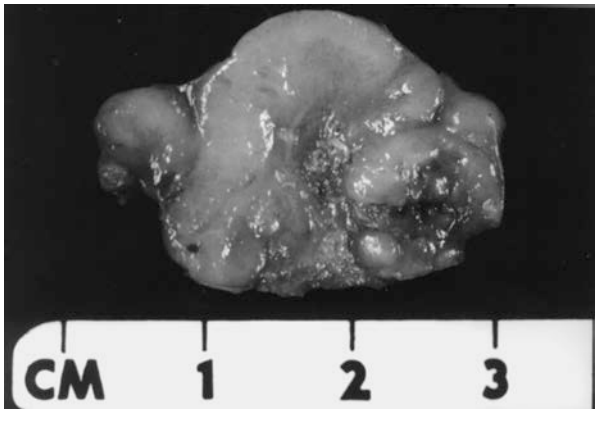


Figure 5.1 Infantile myofibroma. **A:** A 4-year-old boy with progressive forward and downward displacement of the right eye of 14 months' duration owing to a hard palpable mass in the superoanterior orbit. **B:** Surgical specimen. The mass arose from the periorbita and measured 3.0 × 2.5 × 1.5 cm.

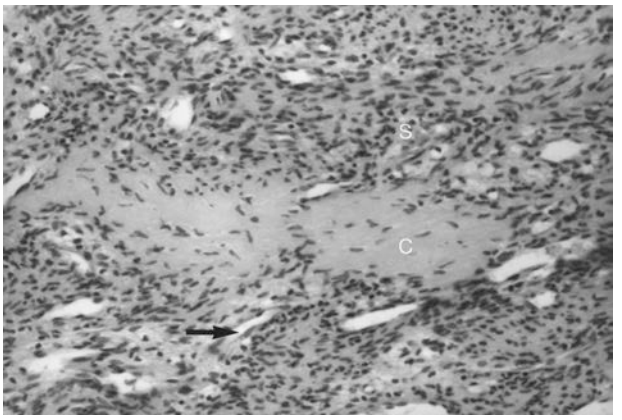


Figure 5.3 Spindle cells (S) of this myofibroma intertwine. Collagen (C) is surrounded by slit-like vascular channels (*arrow*) (hematoxylin and eosin, original magnification ×400).

Immunoperoxidase stains are usually positive for vimentin (a general soft tissue marker) and actin (a marker for contractile protein), the latter a contractile protein. Some observers say these staining properties are variable. Staining is variable also for desmin (a soft tissue marker) but negative for S-100 protein (a marker of neural crest derivatives and other tissue) and leukocyte common antigen (a white blood cell marker).

Ever since Chung and Enzinger (1981) suggested that the tumor cells were intermediate between fibroblasts and muscle cells, the tumor's pathogenesis (fibrous tissue or smooth muscle) has been debated. At present, this discussion is not germane to the clinical course and management of the tumor.

Management

Assuming the myofibroma is primary in the orbit, the ophthalmologist has several treatment options, depending on such factors as size and location of the tumor, severity of visual dysfunction, and the extent of bone erosion. If the mass is located in the anterior orbit and the displacement, motility, and vision of the eye are not seriously compromised, an effort may be made to excise the lesion.

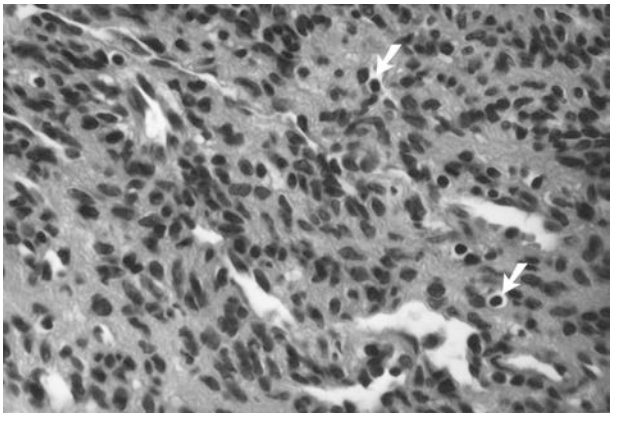


Figure 5.4 The central portion of this myofibroma shows spindle cells, sparse mononuclear cells (*arrows*), and slit-like vessels (hematoxylin and eosin, original magnification ×630).

If the lesion is very large (because of either rapid progression or long duration), the vision and motility of the eye are severely restricted, and the patient is experiencing pain, piecemeal debulking is best. Some tumors of this size may also be undergoing some necrotic degeneration with the tumor in such a semigelatinous state as to be amenable to aspiration. Any tumor, regardless of size or location, which has papilledema or retinal disruption also should undergo debulking. Myofibromas that invade the bone, other than surface erosion, must be debulked, particularly if the sphenoid bone is involved.

Comment

To conclude this section, we should mention a 2 1/2-year-old boy with a sino–orbital desmoid fibromatosis (aggressive juvenile fibromatosis) reported by Maillard and Kountakis (1996). Aggressive juvenile fibromatosis is a benign, poorly encapsulated, infiltrative, firm overgrowth of fibrous tissue, with a propensity to invade bone and soft tissue, occurring in children in the 2- to 8-year age range (and considered rare in the sinuses [Naidu et al., 1991, Thompson et al., 1991]). In these respects, it is similar to the preceding infantile myofibroma.

It differs from myofibroma, however, in several respects, namely, its aggressiveness, which belies its assumed benignity; its recurrence; and, if located near a vital area, its lethality. The authors believe their case was the sixth to be reported wherein the primary locus of the tumor was a paranasal sinus.

Within a month of the child falling and hitting his left cheek, the cheek began to bulge, pushing the left eye upward and deforming the left side of his face. Imaging studies showed a mass in the left antrum with extension into the ethmoid cells and erosion of both the orbital floor and the anterior maxillary wall.

The mass in the antrum was removed surgically within its pseudocapsule, but tumor extension into the orbit was dissected from the periorbita along the floor of the orbit. On re-exploration 3 months later, the sinus cavity had re-epithelialized. However, the infiltrating tumor was still present in the inferior orbit. This was vaporized with the carbon dioxide laser. Following a report that hormonal receptors have been identified in some cases of juvenile fibromatosis (Maddalozzo et al., 1993) adjuvant treatment consisted of a 2-month course of tamoxifen citrate (10 mg twice daily). MRI performed 2 years later showed no recurrence.

NODULAR FASCIITIS

Some years ago, Konwaler et al. (1955) described a circumscribed, subcutaneous tumor-like lesion that was

thought to be a distinct clinicopathologic entity. Although the lesion was alarmingly reminiscent of fibrosarcoma, the authors believed the entity was an inflammatory reaction. This proved a major step in the resolution of the confusion at that time regarding what constitutes a low-grade fibrosarcoma. Numerous clinicians and pathologists subsequently confirmed the basic premise of Konwaler et al. (1955) of an entity that, histologically, looked sarcomatous but, clinically, was benign. This feature was responsible for the term *pseudosarcomatous fasciitis*. In the early years, this term was the title of most descriptions of this lesion.

Incidence

This is a benign, self-limiting tumor composed of rapidly proliferating, immature fibroblasts and myofibroblasts in a cellular matrix with mitotic activity (atypical mitoses are rarely seen). The precise cause of the proliferation is unknown, but its histopathologic pattern supports a reactive process such as that seen with trauma, inconspicuous or otherwise.

It is one of the most common soft tissue lesions among the tumor and tumor-like lesions of fibrous tissues. Enzinger and Weiss (1995), at the Armed Forces Institute of Pathology (AFIP), reviewed >1,000 cases over a 20-year period. In the AFIP series, this tumor was most common in adults aged 20 to 40 years. In the series of 250 cases described by Shimizu et al. (1984), the age range was 1 to 76 years with a mean of 39 years. Sex incidence was nearly equal.

In the 1960s and 1970s, the tumor was extensively studied by physicians anxious to report cases of the recently described clinical entity. Font and Zimmerman (1966) reported ten cases involving the eye and ocular adnexa (eyelids, five cases; periorbital tissues, two cases; subconjunctival tissue overlying the scleral insertion of a rectus muscle, one case; eyebrow, one case; and corneoscleral limbus, one case). In the same year, Tolls et al. (1966) described a case originating in the Tenon capsule (fascia bulbi). Subsequent cases were reported in the eyelid (Levitt et al., 1969), fascia bulbi (Ferry and Sherman, 1974), eyebrow (Meacham, 1974), and episcleral mass (Holds et al., 1990). None of these patients had proptosis. However, one article (Levitt et al., 1969) did use the word ''orbital'' in the title. However, Perry et al. (1975) described a 34-year-old woman with proptosis due to a mass in the superior temporal quadrant of the left orbit. On excision, the mass was not attached to any structure, was encapsulated, and was very vascular. This does not fit the present description of nodular fasciitis.

The best-documented orbital case was reported by Kaw and Cuesta (1993) in a 10-year-old girl with a painless, rapidly growing mass causing medial deviation of her left eye. There was no history of trauma. On surgical exploration, a shiny white, circumscribed, but unencapsulated, firm mass, 2 cm in diameter, was removed from its attachment to the periorbita. Histologic study confirmed the diagnosis of nodular fasciitis.

Clinical Features

Most patients present with a rapidly growing mass or nodule of from 2 to 6 weeks' duration. Around the ocular adnexa and orbit, the lesions are solitary and not associated with pain or tenderness unless the growth reaches a size that pushes on a nerve. The CT scan of the patient of Kaw and Cuesta (1993) simply documented a circumscribed mass. An MRI study was not performed.

Pathology

The histologic variability of this lesion was pointed out in the initial description by Konwaler et al. (1955). Its basic components are proliferating bundles of fibroblasts. In the early lesion, these spindled and ovoid, mitotically active fibroblasts proliferate in a helter-skelter fashion in a loose myxoid matrix containing many intercellular clefts. A rich capillary network is also present, and microscopically, the tumors may infiltrate the orbital muscle. As the tumor matures, the lesion becomes more cellular and compact, and the myxoid matrix is gradually replaced by collagen. The capillaries become less abundant, and some nuclei show prominent nucleoli. In the third stage, fibroblasts are more slender and compressed into whorls and interdigitating bundles similar to fibrous histiocytoma. Collagen deposition increases and the cell nuclei are more hyperchromatic. The content of mononuclear inflammatory cells varies considerably from specimen to specimen. These cellular variants represent a continuum of changes that correlate well with the duration of the lesion, the myxoid subtype having the shortest history and the fibrous subtype having the longest history.

Ultrastructural study reveals cells that seem to combine the properties of the fibroblast (abundant rough-surfaced endoplasmic reticulum and no basement membrane) and the smooth muscle cell (thin cytoplasmic actin filaments with fusiform densities, i.e., myofibroblasts) (Jakobiec and Jones, 1979).

Management

The orbital and adjacent adnexal growths are managed by simple excision.

NASOPHARYNGEAL ANGIOFIBROMA

This long-known, benign rhinologic neoplasm may also be found in the orbital soft tissues. Several sizable, well-documented series of angiofibromas—120 cases by Neel et al. (1973) and 218 cases by Stern et al. (1986)—have been published wherein proptosis or displacement of the

eye occurred. Although the lesion is chiefly a secondary intruder into the orbital domain, this anatomic area may be an even rarer primary locus for the tumor.

Incidence

Neel et al. (1973) in their 120 patients noted orbital invasions in ten patients (8%). Stern et al. (1986) noted orbital involvement in a larger number of patients, in 26 (12%). In the interval since these reports, we have not found another large, well-documented collection of cases in the literature, which could be the basis for statistical analysis. Moreover, we believe that the frequency of orbital spread is much less because of factors not present in the 1970s and 1980s. First is the routine use of the CT scan at the time of the patients' initial visits. The CT scan image shows the full anatomic extent of the tumor and ramifications outside the nasal passage. In turn, this imaging encourages earlier surgery and more complete excision of the primary tumor. Second, surgical technology has been refined.

All 120 patients in the series reported by Neel et al. (1973) were men. Some authors have stated nasopharyngeal tumors always occur in men. However, several reports have noted the tumor's occurrence in women (Finerman, 1951; Osborn and Sokolovski, 1965; Conley et al., 1968; Peloquin et al., 1997). Rarely, patients with this angiofibroma also have familial adenomatous polyposis (Giardiello et al., 1993; Ferouz et al., 1995).

Clinical Features

The common presenting features are some degree of nasal obstruction, facial deformity, and repeated epistaxis. Examination shows a pale, red or reddish blue mass in the pterygopalatine fossa projecting into the roof of the posterolateral nasal cavity. Bulging of the adjacent cheek often is present because of the pressure erosion of underlying bone. A thorough bone imaging on CT scan shows the full extent of the tumor. Initially, some erosion of sphenoid bone occurs behind the sphenopalatine foramen (Lloyd et al., 2000). The deeper the tumor extension is into cancellous bone, the greater the likelihood some remnant of tumor may remain after surgical removal. Because of the high vascularity of the tumor, MRI shows signal voids and strong postcontrast enhancement. Because of its aggressive nature, the tumor rapidly expands into the retromaxillary area, the orbit, and the intracranial vault by a combination of passages through bony fissures and bone erosion. Orbital invasion is heralded by one or more of the following: Reduced vision, displacement of the eye, tearing, and ophthalmoplegia. Intracranial extension often occurs with or near the time of orbital invasion. Such patients have papilledema or optic atrophy.

The one case of angiofibroma in our tumor series was a 16-year-old boy with trouble breathing through the left side of his nose during the preceding 6 to 8 weeks. Two weeks before his referral, his referring physician biopsied a mass in the left nasal passage. The biopsy report indicated that the tumor was an atypical angiofibroma.

On admission, imaging studies revealed a large mass in the left posterior nasopharynx extending into the sphenoid, ethmoid, and maxillary sinuses. Through a lateral rhinotomy, the affected sinuses were exenterated, and the presenting surface of the tumor was treated by cryoablation.

Ten months later, angiography revealed extensive recurrence of tumor in the left nasopharynx, the floor of the middle intracranial fossa, and marked dilation of the ophthalmic vein. The left eye was proptosed 5 mm, and the anterior surface of the sclera was covered by dilated veins (see Fig. 5.5). The area was treated with cobalt 60, 24 Gy, over a 10-day period. At the last follow-up $3\frac{1}{2}$ years later, the tumor had disappeared, and the eye looked almost normal.

Moschos et al. (1998) reported an angiofibroma they considered primary in the orbit. A 14-year-old boy presented with a mass in the left lacrimal sac area. The patient had had a previous surgery for dacryocystitis. Imaging procedures showed erosion of the lower nasal wall of the orbit with displacement of the eye temporally. The mass was totally removed. Pathologic study indicated a nasopharyngeal angiofibroma. We consider the lacrimal sac, anatomically, to be an adnexal structure that is outside the orbit. Therefore, this case is an angiofibroma secondarily invading the orbit. The case of a 15-month-old boy with an angiofibroma, anterior and medial to the lacrimal sac, described by Schick et al. (1998) is anatomically in the same area. The tumor was removed through an endonasal, microscopic–endoscopic approach. Finally, Weprin and Siemers (1991) noted a biopsy-proved juvenile nasopharyngeal angiofibroma first diagnosed in an 11-year-old child. The patient was followed up for 12 years but received no therapy. Total involution of the

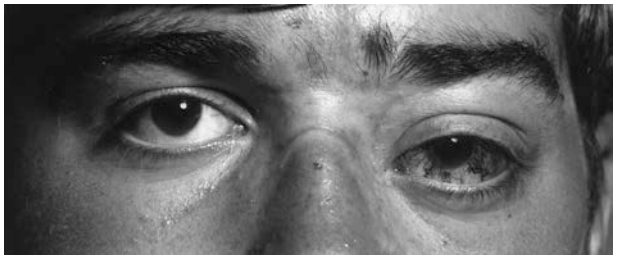


Figure 5.5 Recurrent nasopharyngeal angiofibroma. This 17-year-old man had total excision of a $10 \times 7 \times 4$-cm multilobular mass 10 months previously involving nasopharynx, nasal cavity, sphenoid sinus, retromaxillary space, maxillary antrum, and cheek, all on the left side. Angiography showed an enormous recurrence involving the floor of the left middle intracranial fossa and the orbit, and obstruction of the ophthalmic veins. Note the dilated epibulbar vessels on the bulging, displaced left eye. The recurrent tumor was considered inoperable, but it responded to radiotherapy. The patient was living without further recurrence at follow-up 3 years after this photograph was taken.

lesion occurred. This involution supports the theory that this tumor may resolve with time.

During the past several decades, the effect of sex hormones on the clinical course of angiofibromas has been debated. Two publications on the subject in the rhinologic literature of the 1990s should be noted. Using immunohistochemical methods, Gatalica (1998) examined eight nasopharyngeal angiofibromas for the expression of androgen receptors, estrogen receptors, and progesterone receptors. No estrogen receptors or progesterone receptors were found in the tumor components. Variable weak-positive androgen receptor immunoreactivity was found in a minority of endothelial and stromal cells, similar to normal turbinates. He concluded that the results argued against an important role for androgen receptors in the growth of these tumors. Hwang et al. (1998) performed immunocytochemical studies on 24 nasopharyngeal angiofibromas. Stromal and endothelial nuclear immunostaining was positive for androgen receptors in 18 (73%) of 24 cases, whereas 2 (8.3%) of 24 cases were positive with antibodies to progesterone receptors. None of the samples was positive with antibodies to estrogen receptors.

Pathology

The tumor is a profusion of thin-walled vascular channels of variable size and shape interspersed in a fibrous tissue stroma (see Fig. 5.6). The fibrous tissue consists of a complex proliferation of spindle and stellate cells in the more peripheral zones of the lesion, whereas a less cellular, predominantly collagenous matrix is usually present in the deeper, more central zone. The amount of the vascular component decreased as the extracellular collagenous fibers increased (Liang et al., 2000). In the more proliferative zone of the tumor, the endothelial cells of the vascular channels lie directly against the supporting stroma, without any intervening elastic fiber or smooth muscle cells (pericytes). This probably accounts for the profuse hemorrhage when the tumor is manipulated. In more collagenous areas, spindle cells may layer between vessel wall and stroma. If so, some of these cells probably stain positive to actin, indicative of smooth muscle properties.

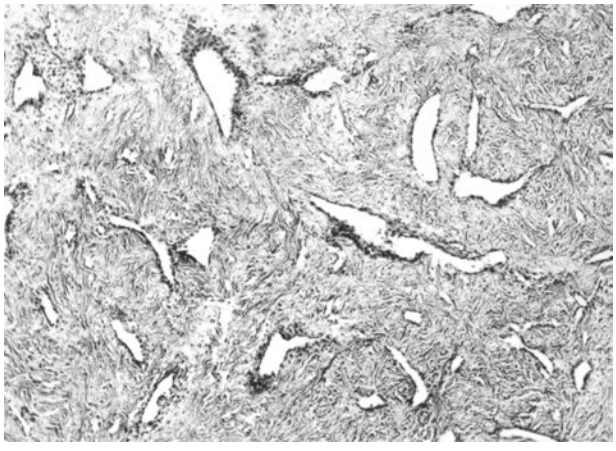


Figure 5.6 In this nasopharyngeal angiofibroma, a dense, cellular, spindle cell stroma supports a mixture of slit-like and irregular, angulated, thin-walled vascular channels. At this magnification, the tissue pattern resembles the spindle cell variant of hemangiopericytoma (hematoxylin and eosin, original magnification ×60).

Management

The role of the ophthalmologist begins when and if the angiofibroma invades the orbit. It is likely that areas other than the orbit show extension of tumor on CT scan imaging. One, two, or more combinations of the following spaces may also be involved: Pterygopalatine fossa, maxillary sinus, sphenoid sinus, anterior intracranial fossa, maxillopterygoid fossa, infratemporal fossa, and middle intracranial fossa. Therefore, the multilocular angiofibroma may encroach on the boundaries of several surgical disciplines such as maxillofacial surgery, rhinologic surgery, plastic and reconstructive surgery, and neurosurgery, in addition to ophthalmology. Various surgical approaches recommended in the literature to remove tumor extensions include endoscopic, subtemporal, midfacial, lateral rhinotomy, lateral orbitotomy, and lateral preauricular temporal approach. For lesions around the cavernous sinus, microdissection has been recommended inasmuch as the tumor tends to push aside the structures rather than fuse with their fascial coverings. Before commencing these major surgical procedures, it is prudent to perform angiography and, if possible, to embolize the feeder vessels to the tumor.

Radiotherapy also is used as initial therapy but in recent years has been reserved for recurrent tumor after surgical removal. Reddy et al. (2001) analyzed 15 patients treated with radiotherapy between June 1995 and March 1996. Six patients received radiotherapy as the initial therapy, and the remaining nine had irradiation for recurrent tumor. All patients were boys between the ages of 11 and 14 years. Eight patients were followed up for 5 or more years, and seven were followed up for 10 or more years. The entire cohort was treated with continuous-course techniques with variable dosages ranging from 540 to 735 Gy. Thirteen patients had complete resolution of tumor within 1 to 39 months (median, 13 months). Two patients had tumor recurrence at 26 months and 28 months. Both these patients received irradiation as initial therapy. Cataract developed in three patients 5 to 10 years after irradiation. All three had tumor invasion of the orbit.

Kuppersmith et al. (2000) treated three patients with intensity-modulated radiotherapy. This technique embraces the concept of computer-controlled radiation deposition and computer-controlled normal tissue avoidance. One patient with an extensive tumor was treated initially with radiotherapy because the tumor was considered unresectable. The other two patients were treated for recurrent angiofibroma 11 months and 13 months after surgical

excision. The tumor in the first case eroded the base of the skull and extended into the pterygopalatine fossa and the area of the cavernous sinus. The tumor received a total dose of 45 Gy in 25 fractions. The mean dose to optic nerves was 28 Gy and to optic chiasm was 17 Gy. Imaging scans showed tumor regression at 15 months. The two patients with recurrent angiofibromas were treated with a total of 45 Gy and 35 Gy. Tumor resolution occurred at 40 months and 6 months, respectively. No further follow-up of the three cases was stated.

Therapeutic options other than surgery include cryotherapy, electrocoagulation, interstitial brachytherapy, and embolization (Spector, 1988); hormonal therapy (Hagen et al., 1994); and chemotherapy (Goepfert et al., 1985).

GIANT CELL ANGIOFIBROMA

Dei Tos et al. (1995) described "seven cases of a morphologically distinctive orbital tumor, occurring in adults and showing histologic appearances intermediate between, but distinct from, (solitary fibrous tumor) and giant cell fibroblastoma (GCF) of soft tissue. We believe that the lesion represents a unique, previously undescribed orbital tumor and, in view of its morphology and its peculiar location, suggest the designation *giant cell angiofibroma of the orbit*. Subsequent cases were reported by Ganesan et al. (1997) and Hayashi et al. (1999). The latter summarized the reported cases, including five of their own cases. The patients in the conglomerate ranged in age from 23 to 78 years (median, 51.5 years), and 13 of a total 16 were men. The orbit was affected in seven cases, the eyelid in five cases, the eyelid and orbit in three cases, and the conjunctiva in one case.

Patients usually present with a unilateral, painless swelling of either the upper or the lower eyelid because of a palpable, soft lump or nodule in the subcutaneous tissue. Less often, the presentation is a displacement of the eye due to a mass in the anterior medial or lateral orbit. The duration of symptoms varied from 6 months to 8 years. The lesions enhance and are easily imaged by CT scan of the anterior orbit and adjacent eyelid.

Grossly, the tumors are soft and relatively well circumscribed and have a reddish hue. Microscopically, the tumor consists of a patternless proliferation of round, oval, and spindle cells with a moderate to high degree of cellularity in a collagenous matrix. The stroma has a rich vascularity. A peculiar feature of the lesions is the pseudovascular spaces, which differ from true vascular channels, lined by spindle, oval, or multinucleated tumor cells instead of endothelial cells (see Fig. 5.7). The giant cells may have a cluster of nuclei in the center of the cell, or more commonly, the nuclei are arranged in a ring around the periphery. Immunohistochemically, the spindle cells and giant tumor cells are markedly positive for CD34 antigen and vimentin. Guillou et al. (2000) believe there is growing evidence that giant cell angiofibroma and solitary fibrous tumor significantly overlap, and it is likely that the former is merely a giant cell–rich variant of the latter.

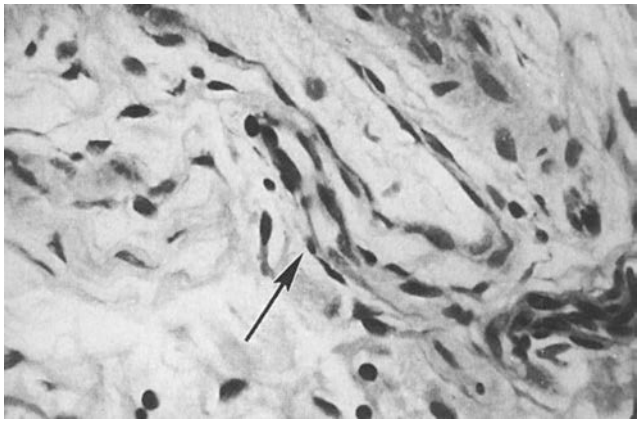


Figure 5.7 In this giant cell angiofibroma, tumor cells line the periphery of a vascular-like space (*arrow*). (Reprinted from Hayashi N, Borodic G, Karesh JW, et al. Giant cell angiofibroma of the orbit and eyelid. *Ophthalmology*. 1999;106:1223–1229, with permission of Elsevier Science.)

These circumscribed angiofibromas can be completely removed without recurrence.

FIBROUS TUMOR

This is a newcomer to our collection of orbital tumors. It was not discussed in the three previous editions of this text. It was first described by Klemperer and Rabin (1931) as a pleura-based fibrous mesothelioma. Subsequent study of the tumor by electron microscopy and immunochemical agents did not confirm a mesothelial differentiation but, instead, a fibroblastic genesis. Furthermore, it was soon evident that the tumor was not localized to the pleura but occurred in diverse sites, including the liver, meninges, nasal passages, skin, thyroid, respiratory tract, soft tissues, and orbit. Our discussion focuses on the tumor's orbital manifestations.

Incidence

The literature contains numerous reports of single cases primary in the orbit. Those publications describing two or more cases are Dorfman et al. (1994), Westra et al. (1994), Lucas et al. (1995), Kim et al. (1999), and Gigantelli et al. (2001). Three publications describe solitary fibrous tumor as a secondary invader of the orbit (Fukunaga et al., 1995; Lucas et al., 1995; Ahn et al., 2001). The primary locus of the tumor in these three cases was the nasal cavity, the lacrimal sac, and the meninges, respectively. Also, there are a few reports of the tumor occurring in extraorbital sites. The fibrous tumor in these areas does not differ from those lesions primary in the orbit, except for their location. Last is

the report of a malignant orbital fibrous tumor by Carrera et al. (2001). In brief, a 64-year-old man presented with a mass in the upper part of one orbit. Two prior resections of the tumor had been performed elsewhere in the 3 years before presentation. On surgical exploration, a malignant tumor was noted, and an exenteration ensued. Thirty-eight months later, multiple recurrent neoplastic nodules were found at the base of the affected orbit. Another surgical resection of the recurrent tumor was performed 13 months later. The patient died soon after, 8 years after onset. The final diagnosis was solitary fibrous tumor with histologic evidence of progressive dedifferentiation to fibrosarcoma. Proof of a malignant degeneration of a solitary fibrous tumor would have been more definite if a photomicrograph of the first surgical excision had been available. Profuse immunostaining with CD34 and vimentin are not proof that the original lesion was a solitary fibrous tumor. Such immunoreactivity is not specific for fibrous tumor.

In a casual review of the literature seeking data on the incidence of solitary fibrous tumors primary in the orbit, we encountered some 16 publications representing 29 patients (through year 1991). Since 1991 Dorfman et al. (1994) reported three additional cases, reaffirming that the orbit is one of the most common locations for extrapleural spread of the tumor. When we add the three patients from our own survey (see Table 3.3), the grand total is 32 patients (13 male, 19 female). The patients ranged in age from 14 to 84 years (median, 46 $^1/_2$ years) (see Table 5.2).

Clinical Features

Patients usually present with unilateral swelling of an upper or lower eyelid. If the lower eyelid is affected, some tearing may be present. A soft lump, mass, or nodule is palpable in the anterior orbital space opposite the swelling. This mass may be large enough to cause some displacement of the eye in a vertical or horizontal plane associated with diplopia. The duration of signs and symptoms may range from 1 month to several years, depending on the patient's tolerance for lid swelling or the degree of diplopia. These tumors rarely locate in the retro-ocular space to such a degree that they cause severe proptosis. If the patient says the palpable lump was partially removed previously, the recurrent tumor may cause some degree of pain. CT scan shows a well-circumscribed, high-density mass with some enhancement. T_1- and T_2-weighted MRI studies show a hypodense mass. The adjacent bone is normal unless the tumor is very large or of long duration. In the latter situation, the bone may show remodeling.

TABLE 5.2
PRIMARY ORBITAL SOLITARY FIBROUS TUMOR BY DECADE OF AGE

Decade of Age (y)	Number of Patients
14–20	3
21–30	7
31–40	4
41–50	7
51–60	3
61–70	7
71–80	3
81–84	1

Pathology

The gross specimen is soft, tan-gray, and well circumscribed. Microscopically, the neoplastic spindle cells are plump, uniform, and usually arranged in a haphazard fascicular pattern with individual cells separated by variable amount of fibrillar collagen (see Fig. 5.8). In some areas, the collagen may be dense and partly hyalinized. The nuclei are ovoid, plump, or spindle-shaped with vesicular chromatin and definite nuclear membranes (see Fig. 5.9). There is usually a prominent background vascular pattern with both thick- and thin-walled vessels. The vessels in some areas may have configurations similar to those of hemangiopericytoma. On immunohistochemical evaluation, the neoplastic cells are positive for vimentin and CD34 antigen (Clayton et al., 2001). The latter is a highly sensitive marker for solitary fibrous tumor, although it is not entirely specific for this tumor.

Management

The circumscription of the tumor and its frequent residence in the more anterior orbital space facilitate its intact

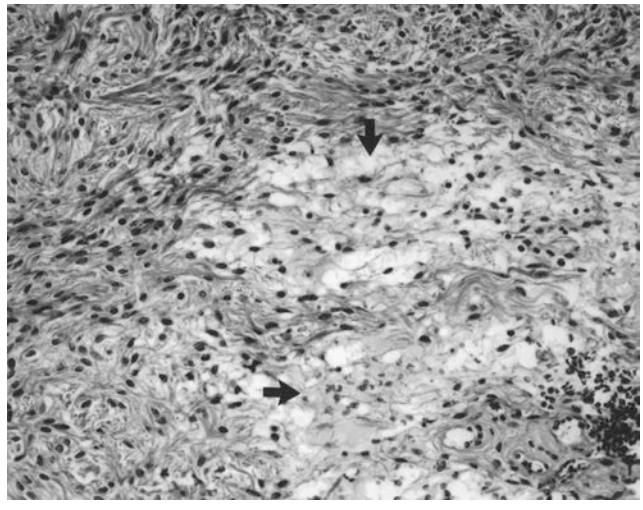


Figure 5.8 Solitary fibrous tumor of orbit demonstrating uniform spindle cells arranged in a haphazard fascicular pattern. Note prominent vascular stroma, which includes several ectatic vessels (*arrows*) (hematoxylin and eosin, original magnification ×110).

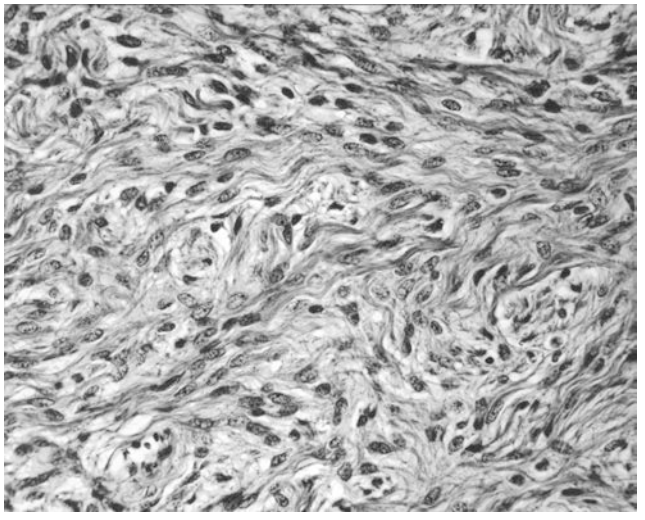


Figure 5.9 Solitary fibrous tumor demonstrating spindle cells with plump, ovoid nuclei and ill-defined cytoplasm; cells are separated from one another by bundles of fibrillar collagen.

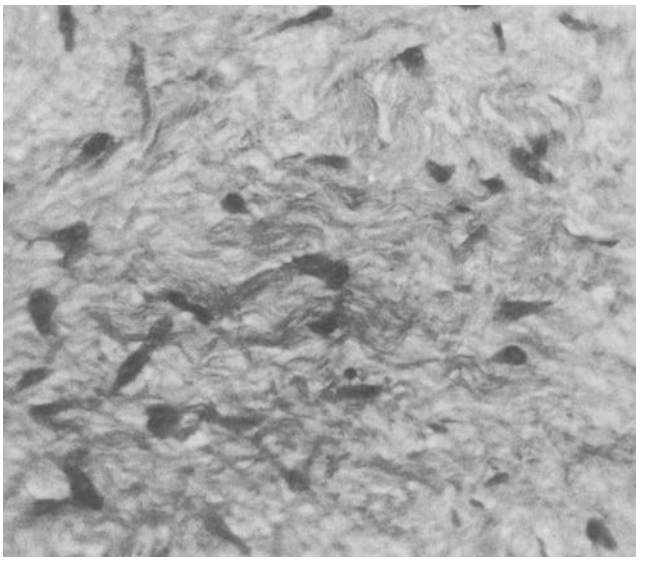


Figure 5.10 A specimen of fibroma from a nonorbital site showing a benign hypocellular tumor of elongated fibroblasts separated by wide bundles of collagen.

removal. Tumors in the posterior orbit are better managed by lateral orbitotomy or orbitocraniotomy. The tumor does not recur if removal is intact. If piecemeal removal is necessary because of the tumor's proximity to the optic nerve, tumor recurrence is likely, although several years may elapse between these events.

FIBROMA

In the 50-year period of our survey (1948 to 1997), we did not observe a patient with a fibroma primary in the orbit. At one time it was thought to be more common in the orbit, than at present. The diagnosis of fibroma decreased in frequency when the diagnostic criteria of fibrous histiocytoma were suggested approximately 20 years ago. What had once been called "fibroma" was now termed *fibrous histiocytoma* in many cases. In addition, many reports of fibroma were never photographically documented. Further review indicated that diagnosis was based only on the quantity of fibrous tissue within the lesion, and the presence of a histiocytic component was ignored. Therefore, the one case of fibroma recorded in the first edition of *Orbital Tumors* proved, on further review, to be a fibrochondroma rather than a fibroma with cartilaginous differentiation. In short, the diagnosis of fibroma had been overstated.

In the present terminology, an orbital fibroma is quite rare. One of the two cases reported by Mortada (1971), a 25-year-old man, and the case described by Case and LaPiana (1975), a 77-year-old man, seem to be true orbital fibromas. In each of these cases, the tumor had been present for at least 3 years, and the principal manifestation was a painless, slowly progressive proptosis. Subsequently, Takamura et al. (1994) reported a 53-year-old man with a fibroma primary in the orbit, although the authors did not include a photomicrograph to support their diagnosis. Fibromas have been known to occur on the surface of the ocular adnexa also.

The fibroma is a benign, well-circumscribed, firm neoplasm with a pinkish tinge. CT scan probably shows a well-delineated mass with slight contrast enhancement, depending on the degree of vascularity. MRI probably shows a mass with low intensity in both T_1- and T_2-weighted images. In the orbit, the tumors may arise from the sclera, the fascial sheath of the extraocular muscles, the Tenon capsule, or the periorbita.

Histopathologically, the tumor consists of a sparse number of fibroblasts with tapered ends and elongated nuclei interspersed among bundles of wavy collagen (see Fig. 5.10). Mitotic figures are rare. The tumor is poorly vascularized except along the interlobular septa.

The preferred management is intact excision. If removal is incomplete, the tumor is prone to recurrence.

FIBROSARCOMA

In the mid-1960s, when the writing of the manuscript for the initial edition of *Orbital Tumors* was under way, the diagnostic criteria for benign and malignant soft tissue neoplasms, as well as various proliferations of fibrous tissue, were becoming more restricted. First, histopathologists excluded tumors composed of cells capable of acting as facultative fibroblasts. Next, many fibromas and fibrosarcomas were reclassified as histiocytic neoplasms, and refinements of histologic criteria segregated the fibromas as a unique

group of tumors distinct from fibrous tissue neoplasms. The advent of immunohistochemistry and cytogenetics made recognition of monophasic fibrous synovial sarcomas and malignant peripheral nerve sheath tumors more accurate (Das Gupta and Chaudhuri, 1998; Weiss and Goldblum, 2001). Revisions of terminology soon followed (Rootman, 1988; Scott et al., 1989). Therefore, the diagnosis of orbital fibrosarcoma is less inclusive and more restricted. At present, too few primary orbital fibrosarcomas that meet these restrictive criteria have been reported in the literature to calculate an accurate incidence of orbital fibrosarcomas.

Clinical Features

In the third edition of this book (1994), we cited cases of primary orbital fibrosarcomas that seemed to meet the present restrictive diagnostic criteria. Eifrig and Foos (1969) reported a 3-year-old girl with a 2-month history of proptosis and blepharoptosis of the left eye due to a rapidly growing mass in the superonasal orbital quadrant that eventually extended to the orbital apex. An orbital exenteration was performed. The histopathologic diagnosis was a well-differentiated fibrosarcoma. Follow-up information did not exceed 6 months. Yanoff and Scheie (1966) described two patients. One, a 66-year-old woman, developed 4 mm of proptosis of the left eye over a 9-month period from a mass in the superonasal quadrant of the orbit. At orbitotomy, the mass was well circumscribed and the tumor was easily removed intact. However, when the diagnosis of fibrosarcoma became known, an exenteration was performed. The mitotic index of the tumor was 1. The exenteration specimen showed extension of tumor into the orbital apex such as was found in the case described by Eifrig and Foos (1969). This patient was observed for 6 years without tumor recurrence. The authors' second case was a 60-year-old man who developed proptosis of the left eye over 1 year. A smooth-surfaced retrobulbar mass was incompletely excised. The histopathologic diagnosis was a well-differentiated fibrosarcoma with a mitotic index of 1. In another 3 years, tumor recurrence necessitated exenteration. The recurrent tumor proved to be a poorly differentiated lesion with a mitotic index of 14. Weiner and Hidayat (1983) discussed five cases of periorbital fibrosarcoma. In two of the patients, the tumor seemed strictly orbital in position, and in the third case, the lesion involved the orbit and an adjacent eyelid. One of the orbital cases occurred in a 3-year-old girl with proptosis of the left eye of 2 months' duration. A mass in the medial orbit was treated with radiotherapy, but the response was unsatisfactory. An exenteration was performed. The tumor showed a mitotic index of 10. This patient was alive and well 32 years later. The second orbital case occurred in an 8-year-old girl with a lump in the left lower orbit that developed over 5 months. The lesion was locally excised but recurred in 1 month. This tumor had a mitotic index of 5. An exenteration of the orbit was then performed, but a second recurrence appeared in 2 months. The latter was treated with radiotherapy. One year later the patient was alive with probable recurrent orbital disease. The third patient, a 4-week-old boy, had massive proptosis of the left orbital contents from a congenital fibrosarcoma. The orbit was exenterated. This tumor had a mitotic index of 2. There was no recurrence after a follow-up of 21 months.

A search of the literature has not disclosed a further case of primary orbital fibrosarcoma until the report of Takamura et al. (1994) who described a 53-year-old man. Likewise, we have added only one case of our own in the last decade to our total cases. Our patient group consists of five cases (four women, one man) over the 50-year period of our survey. The age range was 32 to 78 years (median, 65 years). None of the cases was associated with prior irradiation. Lastly, Ohtsuka and Saito (1996) reported a fibrosarcoma sprouting from and attached to the sclera at the posterior pole of the eyeball in a 56-year-old woman. The tumor also infiltrated the adjacent optic nerve sheath. An exenteration was performed. The specimen stained positive for vimentin, and the mitotic index was 3. One year after exenteration, there was no recurrence.

Clinically, patients present with an insidious, slowly expanding, painless orbital mass. If the tumor is located in the forward part of the orbit, the adjacent eyelid may show some swelling. The process evolves over a period of weeks to months. Onset of pain occurs when and if the size or location of the mass exerts some pressure against a nerve. At this stage, involvement of the preauricular nodes is rare.

Imaging Aspects

In the early stage of a fibrosarcoma's growth—usually the situation when a patient is first seen with an orbital mass—the tumor has no imaging features to differentiate it from some of the benign fibrous tissue tumors of the orbit. The fibrosarcoma is well outlined on CT scan. With MRI, the lesion tends to be homogeneous on T_1-, T_2-, and postgadolinium T_1-weighted images. However, fibrosarcomas of long duration or large size may show a heterogenous pattern on T_2-weighted images with low signal areas of void representing vascular channels and zones of necrosis.

Pathology

Fibrosarcoma differs from the antecedent fibroma and fibromatosis in a greater density of cellularity, nuclear atypia, and hyperchromicity but less extracellular collagen. Mitotic activity may range from two to ten mitoses per 10 high-power fields (Spencer, 1996). The cells are closely packed in an interlacing, intertwining (herringbone) pattern (see Fig. 5.11). The nuclei of fibrosarcoma cells are elongated with pointed ends. Giant cells of bizarre size and shape are rare except for tumors that have been irradiated. The cells stain positive for vimentin (Weiss and Goldblum, 2001).

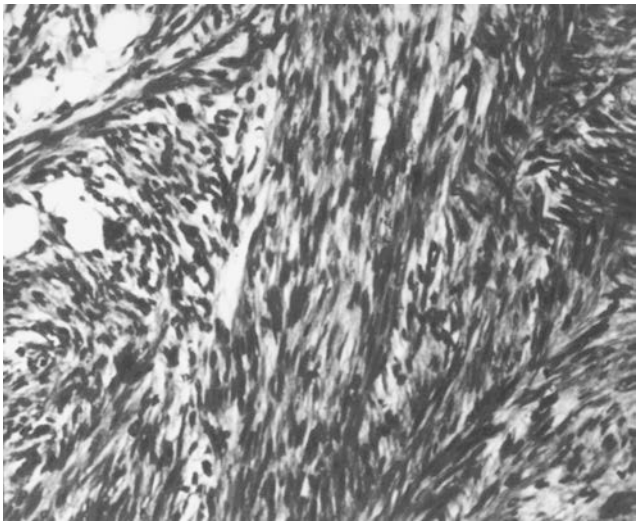


Figure 5.11 This fibrosarcoma shows a herringbone pattern of interlacing fascicles of malignant fibroblasts with occasional mitotic figures (upper left and left center) (hematoxylin and eosin, original magnification ×150).

Management

We believe total exenteration should be performed as the initial procedure on all primary orbital fibrosarcomas as soon as the pathologic diagnosis is known. Only exenteration for those patients with recurrent tumor probably is insufficient to forestall further recurrence. Radiotherapy is used as an adjuvant to wide excision or exenteration for recurrent tumors that were incompletely excised initially. Chemotherapy is proving useful for patients with widespread recurrence such as secondary orbital fibrosarcoma.

Secondary Fibrosarcoma

Our tumor survey includes ten secondary fibrosarcomas. Nine of the tumors originated in either the nasal cavity or paranasal sinuses. One originated in the upper jaw. None was radiation induced. There were six men and four women, ranging in age from 38 to 85 years (median, 60 years).

FIBROUS HISTIOCYTOMA

Fibrous histiocytoma is a descriptive and histologic term for a group of tumors once considered separate histopathologic entities. Kauffman and Stout (1961), studied 39 children with diverse soft tissue mesenchymal tumors and divided them into two groups, depending on the fibroblastic content of the lesion. Between 1963 and 1986, 11 publications discussed the histogenetic enigma of the two principal cell constituents of the tumor. (These publications were referenced in our 1994 edition.) The several possibilities were that both types of cells are derived from completely independent cell lines, fibroblastic cells are derived from histiocytic cells, or histiocytic cells are derived from fibroblasts. The histiocytic origin has now been questioned (Weiss and Goldblum, 2001). In the case of malignant fibrous histiocytoma, a fibroblastic origin is now proposed. In summary, the term *fibrohistiocytic* is descriptive and merely denotes a tumor composed of cells that resemble normal histiocytes and fibroblasts.

Incidence

Almost all data on this facet of the soft tissue orbital fibrous histiocytoma are based on the publication of Font and Hidayat (1982). No other series can match their analysis of 150 cases from the file in the AFIP Registry of Ophthalmic Pathology. The median age of their patient cohort at the time of diagnosis was 43 years (range, 4 to 85 years). The sex distribution was essentially equal, 72 men and 77 women. Forty-eight percent of the tumors were located in the right orbit, and 51% involved the left orbit. The lesions tended to involve the upper part of the orbit more than the lower part. Nine patients had both orbital and paranasal sinus involvement. In such cases, we suspect the tumors originated in the sinuses and spread secondarily into the orbit.

An important conclusion of their study was that fibrous histiocytoma is the most common primary mesenchymal orbital tumor in adults. However, this conclusion was based on a collection of tumors that were probably considered unusual and therefore were sent to the AFIP for definitive diagnosis over a long period. Such data might not represent the true frequency of fibrous histiocytoma in a clinical setting of consecutive cases.

In the third edition of our text, we cited eight single cases of orbital involvement. These, plus the six cases reported by Jakobiec and Tannenbaum (1974), total 14 patients.

Subsequently, we have found several single case reports of benign fibrous histiocytoma in the literature: Larkin et al. (1988) described an infant girl; Ulloa and Anderson (1999) reported a 32-year-old man; and Al-Hazzaa et al. (1996) reported a 44-year-old woman. Single cases of malignant fibrous histiocytoma were reported by Liu et al. (1987) in a 3-year-old girl; Ros et al. (1985) in a 44-year-old man; Hirano et al. (1996) in a 58-year-old man; and Shields et al. (1995) in a 31-year-old man with a multinucleate cell angiohistiocytoma. Finally, the report of eight cases by Jacomb-Hood and Moseley (1991) of Moorfields Eye Hospital includes five women and three men, three benign and five malignant tumors. All were adults, ranging in age from 31 to 65 years (median, 38 years). The 15 cases enumerated in this paragraph plus the 14 in the previous paragraph total 29 cases in the literature.

Fibrous histiocytomas involving the orbital and ocular adnexa, with or without orbital invasion, are probably more common than primary orbital types. The literature includes

reports by Balestrazzi et al. (1991) of a 53-year-old man with a malignant epibulbar tumor and orbital invasion; by Nath et al. (1992) of a 20-year-old woman with a malignant angiomatoid histiocytoma of the eyelid, also invading the orbit; and by Choi et al. (1997) of a 33-year-old man with a benign histiocytoma of the lacrimal sac.

Malignant fibrous histiocytoma may also develop a "second tumor" from an antecedent tumor in the orbital area that undergoes malignant degeneration. Such was the fibrous dysplasia of the adjacent facial bone reported by Cheng and Chen (1997). Total excision of the mass was performed, but the patient refused orbital exenteration and postoperative adjuvant therapy and died 2 years later with tumor recurrence. Shields et al. (2001) also noted malignant fibrous histiocytoma as a second tumor after external beam irradiation of a 5-month-old girl who had enucleation of one eye for retinoblastoma. When the patient was 17 years old, a malignant fibrous histiocytoma developed in the field of irradiation.

At the time of presentation, solely on the basis of physical signs and symptoms, a benign fibrous histiocytoma cannot be differentiated from a fibrous tumor. Likewise, the presentation of a malignant fibrous histiocytoma is similar to that of the preceding fibrosarcoma.

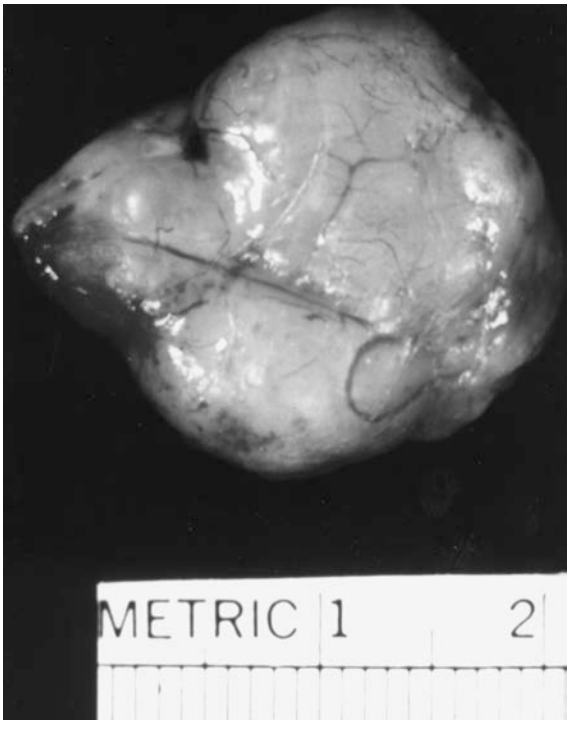


Figure 5.12 This gross specimen of fibrous histiocytoma was lobulated and light purple, with a prominent vascular arcade that coursed over its surface.

Imaging Aspects

Similarities in the composition of fibrous tissue tumors may also perplex the radiologist who tries to differentiate the various subtypes on the basis of their imaging display. Dalley (1999) seems to have the most experience with this dilemma. He wrote:

> "Benign fibrous lesions are usually well-circumscribed and may chronically remodel bone, whereas more aggressive malignant fibrous tumors tend to have infiltrating margins and may destroy bone on CT or MR imaging." With malignant fibrous masses, enhancement patterns on CT scan or MRI may be more inhomogeneous, with avascular or necrotic nonenhancing regions. At MRI, benign lesions tend to be homogeneous on T_1-, T_2-, and postgadolinium T_1-weighted images.
>
> However helpful these clues may be, "determining the extent of orbital involvement remains the primary goal of the radiologist."

Pathology

The gross appearance of a benign fibrous histiocytoma is usually a lobulated, well-circumscribed, firm mass varying in color from grayish white to yellow-tan. The latter coloration reflects a high component of histiocytic cells. Microscopically, the lesion is called a *fibrous histiocytoma* because of a variable admixture of spindle-shaped, fibroblast-like cells, and more ovoid, sometimes lipidized histiocytic cells (Spencer, 1996) (see Figs. 5.12 and 5.13). The dominant constituents of most of these tumors are bundles of elongated fibroblasts set in a dense fibrous stroma with various amounts of collagen interspersed between fascicles. Descriptors such as "storiform," "spiral-nebular," "cartwheel," and "pinwheel" are often applied to this characteristic pattern.

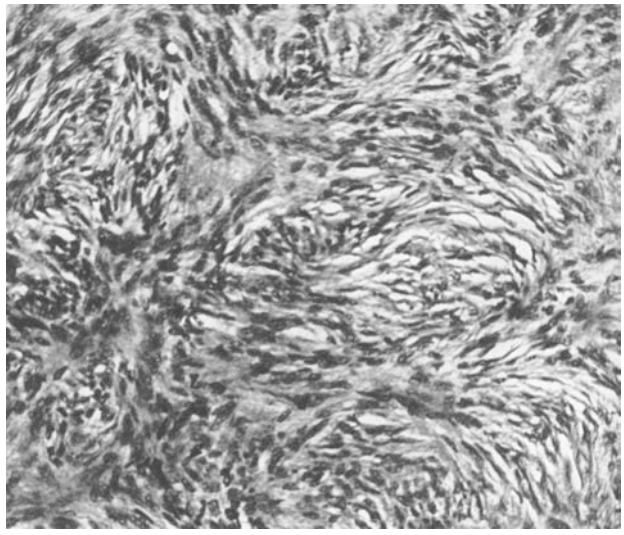


Figure 5.13 In this fibrous histiocytoma, a cartwheel pattern of intertwining, elongated fibroblasts is the predominant characteristic (hematoxylin and eosin, original magnification ×170).

A vascular network of thin-walled, variably sized capillaries may be seen, particularly in tumors from children. Reticulin stain shows a moderately heavy but uneven distribution of reticulin fibers. Most tumors have scattered areas of loose-textured myxoid tissue. The tumors are not encapsulated. Mitotic figures counted on the basis of 40 high-power fields are either rare or absent.

Font and Hidayat (1982) classified their series, based on histopathologic features, as benign, locally aggressive, and malignant types. This categorization is similar to the histopathologic grouping of hemangiopericytomas. Compared with the benign group, the locally aggressive tumors showed no notable nuclear pleomorphism or cellular atypia but did have infiltrating margins, areas of hypercellularity, and mitotic figures not exceeding 20 in the 40 high-power fields. The malignant group, in addition to an increased mitotic index, showed increasing nuclear pleomorphism, cellular atypia, bizarre multinucleated giant cells, areas of necrosis, and an increased amount of lipid within the cytoplasmic vacuoles of the tumor cells (see Fig. 5.14). On the basis of this classification, 63% of their 94 cases were benign, 26% were locally aggressive, and 11% were malignant.

Immunohistochemical analysis may be positive for vimentin and α-antitrypsin and negative for S-100 protein, but this pattern is usually not helpful in distinguishing fibrous histiocytoma from other mesenchymal or closely related lesions (Spencer, 1996).

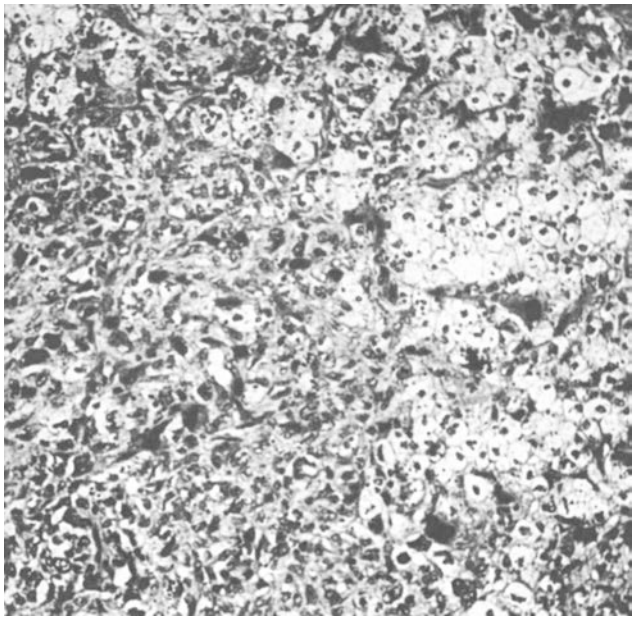


Figure 5.14 In this malignant fibrous histiocytoma, the fibroblastic component (left) and histiocytic-like cells (right) show marked cellularity, cellular pleomorphism, nuclear anaplasia and hyperchromatism, and numerous mitoses (hematoxylin and eosin, original magnification ×100).

Management and Prognosis

Our experience with this tumor is limited to the seven cases in our tumor survey (see Table 3.3)—one benign and six malignant tumors in five men and two women who ranged in age from 19 to 75 years (median, 48 years). The one benign tumor occurred in a 19-year-old woman. It was lodged well forward in the inferior part of the orbit with extension into the lower eyelid. A well-circumscribed, lobulated, light purple mass was removed intact through a subciliary eyelid incision. The patient was followed up for 3 years without recurrence.

The management of the malignant tumors was a different matter. All six arose in a maxillary sinus with invasion of one orbit. All required combined maxillectomy and orbital exenteration. An additional resection of neoplasm in the pterygopalatine fossa was performed in one patient and a partial mandibulectomy in another. Only one patient survived, living 19 years without recurrence. This patient received no adjuvant therapy after the initial surgery. The remaining five patients died with either local recurrence or metastasis of tumor 8, 9, 11, 14 months, and 19 years after surgery. The last patient, over 19 years of life, had successive surgical procedures and biopsies, radiotherapy, radioisotope therapy, and chemotherapy; remissions, recurrences, and multiple metastases. Chemotherapy, using a combination of drugs with a doxorubicin base, was temporarily effective in shrinking the neoplasm, but the tumor recurred several months to several years later. Focal radiotherapy to multiple areas of bone metastasis over the 19 years effectively reduced the pain.

Fortunately, Font and Hidayat (1982) obtained follow-up information on 123 of their 150 patients. Otherwise, the number of cases in the literature would be too few to allow an objective analysis of management and survival. These 123 patients included 74 with benign tumors, 35 with locally aggressive tumors, and 14 from the malignant group. None of the patients in the follow-up group with benign tumor died. Their 10-year survival rate was 100%. The 10-year survival rates of patients with locally aggressive tumor and malignant tumor were 92% and 23%, respectively.

Font and Hidayat (1982) noted a high recurrence rate after incomplete excision of tumor. Their data supported the conclusion that initial complete excision or complete reexcision of a recurrent tumor was adequate management for patients with benign lesions. They recommended orbital exenteration for patients with malignant fibrous histiocytoma. For patients with locally aggressive lesions, exenteration was advised for recurrences. Adjunctive radiotherapy did not seem helpful.

MYXOMA

Although fibrous tissue and collagen are the functional staples of the fibroblast, it is also capable of producing

myxoid tissue. An example of the latter is the benign myxoma. Enzinger (1965) stated: "One might speculate that the myxoma cell is an altered fibroblast that produces an excess of mucopolysaccharides and is incapable of assembling mature collagen." Strong support for such a genesis is the close ultrastructural resemblance of the myxoid cell and the fibroblast. The factors responsible for this monophasic functional deviation of the fibroblast are now known. However, this concept of the tumor's histogenesis is not universally accepted.

Clinical Features

In somatic soft tissues, most myxomas occur in the extremities and the pelvic girdle. In the head and neck area, their most common location is the maxilla or mandible. Table 5.3 summarizes ten cases in the literature, documented by photomicrographs, which have been reported since 1914. The patients ranged in age between 10 and 50 years, with a mean of 29 years. The sex ratio was equal.

The primary myxoma of the orbit is usually a tumor that occurs in adults in the fourth to fifth decade of life. The duration of symptoms and signs before presentation averages 1 to 3 years. However, the temporal onset was 7 years in the case reported by Fuchs (1914) and 3 years for the case described by Blegvad (1944). This attests to its slow, indolent growth. Because of the tumor's soft consistency, its mass has little effect on the function of the visual apparatus, and has 1 to 3 mm of painless proptosis or displacement of the eyeball, unless the tumor is quite large or of long duration. Blegvad's patient experienced an increased hyperopia of 8 diopters over 6 years.

All the cases in Table 5.3 were unilateral and single or slightly lobulated in configuration. The case described by Gifford (1931) was unusual in the botryoid configuration of the tumor. At the initial orbitotomy, seven "shiny, grayish bodies" were removed. At the time of tumor recurrence 4 years later, ten lobules of tumor were excised. Jakobiec and Jones (1979) observed one case that was not described in the literature. And also remind the clinician that true benign myxoma needs to be distinguished from other tumors containing myxomal foci.

The one case in Table 5.3 associated with bone is that of Candy et al. (1991). This was an intraosseous myxoma in the left orbital wall of a 40-year-old woman. The matrix of the tumor did not have a nidus of formative bone, and the consistency of the lesion was the same as that of the soft tissue tumors in the orbital space. The surrounding bone also was normal. This contrasts to the myxomas of the mandible and maxilla wherein the tumor has its origin from the bone.

Imaging Aspects

Several tumors in Table 5.3 were visualized by ultrasonography. The scan showed a cystic tumor with a display similar to cavernous hemangioma. CT scanning showed a well-defined, homogenously isodense mass often adjacent to, or part of, a rectus muscle or optic nerve. With MRI, the tumor was hypointense on T_1-weighted imaging and bright on T_2-weighted imaging. The bright T_2 image was attributed to excessive amounts of mucoid ground substance (Mani et al., 2000). There was little or no enhancement with gadolinium because of the tumor's meager blood supply.

Pathology

Grossly, the tumor is grayish white, soft, somewhat lobulated, poorly circumscribed (with or without a pseudocapsule), and infiltrative with a gelatinous content. Microscopically, the tumor consists of a haphazard arrangement of stellate and spindle cells dispersed in a reticular network containing abundant myxoid ground substance (see Fig. 5.15). With Alcian blue, the myxoid material stains positively for mucopolysaccharides, but this Alcian blue positivity is absent if the specimen is pretreated with hyaluronidase. The vascular supply is meager. Mitotic figures are absent. Immunostaining studies for

TABLE 5.3
MYXOMAS PRIMARY IN ORBITAL BONE AND SOFT TISSUE REPORTED IN THE LITERATURE

Authors (date)	Patient's Sex	Patient's Age (y)	Tumor Location
Fuchs (1914)	Female	40	Soft tissue
Lamb (1928)	Female	16	Soft tissue
Bistis (1931)	Male	29	Soft tissue
Gifford (1931)	Female	25	Soft tissue
Blegvad (1944)	Female	29	Soft tissue
Maria and Marwa (1967)	Male	50	Soft tissue
Krueger et al. (1967)	Male	31	Soft tissue
Lieb et al. (1990)	Male	27	Soft tissue
Candy et al. (1991)	Female	40	Bone
Mani et al. (2000)	Male	10	Soft tissue

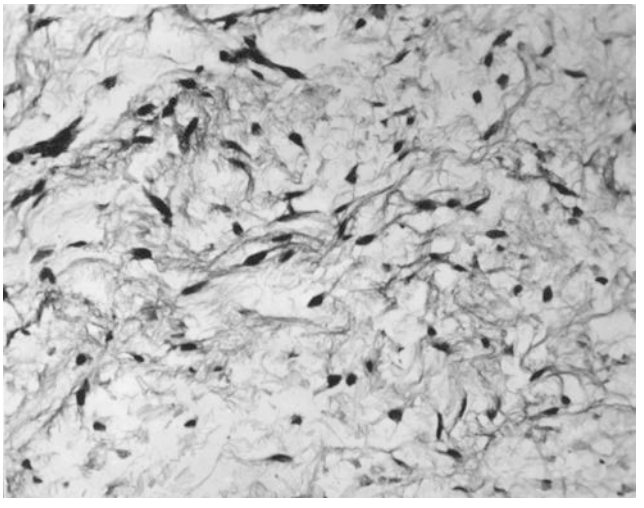


Figure 5.15 This myxoma shows stellate and spindle cells in a delicate framework of mucinous matrix. Specimen is from the anterior thigh of a 71-year-old woman (hematoxylin and eosin, original magnification ×200).

S-100, desmin, and cytokeratin are negative but are strongly positive for vimentin (Lieb et al., 1990).

Management

Surgical removal with complete margins is the management goal, but this may be difficult in some cases because of the poorly demarcated infiltrative margins of the tumor. The tumor tends to recur if excision is incomplete, although it does not metastasize. For the intraosseous myxoma, bone need not be removed other than to gain access to the soft tissue component.

These patients and their primary relatives should also be examined for possible manifestations of the Carney complex (Kennedy et al., 1987), which has substantial morbidity and mortality because of the occurrence of cardiac myxoma. Facial and eyelid lentigines, conjunctival, caruncle, and eyelid pigmentation may precede signs or symptoms of cardiac myxoma. Carney complex is transmitted in a manner consistent with Mendelian autosomal dominant inheritance.

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6 Fibro-Osseous, Osseous, Cartilaginous, Vascular, and Inflammatory Tumors of Orbital Bone

This chapter covers an array of dysplastic, neoplastic, and odontogenic tumors affecting orbital bone. The fibro-osseous group of tumors is discussed first, inasmuch as it is a logical transition between the fibrous tissue tumors of the preceding chapter and the bony and cartilaginous tumors of this chapter.

FIBRO-OSSEOUS TUMORS

These lesions are an admixture of fibrous tissue and osteoid (immature bone that has not undergone calcification). The fibrous tissue usually is the predominant constituent with a content of osteoid that differs quantitatively and structurally from one tumor to another. This group includes fibrous dysplasia, fibro-osseous dysplasia, giant cell granuloma, aneurysmal bone cyst, and ossifying fibroma.

Fibrous Dysplasia

Fibrous dysplasia is a benign lesion characterized by the presence of fibrous connective tissue with a whorled pattern and trabeculae of immature nonlamellar bone. It is not considered a true neoplasm (Spraul et al., 1996). This lesion was first defined by Lichtenstein (1938), but its cause remains unknown. Jakobiec and Jones (1979) suggested the tumor was the result of an arrest of bone maturation at the woven bone stage. Most cases present in childhood or early adolescence. Initially, the disorder was predicted to arrest at puberty. Tanaka et al. (1993) described a boy with craniofacial fibrous dysplasia that showed marked involution at the end of puberty. Now, the tumor is known to progress well into adult life (Horgan et al., 1999).

Incidence

Our current 10-year survey (1988 to 1997) added six more primary orbital fibrous dysplasias (Table 3.2) to those tabulated in the previous editions of this book. The grand total of primary dysplasias observed over 50 years is 12, six males and six females, an incidence of 0.006% among 1,795 tumors (Table 3.3). The age range was 6 months to 63 years, with a median of 19 years. Bibby and McFadzean (1994) also reported a small series of 12 cases from the Leicester Royal Infirmary, London. There were five male and seven female patients. Age at diagnosis ranged from 5 to 45 years, with an average of 18 years. Most commonly involved were the frontal bone (eight patients) and the sphenoid bone (seven patients). Bilateral lesions occurred in three patients. They concluded that fibrous dysplasia is not a disease confined to adolescence but may continue into adulthood and sometimes middle age.

Clinical Features

The symptoms of this lesion depend on the anatomic site of the affected bone, the number of bones affected, the rate and duration of tumor growth, and the soft parts that are compressed, distorted, or displaced by the expanding

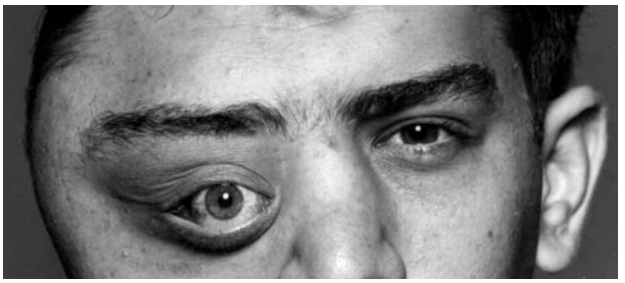

Figure 6.1 Fibrous dysplasia of the right temporal, frontal, malar, ethmoid, and sphenoid bones in a 19-year-old man with progressive proptosis, displacement of the right eye since the age of 8 years, and deformity of the right side of his face since the age of 10 years. The disease continued to progress over a period of 31 years. The patient underwent the last of seven surgical procedures, a craniotomy, at the age of 51 years to alleviate convulsions secondary to encroachment of the tumor on his brain.

bone. The chief manifestation of this lesion is a unilateral, slowly progressive proptosis and displacement of the eye. Beyond this mass effect of the growing tumor on the eye, the presentation depends on the orbital location of the affected bone. If the tumor is well anterior in the frontal, ethmoid, or maxillary bones, the displacement of the eye in a direction opposite to involved bone may be equal to or greater in extent than the proptosis. Such patients may also have grotesque transmogrification of the upper face (see Fig. 6.1). Strangely, some such patients may retain good visual acuity and have little functional impairment of the eye other than a limitation of ocular motility in the field of the growing tumor and epiphora secondary to nasolacrimal duct compression.

As the process extends posteriorly or if the tumor originates either in the posterior extent of the above-mentioned bones or the sphenoid bone, the proptosis increases in proportion to displacement of the eye, and visual function is more seriously affected. These patients more often have annoying, persistent headache or discomfort on the side of the lesion, particularly if there is compression of structures in the orbital apex, reflecting encroachment on cranial nerves III, IV, and VI. Usually, pain is not an important component of the presentation except when the tumor becomes so large that it competes with the displaced eyeball for limited orbital space. Stenosis of the bony optic foramen occurs from expansion of fibrous dysplasia of the sphenoid bone, the periorbita is stretched by a sudden intrusion into the orbital space by tumor from a paranasal sinus, or an unusual rapid growth of tumor. The latter is illustrated in the report by McCluskey et al. (1993). Over a period of only 4 months, a 41-year-old woman developed progressive diplopia, reduced visual acuity, pain in the left orbit, proptosis of 7 mm, and downward and inward displacement of the left eye associated with a large, tender mass in the fossa of the lacrimal gland. The bony mass already had eroded the upper lateral margin and frontal process of the zygomatic bone on the left side.

Other unusual patterns of presentation should be mentioned, particularly patients who experience extreme loss of vision in the affected eye: A 21-year-old woman with visual loss to light perception over 1 week responsive to high dose corticosteroid therapy (Osguthorpe and Gudeman, 1987), a 20-year-old woman with no light perception (Liakos et al., 1979); a 17-year-old woman who became blind in the affected eye 4 hours before admission (Ronner et al., 1982); a 13-year-old boy with counting finger vision (Melen et al., 1980); an 8-year-old boy in our series with no light perception; and a 3-year-old boy also with no light perception (Posnick et al., 1993). However, the nuances of the tumor's presentation, symptoms, and course are about the same for most of the bone tumors in this chapter. In short, they are nonspecific in contributing to diagnosis of the specific type of bone tumor. All the signs and symptoms noted in the preceding text serve as a guide to the correct site for radiographic studies and for biopsies (Unni, 1996). Yuen et al. (2002) reported a third case in the literature of fibrous dysplasia associated with aneurysmal bone cyst.

Imaging Aspects

Computed tomography (CT) scan shows the size, shape, and extent of orbital bone involvement. Anatomic factors may affect the radiographic image of the tumor. In thinner bone, such as the orbital plate of maxillary, ethmoid, and frontal bone, the cortex expands more rapidly and to a greater degree than in thick bone. Therefore, thinner bones tend to show more lucency, cavitation, and compartmentalization of the dysplastic process.

Lucency equates with a lytic, cyst-like pattern of bone expansion. Thick bone (see Fig. 6.2), such as the sphenoid, tends to react in a more solid, sclerotic, and diffuse manner. Also, the dysplasia may transgress suture lines and affect multiple bones that rim the orbital space. In later stages, extension of tumor across the midline of the skull is not uncommon (see Fig. 6.3). Absence of a sharp border between cortical bone and the medullary constituents

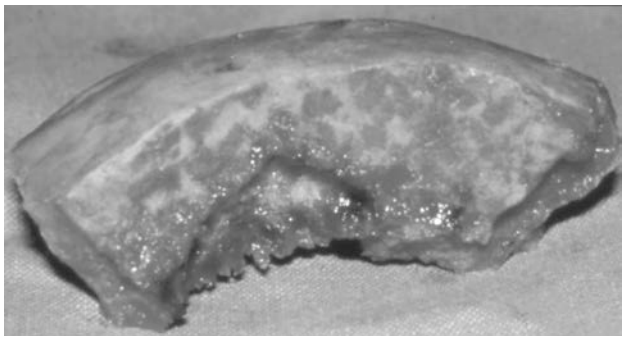

Figure 6.2 A 2-cm-thick piece of bone from the right frontal orbital plate of the man with craniofacial fibrous dysplasia pictured in Figure 6.3. The mottled areas on the cut surface of the bone (above) represent small, irregular, cyst-like spaces that contained a sanguinous fluid. The large cavity (lower left) was filled with tissue that suggested an aneurysmal bone cyst.

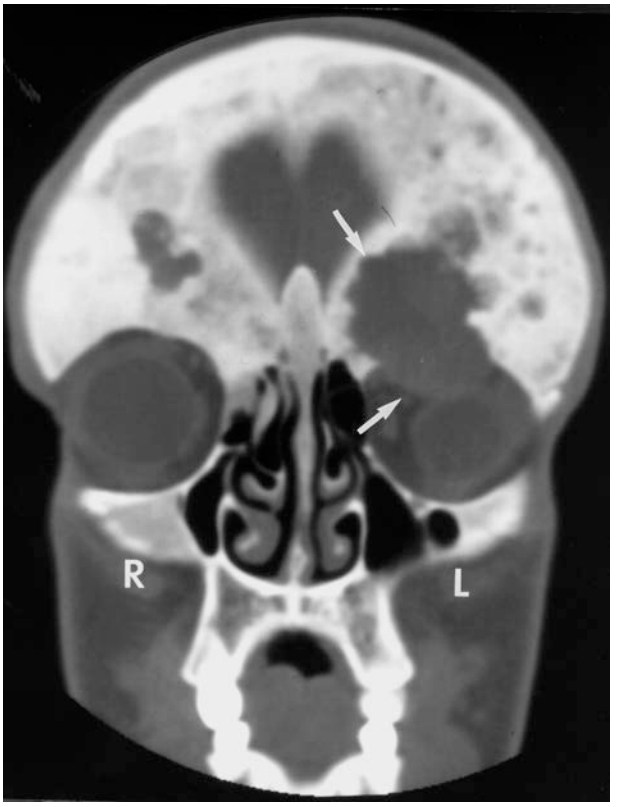

Figure 6.3 Coronal computed tomography scan with contrast enhancement from a patient with fibrous dysplasia shows mottled densities and lucent areas in both frontal bones, greater on the right than on the left. A large cavitary erosion of the left side of the orbital roof (*upper arrow*) by a soft tissue mass (*lower arrow*) extends inferiorly into the left orbital space, causing downward displacement of the eye. On surgical excision, the inferior soft tissue mass suggested an aneurysmal bone cyst.

of the tumor produces a homogeneous smudge on the radiograph. Nevertheless, differentiating intraosseous meningioma from fibrous dysplasia affecting the roof and apex of the bony orbit poses difficulties. Errors in diagnosis caused by excessive reliance on diagnostic imaging occurred on three occasions in a series of 25 patients reported by Hansen-Knarhoi and Poole (1994).

Casselman et al. (1993) reported magnetic resonance imaging (MRI) of five patients with biopsy-proved craniofacial fibrous dysplasia. According to this report,

> Low to intermediate signal intensity was usually seen in the largest part of the lesion on both spin-echo sequences, but smaller regions of hyperintensity on T_1- and T_2-weighted images and intermediate signal intensity throughout a lesion on T_1-weighted images are also seen. All lesions enhanced but only two became iso- or hyperintense compared to fat. High clinical and pathologic activity in three cases correlated with high signal intensity on both spin-echo sequences and with strong enhancement in two of the three. The presence of large veins or sinusoids on pathologic examination did not correlate with the enhancement pattern.

Pathology

Fibrous dysplasia mirrors the early stage of intramembranous ossification of the bones of the skull in which osteoid is formed by mesenchymal-derived spindle cells (fibroblasts). This is illustrated in Figure 6.4, which shows spicules of woven bone interspersed in a stroma of uniform, benign spindle cells. There is no nuclear atypia and mitoses are rare. With polarized light, the woven bone shows an uneven birefringence. If the affected bone had developed normally, osteoblasts would then have appeared at the periphery of the bone elements and would have converted the woven bone into the lamellar form. Multinucleated giant cells are occasionally present. With the passage of time, the stroma may develop acellular myxoid-like zones of degeneration.

Management

When the third edition of this text was written, more vigorous surgical approaches evolved to replace the conservative efforts to remove fibrous dysplasia of orbital bone, which was the norm of prior decades. The aim during the 1980s was to remove all dysplastic bone by staged surgery, to alleviate blindness, if necessary, by decompression of the optic nerve, and to reconstruct or revise the contour of the bony defect.

Surgical management was further refined in the 1990s to remove all dysplastic bone and reconstruct the orbit in

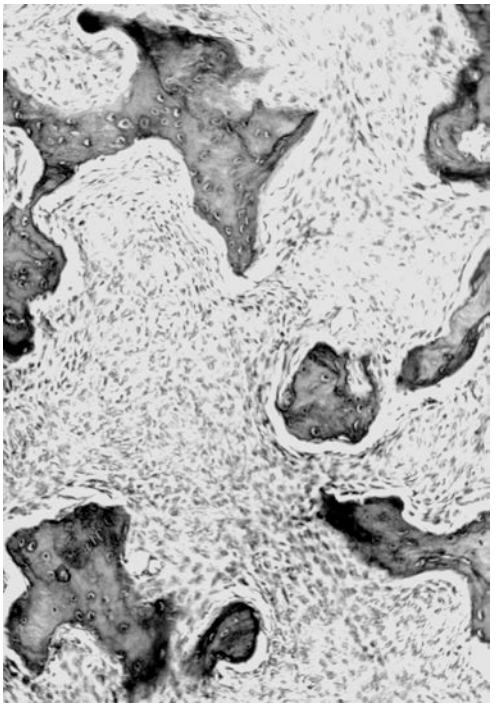

Figure 6.4 Fibrous dysplasia. Irregular contoured islands of woven bone are interspersed in a spindle cell stroma. Unlike ossifying fibroma, there are no osteoblasts rimming the osseous spaces (original magnification ×125).

one surgery and to prevent optic nerve dysfunction by early decompression, rather than delaying surgery until vision was already impaired to some degree (Mahapatra et al., 2003).

Perhaps the largest series of cases relevant to refinements in the surgical management of orbital fibrous dysplasia is that of Yavuzer et al. (2000). One of the coauthors, I. T. Jackson, MD, has had extensive experience in this field over the time of several editions of this text. Yavuzer et al. (2000) treated 32 cases of fronto-orbital fibrous dysplasia during the past 20 years and assessed the results of treatment. The treatment consisted of radical resection of the fibro-osseous tissue, decompression of the optic nerve canal, and reconstruction of the fronto-orbital areas either with noninvolved bone graft or with dysplastic bone that was contoured down or heated in the sterilizer. During follow-up, two tumors recurred, but repeat optic nerve decompression was not required. Overall, the aesthetic results were satisfactory. Patient ages ranged from 2 to 51 years, with a mean age of 16.8 years.

Ricalde and Horswell (2001) also commented on their experience with the surgical management of six patients with fronto-orbital surgery. Their patients ranged in age from 7 to 28 years. Surgery generally involved extensive tumor excision and immediate orbital reconstruction with autogenous bone grafts. Two patients also had reconstructive surgery with resected and treated autogenous bone, which was then immediately replanted using rigid fixation. Three patients had intracranial microsurgical optic canal decompression. All patients received postoperative corticosteroids. Five patients experienced partial relief from their sensory and visual disturbances. One patient who underwent two-wall optic canal decompression had visual loss. They recommended early surgery to avoid the hazards of late-stage decompression.

Papay et al. (1995) addressed the surgical decompression of the bony optic canal in cranial base fibrous dysplasia. Seven coauthors were included, thereby indicating their support for a multispecialty approach for surgery of the anterior cranial base. They described five patients without measurable loss of visual acuity who underwent superior decompression of the optic canal in the course of radical excision of dysplastic bone. However, imaging displays showed early signs of visual afferent defects, venous congestion of the superior ophthalmic vein (color Doppler display), or a combination of these. No ophthalmic morbidity was encountered during the mean follow-up of 18 months.

This more vigorous approach and earlier management of major craniofacial dysplasias have come about chiefly in the past decade. The publications that support these concepts cite one or more of an array of reasons for altering the conservative management stance of former years: To correct deformity of the face and periorbital region, to alleviate headache and pain attendant to expansion of the craniofacial bones, to relieve proptosis of the eye, to forestall further visual loss where such a functional deficit is already present, to alleviate sudden intralesional hemorrhage, and to eradicate malignant transformation of the dysplasia where such malignancy is either proved or suspected. Less direct are the reasons that emphasize the prevention aspects of aggressive and early management such as avoiding the delayed effects of progression of the dysplasia and preventing complications while awaiting spontaneous arrest of the disease. The last-named reasons may be more wishful thinking than factual confrontation with the disease.

In general, the most predictable result of these major surgical ventures is subjective more than objective improvement in the bony disfigurement of the patient's skull or face. Less often is the patient unequivocally pleased with the postoperative position of the eye, particularly if reconstruction of the floor of the orbit was either attempted or necessary. A new, disconcerting, long-lasting diplopia often occurs postoperatively, chiefly because of an unavoidable shift in mechanics of the inferior and superior oblique muscles. Blepharoptosis of some degree and variable duration is almost always a complication of radical surgery of the frontal bone. Even so, the most worrisome problem confronting both patient and surgeon is the ultimate effect on the visual function of the eye. Will the patients with failing vision be better or worse after surgical decompression of the optic nerve? The odds appear to be about even either way. Will the patient without preoperative visual disability lose vision as the result of a surgery involving dysplasia of the sphenoid bone or base of the skull? Here the results are "all or none." Postoperatively, either the visual function is unscathed or the patient is blind. No data are available to answer this question because the cases with favorable outcomes are reported more often than cases that are visual disasters.

The question of the "preventive" purpose of these surgeries should also be addressed. Will early surgery delay progression of the disease? Probably so, although a major drawback in all the reports by enthusiasts for the surgery is the lack of long-term follow-up data. Will the surgery prevent complications while the patient waits for spontaneous arrest of the dysplasia? Probably not!

Our experience with six patients observed over 10 to 32 years may give some clue to the answer to the last question.

Case 1

A 19-year-old man had fibrous dysplasia of five cranial bones on the right side. Although visual acuity of the right eye was normal, early pallor of the right optic disk was present. This was worrisome for future visual loss because of threatened encroachment of dysplastic bone on the right optic canal. This factor, plus the marked disfigurement of the right side of his face and displacement of the right eye (Fig. 6.1), prompted the decision to proceed with craniofacial surgery. Over the next 10 months, five staged surgical procedures were performed to alleviate the

situation. The disfigurement was greatly improved, and the vision remained stable until, 6 years later, proptosis reappeared, pallor of the optic disk increased, and vision dropped to 20/200, all in the right eye. In another 6 years, by the age of 31 years, pallor of the left optic disk also was noted, and a right upper quadrant hemianopsia was present in the visual fields, indicating an optic tract involvement. At the age of 39 years, convulsive seizures commenced, hearing loss on the right side occurred, and the hard palate was involved by the advancing dysplastic process, in addition to further progress in all prior signs and symptoms. At the last follow-up, at the age of 51 years, the patient had undergone another craniotomy to relieve a left hemiparesis secondary to encroachment of the dysplasia on the brain.

Case 2

A 10-year-old girl with fibrous dysplasia involving three bones of the skull underwent a right craniofacial surgical procedure because of persistent headache and right-sided craniofacial disfigurement of 1 year's duration. Subsequently, the patient was free of pain for 4 years and then underwent another craniotomy for recurrence of headache. A pain-free interval of 7 years elapsed before another craniotomy, including a section of a division of the trigeminal nerve, which was necessary for recurrent pain. A fourth craniotomy for recurrent pain was performed at the age of 24 years. The right eye was blind after this surgery. By the age of 29 years, the recurrent head pain was treated with repeated nerve blocks and surgical section of peripheral nerves. The patient was also medicated for temporal lobe epilepsy. Imaging of the skull at this time indicated extension of the dysplasia across the intracranial midline.

Case 3

This 8-year-old boy was blind in the right eye from fibrous dysplasia of the sphenoid bone. A debulking procedure was performed, including unroofing of the right optic canal. Postoperatively, the right eye remained blind. Skull films at the age of 11 years showed recurrent dysplasia in the lesser wing of the right sphenoid bone. At the age of 14 years, the patient was subjectively and objectively stable. However, by the age of 29 years, radiography showed extension of the dysplastic process into the right frontal bone, the right middle intracranial fossa, and the left sphenoid bone. Vision in the left eye was not affected.

All these three patients showed definite progression of their disease into early and late adult life. Two of the three were seriously handicapped by their fibrous dysplasia. The third case seems definitely at risk for eventual intracranial neurologic defects.

Case 4

A 23-year-old woman with 11-mm proptosis of the left eye and fibrous dysplasia of three cranial bones underwent a craniofacial excision of tumor chiefly to relieve disfigurement. The latter was deemed successful until drainage appeared in the operative site 19 months later, following what was considered minor trauma to the left side of her forehead. This was treated with hot packs and antibiotics followed by remission. Over the next 16 years, the patient continued to receive local therapy intermittently because of recurrence of drainage from the surgical site. There had been no further surgical procedures in this interval, and the patient had not experienced any visual difficulty, but information concerning the imaging status of her dysplasia was incomplete.

Case 5

A fibrous dysplasia localized to the orbital plate of the left frontal bone with erosion into the intracranial space in a 15-year-old girl was excised through an anterior orbitotomy. A 2-mm left blepharoptosis was a permanent sequel to the surgery. Ten years later, the patient's ocular and orbital statuses were stable, and there was no obvious progression of the dysplasia. However, follow-up radiography was not done. Even so, she is the only patient among those described herein who had 10 years without some complication of either progressive disease or the surgical procedure.

Case 6

The sixth patient, a 14-year-old girl, underwent excision of a fibrous dysplasia of the ethmoid bone with orbital extension in April 1987. However, follow-up on this patient was only 14 months, too short an interval to objectively assess a disease as resilient as fibrous dysplasia.

Several conclusions seem warranted from the above discussion.

1. A long follow-up period is necessary before judging the arrest or progression of fibrous dysplasia. Well-documented cases of spontaneous arrest of the orbital disease seem to be lacking. A minority of patients with dysplasia limited to either the frontal or maxillary bones seem most amenable to total excision and possible cure.
2. Most of the patients with dysplasia of two or more cranial bones probably have slowly progressive disease for an indefinite period in their life span. Such patients may ultimately have serious neurologic complications, particularly if the sphenoid bone is initially affected. The extension of the disease in such patients probably is related to the unavoidable, limited excision of the lesion that is possible at the base of the skull. At present, there are no standard guidelines or criteria for the management of this distressing and potentially disabling disease, except that a debulking procedure may be considered for some patients with headache or pain.
3. Finally, there is some hope in the medical management of patients with extensive involvement of bone

proximal to vital orbital structures where surgical intervention poses a high risk for functional loss, particularly in children. Yavuzer et al. (2000) have used a bisphosphonate, pamidronate, which seems to arrest invasion of fibrous dysplasia into adjacent normal bone by limiting osteoclastic activity, which causes normal bone resorption. The drug is only a temporizing measure as long as the treatment regimen is maintained. The drug is administered as an intravenous infusion on an outpatient basis. Three doses of 60 mg or 1 mg per kg in children is given at intervals of 1 day to 1 week. This regimen is repeated every 6 months, or more frequently, depending on the patient's clinical picture.

Ossifying Fibroma

Kempson (1966) originally described this neoplasm. Although considered benign, it is also a lesion of aggressive growth. Tumors that originate in the paranasal sinuses or at the base of the skull usually affect the orbit secondarily. The tumor is closely related to fibrous dysplasia and may actually be a variant of fibrous dysplasia. The numerous spherules of bone that are scattered throughout the stroma of the lesion prompted Margo et al. (1985) to add the qualifying term "psammomatoid" to distinguish this tumor from other fibro-osseous tumors.

Incidence

Margo et al. (1985) selected from the file of the Armed Forces Institute of Pathology 21 patients with ossifying fibroma of orbital bone. The average age of their group at the time of initial diagnosis was 17.8 years, with a range of 4 months to 52 years. The sex incidence was equal. Many clinical details of this cohort, including the laterality of the lesion, were not stated.

In the third edition of this text, we culled 14 cases of orbital ossifying fibroma reported by nine authors between 1964 and 1988. The mean age of these patients was 15.5 years, with a median of 10 years. The male-to-female ratio was 9:5. This indicates the prevalence of the tumor in the first 2 decades of life. Two cases of bilateral orbital involvement were included in the survey, a 22-year-old woman (Scott et al., 1971) and an 8-year-old boy (Margo et al., 1986) (see Table 6.1).

Five additional cases of pathologically proved orbital ossifying fibroma have been reported since 1988: A 7-year-old boy (Palma et al., 1988); a 16-year-old boy (Perri et al., 1996); a 12-year-old boy (Takaya et al., 1993); a 29-year-old man (Nakagawa et al., 1995); and a 6-year-old boy (Fakadej and Boynton, 1996).

Clinical Features

The chief manifestation of orbital encroachment is a slowly progressive, painless proptosis and displacement of one eye associated with diplopia. More serious functional and ophthalmic deficits, such as visual loss, optic atrophy, and paralytic strabismus, usually do not occur until the lesion extends into the orbital apex or sphenoid sinus. Such signs and symptoms are also common portents of tumor growth. The tumor's slow evolution was confirmed by the study of Margo et al. (1986). In their group of 21 patients, the average duration of symptoms before initial diagnosis was 4.6 years. Only in four patients was the duration <12 months. This presenting mode is essentially the same as that of a patient in the same age-group with fibrous dysplasia.

Encroachment of the orbital space comes from tumorous expansion of the orbital plates of the frontal, ethmoid, and maxillary bones, roughly in that order of frequency.

TABLE 6.1
OSSIFYING FIBROMA OF ORBITAL BONES: REPORTS OF INDIVIDUAL CASES

Authors	No. of Cases	Sex	Age, y	Orbit
Schwarz (1964)	2	F	9	Right
		F	18	Right
Thomas and Kasper (1966)	1	M	8	Right
Lehrer (1969)	3	M	20	Left
		M	11	Left
		M	50	Left
Scott et al. (1971)	1	F	22	Bilateral
Fu and Perzin (1974)	2	F	7	Left
		M	9	Left
Shields et al. (1983)	1	M	9	Right
Shields et al. (1985)	1	F	14	Left
Margo et al. (1986)	2	M	8	Left
		M	8	Bilateral
Rootman (1988)	1	M	25	Right

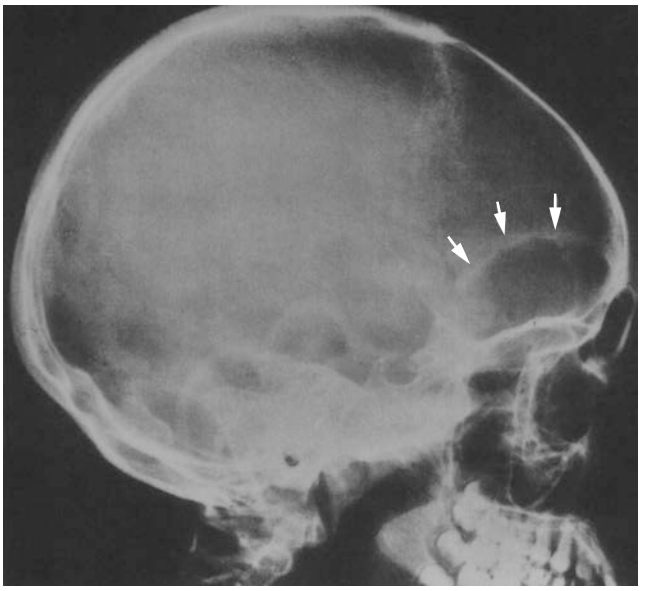

Figure 6.5 Psammomatoid ossifying fibroma. Lateral skull radiograph shows a radiolucent lesion expanding the roof of the orbit (*arrows*) into the anterior cranial fossa. The lesion is encompassed by very thin sclerotic bone. (From Margo CE, Shields JA. Diagnosis of fibro-osseous bone lesions [Letter]. *Ophthalmology*. 1989;96:569–570, with permission.)

Imaging Aspects

Radiography (see Fig. 6.5) and CT scan are the imaging mainstays of fibro-osseous tumors involving the orbit, particularly if more than one bone is affected. The tumor is a destructive process that tends to distort and expand the affected bone but retains a thin, somewhat sclerotic shell of peripheral bone. The lesion is round or ovoid in contour, and on plain film radiography, it appears radiolucent in a solid bone and radiopaque when adjacent to an air-filled sinus. In the early stage, the lesion is confined to one bone and the margins are well defined. With the passage of time, the lesion expands to additional bones, and in its late stages, it may show productive changes that seldom compensate for the early osteolysis.

CT scan shows the patchy-appearing, nonhomogeneous matrix with its mixture of radiodense and radiolucent material. Also, there may be a radiolucent zone between the tumor's matrix and the surrounding unaffected bone, which tends to emphasize the tumor's circumscription. Because of its slow, painless evolution, the lesion may reach considerable size. In 12 of the 21 cases studied by Margo et al. (1985), the average diameter of seven lesions affecting the frontal bone was 5.3 cm and that of five lesions of the ethmoid plate was 5.5 cm. On MRI scans, ossifying fibromas appear heterogeneous and usually show intermediate signal on T_1-weighted and hypointense signal on T_2-weighted MRI. Contrast enhancement is moderate on gadolinium-enhanced T_1-weighted MRI scans (Wenig et al., 1998).

Pathology

Grossly, the tumor has a smooth surface, is covered by a thin shell of sclerotic bone, and, in the orbital plates, tends to be multicystic. It consists of both fibrous and osseous elements, with the former predominating. The fibrous stroma is highly cellular, vascular, and well endowed with fibroblasts with plump nuclei, particularly in tumors of short duration. In older lesions, the fibroblasts are more compressed, with flattened nuclei. Some mitotic activity is present in all lesions.

The most diagnostic features, however, are the size, configuration, and makeup of the numerous spherules of lamellar bone scattered throughout the stroma. Most of these bone elements are ovoid and are surrounded by a delicate pink-staining layer of osteoid, which, in turn, is rimmed by osteoblasts. The rim of osteoblasts is prominent in contrast to their inconspicuousness in typical areas of fibrous dysplasia.

Other histopathologic components of the lesion, such as intercellular collagen, trabeculae of woven bone here and there, and occasional giant cells, are minor in quantity and consistency. Two variants of ossifying fibroma deserve mention. One is the cementifying fibroma that likely originates from cells along the periodontal area of the teeth in the upper jaw. It is also a destructive tumor that, by progression, may secondarily invade the orbit. The calcified material in this lesion is cementum rather than bone. Rarely, these tumors seem to arise in orbital bone, as the tumor did in the 12-year-old boy reported by Takaya et al. (1993). These lesions probably originate from cells capable of producing cementum as well as bone and fibrous tissue. This admixture of tissue could be called a *cemento-ossifying fibroma*.

The other variant is the psammomatoid ossifying fibroma that typically arises in the sinonasal passages and invades the orbit through the ethmoid sinus and medial orbital wall. Their distinctive component is the mineralized or calcified ossicles, of variable size, scattered throughout the bony trabeculae and adjacent cellular stroma (see Fig. 6.6).

Surgical Management

When the manuscript for this section was completed in 1989 for the third edition of this text, we indicated it was likely that, in the future, excision of the tumor would be accomplished in most cases at the time of the initial surgery. This would supersede the multistage surgical procedure used before 1989.

Now, almost all authors writing on the subject of surgical management of ossifying fibroma strongly advocate complete removal of the tumor at the time of initial surgery. If multiple bones are involved, they recommend a multidisciplinary approach to tumor removal by surgeons from the various surgical disciplines accustomed to working in the anterior portions of the skull. They also believe that

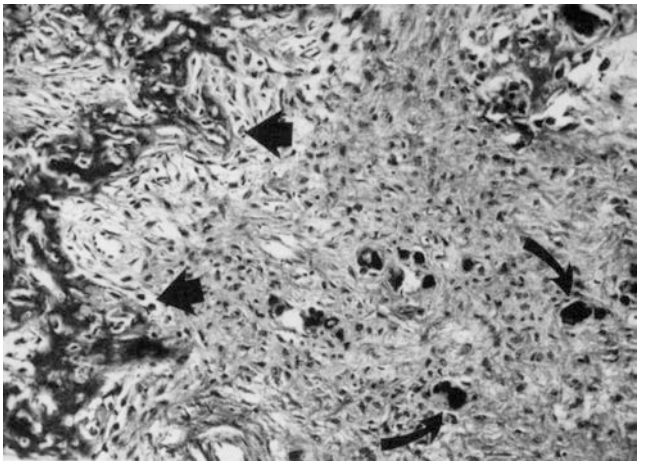

Figure 6.6 Psammomatoid ossifying fibroma shows immature woven bone (*straight arrows*) in a transition area between the small, round ossicle pattern of bone formation and normal bone, which is located toward the left. Several small, round ossicles (*curved arrows*) are also frequent in this transition area (hematoxylin and eosin, original magnification ×160). (From Margo CE, Shields JA. Diagnosis of fibro-osseous bone lesions [Letter]. *Ophthalmology*. 1989;96:569–570, with permission.)

an open (combined craniofacial transfrontal procedure) surgical approach assures complete removal of the tumor compared with endoscopic procedures often used with paranasal sinus disease. The latter is often confounded by postoperative imaging that shows residual tumor. In such cases, these aggressive tumors do recur. Several reports have reviewed surgical options, surgical details, and follow-up data on three or more patients (Blitzer et al., 1989; Lawton et al., 1997; Hartstein et al., 1998).

Fibro-osseous Dysplasia

Unni (1996) favored this designation for a group of non-neoplastic lesions that consist of a large component of tissue elements of fibrous and mesenchymal origin (fibroblasts and spindle cells), both resorption and formation of bone, and giant cells. Three of these lesions are unique, inasmuch as they have essentially the same histopathology but differing clinical features. These are giant cell reparative granuloma, cherubism, and brown tumor of hyperparathyroidism.

Pathology

Grossly, these lesions are soft, spongy, multicystic, and friable with a reddish brown color and gritty consistency. In orbital bone, they are intraosseous and tend to expand the bone. When the fragile exterior is ruptured, the tumor may contain a black, viscous fluid consistent with old blood. The dominant cellular component is the benign fibroblast with benign multinucleated giant cells interspersed throughout the stroma (see Fig. 6.7). There is no cellular atypia. Mitotic figures are present in the fibroblasts but not in the giant cells.

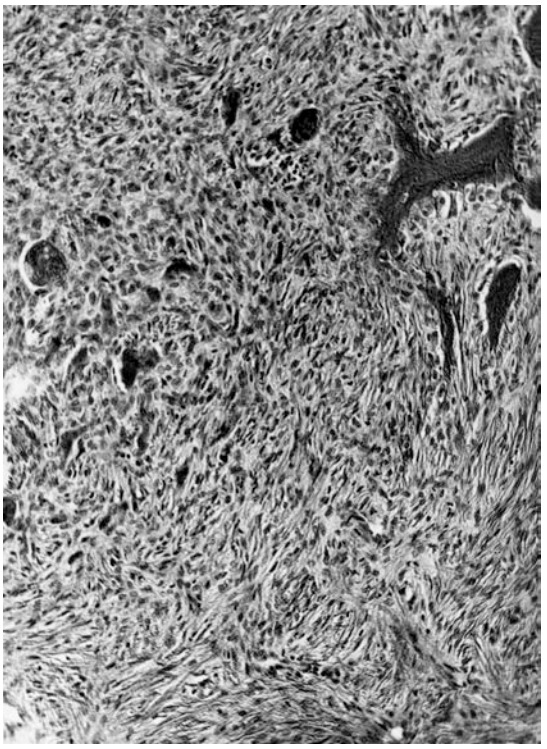

Figure 6.7 In this section from the mandible of a patient with fibro-osseous dysplasia, a few benign giant cells are present, but the histologic pattern is dominated by fibroblastic cells. Osseous metaplasia, almost always present, is seen at the upper right. (From Unni KK. *Dahlin's bone tumors: General aspects and data on 11,087 cases*, 5th ed. Chapter 28, Philadelphia, PA: Lippincott-Raven; 1996, with permission.)

If hemorrhage has occurred, giant cells and epithelial histiocytes tend to cluster around the hemorrhagic zone. Almost all specimens show new bone formation as well as bone destruction. Southgate et al. (1998) showed the multinucleated giant cells in surgical specimens from a case of cherubism to be osteoclasts "since they synthesised tartrate- resistant acid phosphatase, expressed the vitronectin receptor, and resorbed bone." The cause of this cellular response is not known except in the brown tumor of hyperparathyroidism. Here, increased levels of calcium and parathyroid hormone in the peripheral blood cause increased osteolysis.

Giant Cell Reparative Granuloma

When Jaffe (1953) described this lesion, he noted a tendency of the giant cells to surround foci of hemorrhage. He assumed the hemorrhage was secondary to trauma and the giant cells represented some type of healing or reparative process. Subsequently, the association of this tumor with a history of trauma has not been consistently reported, and the word "reparative" has been abandoned by many authors. The present trend is to simply designate the tumor as "giant cell granuloma." However, the lesion

is still considered to be some type of "reactive" process, but the cause remains elusive.

In the skull, the granuloma predominantly affects the mandible, maxilla, and temporal bone, roughly in that order of frequency. Over time, it has also been observed in the frontal, ethmoid, and sphenoid bones, with concomitant orbital encroachment. The orbital lesions are locally aggressive and, along with proptosis, displacement, and some limitation of ocular rotation, are associated with pain, particularly the intraosseous tumors. The expansion of the thin plate of orbital bone stretches the periorbita, thereby causing the pain. In addition, a certain amount of bone destruction produces an additional inflammatory response. By contrast, the presentation of fibrous dysplasia is usually painless unless it is exceptionally aggressive and rapid in growth. The histopathology of this tumor is illustrated in Figure 6.8.

Those cases are either primary in orbital bone or show encroachment of the orbit from a locus of tumor in an adjoining sinus (Sood et al., 1967; Friedberg et al., 1969; Hoopes et al., 1981; Rhea and Weber, 1983; Case Records of the Massachusetts General Hospital, 1984; Chapman, 1984; Sebag et al., 1985; Spraul et al., 1997; Hyver et al., 1998; Mercado et al., 1999). The age range of the 15 patients reported is 5 to 83 years, with an average of 24.2 years and a median of 11.5 years at the time of diagnosis. There were 13 males and 2 females in this group.

CT scan shows an orbital mass with a heterogeneous internal structure and adjacent bone erosion. MRI shows a circumscribed intraosseous cystic mass with internal signals consistent with blood and fluid levels (Mercado et al., 1999).

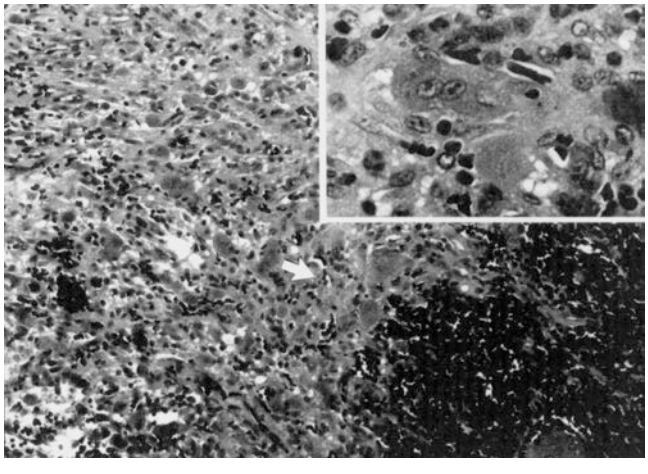

Figure 6.8 An infiltrate of epithelioid histiocytes (*arrow*) and giant cells surrounds a focus of hemorrhage at the lower right (hematoxylin and eosin, original magnification ×50). Inset: Histiocytes are shown at a higher magnification (hematoxylin and eosin, original magnification ×250). (From Unni KK. *Dahlin's bone tumors: General aspects and data on 11,087 cases*, 5th ed. Chapter 28, Philadelphia, PA: Lippincott-Raven; 1996, with permission.)

Most surgeons involved in the surgical removal of these lesions, in and around the orbit, are members of a multidisciplinary surgical team comprising neurosurgeons, head and neck surgeons, otorhinolaryngologists, ophthalmologists, and plastic surgeons. The object of surgery is complete removal of the lesion, and this is usually possible.

Cherubism

In 1933, William Jones, a Canadian radiologist, reported a familial intraosseous multilocular cystic disease of the jaws in three siblings of the same family, characterized by "full round cheeks" and "upward cast of the eyes" that gave the children a "cherubic appearance." Jones coined the term "cherubism," because he thought the children resembled the cherubs frequently painted in Renaissance art.

The histopathology of this lesion is the same as giant cell reparative granuloma and brown tumor of hyperparathyroidism. At birth, the shape of the head and face is normal. At the age of 2 or 3 years, hard, bilateral, symmetric, painless masses usually appear around the angle of the mandible and spread to the ascending rami and body of the mandible. Next, the maxillae are involved, but the extent of the disorder varies from minor lesions to massive involvement of both jaws. The teeth are irregularly placed and may be missing. About 200 cases of cherubism have been reported in the literature, but orbital involvement is infrequent.

Orbital involvement occurs when and if the upper portions of the maxillary bones are involved. This causes bulging of the inferior orbital plate which, in turn, pushes the eyes superiorly. This displacement results in varying degrees of diplopia, tearing, and proptosis. If there is massive involvement of maxillary bones with long-standing upward expansion of the inferior orbital floor, some degree of visual loss occurs from compression of the optic nerve. This is rare, however, either because the disorder spontaneously self-arrests or because the bony deformity is surgically removed before this complication. The disorder usually subsides at puberty, with the affected bone reverting to some semblance of its normal contour. However, there are some exceptions.

One unusual exception was the 27-year-old woman described by Colombo et al. (2001). The patient had a slowly progressive, bilateral superonasal globe displacement and temporal orbital masses of 6 years' duration. Although there was a history of cherubism, her cheeks and jaws appeared normal, and CT scans demonstrated multicystic bony lesions arising from the orbital floors bilaterally. The nature of the masses (cherubism) was confirmed histopathologically. The authors concluded that orbital involvement may develop beyond puberty, after stabilization or regression of the lesions in the jaws. Seven other patients have been reported with orbital involvement: Three by Jones (1933), two by Hawes (1989), one by Carroll and Sullivan (2001), and one by Schultze-Mosgau et al. (2003).

CT scan shows multilocular areas with intervening solid tissue involving the mandible and maxilla with extension along the floor of the orbit.

Anderson and McClendon (1962) established the genetic basis for the disorder. The gene locus was localized to chromosome 4p16.3. Cherubism is a familial disease transmitted in an autosomal dominant manner, with 80% to 100% penetrance and variable expressivity (Peters, 1979).

The management of these cases is a mixture of conservatism and aggressive surgical debulking. In the early stages, if one or two teeth are malformed or partially resorbed, these can be removed. However, if there is major disruption of bone in the tooth-bearing areas, surgical debulking of the osseous lesion is performed. Upward displacement of the eyes caused by expansion of the maxillary bones along the floor of orbital bone can be followed up by CT scans so long as only the anterior orbit is involved. If imaging methods show extension toward the posterior orbit, the anterior maxillary wall can be partly removed for access to the orbit, and the orbital floor debulked subperiostially.

Hyperparathyroidism (Brown Tumor)

von Recklinghausen (1891) described the changes in bone that were subsequently called *generalized osteitis fibrosa cystica*. Twenty years passed before the demineralization of bone, so characteristic of the disease, was associated with enlargement of the parathyroid gland. However, the question of whether the bone disorder caused the hyperplasia of the parathyroid, or *vice versa*, remained in dispute. Amazingly, another 20 years passed before this question was settled, and hyperparathyroidism was identified as the triggering mechanism (Jaffe, 1933).

In the primary form, such as a neoplasm or hyperplasia of the parathyroid gland, the metabolism of bone goes askew, resulting in diffuse demineralization, elevated levels of calcium in the urine and blood, and a diminished serum phosphorus level. In secondary hyperparathyroidism, such as occurs in chronic renal failure, these assay values in serum and urine are reversed. The parathyroid gland responds by secreting parathyroid hormone in larger quantities.

In some cases, whether the cause is primary or secondary, the bone disorder is focal, such as in the orbit, rather than generalized in type. In the focal type, bone resorption is followed by cyst formation and an influx of reactive vascularized fibrous tissue. Hemorrhage and an influx of giant cells ensue. The sum of this process is a radiographically visible tumor of bone that resembles giant cell reparative granuloma and cherubism.

When incised or resected, these lesions are brown. But "brown tumor" is not an appropriate designation because the other two histopathologically similar tumors, giant cell reparative granuloma and cherubism, are also brown. Furthermore, the histopathologic features of the brown tumor are not pathognomonic. Diagnosis is best established by the elevated serum levels of calcium, alkaline phosphatase, or parathyroid hormone and an increased amount of urinary calcium.

Parrish and O'Day (1986) published a review of the literature pertaining to "brown tumor of the orbit." They summarized what little is known about clinical presentation, course, and frequency of the tumor in the orbital bone. They analyzed 12 cases in the literature from 1953 through 1986. There were four males and eight females, ranging in age from 7 to 71 years (average, 30.4 years; median, 24 years). In five of the twelve, the lesion was of the primary type, six were associated with glomerulonephritis, and in one case the type was not stated. All patients presented with either some "swelling" of the eye, proptosis, or a palpable orbital mass. Reduced vision and pain were present in two cases. All cases underwent surgical excision of the tumor.

Two cases were added to this list and detailed in the third edition of this text. One was the 69-year-old woman described by Rootman (1988); the other was our patient, a 27-year-old woman listed as having "brown tumor" in Figure 6.9. The lytic lesion of the patient described by Rootman (1988) was well localized to the roof of one orbit and was completely resected. Histopathologic evaluation and subsequent serum assays of calcium, phosphorus, and parathyroid hormone led to the discovery of a parathyroid adenoma, which was removed.

Several years before presentation in our patient, a tumor had been removed from her right mandible at another institution. This tumor was thought to be a giant cell reparative granuloma. Plain film radiography demonstrated an expanding lesion of the right frontal bone. This osteopathy involved the orbital roof and greater wing of the sphenoid bone. Also, it extended intracranially (see Fig. 6.9A). The tumor was resected through a frontal craniotomy. The tumor also extended into the orbit through a lytic area in the orbital roof (Fig. 6.9B). Subsequent blood serum assays of calcium and phosphorus levels confirmed the diagnosis. One month later, an adenoma of the parathyroid gland was removed. The patient was followed up for 7 years without the development of any additional osteopathy. In retrospect, the jaw and orbital bone lesions probably represented multifocal lesions of hyperparathyroidism.

Finally, Levine et al. (1991) described a 27-year-old woman with hyperparathyroidism secondary to chronic renal failure. She had been receiving hemodialysis treatment for several years. Over the past decade or so, hemodialysis has increasingly been used for treatment of chronic renal failure. Therefore, the number of patients with secondary hyperparathyroidism has increased.

Aneurysmal Bone Cyst

This is a benign lesion of bone. The name *aneurysmal bone cyst* was first applied by Jaffe and Lichtenstein (1942) to differentiate this tumor from a solitary bone cyst. They noted the course of the tumor in two patients.

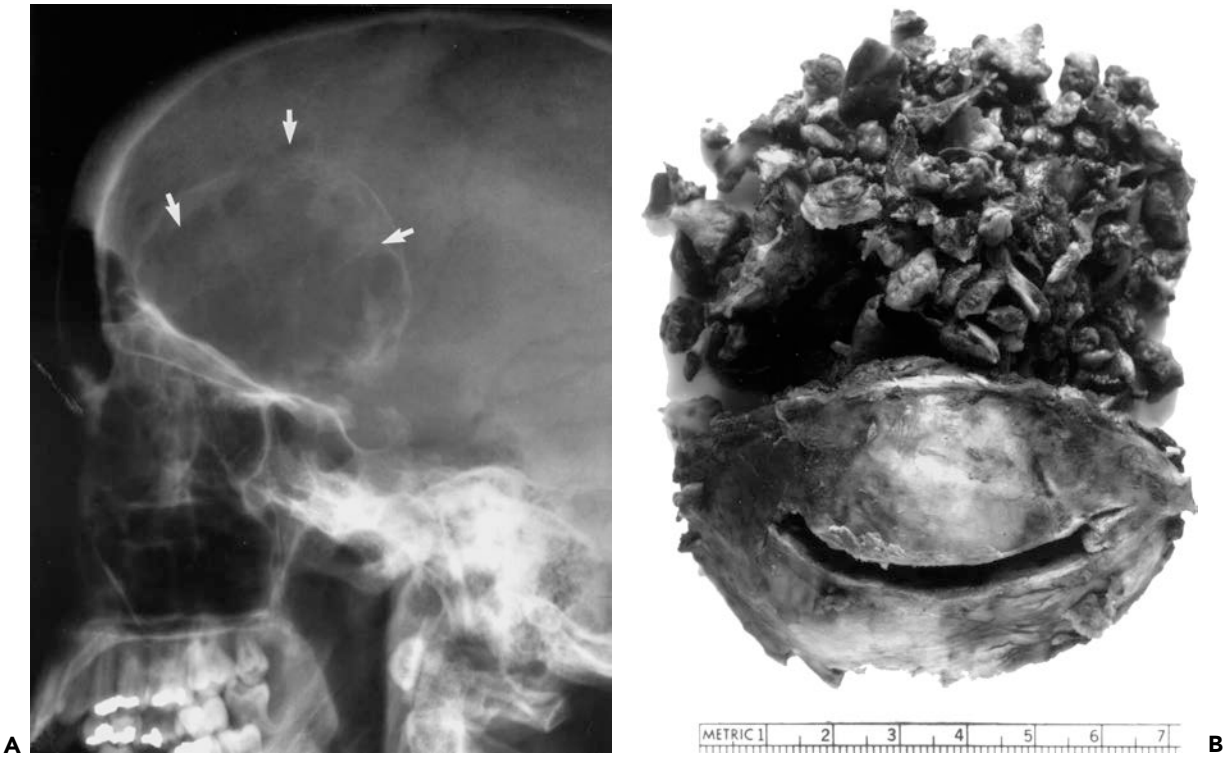

Figure 6.9 **A:** Sagittal radiograph showing an expansile lesion of the frontal bone with involvement of the orbital roof and the greater wing of the sphenoid bone of a 27-year-old woman. Note the large balloon-like, bosselated intracranial extension (*arrowheads*). **B:** *En bloc* resection shows gross specimen, measuring approximately 7 × 6 × 5-cm, attached to the orbital roof. The large upper portion of the lesion was extradural. The tufted configuration of the upper periphery corresponds to the bosselation noted in **(A)**.

Subsequently, there was much debate about the pathogenesis of the lesion.

Now, it is not considered to be either a cyst or a neoplasm. Instead, it probably is a pathophysiologic process that evolves from incomplete resolution of a tumor-associated vascular malformation. In approximately one third of cases, the preexisting lesion can be identified. Most common is the giant cell tumor. Other precursor tumors include osteoblastoma, chondroblastoma, fibrous dysplasia, nonossifying fibroma, solitary bone cyst, fibrous histiocytoma, eosinophilic granuloma, osteosarcoma, and angioma of bone. If no preexisting tumor is known, trauma (hematocele) should be considered. Aneurysmal bone cysts have been described in almost all areas of the skeleton except possibly the bones of the middle ear. Its favorite haunts are the long bones, vertebrae, ribs, and sacrum. We are chiefly concerned with its occurrence in and around the orbit (see Fig. 6.10).

Frequency

In the 1994 edition of this text, we referenced 17 single cases of unilateral orbital aneurysmal bone cyst in the literature from 1968 through 1990 (Fite et al., 1968; Offret et al., 1971; Komorn, 1972; Delorit and Summers, 1975; Powell and Glaser, 1975; Jakobiec and Jones, 1976; O'Gorman and Kirkham, 1976; Yee et al., 1977; Flament and Forest, 1979; Iraci et al., 1980; Ronner and Jones, 1983; Sanerkin et al., 1983; Klepach et al., 1984; Johnson et al., 1988; Rootman, 1988; Carmichael et al., 1989; Hunter et al., 1990).

Seven single cases of aneurysmal bone cysts were reported between 1993 and 2002 (Bealer et al., 1993; Patel et al., 1993; Dailey et al., 1994; Lucarelli et al., 1995;

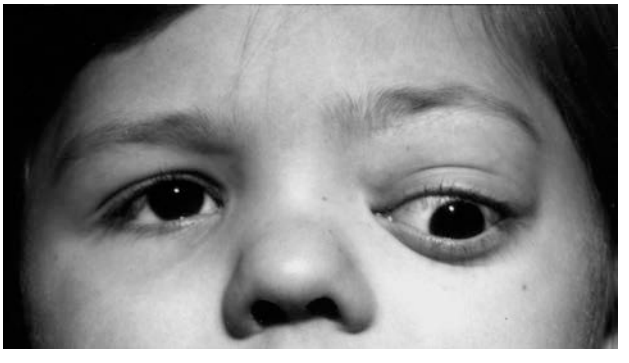

Figure 6.10 Displacement of the left eye caused by an aneurysmal bone cyst in a 5-year-old girl. The cyst occupied the upper third of the orbital space.

Hino et al., 1998; Menon et al., 1999; Senol et al., 2002). Our 50-year survey list includes three cases, which brings the total number of cases to 27.

These patients ranged in age from 11 months to 43 years (average, 13.6 years; median, 11 years). There were 17 females and 10 males. The orbital bone affected was frontal in 15, sphenoid in 6, ethmoid in 4, malar in 2, and maxilla in 1. The salient features of this statistical analysis are the 11:6 female-to-male sex ratio, a median age of 11 years for the presentation of the tumor, and the frequency of frontal bone involvement.

Clinical Features

In most anatomic sites, the principal sign of this tumor is an expansion of bone with subsequent stretching of the covering periosteum. The latter accounts for the principal symptom, pain of increasing severity. However, around the orbit, the bones are not thick enough to support a fusiform expansion of extended duration except for the body of the sphenoid, the base of the zygomatic arch, and the brow area of the frontal bone. Even in these sites, continuous pain of increasing degree is seldom encountered except in patients with involvement of the sphenoid bone. In such patients, ipsilateral headache is a frequent initial symptom of a growing cyst.

Nevertheless, in approximately 40% of the lesions in all orbital sites, pain may be the principal reason for seeking consultation. In these situations, the pain is usually of sudden onset and has been present for only a week or two. Such symptoms probably represent a sudden increase in the size of the lesion and stretching of the periorbita secondary to recent hemorrhage. In reality, the hemorrhage or sudden

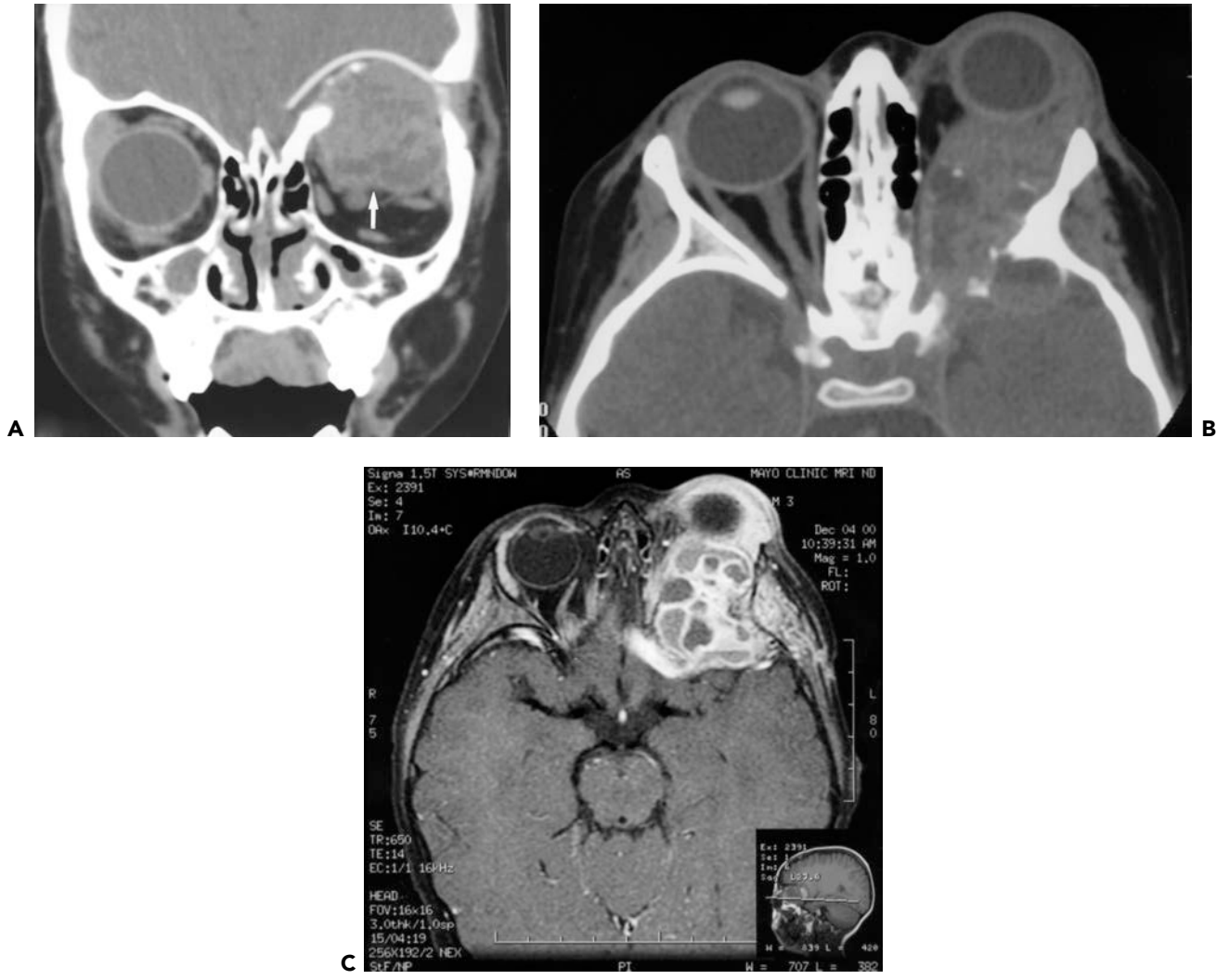

Figure 6.11 Imaging aspects from a 3-year-old boy. **A:** Computed tomography scan (coronal view) of massive tumor with irregular densities in the superoposterior orbit located in the peripheral orbital space between periorbita (*arrow*) and orbital bone. **B:** Axial view showing tumor invasion of the intracranial vault through erosion of the sphenoid bone. **C:** Magnetic resonance imaging axial view showing a ''soap bubble'' configuration.

expansion of tumor is superimposed on an otherwise insidiously growing tumor of unknown duration.

In the approximately 60% of patients without pain or headache, proptosis is the chief presenting symptom owing to the bulk effect of the nonosseous part of the lesion usurping the orbital space. Such is the situation in most patients with frontal bone involvement. These patients show few signs or symptoms other than nonaxial proptosis and some mechanical limitation of gaze in the direction of the expanding mass. Occasionally, these patients may have an episode of ecchymosis of the upper eyelid or transient blepharoptosis if the cyst is located well forward along the orbital roof.

Patients with more serious orbital symptoms, such as optic disk edema, third and sixth nerve palsies, visual decrease, and an afferent pupillary defect, are those with sphenoid bone involvement or an intracranial extension of tumor. Nevertheless, suspicion of an orbital aneurysmal bone cyst is usually based on one of the imaging methods rather than the presenting clinical features.

Imaging Aspects

CT scan is particularly useful in defining the size and extent of lesions located in areas where the bony areas are complex, for example, the base of the skull. Fluid levels are common and may be seen on both CT scan and MRI. MRI seems superior for imaging the hemorrhagic content of the tumor because of its high-intensity signal on T_1-weighted sequence. Also, MRI shows the internal trabeculations and the variable densities within the pseudocompartments of the tumor.

Kransdorf and Sweet (1995) studied the natural history through four evolving radiologic stages: Initial appearance, growth, stabilization, and healing. In skeletal bone, the initial stage is characterized by a well-defined area of osteolysis with discrete elevation of the periosteum. This is followed by a growth phase, in which the lesion grows rapidly with progressive "destruction" of bone and development of the characteristic "blown-out" radiologic appearance. The growth phase is succeeded by a period of stabilization, in which the characteristic "soap bubble appearance" develops, as a result of maturation of the bony shell. Final healing results in progressive calcification and ossification, with the lesion transformed into a dense bony mass. Figure 6.11 illustrates some of these imaging features.

Pathology

The consistency of the nonosseous portion of the tumor has been described as friable, fleshy, fibrous, or granular. This particular characteristic may depend on the age of the mass. The blood-filled spaces visually lack a lining of endothelium. All spaces may be separated by thin, delicate septa of loose connective tissue or by thicker compact bands of fibroblasts containing osteoid. Throughout the tumor are variable mixtures of hemosiderin-filled macrophages, benign giant cells, and lymphocytes. Some mitotic figures may be present (see Fig. 6.12). Calcification may be seen in both the fibrous stroma and chondroid material. The tumor on occasion may be a secondary phenomenon to chondroblastoma or fibrous dysplasia.

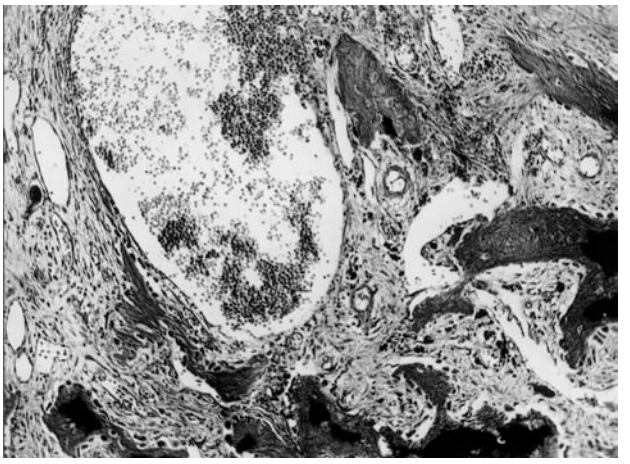

Figure 6.12 Blood-filled spaces are separated by fibrous septa containing bone spicules (original magnification ×110).

Treatment and Prognosis

An orbital aneurysmal bone cyst usually requires only one surgery for satisfactory resolution, provided the surgical intervention is definitive rather than simply exploratory. In the orbit, the thin shell of bone typically covering the advancing form of the cyst in other anatomic sites may be absent. In the latter situation, there is only a covering of periorbita. The soft portions of the tumor are usually easily removed from the periorbita. The underlying defect in bone is curetted lightly, but persistently, to remove all loose, porous bone. Bleeding usually stops when this is accomplished. In cases where the orbital roof has been breached by intracranial extension of tumor, the soft tissue is wiped or sucked away from the covering dura. If this is accomplished, it is rare that a second operation is required. Cure of the lesion also has been reported after simple biopsy or incomplete removal. We do not believe radiotherapy is necessary for orbital lesions. If the lesion recurs, it usually appears within 2 years.

OSSEOUS TUMORS

Osteoma

This section discusses lesions with a predominantly osseous composition. Although the soft tissue component of these tumors exercises some supportive role, it is only a minor portion of the overall bony structure of the growth. It is the osseous feature of these lesions that determines the clinical manifestations and course of the tumor and poses a challenge in their management. The osteoma is the most common of this family of tumors with

orbital orientation, excluding those that have occurred after overzealous irradiation around the cranium.

This lesion is peculiar to the membranous bones of the face and skull. A favorite locale for its orbital presentation is the juncture of the bones of the ethmoidal and frontal sinuses in the anterosuperonasal orbit.

Osteoma has been classified into three types—ivory, mature, and fibrous—depending on the histopathologic proportion of bone to supporting fibrous stroma and the assumed maturity of the tumor. The fibrous type is considered the most immature and may be a continuum of or a link with the aforementioned ossifying fibroma. Apart from some minor variation in age range and rate of growth, the clinical course of the several histologic types is the same. Therefore, this subtyping is of little clinical importance.

In spite of much-published rhetoric and conjecture, the pathogenesis of osteoma is not known.

Incidence

The 50-year Mayo Clinic series includes 12 orbital cases, approximately 0.6% of our total series of pathologically proved lesions. This is a lower frequency than in other large study series (300 or more total orbital tumors) in the literature. Nine patients were men. Although the sex incidence of osteomas of the paranasal sinuses has been widely studied in a large number of patients (male-to-female ratio of 1.6 among 567 cases reported after 1939) (Mansour et al., 1999), that of primary orbital osteomas has usually not been included as a separate ratio.

The same omission in reference to the age range of patients with orbital involvement also occurs. Because osteoma of the orbit is slow growing, the tumor may remain asymptomatic for many years before presentation, thereby concealing the age at onset. Therefore, Grove (1978) noted an age range of 12 to 51 years based on the time of onset of symptoms rather than the time of diagnosis. The age range of our group of 12 patients based on the age at onset was 11 to 71 years (mean, 33.4 years; median, 32.5 years).

In our group of 12 patients, 4 had primary orbital osteomas and 8 had secondary extension of tumor from an adjacent sinus. Actually, primary orbital osteomas are very rare. Andrews (referenced by Cushing, 1927) found eight orbital osteomas among the records of 429,989 cases seen at three major ophthalmologic institutes in New York City.

The paranasal sinuses are, by far, the most frequent source of osteomas of the skull. The most frequent sinuses of origin are frontal (50%), ethmoid (40%), maxillary (6.2%), and sphenoid (3.6%) (Mansour et al., 1999). However, in terms of orbital extension, the ethmoid sinus is the most frequent source of osteoma.

A number of single cases of orbital osteoma have been recorded in the literature since the third edition of this text. All were osteomas of one or more paranasal sinus that secondarily extended into the orbit: A 32-year-old man (Biedner et al., 1988); a 14-year-old boy (Gillman et al., 1997); a 53-year-old woman (Gossios et al., 1999); a 15-year-old boy (Sires et al., 1999); a 66-year-old woman (Mansour et al., 1999); and a 13-year-old girl (Kim et al., 2000).

Chief among the oddities surrounding osteomas are the several references in the third edition linking osteoma of the jaw or skull with Gardner syndrome (Gardner, 1951). This is an autosomal dominant, familial polyposis of the large bowel, with epidermal and sebaceous cysts of the subcutaneous tissues. Also, the orbital osteoma may be a presenting manifestation (proptosis) of the disorder (Tandon et al., 1988). The importance of this association is that a malignant transformation of the intestinal polyposis may occur in nearly 40% of cases (Smith and Calcaterra, 1989; McNab, 1998).

Clinical Features

The anatomic site of orbital encroachment of the growing, expanding mass is the chief determinant in the ultimate pattern of presentation. In this respect, osteomas closely mimic the signs and symptoms of a mucocele in the same location; these were described for mucocele in Chapter 4. Osteomas originating in a paranasal sinus may remain asymptomatic until the sinus is filled with mature bone. Pain becomes a problem when the tumor pushes through the covering plate of bone and extends into the orbit. Osteomas arising in the intracranial vault have more room for unfettered growth and reach "giant" size before invading the orbit. Osteomas from a frontal sinus have one of the optional patterns of proptosis and downward displacement of the eye, the ethmoidal osteoma produces a more lateral shift of the eye, and the rare osteoma rising in the sphenoid sinus produces a modified orbital apex syndrome.

The rock-like consistency of an osteoma arising from the intracavitary surface of the bony orbital plate brings the patient with a primary orbital osteoma to the physician. It is the mechanical obstructive effect on ocular rotation that causes trouble. Biedner et al. (1988) reported a 32-year-old man who was unable to elevate the left eye when adducted (Brown superior oblique tendon sheath syndrome) because of an osteoma that had pushed the trochlea forward. Other cases of monocular, gaze-evoked, or transient loss of vision due to orbital osteoma were reported by Wilkes et al. (1979), Miller et al. (1977), and Gillman et al. (1997). In a patient described by Rootman (1988), an orbital osteoma was responsible for two episodes of subluxation of one eye in a 12-month period. In the 17-year-old boy described by Cecire et al. (1988), the osteoma was so unyielding that it eroded both the ethmoid plate and the periorbita, allowing air to enter the orbit when the patient blew his nose. In the case described by Mansour et al. (1999), cellulitis occurred when an osteoma of the ethmoid sinus broke into the orbit.

Imaging Aspects

CT scan is the procedure of choice to outline the full extent of the osteoma. The hyperdense mass probably shows some expansion of the sinus wall of origin (see Fig. 6.13). Some

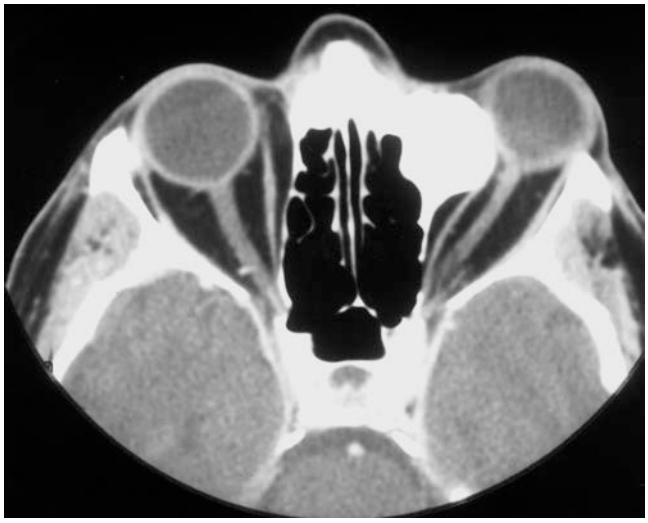

Figure 6.13 The computed tomography scan shows a 3 × 2.5 × 1-cm, hyperdense, smooth-surfaced osteoma along the superomedial, left orbital wall. The mass was completely resected. There was no recurrence 27 months later.

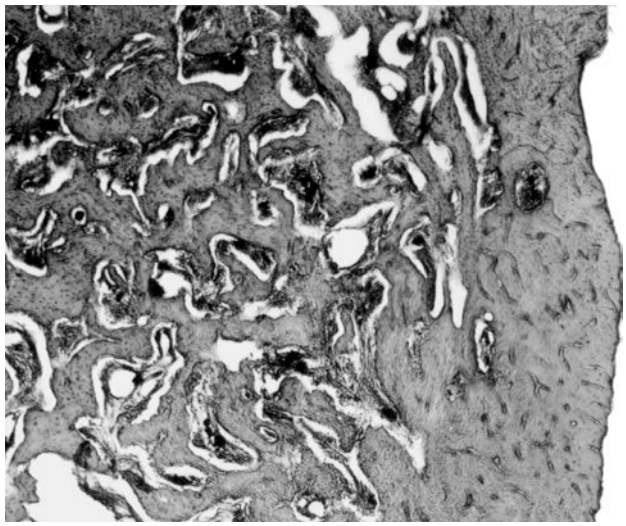

Figure 6.14 In this osteoma, islands of fibrovascular tissue are interspersed among interconnecting lamellae of bone (left). Note the more compact bone along the periphery of the tumor (right) (original magnification ×30).

tumors contain areas of spongy (cancellous) bone. If so, the signal intensity of CT scan is less in these areas compared with the surrounding compact bone (Bilaniuk et al., 1992). The tumor is not associated with bone destruction.

On MRI, the signal void of an osteoma is difficult to distinguish from the signal void of air within the sinuses. However, the periorbital and dural coverings of the orbital plates show enhancement with MRI.

Pathology

The orbital osteoma, simply put, is an overgrowth of bone in the wrong place. Its structure is either cancellous or compact, lamellar bone or a mixture of both, depending somewhat on the site of origin or the maturity of the tumor. In the cancellous type, the trabeculae of bone are thinner, and the loosely arranged fibrovascular matrix is more abundant compared with the compact, eburnated bone (see Fig. 6.14). In the latter, the ivory-like bone is dense and thick, and the scanty fibrovascular component is compressed into tiny spaces, the haversian canals. Tumors arising from the orbital face of the bony wall have a covering of periorbita, whereas tumors of sinus origin also have part of their periphery covered with respiratory epithelium (see Fig. 6.15). Grossly, the compact subtype has an ivory-white, glistening surface, but the cancellous subtype may have a slightly pink hue. Some of the tumors are round and smooth, and others have a knobby, irregular contour (see Fig. 6.16).

Management

Surgical removal of the orbital mass was performed on all 12 osteomas listed in the 50-year survey (Table 3.3). However, ten of these patients underwent surgery before 1988. If the osteoma is located along the medial aspect of the roof or the superior portion of the medial wall and is attached to the cribriform plate, then management becomes quite challenging. If it is necessary to remove the lesion in its entirety because of compression of the medial surface of the optic nerve, intracranial extension, or extension into the superior orbital fissure, an orbitocraniofacial resection may be required, with reconstruction of the cribriform plate. Otherwise, a burring down procedure might be preferable instead of complete removal.

Selva et al. (2003) described a 28-year-old woman with an extensive osteoma arising in the frontoethmoidal sinuses and the orbital roof. The tumor was successfully

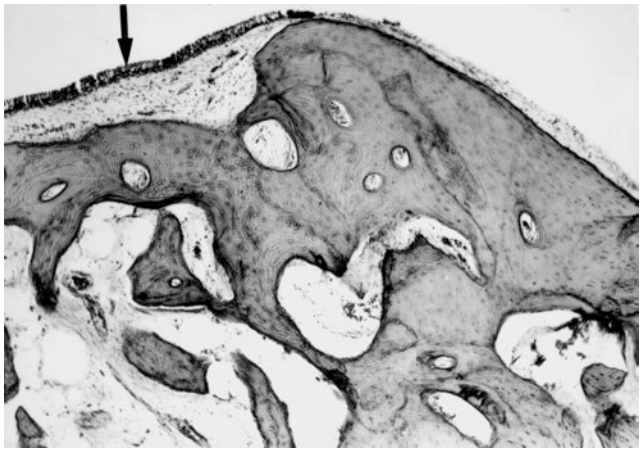

Figure 6.15 This osteoma shows a mixture of fibrovascular tissue and bone covered with ciliated, columnar epithelium (*arrow*) (original magnification ×60).

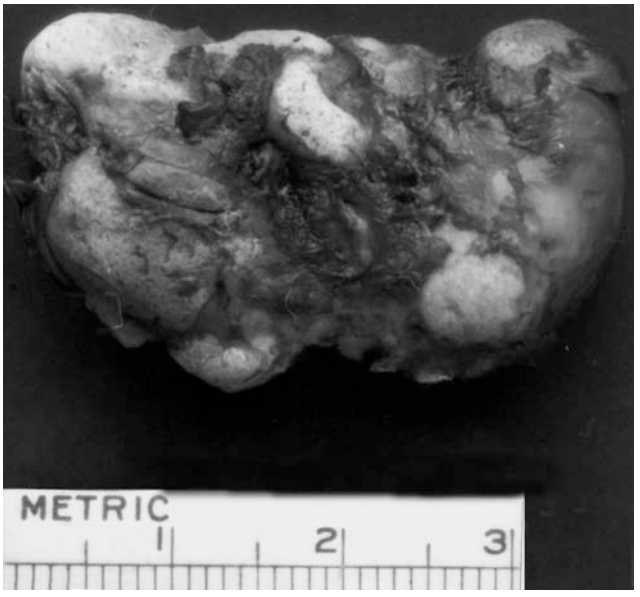

Figure 6.16 Knobby, irregularly contoured orbitofrontal osteoma removed from a 25-year-old man.

removed by means of a combined sinus endoscopic and orbital approach, with the assistance of stereotactic localization. The patient had postoperative ptosis, diplopia, and supraorbital nerve anesthesia, all of which resolved over a 3-month period. A stereotactic-assisted, sino-orbital approach to select frontoethmoidal osteomas may provide a viable alternative for those patients in whom it is desirable to avoid the morbidity of a craniotomy.

Osteoblastoma

This neoplasm is a distinct entity, despite the fact that histologically it may contain areas that are similar to the osteoid osteoma. Some years ago, this tumor was called *osteoid osteoma*, *giant osteoid osteoma*, and *osteogenic fibroma*. The literature abounds with osteoblastomas that have been mistaken for these tumors, including osteosarcomas. Since 1965, the name *benign osteoblastoma* has prevailed. However, some osteoblastomas in nonorbital sites are locally aggressive and associated with much bone destruction. This behavior belies their assumed benignity. In the literature, the terms *aggressive osteoblastoma* and *malignant osteoblastoma* emphasize this problem. There are rare well-documented examples of osteoblastoma undergoing malignant change to osteosarcoma (Unni, 1996).

Perhaps the term should be *osteoblastoma*, not "benign osteoblastoma," to emphasize the rare aggressive lesion. The tumor is most frequently found in vertebrae, femur, tibia, and mandible. Males in the first 3 decades of life are predominantly affected (McLeod et al., 1976).

The orbit is a relatively rare location for this tumor. We have reviewed six cases reported since 1973. In four of these cases, the tumor was primary in the orbital roof (Shepherd et al., 1977; Clutter et al., 1984; Lowder et al., 1986; Leone et al., 1988). The two remaining cases were primary in the ethmoidal sinus with secondary encroachment on the orbital space (Fu and Perzin, 1974; Freedman, 1975). In all six cases, the orbital disease was unilateral. All were documented with histologic descriptions, but one publication did not include a photomicrograph of the lesion.

Among the descriptions of primary lesions was a 10-year-old boy whose tumor eroded the orbital roof but did not invade the brain or breach the periorbita. The lesion was circumscribed but not encapsulated. There was no recurrence 10 months after excision of the mass. The lesion in the 18-year-old reported by Clutter et al. (1984) was also unencapsulated. The lesion was curetted but a definite follow-up was not stated. In the 5-year-old boy described by Lowder et al. (1986), the lesion was excised piecemeal but recurred a year later. The tumor was then completely resected through cranioplasty without recurrence in a follow-up of 4 years. In the 9-year-old girl described by Shepherd et al. (1977), the circumscribed tumor extended into the olfactory groove and the ethmoidal sinus. It was completely removed through craniotomy with no recurrence in a follow-up of 18 months. The two secondary tumors already noted occurred in a 13-year-old boy and a 12-year-old girl.

The median age of these patients was 11 years (range, 5 to 18 years) with a male predominance. This age and sex incidence is not unlike that of extraorbital lesions. Pain was not a prominent feature in the clinical evolution in most of the orbital cases.

The radiographic descriptions of the orbital lesions vary and are not specific for osteoblastoma. Factors such as location, size, and duration of the orbital lesion may influence its radiographic image. In long bones, the lesion appears as an expanding tumor with a radiolucent center and an eggshell-like boundary. However, the orbital roof is so thin that it cannot support the size and configuration of a tumor of this type. Therefore, the lesion is usually atypical when compared with the radiographic appearance in extraorbital sites. In this respect, the tumor resembles an orbital aneurysmal bone cyst.

The fibrovascular stroma varies so much, both in content and quantity, from case to case that it is difficult to describe histopathologic features of a typical case (Lawton and Leone, 1990).

Leone et al. (1988, 1989) described the lesion removed from their patient as follows:

> Sections of the lesion stained with hematoxylin and eosin showed a tumor composed of moderate numbers of immature bone spicules separated by a dense, fibrovascular matrix (see Fig. 6.17). On higher power, many small cells with minimal cytoplasm and densely basophilic nuclei were associated with the bone spicules and admixed with the fibrous tissue. Results of careful examination demonstrated neither significant pleomorphism nor mitotic figures. The small cells were osteoblasts.

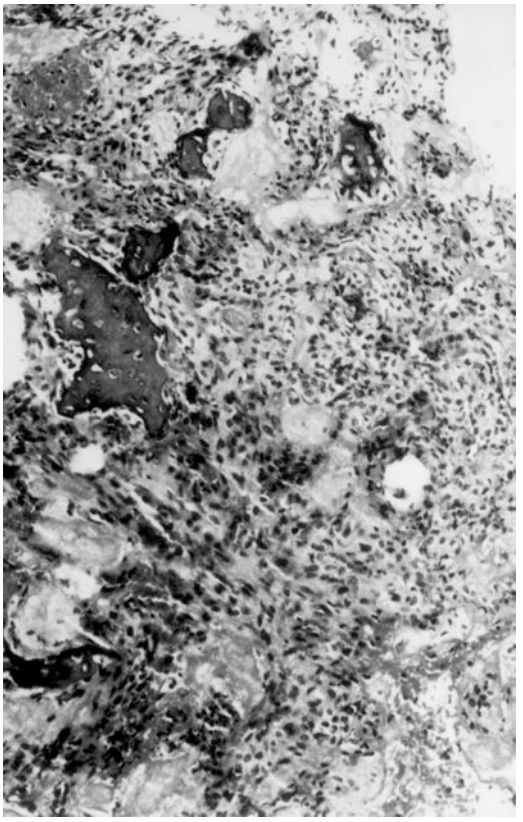

Figure 6.17 This osteoblastoma shows fairly mature bone spicules embedded in a cellular, vascularized matrix of fibroblasts and osteoblasts (hematoxylin and eosin, original magnification ×205). (From Leone CR, Lawton AW, Leone RT Jr. Benign osteoblastoma of the orbit. *Ophthalmology*. 1988;95:1554–1558, with permission.)

Leone et al. (1988) used the following surgical approach to the tumor:

> A transcranial approach using a right frontal craniotomy was undertaken to fully expose the roof of the right orbit. The mass was found between the dura and periorbita with the anterior one half of the roof completely eroded away. The mass was soft, friable, and vascular with bony spicules located primarily at the periphery of the mass. It measured 2 × 3 cm, had no capsule, but was well circumscribed. The soft tissue part of the mass was removed with the Cavitron ultrasonic surgical aspirator (Cavitron, Sudbury, MA) and the bony spicules were manually removed. The defect in the roof was covered with a 1.5-mm thick polypropylene screen.

We have not encountered an orbital osteoblastoma in our 50-year survey, nor have we found any further cases recorded in the literature since the 1988 report of Leone et al.

Osteosarcoma

Most authors consider this neoplasm the most common primary malignant tumor of bone (nonorbital) that typically metastasizes to the lung. Primary and secondary osteosarcomas, particularly the latter, are also frequent residents of the orbit. In the third edition, we analyzed a collection of 13 osteosarcomas for their incidence factors. Our update cohort (1989 to 1997) added five more osteosarcomas, for a total of 18 neoplasms (see Table 6.2). The 18 malignant orbital osteosarcomas comprise 1% of the 1,795 total in our 50-year survey (Table 3.3).

TABLE 6.2
SUMMARY OF INCIDENCE DATA OF ORBITAL OSTEOSARCOMA, 1948 TO 1997

Year Seen	Sex	Age at Onset, y	Source
1949	M	31	Primary
1951	M	53	Secondary
1952	F	1 1/2	Secondary
1956	M	23	Secondary
1962	M	3	Secondary
1970	M	57	Secondary
1971	F	36	Secondary
1976	F	31	Secondary
1979	M	49	Secondary
1979	F	62	Primary
1979	F	64	Secondary
1982	F	18	Primary
1982	F	Unknown	Secondary
1988	F	66	Secondary
1989	F	45	Primary
1993	M	5	Primary
1996	M	16	Secondary
1997	F	19	Secondary

The source of most tumors was the nasal cavity and paranasal sinuses. However, some of the neoplasms were so large and extensive that it was difficult to pinpoint their source. The orbital bones involved, in order of frequency, were sphenoid in seven, frontal in seven, maxilla in six, ethmoid in five, nasal in three, and one each of the malar, temporal, and mandible.

There were eight males and ten females. The age range of our patients near the time of onset was 1 1/2 to 66 years (mean, 33.5 years; median, 31 years). These incidence data are unlike the often-repeated statement in the literature that most cases in the overall skeleton (bones other than the orbit) occur in children, adolescents, and young adults with a male predominance.

Clinical Features

The principal difference in the orbital symptoms of osteosarcoma, when compared with benign bony tumors, was more rapid onset of proptosis and a more alarming degree of functional impairment of the eye. The chief presenting sign or symptom was either proptosis or off-axis displacement of the eye in 13 of 16 patients (81%)

in our group of osteosarcomas. Two additional patients already had one eye removed because of recurrent tumor. In only 7 of 18 patients (39%) was there a visible mass externally in the nasal cavity or nasopharynx or a palpable orbital mass. The remaining symptoms were a miscellany of facial swelling, eyelid swelling, epiphora, epistaxis, nasal discharge, nasal obstruction, orbital pain, facial dysesthesia, and headache. The duration of signs and symptoms before presentation averaged slightly more than 1 year, with a range of 3 to 24 months. One patient had bilateral orbital involvement.

Osteosarcomas affecting the orbit may develop as a malignant transformation of preexisting Paget disease or fibrous dysplasia of the skull or after irradiation of benign, malignant, and inflammatory tumors of the orbit and be associated with the heritable form of retinoblastoma. Goldberg et al. (2000) described an 83-year-old woman with Paget disease of 20 years' duration who developed visual loss (hand motion only) in the right eye and proptosis in the left eye. Imaging studies revealed diffuse pagetoid changes in the cranium associated with bilateral narrowing of the optic canals and an extracranial mass in the left orbit. Diagnosis of osteosarcoma was made by fine-needle aspiration biopsy.

The patient reported by Benedict et al. (1988) (Table 6.2) developed malignant degeneration of a fibrous dysplasia some years after radiotherapy to the affected orbit. As noted, osteosarcoma may be associated with familial retinoblastoma. In such cases, the two tumors share the absence of a suppressor gene at the retinoblastoma locus on the long arm of chromosome 13. Patients with this form of retinoblastoma are at a 10% risk of developing osteosarcoma by the age of 25 years (Draper et al., 1986).

Some authors associate osteosarcoma with preexisting trauma. Long et al. (2000) described an osteosarcoma that developed in bone within a phthisic eye of 20 years' duration in an 86-year-old woman.

Additional interesting cases of orbital osteosarcoma have been described by Misra et al. (2001); Trevisani et al. (1996); Sharma et al. (1996); and Parmar et al. (2001). The case described by Misra et al. (2001) was an 8-year-old boy who developed protrusion of one eye 1 month after an above-the-knee amputation for osteosarcoma of the tibia. Ultrasonography showed a lobulated, nodular, hypodense, retrobulbar mass in the affected orbit. Fine-needle aspiration cytology of the mass showed metastatic osteosarcoma.

The case described by Trevisani et al. (1996) was a 58-year-old man with Paget disease of bone for 23 years and no prior radiotherapy, who developed proptosis and displacement of one eye. CT scan showed an osteolytic lesion involving the entire orbital roof of the affected orbit. An incisional biopsy indicated osteosarcoma.

Sharma et al. (1996) also described another case of metastatic osteosarcoma. A 15-year-old boy had undergone a disarticulation of the left hip. Seven months later, epistaxis and unilateral proptosis occurred. A fleshy, vascular mass was present on the lateral wall of the nose. CT scan showed a mass in the left ethmoid. Biopsy showed features of metastatic osteosarcoma.

Parmar et al. (2001) described two primary orbital parosteal osteosarcomas. This is a low-grade sarcoma that tends to recur locally after excision but has a favorable prognosis. The first patient was a 40-year-old man with an 8-year history of unilateral proptosis and a superotemporal orbital mass. The mass was completely excised and proved to be a well-differentiated neoplasm. The patient remained well 9 months postoperatively. The second patient was a 47-year-old man with a 5-month history of painless swelling of the right lower eyelid. Excision biopsy suggested a well-differentiated parosteal osteosarcoma along the orbital floor. The tumor recurred 3 years later. In another 3 months, the mass demonstrated accelerated growth and an exenteration was performed. Histologic examination showed a high-grade liposarcoma, a very unusual turn of events. The patient was disease free 4 years later.

The sole laboratory analysis of clinical value is determination of the serum alkaline phosphatase level. Abrupt elevation of serum alkaline phosphatase levels in patients with preexisting benign bone lesions may indicate malignant transformation.

Imaging Aspects

On CT scan, the enhancing mass may vary somewhat in density from case to case, depending on the predominance of osseous, cartilaginous, or fibrous tissue components. In addition to bone destruction, the lesions usually show some degree of calcification representing new bone formation. In sites of growth where the background contrast is good, the lesion may show fine linear shadows radiating from the nidus of the mass. These represent finger-like projections of new bone (see Fig. 6.18).

Because of their fast growth and hidden source—the paranasal sinus—the secondary orbital osteosarcoma may reach a considerable size before an orbital presentation evolves. CT scan is important in such cases to outline the full extent of the neoplasm to aid future eradication of the lesion.

On MRI, the tumor appears heterogeneous and demonstrates intermediate signal on T_1-weighted images and mixed signal intensity (hyperintense and hypointense zones) on T_2-weighted images. Osteosarcomas demonstrate heterogeneous enhancement on gadolinium-enhanced T_1-weighted scans (Wenig et al., 1998).

Pathology

In the fifth edition of his text, Unni (1996) reminded us that foci of osteoid must be present in any given section of an osseous neoplasm to warrant a diagnosis of osteosarcoma, although the dominant cellular component of the sarcomatous matrix is of either fibromatous or cartilaginous origin. Osteoid is the unmineralized precursor

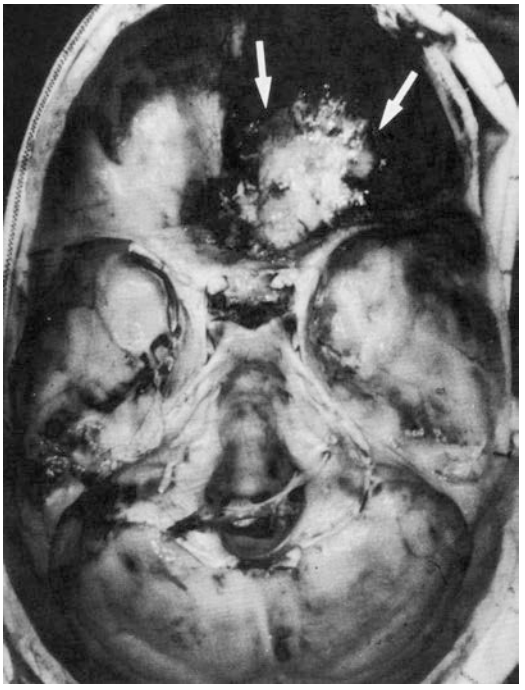

Figure 6.18 Transverse section of skull at autopsy of a 16-year-old girl shows extension of osteosarcoma into the right orbital roof (*arrows*) 1 year after its identification in the right nasal cavity. Note the finger-like projections of tumor along the anterolateral border that radiate from the central mass. The extent of the lesion into the maxillary sinus, right pterygoid fossa, sphenoid bone, and orbit emphasizes the difficulties of surgical removal.

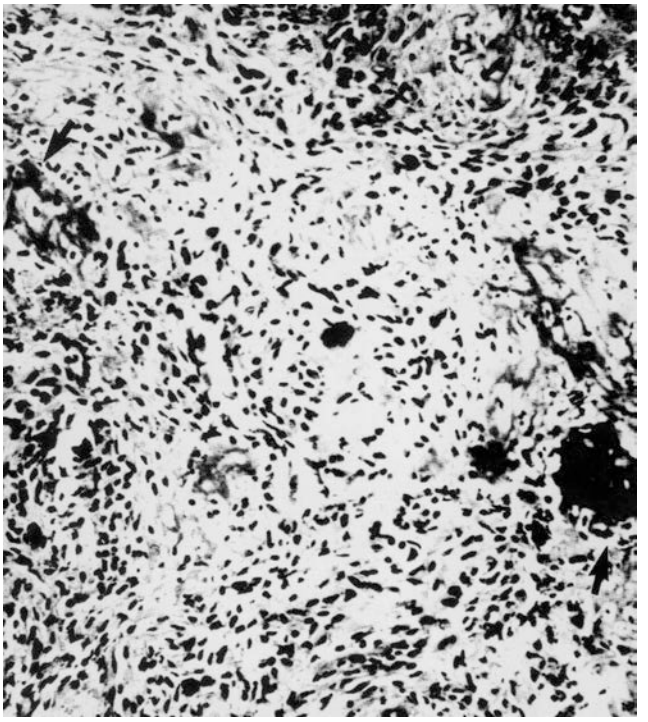

Figure 6.19 Osteosarcoma. Islands of osteoid (*arrows*) in a stroma of spindled cells with hyperchromatic nuclei (original magnification ×250).

of bone. It is a hyalin-like material with irregular contours, surrounded by a rim of osteoblasts, and is eosinophilic (see Fig. 6.19). Osteosarcomas include a sarcomatous stroma intimately admixed with and giving rise to osteoid. Stromal cells show variable anaplasia and are spindled to polygonal in shape. The nuclei are hyperchromatic. Necrosis, invasive growth, and mitotic activity are commonly present.

Management

Presumed osteosarcoma involving orbital bone should be referred to an oncologist, who initiates chemotherapy before surgery, after appropriate evaluation for metastatic disease. The standard drugs involved are doxorubicin, methotrexate, and cisplatin. Each drug is successively administered intravenously at appropriate intervals in the early stages of the treatment cycle. After 9 to 12 weeks, the patient is reevaluated with MRI, CT scan, and bone scans. If these images do not show metastases, surgical eradication can proceed. The pathologist predicts a prognosis based on the extent and degree of tumor necrosis.

Machak et al. (2003) reported 31 patients with non-metastatic osteosarcoma of the extremities after induction chemotherapy who refused surgery and underwent standard, fractionated external beam radiotherapy for local control. The median radiation dose to the limb was 60 Gy (range, 40 to 68 Gy). In an editorial comment, Anderson (2003), a Mayo Clinic oncologist, thought that external beam radiotherapy in combination with chemotherapy may provide "better than expected" local and systemic control.

Ameloblastoma

This epithelial neoplasm arises from primitive, embryonic dental rests in the mandible or maxilla but is not associated with any formed element of mature tooth.

Incidence

Approximately 80% of the tumors arise in the posterior portion of the mandible with age at onset between 33 and 39 years (Hayashi et al., 1997; Mathew et al., 1997) and age range from childhood to ninth decade (Stamatakos et al., 1995). The sex ratio is equal.

The remaining 15% to 20% of cases occur in the maxilla. Nastri et al. (1995), on the basis of their statistical study of 13 cases, found that age at the time of diagnosis ranged from 24 to 70 years, with a mean age of 50 years. This is the basis for their belief that ameloblastomas affect a slightly older age-group than mandibular tumors. In this group were nine women and four men, a female-to-male ratio of 2.25:1.

The orbital ameloblastoma has its origin in the maxilla. Cases with secondary orbital extension described in the literature were a 73-year-old woman (Kyriazis et al., 1971);

an 81-year-old man (Shaw and Katsikas, 1973); a 20-year-old woman (Daramola et al., 1980); a 63-year-old man (Komisar, 1984); a 72-year-old man (Weiss et al., 1985); and a 53-year-old man, a 15-year-old boy, and a 37-year-old woman (Bredenkamp et al., 1989). To these eight cases we can add three men aged 21, 58, and 65 years. In the 11 cases, the men predominated by a ratio of 9:2, and the age range was wide (15 to 81 years). Two of the cases reported by Nastri et al. (1995) had orbital involvement but their age and sex were not stated.

Clinical Features

Ameloblastoma is locally invasive and potentially malignant. Its origin is an upper dental alveolus, and it presents as a painless intraoral swelling. Initially, the growth of tumor is so slow, insidious, and painless that the neoplasm is overlooked until the patient seeks care because of swelling of the upper gingiva or a loose tooth. If the tumor is not completely resected or remains unrecognized at this time, it then spreads to the ipsilateral maxillary antrum. After filling the antral cavity, it erodes one of the walls of the antrum and may extend anteriorly into the cheek, laterally into the infratemporal fossa, medially into the nasal cavity or ethmoid sinus, superiorly into the anterior orbit, or posteriorly into the pterygoid fossa and posterior orbit. This odyssey may take many years to complete and is usually interrupted by many surgical forays to stem the advance of tumor.

Orbital extension is manifested by slight proptosis or displacement of the eye. If the patient is still pain free and there has been no prior oral or maxillary surgery, the orbital extension produces only a mass effect on the orbital contents. However, if pain is present, it is likely the neoplasm has undergone a malignant dedifferentiation and is infiltrating orbital nerves. If there has been some prior resection of tumor, orbital invasion is a sign of recurrent tumor.

Lastly, we note the case described by Hayashi et al. (1997), wherein a 63-year-old woman with an ameloblastoma of the mandible of some 27 years' duration had metastasis of the tumor to the orbital space. Over the 27-year period, the tumor had recurred three times, eventually undergoing malignant transformation. On surgical exploration, the metastatic focus was distinctly separate from the primary locus. There was no other evidence of systemic metastasis.

Imaging Aspects

By the time an ophthalmologist sees a patient with orbital extension, the diagnosis has probably been established. The tumor reaches the orbit by eroding the back wall of the sinus in addition to the orbital plate of the maxilla. CT scans are essential to define the extent of bony destruction at the skull base and to plan a likely surgical approach to the lesion.

Histopathology

The predominant feature is proliferation of epithelial cells with various amounts of surrounding fibrous tissue. Some lesions are quite cellular and have little fibrous connective tissue, whereas others have widely separated epithelial islands with fibrous connective tissue. The epithelial cells usually have a follicular pattern in which the epithelial cells are arranged in a palisading manner at the periphery with loose tissue in the center. The cells at the periphery are columnar, suggestive of basal cells. The latter do not show extensive atypia. Also, a plexiform pattern is present when epithelial cells tend to form anastomosing chords. Some specimens show a mixture of follicular and plexiform arrangements. Occasionally, a cellular variant resembles a spindle cell sarcoma (see Fig. 6.20). Squamous metaplasia may also be present and suggests squamous

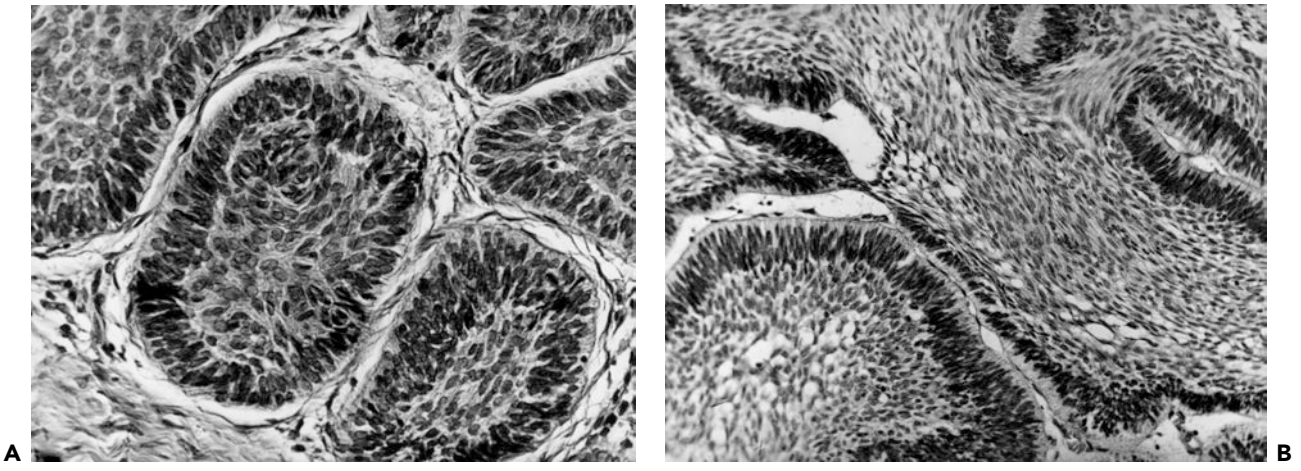

Figure 6.20 **A:** Islands of cells show palisading of columnar ameloblasts (original magnification ×325). **B:** Specimen shows spindling pattern of core cells (original magnification ×200). (From Unni KK. *Dahlin's bone tumors: General aspects and data on 11,087 cases*, 5th ed. Chapter 28, Philadelphia, PA: Lippincott-Raven; 1996, with permission.)

cell carcinoma, but the cells do not show cytologic atypia (Unni, 1996). However, there does not seem to be any correlation between histologic type of ameloblastoma and its subsequent behavior.

Management

Once the tumor has reached the orbital environs and skull base, its most common location, nothing short of a radical, *en bloc* ostectomy can effect a cure. Nastri et al. (1995) considered a temporal surgical approach best suited for radical excision in this area. Postoperative radiotherapy and chemotherapy may be used for recurrent tumor or palliative care.

Prognosis

Once the tumor has extended beyond its origin in the alveolar process of the maxilla, the clinical course may be so deceptively asymptomatic that a patient whose initial tumor was resected may be totally unaware of its insidious advance. One of the patients of Bredenkamp et al. (1989) lived for 15 years before succumbing to the tumor. One of our patients, aged 75 years, died with a huge recurrent tumor along the base of the skull. His neoplasm had been subject to four surgical procedures over a 17-year period.

Death from ameloblastoma 8 years after initial surgery was the fate of another patient of Bredenkamp et al. (1989) and the case described by Kyriazis et al. (1971). The latter patient had lost vision in both eyes before death.

Ewing Sarcoma

This is a malignant tumor of bone long a subject of controversy among pathologists as to its cell of origin. At present, it is considered to be of neuroectodermal origin (Unni, 1996).

Incidence

The neoplasm occurs most commonly in the medullary centers of the long bones of the extremities or the pelvic girdle. Primary tumors of the skull occur in approximately 2% of cases (Wilson et al., 2001), but there are no incidence calculations pertaining to primary tumors of the orbit. Most reported cases of orbital involvement are caused by metastasis from distant sites.

Lam et al. (1999) tabulated nine cases of Ewing sarcoma primary in the orbit that were reported in the literature since the neoplasm was first described. However, we believe two cases in this list are secondary neoplasms of the orbit from primary tumors of the maxillary sinus. The remaining seven cases are summarized in Table 6.3. Cases 8 through 11 are additional cases we culled from the literature. The age range of the 11 patients was 2 to 61 years (median, 10 years; mean, 17.2 years). There were seven males and four females. The patient described by Lam et al. (1999) was the only one with a bilateral tumor. Dutton et al. (2000) also described a 7-year-old boy who had metastasis to the orbit from a primary in the clavicle that had been excised 3 years previously. The cases in Table 6.3 are a mixture of soft tissues, orbital space-occupying sarcomas, and sarcomas of orbital bone.

TABLE 6.3
PRIMARY EWING SARCOMA OF THE ORBIT

Authors	Sex	Age, y
Harbert and Tabor (1950)	M	19
Yamada and Takahashi (1957)	M	61
Alvarez-Berdecia et al. (1979)	M	6
Howard and Lund (1985)	M	14
Woodruff et al. (1988)	M	6
Tewari et al. (1993)	F	10
Kuzeyli et al. (1997)	F	10
Lam et al. (1999)	M	2
Choi et al. (1999)	F	43
Dutton et al. (2000)	M	2
Wilson et al. (2001)	F	17

Clinical Features

The presentation of a tumor with orbital involvement is usually the mass effect of a lesion encroaching on the orbital space. If the tumor is located in a more forward part of the orbit, one or more of the following symptoms or signs are present: Proptosis, displacement of the eye, limitation of ocular motility, or diplopia. A mass may or may not be palpable, and some degree of headache may be present. If the mass is positioned in the extreme infero-postero-medial orbit, the presentation is associated with compression of the optic nerve, resulting in a central scotoma, an afferent pupillary defect, and, perhaps, edema of the optic nerve disk.

Pain, so often noted with tumors of skeletal bone, may be absent in orbital involvement. Pain is caused by the tumor inciting an inflammatory response of the patient's immune system to the destruction of bone. Among the patients in Table 6.3, several were pain free. Case 7, in particular, with an extensive, bilateral, soft tissue Ewing sarcoma, was pain free.

Imaging Aspects

CT scan shows an enhancing, hyperdense, mottled, "moth-eaten" nonhomogeneous soft tissue component associated with erosion, destruction, and calcification of bone. It is difficult to differentiate the CT display of Ewing sarcoma of bone from hemangioendothelioma of bone and angiosarcoma of bone, described later in this chapter. Figure 6.21 shows the soft tissue sarcoma.

Pathology

Grossly, the soft tissue component is gray, moist, glistening, and sometimes translucent with an almost liquid

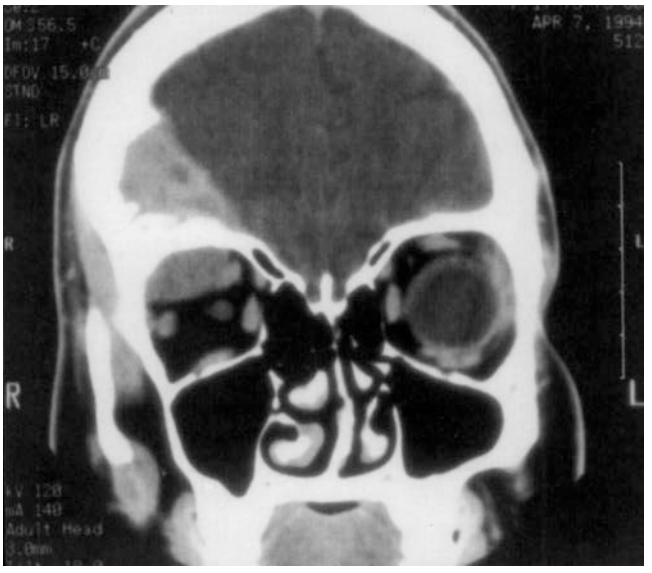

Figure 6.21 Computed tomography scan showing a mass in the region of the right orbital roof with extension into the anterior cranial fossa, temporal fossa, and retrobulbar orbit. (From Wilson DJ, Dailey RA, Griffeth MT, et al. Primary Ewing sarcoma of the orbit. *Ophthal Plast Reconstr Surg*. 2001;17:300–303, with permission.)

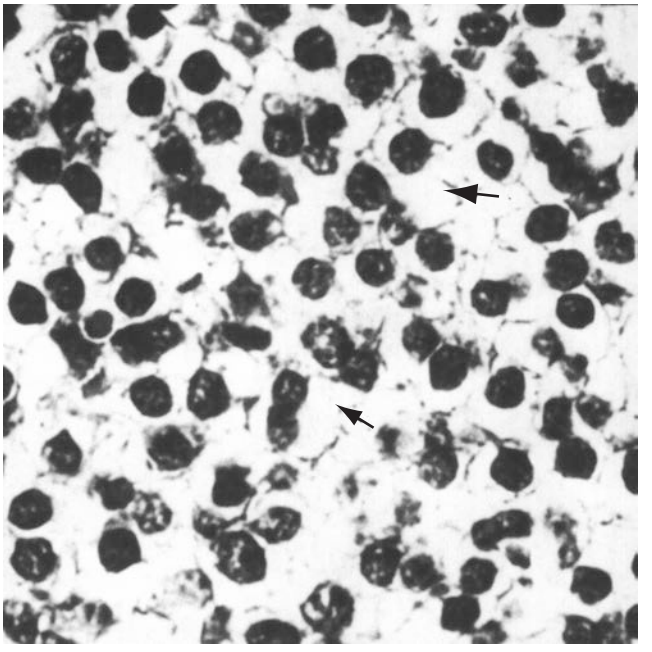

Figure 6.22 These tumor cells are strikingly uniform in a sea of almost featureless clear cytoplasm caused by a high glycogen content, characteristic of this neoplasm. Note the almost indistinct cell boundaries of reticulum (*arrows*) (hematoxylin and eosin, original magnification ×400). (From Nash AD. *Soft tissue sarcomas: Histologic diagnosis. Biopsy Interpretation Series*. New York: Raven Press; 1989, with permission.)

consistency. Histopathologically, the tumor is very cellular, with few intercellular strands of fibrous tissue that tend to compartmentalize the cellular aggregates. The cells are regular in contour with round to oval nuclei. The outlines of the cells are indistinct (see Fig. 6.22).

An immunoperoxidase stain, HBA-71 or MAB0-13, helps to differentiate Ewing tumor from malignant lymphoma and metastatic carcinoma but is not specific. This stain may also be positive for some examples of embryonal rhabdomyosarcoma and lymphoblastic lymphoma. Ewing sarcoma stains negative for neuron-specific enolase, S-100, myoglobin, and desmin (see Fig. 6.23).

Management

Only few tumors in this text—lymphoma is one—have undergone a positive change in management, since our 1994 edition, as has Ewing sarcoma. The refinement of chemotherapy is responsible for the advance in therapy of this sarcoma. Chemotherapy, once used only as an adjuvant to surgery and radiotherapy, may now be the initial therapy in selected cases. Such was the case of the 2-year-old boy of Lam et al. (1999) who was given a 42-week course of chemotherapy for sarcoma of an orbital bone, according to the recommended protocol of the European Intergroup Cooperative Ewing Sarcoma study, followed by radiotherapy (a total of 45 Gy over a 5-week period). The patient was in remission 30 months later without evidence of residual tumor, radiation-induced cataract, keratitis, or retinopathy. No surgery was attempted after the initial biopsy.

Oncologists consider Ewing sarcoma a systemic disease. For that reason, they recommend chemotherapy rather than local excision as the initial treatment once the diagnosis is made by biopsy and histopathologic study. A regimen consisting of vincristine, doxorubicin, and cyclophosphamide alternating with etoposide and ifosfamide is used at Mayo Clinic. A cycle of these drugs is given at 3-week intervals. At about 12 weeks (i.e., 4 cycles), surgery is performed. If

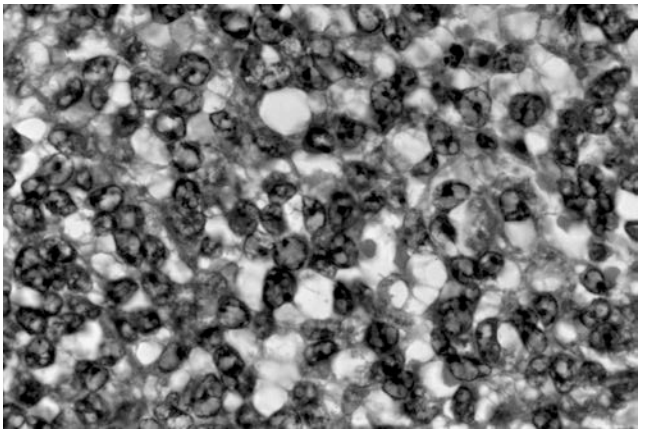

Figure 6.23 Ewing sarcoma showing uniform round nuclei and indistinct cytoplasmic borders (hematoxylin and eosin, original magnification ×60).

surgery can be performed with adequate margins (1 to 2 cm of normal tissue), radiotherapy is not needed. Additional chemotherapy is given after surgery. However, if the tumor is not resectable, radiotherapy is administered to a dose of about 50 Gy. Postoperatively, additional cycles are given at 3-week intervals over a 30-week period, for a total of 42 weeks of chemotherapy.

Prognosis

There are no sizable case series of Ewing sarcoma of the orbit, which have been treated with a chemotherapy regime, similar to the one in the preceding text, to provide an estimate of long-term prognosis. General surgeons, orthopedists, and pediatricians who deal with Ewing sarcoma of skeletal bone agree that chemotherapy has improved prognosis. In most of their reports, chemotherapy has been used as an adjuvant to surgery or in some combination of chemotherapy and radiotherapy. Forthcoming reports, where chemotherapy is used as the initial and principal therapy, may show an even better prognosis.

CARTILAGINOUS TUMORS

Chondroma

Theoretically, a chondroma should not occur in membranous bones such as those of the orbit. Only the body and lesser wing of the sphenoid bone have any notable derivation from cartilaginous precursors, and the trochlea is the only purely cartilaginous structure. Among the orbital chondromas reported in the literature, the origin of the chondroma is not always clear-cut. Therefore, the true incidence of orbital chondroma is not known. We believe the lesion is quite rare. We have seen only 1 case in our 50-year survey (Table 3.3).

This was a 59-year-old man who first observed a lump under the lateral aspect of his right eyebrow 10 years before presentation. Seven years later, several lumps, incompletely removed elsewhere, were diagnosed as fibroma. When first seen at Mayo Clinic, there was downward displacement of the right eye with proptosis of 17 mm (see Fig. 6.24). The superior portion of the eyeball was still covered by a stretched upper eyelid, but the inferior ocular bulb no longer could be protected by an overstretched, lax lower eyelid. A hard, encapsulated, lobulated tumor measuring 2.5 cm was completely removed (see Fig. 6.25). The tumor arose either from the periorbita on the underside of the orbital roof or the floor of the frontal sinus. A diagnosis of chondroma was made. Chondromas are usually asymptomatic except for either a palpable or a visual mass.

Two orbital chondromas have been reported in the literature in the past decade (Faber et al., 1992; Pasternak et al., 1996). The case described by Faber et al. (1992) was a 19-year-old man who had a cartilaginous mass adjacent to the trochlea of one orbit. The mass was removed and proved to be a chondroma. The chondroma described by Pasternak et al. (1996) was attached to the medial orbital wall of a 25-year-old woman.

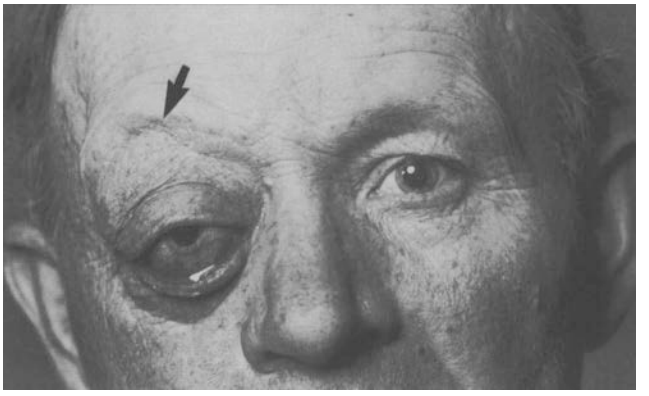

Figure 6.24 Chondroma in a 59-year-old man with recurrent tumor in the superotemporal quadrant of his right orbit. A depression (*arrow*) along the superior orbital ridge indicates the site of previous surgery. A 2.5-cm encapsulated mass was removed through transfrontal craniotomy.

Imaging Aspects

Imaging, usually CT scan, shows a smooth, well-marginated, slightly radiolucent nodular mass containing

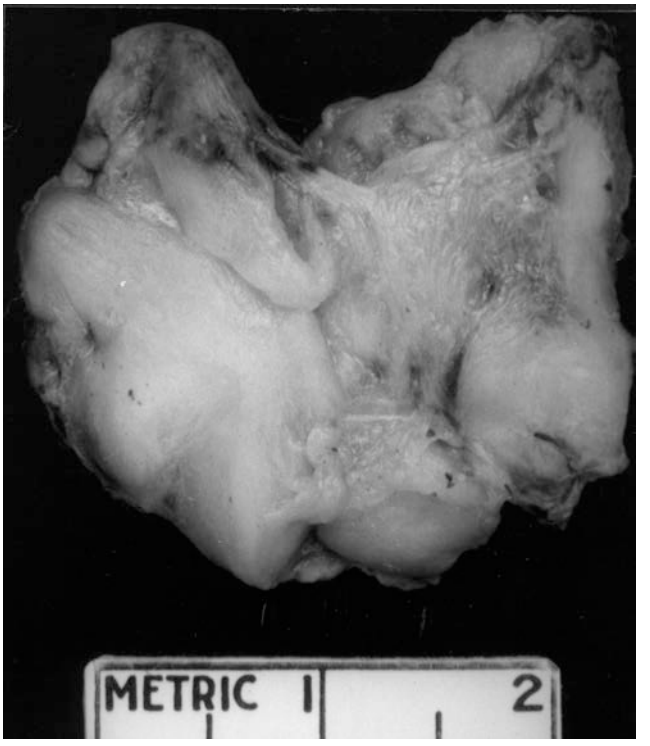

Figure 6.25 The knobby chondroma covered with fibrous tissue removed from the patient pictured in Figure 6.24.

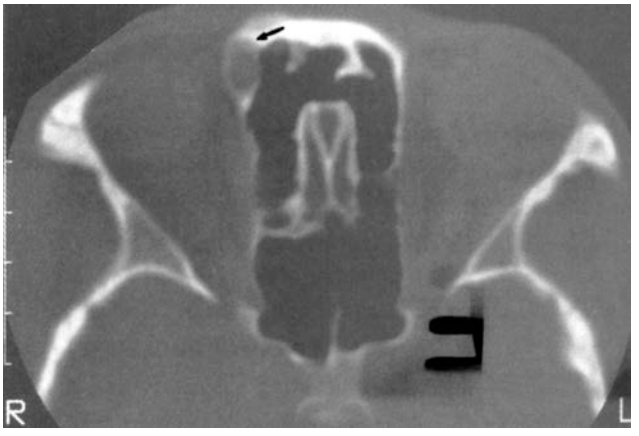

Figure 6.26 Computed tomography scan of a chondroma shows an oval, irregularly calcified, slightly radiolucent lesion within the bone in the right anteromedial orbital wall (*arrow*). (From Pasternak S, O'Connell JX, Verchere C, et al. Enchondroma of the orbit. *Am J Ophthalmol*. 1996;122:444–445, with permission.)

some flecks of calcium proportionate to the size and duration of the tumor. If the lesion is on the surface of the orbital plate, there may be some sclerosis of the underlying bone (see Fig. 6.26).

Pathology

Chondroma is a benign tumor composed of mature hyaline cartilage. The content of hyaline of an enchondroma is slightly less mature. The chondroma has a bluish tinge and a semilucent density. Some fibrous tissue probably is attached to the tumor, serving a supportive function. Each small single chondrocyte has its own lacunae, and the nucleus is round and regular (see Fig. 6.27). Calcification may be seen as fine, purple-tinged granular precipitates in a blue-staining matrix.

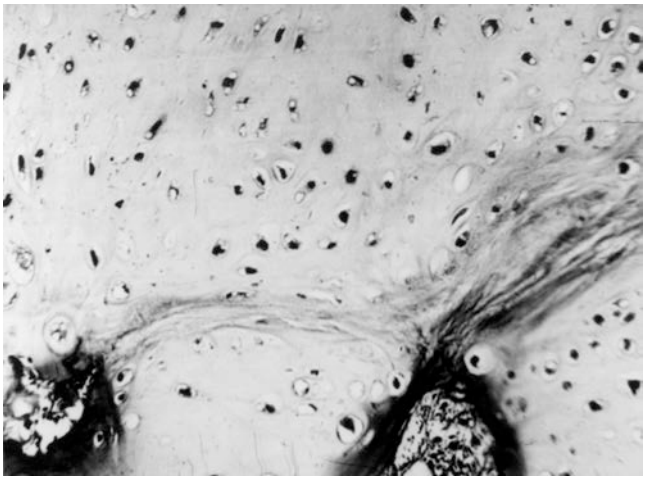

Figure 6.27 Uniform, mature chondrocytes in a matrix of hyaline cartilage (original magnification ×170).

Management

An orbital chondroma usually can be removed intact by blunt dissection because of its firm consistency. If it is more securely attached to an orbital bone, the tumor is easily detached from its base with a hammer and chisel.

Chondrosarcoma

A chondrosarcoma primary in the orbit, not of the mesenchymal type, is rare. Lacking are meaningful data from a sizable series of consecutive orbital chondrosarcomas from a single source. The one positive fact is that primary orbital chondrosarcoma of bone is much less frequent than those encroaching on the orbit from the paranasal sinuses and nasal cavity. The latter are also considered to be rare in the skull area when compared with the frequency of chondrosarcoma in skeletal bone.

We have accessioned eight chondrosarcomas in our 50-year survey (Table 3.3). Two were primary in the orbit. There were six secondary tumors, but none was metastatic to the orbit. The sex distribution of chondrosarcomas was five men and three women. The age distribution was 39 to 64 years, with an average age of 56 years and a median of 63 years. We have not found any computation in the literature of the incidence of primary orbital chondrosarcomas.

Clinical Features

The presentation of a primary orbital chondrosarcoma includes some combination of proptosis, off-axis displacement of the eye, diplopia, some degree of visual impairment (with or without pain), and a palpable mass. The symptoms of the encroachment of the orbit by a secondary tumor are the same as in the preceding text, in addition to preceding nasal obstruction, nasal drainage, epistaxis, or facial paresthesias.

Only a few cases of orbital involvement have been found in the literature. In one of these cases, the origin of the chondrosarcoma was an orbital bone (Potts et al., 1992). The patient was a 33-year-old man who presented with 7 mm of proptosis and inferolateral displacement of right eye of 2 years' duration. CT scan showed a soft tissue mass of uniform translucency in the superomedial orbit. The medial orbital wall was bowed medially by the adjacent mass. An anterior ethmoidectomy revealed an intact orbital periorbita, and a bilobed purple friable tumor was resected. The mass did not have a defined capsule. Histologic examination showed a low-grade chondrosarcoma in one lobe of the tumor; the other lobe was a high-grade malignant fibrous histiocytoma. In short, the tumor was a dedifferentiated chondrosarcoma.

Additional reports provide examples of orbital encroachment by chondrosarcomas of the nose and paranasal sinuses: An 8-year-old boy (Drucker et al., 1990); a 64-year-old woman with Paget disease (Mooy et al., 1999); and a 13-year-old boy (Jakacki and Knisely, 1990).

Imaging Aspects

Chondosarcomas of the orbit, both primary and secondary types, are lytic lesions. The sarcomas, purely of orbital origin, are discovered earlier in their course than secondary sarcomas and are usually the smaller of the two types in size and extent. CT scan is adequate for the imaging of orbital sarcomas. The smaller orbital tumors have a smooth, well-defined border with or without a sclerotic rim. They are usually attached to the orbital surface of the thin, underlying orbital plate and may resemble a soft tissue tumor on CT scan. The lesion may show variable contrast enhancement. The radiolucent matrix often contains mottled, punctate, or irregular densities representing calcification, which is quite typical.

Erosion of the orbital plate occurs around the base of the tumor. If intracranial extension is suspected, MRI is useful. The tumor appears hyperintense on a T_1-weighted sequence and moderately to markedly hyperintense on a T_2-weighted sequence. A displacement of large intracranial vessels by tumor can also be visualized by MRI.

Pathology

Bone pathologists emphasize that a diagnosis of chondrosarcoma should be reserved for those lesions predominantly composed of lobules of hyaline cartilage containing malignant chondrocytes, with allowance for interlobular strands of fibrous stroma, areas of myxoid change, and bands of fibrous tissue mixed with a few osseous trabeculae along the surface interface with normal bone. The latter may be particularly noted in recurrent lesions (see Fig. 6.28). At higher magnification, the cartilaginous lobules show increased cellularity, pleomorphism, and hyperchromicity of the chondrocytes; mitosis; crowding and disorderly distribution of lacunae; and binucleate cells (see Fig. 6.29). Islands of calcification are not common.

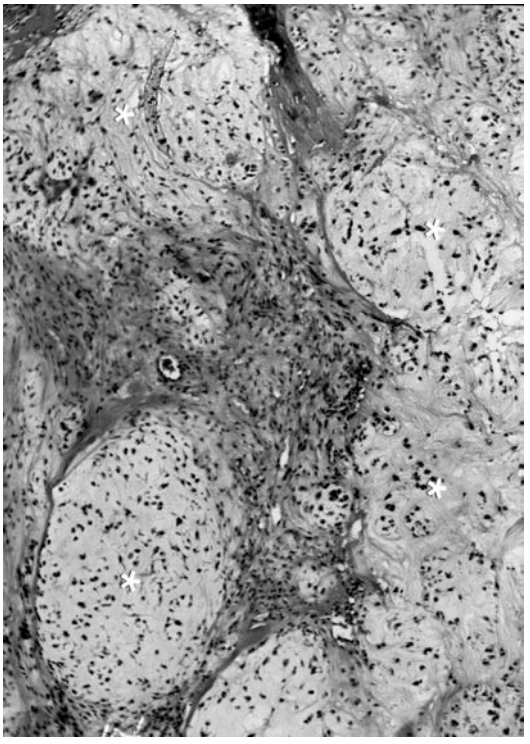

Figure 6.28 In this chondrosarcoma specimen, lobules of hyaline cartilage (*asterisks*) surround a zone of vascular fibromyxoid stroma. The cartilage shows hypercellularity and a disorderly arrangement of pleomorphic chondrocytes (original magnification ×120).

Management

Surgical eradication is the mainstay of treatment for chondrosarcoma at any anatomic site. Even so, the tumor is generally resistant to other forms of treatment, and recurrence is common (Stapleton et al., 1993). For sarcomas that, by imaging methods, seem confined primarily to orbital bone and orbital space, we believe the surgery should be performed by surgeons from two different surgical fields. Therefore, a chondrosarcoma of the medial wall of the orbit requires the involvement of an ophthalmologist and a rhinologist. The surgical approach may be a medial orbitotomy or an external ethmoidotomy. The rhinologist visually determines the presence or absence of any breach in the thin orbital plate that is not seen on a CT scan. If there is any sign of extraorbital extension, further removal of tumor can be done at that time, thereby eliminating a second-stage surgical procedure.

Likewise, if the chondrosarcoma is on the orbital face of the sphenoid bone, a neurosurgeon could be the watchman on the surgical team for intracranial spread. These tumors can be approached through either a frontal craniotomy or a coronal orbitocraniotomy.

In a similar pattern, the ophthalmologist enlists the surgical skills of a maxillofacial surgeon for chondrosarcomas involving either the lateral wall or the floor of the orbit.

Although a primary orbital chondrosarcoma may seemingly be completely removed, a recurrence may appear some months later. If so, further bone can be removed. However, with secondary orbital sarcomas, a more extensive removal of bone probably occurred at the initial surgery and remaining bone may have supported a vital anatomic area. Here radiotherapy may be used except it has little effect on grade 1 chondrosarcomas.

Prognosis

In our experience, the prognosis for patients with orbital involvement by chondrosarcoma is poor. Six of our eight patients died from extension of their tumor. One patient, a 63-year-old woman, was alive without residual or recurrent tumor 2 years after initial surgery, but this follow-up was too short to be of importance, considering the slow growth of chondrosarcoma.

Another survivor was a 59-year-old woman who had a grade 1 chondrosarcoma arising from the surface of the sphenoid sinus at its juncture with the nasal septum in 1959. Each sphenoid sinus was exenterated, the entire

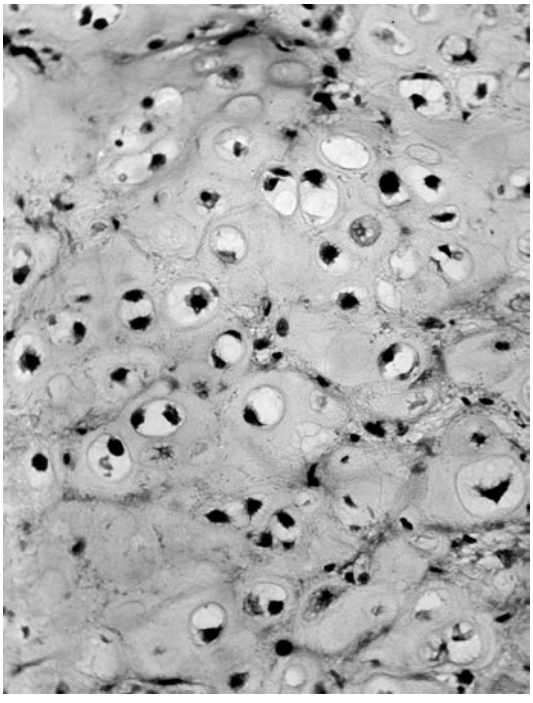

Figure 6.29 Malignant, dark-staining, pleomorphic, binucleate chondrocytes are dispersed in a matrix of hyaline cartilage of this chondrosarcoma (original magnification ×185).

nasal septum was removed, and the nasoethmoidal and nasoantral sinus walls on the left side were resected. The left eye, with its 20/25 vision, was not sacrificed.

The first intraorbital recurrence was noted in 1970. A dome-shaped bony tumor occupying the inferomedial orbital floor on the left side was completely removed, but the functional left eye remained intact.

A second recurrence in the orbital soft tissues posterior to the left inner canthus was noted in 1979. Another local resection of tumor was performed. The patient died of congestive heart failure in 1984. The vision in the left eye was reduced to hand movements, chiefly due to late consequences of prior surgery. At the time of death, there was no objective evidence of further local recurrence or metastasis of tumor.

Mesenchymal Chondrosarcoma

This malignant neoplasm was first described by Lightenstein and Bernstein in 1959. Not a single case of pathologically proved mesenchymal chondrosarcoma primary in the orbit has been recorded in our 50-year review of orbital tumors. Therefore, our discussion of this tumor must be based on the collection of cases reported by others.

Incidence

In the second edition of *Orbital Tumors* (Henderson, 1980), we noted the age and sex of six cases of orbital mesenchymal chondrosarcoma reported between 1966 and 1974. Subsequently, reports of orbital involvement by this neoplasm gradually increased. By the decade of the 1990s, numerous cases of orbital involvement emerged.

Jacobs et al. (1994) reported three new cases of extraskeletal orbital involvement, and they reviewed seven previously reported cases. One of their cases was a 10-year-old girl. This seems to be the youngest case on record. In 1999, two larger series of cases were reported. Khouja et al. (1999) found 16 previously published orbital cases, and Koeller (1999) said that at least 25 cases of orbital mesenchymal chondrosarcoma have been reported in the literature. Our review of the literature supports the findings of Koeller (1999). In 2001, an additional case was reported by Kashyap et al. All authors who have published cases of orbital involvement since 1966 have stated the frequency as ''rare,'' ''extremely rare,'' and ''unusual.'' However, these statements belie the present frequency of orbital mesenchymal chondrosarcoma. If one or two cases continue to be reported each year, this tumor may rival aneurysmal bone cyst and vascular tumor of bone as the most frequent osseous and cartilaginous tumor of the orbit.

Most of these tumors (66%) occur in skeletal locations. The remaining third are located in extraskeletal sites; the orbit is the third most common location (Nakashima et al., 1986; Bagchi et al., 1993). Most orbital tumors occur in late adolescence and young adulthood (between the ages of 18 and 38 years). The youngest case in the literature is a 10-year-old girl reported by Jacobs et al. (1994). Two patients older than 38 years also are known, a 46-year-old and an 84-year-old (Shimo-Oku et al., 1980). The orbital lesions are seen in females by an almost 6:1 ratio.

Clinical Features

In most primary orbital mesenchymal chondrosarcomas, the initial presenting sign is proptosis with some visual impairment. This is due to the frequent location of the tumor in the retrobulbar, intracranial space. If visual impairment is not already present, it soon follows proptosis because of optic nerve compression. There are a few exceptions. One of these is a case described by Koeller (1999), in which the mass was posterior to the lacrimal gland, causing headache and increased lacrimation. As the tumor enlarges, authors have attributed all other secondary known signs and symptoms of orbital tumors to these neoplasms except a palpable mass. One exception (Kashyap et al., 2001) however, is a 45-year-old man with proptosis of 1 year's duration who presented with a hard, palpable mass bulging out of the inferior fornix. Metastasis of the orbital lesion is rare.

Imaging Aspects

The most common location of an orbital mesenchymal chondrosarcoma is the posterior retrobulbar space directly behind the eye. The tumor arises from the orbital reticulum above, below, or to one side of the optic nerve. On CT scan, the tumor's image is a rounded or globular mass roughly

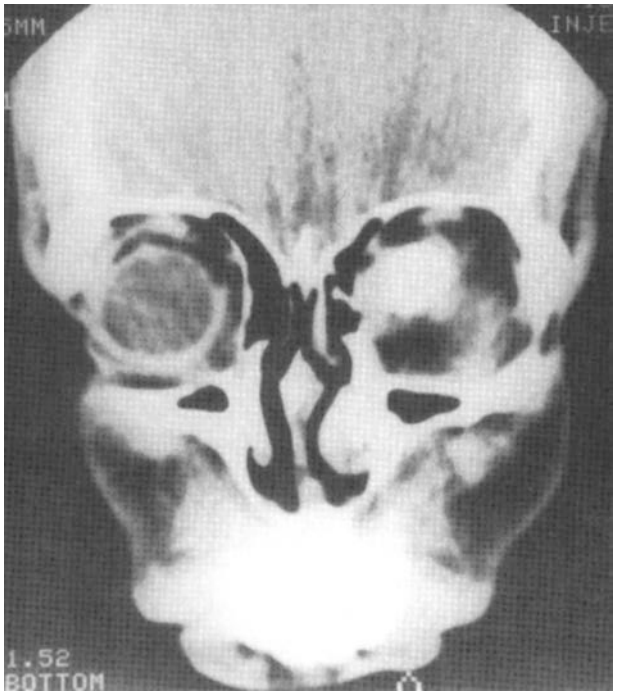

Figure 6.30 Coronal computed tomography scan of a mesenchymal chondrosarcoma showing a well-defined, round, calcified, intracranial mass occupying the center of the orbital space of the right orbit. (From Khouja N, Ben Amor S, Jemel H, et al. Mesenchymal extraskeletal chondrosarcoma of the orbit: Report of a case and review of the literature. *Surg Neurol*. 1999;52:50–53, with permission.)

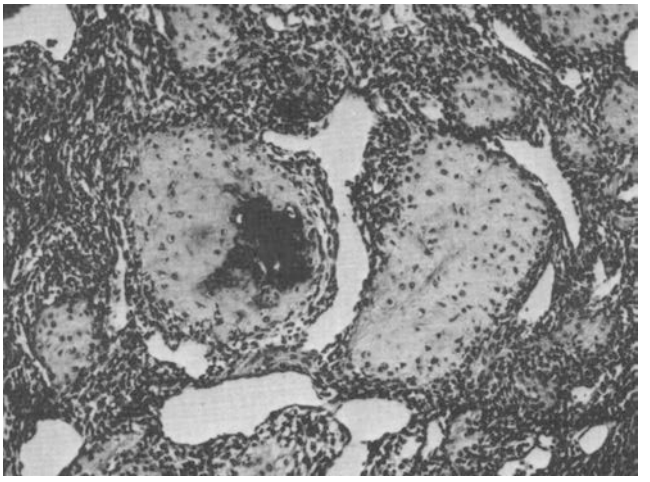

Figure 6.31 Variable-sized lobules of well-differentiated cartilage in this mesenchymal chondrosarcoma are interspersed in a stroma of small, dark-staining, undifferentiated mesenchymal cells. The chondroid lobule (left center) contains a dark mass of calcium (original magnification ×115). (From Guccion JG, Font RL, Enzinger FM, et al. Extraskeletal mesenchymal chondrosarcoma. *Arch Pathol*. 1973;95:336–340, with permission.)

centered in the orbital space. The mass is well marginated with an attenuation factor similar to extraocular muscle (see Fig. 6.30). On dynamic enhanced CT scan study, the tumor has less rapid enhancement than nearby vascular structures. As the tumor enlarges, it pushes the optic nerve from the intraorbital position peripherally toward the surrounding orbital bony plate. However, there is no erosion of bone or invasion of the optic nerve sheath. Likewise, the adjoining extraocular muscle forms a groove or wraps around the expanding mass but remains intact. Calcification varies from mere specks to irregularly positioned clumps and full mineralization of the mass. On MRI, the T_1-weighted image is similar to gray matter, but hypointense to gray matter on T_2-weighted imaging. If the tumor is highly vascular, it produces an early blush on angiographic studies (Koeller, 1999).

Pathology

When Lightenstein and Bernstein (1959) were reclassifying some chondroid tumors pathologically, they noted two specimens that were unusual because of a content of primitive, undifferentiated, pluripotential mesenchymal cells intermixed with distinct islands of mature cartilage in skeletal bone. These tumors do not arise from preformed cartilage as do other cartilaginous tumors. They are responsible for the term *mesenchymal chondrosarcoma*.

In their favorite locations, skeletal bones, these tumors arise from the soft tissue component of the bone. As the tumor increases in size, it becomes lytic to the encompassing bone. However, Dowling, (1964), reported the tumor lodged in an extraskeletal site, the temporalis muscle. The primary orbital sarcomas belong to this soft tissue mesenchymal type of chondrosarcoma.

Grossly, the orbital lesion is gray to pink, well defined, and either round or slightly lobulated. Most lack a capsule but some are well encapsulated. Still others may have a pseudocapsule of fibrous tissue. Depending on the amount of chondroid component, the mass may be quite hard (calcification) or soft in texture. The degree of calcification also varies. The islands of cartilage may vary both in size and number. The mesenchymal cells are small, round, oval, or spindle-shaped with dark-staining nuclei (see Fig. 6.31). A less-common histologic type consists of delicate vascular channels among the closely packed mesenchymal cells that have a hemangiopericytoma-like pattern (see Fig. 6.32).

With immunohistochemical analysis, the well-differentiated chondrocytes of the neoplasm react positively with S-100 protein (Nakamura et al., 1983). And the small round and oval cells react positively with CD99, a cell surface glycoprotein (Granter et al., 1996). On immunophenotypic analysis, the tumor cells are negative for neurofilaments, neuron-specific enolase, glial fibrillary acidic protein, and desmin (Jacobs et al., 1994).

Management

A decade or so after the initial description of the tumor, ophthalmologists eradicated the lesion by exenteration. The result was usually good. Later, with refinements in

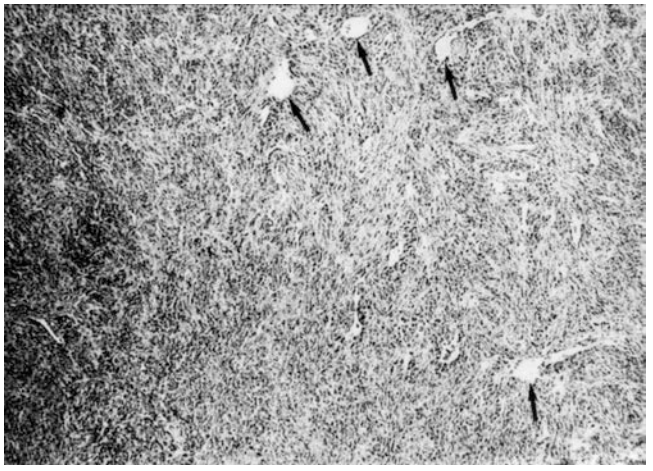

Figure 6.32 Vascular channels (*arrows*) surrounded by mesenchymal cells give a hemangiopericytoma-like appearance to this mesenchymal chondrosarcoma (trichrome, original magnification ×75). (From Jacobs JL, Merriam JC, Chadburn A, et al. Mesenchymal chondrosarcoma of the orbit: Report of three new cases and review of the literature. *Cancer*. 1994;73:399–405, with permission.)

surgical techniques and the wish to preserve the eye, other surgical approaches evolved.

According to Jacobs et al. (1994), in October 1974, they performed an *in toto* removal of the tumor in the posterior orbit by blunt dissection. Three years later, the patient (their case 1) was alive and well without proptosis and with 20/20 vision. They used a lateral orbitotomy approach.

The same approach was used for their case 2 in September 1978 (Jacobs et al., 1994). The tumor was removed using the cryoprobe and blunt dissection. The patient was alive and well without clinical evidence of recurrence in July 1993.

The results of the surgery on their case 3 were quite different (Jacobs et al., 1994). In November 1988, a needle biopsy of a posterior orbital lesion was performed on a pseudoencapsulated mesenchymal chondrosarcoma. Arterial bleeding was so profuse that the surgery was terminated. A week later, an anterior craniotomy with unroofing of the affected orbit was performed. It was not possible to define a surgical plane in the orbital apex, necessitating incision of the capsule and debulking of the tumor. For the residual tumor, the patient received intermittent vincristine, doxorubicin, and cyclophosphamide for 9 weeks. A course of external beam radiation was given totaling a dose of 60 Gy over 46 days. The patient died in June 1989 of *Pneumocystis carinii* pneumonia.

Khouja et al. (1999) experienced a similar disappointment with their patient. In December 1993, a well-encapsulated tumor was macroscopically removed through a subfrontal epidural approach. In March 1995, CT scan showed a recurrence, and a second macroscopic removal of residual tumor was performed through the same approach as the first surgery. The patient also received a radiation dose of 65 Gy. In April 1996, a second recurrence was treated by exenteration.

The lateral orbitotomy and subfrontal approaches have had mixed success in effecting a cure. Because the usual location of this sarcoma is the posterior orbit adjacent to the optic nerve, a surgical team consisting of both an ophthalmologist and a neurosurgeon should remove these tumors using the orbitocraniotomy approach with unroofing of the orbit through a coronal incision. This approach gives a wide view of the surgical field necessary for complete removal of the tumor. Unexpected bleeding can also be managed using this approach.

A recurrent tumor was managed in former years by radiotherapy and chemotherapy, either singly or in combination, but was not very effective. The status of this adjuvant therapy, at present, is not well defined. Exenteration at this stage of therapy is more likely to achieve a cure than repeated surgery.

Chordoma

This is a malignant tumor of bone that arises from vestiges of the notochord after the regression of this fetal structure. The three most common sites along the midline axial skeleton are the sacrococcygeal area, the sphenoccipital area, and the second cervical area. The tumor that secondarily extends into the orbit, the nasal cavity, or both arises from the region of the clivus and dorsum sella.

Clinical Features

Cranial nerve palsy, particularly the sixth nerve, is frequently the first sign of chordoma, the result of the neoplasm spreading along the clivus. A frequent accompaniment is a rather scarce, intermittent, poorly defined pain or headache, probably secondary to early bone erosion. When orbital invasion occurs, proptosis, downward displacement of the affected eye, an afferent pupillary defect, a chiasmal type defect in the visual field, tearing, retro-orbital pain, and diplopia may occur. Later, vision fails, and the optic disk develops pallor. An exuberant extracranial growth of a chordoma along the orbitonasal juncture is illustrated in Figure 6.33. A chordoma of even greater size in the same area of the face was pictured in the report of Flament and Forest (1979). The growth of the tumor is usually slow but relentless.

Reports of chordoma in the ophthalmic literature are sparse and usually limited to single case descriptions. Case reports of this type that we have found in the literature over the period of our 50-year survey are listed in Table 6.4. The 11 cases in the list from 1937 through 1981 were discussed in more detail in the second and third editions of *Orbital Tumors*. The last five cases are recent additions.

Our patient, a 49-year-old woman, presented at another institution with sudden onset of vertical diplopia and proptosis of the right eye with occipital headache, fatigue, and weight loss of 3 months' duration. On the basis

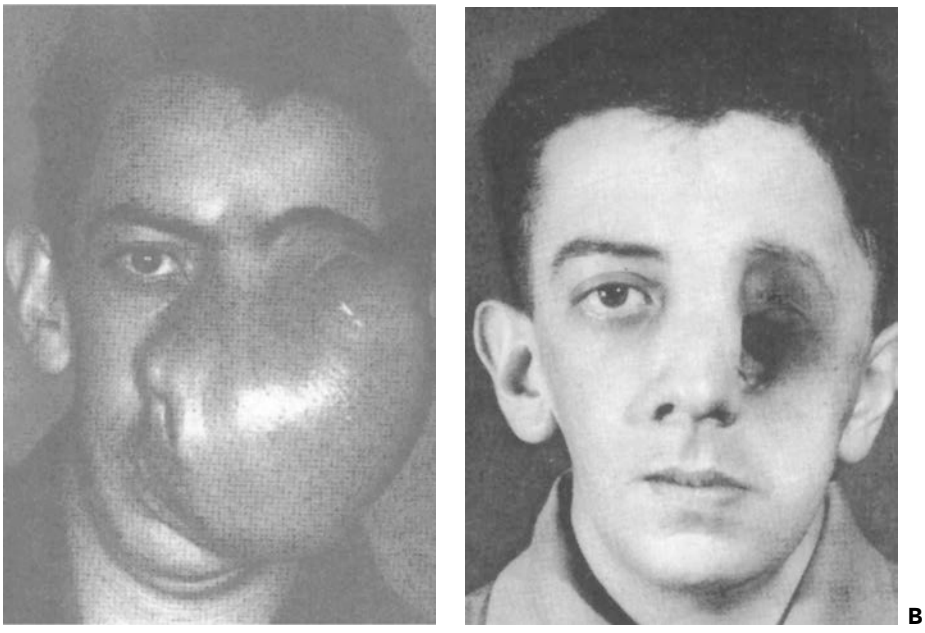

Figure 6.33 **A:** 17-year-old boy with massive distortion of the face from recurrent chordoma. His left eye had been enucleated 2 years previously because of orbital involvement. **B:** Appearance 2 years after removal of recurrent tumor. The patient later had extension of the tumor into the right nasal cavity. (From Crikelair GF, McDonald JJ. Nasopharyngeal chordoma. *Plast Reconstr Surg.* 1955;16:138–144, with permission.)

of imaging scans, a probable diagnosis was made of chordoma of the clivus with secondary invasion of the right orbit. Although vision was 20/20 in each eye, there were also temporal defects in the visual fields. The tumor was partially removed through a combined transethmoidal and trans-sphenoidal approach. The histologic diagnosis was chondroid chordoma. The patient was referred to Mayo Clinic 7 months later for further therapy. Brain radiotherapy was recommended and the patient returned home. Two years later, the patient developed epistaxis. CT scans showed extension of tumor into the medial portion of the right petrous bone, the sphenoid sinus, right middle intracranial fossa, and suprasellar cistern. This was treated with radioactive iodine I 125 implants. Her vision remained 20/20. Her condition continued to decline, and she died 4 years and 9 months after onset. At death, she was blind in both eyes and could no longer swallow.

The patient described by Kasantikul et al. (1998) was a 14-month-old girl with intracranial chordoma involving the left orbit, paranasal sinuses, nasal cavity, hard palate, and unilateral proptosis. The patient's serum α-fetoprotein level was markedly elevated. Moshari et al. (2001) reported a rare ectopic chordoma with an epicenter at the sphenozygomatic suture of the lateral orbital wall of a 63-year-old woman. The tumor had eroded intracranially, invaded the orbit, and compressed orbital soft tissue.

The case described by Fleming et al. (2003) was a 44-month-old girl with a dumbbell-shaped chordoma primary in the cavernous sinus with secondary orbital extension. Ninety-five percent of the mass was surgically debulked. After surgery, the patient received 63 Gy of external beam radiotherapy to the orbit and base of the skull and completed six courses of chemotherapy.

Bouvier and Raghuveer (2001) reported a case of metastatic tumor to the left orbit from a sacrococcygeal chordoma in a 48-year-old man.

Table 6.4 underscores the wide age range of chordoma, at least in regard to the orbit. Therefore, statements that chordomas have a predilection for certain age decades seem irrelevant. Even so, the age tabulation does not objectively reflect the approximate age at onset in some cases. Because of the neoplasm's slow growth, the patient may have had the neoplasm for some years before diagnosis. Such

TABLE 6.4
CHORDOMA WITH ORBITAL INVOLVEMENT

Authors	Sex	Age at Diagnosis, y
Roche et al. (1937)	F	76
Argaud et al. (1937)	M	3
Zeitlin and Levinson (1941)	F	18
Crikelair and McDonald (1955)	M	11
Binkhorst et al. (1957)	F	70
Dyson (1957)	M	57
Kojima et al. (1964)	Unknown	Unknown
Trappe and Weidenbach (1977)	F	18
Daicker (1978)	F	87
Flament and Forest (1979)	M	67
Ferry et al. (1981)	F	26
Henderson (1994)	F	49
Fleming et al. (2003)	F	3
Kasantikul et al. (1998)	F	14 mo
Moshari et al. (2001)	F	63
Deda et al. (2001)	Unknown	Unknown

was the case of the patient described by Binkhorst et al. (1957), wherein radiography had shown a destructive tumor of the sella turcica 12 years before presentation and surgical diagnosis. The sex distribution of the 16 patients in Table 6.4 is predominantly female (female-to-male ratio of 10:4). This is the opposite of the sex ratio (male-to-female ratio of 2:1) for chordomas in all other sites. Bilateral orbital invasion eventually occurs in most cases, either because of unchecked growth or recurrence of tumor after surgical excision or radiotherapy.

Imaging Aspects

The distinctive radiographic features of these neoplasms associated with orbital involvement are invasion and destruction of the sphenoid bone with, in some cases, expansile features. Some portion of the sella is affected in almost all cases. In the course of bone dissolution, some osseous elements may be engulfed by the tumor appearing as matrix calcification. Some sclerosis of tumor edges may also be observed. CT scan and MRI of our patient are illustrated in Figure 6.34.

Pathology

Grossly, the orbital lesions are soft and gray and may be transparent in areas where the covering tissue is thin. On the basis of microscopic appearance, a chordoma is divided into three subtypes: Conventional, chondroid, and dedifferentiated. The conventional type resembles the fetal notochord (see Fig. 6.35). The chondroid type is a slow-growing variant with a substantial chondroid component. The dedifferentiated type may show features that resemble malignant fibrous histiocytoma, fibrosarcoma, osteosarcoma, or high-grade chondrosarcoma.

Management

Chondroma with secondary extension into the nasal passage, paranasal sinuses, or orbit is nearly impossible to surgically eradicate because of its proximity to vascular arcades, large blood vessels, and nerve tracts and nerve bundles located along the skull base. In the ''olden days,'' chordoma of this type was subject to multiple debulking procedures, but removal of tumor was still incomplete. Now, a multidisciplinary surgical team performs the necessary surgery in one procedure, but complete removal of tumor is still elusive.

In such situations, when incomplete removal is suspected, radiotherapy is administered postoperatively as an adjuvant. However, if the surgical team believes there is good gross removal, without any visible major remnants of tumor, radiotherapy is withheld until recurrence 1 or more years later. The radiation dosage is based on the extent of residual or recurrent tumor, the proximity of the eyeball to the radiation field, the age and health of the patient, and the histologic type of the tumor. A new modality in management at some medical centers is use of the Gamma Knife. The number of secondary chordomas treated with the Gamma Knife is insufficient to know its rightful place in the treatment of this tumor.

Chemotherapy has not proved useful (DeVita et al., 2001).

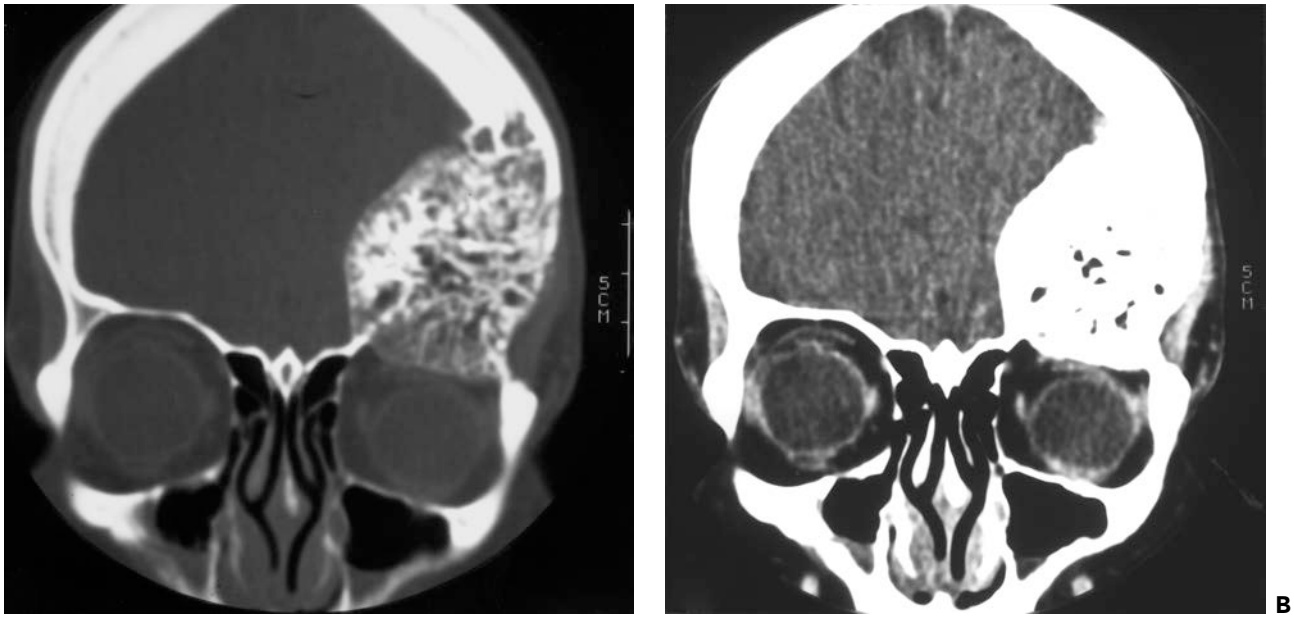

Figure 6.34 **A:** Computed tomography scan of a 44-year-old woman showing a 5-cm expansile bony mass in the left supraorbital frontal area with a central spiculated bone matrix. The mass expanded into the superior orbital space. **B:** Magnetic resonance imaging depicting the radiating pattern of bone with preserved diploic fat.

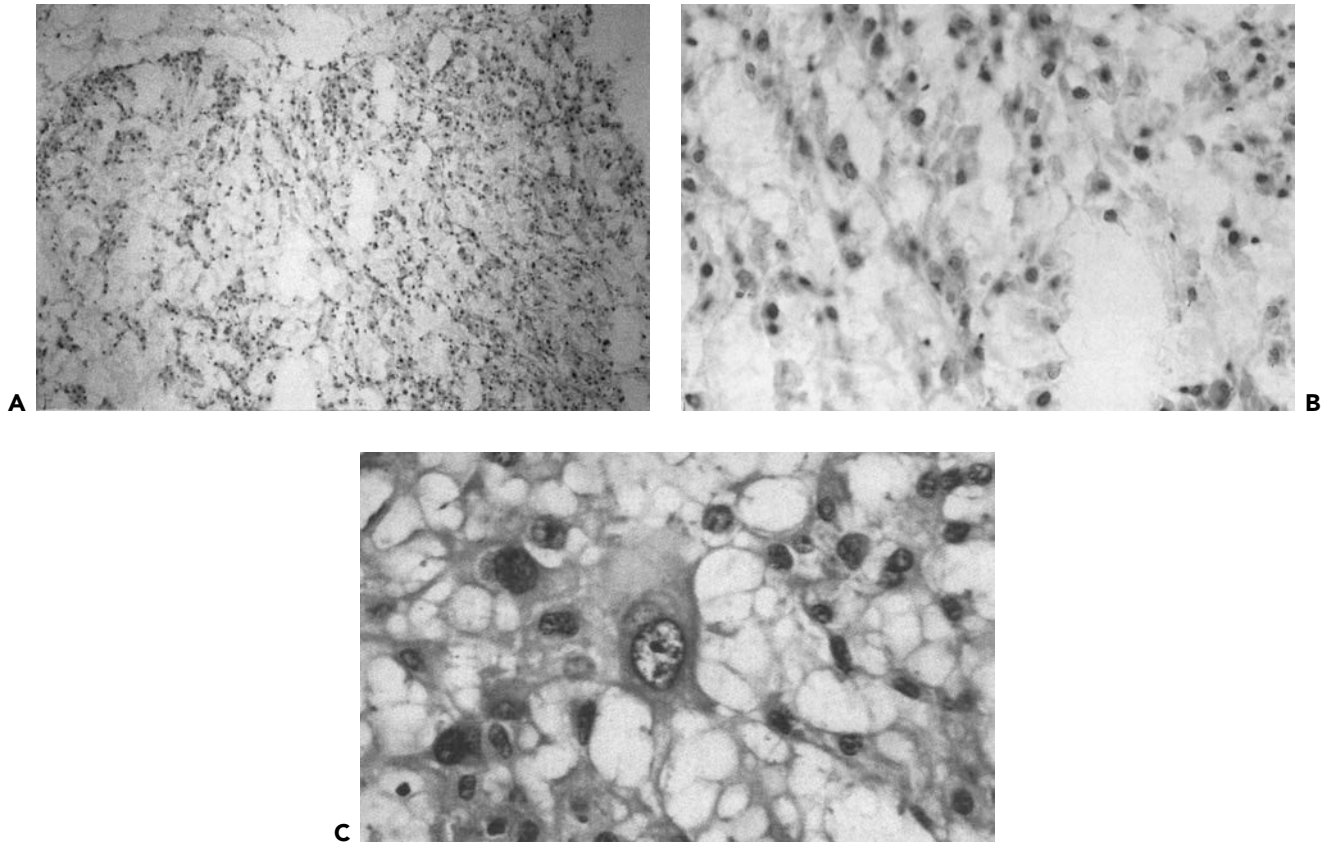

Figure 6.35 Histopathology of chordoma. **A:** Cords and clusters of large polymorphous cells contain an eosinophilic cytoplasm and large, roundish, slightly pleomorphic nuclei. Between the cells, a faintly pale amorphous mass represents mucus extruded by the cells (hematoxylin and eosin, original magnification ×50). **B:** At higher magnification, some of the large cells show vacuoles, giving the typical physaliphorous appearance (center). The pleomorphism of the large, dark nuclei is obvious (hematoxylin and eosin, original magnification ×100). **C:** Higher-magnification photomicrograph shows the large variegated and vacuolated physaliphorous cells characteristic of chordoma (hematoxylin and eosin, original magnification ×400). (From Greenspan A, Remagen W. *Differential diagnosis of tumors and tumor-like lesions of bones and joints*. Philadelphia, PA: Lippincott Williams & Wilkins; 1998:350–357, with permission.)

VASCULAR TUMORS OF THE BONE

All the vascular tumors of the orbital soft tissues discussed in Chapters 10 and 11 may also occur as primary tumors of skeletal bone. However, in orbital bone the three most common vascular tumors are benign capillary and cavernous hemangiomas, and malignant hemangioendothelioma. Because the two benign intraosseous tumors often show a mixture of capillary and cavernous patterns, the histoclassification is of little importance. Pathologists usually just call these tumors *hemangiomas*. We would prefer to discuss them as one tumor.

Hemangioma

Incidence

These data are based largely on documented cases of so-called orbital intraosseous hemangiomas reported in the literature since 1942, when this entity was first described by Rowbotham. Zucker et al. (1989) tabulated age range, sex, and tumor location in the first 16 cases. Relf et al. (1991) added five cases. Subsequently, through 2001, we have found another 10 case reports. Our 50-year tumor survey includes only one hemangioma of bone, making a grand total of 32 cases reported in the literature. However, not all of those cases are true orbital tumors.

If the intraosseous tumor occupies the plate of the orbital bone that encompasses the orbital cavity, is postseptal in location, compresses the orbital contents, and produces proptosis, displacement, or restricted motility of the eyeball, singly or in combination, it can be designated as orbital tumor. The nonorbital lesions present as enlarging, palpable masses along the orbital rim, the fossa of the lacrimal sac, the lateral wall of the orbit, and their proseptal position, verified by CT imaging. These tumors are periorbital, not true orbital tumors.

TABLE 6.5
TRUE INTRAOSSEOUS HEMANGIOMAS OF THE ORBIT, 1942 TO 2001

Authors	Age, y	Sex	Bone
Rowbotham (1942)	66	F	Frontal
Handousa (1947)	36	M	Frontal and parietal
Handousa (1952)	35	F	Ethmoid
	17	M	Ethmoid
Mortada (1964)	48	M	Ethmoid
Chatterji et al. (1969)	47	F	Ethmoid
Clay et al. (1976)	1	M	Frontal
Fouad and Khalifa (1979)	32	F	Frontal
Hook et al. (1987)	31	F	Frontal
Relf et al. (1991)	50	F	Frontal
	59	F	Zygoma
Sood et al. (1992)	50	M	Frontal
	54	M	Frontal
Banerji et al. (1994)	61	M	Frontal and sphenoid
Slaba et al. (1999)	55	M	Sphenoid
Moore et al. (2001)	31	F	Zygoma
Henderson and Garrity (present study)	44	F	Frontal

Among the 32 cases, 17 (53%) qualify as true orbital tumors and are listed in Table 6.5.

All the cases listed in Table 6.5 were unilateral. Their age range was 1 to 66 years, with an average of 42.1 years and a median of 47 years. The sex ratio was essentially equal, nine women and eight men. This sex ratio differed from the prevalence of women among patients with hemangiomas of bone in the skeletal system. Female-to-male ratios of 2:1 and 3:1 have been reported in the literature for patients with skeletal bone hemangiomas.

Clinical Features

The orbital hemangioma of bone behaves more like a hamartoma than a neoplasm. It is slow growing and remodels bone by the simple pressure of expansion rather than lysis, its progression is relatively painless in most cases, it disturbs the function of the tissues in the orbital space by compression rather than by infiltration, it does not metastasize, and once it is completely removed, it does not recur.

Its presentation is that of a mass compressing the structures of the orbital space. One or more of the following signs and symptoms are present: Proptosis, displacement of the eyeball, and restriction of ocular motility. If the sphenoid bone is affected, papilledema and blurring of vision usually occur. In the far forward area of the orbital space, a hemangioma may present as a poorly defined, firm or bony mass along the superior, inferior, or lateral walls just posterior to the orbital system.

Imaging Aspects

Many CT and MR scans reproduced in the literature show the circumscribed, well-defined, soft tissue component of a periorbital hemangioma of bone nestled in its bony cocoon. CT scan of intraorbital hemangiomas of bone are less numerous, and the imaging display is not as sharp when compared with periorbital tumors. A CT scan of coronal sections of a tumor showing extensive involvement of several bones compressing the posterior orbital plate is illustrated in Figure 6.34A.

MRI shows an inhomogeneous web-like pattern of trabeculae with intermediate T_1-weighted signal intensity and high T_2-weighted signal intensity. Within the mass are areas of signal void corresponding to the spaces within the trabeculae. The tumor shows marked enhancement with contrast injection (Fig. 6.34B).

Histopathology

The common cavernous hemangioma of bone has thin, widely spaced bony trabeculations enclosing large, thin-walled vascular cavities lined with a single layer of flattened endothelial cells. The less-common capillary type consists of fine capillary loops encased by a more compact mass of bone. The vascular nature of the tumor is confirmed by the immunoreactivity of the cells with CD34, factor VIII, and vimentin.

Management

The preferred management of the periorbital tumor is *en bloc* excision, including a rim of normal bone. This is accomplished in most cases by an external approach. In the past, some tumors of this type were handled by curettage, but this often resulted in excessive bleeding.

Management of intraorbital hemangioma of bone is a more challenging undertaking. This type usually comes to surgery at a later stage of growth and is much larger, may

affect more than one bone of the orbital plate, is more difficult to approach surgically, and may have a compound blood supply compared with a periorbital lesion. Tumors involving the roof, medial, inferior, and posterior walls usually have some mass effect on anatomic spaces and structures beyond the surgical field of ophthalmology. Tumors of the lesser wing of the sphenoid bone near the skull base are particularly hazardous to approach because of their potential for uncontrolled bleeding during surgical intervention.

The case described by Banerji et al. (1994) was of this type. The tumor involved the roof, medial, and lateral orbital walls, the lesser and greater wings of the sphenoid bone, the planum sphenoidale, the cribriform plate, and the ethmoid sinus on the right side with both intraorbital and intracranial extension. On CT scan, it measured approximately 3 cm. Digital subtraction angiography revealed an arterial supply from the right middle meningeal and ophthalmic arteries. The meningeal artery was embolized.

At surgery, a bicoronal skin flap was reflected anteriorly, and a right frontotemporal craniotomy was performed. A near total excision of the spongy tumor was achieved. Cranioplasty was planned as a second-stage procedure after 6 months.

The hemangioma of bone from our tumor survey occurred in a 44-year-old woman. It was an expansile tumor of the entire orbital roof with intraorbital and intracranial extension measuring 5 cm. Preoperatively, an angiogram was not thought to be necessary. The surgical team was composed of a neurosurgeon, an ophthalmologist, and a head and neck plastic and reconstructive surgeon.

In brief, a large coronal skin incision was made, and the skin flap was reflected anteriorly. Multiple burr holes were placed around the tumor. A rongeur was used to remove honeycomb-like pieces of bony tumor. Bone wax was placed in the burr holes. Some bone was also removed inferiorly along the lateral orbital wall. The defect in bone now measured 9×6 cm.

Next, a full-thickness piece of bone was harvested from the parieto-occipital area, of similar size and contour as the defect in frontal bone. The outer cortex of the donor bone was split from the inner cortex and secured in the surgical site. The inner cortex was replaced in its original location. There was no recurrence over a 3-year period of observation.

Radiotherapy should not be used as an optional management of these benign tumors.

Hemangioendothelioma

In the fourth edition of Dahlin and Unni's (1986) text, *Bone Tumors*, they used the terms *hemangiosarcoma* and *hemanigioendothelioma* "interchangeably in this discussion because there is no valid method of differentiating one from the other." These two entities were previously considered differing types, but closely related, vascular tumors of bone. Furthermore, in his discussion the term *angiosarcoma* was sometimes used in parentheses immediately after the word "hemangioendothelioma." This usage of the terms inferred that angiosarcoma was still regarded as another synonym in some cases.

In the fifth edition of *Bone Tumors*, Unni (1996) added the synonym *low-grade angiosarcoma* to the intermixed designations *hemangiosarcoma* and *hemangioendothelioma*. These three terms describe this bone tumor as a low-grade malignancy. Later, in the same chapter, Unni gave "angiosarcoma of bone" separate status worthy of a subchapter. He considered angiosarcoma at the most malignant end of the spectrum of vascular tumors.

With terminology standardized, more or less, calculating how often this tumor affects the orbit may be possible in the future. Many of the cases reported in the literature in the past no longer correlate with current nomenclature or our stricter orbital tumor criteria of an intraosseous, expanding tumor located in the portion of orbital bones encompassing the orbital space.

Too few hemangioendotheliomas of the above type have been reported at this time to calculate frequency, age range, and the like. Nevertheless, we should update the reader on the subject. Three cases have been reported in the literature wherein the expanding hemangioendothelioma of bone encroached on the orbital cavity. The first case was detailed in our third edition. Here, we recap the salient features of this case.

Friendly et al. (1982) described a 5-year-old girl with a painless swelling of the left brow and downward displacement of the left eye of several months' duration caused by a smoothly contoured, hard mass along the inner aspect of the superior orbital rim. Standard radiography showed an osteolytic lesion. An exploratory orbitotomy revealed an intraosseous hemangioendothelioma of bone. The bone cavity was curetted. Progression of the bony defect necessitated wider excision 4 months later. Two additional neurosurgical excisions of bone were performed 2 and 10 months later. This third excision was followed by intensive radiotherapy. There was no local recurrence or metastasis at the 5-year follow-up interval.

Lyon et al. (1992) described a $3\frac{1}{2}$ -month-old boy who presented with a palpable mass along the infraorbital rim of 3 days' duration. The left globe was displaced superiorly without axial proptosis. CT scan showed a large, fairly well-demarcated mass in the adjacent orbital space with destruction of the maxillary and zygomatic bones. A biopsy was performed through an inferior fornix incision. Considerable bleeding was controlled by thrombin-soaked gelatin sponges and unipolar electrocautery. The histopathologic diagnosis was intermediate (grade 2) malignant hemangioendothelioma, which was confirmed by an outside consultant. Through a modified Weber-Ferguson incision, an *en bloc* excision of the tumor was performed. All margins of the specimen were free of

tumor. After 20 months' follow-up, ocular fixation and motility were normal, as were CT scan, chest radiograph, and bone scan.

Koh and Yoo (2001) described a 20-year-old woman who presented with a 1-year history of proptosis of the left eye. Neuroradiologic imaging revealed a left temporosphenoidal, extra-axial, expansile mass with heterogeneous enhancement associated with erosion and destruction of the temporal and sphenoid bones. The orbital contents were compressed without any sign of infiltration. Angiography demonstrated marked neoplastic angiogenesis from the middle meningeal artery and other branches of the left external carotid artery. Preoperative embolization was unsuccessful. The lesion was totally excised in two stages over a 2-week interval. Bleeding was profuse. A follow-up was not stated.

None of the above patients had a tumor elsewhere, either in the skull or skeletal bone. Multicentricity of the tumor is not uncommon (Lyon et al., 1992). The clinical course of hemangioendothelioma of bone is between hemangioma and angiosarcoma, discussed in the same order in this chapter (Kleer et al., 1996). However, the biological behavior of the hemangioendothelioma is difficult to predict on the basis of histopathologic typing (Unni, 1996). Many authors find it difficult to differentiate the spectrum of benign and malignant vascular tumors of bone by radiologic studies. The consensus is that resection of the tumor is still the primary goal of therapy.

Histopathology

On histologic examination, hemangioendothelioma reveals endothelial cells with abundant, faintly eosinophilic or amphophilic cytoplasm. The interanastomosing vascular channels, often arranged in an antler-like pattern, are delimited by a basal membrane. Markedly pleomorphic endothelial cells, with hyperchromatic nuclei and prominent nucleoli, are attached to this membrane. Individual cells may exhibit intracytoplasmic lumina of variable size, whose diameters often approximate that of an entrapped erythrocyte. Larger lumina appear to be formed as the result of fusion of their smaller intracytoplasmic counterparts. A residual strand of attenuated cytoplasm frequently bridges the opening. Although mitotic figures may be absent, one or two figures per 10 high-power fields are usually seen. An inflammatory infiltrate is often present, consisting of various percentages of eosinophils, lymphocytes, and plasma cells (see Fig. 6.36). Rarely, eosinophils predominate and other inflammatory elements are virtually absent. Small foci of hemorrhage or necrosis may be observed. The stroma typically varies from fibrous to myxoid and may appear more hyalinized, thereby resembling a hyaline cartilage-like matrix. That the cells composing these tumors are differentiated is evident from their frequent positive immunohistochemical staining for factor VIII and for the lectin *Ulex europaeus* (Unni, 1996).

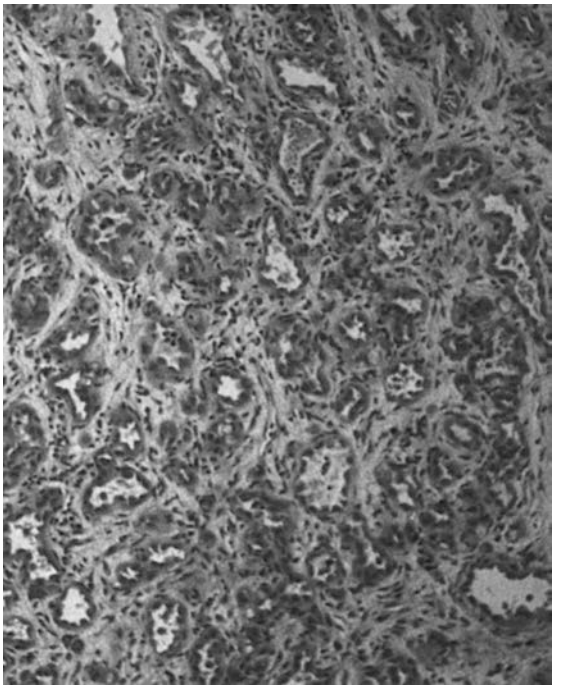

Figure 6.36 A fibrous stroma is filled with proliferating vascular channels that are lined by plump endothelial cells that lack pleomorphism or extensive mitotic activity (hematoxylin and eosin, original magnification ×40). (From Greenspan A, Remagen W. *Differential diagnosis of tumors and tumor-like lesions of bones and joints.* Philadelphia, PA: Lippincott Williams & Wilkins; 1998:350–357, with permission.)

Angiosarcoma

This neoplasm is the most malignant vascular tumor. It is an aggressive malignancy, characterized by frequent local recurrence and distant metastases (Unni, 1996). In the Mayo Clinic series of 11,087 cases of bone tumors (Unni, 1996), the angiosarcoma affecting only soft tissue, commonly involved the skin (33%) and soft tissues (24%). However, angiosarcoma involved bone in only 6% of cases. Angiosarcomas of the cranium are uncommon, averaging 2.5% in two large combined series of 2,110 cases of primary bone tumors (Shuangshoti et al., 1988). Intraosseous angiosarcomas of the bony orbital plates are even more rare. We have found only two well-documented cases in the literature. Here, we describe these two cases in more detail.

The first case, described by Shuangshoti et al. (1988), was a 32-year-old man with progressive left proptosis for 1 year with no other associated signs or symptoms. Radiography showed destruction of the lesser wing of the sphenoid bone, posterior wall of the orbit, and orbital roof. A left frontotemporal craniotomy disclosed an intraosseous, extradural, nonencapsulated, highly vascular, friable tumor. One surface of the lesion was firmly adherent to dura mater, and another area of tumor was adherent to the superior aspect of the eyeball. The adjacent brain tissue was free from tumor infiltration. The entire neoplasm

and affected bone were removed, accompanied by profuse bleeding. CT scan showed no evidence of tumor 9 months after surgery. There was no long-term follow-up. No radiotherapy was given to this patient.

Lopes et al. (1999) described a 43-year-old man with a 3-month history of an enlarging, painless, right temporal mass. No other ocular abnormality was present. Neuroimaging pictured an enhancing, destructive mass of the greater wing of the sphenoid bone with lytic extension into the orbit, temporal bone, and infratemporal fossae, which was infiltrating the dura mater but did not produce any abnormality of the brain parenchyma.

These findings were confirmed on surgical intervention. A right fronto-pteriono-temporal craniotomy disclosed an intraosseous, nonencapsulated tumor. The entire neoplasm was removed *en bloc* with large margins and resection of dura mater. The dural defect was grafted with temporal fascia. Exenteration of the eye was performed, and the "external orbital arch" was removed and reconstructed using a parietal bone graft. Neither radiotherapy nor chemotherapy was administered. CT scan and MRI showed complete resection without recurrence 12 months after surgery.

There is no evidence in the current literature of better control of these neoplasms than wide surgical resection if technically possible.

Histopathology

The neoplasm is a highly vascular collection of anastomosing vascular channels lined by plump, cuboidal ovoid cells having pleomorphic and hyperchromatic nuclei. The cells have a tendency to form papillae (see Fig. 6.37). The stroma is loose, myxomatous tissue containing an

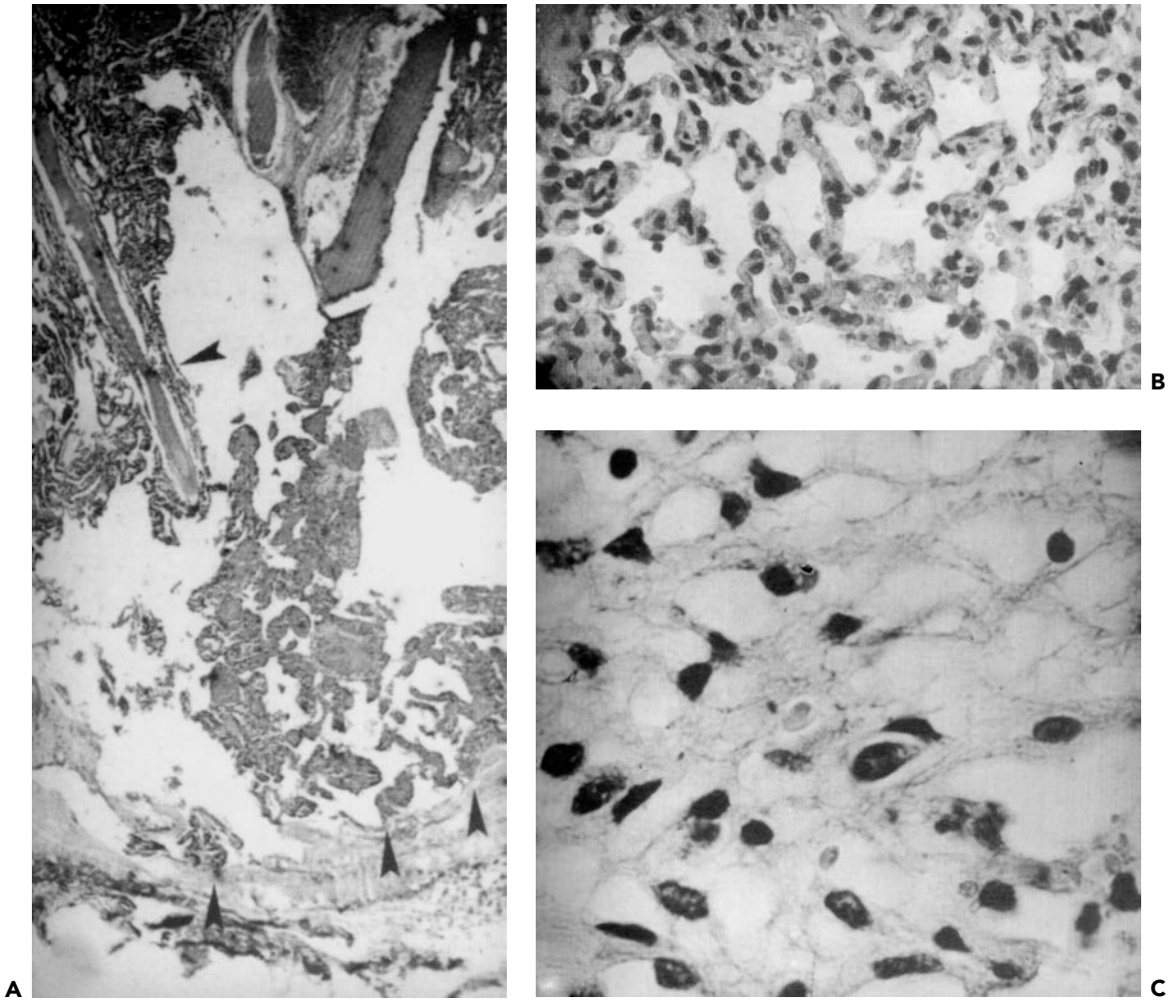

Figure 6.37 **A:** The angiosarcoma invades bone trabecula (*upper arrow*) and dura mater (*lower arrows*) (hematoxylin and eosin, original magnification ×44). **B:** Anastomosing cords of pleomorphic endothelial cells (hematoxylin and eosin, original magnification ×327). **C:** Stellate and spindle-shaped cells lie within the loose myxomatous matrix of the tumor (hematoxylin and eosin, original magnification ×886). (From Shuangshoti S, Chayapum P, Suwanwela N, et al. Unilateral proptosis as a clinical presentation in primary angiosarcoma of skull. *Br J Ophthalmol*. 1988;72:713–719, with permission.)

admixture of stellate, elongate, and spindle-shaped cells. If the proliferation of these cells masks the outline of the vascular channels, the channels can be defined by a reticulin stain. Finally, the endothelial nature of the tumor can be defined, in most cases by immunochemical evidence of factor VIII–related antigen.

INFLAMMATORY TUMORS

Infantile Cortical Hyperostosis

The first description of this tumor was made by Caffey and Silverman (1945). In those early years, eponyms such as "Caffey de Toni-Silverman," "Caffey-Smyth," and simply "Caffey" were used to describe the tumor. Infantile cortical hyperostosis is an inflammatory disorder of bone. However, at the time of presentation, its onset is easily mistaken for a neoplasm.

In the skeletal system, the tumor affects long bones, ribs, scapula, and clavicle. In the skull, infantile cortical hyperostosis is most common in the mandible. Orbital involvement is less common but is the reason for discussion of the tumor in this text. Its etiology is unknown, but some cases seem to have a familial predisposition.

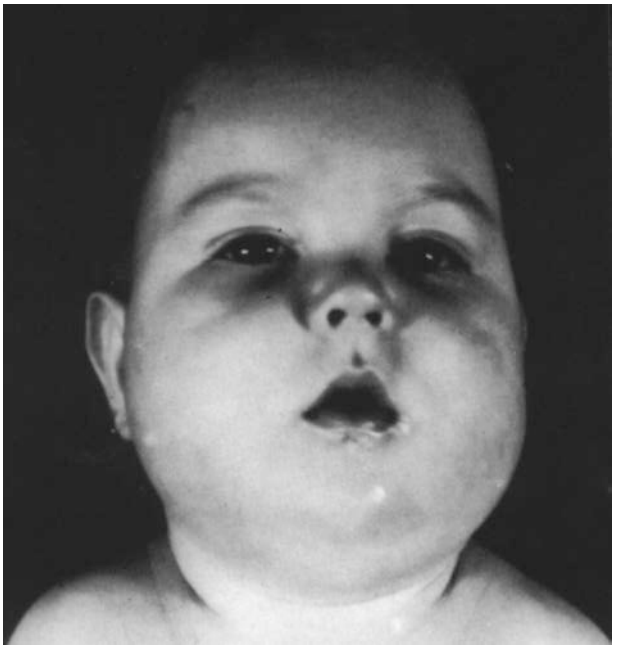

Figure 6.38 Classic facial appearance of a patient with infantile cortical hyperostosis. (From Minton LR, Elliott JH. Ocular manifestations of infantile cortical hyperostosis. *Am J Ophthalmol.* 1967;64:902–907, with permission.)

Clinical Features

Iliff and Ossofsky (1962) were the first to report a case affecting the orbit. Other orbital examples have been published by Bywaters et al. (1963); Minton and Elliott (1967); Galyean and Robertson (1970), and Rogosin et al. (1999). Infantile cortical hyperostosis usually appears before the age of 5 months, and the mean age at onset may be around 9 weeks.

Periorbital edema, either of the eyelids or along the lateral wall of the orbit, is the initial sign of orbital infantile cortical hyperostosis. This suggests cellulitis but the skin is not erythematous. A painful nodule may be palpable in the more forward portion of the frontal, malar, or temporal bone overlying the bony lesion (the orbital plates at the skull base do not seem to be affected by the tumor). The conjunctiva may be chemotic and have a slightly reddish hue, another finding suggestive of an inflammatory response. Proptosis may be slight. The infant probably is restless, irritable, and feverish. Laboratory findings show an elevated sedimentation rate, leukocytosis, slight anemia, and thrombocytosis.

Orbital hyperostosis is often accompanied by lesions of one or both mandibles (see Fig. 6.38). Although involvement of the mandible is absent, the orbital bone may be but one of a series of bones affected by the tumor. The patient described by Rogosin et al. (1999) illustrates this progressive feature. A 40-day-old girl was hospitalized for what proved to be cortical hyperostosis. Within a few days, the infant developed lesions of the right orbit and right mandible. Involvement of the left mandible soon followed. After all these lesions spontaneously resolved, the right clavicle was involved 1 month later.

Recurrences are common in other bony locations. The same bone may be afflicted more than once over a period of years. The lesions tend to undergo spontaneous resolution over a period of 1 to 3 months.

Imaging Aspects

The distinctive feature, either on radiography or CT scan, is the gross thickening of orbital bone due to the reactive change on the periosteal surface and thickening and sclerosis of the cortex of the affected bone.

Histopathology

Jakubikova et al. (1994) believe that inflammatory changes in the afflicted bone are caused by obliteration of small arteries in the bone's vascular supply. This is the result of proliferation of the intima of arterioles producing hypoxia, hyperostosis, and swelling. Figure 6.39 is a micrograph of some of these features.

Management

A number of drugs have been used in the treatment of these orbital tumors, with or without mandibular involvement. Because the disorder undergoes spontaneous resolution, it is not known whether any of these medications are more effective than no drugs at all. No therapeutic control studies have been done on this question. There is no unanimity that one drug is specific for infantile cortical hyperostosis.

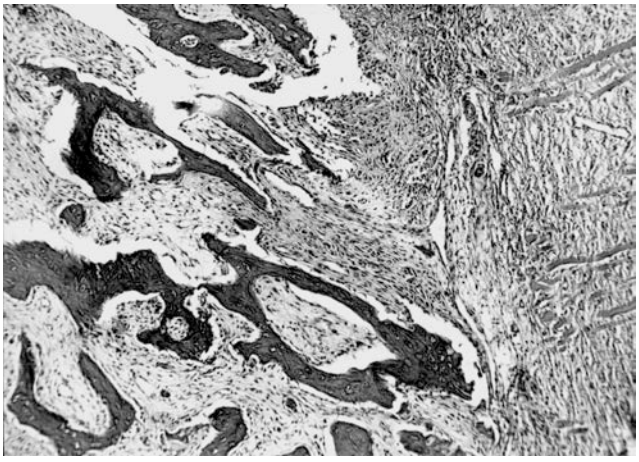

Figure 6.39 Section from the periosteal surface of bone shows chronic inflammatory reaction with fibrous tissue proliferation and marked reactive new bone formation (hematoxylin and eosin, original magnification ×100).

Analgesics and anti-inflammatories may be given to an infant with supplementary intravenous fluids to combat dehydration during the stage of fever.

In the sporadic form of the disorder, recurrence is unpredictable. In the familial type, recurrences and exacerbations are more common.

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7 Tumors of Primitive Mesoderm, Striated Muscle, Adipose Tissue, and Smooth Muscle

EMBRYONAL RHABDOMYOSARCOMA

This malignant tumor in the orbit was once considered a rare tumor of striated muscle. The present consensus holds that, in most patients, the usual source of the tumor is not adult striated muscle. Instead, the tumor recapitulates the primitive, multipotential nature of embryonal tissue. This characteristic is compatible with the high incidence of the neoplasm in children and adolescents and prompted the name *embryonal rhabdomyosarcoma*.

The tumor is not uncommonly found in neonates and, also, occasionally in adults. The revised histogenesis explains the changes in the incidence, treatment, and course of the lesion that have occurred during our 50-year tumor survey. References pertaining to the tumor have also increased manyfold in this interval.

Incidence

During the 50-year period 1948 to 1997, we collected information on 54 orbital rhabdomyosarcomas (26 primary, 27 secondary, one metastatic). When we omit the one metastatic tumor from the data, the remaining 53 rhabdomyosarcomas were 2.9% of our total 1,795 tumors (Table 3.3). There were 35 males and 18 females, nearly a 2:1 ratio. The age range of this sample was 1 to 39 years, with an average of 12.3 years and a median of 9 years. These age data confirm the generally held view that rhabdomyosarcoma is the most common orbital malignancy in the first two decades of life. Histologically, 48 tumors were embryonal, 2 alveolar, and 2 pleomorphic. One was not subclassified, and the paraffin block was no longer available for a second review.

Oberlin et al. (2001) published the experience of four international collaborative groups—Rhabdomyosarcoma Study Group, International Society of Paediatric Oncology Sarcoma Committee, German Collaborative Soft Tissue Sarcoma Group, and Italian Cooperative Soft Tissue Sarcoma Group. Collectively, these groups studied 306 patients with orbital rhabdomyosarcoma. The median age of these patients was 6.8 years.

Clinical Features

Ninety-one percent (48 out of 53) of the orbital rhabdomyosarcomas in our 50-year survey were the embryonal type. Herein, we chiefly discuss the clinical features of this age-group.

The most common clinical features are a painless proptosis of one eye of rather sudden onset, soon followed by swelling of one or both eyelids, chemosis of conjunctiva, mechanical impairment of ocular motility in one direction of gaze, and nonaxial displacement of the eye.

As a rule, symptoms develop rapidly in young patients, with the affected eye and adnexa showing obvious progression by the day or week, rather than by the month. At onset, the puffy edematous eyelids show a bluish tinge that soon changes to a reddish purple hue giving way to an alarming red color that suggests an inflammatory process (see Fig. 7.1).

Figure 7.1 Red, slightly violaceous, edematous eyelids concealed a proptosed left eye of 3 weeks' duration in a 4-year-old boy. The marked edema of the eyelids was disproportionate to the short duration of the process.

There is no increase in local heat, however, and the process is painless unless a number of weeks have elapsed since onset. Affected patients are not febrile nor do the children look sick, as would be the case in children with orbital cellulitis, neuroblastoma, or Langerhans histiocytosis, which occur in this age-group. Often, the concerned parents of an affected child attribute the puzzling proptosis and swollen eyelid to trauma, although such trauma is either not well substantiated or is so trivial that it is not etiologically important. The swollen eyelid may partially conceal the proptosis and resist palpation. Grossly, the tumors are well defined.

The embryonal rhabdomyosarcoma is noted for unusual presentations as well as association with other benign and malignant neoplasms and other disorders of children. Onderoglu et al. (1999) described multiple masses of a solid tumor in a fetus at the 33rd week of gestation, involving the liver, orbit, and maxillary sinus and detected by ultrasonography. The presumptive diagnosis was rhabdomyosarcoma, which was later confirmed. Chams et al. (1988) described a case in a 1-day-old infant.

Hadjistilianou et al. (2002) reported two infants, aged 2 months and 11 months, with orbital rhabdomyosarcoma associated with neurofibromatosis type 1. Muwakkit et al. (2002) noted a simultaneous occurrence of Wilms tumor and rhabdomyosarcoma in two patients, and Armstrong and Sclar (1999) described a 16-year-old girl with orbital rhabdomyosarcoma who developed bloody diarrhea during chemotherapy. She was found to have a familial adenomatous colonic polyposis.

Metastatic rhabdomyosarcoma may also involve the orbit. Amato et al. (2002) reported metastasis to the right orbit in a 29-year-old man 18 months after the initial tumor in the left orbit had been treated with chemotherapy and radiotherapy. Simpson et al. (1999) noted a metastatic tumor presenting as an isolated lateral rectus muscle restriction. The one case in our tumor survey metastasized from the testes of a 29-year-old. Fekrat et al. (1993) described a 27-year-old woman with metastasis of an alveolar rhabdomyosarcoma to the orbit.

Earlier we noted the tendency of embryonal rhabdomyosarcoma to occur in individuals older than the second decade. Our 50-year survey included three patients in the fourth decade with rhabdomyosarcoma. One patient was 36 years old, and two others were each 39 years old. Other individuals in this age range have been reported in the literature.

The third through seventh decades are the age range for pleomorphic "striated muscle" rhabdomyosarcoma of adults. We have only one patient with the pleomorphic tumor in our survey, and our experience with the multifaceted clinical features of this histologic type is too limited to write a comprehensive review. Readers who encounter a pleomorphic rhabdomyosarcoma may be interested in the review of Furlong et al. (2001). These authors published a thorough clinicopathologic study of 38 cases from multiple anatomic areas, including one orbital case. There were 28 men and 10 women with a mean age of 52 years and a median of 54 years. They conclude that the tumor is a high-grade sarcoma with an aggressive clinical course. The spindle cell variant also tends to affect adults and has a good prognosis.

Imaging Aspects

Computed tomography (CT) scan of this tumor is important because it shows the tumor's size, configuration, location, and the presence or absence of bone destruction. These tumors may occur anywhere in the orbital space but favor the superonasal quadrant. Small tumors are usually fairly well defined, may even appear circumscribed, and show mild to moderate contrast enhancement (see Fig. 7.2).

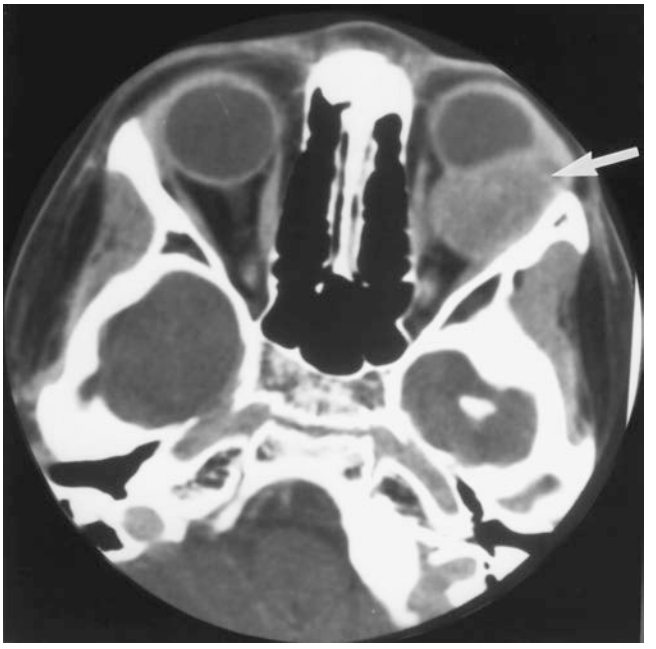

Figure 7.2 Axial computed tomography scan of a primary rhabdomyosarcoma shows a homogeneous, slightly enhancing mass (*arrow*) in the left posterior, superolateral orbit of a 10-year-old boy who was symptomatic for only 2 weeks. The tumor measured 30 × 25 × 20 mm.

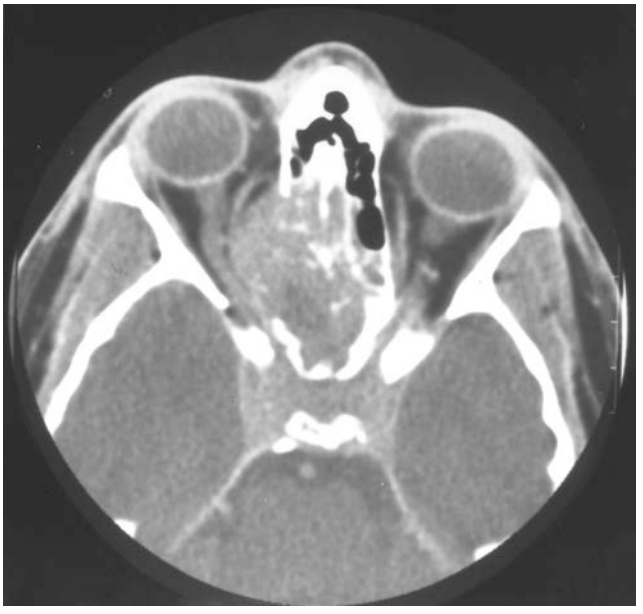

Figure 7.3 Axial computed tomography scan shows a large soft tissue mass in the right ethmoid sinus with destruction of the adjacent medial orbital wall, extension into the orbital cavity, and spread to the opposite ethmoid of 2 months' duration in a 17-year-old boy.

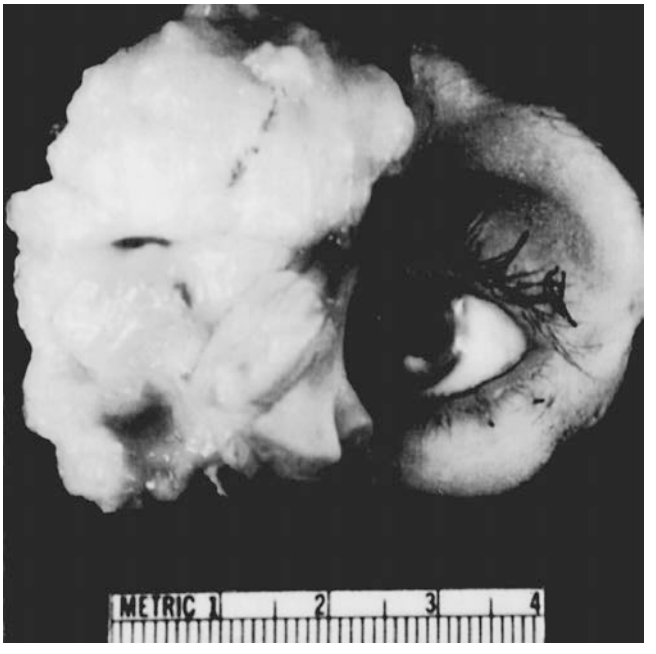

Figure 7.4 Exenteration specimen of an embryonic rhabdomyosarcoma shows a large, fleshy, grayish white, infiltrative tumor.

Large tumors have irregular contours and show marked contrast enhancement. The degree of enhancement is probably related to the volume of blood supply.

If bone destruction is present, the medial orbital wall and thin portion of the lateral wall are most often affected. Osseous involvement is always present when secondary tumors from the nasal passage, a paranasal sinus, or the intracranial vault invade the orbit (see Fig. 7.3). Bone destruction frequently accompanies recurrence of a primary orbital rhabdomyosarcoma and was present at the time of presentation in about one third of our patients with primary orbital tumors. A primary rhabdomyosarcoma with osseous or paranasal involvement is staged in a more serious category for the purpose of the Intergroup Rhabdomyosarcoma Study compared with a tumor without bone encroachment.

Magnetic resonance imaging (MRI) shows an isotense or slightly hypotense lesion compared with brain on a T_1-weighted scan. T_2-weighted scan shows a hypertense signal. Radiologists Mafee et al. (1998) believe a CT scan or MRI "baseline" scan is essential after completion of therapy. The scan is specific for showing recurrence of tumor that otherwise may not be clinically suspected.

Pathology

Grossly, the tumor is soft and varies in color from grayish white to yellow tan or reddish tan. It may be obviously infiltrative (see Fig. 7.4) or deceptively circumscribed (see Fig. 7.5). Although the latter tumor mass can often be removed intact despite its fragile consistency, the surrounding orbital tissue shows microscopic spread of tumor beyond the line of circumscription.

Various cell types and growth patterns characterize this neoplasm. The cell morphology may range from small, undifferentiated round cells to increasingly differentiated

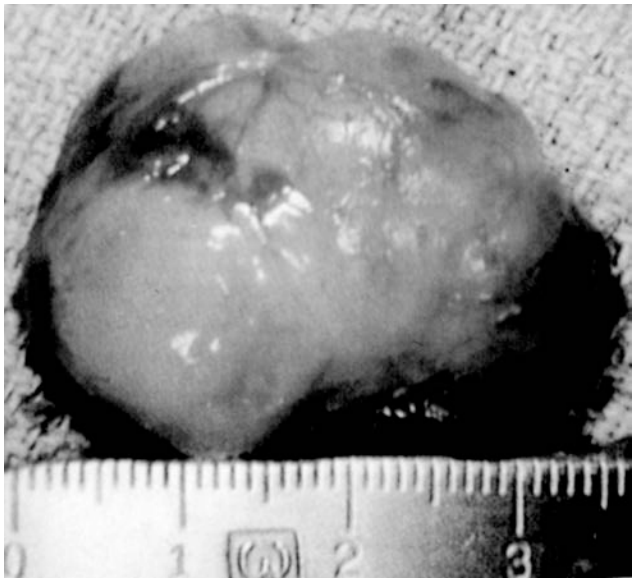

Figure 7.5 This 35-mm embryonal rhabdomyosarcoma is reddish yellow, slightly lobulated, soft, and moderately circumscribed, apparently removed intact from a 4-year-old boy. However, residual tumor was visible microscopically in surrounding orbital tissue.

types, including spindle-shaped cells, strap cells, racquet cells, tadpole cells, spider cells, and giant cells. In general, cross-striations are seen only in better-differentiated tumors. The histologic types are subclassified as embryonal, alveolar, and pleomorphic. The term *botryoid* is applied to the gross grape-like appearance of the rare submucosal mass that may appear in the epibulbar tissues. This is usually of the embryonal type.

The embryonal type (see Fig. 7.6A) shows some combination of undifferentiated small round cells admixed with cells attempting rhabdomyoblastic differentiation. These latter cells may be small and round with deeply eosinophilic cytoplasm that is acidophilic or spindle-shaped with hyperchromatic nuclei and acidophilic cytoplasm. Other cells include elongated strap cells with one or two nuclei arranged in tandem. Intermingling streams of spindle cells may be associated with a myxoid stroma. Intracellular glycogen, which can be demonstrated in most rhabdomyosarcomas, is sparse in this poorly differentiated embryonal form. The spider cells are examples in which the intracellular glycogen has been moved by fixation.

Those embryonal tumors in which fascicles of spindle cells predominate have a higher degree of differentiation. Within the elongated strap cells, one or two nuclei are arranged in tandem, and the cytoplasm is acidophilic. Well-marked cross-striations may be visible with hematoxylin and eosin stain.

The alveolar type, which is the second most common type, is so called because the framework is similar to that of the lung. The tumor cells are similar to those found in the embryonal form and are present within the alveolar spaces and cling to the fibrous connective tissue septa (Fig. 7.6B). It is not uncommon to find an alveolar pattern as a small focus in a tumor that is predominantly of the embryonal type. The alveolar subtype is thought to have the worst prognosis, regardless of its location or stage.

Management

As chemotherapy has improved, attempts have been made to spare radiation therapy in a select group of patients (Alvarez Silvan et al., 1996; Lackner and Urban, 1997). Nowadays, however a patient living in the United States who presents with an orbital tumor that, on biopsy, is an embryonal rhabdomyosarcoma may become part of a therapeutic protocol of some state, regional, or national rhabdomyoma study group. The orbital lesion has a more favorable prognosis compared with rhabdomyosarcoma in many other organs and anatomic sites because of the absence of multiple, systemic foci of tumor.

The Mayo Clinic Section of Pediatric Oncology recommends a staging workup, which includes "CT or MRI at the primary site, evaluation of lymph nodes, chest CT scan, bone scan, and bilateral marrow aspirant biopsy." If there is no metastatic spread of the tumor, the patient is staged into one of three clinical groups: Group 1, complete surgical excision of tumor with no microscopic residual tumor; group 2, microscopic residual tumor; and group 3, gross residual disease. If the tumor has undergone an incisional biopsy and then been debulked, it belongs in group 2. If the tumor is large, frankly infiltrative, and not debulked after biopsy, it belongs in group 3.

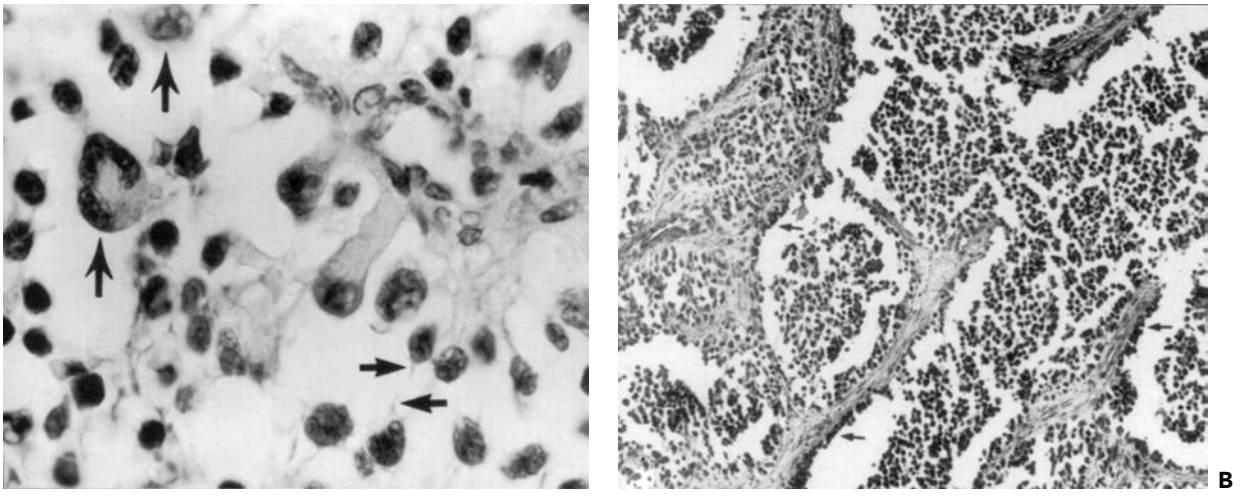

Figure 7.6 Embryonal rhabdomyosarcoma shows a variety of cell types. **A:** Note a large strap cell (*center*) with a large nucleus at the lower pole, a spiderweb cell (*upper left arrow*), and a large, multinucleated cell (*left center arrow*). Many of the cells had a wispy extension of cytoplasm (*lower right horizontal arrows*), suggesting a tadpole-like contour. The size and shape of the hyperchromatic nuclei differ (original magnification ×600). **B:** Another area of the same tumor shows alveolar features. Note the orderly row of cells clinging to the connective tissue septa along the periphery of the cell clusters (*arrows*) and the loose arrangement of the cells in the center of the cell clusters (original magnification ×90).

In the past we encountered cases that were operated on within 3 weeks of onset; the tumor was small, located in the retrobulbar space, and grossly circumscribed. With careful dissection and the use of cryoextraction, the surgeon may believe the tumor has been removed intact, but the tumor's circumscription may be deceiving. Bits of tissue from the adjoining retrobulbar tissue may show microscopic spread on further microscopic study. True "complete excision" of an orbital rhabdomyosarcoma is probably rare, except for an exenteration.

No radiotherapy is used for group 1 cases. This group implies clear surgical margins. Radiotherapy of 36 Gy is administered for group 2. For group 3, 45 Gy of radiotherapy is given at week 3. Two drugs, vincristine and actinomycin, are administered initially. Cytoxan may be added to the regimen if lymph nodes are involved. A more aggressive treatment protocol is needed for an alveolar rhabdomyosarcoma of the orbit.

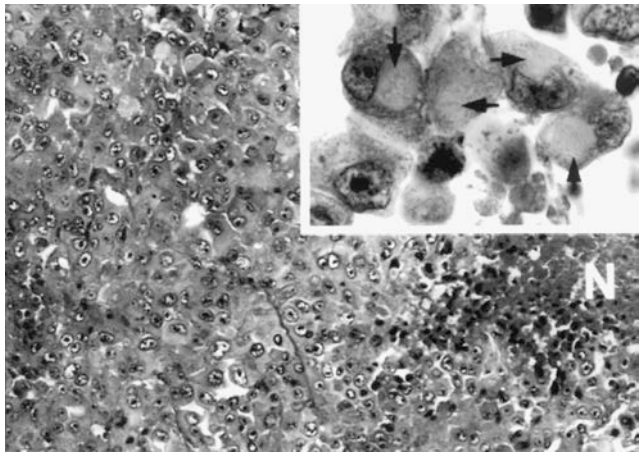

Figure 7.7 This recurrent rhabdoid orbital tumor is composed of poorly differentiated cells with copious cytoplasm continuing filamentous inclusions with prominent nucleoli. N marks the focus of necrosis (hematoxylin and eosin, original magnification ×50). Inset: Arrows denote filamentous cytoplasmic inclusions (hematoxylin and eosin, original magnification ×250). (From Gunduz K, Shields JA, Eagle RC Jr, et al. Malignant rhabdoid tumor of the orbit. *Arch Ophthalmol*. 1998;116:243–246, with permission.)

RHABDOID TUMOR

Rhabdoid (from the Greek, *phabdo-eides*, like a rod, rod-shaped) is usually a primary tumor of the kidney in children <1 year of age. Basically, it is another member of the clan of poorly differentiated, mesodermal, small, round cell tumors. Initially, Beckwith and Palmer (1978) thought it was a sarcomatous variant of Wilms tumor and named it *rhabdomyosarcomatoid tumor* because of its light microscopic resemblance to embryonal rhabdomyosarcoma. Later (Haas et al., 1981), on the basis of ultrastructural study of 11 examples available from the National Wilms Tumor Study, the neoplasm was considered a distinct entity separate from rhabdomyosarcoma and given the name *rhabdoid tumor*.

Subsequently, tumors with a histologic appearance similar to that of rhabdoid tumors arising in the kidney have been described in virtually every extrarenal anatomic site. Carcinomas of various types may also have rhabdoid features. The term *extrarenal rhabdoid tumor* as it pertains to soft tissue should be used for tumors with predominant rhabdoid morphology and in which no other clear line of differentiation can be documented (Weiss and Goldblum, 2001).

The presentation of a rhabdoid orbital tumor is so similar to a rhabdomyosarcoma (see Fig. 7.7) that it is impossible to differentiate them at this early stage. A primary rhabdoid tumor of the orbit is very rare. Rootman et al. (1989) seem to be the first to report such a case. This was a 6-week-old boy with rapidly progressive proptosis since the age of $1\frac{1}{2}$ weeks. The proptosis of the child's left eye measured 10 mm. CT scan showed a large, nonenhancing retrobulbar mass with expansion of the orbital walls and extension of tumor into the superior and inferior orbital fissures. The tumor was debulked with a suction fragmentation device. The patient was treated with a combined course of radiotherapy (41 Gy) and chemotherapy. The child was alive and well without recurrence or second tumor 24 months later. The second case was a 47-year-old man (Johnson et al., 1991) who presented with increasing hyperopia and monocular diplopia of 3 months' duration. A circumscribed, firm tumor within the sheath of the left lateral rectus muscle was resected. Postoperatively, he received 50 Gy of radiotherapy in 25 fractions. There was no recurrence of tumor 18 months postoperatively.

A third patient, a 3-year-old girl (Gunduz et al., 1998), did not fare as well as the two preceding patients. The biopsy diagnosis was made after a 3-week history of proptosis of the right eye. Despite initial chemotherapy and radiotherapy, she had massive orbital recurrence 6 months later, and an exenteration was performed. Aggressive chemotherapy with a combination of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide phosphate was continued. At 17 months' follow-up, orbital debulking surgery with externalization of the maxillary sinus was performed because of massive tumor recurrence. The child died 28 months after her initial diagnosis from tumor invasion of the central nervous system.

A fourth case (Niffenegger et al., 1992) was a 50-year-old man with a rapidly growing mass in the area of the right lacrimal gland. A wide local excision of a yellow mass was performed. A workup for metastases was negative, and orbital exenteration was then performed. Five weeks after exenteration, 45 Gy of radiotherapy was delivered in 25 fractions over 40 days. Six weeks after completion of radiotherapy, the patient was started on systemic chemotherapy, including cycles of actinomycin, doxorubicin, cyclophosphamide, and vincristine. Fifteen

months later, the patient had no evidence of either local recurrence or distant metastases.

Stidham et al. (1999) reported a primary malignant rhabdoid tumor of the orbit in a neonate. Walford et al. (1992) described an intraorbital rhabdoid tumor arising in the right orbit of a 3-year-old boy previously treated for bilateral retinoblastoma. The patient first presented at the age of 2 months. The left eye was enucleated, and the right orbit was treated with radiotherapy (lateral field, 45 Gy). Recurrent tumor was noted 27 months later in the right orbit. The patient was treated with chemotherapy and additional radiotherapy but failed to respond. He died as the result of intracranial tumor progression.

Imaging Aspects

With CT scan, the cases of Rootman et al. (1989) and Gunduz et al. (1998) showed a poorly defined, homogeneous, nonenhancing mass in the retrobulbar space. If the tumor is quite large, there may be thinning of the orbital bones with some expansion of the orbit.

Pathology

These tumors are highly malignant with rapid growth, and the mortality rate is high. Grossly, the orbital tumor appears pale tan to white and is likely to be circumscribed to some degree. However, if it has been present for >3 to 4 weeks, it may be widely infiltrative.

The light microscopic features are sheets or nests of round, oval (epithelioid-like) cells with eosinophilic cytoplasmic filaments, eccentric nuclei, and "owl eye" (Spencer, 1996). The hyaline-like globules of cytoplasmic, intermediate filaments may be so large as to indent the nuclei. Vimentin staining is usually positive. Other immunostaining may be variable.

Management

Once the incisional biopsy is positive for rhabdoid tumor, an oncologist should be contacted quickly to oversee the patient's staging workup. When the workup is completed, the oncologist may recommend one of the current protocols of therapy used by the Intergroup Rhabdomyosarcoma Study. The therapy involves some combination of chemotherapy, surgical excision, and radiotherapy. However, too few cases of orbital rhabdoid have been treated and followed up over an adequate period of time to have a standard, uniform consensus as to sequence of treatment entities, dosage, and duration of therapy.

RHABDOMYOMA

Terminology

Rhabdomyoma is a benign neoplasm of striated muscle that occurs most commonly in the heart of infants. Extracardiac rhabdomyomas are divided into four different types on the basis of histologic differences, the patient's age, and the organ or area of the body affected. Ophthalmologists need to be concerned only with the adult and fetal types.

Neoplasms of striated muscle relevant to this discussion include, in ascending order of their histologic differentiation toward normal adult striated muscle, embryonal rhabdomyosarcoma, fetal rhabdomyoma, pleomorphic rhabdomyosarcoma, and adult rhabdomyoma, the best differentiated (Knowles and Jakobiec, 1975). Some authors regard fetal rhabdomyoma as the benign counterpart of embryonal rhabdomyosarcoma and adult rhabdomyoma as the benign counterpart of pleomorphic rhabdomyosarcoma. The qualifier "adult" seems to be based on this classification. However, in this regard, it is a misnomer because this well-differentiated tumor also occurs in children.

Clinical Features

The so-called adult rhabdomyoma presents as a slow-growing, painless, solitary, round or polypoid mass in the head and neck region. Here it principally affects the pharynx or larynx, causing hoarseness or difficulty in swallowing (Weiss and Goldblum, 2001). Two cases of orbital involvement have been well-authenticated (Knowles and Jakobiec, 1975; Hatsukawa et al., 1997).

The case described by Knowles and Jakobiec (1975) was an 8-year-old boy who presented with a 3-month history of a painless, firm, enlarging mass in the left upper eyelid. At surgery, an encapsulated, multilobulated mass was found arising from the medial rectus muscle. (The tumor's attachment to the orbital muscle differentiates it from embryonal [undifferentiated] rhabdomyosarcoma in the same age-group.) Four months later, the patient returned with a pea-sized lesion overlying the insertion of the medial rectus muscle. This lesion was thought (mistakenly) to be an embryonal rhabdomyosarcoma, and an orbital exenteration was performed. Twenty-five years later, the patient was alive and free of recurrence.

The case described by Hatsukawa et al. (1997) was a 16-month-old boy with painless proptosis (3 mm) of the right eye of 1 month's duration. On lateral orbitotomy, an engorged lateral rectus muscle was noted. The orbital mass was partially excised from its attachment to the muscle. One year after surgery, CT scan did not show any regrowth of tumor.

Kapadia et al. (1993) studied 24 fetal rhabdomyosarcomas that presented as well-defined solitary masses arising within the soft tissue or mucosa of the head and neck and displayed a greater degree of maturation and a wider morphologic spectrum than previously recognized. In this summary of cases, one patient, an 18-year-old man, was listed as having an orbital mass associated with proptosis and decreased vision. No other clinical features of this case were stated. However, the histologic specimen, illustrated in the article, was removed from the periorbital area. This

case may be a primary tumor of the eyelid with secondary invasion of the orbital space. Kapadia et al. (1993) made an important observation; that is, fetal rhabdomyomas occur in a broader age range and histologic spectrum than previously recognized. Eleven tumors (46%) occurred in patients older than 15 years.

Our 50-year tumor file includes no orbital rhabdomyomas.

Imaging Aspects

We have found only one CT scan of an orbital rhabdomyoma in the literature (see Fig. 7.8). This showed an irregularly contoured, somewhat mottled mass in the right orbital apex that extended forward along the medial and lateral rectus muscles. The mass did not enhance after contrast injection. A plain skull film did not show bony erosion (Hatsukawa et al., 1997).

Pathology

The so-called adult-type rhabdomyoma is a gray-yellow, fibrous mass composed of mature but disorganized striated muscle fibers with a mixture of collagen fibers. Cellular details are illustrated in Figure 7.9. There is no nuclear atypia. Metastases are absent. Immunohistochemically, the cells stain positively for myoglobin, desmin, and muscle-specific actin but are positive less commonly for vimentin and S-100 protein (Weiss and Goldblum, 2001).

According to Kapadia et al. (1993), so-called fetal rhabdomyomas of soft tissues are grossly circumscribed, soft, and gray white to tan pink with a mucoid glistening cut surface. The tumors are unencapsulated. Their histologic picture is quite different from adult-type rhabdomyomas. Overall, the fetal type shows a spectrum of skeletal muscle differentiation ranging from the ''classic'' immature tumors to those lesions with more advanced rhabdomyoblastic maturation. They refer to the latter group as *intermediate* differentiation, a degree that never completely recapitulates the appearance of normal adult skeletal muscle. The intermediate type is illustrated in Figure 7.10. This specimen is from the 18-year-old man described previously.

The immature classic type is composed of an admixture of haphazardly arranged, slender skeletal muscle fibers with rare cytoplasmic cross-striations and undifferentiated round, spindled, serpentine cells in a myxoid stroma. All 24 specimens the authors examined had cross-striations.

Figure 7.9 Rhabdomyoma is composed of large, round polygonal cells with acidophilic, granular cytoplasm and large, vesicular, peripherally placed nuclei (trichrome, original magnification ×375). (From Knowles DM II, Jakobiec FA. Rhabdomyoma of the orbit. *Am J Ophthalmol*. 1975;80:1011–1018, with permission.)

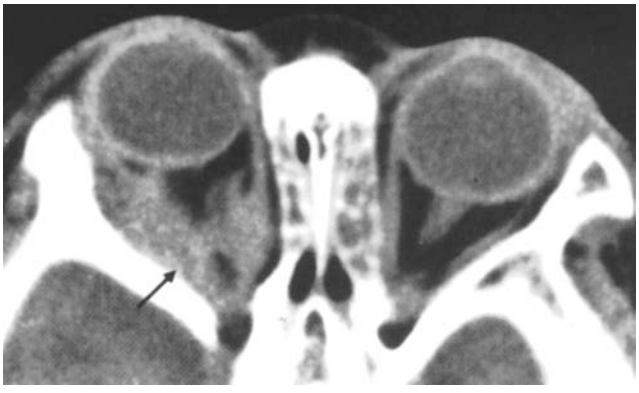

Figure 7.8 Axial computed tomography scan shows an irregular right retrobulbar mass (*arrow*). The tumor did not enhance after contrast injection. (From Hatsukawa Y, Furukawa A, Kawamura H, et al. Rhabdomyoma of the orbit in a child. *Am J Ophthalmol*. 1997;123:142–144, with permission.)

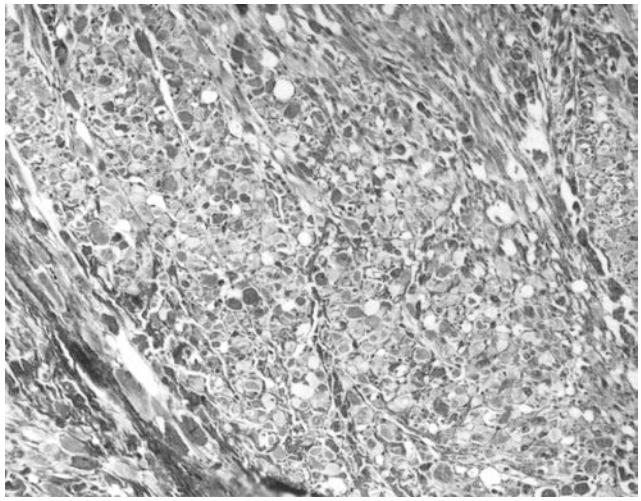

Figure 7.10 An ''intermediate'' fetal rhabdomyoma from the periorbital region shows a fascicular arrangement of cells with abundant eosinophilic cytoplasm and rare cytoplasmic vacuolation (original magnification ×75). (From Kapadia SB, Meis JM Frisman DM, et al. Fetal rhabdomyoma of the head and neck: A clinicopathologic and immunophenotypic study of 24 cases. *Hum Pathol*. 1993;24:754–765, with permission.)

Immunohistochemical stains were positive for myoglobin, desmin, and muscle-specific actin.

Management

A guarded debulking or partial excision of the tumor seems to suffice, taking care to preserve, as much as possible, the affected extraocular muscle.

MALIGNANT MESENCHYMOMA

Terminology

The present concept of mesenchymoma evolved from the interest of Stout (1948) in the morphology and classification of soft tissue sarcomas, particularly in children. Working only with the media of light microscopy and tissue culture (electron microscopy was in its infancy), he unified a number of poorly differentiated, unclassified sarcomas of mixed morphology and applied the simple term *mesenchymoma* to this new conglomerate of tumors. This name brought order into a disordered field of complex, compound names that had previously been used to designate the multiple histologic features of these sarcomas. It is likely that the term *mesenchymoma* was borrowed from an earlier publication of Klein (1932).

Stout (1948) restricted the name to a tumor containing two or more elements of mesenchymal derivation, in which each element alone might be considered a primary malignant neoplasm. The definition excluded the malignant fibroblast-like components that were common to all the primary sarcomas in the study. The tissue elements most commonly found in these tumors were mixtures of leiomyosarcoma and liposarcoma as well as rhabdomyosarcoma and liposarcoma.

In reference to the histogenesis, Stout (1948) suggested the tumor was the result of a dysontogenetic fault, a way of acknowledging a "borderline of embryology and pathology" (Dehner, 1986). This would be an attractive explanation for those mesenchymomas occurring in later life. However, this theory does not explain most mesenchymomas in elderly adults. For the latter, it seems more plausible to regard their origin from primitive and uncommitted mesenchymal elements that have differentiated along multiple cell lines (Enzinger and Weiss, 1988).

Enzinger and Weiss (1988) were supportive of Stout's (1948) original definition and stated "a judicious approach is mandatory in making this diagnosis" to prevent it from becoming a "wastebasket" for poorly differentiated sarcomas. In 1988, this definition might well have become a standard for future diagnosis and classification. However, some subsequent authors wished to add other tissue entities of mesenchymal derivation that nullified data pertaining to incidence.

Case Reports

Nash and Stout (1961) published their tabulation of 42 cases of malignant mesenchymoma in children from the surgical pathology file of Columbia University College of Physicians and Surgeons. Two of these cases involved the orbit. One was a 6-year-old girl. Her tumor was a mixture of undifferentiated rhabdomyosarcoma and leiomyosarcoma. No details of either the clinical features or the presentation were stated. The case was managed with radiotherapy, administration of nitrogen mustard, and orbital exenteration. The child had several recurrences and died 1 1/2 years later with metastases to the brain and mediastinum. The histopathology of the rhabdomyosarcoma was what is now classified as the embryonal type. The histopathology of the leiomyosarcoma was not described.

Their other case was a 6-year-old boy with a tumor composed of undifferentiated chondrosarcoma associated with unrecognizable and unclassified mesenchymal tissue. The lesion was partially excised. The tumor recurred and the patient died 10 months later with metastasis to the liver and lungs.

Vlvo (1968) described a 28-year-old man with an orbital mass that may have qualified as a mesenchymoma on the basis of Stout's (1948) strict histologic standards. Over a 2-month period, the patient's left eye was luxated by the rapidly growing tumor that also produced complete ophthalmoplegia. Biopsy revealed a mesenchymoma composed of elements of a pleomorphic, adult-type rhabdomyosarcoma and liposarcoma. An orbital exenteration was performed. No radiotherapy was given. After 1 1/2 years there was no recurrence or metastasis.

We have found no additional cases of orbital mesenchymoma reported in the English language literature since 1968.

In the future, if an ophthalmologist encounters a histologically proved orbital mesenchymoma, an oncologist should be contacted. This physician can recommend the current chemotherapy regimen available to treat this tumor.

MALIGNANT ECTOMESENCHYMOMA

This orbital tumor is a very rare soft tissue neoplasm that is generally believed to arise from ectomesenchyme. It is composed of a mesenchymal element (most often rhabdomyosarcoma) and a neuroectodermal element (neuroblastoma, ganglioneuroblastoma, ganglioneuroma). It occurs predominantly but not exclusively in infants and children.

Case Reports

Matsko et al. (1992) observed a 5-year-old girl with a painless, rapidly enlarging mass in the superior nasal quadrant of the right orbit. The firm, palpable mass produced 7 mm

of blepharoptosis and downward displacement of the eyeball. MRI revealed a mass primarily in the preseptal space of the eyelid, which extended posteriorly over the globe to the equatorial area. The tumor was debulked through an anterior orbitotomy. The patient was treated according to the Intergroup Rhabdomyosarcoma Study III regimen. In brief, the patient was treated initially with dactinomycin for 5 days. Ten days later, 45 Gy of radiotherapy was administered in 1.8-Gy fractions. Subsequently, alternating courses of dactinomycin and vincristine were given. The tumor resolved. Subsequently, the patient was well without recurrence or secondary tumor.

The case described by Bittinger et al. (1997) was a 5-year-old boy with proptosis of the left eye. Imaging showed a large mass in the nasal quadrants of the affected orbit, which infiltrated the medial rectus muscle. The mass was completely removed. The bony orbit was intact. The patient was treated with the Intergroup Rhabdomyosarcoma Study III regimen. The patient was well and tumor free 12 months after presentation.

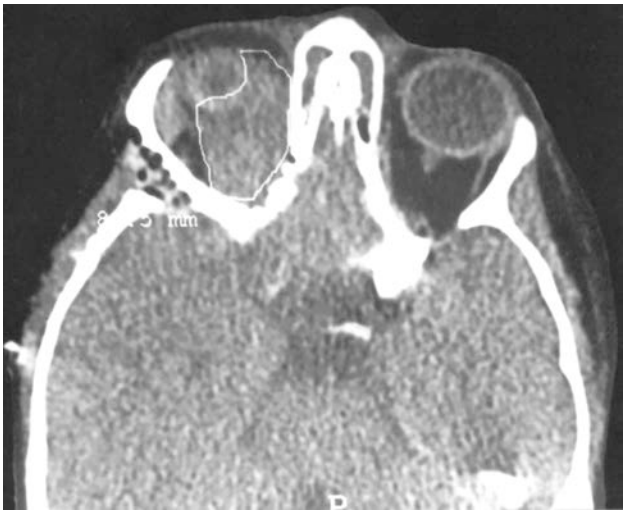

Figure 7.11 Computed tomography scan shows a large, isodense mass filling the nasal quadrant of left orbit and engulfing the medial rectus muscle. (From Bittinger A, Rossberg C, Rodehuser M. Primary malignant ectomesenchymoma of the orbit. *Gen Diagn Pathol.* 1997;142:221–225, with permission.)

Imaging Aspects

CT scan of the patient described by Bittinger et al. (1997) showed an isodense, poorly circumscribed mass filling the nasal orbit and infiltrating the medial rectus muscle (see Fig. 7.11). MRI of the patient described by Matsko et al. (1992) showed a well-circumscribed mass of low intensity on T_1-weighted imaging (see Fig. 7.12A) and marked enhancement on T_2-weighted imaging with extension of the mass into the nasal orbit (Fig. 7.12B).

Pathology

Grossly, the tissue specimen from the case reported by Matsko et al. (1992) consisted of a white, friable, minimally vascularized mass. The mesenchymal component of the tumor was a rhabdomyosarcoma with marked pleomorphism and many mitotic figures. This lesion included cells that were positive for immunocytochemical markers of skeletal muscle differentiation, including desmin, vimentin, and muscle-specific actins. The neuroectodermal component was a neuroblastoma composed of cells positive for markers of neuroendocrine differentiation, including chromogranin, neurofilaments, and nerve growth factor receptors.

The tissue specimen from the case reported by Bittinger et al. (1997) also included loosely arranged rhabdomyosarcomatous elements. The other components of the tumor were ganglioneuromatous cells with one or two nuclei, central nucleoli, and broad eosinophilic cytoplasm. These cells were positive for S-100 protein, glial fibrillary acid protein, and neurofilaments.

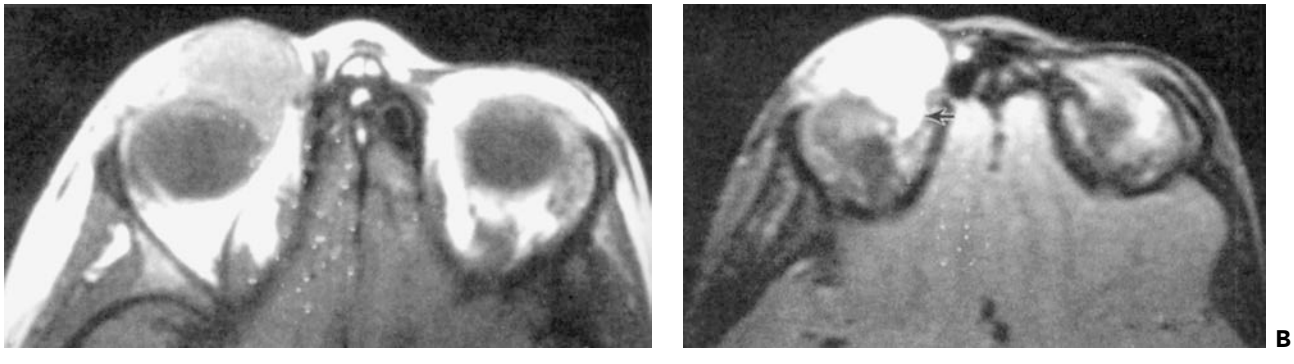

Figure 7.12 **A:** T_1-weighted magnetic resonance imaging demonstrates low signal intensity of the tumor in the right upper eyelid. **B:** T_2-weighted magnetic resonance imaging shows marked enhancement of the mass and its extension into the superior nasal quadrant of the right orbit (*arrow*). (From Matsko TH, Schmidt RA, Milam AH, et al. Primary malignant ectomesenchymoma of the orbit. *Br J Ophthalmol.* 1992;76:438–441, with permission.)

LIPOMA

Terminology

This tumor is composed of mature fat and represents the most common mesenchymal neoplasm (Enzinger and Weiss, 1988). Owing to the wide distribution of adipose tissue throughout the body, the tumor may occur anywhere. Surgically speaking, the tumor is often classified according to location such as superficial, cutaneous, deep-seated, parosteal, neural, hernial, intramuscular, and associated with tendon sheaths. Histologically, the tumor often includes an admixture of other tissue elements, which, rightly or wrongly, is reflected in terms such as fibrolipoma, spindle cell lipoma, angiolipoma, angiomyolipoma, and myxolipoma. Finally, the tumors may be single or multiple, non-neoplastic, hamartomatous, or familial proliferations of mature fat. Enzinger and Weiss (1988) summed up all such categorization as "largely speculative and of little practical consequence."

Incidence

Although the orbital reticular tissues are generously endowed with adipose tissue, true lipomas primary in the orbit are as uncommon as lipomas elsewhere are regarded as common. In the older ophthalmic literature, many putative lipomas of the orbit were not histologically documented by the finding of some evidence of encapsulation. Since these tumors were indistinguishable from normal orbital fat, the diagnosis was based only on a surgeon's statement. In addition, because of the limited orbital exposure attendant to many orbitotomies during such years, many "lipomas" represented instances where fat was removed in the belief that such tissue represented the true tumor. Many, but not all, orbital lipomas reported in the literature before 1970 must be regarded with reservation.

Subsequently, well-documented orbital cases are a spindle cell lipoma in a 42-year-old woman described by Johnson and Linn (1979); a spindle cell lipoma in a 20-year-old woman described by Bartley et al. (1985); an angiolipoma in a 3-year-old girl described by Feinfield et al. (1988); a 35-year-old man described by Koganei et al. (1988); a 61-year-old man described by Small et al. (1979); and a 35-year-old man described by Brown et al. (1991). The four primary orbital lipomas from our 50-year survey can be included in this group. Three of these cases were men, aged 37, 59, and 27 years, and one 20-year-old woman. The 27-year-old man was also reported by Bartley et al. (1985). The age range of the nine cases noted in this paragraph was 3 to 61 years, with a median of 35 years. Five were male and four female.

Clinical Features

The presentation of a primary orbital lipoma is usually a painless, slowly enlarging mass producing proptosis or displacement of the eye with or without diplopia, of 3 to 15 months' duration. The mass is preceded in some cases by fullness of an eyelid of the affected orbit.

Some exceptions to this benign presentation have little effect on ocular function because of the lipoma. The 63-year-old man described by Sabates et al. (1990) lost all sight in his right eye over an 8-year period associated with a profound optic atrophy. Imaging studies showed enlargement of the optic canal caused by a mass encircling the intracanalicular portion of the optic nerve with extension posteriorly into the ipsilateral optic chiasm.

Small et al. (1979) noted a lipoma in the frontal bone of a 61-year-old man, which produced marked bony metaplasia, mistakenly assumed to be a fibrous dysplasia over a 17-year period of observation, with extension into the right orbit. The downward displacement of the eye was first noted at the age of 6 years.

Another case was the 35-year-old man with 17-mm proptosis of the left eye reported by Brown et al. (1991) and caused by a huge fat-like mass that produced metaplasia of adjacent orbital bone and extended through the superior orbital fissure into the middle cranial fossa (see Fig. 7.13A). This tumor was also first manifest in childhood by a progressive malposition of the affected eye and had been present since birth. At surgery, the tumor lacked encapsulation. This feature, combined with the age at onset, prompted the authors to propose the term *lipomatous hamartoma*. Orbital lipomas, understandably, may reach considerable size. The lipoma reported by Koganei et al. (1988) measured $42 \times 34 \times 32$ mm.

Imaging Aspects

The attenuation void of these tumors on CT scan and the high-intensity T_1-weighted signal with MRI (Fig. 7.13B) are compatible with orbital adipose tissue. Some tumors, particularly the angiolipomas, show variable degrees of enhancement with contrast on CT scan. Other lipomas may show spots of altered attenuation or variable densities depending on the admixture of other tissue elements. The T_2-weighted MRI cannot be differentiated from a collection of orbital blood.

Pathology

Grossly, these tumors are circumscribed with a yellowish white or yellow-tan hue, less yellow than the color of normal fat. These characteristics aid in their dissection from surrounding fat, except that some tumors are so large and the orbital space is so compact that intact removal is often not possible without undue trauma to neighboring nerves and muscles. In the orbit, the tumors tend to be less lobulated than in other anatomic sites. If the tumor is removed intact, some slight encapsulation is evident, a feature that is lost with biopsy or piecemeal removal.

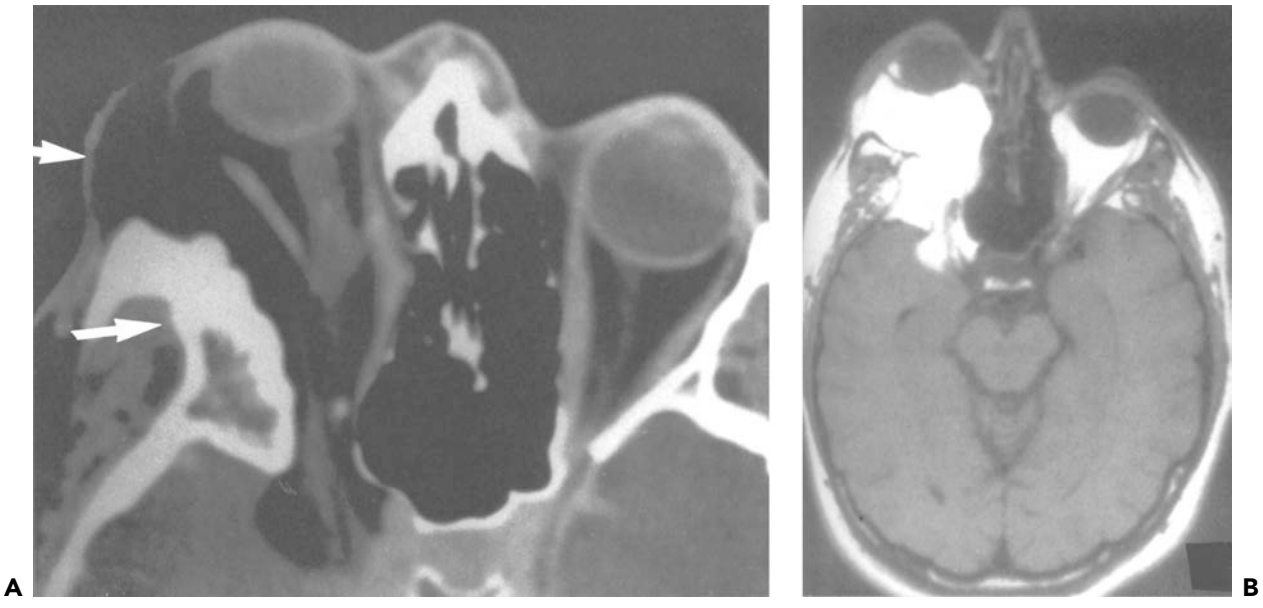

Figure 7.13 Lipomatous hamartoma. **A:** Computed tomography scan shows a large radiolucent mass (*upper arrow*) along the right lateral wall of the orbit compressing the lateral rectus muscle medially and extending through the superior orbital fissure into the middle cranial fossa (*lower arrow*). The lateral orbital wall shows marked thickening. **B:** Magnetic resonance imaging documents the configuration and extent of the mass on T_1-weighted image. (From Brown HH, Kersten RC, Kulwin DR. Lipomatous hamartoma of the orbit. *Arch Ophthalmol.* 1991;109:240–243, with permission.)

Histologically (see Fig. 7.14), the tumor is composed of mature adipocytes that are somewhat larger than ordinary fat (Enzinger and Weiss, 1988). The content of other tissues of mesenchymal origin, such as spindle cells, fibroblasts, collagen, and myxoid foci, may vary considerably. In the ordinary orbital lipoma, the delicate, intraseptal vascular network may be deceivingly inconspicuous, probably owing to the compression factor of the crowded orbital space. However, the true vascularity of these tumors is quickly evident if the tumor's encapsulation is breached during orbitotomy. The ensuing hemorrhage and the need for continuing hemostasis proves a frustrating handicap to total removal of the tumor.

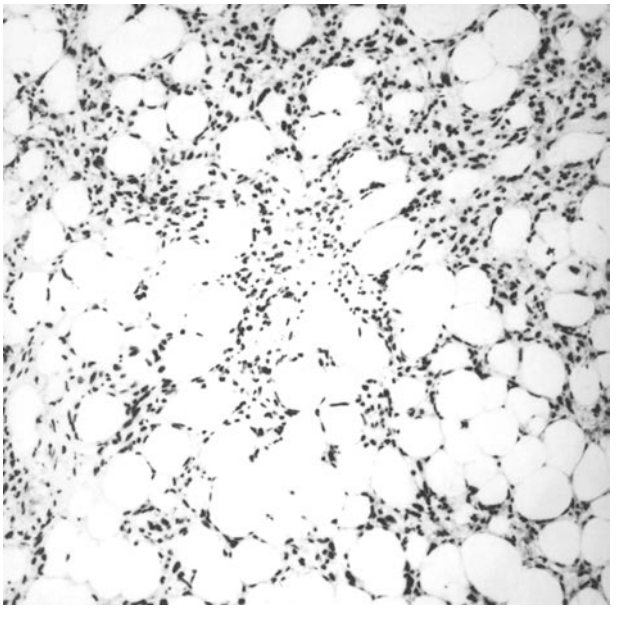

Figure 7.14 In this spindle cell orbital lipoma, mature adipocytes are interspersed in a delicate stromal net of benign spindle cells (original magnification ×160).

With immunohistochemical analysis, adipocytes of both benign and malignant fatty tumors stain positively for vimentin and stain variably for S-100 protein. More recently, an antibody to the adipocyte lipid-binding protein p422 (also known as *aP2*), a protein expressed exclusively in preadipocytes late in adipogenesis, has been found to stain only lipoblasts and brown fat cells, as well as liposarcomas. The diagnostic utility of this antibody has yet to be proved (Weiss and Goldblum, 2001).

Management

Intact surgical removal is the preferred management. This is best performed either by an orbitocoronal or a lateral orbitotomy that gives the widest field for dissection. Two of our patients had intact removal through a frontal craniotomy and a lateral orbitotomy. A third patient had piecemeal removal through a frontal craniotomy but was lost to subsequent follow-up. An anterior brow approach resulted in only a partial removal in the fourth patient. Recurrence required further excision 22 months later.

LIPOSARCOMA

This is a malignant tumor of primitive mesenchymal lipoblasts that, because of their pluripotential character, may recapitulate differing phases in the functional evolution of normal fat in any given liposarcoma. Therefore, it is difficult to define a typical liposarcoma. Most pathologists believe the tumor has its own pathogenesis rather than being a malignant transition from a preexisting lipoma. It is one of the most common soft tissue sarcomas of adults. Most often they arise from the deep soft tissue of the extremities or the retroperitoneum. They are much less frequent in the head and neck. They rarely occur in children. Our discussion here is limited to liposarcoma occurring in the orbit.

Incidence

In a series of 645 biopsies of orbital tumors collected between 1962 and 1982, Shields et al. (1984) found only two liposarcomas, 0.3%. Our 50-year compilation of orbital tumors at Mayo Clinic included six liposarcomas, also 0.3%. However, the frequency of only 0.3% is deceiving as we count the number of orbital liposarcomas reported in the literature since 1963. At the time of the publication of the study by Enzinger and Weiss (1988), there were a half dozen or so detailed reports of primary orbital liposarcomas in the literature. Ten additional cases were reported in three publications (Lane et al., 1988; Jakobiec et al., 1989; McNab and Moseley, 1990). Subsequently, one case was reported by Favrot et al. (1994), seven cases from one institution by Cai et al. (2001), and our six cases, for a total of 30 or more cases. This number is much larger than many other individual tumor groups in this text. In reality, orbital liposarcoma may not be as rare as has been stated in the literature.

In the combined 10 cases of Lane et al. (1988), Jakobiec et al. (1989), and McNab and Moseley (1990), the age and sex of individual patients was stated. If the 6 adults in our series with similar data are included, the total was 16 adults, 8 males and 8 females. The age range was 17 to 71 years with a median of 31.5 years. Liposarcoma is very rare in children, with only one case, a 5-year-old boy, having been reported by Quere et al. (1963).

Clinical Features

Liposarcoma and lipoma produce a similar effect on the involved eye at the time of presentation, namely, proptosis or displacement of the eye with or without diplopia and little, if any, impairment of vision. An exception may be a patient with a tumor in the orbital apex that compresses the optic nerve causing both pain and impairment of vision (see Fig. 7.15). The duration of symptoms before presentation may be a bit shorter than those preceding lipoma. Both benign and malignant types may reach considerable size.

Figure 7.15 Exenteration specimen from a myxoid liposarcoma shows a large, yellow-hued, invasive, multilobulated tumor that encompassed globe, surrounded optic nerve, and invaded extraocular muscles. Most of the lobules were firm, but some were semimyxoid in consistency. The neoplasm measured approximately $50 \times 30 \times 22$ mm.

Liposarcomas metastatic to the orbit from nonorbital sources have been reported by Enterline et al. (1960); Abdalla et al. (1966), and Fezza and Sinard (1997). The case described by Enterline et al. (1960) was unusual; metastasis developed 16 years after initial diagnosis in a 53-year-old woman.

Lipomas that undergo malignant transformation to liposarcoma have been reported in the literature. Weiss and Goldblum (2001) believe these are, in reality, liposarcomas in which inadequate sampling led to underdiagnosis of malignancy in the original material. These authors also believe that liposarcoma-like lesions in children are apt to represent lipoblastoma, a fetal form of lipoma.

Pathology

The common link among the various types of liposarcoma is the lipoblast. The degree of differentiation of this cell is a principal determinant for classifying the tumor and judging its clinical behavior. Other histologic features may also play some role in classification such as the relative content of lipid in the cells, the amount of extracellular mucinous material, the overall degree of cellularity, and degree of cellular pleomorphism (Enzinger and Weiss, 1988). In nonorbital sites, the location of the tumor may also influence prognosis.

Since 1994 (Weiss, 1994), liposarcomas have been classified on the above characteristics into five histologic subtypes, namely, pleomorphic, round cell, myxoid, dedifferentiated, and well-differentiated types. This classification may be subject to further grouping of the five subtypes and to exceptions such as a mixture of several subtypes in one tumor.

Most orbital liposarcomas are the myxoid type (see Fig. 7.16). All subtypes tend to have some lobular

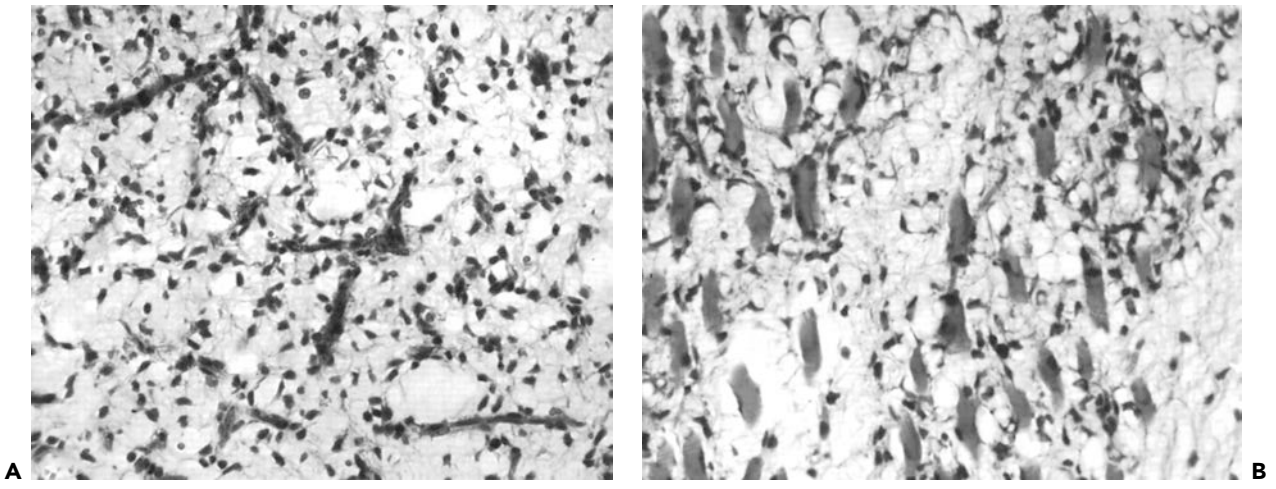

Figure 7.16 Myxoid liposarcoma. **A:** Numerous lipoblasts of varying size and a capillary network (dark, linear structures) are interspersed in a myxoid stroma. The vascular pattern is distinctive and appears as plexiform strands between the foamy cells (original magnification ×245). **B:** Extensive invasion of extraocular muscles (original magnification ×285).

configuration and are either poorly circumscribed or obviously invasive of extraocular muscle. The consistency of the tumor lobule may be firm or gelatinous. In color, the tumor varies from gray to yellow white, depending on the relative mix of lipoblasts and myxoid matrix. It is beyond the field of the ophthalmologist to know the histologic nuances of the five subtypes. This is the domain of the pathologist.

Imaging Aspects

An attempt to construct a representative CT scan display of this tumor is confounded by conflicting descriptive phrases in the literature such as a "radiolucent mass," "a mass of greater density than surrounding fat," "mottled densities," "streaky radiographic densities," "a mass with coexistent increased and decreased densities," "pseudocystic component," "pseudocapsule," and "reticulated densities." Such confusion merely reflects the variable histologic morphology among tumors or the differing cytologic infrastructure within the same tumor. Suggestions that a preoperative diagnosis of liposarcoma is possible, based on CT scan characteristics, are more fiction than fact.

There is only one imaging feature common to all scans, that is, the intimate association of the tumor with extraocular muscle. MRI probably shows hyperintense signals similar to those of normal surrounding orbital fat on T_1-weighted images and hypointense signals on T_2-weighted images.

Management

Over the last 40-some years, some type of surgery has been the primary therapy for an orbital liposarcoma. These procedures include "wide excision with clear margins," "exenteration," "orbitocraniotomy," and "subtotal excision." Some, but not all, surgical eradications have been followed by radiotherapy. In general, there are too few cases in the literature managed by one or another of the above surgical regimens to propose a standardized management. Furthermore, the follow-up is relatively short in many cases.

Jakobiec et al. (1989) summarized their management of five cases. Three of their cases required orbital exenteration after local recurrence, and two refused exenteration. None of the patients experienced regional or distant metastases with follow-up of 1 to 7 years (mean, 5.2 years). We do not know of any other report wherein the patient was treated only with radiotherapy.

Our experience with the management of this tumor is less favorable. We have adequate follow-up data on four of six patients. The first patient was a 29-year-old man. In April 1956, a circumscribed mass (myxoid liposarcoma) that was adjoining the left superior and inferior oblique muscles was removed intact. Radiotherapy was given, 56 Gy in four fractions, over a 3-month period. In July 1970, the patient was living without recurrence.

The second patient was a 61-year-old man with a tumor (myxoid liposarcoma) filling the left antrum with secondary spread into the left maxilla, nasal fossa, and left orbit. He underwent excision of all soft tumor tissue and enucleation of his left eye in May 1955. No postoperative radiotherapy was administered. The patient died with recurrence in June 1961.

The third patient was a 17-year-old boy who in August 1962 underwent exenteration of a large retrobulbar mass (myxoid liposarcoma measuring $5 \times 3 \times 2.5$ cm) in the left orbit. In January 1969, an extensive recurrence involving intracranial and extraorbital structures occurred. The tumor was considered unresectable.

The fourth patient was a 33-year-old man who underwent exenteration of the right orbit for a liposarcoma, type unknown, in July 1983 at another institution. Postoperatively, 50 to 60 cGy was given. We first saw the patient in January 1989 with recurrent tumor in the orbit with lytic destruction of frontal bone and soft tissue extension of tumor into adjacent frontal sinus and nasal bones. The liposarcoma had undergone a dedifferentiation into a highly malignant tumor type. There followed a craniofacial resection (February 1989), a frontal craniotomy (March 1989), and a frontal craniotomy (April 1989). In December, the patient had developed multiple metastases.

Cai et al. (2001) also have follow-up data on five of their series of seven patients with primary orbital liposarcomas. Some type of surgery was the primary procedure in all five patients. Total exenteration was performed on one patient with a pleomorphic tumor and another patient with a well-differentiated neoplasm. Both patients were alive at last follow-up with no sign of recurrence 65 months (pleomorphic tumor) and 108 months (well-differentiated tumor) after surgical removal. One patient underwent a "marginal" excision of a well-differentiated tumor and was living without recurrence 53 months later. A fourth patient had six partial resections of a well-differentiated tumor and was alive with recurrent disease 204 months later. The fifth patient had a subtotal exenteration plus radiotherapy of a well-differentiated tumor but died of another cause 13 months later.

In summary, total exenteration alone appears to be the best primary surgical procedure to treat orbital liposarcoma of all histologic types. Postoperative radiotherapy appears to be inadvisable. Should recurrence appear, it is probably due to an incomplete exenteration wherein sarcoma cell remnants probably remained surrounding the severed end of the proximal portion of the optic nerve at the anterior entrance of the optic foramen. In the future, the posterior portion of the exenteration specimen surrounding the severed optic nerve should be examined for microscopic evidence of sarcoma. If present, the optic foramen should be unroofed and the remaining optic nerve excised up to the chiasm.

At present, radiotherapy may be reserved only for recurrences and, if necessary, given in a dosage of approximately 0.5 Gy. Chemotherapy has not been successful.

Immunohistochemical stains may vary among the differing histologic types of liposarcomas.

LEIOMYOMAS

The reader of this text may wonder why the title of this section is written in plural number. There seem to be two types of leiomyomas peculiar to the orbit, which differ in their orbital location, histopathologic makeup, and probable etiopathogenesis. Both types are benign neoplasms. The two types are the leiomyoma of smooth muscle origin and the leiomyoma that may have a vascular genesis.

Smooth Muscle Leiomyoma

The smooth muscle of the orbit and adnexal tissue is scant. It consists chiefly of the tarsal muscle of the upper and lower eyelids, and the Müller muscle along the floor of the orbit. Nath and Shukla (1963) suggested the capsulopalpebral muscle of Hesser as a probable source of histogenesis.

This tumor usually presents as a slowly enlarging, painless mass in the anterior portion of the orbit of some 8 to 12 months' duration in a young adult. The mass is firm to palpation and tends to extend forward into the adjoining eyelid. There is little, if any, impairment of visual function, perhaps some slight displacement of the eye, and puffiness of the affected eyelid.

CT scan (see Fig. 7.17) shows thickening of the eyelid tissues, but the bulk of the lesion is in the anterior orbit just posterior to the orbital rim. The mass does not enhance with contrast. There is no bone destruction or remodeling.

The histopathologic features of the tumor are illustrated in Figure 7.18. Spindle cells stain positively for muscle actin, desmin, and vimentin. The lesions are not encapsulated.

Because the presentation of a leiomyoma is in the forward orbit, the tumor is smaller and discovered earlier than the larger vascular leiomyoma in the retrobulbar space. The tumor described by Jolly et al. (1995) was totally excised, although it was not encapsulated, without recurrence 15 months later. These authors thought this patient, a 42-year-old man, was the fifth reported case of a leiomyoma involving the anterior orbit. They do not mention the authors of the preceding four cases.

Vascular Leiomyoma

Synonyms for this tumor include "venous hemangioma," "hemangioleiomyoma," and "angiomyoma." These names emphasize a major vascular component of this benign

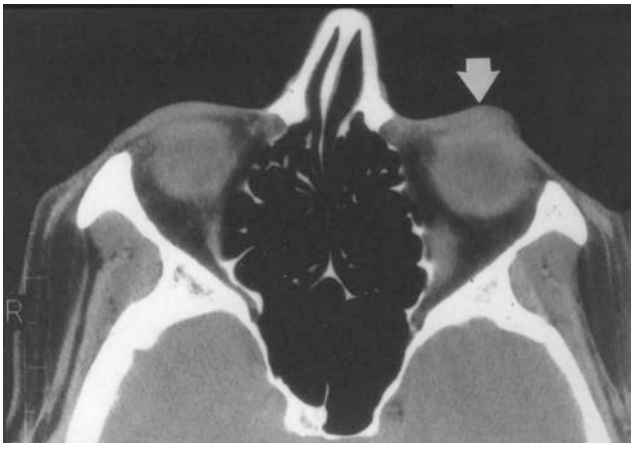

Figure 7.17 Computed tomography scan shows mass (*arrow*) in left lower eyelid and anterior orbit. (From Jolly SS, Brownstein S, Jordan DR. Leiomyoma of the anterior orbit and eyelid. *Can J Ophthalmol.* 1995;30:366–370, with permission.)

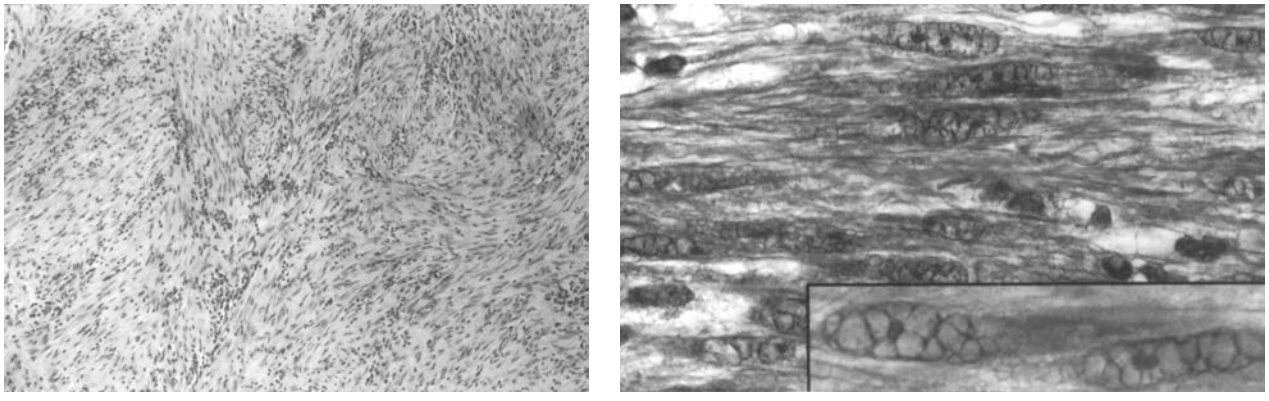

Figure 7.18 Leiomyoma. **A:** Bundles of spindle cells are arranged in an interlacing manner separated by a variable amount of collagenous stroma. Capillaries are inconspicuous (hematoxylin and eosin, original magnification ×100). **B:** The spindle-shaped cells contain blunt-ended, cigar-shaped nuclei and longitudinally oriented, nonstriated intracytoplasmic filaments (Masson trichrome, original magnification ×1,000). Inset: Numerous vesicles and prominent nucleoli are present in nucleus (Masson trichrome, original magnification ×1,600). (From Jolly SS, Brownstein S, Jordan DR. Leiomyoma of the anterior orbit and eyelid. *Can J Ophthalmol*. 1995;30:366–370, with permission.)

neoplasm. Stout (1937) introduced the term *vascular leiomyoma* to describe a smooth muscle tumor with a prominent vascular component that occurs in areas other than the skin. Over time, *angiomyoma* seems to have become the favored name.

Over the next 40 years, several case reports of this tumor, which occurs chiefly in the posterior orbit, were published under the term *leiomyoma*. Recent review of these earlier studies suggests they were examples of Stout's vascular leiomyoma, although his term was not used. One publication in 1975 noted their occurrence also in the eyelid, although no description or photography of the eyelid lesion was given. Calling the angiomyoma a leiomyoma has resulted in confusion in terminology and cataloging of the tumor according to its histopathologic makeup. The angiomyoma probably arises from the muscle layer associated with postcapillary venules and veins, particularly in view of the tumor's vascularity and posterior location within the orbit (Spencer, 1996).

In our previous edition (1994), we surveyed a dozen or so orbital leiomyomas (angiomyomas) and noted an age range of 5 to 45 years. There was no sex predilection. Subsequently, four more cases of this tumor, primary in the orbit, have been reported: A 9-year-old boy (Carrier et al., 1993); a 56-year-old man (Badoza et al., 1999); a 25-year-old man (Wiechens et al., 1999); and a 9-year-old boy (Kulkarni et al., 2000).

The patient described by Kulkarni et al. (2000) had an orbital apex tumor with intracranial extension of 8 months' duration that was partially excised. Four years later, there was anterior extension of the intraconal tumor in the posterior orbit. Also there was some extension into the middle cranial fossa. A frontotemporal craniotomy was performed, and the tumor was excised.

The 25-year-old patient described by Wiechens et al. (1999) had extension of his orbital tumor into the adjoining maxilla. This tumor was of nearly lifelong duration and was heavily calcified at the time of total resection.

The presenting clinical picture of this neoplasm is a slowly progressive proptosis or displacement of the eye of several months' to several years' duration. The degree of visual dysfunction produced by the tumor's growth is proportionate to the time before presentation and size of the lesion attained at the time of surgical removal. Most patients note intermittent episodes of pain or discomfort. In our patient, a 9-year-old girl, pain was associated with exercise (Henderson and Harrison, 1970).

CT scan shows an oval or round, circumscribed mass in the retrobulbar space that with contrast enhancement has a mottled appearance (see Fig. 7.19). Some tumors occur in the orbital apex, pushing an extraocular muscle or optic nerve to one side but not invading these structures. MRI (see Fig. 7.20) shows a well-circumscribed mass that is isointense to gray matter on T_1-weighted image and becomes hyperintense on T_2-weighted images. Some lesions, because of their profuse vascular component, may exhibit high-velocity flow on Doppler ultrasonography.

Grossly, the tumors have a gray-tan color and are encapsulated. The smooth muscle cells are arranged in bundles interspersed with varying amounts of collagen and foci of myxoid tissue (see Fig. 7.21). Tumors of long duration may have plaques of calcium, remnants of a previous intralesional hemorrhage. The nuclei are rod- or cigar-shaped and show some degree of palisading. Trichrome stain demonstrates intense cytoplasmic eosinophilic and longitudinally oriented, nonstriated myofibrils that are the diagnostic features of these tumors. Reticulin fibrils wrap around the

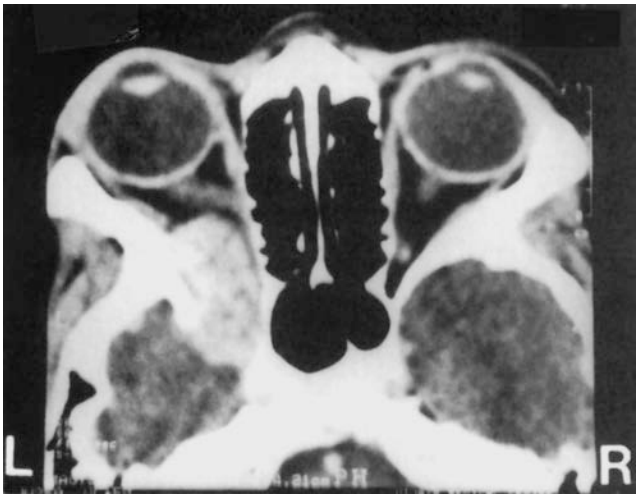

Figure 7.19 Contrast-enhanced computed tomography scan shows a well-circumscribed mass at the left orbital apex pushing the optic nerve medially. Note expansion of the superior orbital fissure and extension of the tumor into the middle cranial fossa. The numerous imaging voids in the display probably represent the vascular sinusoids of the tumor. (From Kulkarni V, Rajshekhar V, Chandi SM. Orbital apex leiomyoma with intracranial extension. *Surg Neurol*. 2000;54:327–330, with permission.)

cells, corresponding to the basement membrane. Vascular spaces of irregular size and shape are scattered throughout the tumor.

The preferred management is complete excision. The tumor in our 9-year-old patient was removed intact from the inferior retrobulbar space. The surgery was accompanied by profuse bleeding throughout the procedure. Although encapsulated, angiomyomas at the orbital apex tend to adhere to extraocular muscles, optic nerve, and periorbita joining the superior orbit. These lesions are frequently incompletely removed lest optic nerve dysfunction occur postoperatively. When the tumor recurs, it is best to attempt full excision through an orbitocranial, bicoronal approach. The tumors are resistant to radiotherapy. If radiotherapy is used to treat a recurrence, malignant degeneration of the tumor is likely.

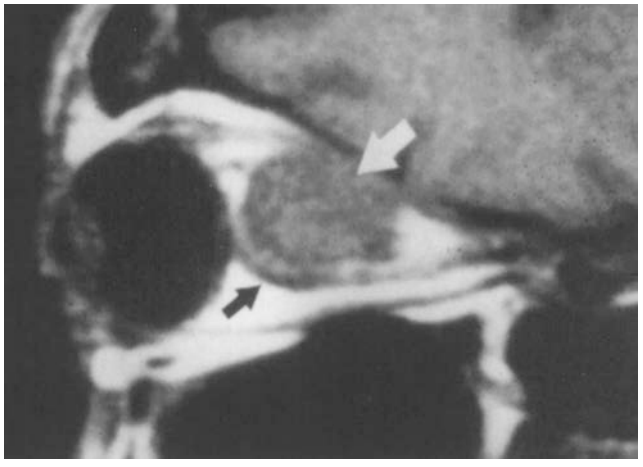

Figure 7.20 Sagittal T_1-weighted magnetic resonance image shows optic nerve (*black arrow*) that is displaced but not invaded by the well-defined orbital mass (*white arrow*). (From Badoza D, Weil D, Zarate J. Orbital leiomyoma: A case report. *Ophthal Plast Reconstr Surg*. 1999;15:460–462, with permission.)

LEIOMYOSARCOMA

This malignant neoplasm has its origin either from the smooth muscle components of the eyelid or a more vascular genesis from the muscle layer of veins and venules in the retrobulbar orbital space. The latter origin probably corresponds to the vascular leiomyosarcoma of Weiss and Goldblum (2001), occurring in nonorbital sites. However, the orbital leiomyosarcomas are fewer in number than the preceding leiomyomas, and no attempt has been made to differentiate the sarcomas on the basis of histology or clinical features as we have done with the leiomyomas. The sarcomas are lumped together as one term and are so referenced. The leiomyosarcoma is believed to arise *de novo* rather than occur as a malignant transformation of a preexisting leiomyoma, unless the latter has been treated with radiotherapy.

Meekins et al. (1988) found six prior reports of primary leiomyosarcoma in the literature: A 48-year-old woman (Kojima and Sakai, 1972); a 68-year-old woman (Tsuchiya et al., 1977); a 36-year-old man (Wojno et al., 1983); a 51-year-old woman (Terry, 1934); and two women aged 58 and 59 years (Jakobiec et al., 1975). The median age of these six patients and the 82-year-old woman reported by Meekins et al. (1988) was 57 years (range, 36 to 82 years). The predominant female sex incidence and age range of orbital leiomyosarcoma is comparable to the data concerning leiomyosarcomas in nonorbital sites (Weiss and Goldblum, 2001). The age range of patients with orbital leiomyomas is considerably younger and without a sex predilection.

Additional cases noted in the literature since the report by Meekins et al. (1988) are a 75-year-old woman (Arora and Betharia, 1990); a 78-year-old woman (Ichikawa et al., 1996); and an 84-year-old woman (Wiechens et al., 1999).

Three reports of leiomyosarcomas metastatic to the orbit have been published in the past decade (Conlon et al., 1994; Matsumoto et al., 1995; Logrono et al., 1997).

Also, in their 1988 review of the literature, Meekins et al. (1988) noted three cases of radiation-induced leiomyosarcoma in patients treated for retinoblastoma. Additional cases were reported by Mihara et al. (1991) and Klippenstein et al. (1999).

The clinical presentation of a leiomyosarcoma and a benign leiomyoma are the same except the malignant tumor occurs in an older patient, and some, but not all, may have some degree of pain or discomfort.

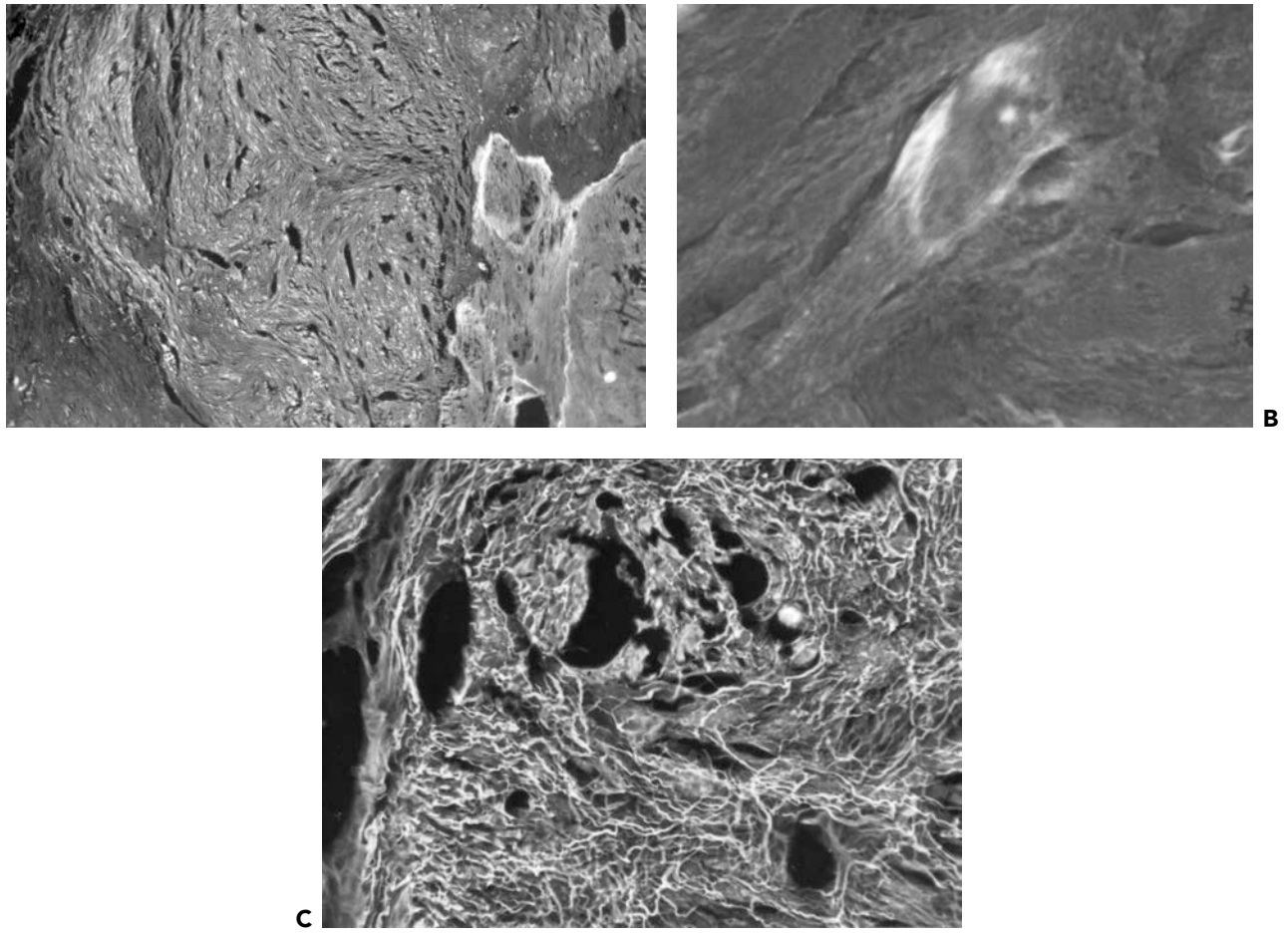

Figure 7.21 **A:** Interlacing bundles of smooth muscle cells stream from a wall of irregular vascular spaces lined by endothelium. The lighter-staining areas are connective tissue, the darker areas are calcification (hematoxylin and eosin, original magnification ×55). **B:** Fine, discrete, longitudinal striations (myofibrils) in this tumor section (Mallory phosphotungstic acid hematoxylin, original magnification ×1,200). (From Henderson JW, Harrison EG, Jr. Vascular leiomyoma of the orbit: Report of a case. *Trans Am Acad Ophthalmol Otolaryngol*. 1970;74:970–974, with permission.) **C:** Large, irregular, contoured vascular channels (hematoxylin and eosin, original magnification ×135).

CT imaging shows the size, shape, and location of a mass, usually in the retrobulbar space. This is helpful in planning the eventual surgical approach. Otherwise, no single imaging display is typical of a leiomyosarcoma. The lesion may look solitary or multilobular, the margins may appear circumscribed or infiltrative, and the matrix may be homogeneous or inhomogeneous, depending on the vascularity of the tumor. In short, the image of a leiomyosarcoma is indistinguishable from that of other orbital sarcomas.

A leiomyosarcoma shows a prominent vascular component, on both gross and microscopic examination. The leiomyosarcoma cell is elongated and has abundant cytoplasm that varies from pink to deep red with hematoxylin and eosin stain. Of greater diagnostic value is the Masson trichrome stain, which demonstrates the numerous, deep red, usually parallel myofibrils that run the length of the cell. These striations are purple if stained with phosphotungstic acid hematoxylin. The nuclei are centrally located and cigar-shaped. Some cells may also show perinuclear vacuoles that indent or distort the nucleus. The cells are generally arranged in fascicles or intertwining bundles (see Fig. 7.22).

In judging the degree of malignancy, several sections of the tissue specimen should be studied, and the number of mitotic figures should be counted and averaged per 100 high-power fields. A correlation between the mitotic index and the clinical course of the orbital leiomyosarcoma has not been well standardized.

The prognosis for a patient with an orbital leiomyosarcoma is generally poor. The possibility for cure is total excision of the tumor. This is easier said than done, except by exenteration. The removal of a large, friable, unencapsulated tumor may even be beyond the skills of a multispecialty surgical team. If exenteration is necessary, the earlier it is done, the better. However, if the tumor is solid,

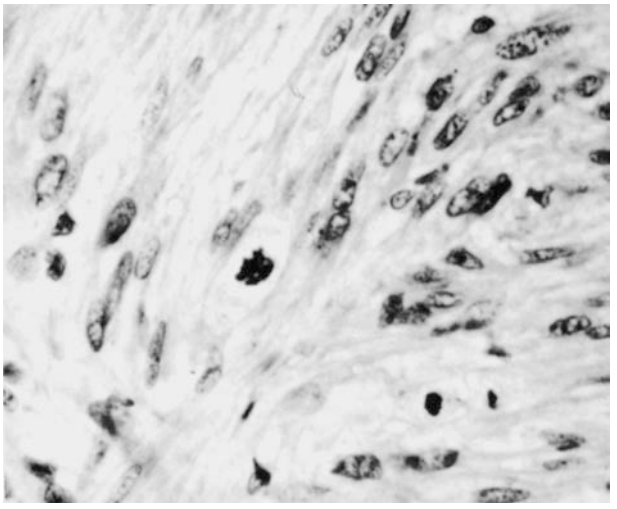

Figure 7.22 Interdigitating fascicles of spindle-shaped cells with elongated nuclei, stippled chromatin, and long, thin, eosinophilic cytoplasmic borders. Note mitotic figure in center of field (hematoxylin and eosin, original magnification ×400). (From Meekins BB, Dutton JJ, Proia AD. Primary orbital leiomyosarcoma: A case report and review of the literature. *Arch Ophthalmol*. 1988;106:82–86, with permission.)

small, and encapsulated, it can be totally removed through a lateral orbitotomy, a transfrontal approach, or a coronal orbitofrontal craniotomy, depending on its orbital location.

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8 Tumors of Peripheral Nerve Sheath Origin

The origin of many tumors in this text is linked, wholly or in part, to mesoderm. However, nerve sheath tumors arise from neuroectodermal tissue. Ophthalmologists are principally interested in the benign proliferation of elements of the sheaths of branches of the cranial, motor, and sensory nerves that traverse the orbital space. These disorders are the solitary neurofibroma, neurofibromatosis type 1, and schwannoma. They have one feature in common, that is, a tendency to undergo malignant transformation. The malignant forms are lumped together under the broad term *malignant nerve sheath tumor*.

These four types of orbital nerve sheath neoplasms are the most protean and ubiquitous of the numerous tumor families in this text. The incidence of nerve sheath tumors among the total tumors in our 50-year survey (see Chapter 3) is 3.5% (63/1,795). In their various guises, these tumors may be associated with optic nerve glioma, buphthalmos, iris nodules, hamartomas of the choroid, posterior capsular cataract, asymmetry of the facial bones, hypoplasia of adjacent paranasal sinuses, dysplasia or dysgenesis of the sphenoid bone, and eyelid tumors.

SOLITARY NEUROFIBROMA

Solitary neurofibroma may also be called *isolated neurofibroma*.

Incidence

Nine neoplasms in our series were the solitary type. The age at onset was known in eight of the patients, ranging from 20 to 58 years (median, 45.5 years). Sex incidence was equal. Two of these patients had more than one solitary lesion in the unilateral orbit (see Fig. 8.1). Multiple forms of this lesion have also been reported in the literature (Gurland et al., 1976; Krohel et al., 1985; Shields et al., 1990; Meyer and Wobig, 1992). Shields et al. (1990) encountered three separate neurofibromas in one orbit. The case described by Meyer and Wobig (1992) was unusual, a solitary neurofibroma in each orbit. This patient also had several features suggestive of multiple endocrine neoplasia type 2B. Multiple neurofibromas are usually associated with neurofibromatosis type 1 (NF1).

Clinical Features

The usual orbital location of a solitary neurofibroma is the supraorbital frontal branch of the trigeminal nerve. Second in frequency is the maxillary branch. Multiple tumors in patients also involve other nerves transversing the orbit (see Fig. 8.2). The tumor is slow-growing. The usual pattern of presentation is a progressive unilateral proptosis of 1 or more years' duration. The tumor exerts a mass effect on the eye, and the eye's displacement is opposite the growing mass. Initially there is no pain, but pain of variable degree develops as the tumor expands the covering perineurium and epineurium of the nerve. Visual acuity is little affected.

One of our patients, a 52-year-old woman, had quite a different presentation. A year before admission she had noted slight proptosis of the left eye. One month later, she had a sudden, marked reduction in vision in the affected eye. She was treated for optic neuritis, without effect. On presentation, vision was reduced to counting fingers associated with pallor of the left optic disk and a cecocentral scotoma. Her neurofibromas proved to be localized to the apex of the left orbit.

Imaging Aspects

The ophthalmologist may have some trouble differentiating between a solitary neurofibroma and a cavernous hemangioma on computed tomography (CT) scan. Both lesions have about the same degree of enhancement, are well outlined, have similar homogeneity, and are located in the retrobulbar space. However, on anteroposterior and

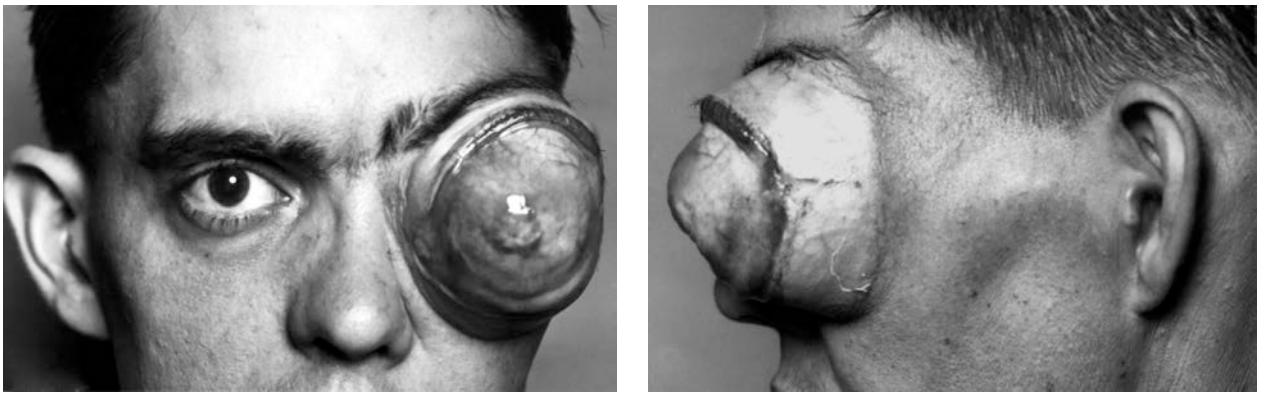


Figure 8.1 Front and side views of a huge neurofibroma in a 32-year-old man that developed slowly over a period of 15 years. The left eye was blind. The patient asked to have the orbital mass removed because of increasing pain. An exenteration was performed. The tumor measured $8 \times 7 \times 6$ cm.

sagittal views, the neurofibroma is more rounded in shape and positioned more forward in the retrobulbar space. Indeed, the front edge of the neurofibroma may overlap the rear edge of the eyeball. Other features of a neurofibroma are noted in Figure 8.3.

Pathology

A gross specimen is illustrated in Figure 8.4. The basic unit of the localized neurofibroma is a myelinated or nonmyelinated peripheral nerve axon covered by intertwining Schwann cells, which are intimately associated with collagen strands and surrounded by a matrix of mucopolysaccharide, capillaries, and endoneural fibroblasts, all in varying ratios (see Fig. 8.5). This tissue complex causes a fusiform or oval intraneural expansion of the involved nerve. The tumor is circumscribed, is grayish white, and has a firm fibrous consistency. With low-power light microscopy, the distinctive feature is wavy interlacing bundles of collagen interspersed with spindle-shaped cells and separated by a mucopolysaccharide-rich material (see Fig. 8.6A). Under higher power, the mixture of spindle cells can be differentiated into endoneural fibroblasts and those with comma-shaped nuclei (Schwann cells). This arrangement may be compact and cellular or loose-textured

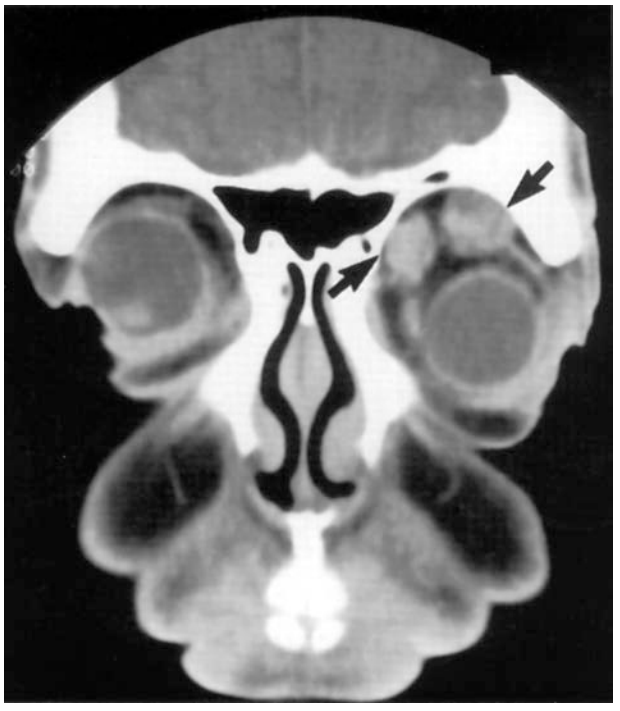


Figure 8.2 Multiple neurofibromas. Coronal computed tomography scan shows two circumscribed tumors (*arrows*) in the left orbit of a 42-year-old man. At orbitotomy, the masses were connected by a small isthmus of tissue.

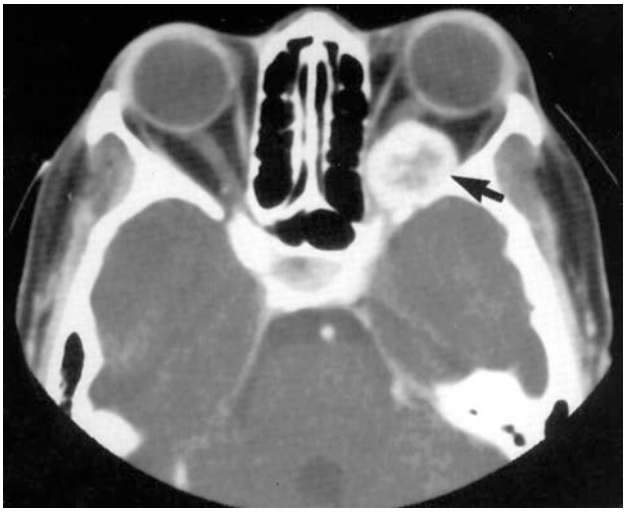


Figure 8.3 Axial computed tomography scan shows an enhancing circumscribed mass in the apex of the left orbit (*arrow*) with a hypodense center that remodeled and expanded orbital bone of a 52-year-old woman with proptosis of 1 year's duration. Vision was reduced to counting fingers secondary to optic nerve compression.

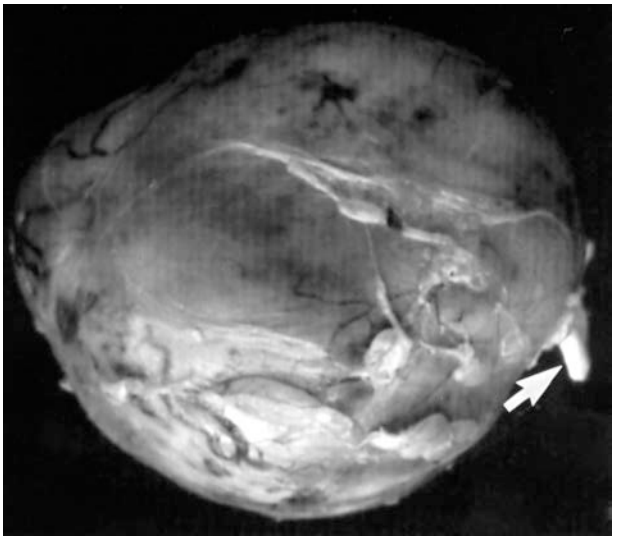


Figure 8.4 Gross specimen of a circumscribed, oval expansion of an orbital nerve. At the right (*arrow*) is the pigtail segment of normal nerve from which it arose. Specimen measured 2 × 2.5 × 2 cm.

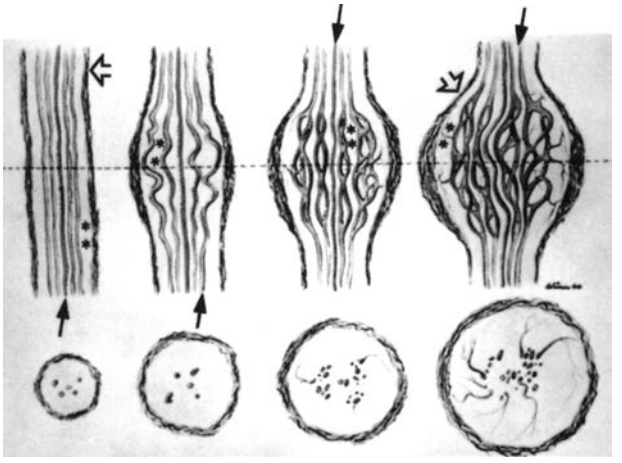


Figure 8.5 Diagrammatic representation of progressive phases (left to right) of the tumor's growth that spreads the Schwann cell cylinders (*arrows*) apart. Perineurium (*arrowheads*) is thickened. *Asterisks* indicate endoneural tissue. Cross-sections through the level of the *dotted line* are shown at the bottom of the illustration. (From Harkin JC, Reed RJ. Tumors of the peripheral nervous system. In: *Atlas of tumor pathology, Second Series, Fascicle 3*, Washington, DC: Armed Forces Institute of Pathology; 1969, with permission.)

and myxoid in appearance. Capillarity is not a prominent feature of this tumor compared with the plexiform neurofibroma. The axonal component of these tumors can be identified with the Bodian stain (colloidal silver), and the matrix can be stained with Alcian blue (a copper-containing dye). A neurofibroma containing spherical tactile-like bodies is illustrated in Figure 8.6B. Immunohistochemically, the tissue stains positive for S-100 protein.

Here, we should mention the diffuse neurofibroma that many pathologists consider a distinct type of nerve sheath tumor. Histopathologically, it has cellular components similar to those of the solitary neurofibroma, but it is an infiltrating, extraneural neoplasm that expands along connective tissue septa and intercellular spaces, replacing orbital fat and permeating extraocular muscle (see Fig. 8.7). Its clinical behavior and management are more akin to those of a schwannoma. From a practical standpoint, other authors choose to combine these tumors in their discussion of schwannoma.

Management

The solid makeup of the solitary tumor facilitates its intact removal. If it can be removed intact, it does not recur.

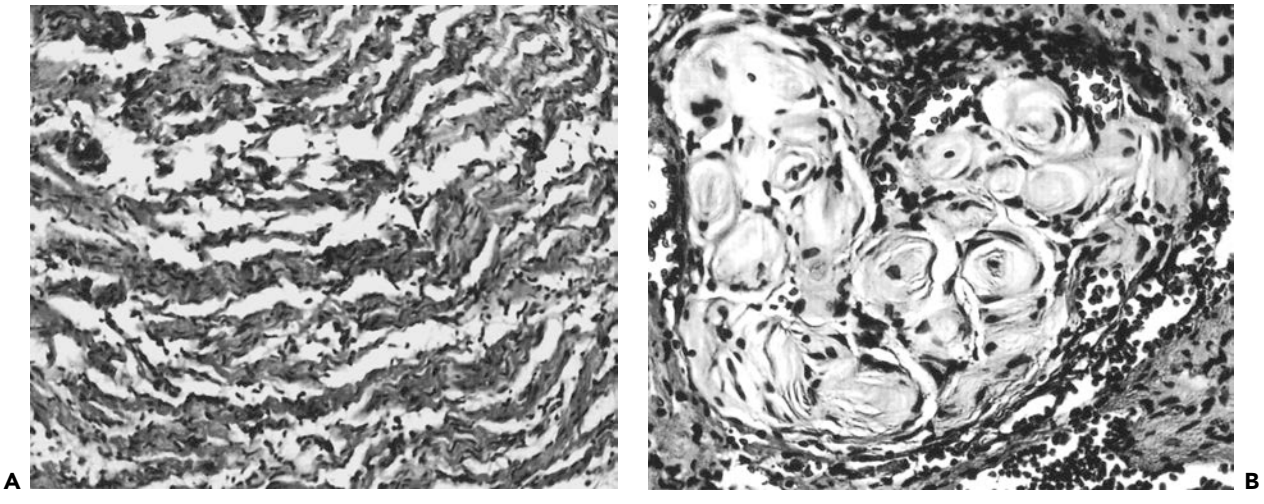


Figure 8.6 **A:** Wavy bundles of collagen interspersed with Schwann cells and endoneural fibroblasts and separated by a mucinous-myxoid matrix (original magnification ×130). **B:** Some areas may contain spherical tactile-like corpuscles (original magnification ×200).

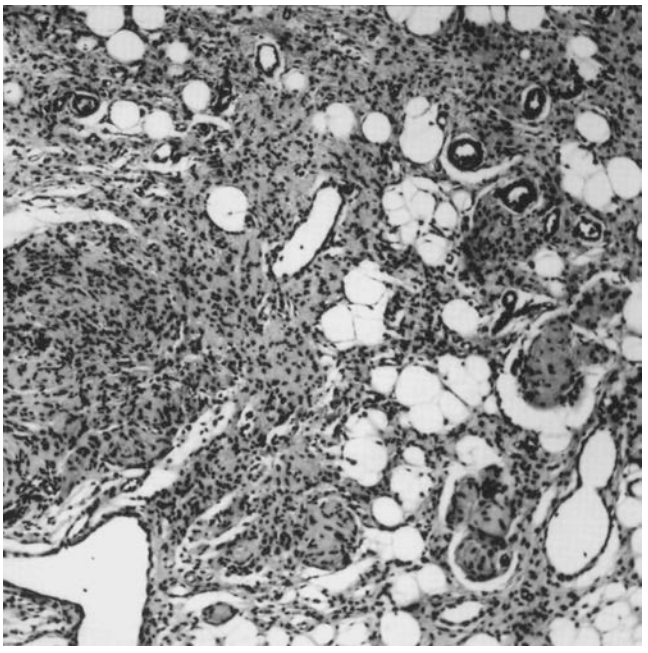


Figure 8.7 Diffuse neurofibroma. Note the nerve tissue permeating orbital fat and surrounding blood vessels (original magnification ×65).

Excision is reasonably free of bleeding. In the surgical management of nerve sheath tumors, care should be taken to identify the involved nerve as a sensory nerve rather than a motor nerve before resecting it.

NEUROFIBROMATOSIS TYPE 1

The plexiform neurofibroma is the hallmark of the orbital form of NF1, a peripheral nerve sheath subset of von Recklinghausen neurofibromatosis, first described by von Recklinghausen (1882). The latter is an autosomal dominant abnormality that may involve multiple organ systems. The genetic defect is located on chromosome 17.

Incidence

Our 50-year survey includes 31 pathologically proven plexiform neurofibromas (see Table 3.3). This frequency was approximately three times (31:9) that of neurofibroma and 1 1/2 times more common than schwannoma. The sex incidence was nearly equal, 17 men and 14 women.

The age of the patient when first seen at Mayo Clinic is a meaningless statistic because it does not represent the true age at onset. The age at onset was known in 30 of our patients. The plexiform subset of the tumor is predominantly a disorder with an onset in infancy or childhood. In nearly half our patients (13/30), the tumor was present at birth. Onset at 6 months or earlier occurred in another four patients.

Clinical Features

A thickening or palpable lump in the upper eyelid is the usual sign that brings the infant or child to the attention of a pediatrician or an ophthalmologist. The droopy eyelid may conceal a slight degree of proptosis or displacement of the underlying eye. If further examination of the patient's body surface reveals several *café au lait* spots, it is likely the patient will later show other signs or symptoms of generalized NF1. The growth of the tumor is slow. The hypertrophy of the eyelid becomes more localized to its lateral third, and a tumor consisting of cords is palpable. The uneven growth of tumor gives the affected eyelid a sinuous curve. Downward displacement of the eye soon follows owing to extension of the tumor through the orbital septum into the anterosuperior orbit. If the eyelid is particularly thick, it may conceal the subtle malposition of the eye at the time of presentation, unless a simultaneous bulging buphthalmic eye is present. Eventually, by adolescence, the eyelid tumor may further extend into the neighboring temple or the forehead or fill the orbit with a ropy mass likened to a "bag of worms." With such progression, some mild degree of pain or discomfort may occur because of the localization of orbital neurofibroma in the sensory nerves.

Another pattern of presentation is a proptosed eye associated with pulsation, with or without a palpable mass. The pulsation is best appreciated by viewing the affected eye from its lateral side. The pulsation is caused by incursion of brain tissue into the orbit, secondary to the absence (dysgenesis) of the wings of the sphenoid bone.

Less frequent is the association of optic nerve glioma and the plexiform neurofibroma. Optic nerve glioma is one of several tumors of the central nervous system that present this association. Incidence estimates in the literature range from 10% to 50%. Probably the most accurate survey is the prospective study by Lewis et al. (1984). Their study comprised 217 patients aged 4 weeks to 69 years, and diagnosis was based on stringent criteria.

The incidence of glioma confined to the optic nerves was 10% (22/217). The mean age of this subgroup with radiographic diagnosis of unilateral or multicentric optic nerve glioma was 20.8 years. There was no difference in the sex incidence. Whatever the true incidence of unilateral cases, bilateral optic nerve glioma is considered virtually pathognomic of von Recklinghausen syndrome (Stern et al., 1980).

Several case reports of NF1 have appeared in the literature since our third edition. The first report (Mamalis et al., 1988) was an 8-month-old girl with a tumor that extended from the cavernous sinus into the left orbit involving the optic nerve, extraocular muscles, and eyelid. This case was unusual in that glaucoma developed before clinically evident eyelid manifestations.

The second case (Pittet et al., 1997) was most unusual. This patient, a 15-year-old girl from West Africa, was first seen with a slowly growing gigantic facial tumor since the

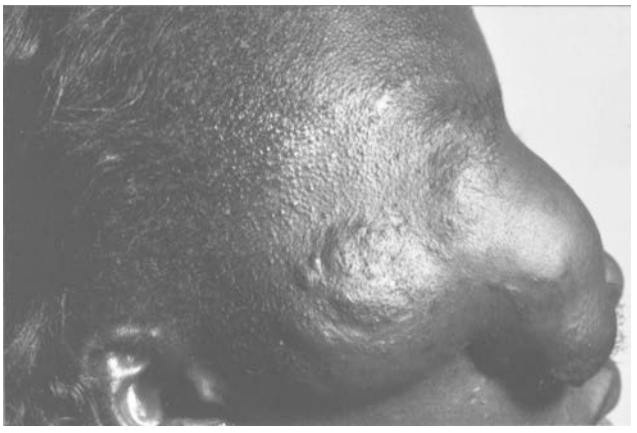


Figure 8.8 Side view of 15-year-old girl showing marked deformity, thickening, and ptosis of right eyelid that completely obscures the right eye.

age of 5 years (see Fig. 8.8). The mass originated in the right orbital area and completely covered the right side of her face. The pendulous mass extended further inferiorly to the middle of her chest. It measured 35 × 12 cm. The first surgical procedure was excision of the protruding mass. The specimen weighed 2,500 g.

The third case (Tada et al., 1998) was a 10-year-old boy with slowly progressive protrusion of the right eye since birth. Exophthalmos measured 15 mm. Imaging studies showed a diffuse, retrobulbar orbital mass that extended into the cavernous sinus through the superior orbital fissure, indicating the tumor was associated with cranial nerves III, IV, V, and VI rather than the optic nerve. Initial diagnosis of NF1 was made because of multiple *café au lait* spots on the skin of the trunk.

Two of our patients with NF1 are depicted in Figures 8.9 and 8.10.

Hadjistilianou et al. (2002) reported two children with NF1 associated with embryonal rhabdomyosarcoma of the orbit. The first patient was a 4-year-old child who presented with a rapidly progressive proptosis of the left eye. Imaging studies revealed right sphenoid wing agenesis and an orbital mass. At orbitotomy, the mass stained positively for immunostains MyoD1, vimentin, and desmin and negatively for S-100 protein. The second patient was 14 months old with a tumor of the right medial rectus muscle that stained positively for vimentin and desmin and negatively for S-100 protein. The child also had a family history of NF1 and ten *café au lait* spots on the trunk, which met the criteria for diagnosis of NF1.

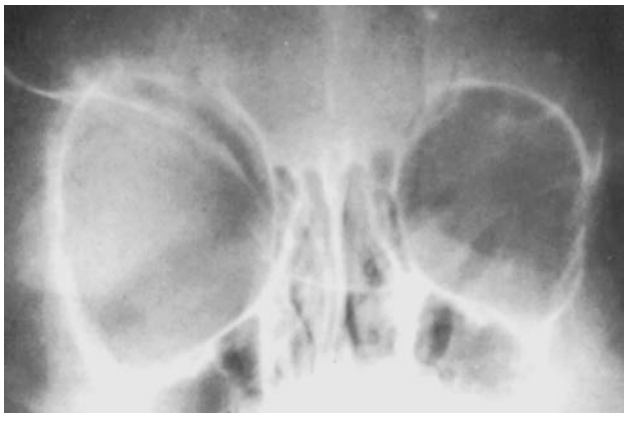


Figure 8.9 Marked enlargement of right orbit in a 4-year-old child.

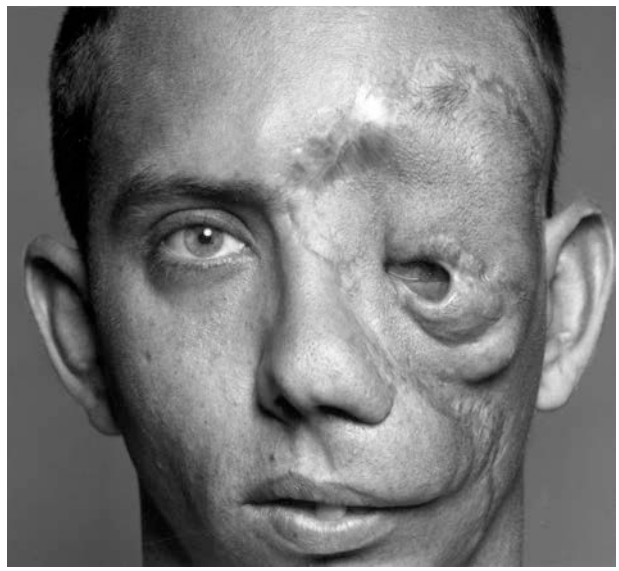


Figure 8.10 This patient with NF1 underwent numerous surgeries to correct deformity of left eyelids to little avail.

The report by Farris and Grove (1996) described in detail the clinical features associated with NF, their clinical evolution, the myriad associated anomalies, and management of a series of ten patients followed up till the age of 18 years. This publication includes 133 references.

In 1987, the National Institutes of Health proposed strict criteria for the diagnosis of NF. A revision by Mulvihill et al. (1990) defines the diagnostic criteria as two or more of the following:

1. Six or more *café au lait* macules >5 mm in greatest diameter in prepubertal patients and >15 mm in greatest diameter in postpubertal patients
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal regions
4. Optic glioma
5. Two or more Lisch nodules
6. A distinctive osseous lesion, such as sphenoid dysplasia, or thinning of the long bone cortex with or without pseudarthrosis
7. A first-degree relative (parent, sibling, or offspring) with NF by the above criteria

Subsequently, Farris and Grove (1996) proposed an eighth addition to the above scheme, namely, a distinct defect on chromosome 17.

Imaging Aspects

When obtaining a good CT scan image may be difficult, particularly in infants and children, skull radiography is still a valued adjunct to diagnosis. In small children with unilateral proptosis and a poorly defined, palpable orbital mass, the skull film may show an enlargement of the bony orbit or, a more positive diagnostic sign, an absence of one or both wings of a sphenoid bone (see Fig. 8.11). In older patients, CT images show all these defects. Figure 8.12 shows the homogeneous, contrast-enhancing character of a multilobular lesion. Magnetic resonance imaging (MRI) demonstrates heterogeneous hypointensity on T_1-weighted images relative to orbital fat, but high signal intensity on T_2-weighted images relative to orbital fat. The tumor may show a variable degree of contrast enhancement better seen with fat-suppression techniques.

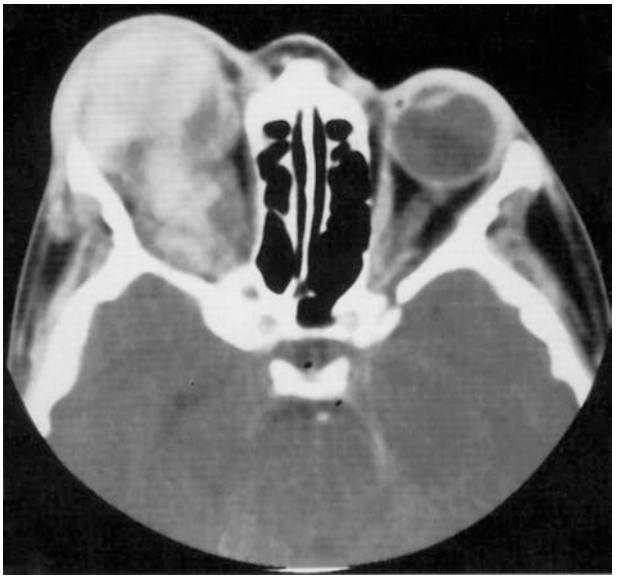
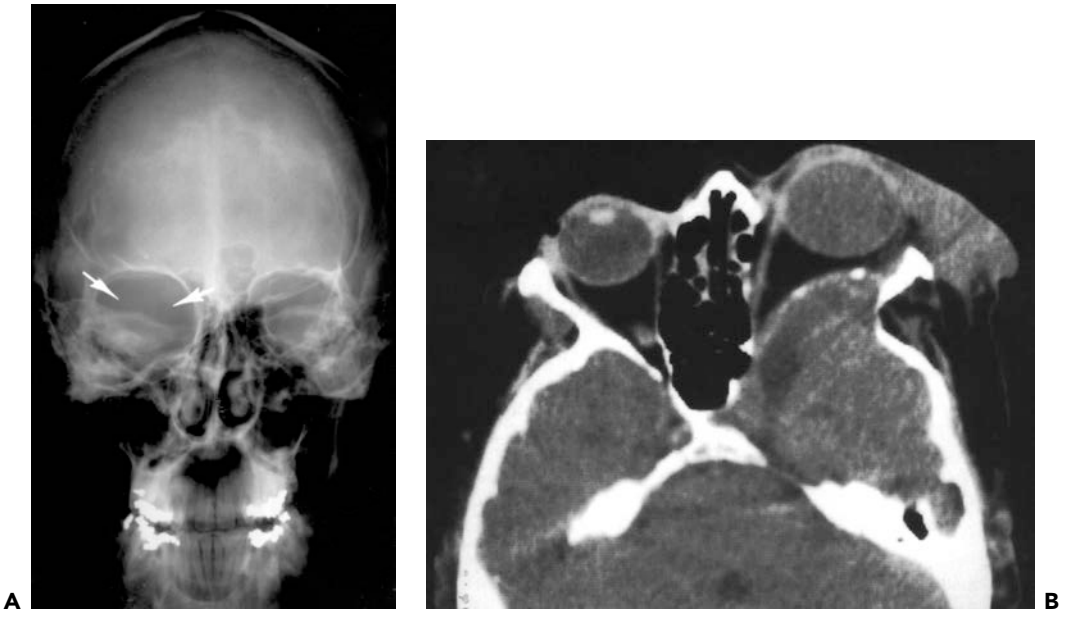


Figure 8.12 Axial computed tomography scan shows inhomogeneous mass in the right orbit of a 17-year-old woman. The tumor partially obscured the proptosed eye and caused expansion of the orbital wall. A diagnosis of von Recklinghausen disease was made in infancy. Episodes of subluxation of the proptosed eye commenced at the age of 14 years.

Pathology

Like its kin, the solitary neurofibroma, the plexiform neurofibroma is grayish white in color. Basically, the plexiform subtype is an exuberant overgrowth of all tissue components of the affected peripheral nerve branch (see Fig. 8.13). However, unlike the solitary tumor, which is covered by Schwann cells, the plexiform subset is surrounded by perineurium. The tumor's exuberant



A **B**

Figure 8.11 **A:** Plain film of orbit of 21-year-old man with progressive displacement of the right eye since birth. The lesser and greater wings of right sphenoid bone (*arrows*) are absent, and the orbit is enlarged. The patient had some pulsation of the eye. **B:** Axial computed tomography scan of a 44-year-old woman shows enlargement of the left orbit, absence of the greater and lesser wings of the sphenoid bone, herniation of contents of the middle cranial fossa into the posterior orbit, enlargement of the left eye, and thickening of tissues of the forehead and upper eyelid. The patient had progressive disease since birth.

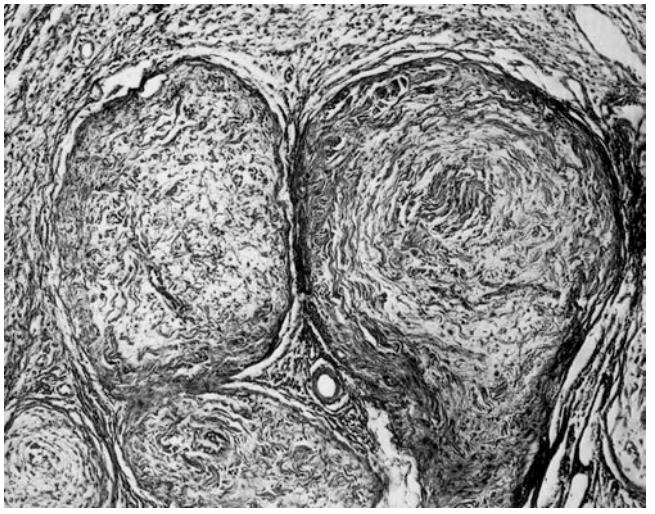


Figure 8.13 Gigantic nerve-like structures and their surrounding perineurium are nestled in a matted mass of connective tissue. This hyperplasia gives the specimen an organoid appearance (original magnification ×35).

hyperplasia causes kinking, twisting, and tortuosity of adjoining bundles, giving the tissue an organoid appearance. This convoluted mass of knobs, lumps, nodules, and interconnecting strands resembles a "bag of worms." An added feature is the tumor's vascularity compared with the nonplexiform type. This vascularity is a serious hurdle in the surgical manipulation of this tumor. The perineural cells stain positive for S-100 protein.

Management

Farris and Grove (1996) summarized this aspect of the tumor saying:

> "The experience with our ten patients has shown that orbital and eyelid characteristics of (neurofibromatosis) are progressive, with most patients ultimately undergoing surgery. However, treatment must be individualized to the patient. Once surgery has begun for orbital and eyelid (plexiform neurofibromas), both the surgeon and patient must be well aware that multiple procedures may be expected due to the progressive nature of the tumor. Surgery is palliative, not curative, and usually consists of debulking procedures with reconstruction and ptosis repair."

Nowadays the removal of the tumor is a challenge, not only to a surgical team comprising three to five surgical disciplines, but therapy is not complete until some effort is made to restore the bony configuration of the orbit and face.

SCHWANNOMA

This tumor was separated from the large family of neurofibromas by Verocay (1910) and given the name *neurinoma* (nerve fiber tumor). This was the favored designation for the next 30 years or so, until it was replaced by other names. Even so, scattered reports of neurinoma persist in the literature, particularly reports by European authors. Masson (1932), used the term *schwannoma*, implicating the presumed cell of origin (Schwann cell) of the tumor. This initiated controversy concerning the tumor's genesis, culminating in the name suggested by Stout (1935), *neurilemoma*. This term straddled the issue by implicating both cellular components (fibroblast and Schwann cell) of the nerve sheath. Some 30 years later, electron microscopy identified the Schwann cell as the principal histologic component of the tumor.

Incidence

There are 20 schwannomas (19 primary, 1 secondary) in our 50-year orbital tumor survey (see Chapter 3), an incidence of 1% (20/1,795) in the consecutive, pathologically verified tumor series. The sex incidence in our series is equal. Over this 50-year period, the schwannomas in our survey occurred over a wide age range. Table 3.4 indicates a nearly equal distribution of orbital patients from the second through eighth decades. This is contrary to statements in the literature that schwannoma of the skeletal system is most common in the 20- to 50-year age range. Some publications seem unaware that the tumor has also been reported in the first age decade: Capps et al. (1990), an 8-year-old girl, and Cantore et al. (1986), two children aged 2 and 4 years. The youngest patient in our orbital series was 15 years old, and the oldest was 77 years old. There is a high incidence of the benign tumor in patients with neurofibromatosis type 2 (NF2).

Clinical Features

The schwannoma closely parallels the solitary neurofibroma in most clinical aspects. These similarities include presentation and duration, size and distribution in the orbital space, effect on ocular function, intermittent pain, imaging aspects, occurrence of multiple forms, course, management, recurrence after incomplete removal, and lack of any single feature pathognomic of the tumor.

Several cases of schwannoma have been reported in which the clinical presentation was a bit more diverse than usual. Two different authors, Lam et al. (1997) and Tsuzuki et al. (2000), each reported a single case of cystic schwannoma. In the case described by Lam et al. (1997), the tumor in a 54-year-old man mimicked an orbital mucocele in its imaging aspects. Likewise, the image display of the case described by Tsuzuki et al. (2000) was that of a single cyst in a 62-year-old woman.

Capps et al. (1990) reported an 8-year-old girl with an intravascular schwannoma lodged within the medial rectus muscle of one orbit. Faucett et al. (1989) reported a gasserian ganglion with orbital extension. More unusual

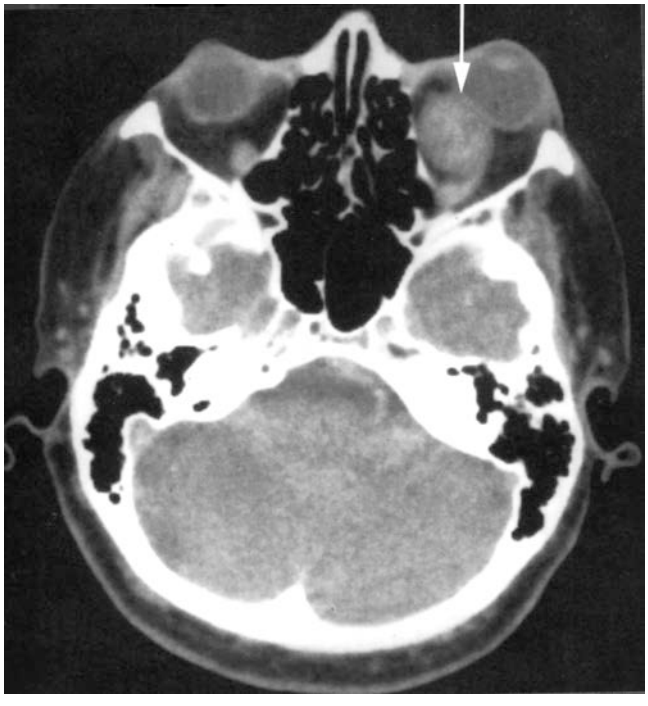


Figure 8.14 Axial computed tomography scan shows a contrast-enhancing, oval, well-demarcated mass (*arrow*) indenting the wall of the eyeball in the left medial orbit of a 71-year-old woman. Several hypodense areas in the mass corresponded to zones of cystic-like degeneration found on subsequent histopathologic study.

was the case of Shen et al. (1993), a schwannoma involving cranial nerve III along the cavernous sinus with orbital extension.

Imaging Aspects

Figures 8.14 and 8.15 show several CT scan and MRI features. On CT scan, the schwannoma is usually oval or spindle-shaped, which helps differentiate it from the more rounded images of the solitary neurofibroma and the cavernous hemangioma. The lesion is well circumscribed. According to Shen et al. (1993), the histologic Antoni A portion of the tumor showed intermediate signal intensity with both T_1- and T_2-weighted images and exhibited postcontrast enhancement. The Antoni B part revealed hypointensity on T_1-weighted images and hyperintensity on T_2-weighted sequence but showed no contrast enhancement.

Pathology

Grossly, the schwannoma is a well-encapsulated tumor with a yellow tan to reddish gray color. It is a smooth, oval or fusiform, uninodular mass if its growth in the retrobulbar space is relatively unimpeded. If it expands in a more confined space, its surface becomes irregular, knobby, and somewhat multilobulated (see Fig. 8.16). The tumor grows by simple expansion and pushes the axons of the affected nerve toward the periphery of the enlarging mass (see Fig. 8.17). The affected axons may be stretched haphazardly over the surface like wisps of thread or be collected in relatively intact bundles located eccentrically along one surface of the mass. The cells show intense, uniform immunostaining for S-100 protein.

The main point of dissimilarity between schwannoma and solitary neurofibroma is their pathology. The makeup of the schwannoma is almost exclusively the Schwann cell. These elongated cells with their eosinophilic cytoplasm may proliferate in wavy, flowing fascicles or whorled bundles. Classically, solid cellular areas with an orderly arrangement of palisading nuclei (Antoni A pattern) alternate with less orderly areas of myxoid-like texture composed of stellate or ovoid cells (Antoni B pattern) (see Fig. 8.18). The nuclei may be slender or spindled in configuration in the compact Antoni A areas but are ovoid or stellate in character in the Antoni B zones. The

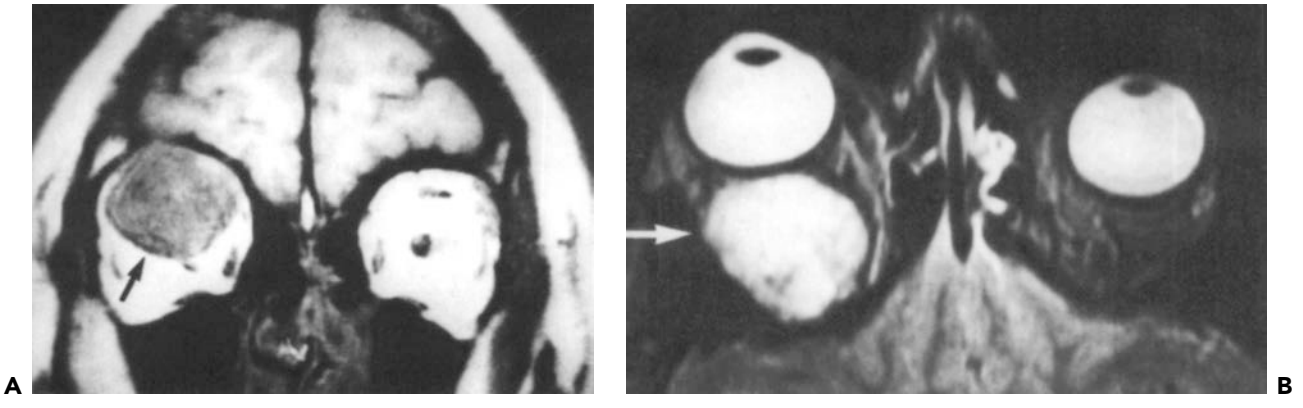


Figure 8.15 **A:** Superior orbital mass (*arrow*) shows low intensity on T_1-weighted coronal magnetic resonance imaging (MRI). **B:** Axial projection of same tumor (*arrow*) shows high signal intensity on T_2-weighted MRI. (From Bergin DJ, Parmley V. Orbital neurilemoma. *Arch Ophthalmol.* 1988;106:414–415, with permission.)

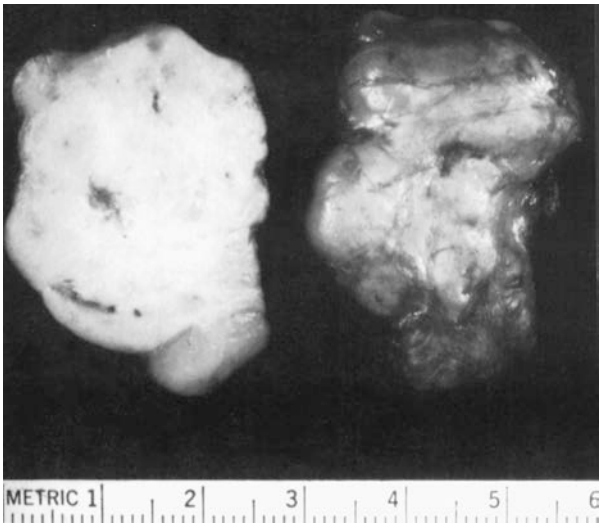


Figure 8.16 Two large schwannomas, the larger of which (left) from a 77-year-old woman measures 4 × 3 × 2 cm. Its cut surface shows a small area of hemorrhage and cyst-like degeneration at its center. The tumor was remarkably firm, considering its long duration (25 years). The surface of the second tumor (right) is irregular and slightly bosselated in keeping with resistance to its expansion by a fellow tumor and the cramped confines of the orbital space.

cytoplasm has a fibrillary character, but the cytoplasmic borders are indistinct. With appropriate stains numerous reticulin fibers can be demonstrated running parallel to the axis of the cells. The tapered thread-like poles of the elongated parallel Schwann cells tend to interdigitate. Such

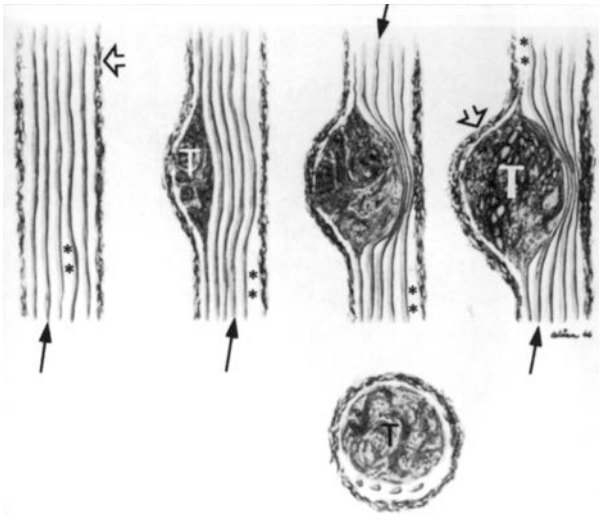


Figure 8.17 Diagrammatic representation of progressive phases (left to right) of the tumor's growth, which compresses the nerve around its periphery. The circular figure at the bottom represents a cross-section of the tumor on the far right. Also evident are epineurium (*arrowheads*), Schwann cell cylinders and nerve axons (*arrows*), endoneurium (*asterisks*), and tumor (T). (From Harkin JC, Reed RJ. Tumors of the peripheral nervous system. In: *Atlas of tumor pathology, Second Series, Fascicle 3*, Washington, DC: Armed Forces Institute of Pathology; 1969, with permission.)

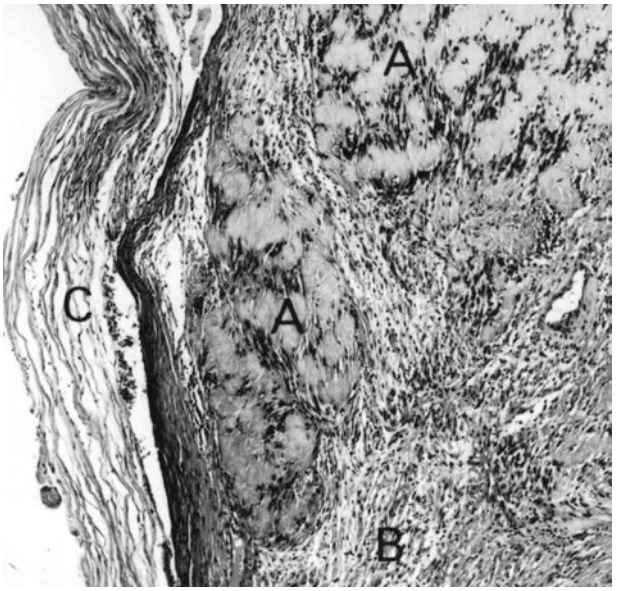


Figure 8.18 Schwannoma shows the palisading nuclei of the Antoni A pattern (A), the loose-textured Antoni B tissue (B), and the peripheral capsule (C) (original magnification ×100).

interconnecting areas of cell processes have an acellular appearance and, when surrounded by orderly rows of similarly aligned nuclei, are called *Verocay bodies*. Malignant change of a schwannoma is quite rare.

Management

The capsule of the tumor is rather tough. Therefore, its intact removal is generally not too difficult, severing the sensory nerve fore and aft. However, bleeding may be a problem, as it is with most nerve sheath tumors. If a motor nerve is affected, the tumor must be stripped away from the overlying nerve branches by microdissection. Management is further complicated by the frequent requirement for craniotomy for adequate exposure (Cockerham et al., 1999). Lesions are often situated in the orbital apex and can extend intracranially through the superior orbital fissure which is a clue to a peripheral nerve sheath origin.

MALIGNANT PERIPHERAL NERVE SHEATH TUMORS

Malignant tumors arising from the prior neoplasms are collectively referred to as *malignant peripheral nerve sheath tumors* in this chapter. This term replaces a number of earlier terms, including *malignant schwannoma, neurofibrosarcoma*, and *neurogenic sarcoma*. Because malignant peripheral nerve sheath tumors recapitulate the appearance of various cells of the nerve sheath, they range in appearance from tumors that resemble a neurofibroma to those almost indistinguishable from a fibrosarcoma (Weiss and Goldblum, 2001).

Most lesions may arise from plexiform neurofibromas in association with NF1. The tumor might show such a mixture of cell types that it was not always possible to assign a specific cell of origin in many cases. In short, in the course of its malignant transformation, the tumor loses some of the cell specificity that was characteristic of its benign state.

Clinical Features

The best comprehensive review of the orbital features of this malignant tumor is still the one published by Lyons et al. (1989). They found only 13 well-documented cases in the literature and added three of their own. Their total included eight cases from the file of the Armed Forces Institute of Pathology before 1975, which were analyzed by Jakobiec et al. (1985). The latter is the best documented series from a pathologic point of view. Ten of the 13 cases arose from the supraorbital (frontal) branch of the trigeminal nerve. All reported cases, including the three cases reported by Lyons et al. (1989), have been in adults. One of the three cases in our 50-year file of orbital tumors was also included in the review by Lyons et al. (1989). All the cases have been in adults ranging in age from 19 to 76 years.

There have been a surprising number of case reports since 1989. Two were published in 1997, and both were in children. The first, by Fezza et al. (1997), was a 4-day-old male infant with Kartagener syndrome who was found to have a large, primarily extraconal mass in the superior temporal right orbit. The newborn underwent an exenteration, and the tumor was removed with clear margins. The tumor itself was invading the extraocular muscles, adjacent fat, and periosteum over the lateral orbital rim. The underlying bone was normal. Only rare mitoses were identified. There was no tumor recurrence after 27 months of follow-up. The second report, by Morton et al. (1997), described a 5-year-old boy who had what was initially thought to be "fibromatosis" of the left orbit. The tumor had been excised but recurred 18 years later. The recurrence was heralded by severe left orbital pain after periorbital trauma. He was treated with an exenteration, and only limited follow-up was described. The following year, Tada et al. (1998) reported a 10-year-old boy with unilateral proptosis since birth. A diagnosis of NF1 had been made previously on the basis of multiple *café au lait* spots on the skin of his trunk. On orbitotomy, a diffuse mass, rather than a discrete one, wrapped around the optic nerve. The tumor extended posteriorly into the cavernous sinus. The tumor was removed through a frontocraniotomy. At last follow-up, the patient had been well for 2 years.

Dutton et al. (2001) described a 6-year-old boy with NF1 who received irradiation for presumed bilateral optic nerve and chiasmal gliomas and in whom a malignant tumor later developed. Exenteration with extirpation of the entire contents of the orbit was performed six times. The tumor recurred after each surgical procedure until the patient died of malignancy 11 years later.

A third case is that reported by Eviatar et al. (1992) occurring in a 15-month-old boy, the youngest patient on record. At orbitotomy, a bilobed tumor was completely excised. One lobe proved to be a circumscribed, but not encapsulated, myxoid neurofibroma to which the lobe of malignant peripheral nerve sheath tumor was attached. The standard treatment at that time included options of orbital exenteration, chemotherapy, and radiotherapy, but all were refused. The patient was tumor free 9 years later. The patient did not have NF1.

The most recent report (Briscoe et al., 2002) is that of another child, an 11-year-old girl, who noted rapidly progressive proptosis of the left eye and visual loss from optic nerve compromise. There was no mention of any pain or sensory changes. Imaging demonstrated an intraconal mass in the inferotemporal quadrant. She was treated with an exenteration followed by radiotherapy. After 4 years' follow-up, she had no evidence of recurrent disease.

Almost all these malignant tumors are associated with orbital pain. If, on presentation, a patient is known to have a painless orbital mass but later develops pain, it probably indicates a malignant transformation of the mass, or it has enlarged to such a size that the bony orbit no longer can accommodate the tumor's growth.

These tumors metastasize to the lung.

Imaging Aspects

Results from CT scan, MRI, and ultrasonography have all been described for malignant peripheral nerve sheath tumors. Morton et al. (1997) reported echography that showed a low-reflectivity lesion with a highly reflective surface. Central echolucency corresponded with intralesional hemorrhage. Briscoe et al. (2002) described MRI findings of a homogenous signal on T_1-weighted images and small cystic areas visible on the T_2-weighted images. There was diffuse enhancement after contrast administration with focal areas of more intense enhancement. The case reported by Eviatar et al. (1992) was described as bilobed without bone destruction.

Pathology

Patients with NF1 are at increased risk to develop these tumors. The pattern of cellular proliferation in these malignant tumors may be so diverse that to attempt a uniform description is almost futile. Under low-power magnification, the lesion usually resembles the flowing fascicles of a fibrosarcoma. However, in patients who also have NF, the pattern may resemble a disorderly arranged neurofibroma. At the outset, it is probably more important to recognize the features of a malignant tumor rather than to worry about the principal cell of origin. Figure 8.19 shows the basic malignant aspects of these tumors. The nuclei vary greatly in size and shape, and the specimen, overall, is very

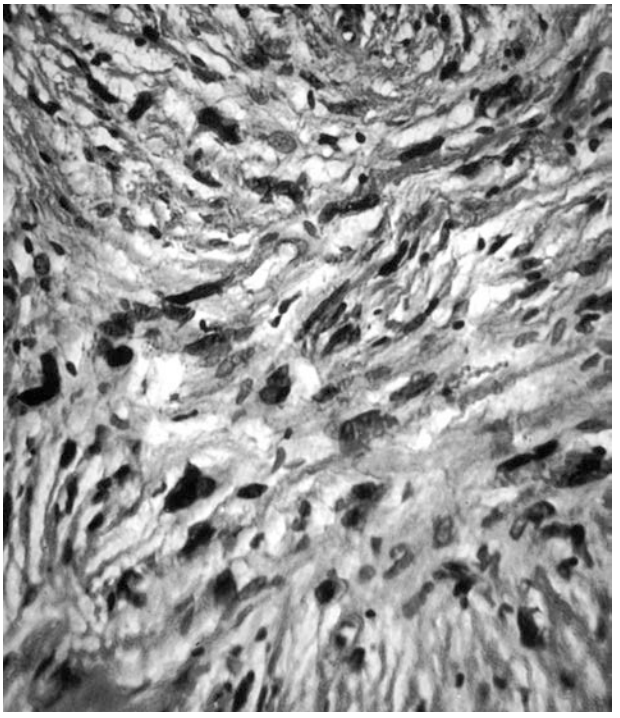


Figure 8.19 An interweaving fascicular pattern with increased cellularity, hyperchromatism, mitotic activity, and marked pleomorphism (original magnification ×300).

cellular. Some spindle-shaped nuclei are plump with a delicate chromatin; other nuclei are oval, vesicular, and lightly staining; and still others are narrow, slightly curved, somewhat hooked or comma-shaped, and very hyperchromatic. The cell boundaries are indistinct, but the intervening collagen fibers are prominent and impart an appearance of interweaving fascicles of cells. Pronounced nuclear palisading, such as was seen in the neurilemoma, is not present in most malignant lesions. Other growth patterns described in the literature have been nodular, plexiform, curlicue, epithelioid, and whorls of cells. Relatively hypocellular myxoid zones with a more random, nonparallel distribution of cells may also be seen. Any given tumor may contain heterologous elements of bone or cartilage. Perineural extension is the common mode of spread, but invasion of surrounding soft tissue is also seen. Most observers consider the number of mitoses to be of lesser importance in diagnosis than the features already noted. Immunostaining with S-100 protein is present but is less uniform, focal, or sparse when compared with neurilemoma, and immunostaining for p53 is present in most cases.

Several other antigens useful for identifying nerve sheath differentiation are Leu-7, PGP 9.5, and myelin basic protein (Weiss and Goldblum, 2001).

Management

For many years, the principal mode of management has been orbit exenteration. Nevertheless, recurrences of tumor are common because of unseen malignant cells that spread posteriorly along the nerve sheath through the bony fissures into the intracranial vault. However, if the patient is lucky enough to have a well-circumscribed malignant lobe still attached to a circumscribed lobe of benign tumor, such as described in the preceding text, intact removal of tumor may suffice, providing rogue malignant cells have not already shed into the retrobulbar fat. Chemotherapy of the tumor is not well defined.

MALIGNANT TRITON TUMOR

A definition of this tumor, used by most authors, is the one proposed by Woodruff et al. (1973), that is, "a malignant schwannoma with rhabdomyoblastic differentiation." The name "Triton" evolved from the experimental study of transplanted nerves on the dorsal surface of the Triton salamander (Locatelli, 1925).

There are two types of Triton tumor. The first type is found in patients with NF2, who are young and have a marked male predominance, and is usually located in the head and neck. The second type, by contrast, is found in those without von Recklinghausen disease, who are older and predominantly female, and is frequently located on the patient's trunk.

Case reports of orbital involvement by malignant Triton tumor are almost nonexistent. Victoria et al. (1999) conducted a search of the literature for all cases of this tumor affecting the areas of the head and neck. They reviewed the data on 26 cases in the literature between 1932 and 1999. Their list included one case with orbital disease, a 66-year-old woman with a bleeding mass in the left nasal cavity (Bhatt et al., 1991). Proptosis of 2.5 mm of the left eye was also present. On surgical exploration, a fleshy gray mass was found centered in the left posterior ethmoid sinus. The tumor extended laterally to the optic foramen and inferiorly to the maxillary sinus. The tumor was grossly excised. Pathologically, the Triton tumor was considered low-grade. The patient declined any further radical surgery. Image scanning suggested some tumor regrowth in the posterior ethmoid, but the woman had no symptoms 27 months after surgery. The patient did not have NF.

In their search of the literature, Victoria et al. (1999) overlooked the Triton tumor that we described in some detail in our third edition (1994). This was a child who was known to have *café au lait* spots and auxiliary freckles since infancy. At the age of 3 years (1975), he was noted to have an impairment of vision, a suprasellar mass, and bilateral enlargement of the optic canals. Surgical exploration revealed a grade 1 astrocytoma of the right optic chiasm and left optic nerve. The chiasmal glioma was treated with 9.3 Gy.

At the age of 8 years (March 1980), a mass in the right temporalis fossa was resected, and a diagnosis of neurofibrosarcoma was first made. Visual acuity at this

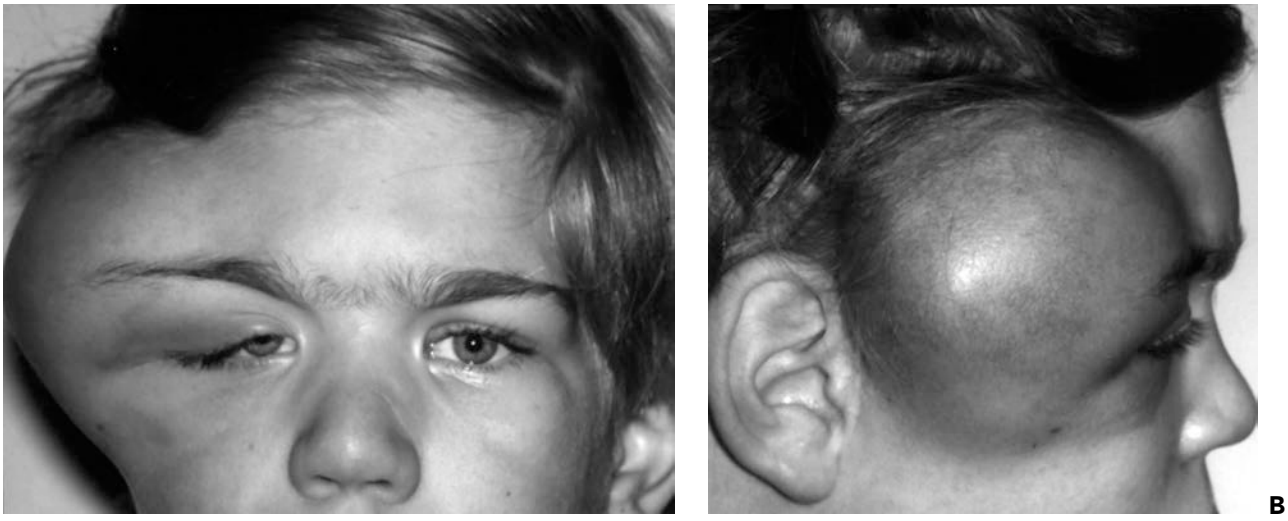


Figure 8.20 Front **(A)** and side **(B)** view of a 9-year-old boy with large, recurrent tumor in the right temporalis fossa with extension into the forehead, periorbital area, and upper face. The right eye was displaced medially.

time was 20/200 in the right eye and counting fingers in the left eye. In November 1980, a second resection was performed to remove recurrent tumor.

In May 1981, when the boy was 9 years old, he was seen at Mayo Clinic because of a tennis ball–sized recurrent mass in the right temporalis fossa of 2 months' duration (see Fig. 8.20). Combined angiography and CT scan showed a vascular mass arising in the region of the right pterion with erosion of adjoining sphenoid wing and lateral orbital wall. The tumor extended into the right lateral orbit and middle intracranial fossa and inferiorly into the facial area (see Fig. 8.21). Through a coronal approach, the skin was dissected from the dome of the tumor, and a craniofacial orbital resection was performed, including all visible tumor, portions of temporal and zygomatic bones, lateral orbital wall, and upper portion of mandible. Histopathologic examination revealed a malignant neurofibrosarcoma with rhabdomyosarcomatous and immature cartilaginous differentiation (see Fig. 8.22).

In August 1981, a partial reconstruction of the orbit and skull was performed using split rib and skull bone grafts and scalp rotation flaps. Multiple biopsy specimens from the prior tumor sites showed no tumor. In November 1981, the tumor recurred in the right temporozygomatic and periorbital areas. Scalp nodules over the left occiput were positive for malignant tumor on biopsy. CT scan showed additional extension of tumor into the right retromaxillary region and the middle and anterior cranial fossa and an exophytic mass projecting into the atrium of the left lateral ventricle. The child died in January 1982.

We have searched the English-language literature but have found no additional cases of orbital involvement.

Management

Complete surgical excision is the principal management mode. The surgical options are the same as described

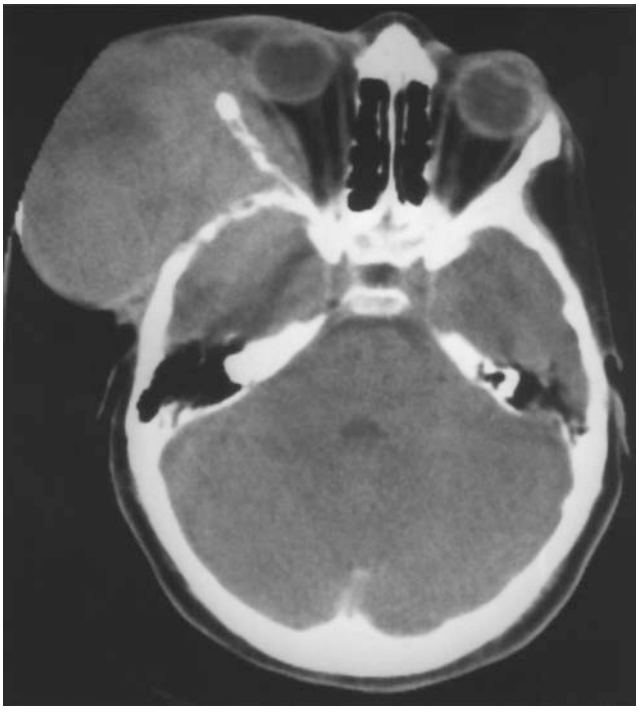


Figure 8.21 Axial computed tomography scan of the patient in Figure 8.20 shows a huge, slightly inhomogeneous tumor occupying the right temporalis fossa, right orbit, and right middle fossa. The mass is isodense to brain.

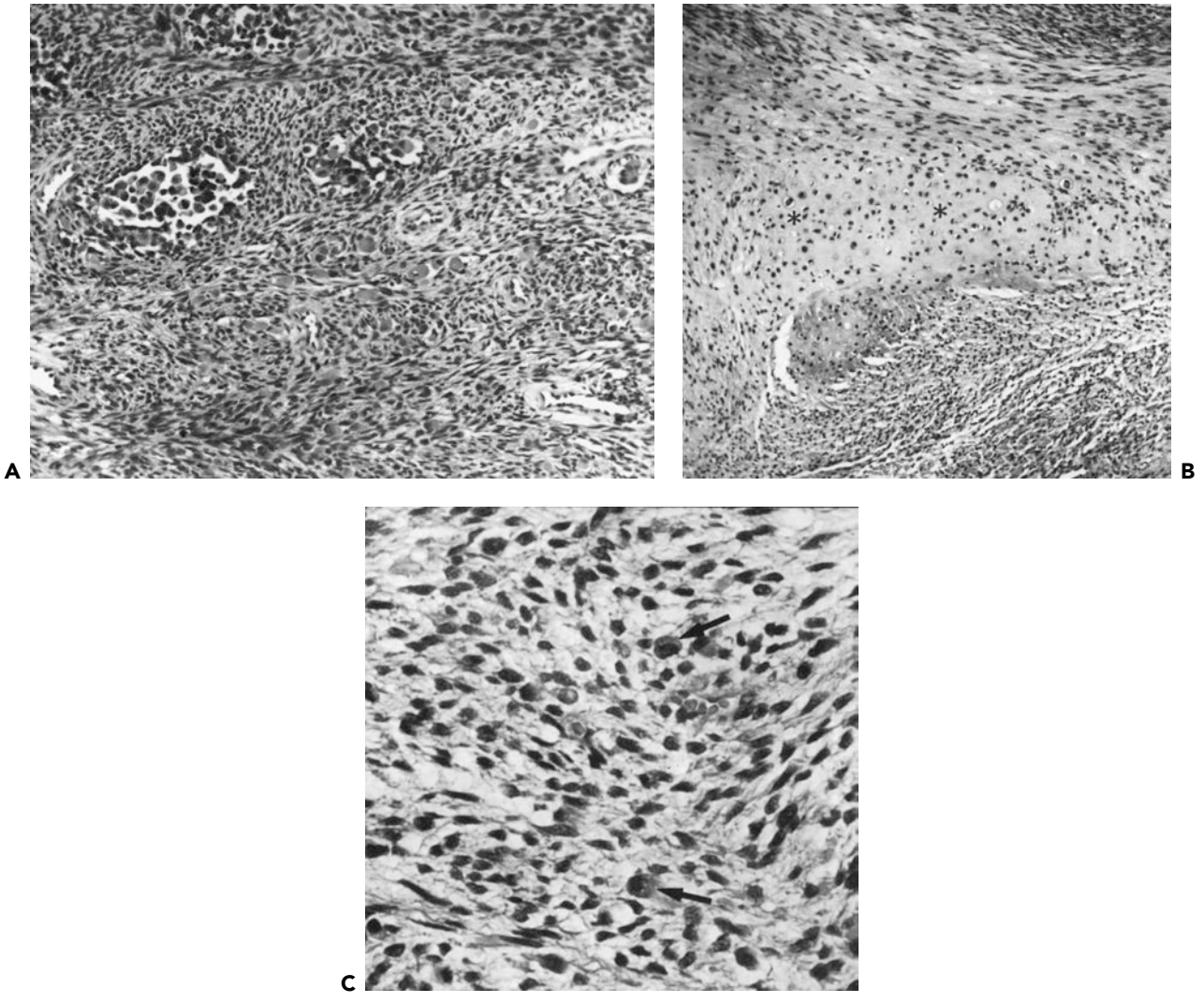


Figure 8.22 **A:** Islets of rhabdomyoblastic differentiation are interspersed in a very cellular stroma of fascicles and whorls of spindle-shaped cells that have nuclei of various shape and size. A collection of more isolated rhabdomyoblasts is present in the center. Note the large round nuclei and abundant cytoplasm of the various rhabdomyoblasts (original magnification ×160). **B:** A horizontal peninsula of cartilaginous differentiation (*asterisks*) extends from left to left center (original magnification ×100). **C:** Scattered rhabdomyoblasts (*arrows*) are present in this section. Note the elongated, thin, slightly curved nuclei of a patch of Schwann cells (lower left) (original magnification ×400).

for eradication of the preceding malignant peripheral nerve sheath tumor. We do not recommend adjuvant radiotherapy. However, if the tumor recurred, radiotherapy may be used only for its palliative effect. We know of no cases with orbital involvement that have been treated successfully with chemotherapy.

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Malignant Triton Tumor

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9 Primitive Neuroectodermal Tumors

In this chapter, we describe neoplasias of several neural, neuroglial, and neuroganglionic tissues that share an ancestry from the primitive epithelium of the neural tube. This heterogeneous group may involve the orbit as primary, secondary, or metastatic growths.

RETINOBLASTOMA

Retinoblastoma develops from primitive embryonal retinal cells, either photoreceptors or neuronal types. The tumor may display evidence of photoreceptor differentiation (Flexner-Wintersteiner rosettes) or show areas of glial differentiation (Atchaneeyasakul and Murphree, 2001; Biswas and Shanmugam, 1996). As in the previous editions of this text, our discussion chiefly concerns the extraocular and orbital extension of the intraocular retinoblastoma.

Incidence

Calculation of the true incidence of retinoblastoma is complex. There are many variables to consider, such as the size of the sample (a minimum of 100 cases), the age and sex of the children, their race, analysis of the data, basis of diagnosis (clinical or pathologic), unilateral or bilateral involvement, hereditable or spontaneous type, and estimation of the population at risk. Most commonly, the incidence is reported as the number of cases of tumor diagnosed in a period per live births for that period (Suckling et al., 1982). The lack of a worldwide uniform tumor registration protocol makes it difficult to attain an accurate calculation of incidence.

In the 40-year period between 1931 and 1971, many estimates of the frequency of retinoblastoma were published. In a population-based study, Bishop and Madson (1975) compiled a list of some of the publications during the 40-year time period (see Table 9.1).

We have not examined each publication in this table to determine which of the variables listed in the prior paragraph were or were not included in their survey. Retinoblastoma appears to have become more frequent between 1951 and 1971.

Tamboli et al. (1990) estimated the incidence of retinoblastoma in the United States from data on 220 cases in the files of the National Cancer Institute in Bethesda, Maryland (1974 through 1985) and compared these cases with previous US population studies. They concluded the incidence of retinoblastoma was almost uniform from 1974 to 1985. Riley (written communication, 2003) analyzed the 475 consecutive cases of retinoblastoma (1983 to 2002) in the registry of the King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia. This registry includes only children of Saudi Arabian descent. He concluded that, over the 19-year period, there had been no change in the incidence of retinoblastoma in their population-based study.

A register-based study of male and female patients born in the Netherlands between 1862 and 1995 was undertaken by Moll et al. (1997). Nine hundred and ninety-five patients were analyzed by a group of nine authors, including ophthalmologists, biostatisticians, epidemiologists, geneticists, and functional morphologists. Since 1945, the incidence of retinoblastoma appears to have stabilized (1 per 17,000 live births). Further, no significant differences in the incidence between males and females were found.

If the true incidence of retinoblastoma in the United States has not changed significantly in the past several decades, it is reassuring to believe that the retinoblastoma gene is not mutating to increase the number of cases of the tumor.

TABLE 9.1
FREQUENCY OF RETINOBLASTOMA

Author	Country/State	Period of Survey	Frequency
Falls and Neel (1951)	Michigan	1938–1947	1:20,288
Bohringer (1956–1958)	Germany	1925–1954	1:23,800
Macklin (1959)	Ohio	1940–1956	1:23,287
Bech and Jensen (1961)	Denmark	1928–1957	1:19,000
Schappert-Kimmijser (1966)	Holland	1950–1959	1:15,230
Suckling et al. (1970)	New Zealand	1948–1968	1:17,500
Barry and Mullaney (1971)	Ireland	1955–1970	1:26,595

(Modified from Bishop JO, Madson EC. Retinoblastoma: Review of the current status. *Surv Ophthalmol*. 1975;19:342–366, with permission.)

In the 7-year interval between the first and second editions of *Orbital Tumors* (1973 and 1980), 1,100 cases of intraocular retinoblastoma were observed and treated (Rootman et al., 1978; and others). This collection of data corresponded to the era when enucleation was the preferred treatment of unilateral retinoblastoma. Orbital involvement of retinoblastoma varied from 8% to 10% of the total sample.

Soon thereafter, chemotherapy superseded enucleation as the primary treatment for intraocular retinoblastoma, and the number of enucleated eyes available for pathologic studies diminished. In the past 2 decades, many eyes have been salvaged that otherwise would have been enucleated. However, not all eyes with orbital involvement respond to conservative, nonsurgical therapy, and the affected eye must be removed. Besides, such eyes have been enucleated at other institutions. Earlier diagnosis of intraocular tumors has likely reduced the number showing orbital involvement. Neither sex has a higher incidence of retinoblastoma; unilateral retinoblastoma occurs more than three times as often as bilateral disease (Pendergrass and Davis, 1980), and incidence of bilateral disease is the same in whites and blacks (Tamboli et al., 1990).

Most retinoblastomas are diagnosed before the patient reaches the age of 3 (Robertson, 2003) to 4 (Zimmerman, 1985) years. However, Shields et al. (1991) noted that 8.5% of patients among their 400 consecutive cases with retinoblastoma were older than 5 years.

Clinical Features

In the United States, leukocoria, often associated with strabismus, is the principal presenting sign of retinoblastoma. Orbital extension occurs sometime after or during treatment of the intraocular tumor. The presenting symptom is a painless proptosis that heralds a retrobulbar mass. If an implant has been placed in the orbital socket after enucleation, the need for frequent adjustment of the prosthesis or its extrusion is indicative of an orbital mass. A vitreous hemorrhage in an older child may conceal an unsuspected retinoblastoma that is discovered after a vitrectomy for a nonclearing hemorrhage. In developing countries, retinoblastoma may present as an orbital tumor rather than an intraocular lesion. In such cases, a large, reddish black, friable mass may bulge out beyond the confines of the eyelid.

Imaging Aspects

Although >90% of intraocular retinoblastomas show intralesional calcification with computed tomography (CT) scan, calcification is rarely present in the extraocular extension (Kaufman et al., 1998). Nevertheless, CT scan shows the size and position of the retrobulbar mass. Magnetic resonance imaging (MRI) may be more useful in determining the degree of optic nerve involvement. The orbital extension is hyperintense on T_1-weighted images and hypointense on T_2-weighted images.

Pathology

Figures 9.1 and 9.2 illustrate two of the routes of extraocular extension of an intraocular retinoblastoma. Other routes of escape are the short and long ciliary nerves and the direct breaching of the wall of the eye manifested by episcleral nodules. When such bluish pods are visible, it is likely that subclinical microscopic spread of retinoblastoma has occurred into the retrobulbar tissue. Invasion of the choroid by the intraocular mass is probably a source for distant metastasis that may precede direct orbital extension. The presence of tumor along the line of transection of the optic nerve or tumor cells along the pial surface of the nerve suggests probable intracranial seeding of neoplasm.

The retinoblastoma is neuroblastic in origin and may arise in any of the nucleated layers of the retina. Immunohistochemical studies with interphotoreceptor retinoid-binding protein antibodies and with neuron-specific enolase support the neuronal origin of the tumor (Rodrigues et al., 1987). Glial differentiation, although demonstrable in tissue cultures of retinoblastoma cells (Kyritsis et al.,

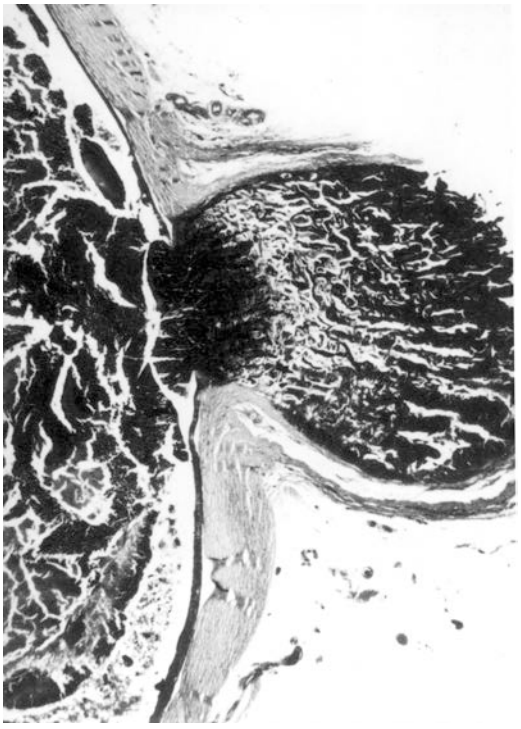


Figure 9.1 Orbital involvement most commonly results from penetration through the lamina cribrosa and spread in the optic nerve (original magnification ×10).

1984), has not been convincingly demonstrated in intraocular tumor cells (Lane and Klintworth, 1983) or within orbital extensions of the tumor.

The intraocular tumor may show varying degrees of differentiation and the formation of fleurettes and rosettes of the Flexner-Wintersteiner type, representing an attempt to produce photoreceptor cells. This high degree of differentiation is not observed in the orbital extension of the

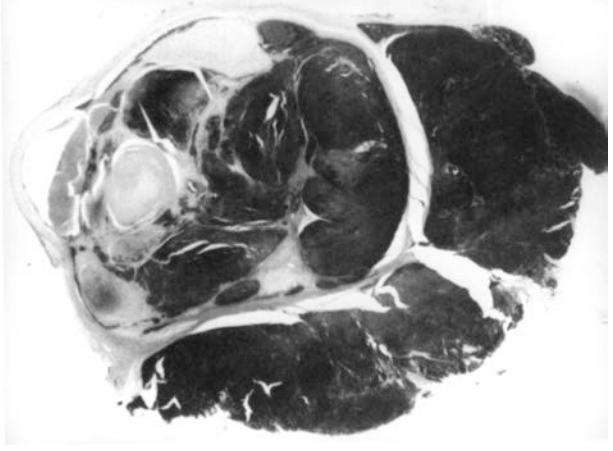


Figure 9.2 Massive orbital invasion apparent along the emissary vascular channels rather than through the optic nerve (original magnification ×2½).

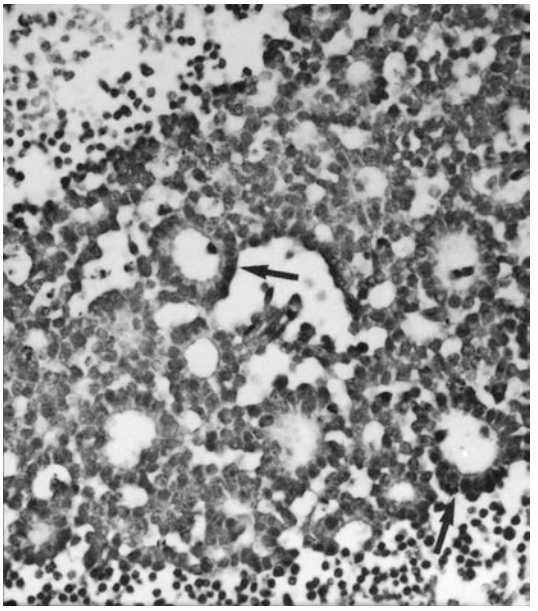


Figure 9.3 A sheet of small, dark cells with hyperchromatic nuclei and Flexner-Wintersteiner rosettes (*arrows*) bordered by areas of necrosis (upper left and lower right) (original magnification ×400).

tumor, and the small dark cells with their hyperchromatic nuclei and multiple mitotic figures are dispersed in sheets (see Fig. 9.3). Necrosis, with or without calcification, is a prominent feature, and DNA liberated from the necrotic tumor cells is seen as a blue ring in the blood vessel walls with the hematoxylin and eosin stain.

Management

Commencing in the late 1980s and early 1990s, chemotherapy became the preferred initial therapy for the nonsurgical management of retinoblastoma. Our third edition of *Orbital Tumors* (1994) noted the drug combination protocols in use for cases of intraocular, orbital, and intracranial tumors. Gradually, adjustments such as local therapy applied to the intraocular mass and radiotherapy to the overall orbit have been added to treatment protocols.

Local ("focal") treatment to the intraocular tumor may include either hyperthermia or photocoagulation through the transpupillary route and/or cryotherapy and brachytherapy applied to the exterior of the globe. Finally, external beam radiotherapy to the globe and orbit may be necessary. Focal therapy alone may be given if the diagnosis is early and the intraocular tumor is small enough to be within the tolerance level of the eye to the local agent chosen for administration.

However, our main concern in this text is the treatment of patients with invasion of the orbit, the optic nerve, or both. This invasion occurs at the most advanced stage of local disease. The rationale for the initial use of chemotherapy is the observation that it sensitizes the

tumor bulk to the adjuvant modalities administered during or after chemotherapy. This mode is termed *chemoreduction*. At present, there is no uniform standard of the type or number of chemical agents used or the duration of the cycles of chemotherapy administered in a given time span. Some physicians recommend a combination of these drugs, that is, carboplatin, vincristine, and etoposide; others combine just two of these agents. Some physicians defer the use of a focal adjuvant on the intraocular tumor until some reduction in the overall bulk of the neoplasm by chemoreduction is observed. Others combine focal and systemic chemotherapy simultaneously. Whichever type of protocol is elected, it should be administered in close interaction with a pediatric oncologist who is knowledgeable about the adverse effects of these powerful chemical agents.

Sooner or later, these patients have external beam radiotherapy. At Mayo Clinic, the radiation equivalent of 45 Gy has been administered over a period of years. Irradiation should be used within 6 months of chemotherapy. If brachytherapy has been used during the course of chemotherapy, the total dose of irradiation should be reduced. Schvartzman et al. (1996) believe adjuvant irradiation is of value in preventing metastasis in patients who had invasion of the optic nerve. If these complex treatment protocols fail or disease recurs after an initial favorable response, enucleation is the last resort. Enucleation is also indicated for patients who, on presentation, have advanced retinoblastoma, that is, more than half the retina is affected by tumor, subretinal fluid and vitreous seeding are present, and visual acuity is markedly reduced. From reports in East Indian journals, eyes with advanced retinoblastoma at the time of presentation are almost the norm.

Prognosis

We have been pleased to read many publications in the literature from the 1990s and the early years of this century that emphasize the increasing survival of patients with retinoblastoma. This increased survival parallels advances and refinements in chemotherapy and its adjuvants over this time span. Robertson (2003) estimates that, at present, 95% of patients survive the malignant neoplasm. This estimate is probably based on patients with an intraocular tumor that has not spread beyond the interior of the eye.

Estimating the survival of patients with orbital extension (including the optic nerve) is unreliable. First, the number of cases of advanced retinoblastoma in North America is relatively small compared with the numbers in India and Africa. Second, these few cases have been treated with a variety of protocols, that is, from 2 to 12 cycles of chemotherapy with or without focal adjuvants. Questions remain about whether adjuvant therapy was administered simultaneously with or after chemotherapy. The same variables can be applied to the use of radiotherapy. Finally, some cases have been treated only with external beam radiotherapy (no chemotherapy). Trying to analyze such a hodgepodge is akin to comparing the proverbial apples and oranges. Robertson (2003) has noted that with extraocular extension and orbital involvement, a morbidity rate as high as 90% has occurred at 2-year follow-up.

What is needed now is an international study group composed of retinoblastoma experts who can establish standard protocols for the management of orbital diseases, provide a uniform system for analyzing data, and the required duration of follow-up observation.

Whether the ophthalmologist is dealing with local intraocular retinoblastoma or advanced disease, patients need to be kept under observation for a long time. Goto et al. (2002) reported recurrences of neoplasm 12 years after brachytherapy, and Shields et al. (2002) noted recurrence 25 years after external beam radiotherapy. Our fervent hope is that a new method of treatment will evolve that will eliminate the use of external beam radiotherapy in children with retinoblastoma.

MEDULLOEPITHELIOMA

Synonyms for medulloepithelioma are "diktyoma," "teratoneuroma," and "teratoid malignant medulloepithelioma." This neoplasm may arise from the primitive neuroepithelium of the forebrain, along the course of the optic nerve, or from the intraocular ciliary body. The neoplasm has a multipotential cellular diversity, may be benign or malignant, and nonteratoid or teratoid type. A teratoid type contains one or more heteroplastic elements such as brain tissue and cartilage. Most publications discuss the medulloepithelioma in its most common location, the ciliary body. Here, most neoplasms are benign. A minority is malignant, but the degree is less than the tumors of the brain and optic nerve. Our concern, in this chapter, is the medulloepithelioma arising in the optic nerve. From this source, the tumor may extend into the orbital space or the intracranial vault, or retrograde into the eyeball.

Incidence

A medulloepithelioma of the optic nerve is very rare. This neoplasm has not been seen at Mayo Clinic during our 50-year collection of 1,795 consecutive, pathologically proved orbital tumors. Only a few well-authenticated cases originating in the optic nerve have been reported in the literature. Among these were a $4\frac{1}{2}$-year-old boy (Reese, 1957), a newborn (Andersen, 1971), a 6-year-old girl (Green et al., 1974), a 2-year-old boy (O'Keefe et al., 1997), and a 3-year-old boy (Biswas et al., 1999). Harry and Morgan (1979) noted the neoplasm associated with a buphthalmic eye. Congenital cases have also been reported (Steinkuller and Font, 1997; Chidambaram et al., 2000).

Clinical Features

All reported cases have been unilateral and sporadic. All the children with medulloepithelioma, except those with congenital tumors, have almost the same presenting signs and symptoms as those with optic nerve glioma. Indeed, these cases were initially thought to be optic glioma until an invasive biopsy was performed. The presenting signs and symptoms include proptosis, displacement of the eye, some impairment of ocular motility, a dilated pupil, and some ophthalmoscopic abnormality of the optic disk. The intraocular tension may be elevated in some cases. However, at the time of discovery, children with medulloepithelioma tend to be a bit younger than the average age of children with optic glioma.

Imaging Aspects

In the article by Biswas et al. (1999), the CT scan of a 3-year-old patient (see Fig. 9.4) shows a well-defined, intraconal, homogeneous, hyperdense, enhancing lesion involving the optic nerve with bowing of the medial orbital wall that extends intracranially through the apex of the orbit and involves the left cavernous sinus. Axial T_1-weighted MRI showed the mass to be hypodense.

Pathology

These tumors contain cellular elements that closely resemble medullary epithelium and are derived from the optic vesicle, optic cup, retinal pigment epithelium, nonpigmented and pigmented ciliary epithelium, vitreous, and neuroglia. The color of the neoplasm may depend on the content of pigmented ciliary epithelium (Spencer and Rao, 1996). All tumor cells have variable cytologic characteristics.

The heterogeneous cellular makeup of any given medulloepithelioma may depend on its location. Tumors of the optic nerve are prone to contain more undifferentiated elements such as those seen in retinoblastoma. Malignant tumors are more common than benign lesions in this location. The components of a neoplasm affecting the ciliary body are composed of more mature cellular components. Here benign medulloepitheliomas are more common than malignant types.

The proliferating medullary epithelium is arranged in cords and sheets separated by cystic spaces and lined by a single layer of epithelium. These cysts contain hyaluronic acid (see Fig. 9.5). If these cysts are located on the surface of the tumor, they may break off and become free-floating in the vitreous. Malignant tumors may not differ significantly from benign lesions. Invasiveness and number of mitotic figures are criteria for malignancy.

Management

There is no standard pattern of management for an orbital medulloepithelioma. Too few cases are available to judge the effectiveness of exenteration, chemotherapy, and radiotherapy, either alone or in combination. The 6-year-old patient reported by Green et al. (1974) was living without metastasis 18 months after exenteration of the orbit. The 4-year-old patient described by Reese (1957) underwent enucleation. Nine months later, there was an orbital recurrence. A second surgery was performed

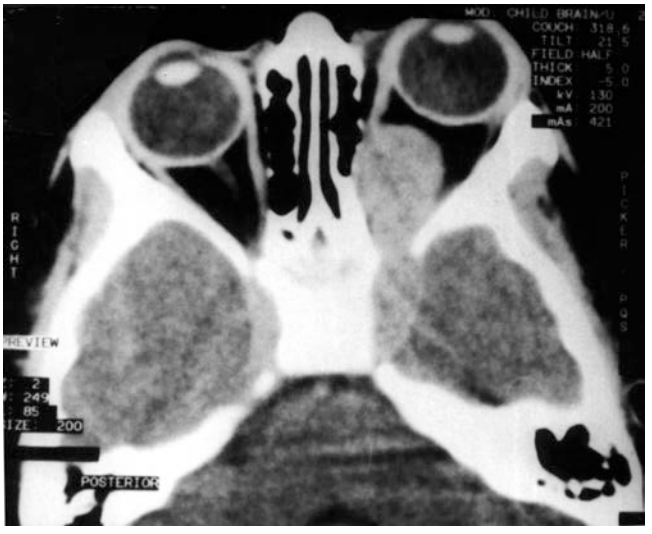


Figure 9.4 Computed tomography scan showing a well-defined, intraconal, homogeneous, hyperdense, enhancing mass extending intracranially through a widened orbital fissure and involving the left cavernous sinus. (From Biswas J, Bhushan B, Jayakumar N, et al. Teratoid malignant medulloepithelioma of the optic nerve: Report of a case and review of the literature. *Orbit*. 1999;18:191–196, with permission.)

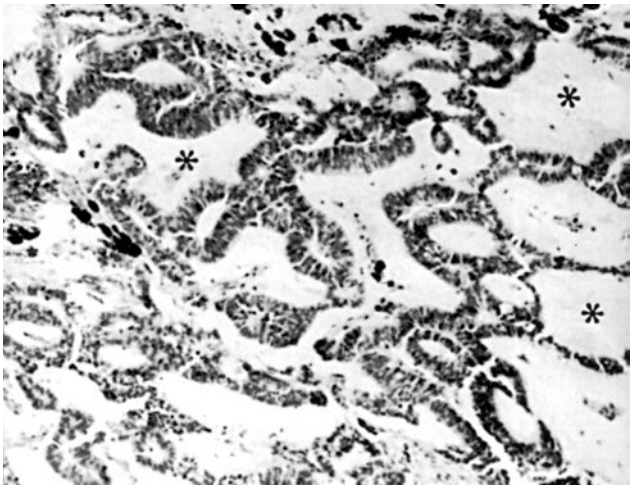


Figure 9.5 Typical cords of medullary epithelium separated by a zone of vitreous-like tissue (*asterisks*) in the optic nerve of a 5-year-old girl (hematoxylin and eosin, original magnification ×380). (From Spencer WH, Rao N. Medulloepithelioma. In: Spencer WH, *Ophthalmic pathology: An atlas and textbook*, Vol. 1, 4th ed. Philadelphia, PA: WB Saunders; 1996:607–608, with permission.)

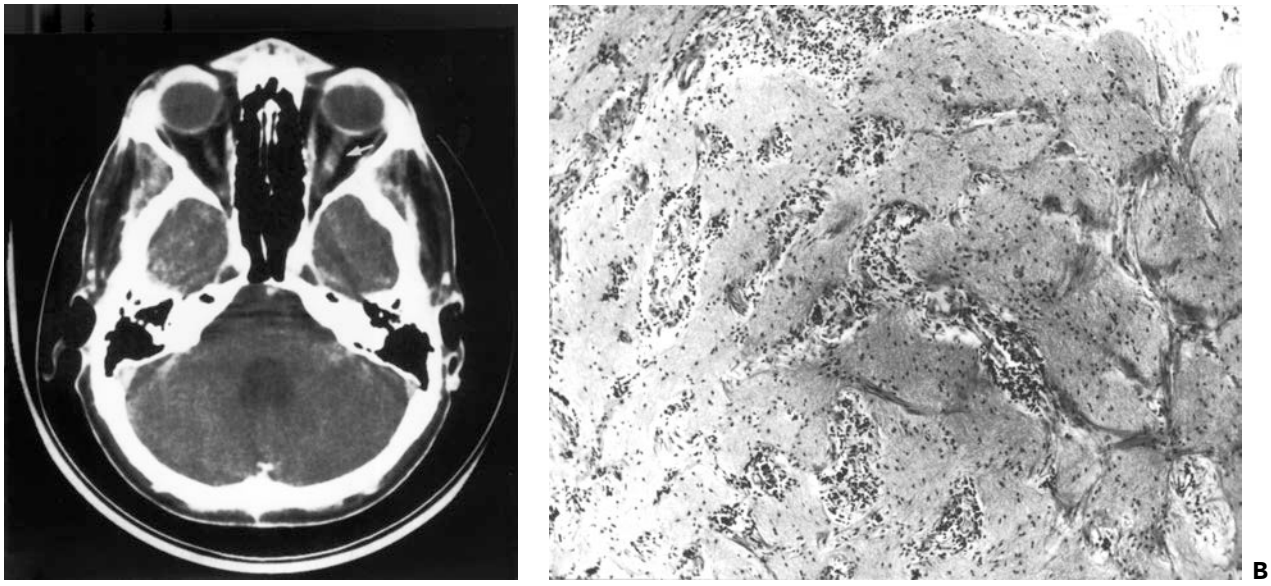


Figure 9.6 Metastatic medulloblastoma. **A:** Axial computed tomography scan demonstrates enlargement of the optic nerve (*arrow*). **B:** Subsequent biopsy revealed a malignant small cell neoplasm infiltrating the optic nerve that was consistent with metastasis (original magnification ×100).

and irradiation was given. No evidence of tumor was found 8 months later. The 2-year-old boy reported by O'Keefe et al. (1997) underwent enucleation because of a presumed retinoblastoma. On histologic study, a medulloepithelioma of the optic nerve was found. Further tumor resection was performed. Radiotherapy and chemotherapy were also administered. Four years later, there was no evidence of recurrence. The 3-year-old patient reported by Biswas et al. (1999) was treated with external beam radiotherapy of 4,600 Gy in 20 fractions. No surgery was performed. Seventeen months after surgery the child was well without systemic metastasis but a month later brain metastasis occurred and the child died.

MEDULLOBLASTOMA

Medulloblastoma is a neoplasm of the cerebellum and is not to be confused with medulloepithelioma. The medulloblastoma arises from the fetal granular layer of cells that covers the cerebellar cortex and is present at birth. Normally, this layer disappears during the first year of life. Metastasis from a medulloblastoma to the intraorbital portion of the optic nerve accounts for the one case of this tumor type in our orbital tumor study. This was a 19-year-old man who underwent removal of a midline medulloblastoma of the cerebellum in January 1984 (Garrity et al., 1989). Postoperatively, the patient was treated with radiotherapy, 55 Gy to the posterior cranial fossa and 37 Gy to the spinal cord. In April 1986, decreasing vision of the left eye was noted. Two months later, a visual acuity of 20/400 in the left eye was recorded. There was marked restriction of the visual field in the left eye, and 4 diopters of papilledema were noted. A CT scan (see Fig. 9.6A) showed enlargement of the left optic nerve. A biopsy of the enlarged nerve revealed a malignant small cell neoplasm consistent with metastatic medulloblastoma (Fig. 9.6B). Another 50 Gy of radiotherapy was given to the left optic nerve, supplemented with chemotherapy. Extensive metastasis to the spinal cord was demonstrated in February 1988, and the patient died 5 months later.

INTRAORBITAL OPTIC NERVE GLIOMA

The nerve of the anterior visual pathway extending from the optic papilla to the geniculate bodies is morphologically and functionally a tract of the central nervous system comparable to the white matter of the brain. This nerve tract is surrounded by the same coverings as the brain, and the extrinsic supporting structures are vascular connective tissue septa and neuroglial cells.

It is the abnormal proliferation of supporting neuroglial cells to which the term *glioma* has been applied. Gliomas may arise anywhere in the central nervous system. Our discussion of the subject mainly concerns the glioma of the optic nerve rather than the manifestations of glioma of the optic chiasm or optic tract. Furthermore, our emphasis is directed chiefly to the intraorbital portion of the optic nerve because it is the glioma in this location that most closely mimics the clinical manifestations of a true orbital tumor.

The present trend is to regard these gliomas as true neoplasms rather than as hamartomas.

Incidence

Our 40-year survey (1948 to 1987) of consecutive cases of orbital tumors, published in the third edition of *Orbital Tumors* (1994), encompassed the era in which enucleation of the eye was the preferred management of an intraorbital optic nerve glioma. Therefore, the neoplasm was available for histologic verification. There were 34 gliomas in this survey. At the time, this represented 2.4% of our total 1,376 tumors. The tumor was the second most frequent orbital tumor in children at that time. Sixty-eight percent of our gliomas were seen in the patients' first decade of life. The age range of our patients was 2 months to 46 years, with a mean of 8.5 years and a median of 5.5 years.

Another massive review of this feature of the neoplasm was also published by Dutton (1994). His survey was based on 2,297 cases from the world's literature up to 1992. The optic nerve glioma occurred in 1.5% to 3.5% of all orbital tumors. The sex distribution was equal. Overall, 70% of patients presented in the first decade of life. Twenty-nine percent of gliomas were associated with neurofibromatosis, and among neurofibromatosis patients, optic nerve gliomas were detected in approximately 15%. Since these publications, update reports on the frequency of orbital optic nerve glioma have declined, particularly in the Americas and Europe, because chemotherapy and radiotherapy have replaced enucleation of the eye as the preferred initial management option. However, in Asia and Africa, cases of advanced glioma at the time of presentation (painful, marked proptosis, and blindness) seem more common. Here, enucleation is the only possible management option.

Clinical Features

The presenting pattern of an intraorbital glioma is almost always one or a combination of a painless proptosis of one eye (see Fig. 9.7), some displacement of the eye, some degree of visual dysfunction, and a disturbance of ocular motility. If the child is too young for visual acuity assessment, a visual-evoked potential can indicate the degree of visual impairment. This test also serves as a baseline for judging the progress of the tumor in this age-group of children. The latency of the visual-evoked potential increases as the neoplasm enlarges (Ng and North, 2001). Other subsequent signs and symptoms of glioma are an afferent pupillary defect and pallor or papilledema of the optic disk, and strabismus may develop. In our small cohort of patients, papilledema was more common than pallor in the intraorbital glioma, but the reverse was noted in the chiasmal-type gliomas. Older children have a central scotoma and some degree of achromatopsia.

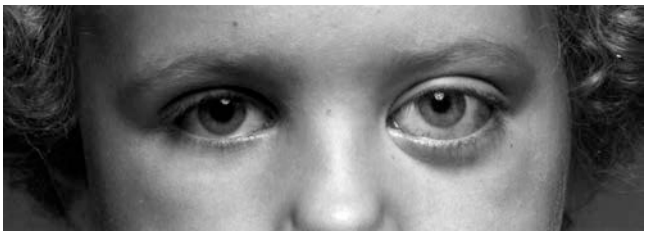


Figure 9.7 Upward displacement, subtle baring of the sclera, and slight proptosis of the left eye with vision reduced to light perception of 1 month's duration in a 4-year-old girl. Chronic papilledema and moderate pallor of the left optic disk were also present.

Imaging Aspects

At present, CT scan is the most useful imaging mode for the initial diagnosis of a presumed orbital optic nerve glioma. It pictures the size, shape, and extent of the neoplasm. Gliomas are usually globular (see Fig. 9.8), fusiform (see Fig. 9.9), or lobular in shape. The lobular glioma is the result of bending or buckling of the expanding nerve within the confined orbital space (see Fig. 9.10). The glioma is usually isodense, with minimal degrees of contrast enhancement, varying between 20% and 25%. The glioma is also well marginated because the dural covering, although stretched, contains the tumor within the nerve sheath. However, in long-standing gliomas, the density becomes less uniform and associated with areas of low attenuation suggesting a cyst-like degeneration (see Fig. 9.11).

MRI is best reserved for the follow-up period. It reveals changes in the size of the tumor and any extension of the mass toward the chiasm. The gliomas have slightly prolonged T_1- and T_2-weighted relaxation times

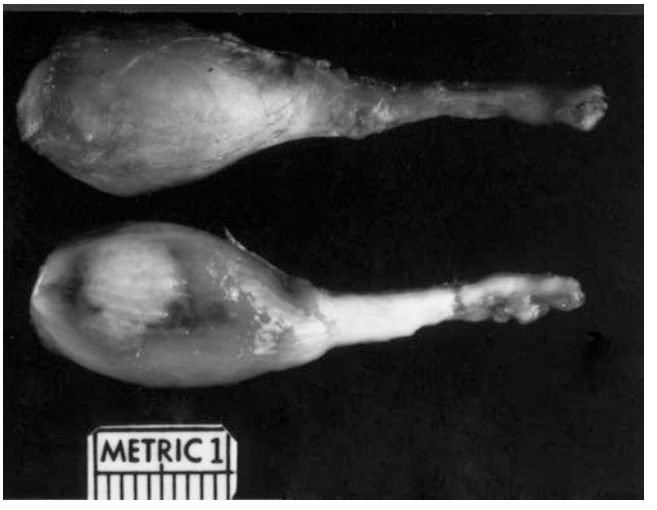


Figure 9.8 A globular glioma from a 12-year-old girl showing the external surface above and cut surface below. The rounded portion of the tumor (left) abutted and indented the back surface of the eyeball.

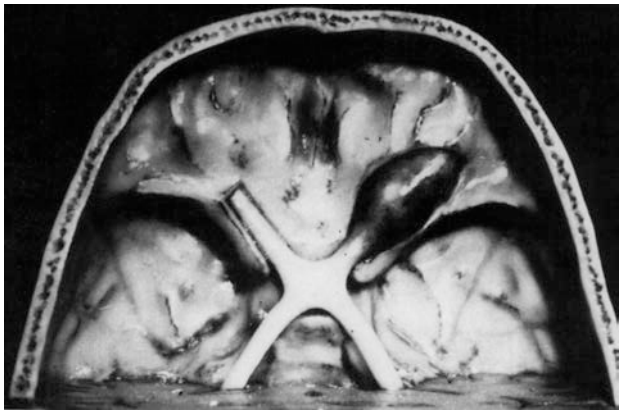


Figure 9.9 Model of a fusiform glioma of the orbital portion of the optic nerve.

(Shen et al., 2001). As a result, the tumor on the T_1-weighted image appears isodense or slightly hypointense compared with white matter. Areas of mucinous degeneration and necrosis appear hypointense. On T_2-weighted images, the signal intensity may show greater variability but usually appears hyperintense compared with white matter.

In lieu of a diagnostic incisional biopsy of the orbital glioma, several ophthalmologists and radiologists discuss their reliance on the differing radiographic features of optic nerve glioma and the orbital nerve sheath meningioma, particularly in older children and adults, for accurate diagnosis. The principal radiographic features of a meningioma surrounding the orbital optic nerve are a greater degree of contrast enhancement than a glioma, calcifications corresponding to the inherent psammoma bodies, and, of most importance, a characteristic tumor blush when studied by angiography, a feature absent in glioma. Unfortunately, some gliomas have an arachnoid hyperplasia that may give a false appearance of vascularization, thereby nullifying this assumed diagnostic clue (Liauw et al., 1996). A diagnosis of an orbital optic nerve neoplasm by radiographic imaging, even among those skilled in the nuances of imaging, is at best only presumptuous.

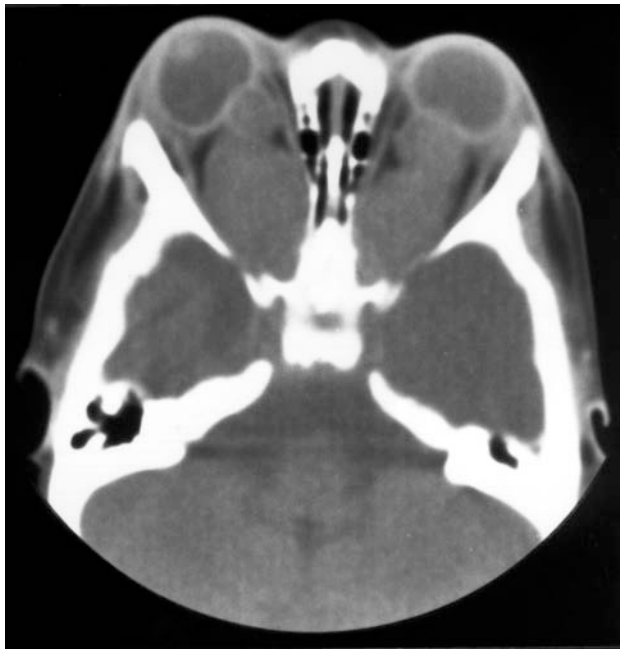


Figure 9.10 Axial computed tomography scan without contrast shows large, bilateral, isodense lobulated tumors filling the retrobulbar spaces and extending from the posterior margins of the eyeballs to the optic foramina. Note the indentation of the posterior wall of each eye by the tumors. The patient was a 5-month-old boy with bilateral ocular nystagmoid movement since birth.

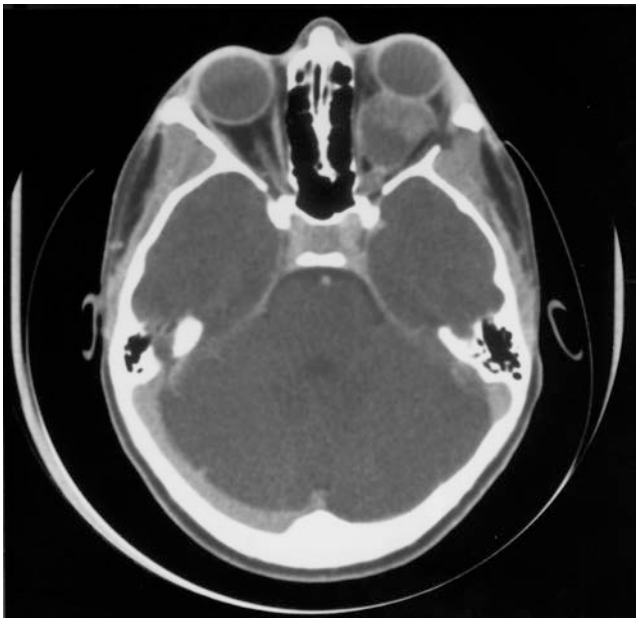


Figure 9.11 Axial computed tomography scan shows a large, well-marginated mass in the retrobulbar space of the left orbit associated with proptosis in a 3-year-old girl. The mass has areas of low attenuation adjoining areas of contrast enhancement suggesting cyst-like degeneration. There is no optic canal enlargement or chiasmal involvement. A biopsy diagnosis of optic nerve glioma was made when the patient was 6 years old. She received no subsequent therapy. At orbitotomy, the mass was a partially necrotic, gelatinous glioma with a large cyst-like component (coalescence of microcysts).

Association with Neurofibromatosis

Over time, a number of publications have discussed this subject. We briefly summarize those reports that included an analysis of >100 cases.

In the article by Crowe and Schull (1953), 635 (29%) of 2,186 published cases with clinical data demonstrated signs of neurofibromatosis type 1 (NF1). The authors believed the true incidence of NF1 may be considerably higher because most studies failed to mention the presence or absence of this disease in their patients.

Chutorian et al. (1976) reported that patients with NF1 may have a higher incidence of bilateral optic gliomas than those without NF1.

Of the 318 patients described with glioma confined to the optic nerve by Imes and Hoyt (1986) and Listernick et al. (1989), only seven patients (2.2%) had bilateral disease with no detectable tumor crossing the chiasm.

Alvord and Lofton (1988) analyzed 155 cases of intraorbital optic nerve gliomas, including patients with and without NF1. None of the patients of either type who underwent a complete excision of the tumor with a microscopically clean proximal stump had a recurrence. However, when the surgical stump was not free of tumor cells or had not been examined at all, the tumor was prone to recurrence because of chiasmal spread. In patients without NF1, the recurrence rate was 5%. In those with NF1, the recurrence rate was 10%.

Pathology

The most common type of glioma affecting the orbital nerve in children is the juvenile fibrocystic astrocytoma, grade 1. It is benign and very slow growing. Its growth often comes to a spontaneous halt, and it remains an intraorbital mass. If growth continues, the neoplasm extends through the bony optic foramen and invades the intracranial portion of the optic nerve. The origin of the tumor is the glial cell of the intraneural, septal supportive network. The proliferating tumor cells may have vesicular or hyperchromatic nuclei (see Fig. 9.12). A minimal amount of cytoplasm may be evident in some cells.

Intracellular, irregularly shaped, eosinophilic processes may be present in association with thickened cytoplasmic glial filaments. These degenerative masses are Rosenthal fibers (see Fig. 9.13). Their presence is characteristic of a low-grade astrocytoma, but they are not specific for this tumor.

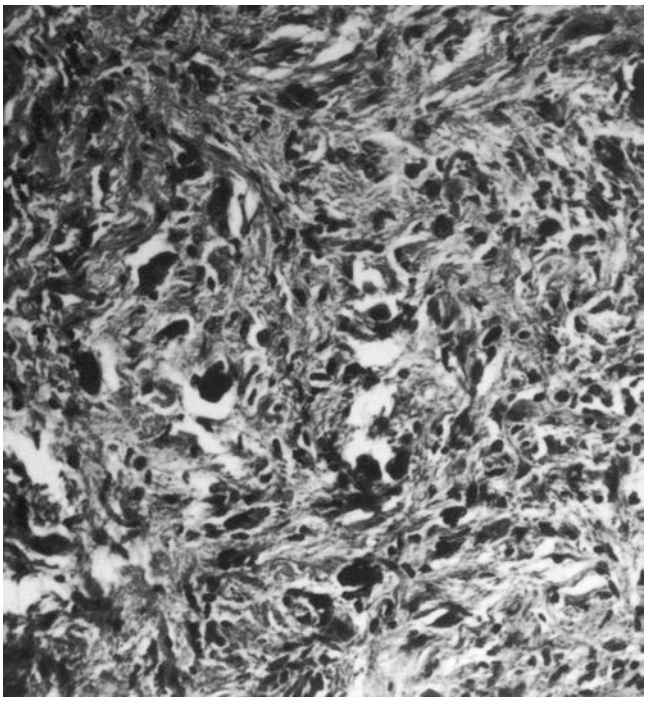
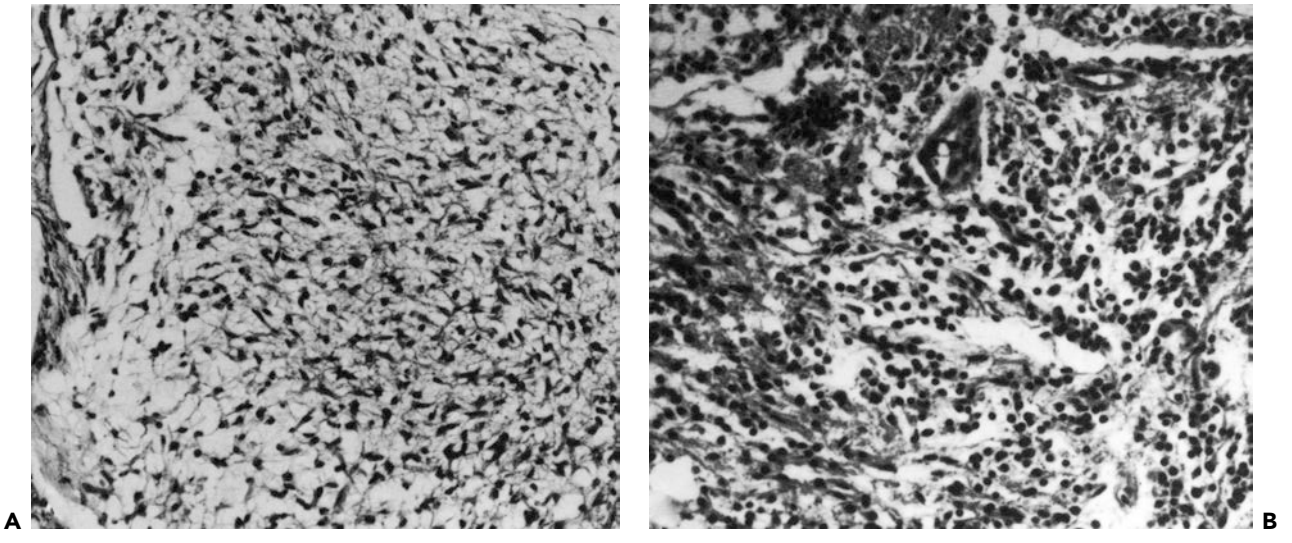


Figure 9.13 Grade 3 astrocytoma showing mitotic figures, increased cellularity, cellular anaplasia, and pleomorphism. Irregular-shaped, amorphous, dense-staining structures are Rosenthal fibers (original magnification ×155).

Areas of the tumor remote from the vascular supply may undergo microcystic degeneration (see Figs. 9.13 and 9.14), and the foci of pooled mucopolysaccharide are visible on



A **B**

Figure 9.12 **A:** The glioma is composed of fine fibrillary astrocytes (original magnification ×155). **B:** Small, regular, rounded nuclei suggest the pattern of an oligodendroglioma (original magnification ×155).

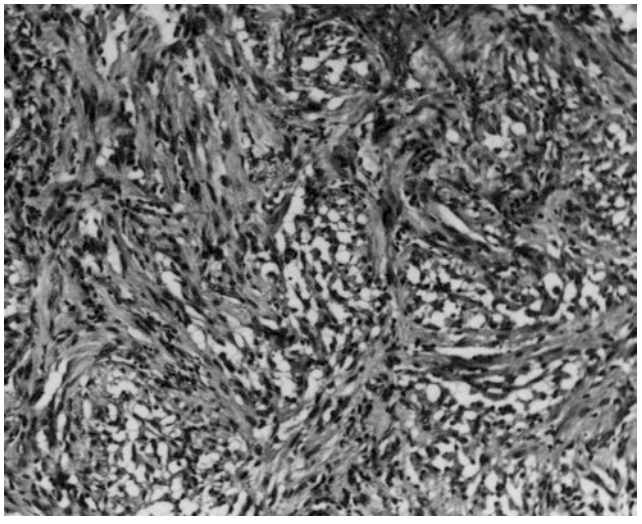


Figure 9.14 Grade 2 neoplasm is more cellular and cytoplasmic processes are coarser, imparting a more fibrous appearance. Numerous microcysts are evident (original magnification ×100).

CT scan. Microcalcospherites are occasionally seen within the stroma.

The tumor cells promote a reactive response of the leptomeningeal cells so that the pial septa thicken, as do the surrounding leptomeninges. This adds to the increasing diameter of the nerve (see Fig. 9.15). Several authors believe this hyperplasia is a feature indicative of associated NF and that intraneural growth without hyperplasia is characteristic of an isolated optic nerve glioma. In the past, biopsy material from the peripheral portion of the nerve has been misinterpreted as fibrous meningioma.

A less common type of glioma of the optic nerve occurs in adults (>20 years old). It is a highly malignant neoplasm, an anaplastic astrocytoma that is infiltrative, grows rapidly (early blindness), and causes death by growing proximally into the intracranial portion of optic pathways. The tumor shows nuclear pleomorphism, mitotic activity, endothelial proliferation, and necrosis. Its most common location is the chiasmal portion of the visual pathway.

Management and Course

If, on initial examination, a child has several signs or symptoms of an optic nerve glioma and a routine orbital CT scan shows a well-marginated mass within the confines of the intraorbital optic nerve, a presumptive diagnosis of a low-grade optic nerve glioma is made. If, on further analysis of the CT scan, there is no evidence of proximal expansion of the mass into the optic foramen, an incisional biopsy is not done.

The parents should be told that it is likely the tumor is benign and will not metastasize, but over succeeding months or years, complete loss of vision will occur. The tumor will grow slowly, and there will be no pain. The parents can also be told that the tumor, at this stage, could be surgically removed, but this would result in immediate and total blindness. Instead, we favor no treatment, thereby allowing preservation of vision as long as possible. We do not recommend radiotherapy or chemotherapy. We also prefer a follow-up visit in 6 months. At this time, an MRI scan can be performed to provide more precise information as to the presence or absence of intracranial extension of tumor. If negative, the child can be followed up at yearly intervals with successive MRIs. If at any time in the follow-up interval, invasion or extended growth along the nerve is shown, surgical removal is our choice of therapy. A frontal orbitocraniotomy with unroofing of the orbit can be performed. The superior wall of the long optic canal and a long piece (short of the chiasm) of the optic nerve and the tumor can be removed. With careful dissection, the eye can be salvaged. If the proximal end of the nerve is free of tumor cells microscopically, the patient can probably be cured.

Rush et al. (1982), studied 33 histologically verified optic nerve gliomas that had been removed between 1919 and 1973. Twenty-three patients underwent total excision of tumor without supplementary radiotherapy. Nine patients, whose tumors were incompletely excised, received supplementary radiotherapy. One patient received no therapy. Five of these patients died: Four of the nine who underwent incomplete surgical removal of tumors and the one patient with no treatment. The remaining 28 patients were still living at the conclusion of their follow-up. Their mean survival interval was 17 years; the longest survival was 44 years and the median was 16 years. Rush et al. (1982) rightfully concluded that survival was significantly associated with completeness of surgical excision.

The malignant optic nerve glioma is, chiefly, primary in the chiasm. Its incidence, clinical features, therapy, and course are beyond the scope of this review.

Over the many years that an intraorbital optic nerve glioma has been known, instances of its spontaneous regression have been occasionally noted. Parsa et al. (2001) reviewed 13 cases of spontaneous regression of optic gliomas documented by serial neuroimaging and collected internationally from 12 medical centers. All tumors met radiologic criteria for diagnosis. Three of the 13 cases showed involvement of the orbital portion of the optic nerve, either as an isolated tumor or a participant in thickening of the nerve from the eyeball to the chiasm. However, only one of these cases was verified histologically. The biopsy report was a pilocytic astrocytoma grade 1 in a 4-year-old girl with thickening of the entire right optic nerve. No treatment was offered. At the age of 17 years, her vision was 20/30 in the affected eye, and an MRI showed only trace enlargement compared with the left optic nerve. The other 10 cases in their series involved the optic chiasm. Some cases in the literature reporting regression of tumor after incomplete excision may have been surgically induced.

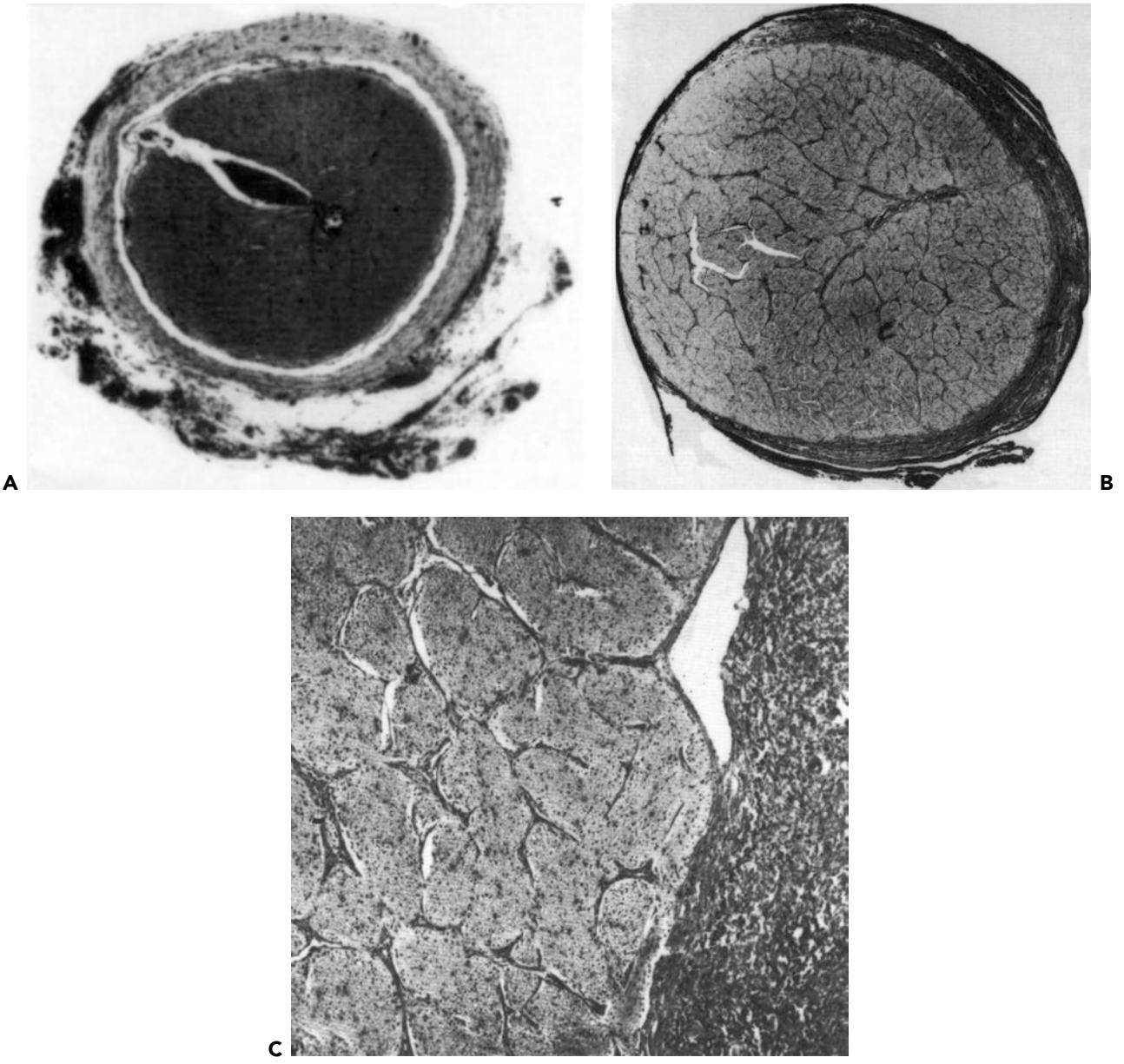


Figure 9.15 **A:** Normal optic nerve (original magnification ×6). **B:** Symmetric enlargement of the nerve reflected in the increased thickness of the individual nerve fascicles compared with (A) at the same magnification (original magnification ×6). **C:** Optic nerve (left) and perineural proliferation of the arachnoid cells and connective tissue (right) that is not part of an optic nerve glioma (original magnification ×4).

NEUROBLASTOMA AND GANGLIONEUROBLASTOMA

These tumors are derived from the sympathogonia of neural crest origin that are destined to populate the sympathetic nervous system. If it can be said that the neuroblastoma represents a first step in maturation from the primitive neural crest cell, the ganglioneuroblastoma represents the second rung of the ladder of differentiation. Other primary sources are the thoracic, cervical, or pelvic sympathetic nervous system chain. Both tumors are considered malignant, but the mature third sibling in this family, the ganglioneuroma, is benign. Our further remarks chiefly concern the metastatic orbital neuroblastoma.

Incidence

In approximately 55% of cases, the primary site of the tumor is the adrenal gland. Approximately 70% are neuroblastomas, 25% are ganglioneuroblastomas, and 5%

are ganglioneuromas (Al-Mulhim, 1998). Most of these neoplasms that metastasize to the orbit come from the adrenal gland or retroperitoneum. Metastasis to all sites occurs in 35% to 50% of all cases.

All tumors reported in the literature that involve the orbit are the metastatic type except for one case. This was a well-documented case of a "differentiated" neuroblastoma "primary" in the orbit, reported by Jakobiec et al. (1987). This tumor occurred in a 49-year-old woman with the tumor localized to the left orbit. Over a 12-year period, she underwent five subtotal excisions, orbital radiotherapy, and finally exenteration. However, Bullock et al. (1989) reported what was thought to be a second case of a primary orbital neuroblastoma in a 35-year-old man. On subsequent review, this case was reclassified as an orbital carcinoid tumor (Font et al., 1991).

We never encountered an orbital neuroblastoma in an adult in our 50-year survey of orbital tumors. All our 19 patients were <10 years of age at the time of diagnosis. The age range was 4 months to 9.9 years, with the majority, 52% (10 out of 19), in the age-group of 1 to 4 years. The distribution of the remaining nine patients was approximately equal in patients younger than 1 year and older than 4 years.

It was the fourth most common tumor in the first decade of life and the second most common orbital tumor in childhood (Table 3.4). The tumor has also been reported at birth (Nelson, 1969). There are 12 males and 7 females in our group. In 42% (8 out of 19), the orbital disease was bilateral. This agrees with a 40% bilaterality widely quoted in the literature. Strangely, in the remaining 11 unilateral tumors, the left orbit was affected in all but one patient.

Our 19 metastatic orbital neuroblastomas represented an incidence of 1% (19 out of 1,795) of the total tumors in our 50-year tumor survey and 12% (19 out of 155) of total metastatic tumors.

Clinical Features

Myriad signs and symptoms are associated with lodgment of a metastatic deposit of neuroblastoma in the orbit or the adnexa. In a study of the ophthalmic manifestations of metastases in 47 patients with proved neuroblastoma, Belgaumi et al. (1997) noted the three most common signs, roughly in their order of frequency, were proptosis (60%), periorbital ecchymosis (40%), and Horner syndrome (17%). Subconjunctival hemorrhage is less common. The periorbital ecchymosis is secondary to necrosis within the rapidly evolving tumor.

Other less common ophthalmic manifestations are ocular motility disturbances, drooping of the upper eyelid, papilledema, and a lump either in the temporal fossa or over the zygomatic bone on the affected side. The lumps usually indicate invasion of underlying bone (see Fig. 9.16). A palpable soft tissue orbital mass was present in <50% of our 19 cases. Although the proptosis is painless,

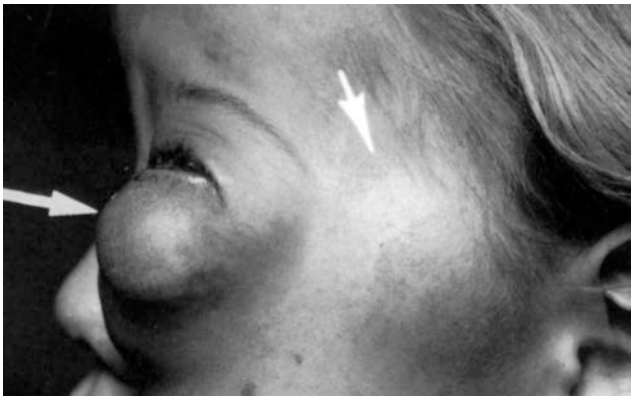


Figure 9.16 Side view of 3-year-old girl with tumor masses overlying the left zygoma (*horizontal arrow*) and along the lateral aspect of orbit (*vertical arrow*).

these patients are sick children. Other systemic signs and symptoms, if not already known, are unexplained fever, chronic runny nose, irritability, listlessness, opsoclonus, and a tendency of the child to cling to a parent. The ocular examination must frequently be conducted with the child's head nestled against the parent's chest.

Many ophthalmologists who write about these neoplasms tend to overlook the possible diagnostic value of the ophthalmologic manifestations of the tumor, saying, "The systemic neuroblastoma was already known." These patients were seen previously by a pediatrician. However, proptosis and periorbital ecchymosis were the presenting features of an undiscovered extraorbital neuroblastoma. The ecchymosis, in particular, is striking (see Fig. 9.17). It is bright red. However, it is not pathognomic. Children may also show discoloration of the eyelids with leukemia, granulocytic sarcoma, rhabdomyosarcoma, and Langerhans histiocytosis. The discoloration of the periorbita associated with rhabdomyosarcoma has a bluish hue. The seepage of hemorrhage into the eyelid from either orbital leukemia or histiocytosis is a dusky red color,

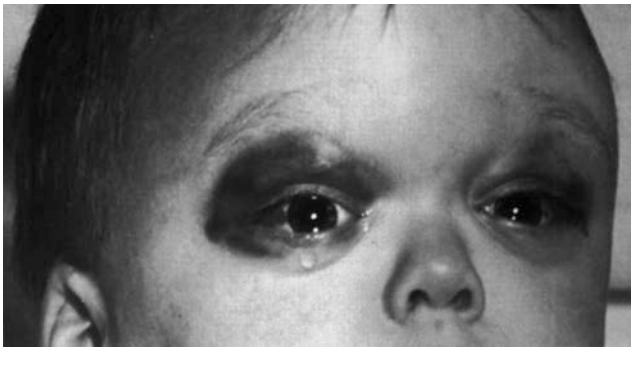


Figure 9.17 Bilateral ecchymosis and periorbital edema were the initial signs of a subsequently discovered abdominal neuroblastoma in a 2-year-old boy. Bilateral proptosis was also present.

and a tinge of green may be present in the effusion from granulocytic sarcoma. Parents whose child was first seen by an ophthalmologist may have been surprised to learn their child also had an abdominal mass.

The rapidity of onset was another common event. In our series, the duration of ophthalmic signs and symptoms was 4.2 weeks. In this respect, the presentation resembles rhabdomyosarcoma, but the median age of patients with rhabdomyosarcoma is 6 years in our series, whereas the median age of metastatic neuroblastoma is 2 1/2 years. Patients with primary orbital rhabdomyosarcoma do not look or feel as ill as patients with neuroblastoma.

In a systemic evaluation, the catecholamine values in urine are elevated in 80% to 90% of patients (Enzinger and Weiss, 1988). Bone marrow biopsy is usually positive for neuroblastoma cells. Last, an ipsilateral appearance resembling Horner syndrome and heterochromia should, in the absence of other orbital pathology, alert the physician to probable foci of tumor in the cervical region.

We should mention some publications that reported out-of-the-ordinary findings. Belgaumi et al. (1997) analyzed their 47 patients with metastatic neuroblastoma to determine the frequency of blindness. Eight of their 47 patients developed blindness in at least one eye at some point during the course of their disease. Subsequent chemotherapy, radiotherapy, and high-dose corticosteroids, alone or in combination, failed to restore vision in these patients.

Another interesting report is that of Bohdiewicz et al. (1995) who examined a 10-month-old child with bilateral periorbital edema and ecchymosis. Background information suggested the patient was a victim of battered-child syndrome. Initial radiographs of the skull, chest, spine, and appendicular skeletal system were negative for fractures. Head CT scan and abdominal ultrasonography were described as "negative." However, scintigraphic radioisotope bone scan revealed increased activity around the orbits (see Fig. 9.18). Several days later, a bone marrow biopsy was positive for neuroblastoma and a meta-iodobenzylguanidine (MIBG) "superscan" refers to abnormal MIBG uptake in the skeleton and decreased uptake in liver, bladder, and heart. After a 5-month course of chemotherapy, follow-up scans of orbit and abdomen were normal.

Wilson et al. (2003) described a 6-year-old girl with recurrent neuroblastoma of the spine who was referred for vaccination of an interleukin 2 and lymphotactin gene-modified allogeneic cell preparation. At the age of 4 years, this child had received multiagent chemotherapy for disseminated neuroblastoma. Within 24 hours of the initial vaccination, she developed periorbital edema and erythema of right upper eyelid. A CT scan showed a cystic lesion in the subperiosteal orbital space. Biopsy of the mass revealed a necrotic neuroblastoma. The authors believe this case represents the first description of occult orbital metastasis detected after administration of an antitumor vaccine.

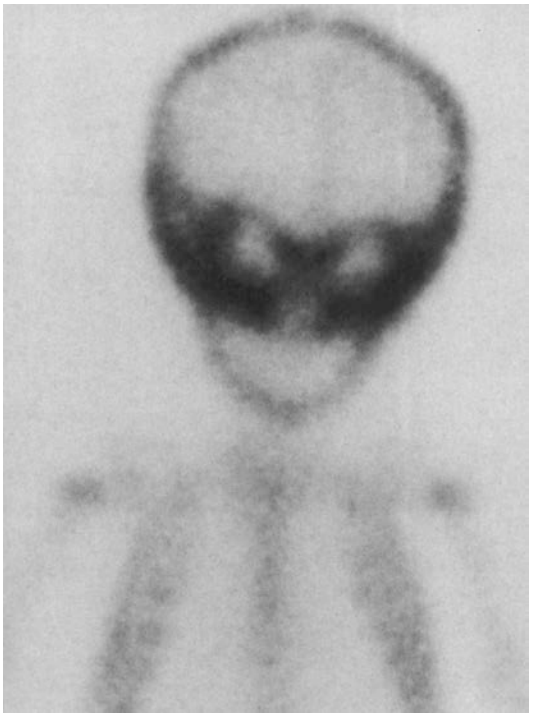


Figure 9.18 Scintigraphy (anterior view) 3 hours after technetium Tc 99m—MDP administration clearly demonstrated abnormal increased activity around both orbits ("bone scan raccoon eyes") and abnormal activity throughout the right humerus.

Imaging Aspects

CT scan is very helpful in showing both soft tissue and bony components of orbital metastases. Metastasis usually involves the zygoma and lateral orbital walls with adjacent intraorbital and extraorbital soft tissue masses (see Fig. 9.19). The soft tissue metastasis is irregular, homogeneous, and slightly hyperdense.

In the preceding paragraphs, we have noted the usefulness of scintigraphy in demonstrating foci of metastasis other than in obvious locations. These imaging agents, methylene diphosphonate (MDP) and MIBG, may reveal an unsuspected metastasis that alters the staging of the tumor. In addition to the radioisotopes already noted, Spottswood et al. (2001) used indium-labeled pentetreotide in radionuclide imaging of patients with neuroblastoma although Shalaby-Rana et al. (1997) noted that indium-labeled pentreotide is less sensitive than MIBG for detecting active disease but may correlate with prognosis.

Pathology

Grossly, the orbital metastasis is a soft, friable, poorly circumscribed mass. Its color is either a red gray or bluish red. The texture may be slightly gritty.

The metastatic neuroblastoma is chiefly composed of embryonal neuroblasts. The individual cells are about the size of a small lymphocyte. The nucleus of each cell is the

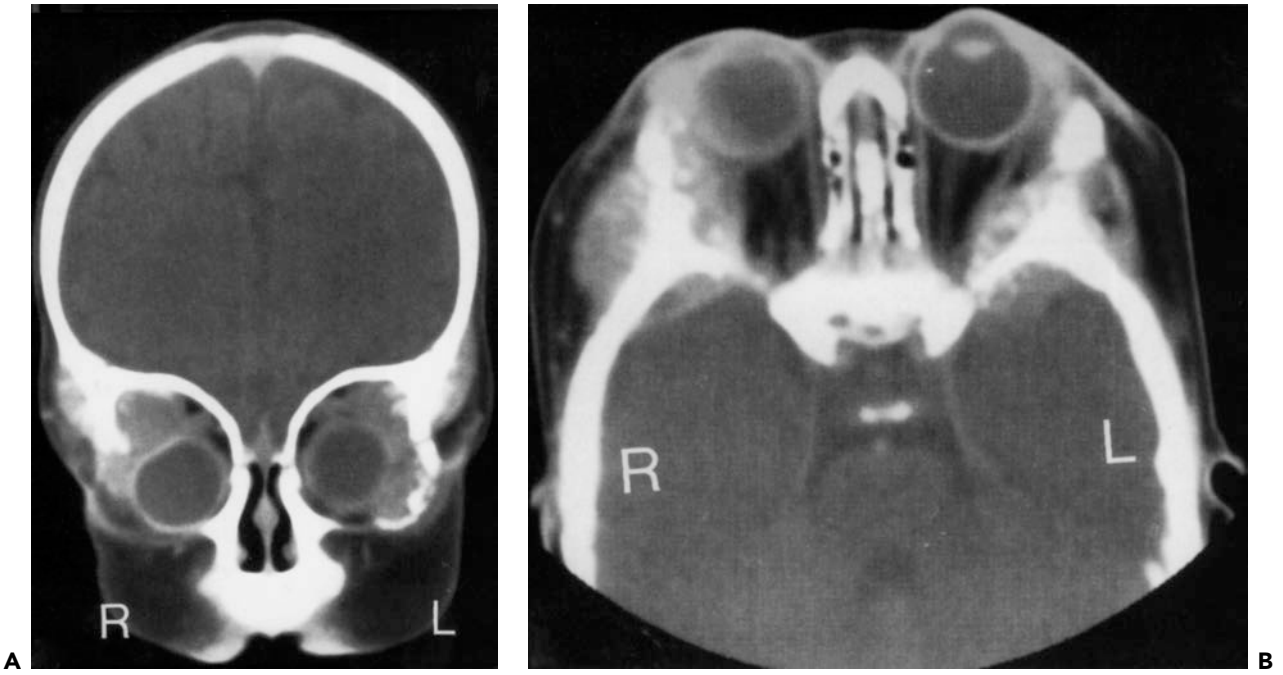


Figure 9.19 Metastatic neuroblastoma. Axial **(A)** and coronal **(B)** computed tomography scans of a 7-month-old child show bilateral, irregular, inhomogeneous, enhancing soft tissue masses with calcific-like densities in the lateral and superior orbits with extraorbital extension. Lytic destruction of the lateral orbital walls and greater wings of the sphenoid bones indicate a malignant process. On the right side are marked displacement and indentation of the globe.

predominant feature. It stains deeply, is round or oval, is surrounded by a space almost devoid of cytoplasm, and has a very indistinct border. The cells are arranged in sheets or clumps, and the stroma consists of a tangled net of cell processes (neuropils). The tumor has likely undergone some differentiation and has a haphazard arrangement of a few Wright rosettes. These are circular cell structures enclosing a featureless core of cell processes. The tumor may have large areas of hemorrhage and necrosis (see Fig. 9.20). Some metastases may contain a smattering of ganglion cells.

The primary tumor, whatever its location, that spawns the orbital metastasis is probably a more differentiated lesion than its offspring. Here, foci of ganglionic differentiation are seen within sheets of neuroblasts, or there is an admixture of immature neuroblasts with clusters of variably differentiated ganglion cells (ganglioneuroblastoma) set in a fibrillary stroma (see Fig. 9.21). Binucleated cells in the ganglionic portion of the tumor also may be present.

Immunohistochemical findings are quite variable. According to Weiss and Goldblum (2001), a number of neuroectodermal antigens can be identified in neuroblastomas, although generally, the extent and intensity are functions of the level of differentiation. Neuron-specific enolase is positive in many of these tumors but is not pathognomic. Neurofilament protein, an intermediate filament, can also be identified, but its immunoreactivity depends on the degree of differentiation of the tumor. S-100 protein is strongly positive in the ganglioneuromatous portion of the lesion. Other markers that may be useful in diagnosis are protein gene product 9.5, chromogranin, vasoactive intestinal peptide, and synaptophysin.

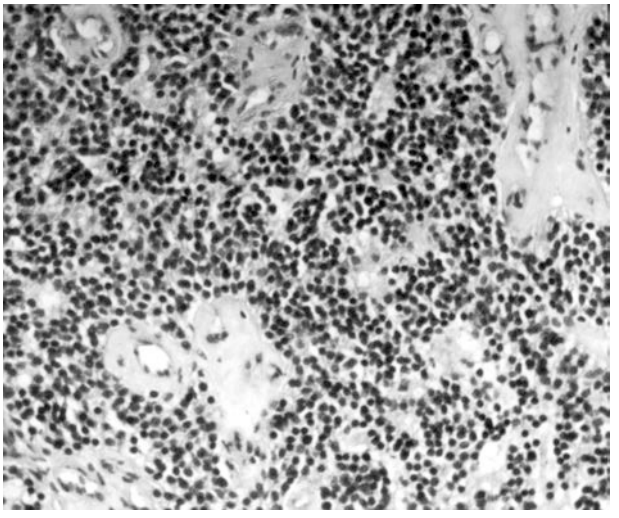


Figure 9.20 The embryonal neuroblast is a small, round cell arranged in sheets or clumps with hyperchromatic nuclei and indistinct cell borders intermixed with a stroma of featureless mats of tangled cell processes (left of center). Note prominent fibrovascular network (upper right) (original magnification ×165).

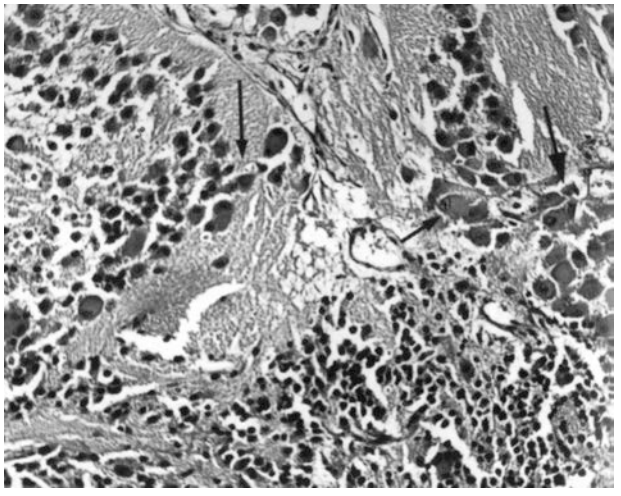


Figure 9.21 In this ganglioneuroblastoma, immature neuroblastic cells (bottom) merge with clusters of sympathetic ganglion cells (*arrows*) in a fibrillary stroma (original magnification ×130).

Management and Course

Among soft tissue tumors, the metastatic neuroblastoma is now considered the most malignant in the realm of childhood oncology. This has not always been the prevailing opinion. During the first 35 to 40 years of our orbital tumor study, a multitude of reports analyzed the effectiveness of various therapies such as surgery, radiotherapy, and chemotherapy, administered alone or in combination. The introduction of chemotherapy, in particular, was considered to have a beneficial effect, and among some reports, chemotherapy was considered a cure on the basis of 2-year studies. However, the passage of time, based on a 5-year follow-up, proved the recurrence and death rates to be no different than in patients who received no therapy. Oncologists now seem to agree that survival rates remained relatively unchanged, a finding that contrasted with the improving prognosis of other childhood sarcomas.

Over the past 15 years or so, it has become apparent that most cases of neuroblastoma, at the time of presentation, have widespread metastases. The introduction of diagnostic scintigraphy during this interval revealed occult foci of metastases that were unknown to oncologists in prior years. The orbit was one of the areas included in this occult group.

Subsequently, pediatricians and oncologists have been making positive strides to improve the dismal prognosis of neuroblastoma. The first major step, long overdue, was to merge the many study groups that were independently overseeing differing protocols for the therapy of neuroblastoma.

The resulting meld was the Children's Oncology Group (COG). The group includes about 22 study centers in the United States and some type of exchange with 3 centers in western Australia. Also, there is a central office for statistical evaluations. There are strict considerations for diagnosis and eligibility criteria. The study protocol defines the guidelines for surgery, radiotherapy, pathology, biology, and chemotherapy. Their treatment protocol is altered for low-risk and high-risk patients on the basis of the known recurrence rate. Patients with orbital metastasis are in the high-risk group. It will be several years before we know the recommendations of the COG study.

In summary, the management of metastatic neuroblastoma is the domain of the pediatric oncologist.

GANGLIONEUROMA

This is a benign, well-encapsulated neoplasm of mature ganglion cells. It may occur anywhere along the sympathetic nerve axis. In this locale, these tumors outnumber neuroblastomas by approximately 3:1 (Stout, 1947). Ganglioneuroma and neuroblastoma also differ in their location and age distributions. Most ganglioneuromas are diagnosed in patients older than 10 years and are most frequent in the posterior mediastinum followed by the retroperitoneum. They are infrequent in the adrenal gland in contrast to neuroblastoma. Most ganglioneuromas develop *de novo* rather than by maturation in a preexisting neuroblastoma (Weiss and Goldblum, 2001).

In the orbit, they are very rare. We do not have a single ganglioneuroma in our 50-year collection of orbital tumors. Toppozada (1958) reported a 4-year-old girl with a primary ganglioneuroma along the left infraorbital nerve that secondarily invaded the inferior orbit and eroded the superior maxilla. Lloyd et al. (1998) reported an interesting case in a 3-month-old girl with a left orbital embryonal rhabdomyosarcoma that was successfully treated with chemotherapy and irradiation. Eight years later, a ganglioneuroma developed in the same area and it was treated surgically. However, it recurred when the patient was 19 years old. All initial and successive tumor specimens were reexamined immunohistochemically, but the diagnoses were all correct.

The tumor has low attenuation on CT scans and low signal intensity on T_1-weighted images and high signal intensity on T_2-weighted images (Johnson et al., 1997).

Grossly, ganglioneuromas have a fibrous capsule. Histologically, the tumor has a uniform appearance consisting of a stroma of Schwann cells with mature ganglion cells interspersed throughout (see Fig. 9.22). The ganglion cells have a voluminous cytoplasm that stains pink and may contain one to three nuclei (Weiss and Goldblum, 2001). Ganglioneuromas may also undergo malignant transformation.

ECTOMESENCHYMOMA

This is a malignant tumor of primitive pluripotential neural crest cells with two components. The mesenchymal element is an embryonal rhabdomyosarcoma, and the neuroectodermal element is one of the neoplasms discussed in this chapter. We reference two tumors of these types.

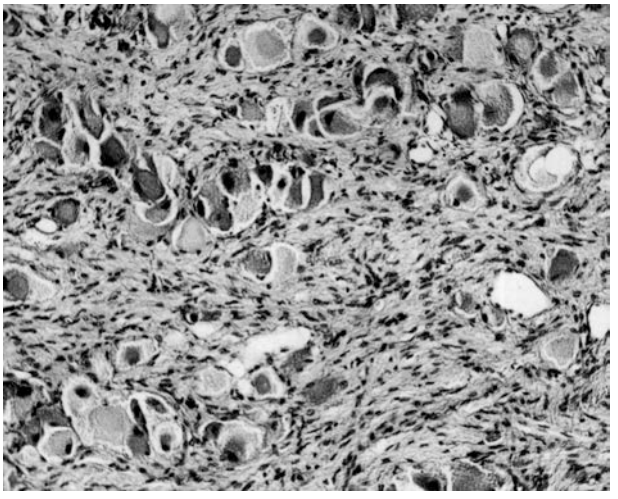


Figure 9.22 Small clusters of mature-appearing ganglion cells are interspersed in a matrix of Schwann cells and fibrous tissue in this specimen from a retroperitoneal mass (original magnification ×110).

Matsko et al. (1992) described a tumor mixed with a neuroblastoma. This occurred in a 5 1/2-year-old girl with rapidly developing ptosis of the right upper eyelid and an enlarging mass in the superior nasal quadrant of the orbit of 10 days' duration. A mass was palpable beneath the superior orbital rim. Imaging showed a preseptal mass that extended posteriorly into the orbit. A trans-septal anterior orbitotomy was performed, debulking the tumor. Immunohistochemical analysis showed one tumor was positive for markers of skeletal muscle differentiation, including desmin, vimentin, and muscle-specific actin. The other tumor was positive for markers of neuroendocrine differentiation, including chromogranin, neurofilaments, and nerve growth factor receptors. The patient was treated with one of the Intergroup Rhabdomyosarcoma Study regimens and was well without tumor recurrence at 18 months' follow-up.

In the second tumor, reported by Bittinger et al. (1997), the neuroectodermal component was a ganglioneuroma. This occurred in a 5-year-old boy with proptosis of the left eye. An orbitotomy revealed a large retrobulbar mass adherent to surrounding tissue and muscle. The tumor was totally removed. On immunohistochemical analysis, the rhabdomyosarcoma element was positive for the same tumor markers described for the preceding tumor. The cell population for the ganglioneuroma was positive for S-100 protein, glial fibrillary acid protein, and neurofilaments. The patient was treated with a protocol of the Rhabdomyosarcoma Study Group. The patient was tumor-free 12 months after presentation.

ESTHESIONEUROBLASTOMA

A synonym for esthesioneuroblastoma is olfactory neuroblastoma.

This is a malignant neoplasm originating from the olfactory placode in the upper reaches of the nasal vault. Because of this location, it frequently erodes the thin surrounding bone early in its course and invades the intracranial vault and orbital space. Our discussion centers on its orbital location.

Incidence

Adults are usually affected, with the highest frequency in the fifth and sixth decades; men and woman are equally affected (Weiss and Goldblum, 2001). Argiris et al. (2003) reported 16 patients recorded in a tumor registry database between 1981 and 2000. The mean age of their patients was 42 years. Our 50-year database (1948 to 1997) has 15 cases. In reference to the total orbital tumor, the frequency of esthesioneuroblastoma was 0.8% (15 out of 1,795) and 2% (15 out of 737) of total secondary tumors. The mean age of this group was 43.7 years. One patient had bilateral tumors.

Clinical Features

The classical features of presentation of a primary tumor within the nose are nasal obstruction or rhinorrhea with or without epistaxis. The presenting features of orbital invasion vary. In one subset, periorbital pain, headaches, fairly rapid loss of vision, variable cranial nerve palsies, afferent pupillary defects, and papilledema heralded a neoplasm invading the orbit from the region of the posterior ethmoid or sphenoid sinuses. In the other subset, the pattern was proptosis, swelling of eyelid, excessive tearing with or without some injection of the globe, and preservation of visual acuity, the result of an esthesioneuroblastoma penetrating the orbit from the anterior ethmoid sinus or the anterior orbital roof.

All observers agree the tumor is uncommon in children younger than 10 years. Two reports in the latter category have been published in the past 10 years. Bobele et al. (1994) observed a 3-year-old boy with tumor of the paranasal sinuses and both orbits and extension involving both frontal lobes. They reviewed the literature and found only 12 other cases documented in patients <10 years old. The case described by Arora et al. (1999) was a "young" male with bilateral proptosis, bitemporal hemianopsia, erosion of the sella, and an intracranial mass.

Curiously, levels of urinary catecholamines are usually not elevated in these patients as would be expected in those with peripheral neuroblastoma (Jakobiec and Font, 1986).

Imaging Aspects

CT scan of a soft tissue mass in the superior nasal vault is quite characteristic of the primary tumor. The mass is homogeneous with relative uniform enhancement. If there is bone erosion, CT scan shows some molding of

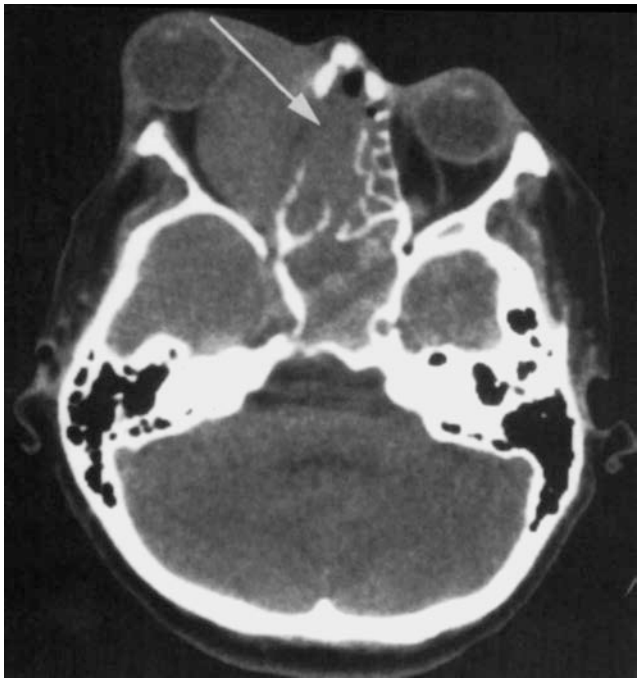


Figure 9.23 Computed Tomography scan without contrast shows a large, isodense, homogeneous tumor in the nasal cavity and ethmoid sinus of a 55-year-old patient with extension into the right orbit (*arrow*) and sphenoid sinus.

bone. If invasion of bone has occurred, the CT scan shows the extent of tumor and its possible resectability. In the case of tumor extension, the CT scan may show flecks of calcium in the image display. Figure 9.23 shows a CT scan

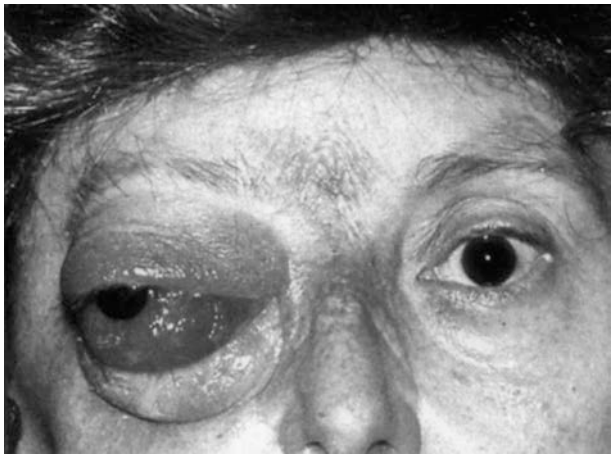


Figure 9.24 Recurrent tumor in a 55-year-old woman with marked proptosis and light perception of right eye of 9 months' duration. Twenty and 18 years previously, surgical procedures had been performed, including right maxillectomy.

from a 55-year-old woman with orbital involvement (see Fig. 9.24).

Pathology

Grossly, the tumors are a fleshy, gray polypoid masses with a spectrum of pathologic features, that is, some lesions resembling childhood neuroblastomas and other tumors resembling paragangliomas (Weiss and Goldblum, 2001). Hirose et al. (1995) believed these neoplasms have characteristics of both classic neuroblastoma and paraganglioma (see Fig. 9.25).

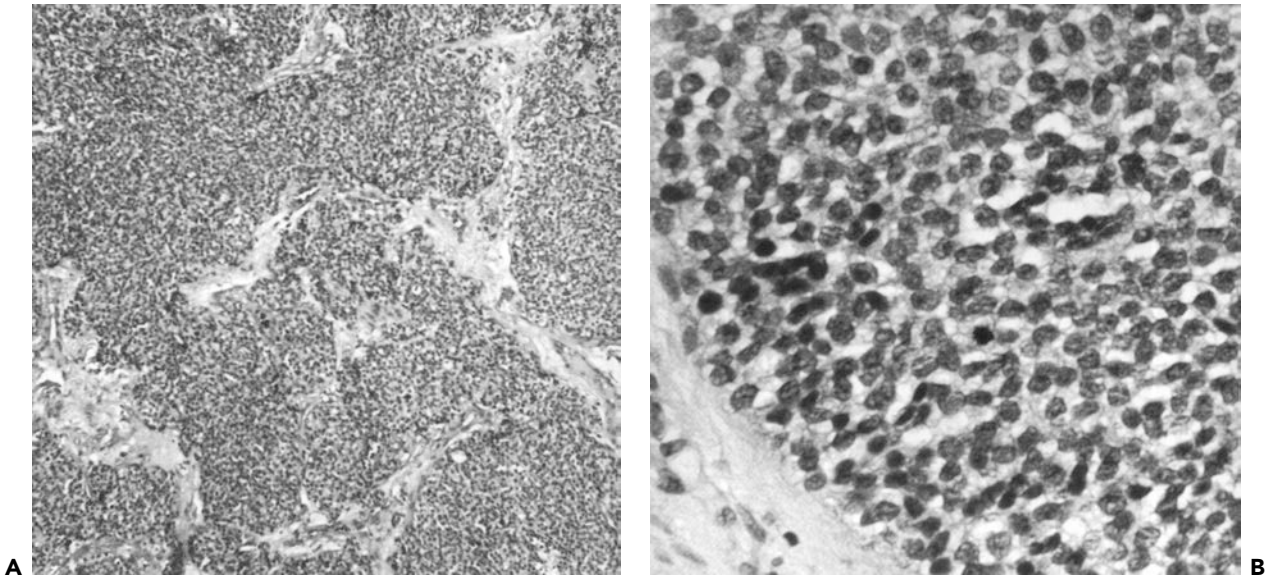


Figure 9.25 **A:** Clusters and lobules of small round neuroblasts and neurocysts separated by septa of vascularized connective tissue and fibrillar extensions from cells. There are no rosettes (original magnification ×100). **B:** The nuclei are round or oval with large nucleoli and well-defined nuclear membranes. The cytoplasm is scant, and the cell membrane is indistinct. A primitive rosette is present (upper right center) (original magnification ×640).

Management and Prognosis

At present, surgical eradication of the esthesioneuroblastoma seems to be the initial therapy preferred by physicians working in this field. This is the domain of the head and neck surgeon. Treatment of the tumor and survival depend on the stage of the disease. The staging system proposed by Kadish et al. (1976) is widely used. He proposed three categories. The orbital lesion is placed in stage C, the stage with the worst prognosis. Stage C includes patients with tumor extension beyond the nasal cavity and sinuses. The survival rate of these patients is 46.7% compared with the most favorable stage (tumor limited to the nasal cavity) with a 90% survival (Elkon et al., 1979). Hirose et al. (1995) believed that metastatic disease is linked to histologic subtype. None of four patients with paraganglioma-like tumors developed metastases, but four of four patients with neuroblastoma-like tumors in addition to 7 of 13 patients with tumors combining paraganglioma and neuroblastoma components were positive for metastatic disease.

Most surgeons favor a combined craniofacial approach for removal of the orbital extension of the tumor with an attempt to preserve the eye. However, the role of radiotherapy (preoperative or postoperative) and chemotherapy, in particular, has not been standardized. In the analysis of survival data, we should be aware that delayed recurrence is common. Three of the 15 patients in our tumor survey had late recurrence of tumor. The first patient was a 17-year-old girl with generalized metastases who died 24 years later. The second patient was 55 years old at the time of initial diagnosis and died 25 years later with intracranial extension. The third patient was 60 years old at the time of initial diagnosis but succumbed to tumor extension 28 years later.

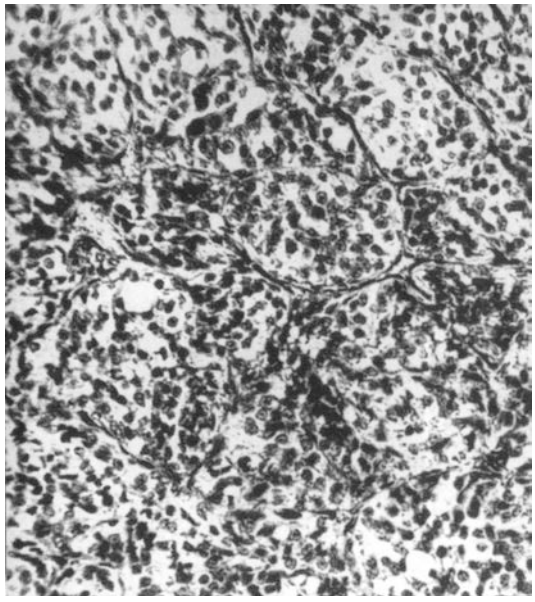


Figure 9.26 Alveolar-like nests of cells demarcated by fine fibrovascular septa (original magnification ×130). (From Ashley DJB. *Evans' histological appearance of tumours*, 4th ed. Edinburgh: Churchill Livingston; 1990:111, with permission.)

NONCHROMAFFIN PARAGANGLIOMA

A synonym for nonchromaffin paraganglioma (NCP) is "glomus body tumor" (a small histologically recognizable body composed primarily of fine arterioles connecting directly with veins and possessing a rich nerve supply). According to Archer et al. (1989), a normal glomus body is very small, 0.1 to 0.5 mm in diameter. A structure of this type has been identified on the orbital floor in serial sections from a newborn infant (Mawas, 1936). If such a tiny structure is located in the normal orbit, its discovery has eluded contemporary anatomists. The orbital NCP may arise from a hamartomatous nest of ganglion cells, located adjacent to an extraocular muscle in the retrobulbar fat. Here, it can parasitize the blood supply of the nearby muscle, if needed, for its growth.

Incidence

The NCP is a very rare tumor of the orbit. The incidence of orbital NCP relative to nonorbital paraganglioma and other orbital tumors is not known. Our 50-year collection of histologically proved orbital tumors does not include a single case of paraganglioma. Approximately, 3 dozen cases have been reported in the literature since the first orbital paraganglioma was described by Fisher and Hazard (1952). However, the total was drastically reduced when Font et al. (1982) reclassified 16 as alveolar soft-part sarcoma. In those years, the histologic patterns of paraganglioma and alveolar soft-part sarcoma were so alike, using light microscopy, that it was difficult to distinguish them (see Fig. 9.26). Subsequently, electron microscopy provided a clue. Ultrastructurally, the NCP contains neurosecretory granules characterized as spherical membrane cytoplasmic inclusions from 80 to 250 nm in size (see Fig. 9.27). This finding is important in differentiating NCP from alveolar soft-part sarcoma.

Archer et al. (1989) reviewed the 13 cases of NCP identified by Font et al. (1982) and included a case of their own. In this series, the age range at presentation was 3 to 68 years, with an average of 36 years. Six patients were female, and eight were male. In this group, the patient of Archer et al. (1989) was unusual. This patient was diagnosed as having a glomus jugulare tumor at the age of 25 years who presented 14 years later with an orbital NCP. Multiple-site involvement of nonorbital paragangliomas has also been noted by DeVita et al. (1989).

Clinical Features

The presenting signs and symptoms are those of a retrobulbar mass, namely, proptosis, displacement of the

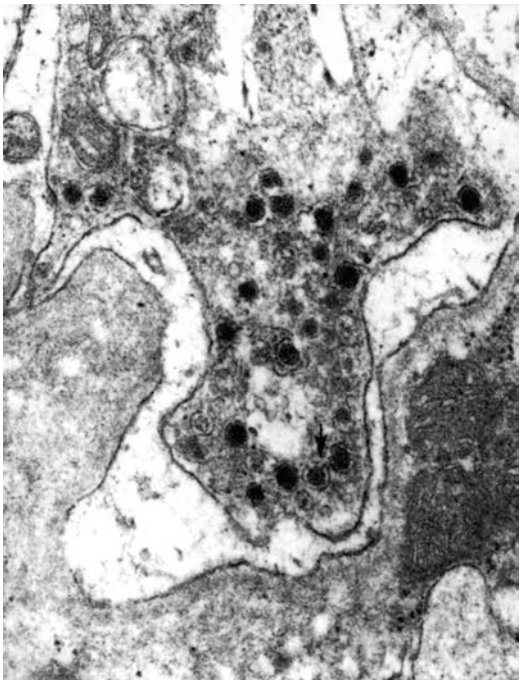


Figure 9.27 Dense-core granules within the cytoplasm of tumor cells (original magnification ×11,500). (From Bednar M, Trainer TD, Aitken PA, et al. Orbital paraganglioma: Case report and review of the literature. *Br J Ophthalmo.* 1992;76:183–185, with permission.)

eye, visual loss, and papilledema. However, nothing in this pattern suggests the presence of an NCP unless the patient experiences a throbbing sensation as well.

Imaging Aspects

CT scan shows a well-circumscribed, uniformly enhancing, isodense mass (Neufeld et al., 1994). In some cases, the image display may also show prominent veins. If so, carotid angiography probably shows an intensive blood supply. MRI shows a salt-and-pepper appearance of the matrix of the tumor (Bednar et al., 1992).

Pathology

This benign, well-circumscribed tumor may be associated with a prominent feeding vessel. The cells are usually polygonal in shape, arranged in clusters or nests, and separated and surrounded by a delicate fibroreticulin network. This pattern gives the specimen an organized appearance. The nuclei are round or oval and have a stippled appearance. Few, if any, mitotic figures are present. The cytoplasm is faintly eosinophilic. There are no cytoplasmic periodic acid-Schiff-positive inclusions, such as those encountered in alveolar soft-part sarcomas. The hallmark of the tumor is the presence of membrane-bound, dense-core, secretory granules when the specimen is studied ultrastructurally. Melanin has been reported in one case (Paulus et al., 1989).

Immunohistochemical stains are positive for neuron-specific enolase, neurofilament protein, chromogranin, and synaptophysin. Staining is negative for glial fibrillary acidic protein, S-100 protein, and vimentin. Chetty et al. (1998) examined 18 extra-adrenal paragangliomas and seven adrenal pheochromocytomas to determine their immunoreactive response to commercially available cytokeratin antibodies. Among these tumors, there was one orbital paraganglioma. It showed strong immunopositivity with CAM 5.2 and AE 1/3.

Management

A consensus favors surgical excision of the paraganglioma. This neoplasm is also radiosensitive. Radiotherapy may be reserved for unresectable, incompletely removed, and recurrent tumors, although no standards have evolved for the dosage of irradiation. The prognosis seems favorable for these tumors localized to the orbit.

GRANULAR CELL TUMOR

The principal histologic feature of this benign tumor is a granular cytoplasm. It may occur anywhere in the body, including the brain. Since its identification by Abrikossoff (1926), its histogenesis has been an enigma. Since the advent of electron microscopy and immunohistochemical analysis, it has been the subject of further scrutiny to determine its cell of origin.

At present, most tumors are positive for S-100 protein with immunostaining. This reaction strongly supports a kinship of the tumor with the Schwann cell. Because of this staining trait and the tumor's frequent association with muscle in nonorbital sites, many observers believe it should be classified with the peripheral nerve sheath tumors. However, no other features align it with either the nerve sheath tumors or neurofibromatosis. McNab and Daniel (1991) observed an orbital tumor that had the light and microscopic appearance of a granular cell tumor. The positive immunostaining of its cell cytoplasm and its negative reaction to S-100 protein corroborate the ultrastructural localization of intermediate filaments and support a possible origin from astrocytes.

In one orbital case (Moriarty et al., 1983), immunohistochemical stains revealed the presence of chorioembryonic antigen, which was interpreted as a primitive cell of origin, probably related to mesenchymal cells. We believe the orbital granular cell tumor is a neural tumor derived from the tissue of the primitive tissues of the neural tube, which is also capable of spawning tumors of ectodermal, mesenchymal, histiocytic, and astrocytic types.

Incidence

This tumor has a widespread distribution in many anatomic sites and organs. Approximately 10% to 15% of patients

TABLE 9.2
GRANULAR CELL TUMORS PRIMARY IN THE ORBIT

	Summary of Case Reports			
Publications	**Age, y**	**Sex**	**Laterality**	**Duration**
Chaves et al. (1972)	15	M	Left	2 mo
Dhermy et al. (1980)[a]	52	M	Right	2 y
Dolman et al. (1987)[a]	44	M	Right	1 mo
Drummond et al. (1979)[a]	43	F	Left	3 mo
Goldstein et al. (1982)	51	F	Right	1 mo
Jaeger et al. (1987)[a]	71	F	Left	1 mo
Karcioglu et al. (1988)[a]	65	F	Right	2 y
Moriarty et al. (1983)[a]	37	M	Left	1 y
Morgan (1976)[a]	52	M	Left	2 y
Morgan and Fryer (1969)	55	F	Right	8 mo
Shimoyarma et al. (1984)	42	Unknown	Left	Unknown
Singleton and Nettleship (1983)	42	F	Left	2 y
Timm and Timmel (1966)	31	F	Left	2 y

[a]Ultrastructural study.

have lesions at multiple sites. Multiple tumors may appear synchronously or over a period of many years.

At the time of survey by Moseley (1991), 500 cases of granular cell tumor had been reported since 1926, but only approximately 3% arose in the orbit.

In Table 9.2, we reproduce a list of granular cell tumors primary in the orbit from our third edition (1994). These 13 cases were selected from the literature for 1966 through 1988. These cases were documented on the basis of descriptive details and photomicrographic and ultrastructural studies, which were included in the original report. In Table 9.3, we list cases of primary orbital granular cell tumors reported since 1988. The latter patients were subject to electron microscopy and immunohistochemical study. This entire group was associated with an extraocular muscle, and immunostaining indicated a strong Schwann cell derivation.

Combining the data in Tables 9.2 and 9.3, the age range of the 17 patients listed was 15 to 71 years at the time of presentation, with a mean of 43.7 years and a median of 44 years. Most patients (10 out of 17) were clustered in the fifth and sixth decades. There were ten females and six males. In one case, the age was not stated. In Table 9.3 are listed single cases within or partially affecting the medial rectus, the orbital portion of the levator, inferior oblique, and inferior rectus muscles.

Another case described by McNab and Daniel (1991) showed all the light microscopic features of a granular cell orbital tumor. It was not included in Table 9.3. This tumor occurred in a 4-year-old girl. This tumor was closely associated with the optic nerve and showed positive immunostaining but a negative response to S-100 protein, suggesting an astrocytic origin.

Clinical Features

In addition to the usual anamnesis—proptosis displacement of the eye, ocular motility disturbance, and diplopia—of a patient with a retrobulbar mass at the time of presentation, additional features were chiefly visual

TABLE 9.3
GRANULAR CELL TUMORS PRIMARY IN THE ORBIT, 1989 TO 1995

	Summary of Case Reports				
Publications	**Age, y**	**Sex**	**Laterality**	**Duration**	**Muscle**
Allaire et al. (1995)	35	F	Right	Unknown	IR
McNab and Daniel (1991)	27	F	Right	1 y	L
	54	M	Left	10 mo	IO
Polito et al. (1991)	58	F	Right	Unknown	MR

IR, inferior rectus; L, levator; IO, inferior oblique; MR, medial rectus.

impairment and a palpable orbital mass. The orbital mass was invariably described as hard. However, there was no associated pain. Many of these signs and symptoms are peculiar to a granular cell tumor.

Imaging Aspects

These tumors usually involve an extraocular muscle. With CT scan, the tumor is well defined and enhances with gadolinium-DTPA. With MRI, the involved muscle is homogenously isodense on T_1-weighted imaging. On T_2-weighted images, the muscle enhances slightly with gadolinium but is hypodense relative to orbital fat (Hashimoto et al., 1997).

Pathology

The literature includes differing descriptions of the gross features of this tumor. It has been described as a small, nodular, smooth, well-circumscribed mass; a rounded, poorly circumscribed lesion adherent to adjoining muscle; and an infiltrating mass.

With light microscopy, the tumor consists of uniform round, oval, or polyhedral cells arranged in nests and clusters and separated by connective tissue septa of varying thickness (see Fig. 9.28). The cells have central or paracentral basophilic nuclei with an occasional nucleus showing an eosinophilic nucleolus. The nuclei are small relative to the size of the cell. A distinguishing characteristic is a pale, acidophilic, coarsely granular cytoplasm. The granular cytoplasm probably reflects the high content of electron-dense lysosomes that are seen on ultrastructural study.

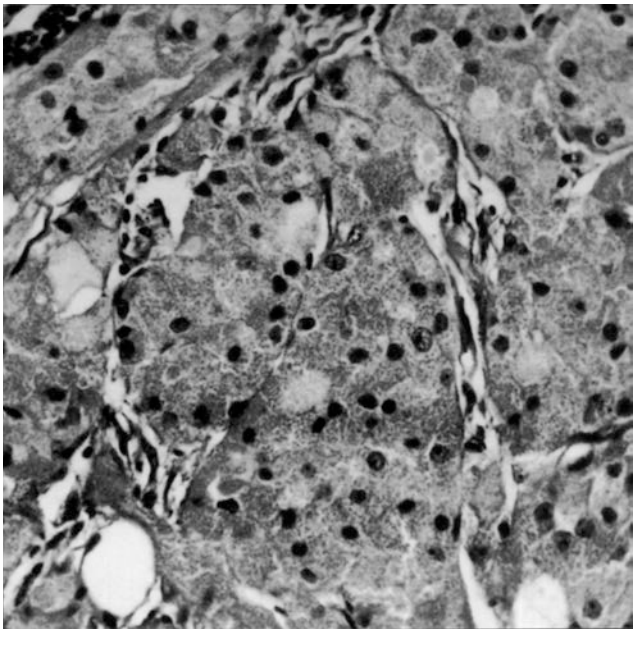


Figure 9.28 Clusters and nests of uniform, round, oval, and polyhedral cells in a pseudoalveolar pattern with a coarsely granular, acidophilic cytoplasm and small nuclei separated by connective tissue septa (vertical strands, right and left center) of varying thickness (original magnification ×245).

With immunostaining, the tumor is positive for S-100 protein, myelin, myelin-associated glycoprotein, and neuron-specific enolase. The positive reaction to S-100 protein strongly supports a kinship of the tumor with the Schwann cell. The positive myelin reaction may indicate a content of modified Schwann cell membrane (Ghadially, 1985).

On ultrastructural study, the tumor hallmarks are the single-membrane-bound, electron-dense, and electron-lucent bodies, which vary greatly in size, density, and shape. Also of note are the membrane-bound angulate bodies found in the interstitial cells that stain with myelin. A basement membrane often surrounds clumps of cells where they abut connective tissue septa but may not extend between adjacent individual cells.

A rare malignant granular cell tumor of the orbit was reported by Friedman et al. (1990). It was located at the orbital apex, and immunohistochemical analysis suggested a Schwann cell origin. The tumor regressed after radiotherapy.

Management

We have had no experience with this tumor. In the literature, surgeons who have treated this tumor recommend excision of the orbital mass. Because of the close association of the tumor with an extraocular muscle, removal of the tumor without permanent impairment of muscle function might be difficult. Fortunately, some of the tumors of the nodular, well-circumscribed type that are completely embedded within the muscle can be shelled out with minimal trauma to the muscle. These tumors are described as pale in color and "hard" in consistency. The consensus is that this "total excision" results in a cure. However, the follow-up of such cases is usually 2 or 3 years. Only one case in the recent literature was followed up for 6 years without recurrence. We do not know what happens to the infiltrative tumors that are incompletely excised. Follow-up reports are few. Nor do we know the therapeutic efficacy of radiotherapy. Karcioglu et al. (1983) believed the tumors are radioresistant.

MELANOTIC NEUROECTODERMAL TUMOR OF INFANCY

This tumor is known by several names. It was first described as a *congenital melanocarcinoma of the maxilla* (Krompecher, 1918). Other names are *retroblastic teratoma, melanotic progonoma, melanotic ameloblastoma*, and *melanotic adamantinoma*. Currently, the tumor is catalogued in library files as *melanotic neuroectodermal tumor*. It was named *retinal*

anlage tumor by Halpert and Patzer (1947) to emphasize the resemblance of tissue elements to primitive optic vesicles. Zimmerman (1985) proposed the term *pigmented retinal choristoma*.

These names reflect differing opinions on the histogenesis of the neoplasm. At present, most observers favor the hypothesis of origin from neuroectoderm. A minority, including ophthalmologists, favor the hypothesis of origin from tissue elements related to primitive optic vesicles. It seems needless to debate a specific cell of origin inasmuch as the primordium is probably a primitive neural crest cell that is capable of spawning multiphenotypic tissues of epithelial, melanocytic, and neural type in variable proportion. It is the same tumor regardless of name.

Clinical Features

This is a pigmented neoplasm that most frequently involves the maxilla. The neoplasm may also affect many other tissues and anatomic areas. Cutler et al. (1981), in an exhaustive review of the literature, detailed 138 cases according to the patients' ages, sex, tumor site, and date of report. Ninety-five (68.8%) were located in the maxilla. The overwhelming majority of tumors (95%) occurred in children <1 year of age, and 92.8% involved the head and neck region. No sex predilection was found. No cases localized to the orbit were listed.

We are aware of four reports in the literature of melanotic neuroectodermal tumors affecting the orbit. Koudstaal et al. (1968) described a 6-week-old boy with a progressively enlarging mass of the right temporal and zygomatic bones. The nontender mass measured 6×5 cm. Radiography revealed the apparent destruction of the lateral wall of the orbit. On surgical intervention, a black-gray tumor was removed. The tumor infiltrated bone, but neither the overlying skin nor orbital soft tissues were invaded by it. Tiny papillary offshoots of tumor into adjacent bone were removed with a dental excavator. No follow-up was included in their discussion of the case.

The case reported by Templeton (1971) was a 5-month-old infant who presented with a woody, hard mass of the left orbital zygoma. At surgery, a charcoal mass was found infiltrating the zygomatic bone. The tumor was "scraped" away from surrounding bone. There was no infiltration of orbital soft tissues or maxillary bone. The child was noted to be in good health 3 months later.

A 5-month-old boy presented with a bulging mass overlying the left zygoma in the report by Hall et al. (1979). It enlarged rapidly during the next 5 days. Skull radiography showed a lytic lesion of the left zygoma. The mass was hard and immobile. CT scan showed moderate enhancement after injection of contrast dye. A radical excision of a cheesy brown, nonhemorrhagic tumor was performed. There were no signs of recurrence during the 1-year follow-up.

A 4-month-old boy was first seen by Lamping et al. (1985) in December 1973 because of fullness of the right upper face, which appeared shortly after birth. Over the previous 10 days, the swelling had increased. Examination revealed two palpable masses, one in the area of the right zygoma and the other overlying the parietal bone. Skull and orbital tomograms showed osteoblastic lesions in both locations. The lesion involving the zygoma and sphenoid bone was removed by a craniectomy. A second-stage procedure 9 days later removed the parietal bone tumor. There were no recurrences over a 10-year period of follow-up.

These four tumors have many traits in common. All four patients were <1 year of age and had involvement of the zygomatic bone. The tumors were fast growing and hard to palpation but painless. Three of the four lesions showed marked bone destruction, but no infiltration of overlying skin or surrounding soft tissues. All the cases were amenable to wide excision.

Initially, the tumor was considered benign but, over time, a half-dozen or so malignant tumors have been reported. In addition, the tumor is known to occur in older children and adults.

Pathology

This tumor is composed of a variety of tissue phenotypes. Its color ranges from a slate gray through brown to blue black. It is an unencapsulated, infiltrative lesion. A prominent feature is the alveolar, cleft-like, or vesicular spaces lined by cuboidal cells containing varying amounts of melanin pigment. These cuboidal cells have microscopic features of both epithelial and melanocytic cells, features similar to retinal pigment epithelium. Zimmerman (1985) believes the melanin granules of retinal pigment epithelium and the melanotic neuroectodermal tumor are the same type. Some micrographs in the literature show these cells as flat rather than cuboidal. The pigmented cells of the tumor are separated from a surrounding, dense, fibrillary stroma by a basement membrane. In the center of the spaces are clumps of small, round cells resembling those of a neuroblastoma intermixed with a neurofibrillary material. Some of these neuroblastoma-like cells may be seen as isolated nests in the dense stroma (see Fig. 9.29).

With immunohistochemical analysis, the tumors are positive for cytokeratin, HMB45, and vimentin, mainly in the large cell epithelial component. The small neuroblastic cells are positive for neuron-specific enolase in approximately 50% of the cases. The tumor cells are negative for chromogranin and desmin (Kapadia et al., 1993).

Management

Complete surgical excision, including all bone infiltrated by tumor, was performed on the four melanotic ectodermal tumors noted previously in this chapter. However, the follow-up period was relatively short to determine the frequency of recurrences.

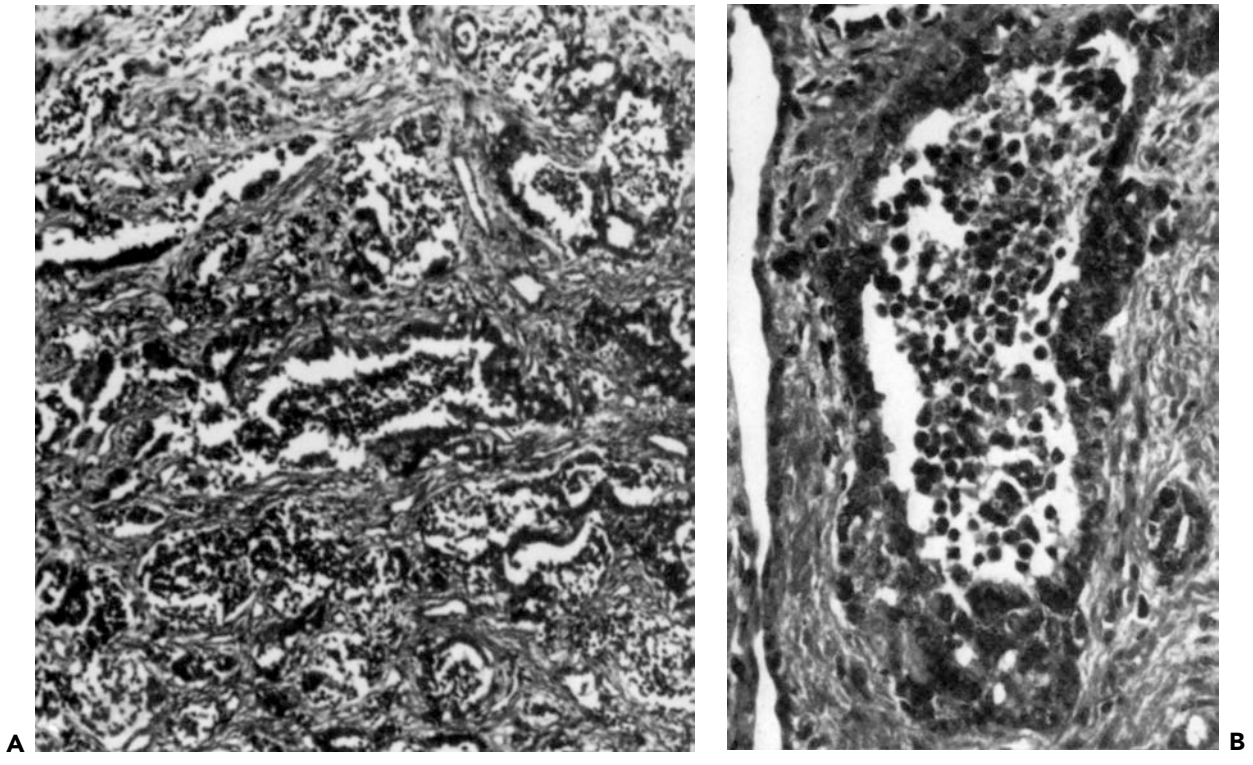


Figure 9.29 **A:** Compact nests and clumps of small cells with basophilic nuclei amid clefts and spaces rimmed by larger cells containing pigment granules and interspersed in a dense, vascularized stroma (original magnification ×125). **B:** A higher magnification shows two populations of cells. The alveolar-like space is lined by the large cuboidal cells containing pigment granular reminiscent of retinal pigmented epithelium. The central space is filled with smaller, uniform basophilic cells with scanty cytoplasm resembling neuroblasts (original magnification ×500). (From Lamping KA, Albert DM, Lack E, et al. Melanotic neuroectodermal tumor of infancy (retinal anlage tumor). *Ophthalmology*. 1985;92:143–149, with permission.)

PRIMITIVE NEUROECTODERMAL TUMORS

The probable origin of these tumors is the neural crest. These neuroectodermal tumors are malignant, poorly differentiated lesions that may be composed of primitive neuroepithelial, ependymal, and neuroglial cells and tissues. *Primitive neuroectodermal tumor* (PNET) is a broad term that includes a wide array of lesions with varying differentiating potential affecting both the central and peripheral sympathetic nervous systems (Dehner, 1986). Some authors have a tendency to add the word "peripheral" to the tumor primary in the orbit. Most authors who discuss this group of tumors seem satisfied with the present terminology. However, as pathologists learn more about these tumors, more specific names may evolve for the variable histologic types in other widespread anatomic areas.

Incidence

The eight cases of primary PNET we found in the literature are summarized in Table 9.4. The age range is wide (1 to 52 years) with a median of 8.5 years. The sex incidence is equal. The data relevant to the orbital location of the tumor are of interest. In all cases except one, the tumor was adjacent to an orbital wall. The lateral orbital wall was the site affected in five of seven cases. The one intraconal tumor occurred in a microphthalmic eye of a 5-year-old patient. The frequency of orbital involvement among a large cohort of tumors in other peripheral anatomic locations has not been published to our knowledge. Orbital occurrence is probably very rare.

Clinical Features

The presenting sign in all cases was proptosis. In four of the eight cases, for which the duration of the proptosis was stated, the disorder evolved over a period of 3 weeks to 2 months. In only one case was a mass palpable. This was a case of involvement of the zygoma bone. The patient noted mild pain on proptosis. Pain was absent in all other cases. Excluding the patient with the palpable mass, the diagnosis of orbital tumor was made by imaging scan. In most cases, perhaps because of the short duration of the tumorous growth, the eyes of these patients had few, if any, signs of functional involvement. The latter does

TABLE 9.4
PRIMARY ORBITAL PRIMITIVE NEUROECTODERMAL TUMORS, 1965 TO 1999

	Summary of Case Reports		
Publication	**Age, y**	**Sex**	**Orbital Location**
Howard (1965)	<1	M	Inferior
Shuangshoti et al. (1986)	52	M	Lateral
Wilson et al. (1988)	7	F	Superior
Arora et al. (1993)	13	F	Lateral
Arora et al. (1993)	4	M	Lateral
Singh et al. (1994)	10	F	Lateral
Kiratli et al. (1999)	28	M	Lateral
Alyahya et al. (1999)	5	F	Intraconal

not apply, of course, to the known case of a preexisting microphthalmos.

Here, we should note a unique report (Hyun et al., 2002) of a 37-year-old woman whose primary orbital PNET was resected and treated further with chemoradiation. Three years later, liver metastasis developed.

Imaging Aspects

CT scan shows the size, contour, and position of the tumor in relation to orbital bone. CT scan with contrast is ideal for showing the degree of bone destruction caused by the tumor. Figure 9.30 illustrates the magnetic resonance of PNET in a 28-year-old patient.

Pathology

Grossly, the tumor is white, firm, and unencapsulated. However, there was no uniformity in the histologic descriptions of the eight tumors tabulated above, and no two were alike. Most cases were composed of small, round, undifferentiated cells with vesiculated, hyperchromatic nuclei and poorly defined cytoplasm. In several cases, the cytoplasm was basophilic, but in one report, it was eosinophilic. Homer-Wright pseudorosettes were present in one case but were absent in two cases. Background neurofilaments were absent in two cases but were present in three cases identified by negative or positive staining with neuron-specific enolase immunostaining. Mitoses were noted in two cases but were absent in one case. With electron microscopy, pleomorphic, dense-staining granules were noted in one case. Immunostaining was positive for cytokeratin (one case), epithelial membrane antigen (two cases), glial fibrillary acidic protein (one case), S-100 protein (one case), MIC2 (one case), and synaptophysin (one case). Negative staining was evident with S-100 protein (one case), muscle-specific antigen (one case), and synaptophysin (one case). These divergent analyses were probably the results of authors' reviewing tumors in various stages of differentiation and tumors that featured diverse tissue phenotypes.

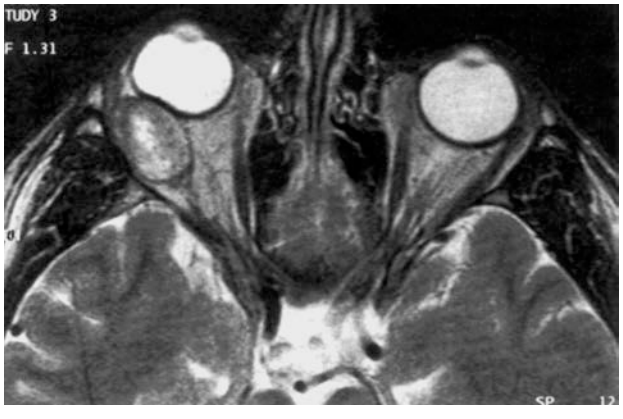


Figure 9.30 T_1-weighted axial magnetic resonance imaging of the orbits after contrast injection showing a well-delineated right lateral orbital mass, which is hypointense relative to orbital fat. The tumor indents the globe. There is no bony defect. (From Kiratli H, Bilgic S, Gedikoglu G, et al. Primitive neuroectodermal tumor of the orbit in an adult. A case report and literature review. *Ophthalmology*. 1999;106:98–102, with permission.)

Management

Seven of the eight cases of orbital involvement listed in Table 9.4 underwent some type of surgical intervention as their initial treatment. The tumors were removed by *en bloc* resection, wide excision, gross removal, simple resection, or exenteration in six cases. A seventh case with bone invasion (Singh et al., 1994) had only an incisional biopsy. Three of the six patients with tumor removal (two cases reported by Arora et al. (1993) and the one case reported by Kiratli et al. (1999)) had no further treatment.

An orbital exenteration was performed on the patient described by Wilson et al. (1988). The exenteration was combined with excision of an intracranial, subfrontal extension of the tumor. Radiotherapy, 35 Gy, was administered after surgery and was supplemented later with a 92-week course of chemotherapy.

After wide excision of tumor, the 5-year-old patient reported by Alyahya et al. (2000) received a six-drug chemotherapy protocol over a 27-week period followed by 45 Gy of radiotherapy.

After surgery, the 52-year-old patient described by Shuangshoti et al. (1986) was treated only with 52 Gy of radiotherapy over 1 1/2 months.

After incisional biopsy, the case reported by Singh et al. (1994) was treated under Children's Cancer Group protocol 7007, which included six courses of vincristine, doxorubicin, and cyclophosphamide, alternating with ifosfamide and etoposide. When the chemotherapy course was completed, the patient received 49.6 Gy over 27 fractions.

There was no follow-up on the two patients reported by Arora et al. (1993). The other five patients described in the preceding text were living in follow-up periods ranging from 6 to 45 months. These follow-up periods are too short to know the frequency of either recurrence or metastasis. We remind the reader of the patient described by Hyun et al. (2002) who had metastasis of a primary orbital primitive neuroectodermal tumor 3 years after combined treatment with surgery and chemoradiation.

What was the outcome for the one patient listed in Table 9.4 who was treated with radiotherapy after initial biopsy? This 8-month-old boy described by Howard (1965) received 2,200 roentgens to the right orbit. The child had two subsequent local recurrences that were surgically removed, and treatment was supplemented with additional radiotherapy. The child died 14 months later with widespread metastases.

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10 Vascular Hamartomas, Hyperplasia, and Neoplasms

This chapter includes an array of vascular tumors resulting from new formation of vessels, proliferation of tissue components of the vessel wall, and hyperplasia of cellular elements ordinarily concerned with the genesis of vascular tissue. These vasculogenic lesions comprise the largest group of primary orbital tumors in our survey. We realize that, in the past, two of the groups (capillary and cavernous hemangiomas) have been considered as phases of the same tumor, the former being a predecessor for the latter. However, on the basis of their differing ultrastructural makeup and their distinctive clinical aspects, it is now obvious that they should be considered separate tumors, a format not followed in prior editions of this text. The literature has not been as active in this area of orbital tumefaction as in other areas; however, there have been some noteworthy publications. Harris (1999), writing on behalf of the Orbital Society, framed the issue of "vascular malformations" on the basis of their hemodynamic features. This is particularly germane to lymphangiomas and varices, which will be considered later in this chapter. The vascular malformations, which are tumefactions based on established vascular channels, will be reviewed in the next chapter.

CAPILLARY HEMANGIOMA

Synonyms for this cellular tumor are *infantile hemangioma*, *hypertrophic hemangioma*, *cellular hemangioma*, *juvenile hemangioma*, *angioblastic hemangioma*, and *benign hemangioendothelioma*. There is strong evidence that some are hamartomatous because of their presence at birth and their association with an enlarged orbit. These signs indicate their perinatal development. This hamartogenesis could reasonably be extended to the orbital lesions that so commonly commence in the first 2 months of life. However, those capillary hemangiomas, surgically verified in older children and adolescents, are more likely to be true neoplasms. Regardless of how these are classified, there have been two interesting papers regarding pathogenesis with reference to the placenta. Burton et al. (1995) noted that there was a threefold higher incidence of hemangiomas in a group of infants exposed to transcervical chorionic villus sampling when compared to the incidence in the amniocentesis group, which approximated the incidence in the general population. From the group of 432 returned questionnaires it was found that all the hemangiomas were cutaneous with the exception of one laryngeal hemangioma. It was not readily apparent why this was so. The life cycle of an infantile hemangioma was noted to have similarities to a placenta in that there is a perinatal presentation, rapid growth, and eventual involution. (North et al., 2002) discovered similarities involving the vasculature and the tissue-specific markers between an infantile hemangioma and a placenta. The authors postulated two potential mechanisms for a placenta-hemangioma connection. The first was a somatic mutation or abnormal local inductive influence, giving rise to the hemangioma but the second more intriguing hypothesis was that placental tissue might embolize and give rise to the hemangioma. This might also serve as an explanation for a higher incidence of hemangioma after chorionic villus sampling as described in the preceding text.

Incidence

First, we should emphasize that our series of 34 capillary hemangiomas were located, all or in part, posterior to the orbital septum. Therefore, our incidence data will differ from other surveys that follow the common practice of analyzing adnexal (eyelids, caruncle, and upper face) and orbital capillary hemangiomas together. We will note in the following text some of the features that distinguish the orbital lesion from the kindred tumors that are solely confined to the eyelids and upper face.

Tables 3.1 to 3.4 record the data pertinent to orbital capillary hemangioma. This tumor comprises 1.9% (34 out of 1,795 cases) of our total series in which the sex incidence and the laterality are equal. It is not only the most common tumor in the first decade but also in the first year of life. In the patient population aged 15 years or less, it is the third most common tumor (30 out of 213 cases, 12.7%). The age of onset is 2 months of age or less in 26 out of 34 cases, 76%, including 8 neonates (24% of the total) with tumors present at birth. Of the eight patients, who are older than 2 months of age at the time of onset, the age range is 4 months to 26 months. The age of presentation in this group varied greatly, reflecting the rapidity of growth and the degree of parental concern. In 27 out of 34 patients (79%), the tumor was palpable in the anterior orbit with or without some extension into the substance of the eyelid. In the seven remaining cases (21%), the tumor was located in the retrobulbar space and could not be palpated. In 8 out of 34 cases (24%), the tumors were located in one of the inferior quadrants of the orbit; in the others they were located in one of the superior orbital quadrants.

Two other surveys of this subject should also be noted (Haik et al., 1979, 1994). In the earlier paper, the authors had studied the clinical records of 101 patients with capillary hemangiomas of the eyelid, upper face, and eyebrow in addition to orbital lesions. The general thrust of their incidence data was similar to our series except for the sex ratio. In their series, there was a preponderance of women in a ratio of 3:2, whereas in our series the ratio was equal. Other publications based on a smaller number of cases also stress the prevalence in girls. Inclusion of hemangiomas in nonorbital sites such as the eyelid, eyebrow, and upper face in the reports of Haik et al. (1979) and others may account for the slight difference in the above sex ratios. The second paper (Haik et al., 1994) was an extensive literature review that does not change any of the comments mentioned in the preceding text.

Clinical Features

The principal presenting feature of capillary hemangioma in the anterior orbit of an infant is a *unilateral, enlarging, painless, compressible swelling of the overlying eyelid associated with displacement of the eye in a direction opposite to the position of the lesion*. The swelling conceals a mass with indistinct borders behind the orbital septum. The mass becomes more distinct as it pushes forward into the eyelid (see Fig. 10.1). The swelling is bluish in color but may be purplish red if the hemangioma involves the subcutaneous tissue of the affected eyelid also. There is no proptosis as a rule. Almost invariably, the parents have noticed that the mass increases in size, and the bluish overtones become more vivid when the child cries (see Fig. 10.2). As the problem progresses, the swollen upper eyelid begins to cover the visual axis and displacement of the eye increases. The growth of the tumor may be so rapid and the soft tissue swelling so great that the eye is hidden by the time the infant is seen in consultation (Fig. 1.6).

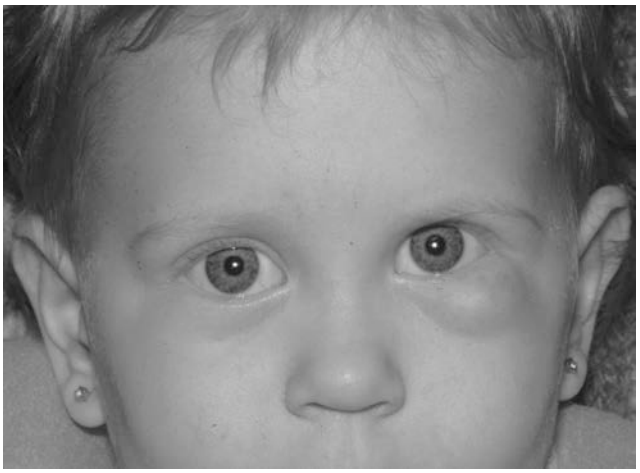


Figure 10.1 A well-demarcated, bluish capillary hemangioma in the left lower eyelid of a 17-month-old girl that was first noted at 2 months of age. Intralesional corticosteroid injections were administered at 4 months of age and 7 months of age with temporary arrest followed by regrowth of tumor. Note upward displacement of left eye due to additional tumor in left inferior orbit, confirmed by computed tomography.

The orbital teratoma is another tumor that may grow rapidly in the neonatal period. In teratoma, the eye is proptosed by the enlarging mass, but in capillary hemangioma, the eye is pushed to one side and the tumor protrudes. In the retrobulbar hemangioma of older infants and younger children, a differential diagnosis involving rhabdomyosarcoma and metastatic neuroblastoma must also be considered. The child with metastatic neuroblastoma whines and is irritable and sick. A runny nose may be present. The examination procedure annoys them, and they tend to cling to their parents possibly because of malaise and aching bones. Ecchymotic splotches are frequent in the eyelid overlying the protruding mass (Fig. 1.12).

The rhabdomyosarcoma poses a more difficult differential. The children affected by the same appear in good health, and there are no systemic or external clues that might suggest a lurking malignancy of the orbit. However, the parents often blame some putative injury for the child's puzzling proptosis. Neither the mass nor the puffy eyelid tends to enlarge with the Valsalva maneuver. The skin of

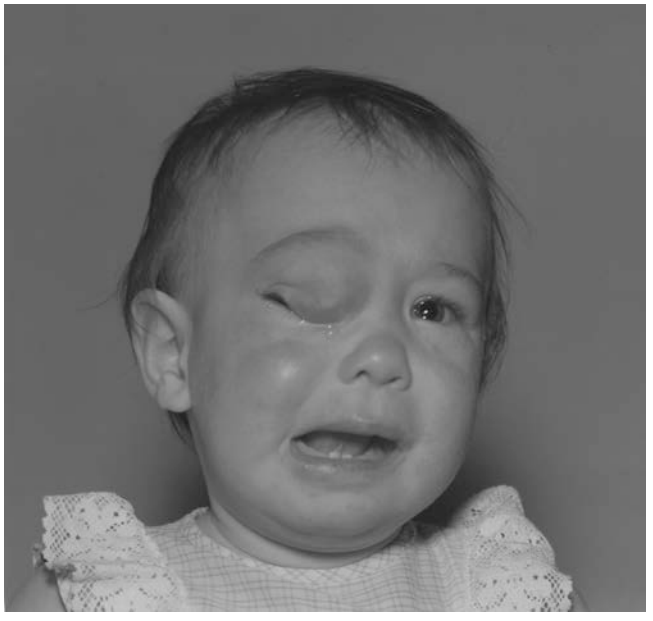


Figure 10.2 Capillary hemangioma in upper nasal quadrant of right orbit and eyelid in an 11-month-old girl. Crying causes the tumor to increase in size and cover eye as eyelid swells. Swelling of the right cheek reflects enlarged blood supply through external carotid system.

the affected eyelid takes on a dusky red hue after several weeks' growth of tumor, rather than the bluish tinge of the eyelid that conceals an orbital hemangioma (Fig. 1.2B) The computed tomography (CT) scans of the two tumors have similar features except that some bone erosion may be present if the rhabdomyosarcoma is localized along a bone surface. A capillary hemangioma opacifies rapidly and more profusely than rhabdomyosarcoma because of a more direct expanded arterial supply. Haik et al. (1994) mentioned that arteriography can be helpful though not in diagnosis but in managing exceptional hemangiomas by identifying the feeding and draining vessels, should ligation ever become a consideration.

Further examination of an eye displaced by an orbital capillary hemangioma will usually show a significant astigmatism when compared to the unaffected eye. The pressure of the hemangioma steepens the corneal curvature in a direction perpendicular to the axis of the astigmatism (Robb, 1977; Stigmar et al., 1978). In the older child, where some quantitative assessment of vision is possible, the visual acuity of the affected eye will be reduced. Ophthalmoscopy of such eyes, however, does not show any consistent feature that contributes to the diagnosis of orbital hemangioma.

For some reason, the capillary hemangioma of the orbit is associated less often with hemangiomatosis when compared to the hemangiomas of the eyelid and face. The infant with a hemangioma of the eyelid is prone to strawberry hemangiomas on the trunk, extremities, or scalp. We do not know of any orbital hemangiomas associated with visceral hemangiomatosis (Kasabach-Merritt syndrome) unless there is also a large facial hemangioma. In this syndrome, thrombocytopenia and bleeding are the results of entrapment of platelets within the hemangioma of the viscera (Jakobiec and Jones, 1979).

The course of these tumors of the orbit is one of growth that merges into a plateau of inactivity (arrest) followed by regression. However, the rate of growth, the maximum size attained by the tumor, the period of arrest, the degree of regression, and the final age of resolution are unpredictable. Reports analyzing these factors vary greatly. Our own series is of little help in quantifying these factors because it is skewed toward the lesions that continue to grow, the tumors that resist therapy, and those hemangiomas that do not involute.

The presenting pattern of an older child with a capillary hemangioma in the retrobulbar space differs from that described in the preceding text. Here, the course of events is more benign. The growth of tumor is slower; the lesion is more circumscribed; proptosis rather than displacement of the eye is common; and no mass is palpable. As the situation progresses, diplopia develops owing to restricted movement of the eye toward the site of the tumor. Gradually, secondary displacement of the proptotic eye appears, visual blurring occurs secondary to the mass effect of the lesion, and enlargement of the orbit is seen on radiography. In brief, the course is similar to the growth pattern of a cavernous hemangioma in the same location.

An unusual case with a growth pattern of the latter type was reported by Lyness and Williams (1986) in a 23-year-old woman. For many years, a small, translucent, and painless "blister" had been present overlying the patient's left lateral rectus muscle. Onset of discomfort brought her for consultation. Six millimeters of proptosis was found, and with computed tomography a large soft tissue mass occupied most of the length of the affected muscle. Partial excision of a bluish tumor in the substance of the muscle was performed. The histopathologic diagnosis was intramuscular hemangioma of the small vessel (capillary) type. In retrospect, it is likely that this hemangioma had been slowly expanding over a period of many years.

We saw one patient with biopsy proved intramuscular hemangioma. A 26-year-old woman noted gradual but slow progressive proptosis of the right eye. A few years later, she developed hyperthyroidism and she was treated with antithyroid medication. The medication was subsequently stopped and the thyroid function normalized with no additional therapy required. We examined her at the age of 36 years for thyroid-related ophthalmopathy. The course of her disease had been gradually progressive over the 10 years since onset. There was no pain, diplopia nor any changes with Valsalva maneuver; however, the globe did seem subjectively "irritated". The vision was normal and 5 mm proptosis was measured. The CT scan showed an abnormality confined to the medial rectus muscle. (see Fig. 10.3). At surgery, the gross appearance of the muscle

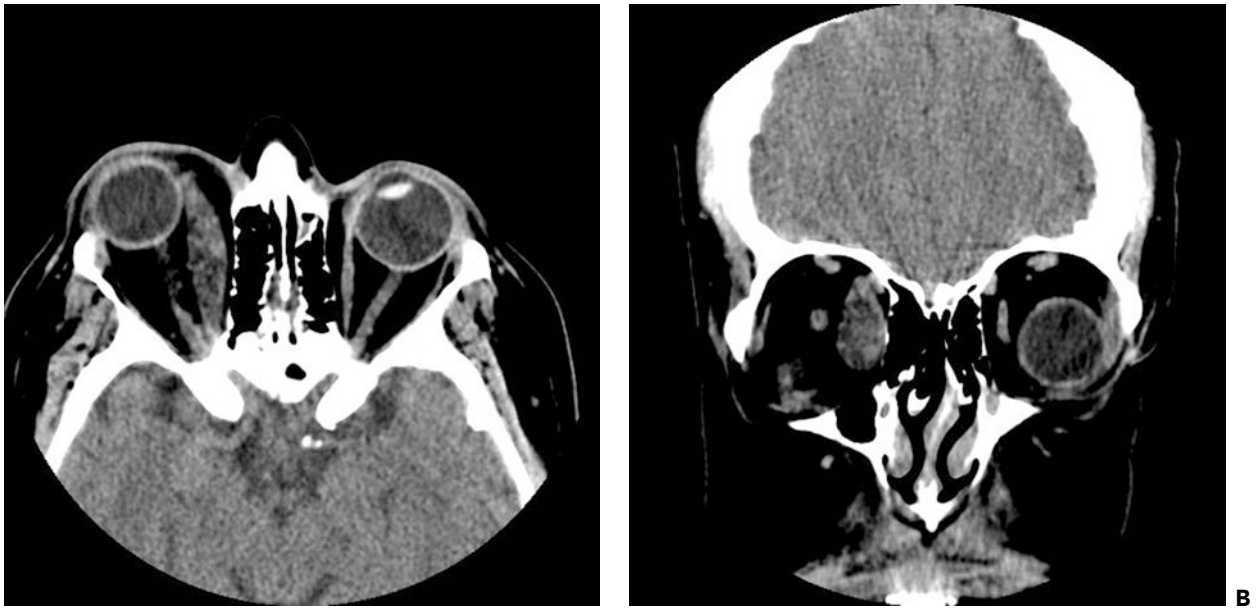


Figure 10.3 Axial **(A)** and coronal **(B)** computed tomography scan (unenhanced) in a 36-year-old woman with intramuscular hemangioma of right medial rectus muscle. Axial scan demonstrates that the entire length of the muscle is involved. The muscle is thickened with inhomogeneous consistency. Coronal computed tomography scan shows tear drop shaped enlargement of medial rectus muscle.

was purple-red with visible vessels. Retrobulbar triamcinolone injections reduced the irritation for 9 years at which time another injection was given with satisfactory results.

Imaging Aspects

CT scan demonstrates many of the expected features of the capillary hemangioma. Often, the orbit is enlarged and this is evident on the scan. Use of contrast shows vivid enhancement, confirming the lesion's vascularity and its infiltrative nature. The lesion can have irregular borders if located either in the eyelids or retrobulbar space, but appears somewhat circumscribed when squeezed between the resistant eyeball and orbital wall (see Fig. 10.4). As a rule, the younger the child, the greater is the enhancement (Sklar et al., 1986). Small phleboliths are occasionally seen in these lesions. Magnetic resonance imaging (MRI) of this tumor is illustrated in Figure 10.5. Ultrasonography in the hands of a trained echographer is a useful method for diagnosis in the infant age-group. The ultrasonogram shows a variable pattern mix of high and low reflectivity (see Fig. 10.6) owing to the irregular, intrinsic makeup of the tumor lobules of tumor containing closely packed lumens of differing diameter cordoned by fibrous septa of variable width that contain dilated vessels. Doppler analysis confirms the profuse blood supply of these tumors.

Pathology

The principal event that has occurred in this field since our discussion in the previous edition has been the study of Iwamoto and Jakobiec (1979). They examined, by transmission electron microscopy, three tissue specimens of capillary hemangiomas in children and four tissue specimens of cavernous hemangiomas in adults. Their work established a pathologic basis for classifying capillary hemangioma and cavernous hemangioma as separate

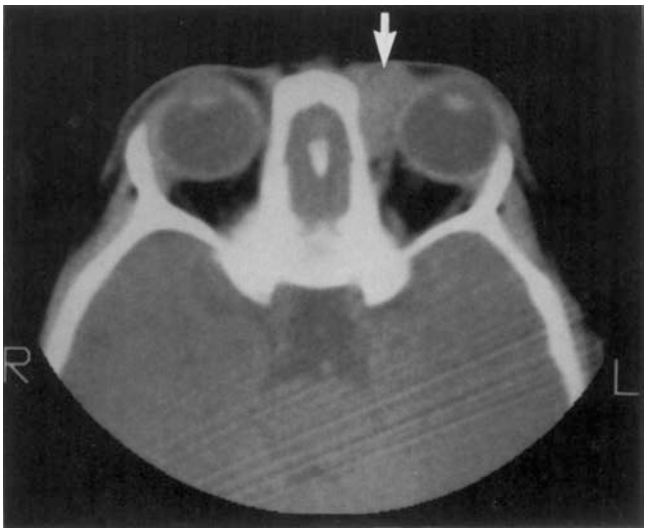


Figure 10.4 Axial computed tomography scan of a capillary hemangioma in an 8-month-old boy shows a homogeneous, enhancing mass in anteromedial left orbit (*arrow*) overlying medial rectus muscle with lateral displacement of the eye. Mass tends to conform to the surfaces of adjacent bone and eyeball indicating a compressible morphology. No bone erosion. Fullness of superonasal eyelid had been present for four months.

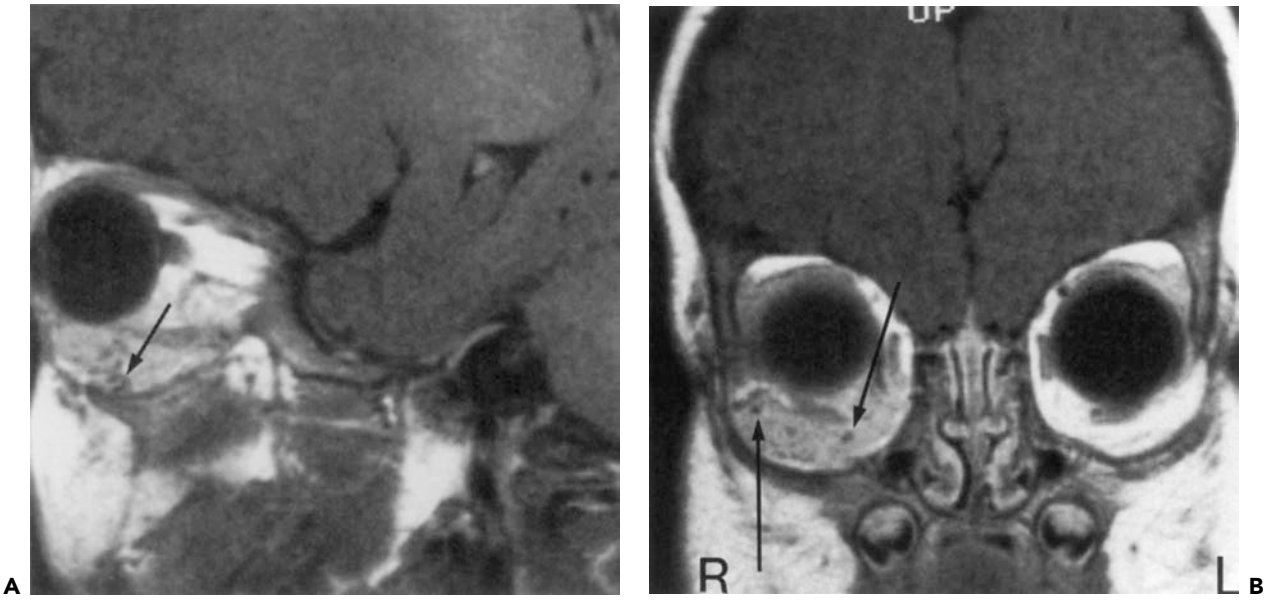


Figure 10.5 Magnetic resonance images at TR = 600 ms and TE = 17 ms of surgically verified capillary hemangioma in the right inferior orbit of a 5-month-old boy. **A:** Sagittal view: The lesion engulfs the inferior rectus muscle and has poorly defined margins. The tortuous, hypointense area (*arrow*) represents a tiny blood vessel. **B:** Coronal view: Shows minimal but homogeneous enhancement. The mass is hypointense compared to the orbital fat in the other orbit. The right orbit is slightly enlarged. The tiny circular voids (*arrows*) represent vascular spaces.

nosologic entities. Previously, many observers either had regarded one tumor as a precursor of the other or both tumors as modulations of each other. Iwamoto and Jakobiec demonstrated definite ultrastructural differences in the two tumors. The *principal difference was a mantle of pericytes serving a support function for the endothelial cells of capillary hemangioma, whereas multiple layers of smooth muscle cells provided support for the endothelial lined spaces of cavernous hemangioma*. The endothelial cells in both tumors were separated from these support tissues by basement membrane material.

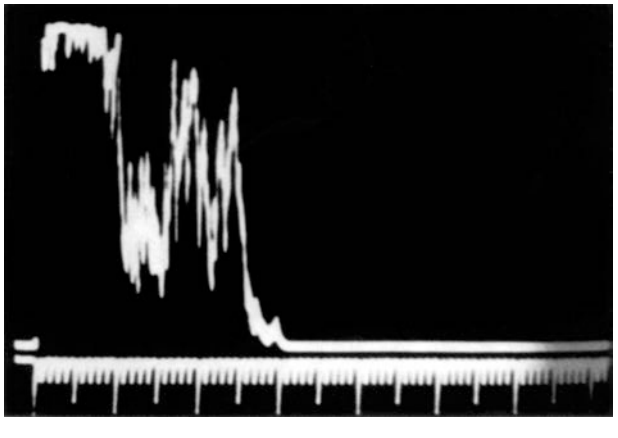


Figure 10.6 Paraocular A-mode echography of capillary hemangioma showing a variable pattern of reflectivity. Compare to Figure. 10.10. (From Sklar EL, Quencer RM, Bryne SF, et al. Correlative study of the computed tomographic, ultrasonographic, and pathologic characteristics of cavernous versus capillary hemangiomas of the orbit. *J Clin Neuroophthalmol*. 1986;6:14–21. By permission.)

By light microscopy, the makeup of capillary hemangioma is essentially similar in all cases. In the most immature stage, the proliferating endothelial cells are so profuse that, under low power, the variable-sized lobules of cells look like a solid tumor. The lobules of tumor are separated by distinct but unevenly arranged septal connective tissue. Under higher power, some mitosis is evident, but the cells, although large, are uniform in appearance. The nuclei are irregularly oval and resemble the nuclei of primitive fibroblasts, except for lack of nucleoli. The borders of the tumor are indistinct and infiltrative. The lumens of the primitive capillaries are narrow and do not seem capable of any circulatory function.

This appearance quickly changes as the tumor rapidly enlarges. It loses its solid look, capillary-sized channels appear, intraluminal clumps of erythrocytes are evident, and the individual endothelial cells become smaller but more distinct (see Fig. 10.7). At this stage, the tumor margins are slightly more circumscribed, and the feeding and draining vessels traveling along the connective tissue syncytium are prominent. Reticular stains at this stage clearly outline the basement membrane that compartmentalizes individual capillary units.

Eventually, involution, either spontaneous or therapeutically induced, sets in. The connective tissue septa thicken;

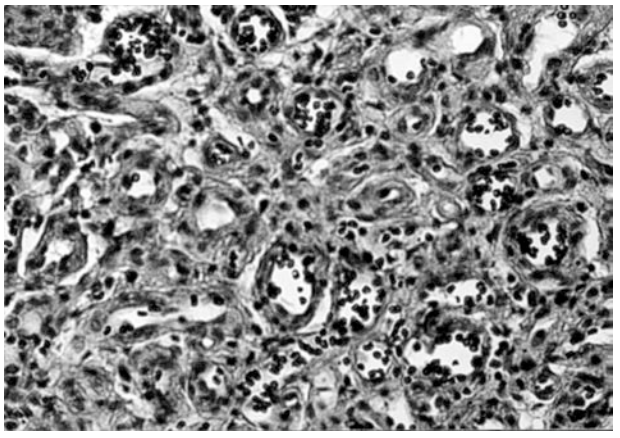


Figure 10.7 Capillary hemangioma: Capillary-size channels are lined with endothelial cells and contain intraluminal erythrocytes (hematoxylin and eosin; ×300).

they are less vascularized, and more fibrosed. The endothelial cells tend to flatten, capillary lumens become ectatic and enlarged, intralesional fat deposition is evident, and occasional interstitial macrophages may appear (see Fig. 10.8). This sclerosing stage resembles the appearance, in miniature, of a cavernous hemangioma in an adult and is responsible for the incorrect diagnosis, in past years, of cavernous hemangioma in children.

Treatment and Prognosis

The current popular remedy is an intralesional injection of a combination of synthetic corticosteroids. The combination is usually a mixture of a long-acting and rapid-acting corticosteroid such as triamcinolone and bethamethasone sodium phosphate. The treatment is easily administered and can be repeated. There is an ever increasing volume of literature on this subject since it was introduced by Kushner (1979). These reports generally recount the location and technique of administration and the clinical response of the treated tumor. The injections are usually confined to eyelid tumors. Therefore, information on the use of this remedy in orbital lesions is sparse.

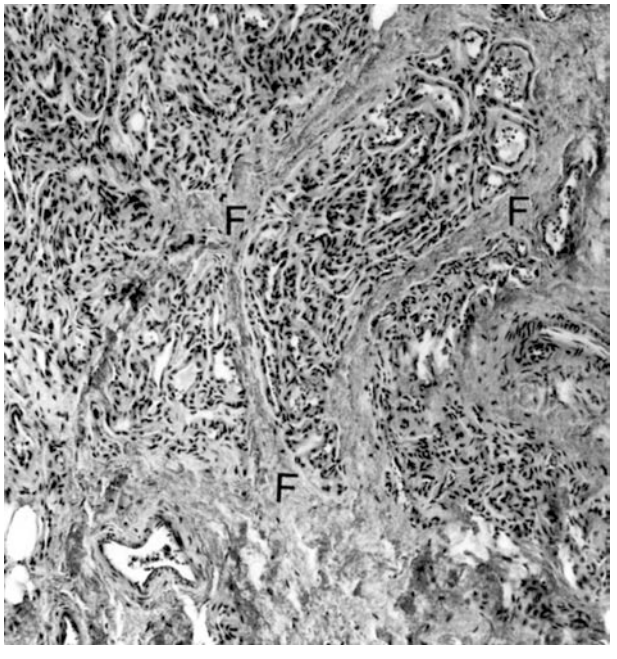


Figure 10.8 Sclerosing capillary hemangioma: Lobules of tumor are separated by fibrous tissue bands (F) (×100).

There is a natural reluctance of many clinicians to thrust a needle into a suspected hemangioma posterior to the orbital septum chiefly because of possible uncontrolled bleeding or worrisome hematoma. Other drawbacks are whether the injection can be properly localized to the mass and the ever present risk of ocular embolism from an inadvertent arterial injection (Shorr and Seiff, 1986). Finally, many clinicians disapprove of any intraorbital injection without a preliminary biopsy.

There are several options for handling these situations where the tumor is entirely intraorbital. One consideration applicable to hemangiomas in the anterior orbit is to perform the injection with ultrasonic-assisted guidance such as described for fine-needle orbital biopsy in Chapter 2. Another option is to proceed with an orbitotomy and, with the lesion exposed, proceed with an intralesional injection with or without preliminary biopsy. We have also used this opportunity to apply bipolar cautery to the exposed lesion on occasion. Lastly, other than simple observation, one could consider treatment with systemically administered corticosteroids or subcutaneous interferon α-2b.

For those orbital hemangiomas that extend into the substance of the eyelid, both the superficial and deep components can be injected; alternatively the eyelid component can receive the injection and the orbital extension can be treated with systemic corticosteroids. All of these options have probably been used in the treatment of capillary hemangioma, but there are an insufficient number of orbital cases treated by any one method to report any meaningful data.

Systemic corticosteroid therapy has been used for both orbital and adnexal hemangiomas since 1970 (de Venecia and Lobeck, 1970). Most such cases have been infants, and the drug dosage has been managed by a pediatrician. The initial response to such therapy has been favorable in a large number of cases but marred by the annoying "rebound" growth of tumor in a significant subset of patients after the drug is discontinued. Hastings et al. (1997), while reviewing their experience with interferon α-2b, noted that the literature estimates a favorable response in 60% of patients treated with oral steroids. The response rate to intralesional steroids was approximately 80%. O'Keefe et al. (2003) reported that intralesional injections are a safe and effective treatment although skin atrophy and eyelid necrosis have been reported (Sutula et al., 1987; Townshend and Buckley, 1990). Of course, the

corticosteroids can again be administered over another several weeks or months until such time as the volume of tumor subsides to the desired level. If the tumor continues to regrow after each series of treatment or arrest of tumor cannot be accomplished with low-dose maintenance therapy, the patient, the physician, and the parents soon become corticosteroid-dependent although only one of the triumvirate is receiving the drug. Such a prolonged treatment then becomes no better than if no treatment had been given initially and, instead, the infant is simply observed. In short, the maximum amount of drug to achieve arrest of tumor growth should be determined initially. If the lesion has not responded or continues its rebound behavior when that goal is reached, another therapy should be tried.

Another systemic therapy, interferon α-2b, is an option. This drug is given as a daily subcutaneous injection for 3 months, and it is thought to interfere with some of the many growth factors identified in capillary hemangiomas during the proliferative growth phase (Hastings et al., 1997). Loughnan et al. (1992) first reported their successful experience in a 4-month-old girl with a massive orbital capillary hemangioma. The lesion had been resistant to both oral and intravenous corticosteroid treatment. Hastings et al. (1997) later reported results from a group of 40 patients followed up. Sixteen patients had ocular dysfunction from the hemangioma and 15 patients completed the treatment. On average, tumor volume decreased by 82%. The authors noted that the drug was well tolerated with no significant side effects although neutropenia and elevated liver function tests were common.

Other Therapies

Over the 40-year period covered by our collection of tumors, the authors have participated in all the therapeutic modalities, which at one time or another, were considered appropriate. Therapies of earlier years such as sclerosing solutions, cryotherapy, surgical diathermy, and applications of radium plaques no longer need be considered.

Surgery

Thirty-five to 40 years ago, surgical excision was the procedure of choice frequently. It was performed through an anterior orbitotomy. Although hemorrhage during the surgery was always a problem, the surgeon usually managed removal of a sufficient portion of the tumor to hasten its involution (Pasyk et al., 1984). However, postoperatively, there followed such a trail of cicatrix that permanent functional or cosmetic impairment of the eye was the rule. There followed a period in which radiotherapy was the principal therapeutic mode (see subsequent text).

The localization and image visualization of hemangiomas by CT has renewed interest in their surgical removal in the past 15 years. This, combined with present-day surgical techniques, has reduced the complications attributed to surgical intervention. Today, surgical excision is a reasonable treatment option when other therapies have failed. It is the treatment of choice when a rhabdomyosarcoma rather than a hemangioma is suspected. It can also be recommended as the primary treatment for hemangiomas in the retrobulbar space, particularly in older children. An anterior orbitotomy is also an attractive option as a preliminary to intralesional injection of those accessible hemangiomas in the anterior orbit. One could also consider combining a surgical exposure with the use of the carbon dioxide laser for those massive, diffuse hemangiomas that overwhelm the contents of the orbit by their size. Intralesional laser therapy probably represents an evolutionary step in the management of this tumor. Burnstein et al. (2000) treated 100 pediatric patients with capillary/cavernous hemangiomas. An incision was placed into the skin overlying the tumor and the laser fiber was introduced into the tumor. Both the neodymium-doped yttrium-argon-garnet (Nd:YAG) and potassium-titanyl phosphate (KTP) lasers were used with no difference detected between the two types. Two patients with midface lesions had facial nerve weakness and 20 patients had superficial necrosis of the hemangioma with ulceration. Although this treatment may be helpful with extremely large, disfiguring tumors, the orbital region may not be an optimal location for this treatment modality.

Radiotherapy

Radiotherapy, in the form of intracavitary radon seed implantation, was the principal therapy for anteriorly positioned tumors in the period 1951 to 1970. Eleven of the 30 patients in our series were so managed. We used relatively weak seeds, 0.22 to 0.3 mc strength. One to three seeds were placed to encompass the assumed area of the lesion. If multiple seeds were necessary, they were positioned so that the principal radius of γ-radiation of each seed would not overlap the other. The amount of radiation reaching the nearest periphery of the lens was considered the critical measurement. This dosage was in the range of 172 to 744γ-roentgens. Four of these patients have been followed up for 10, 12, 17, and 21 years. None of the four showed any sign of cataract although we did examine a patient treated elsewhere with radon seeds and who developed extensive basal cell carcinomas of the eyelid.

Two more patients were treated with external beam orthovoltage radiation. One received a total of 480 R to one orbit and the other patient received 1,000 R. The last named has been followed up for 40 years. These patients have neither cataract nor malignancy. These patients did not have the serious cicatricial complications that were seen in the group treated with surgical excision. However, the percentage of patients who developed some degree of amblyopia was about the same in the two groups.

Our experience in this small group tends to refute the dangers frequently attributed in the literature to radiotherapy in infants. We suspect that the misuse of high doses of radiation so common in the decades 1930 to 1960

was responsible for reports of radiation damage and sarcoma. Such complications were not an uncommon event in the long-term follow-up of patients with retinoblastoma who had been so managed.

Embolization

A well-documented resume of this modality is the report of Kennedy (1978) of a 14-month-old girl with a large orbital hemangioma that had resisted numerous therapies since the age of 4 months. Angiography demonstrated three areas of hemangioma in the right orbit with extension into the superior portion of right maxillary sinus. The tumor received its vascular supply from both the internal carotid and external carotid systems. First, transcatheter arterial embolization was performed with tiny silicone pellets through the right internal maxillary and external carotid system. Next, the external carotid artery was ligated. Five days later a clipping of the right ophthalmic artery was performed. At 3 1/2 years of age, an extensive resection of larger tumor residues was performed.

No Therapy

A management scheme of "watchful waiting" or "intelligent neglect" is probably the best of all, except that this ideal is compromised by the wish to halt the shoving and pushing of the tumor on the eye, the need to alleviate obstruction of the visual axis by a closed eyelid, and the urgency of parents to "do something." The parents can sometimes be mollified by the suggestion of a second opinion from their pediatrician, if neither of the first two factors is in play. It is the need to try to prevent some degree of amblyopia that prompts most clinicians to alleviate the struggling eye. At this point, there is a choice of any or all of the above therapies. Even so, once treatment is deemed necessary, the parents must be warned that *a few of these tumors—owing to their contrary, perverse, obstinate, and stubborn character—will always defy and resist involution no matter what treatment is attempted*.

CAVERNOUS HEMANGIOMA

A multitude of case reports, reviews, and surveys have been published concerning the vascular neoplasms of the orbit, particularly cavernous hemangioma. The latter is a common tumor. It is well known and is particularly suited for surgical removal. Probably, more has been written about this lesion than any other individual tumor mentioned in this text. It would be unusual to find an ophthalmologist who has not participated in the workup, supervised the care, or considered the differential diagnosis of a patient with an orbital cavernous hemangioma. Those clinicians particularly interested in the subject might well ask, "What can be said about this tumor that already has not been said?" The answer is, "very little!" Therefore, we will treat the salient features in a more summary fashion and devote much of the discourse to those features of the tumor that may vary from its well-known clinical pattern.

Incidence

It is the most common benign neoplasm of the orbit in adults, a feature also noted in our prior texts. Its incidence in our present series (Table 3.3) is 4.3% (82 out of 1795) of the total. In the 1978 series its incidence was 4.7% (36 out of 764) of the total. This underlines its constant prevalence among orbital tumors over a period of time. Its incidence among primary orbital tumors is 14.1% (82 out of 574).

The sex incidence is slightly in favor of women, being 37 men and 44 women (Table 3.3). It occurs most frequently in the fifth decade (33 patients) (Table 3.4), with approximately 50% less in the fourth and sixth decades (18 and 13 patients, respectively). These three decades account for 81% (66 out of 81) of the total. The youngest in our series was a 24-year-old woman whereas the oldest was a 75-year-old woman. The tumor was unilateral in all cases, and there was no significant predilection for either orbit.

All patients have some degree of malposition of the eye, either proptosis or displacement. Proptosis is present in 92% and displacement is present in 25% of the 81 cases. The degree of proptosis averaged 5.2 mm and is approximately equal (5.3 mm in women, 5.1 mm in men) in the two sexes. The latter figures tend to refute a prior impression that men tend to have more proptosis than women because of a longer interval before presentation. However, the two patients who have a proptosis >10 mm are men.

A palpable mass was present in 34% of patients, with the majority in the inferior temporal quadrant. In the remaining 66%, the mass was in the retrobulbar space. We are rather dubious of the value of data pertaining to duration of symptoms prior to presentation. The patient's memory is sometimes indefinite, and, on many occasions, a patient's estimate does not jibe with the opinion of a spouse or relative. In 25% of our patients, the tumor, surprisingly, had been present for less than a year. In the remainder, with symptomatology of 1 year or longer, the duration of symptoms averaged 3.5 years.

The second most common symptom was some disturbance of vision and was present in 55% of our patients. It was usually manifest as a decrease in myopia or an increase in hyperopia. A few exceptions to this tumor-induced refractive error will be noted in the subsequent text. An ocular motility disturbance was noted in 35% of total patients.

The most common finding on ophthalmoscopy was choroidal folds (40%) followed in decreasing frequency by optic disk edema (22%), and either pallor or atrophy of the optic disk (8%). Although there was some correlation between choroidal folds and the induced hyperopia, the relationship was not absolute.

Increasingly, we have been seeing patients referred with an incidental orbital tumor. By definition, there is a lack of symptoms and the mass is found when performing cranial imaging for a myriad of reasons, none related to the eye/orbit. We have one patient in this category; however,

the examination revealed evidence of a swollen disk, despite a 20/20 vision. In this instance, we recommended surgery although as Orcutt et al. (1991) reported, we are currently following many patients with asymptomatic lesions.

The only other collection of cases similar to our own is the in-depth study of Harris and Jakobiec (1978). They reviewed 66 surgically verified tumors spanning an interval of 39 years, 1937 to 1976. The incidence data of the two series is strikingly similar except for the following: The sex prevalence of the Harris and Jakobiec series favored women to men in a ratio of 7:3, whereas our ratio was 1:2:1. We do not have an explanation for this difference. In the Harris and Jakobiec study, 73% of patients had proptosis, whereas in our series the incidence was 92%. In the modalities of age range, the average proptosis, the duration of symptoms prior to presentation, and the frequency of visual disturbances, the data of the two studies was surprisingly close. This underscores the predictability of behavior of these neoplasms.

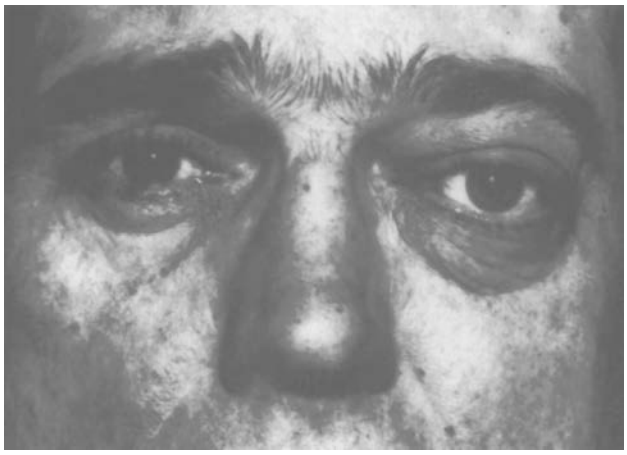


Figure 10.9 A 43-year-old man with several presenting features of a retrobulbar cavernous hemangioma of the orbit of 1-year duration. The left eye was proptosed 8 mm with downward and slight lateral displacement due to tumor in orbital apex medial to optic nerve. Choroidal folds were present, but there was no visual disturbance. (From Henderson JW, Farrow GM, Garrity JA. Clinical course of an incompletely removed cavernous hemangioma of the orbit. *Ophthalmology*. 1990;97:625–628, with by permission.)

Clinical Features

The orbital cavernous hemangioma represents the classical and predictable presentation of a benign orbital neoplasm. The salient feature is a painless, unilateral, nonpulsatile, reasonably slow, progressive proptosis affecting either orbit of a patient in the middle age range. The eyelid will look normal except for slight puffiness, and the functional and anatomic relationship between the eye and eyelids is maintained. Sooner or later, if the tumor is located in the anterior orbit between the eye and nearby bony wall, displacement of the eye develops in approximately 40% of patients. The displacement is opposite to the position of the tumor if the lesion is located in the anterior orbit, but with the retrobulbar hemangioma, the eye will eventually be displaced forward (see Fig. 10.9).

The second most common feature in approximately 50% of patients was some decrease in vision owing to an increasing hyperopia or decreasing myopia induced by the growing tumor pressing on the back of the eye effectively shortening its axial length. This alteration of refraction was closely, but not absolutely, correlated with the appearance of choroidal folds. As a general rule, Friberg and Grove (1983) found that choroidal folds were more likely with greater amounts of exophthalmos or anteriorly located tumors and that the pattern of the folds generally reflected the location of the tumor within the orbit. The shift toward hyperopia was noted with intraconal tumors although extraconal tumors tended to have higher astigmatism. Edema, pallor, or atrophy of the optic disk in a lesser number of patients was usually a tip-off to a close approximation of the tumor to the optic nerve. These patients also have an afferent pupillary defect, some color vision insufficiency, and a visual field defect.

A palpable mass and some degree of ocular motility weakness usually correlate with the onset of displacement of the eye. The motility deficit was usually manifest when gaze was directed toward the position of the tumor. Retrobulbar lesions were seldom palpable.

Some exceptions and interesting variables in the above pattern should also be mentioned. The eye is not always white. An epibulbar red spot, slight dilation of the epibulbar vessels, or a bluish tinge overlying the tendinous insertion of an extraocular muscle is occasionally seen. Three of our patients had recurring subconjunctival hemorrhage at irregular intervals. In one patient, this cosmetic embarrassment prompted the decision to proceed with surgical removal of the tumor.

Amaurosis fugax was observed in three patients in some positions of extreme gaze. This gaze-evoked amaurosis was transient with recovery of vision when the eye was redirected to primary gaze. The phenomenon is probably an ischemia of the optic nerve as it impinges on the retrobulbar mass in the course of the eye's excursion (Orcutt et al., 1987). We suspect it is related more to the proximity of the nerve to the surface of the tumor rather than to the tumor size. Rootman and Graeb (1988) also observed transient visual obscurations in 2 of their 12 patients with cavernous hemangioma.

Exacerbation of symptoms with pregnancy has been reported by Zauberman and Feinsol (1970), Harris and Jakobiec (1978), and others and was present in three of our series.

A disturbing feature was the mention of headache by ten of our patients. It was not well localized (''rather deep'') and not well defined in character or severity. However, it seemed sufficiently persistent to warrant its inclusion in the anamnesis. Perhaps it was related to the degree of resistance encountered by the tumor in its area of growth.

This seemed to be the factor in two women reported by Costa e Silva and Symon (1984). In both, severe headache was localized to the temporal area of their affected orbit owing to a cavernous hemangioma expanding within the optic canal. Neither of these patients had proptosis, because the tumor did not extend into the orbital cavity. From the 21 patients included from the 1988 to 1997 interval, there were three patients with prominent but vague peri-orbital headaches. Two of the three had a past history of migraines; two of the three had swollen discs; and two of the three had no proptosis. The headaches either resolved or markedly improved following surgery.

Of more grave concern were four patients with 20/200 or less vision in the affected eye at time of presentation, associated with a large central scotoma, some degree of optic disk pallor, and an afferent pupillary defect. The duration of their orbital problem ranged from 4 to 14 years, and they were considered diagnostic puzzles until an orbitotomy revealed a cavernous hemangioma in the retrobulbar space. Had CT scan or MRI been available at the time they were first seen, permanent loss of vision would probably have been forestalled by earlier diagnosis and surgical intervention.

We have not encountered multiple cavernous hemangiomas as described by Harris and Jakobiec (1978) in one of their patients. Other reports of multiple tumors must be considered with considerable reserve. These might be examples of a cystic lymphangioma or venous angioma, the latter clustered around the periphery of an orbital vascular malformation.

The clinical features of the cavernous hemangioma of orbital bone will be noted in Chapter 6.

Imaging Aspects

In the years when plain film radiography was the principal imaging resource, slight enlargement of the orbit was noted in many cases. However, such enlargement was also seen in other benign orbital tumors of long duration and, therefore, did not contribute significantly to differential diagnosis. The enlargement of the orbit associated with cavernous hemangioma was never of striking degree when compared to that seen in capillary hemangioma. At present, orbital enlargement, as seen with newer imaging techniques, does not seem to have any prognostic relevance.

Reference has been made to the publication of Sklar et al. (1982) in Figure 10.6 of the prior subchapter, wherein the echographic features of capillary and cavernous hemangioma were contrasted. The pattern of cavernous hemangioma (see Fig. 10.10) is that of a well-marginated mass with uniformly high reflectivity on A-mode scan corresponding to the intralesional septa that separate the cavernous spaces filled with stagnant blood. Doppler analysis combined with A-mode sequences is more subdued when compared to capillary hemangioma because of the reduced blood supply of a cavernous hemangioma.

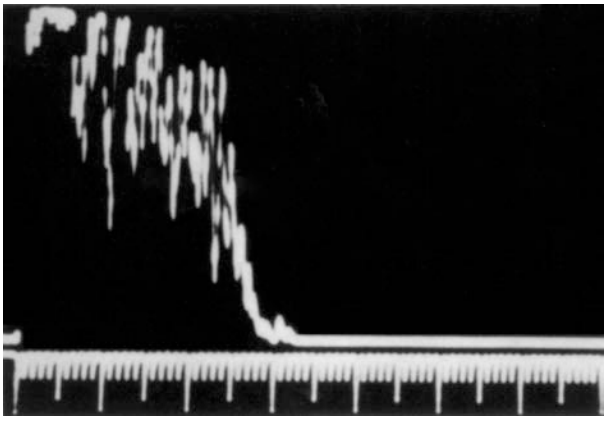


Figure 10.10 Paraocular A-mode echography of cavernous hemangioma showing uniformly high reflectivity corresponding to the intralesional septa that separate the cavernous spaces. Compare to Fig. 10.6. (From Sklar EL, Quencer RM, Bryne SF, et al. Correlative study of the computed tomographic, ultrasonographic, and pathologic characteristics of cavernous versus capillary hemangiomas of the orbit. *J Clin Neuroophthalmol*. 1986;6:14–21, with permission.)

On the CT scan this lesion is a well-demarcated, smoothly marginated, homogeneous mass of increased density (see Fig. 10.11). It may be round, ovoid, oblong, or even acorn-shaped, the latter configuration conforming to the contour of the posterior bony orbit. The tumor is usually slightly less dense than the extraocular muscles. The unenhanced image may show less dense intralesional areas, suggesting lobulation or compartmentalization. Contrast medium does not enter these tumors as easily as capillary hemangiomas and may be quite variable in degree (Savoiardo et al., 1983). There is a tendency to overstate the enhancement factor in the CT scan diagnosis of cavernous hemangioma. Hemangiopericytoma and neurilemmoma may also show many of the above features on CT scan. Therefore, a CT scan diagnosis is only presumptive. CT scan showed a phlebolith in the tumor of one of our patients.

Fries and Char (1988) reported a bilateral cavernous hemangioma based on the CT scan and MRI of bilateral orbital masses in a 48-year-old man. A larger bilobed tumor was removed from the right orbit, and the diagnosis of cavernous hemangioma was histopathologically confirmed. However, the nature of the solitary tumor in the other orbit was not surgically confirmed. This mass could also be a neurilemmoma, a solitary neurofibroma, or a hemangiopericytoma on the basis of similar imaging characteristics of these neoplasms when compared to cavernous hemangioma.

Char and Norman (1985) observed that in almost all cases of large retrobulbar cavernous hemangiomas, CT scan will show sparing of a triangular space at the orbital apex. On the contrary, we have observed filling of the orbital apex by tumor in several instances. One such case is illustrated in Figure 10.12.

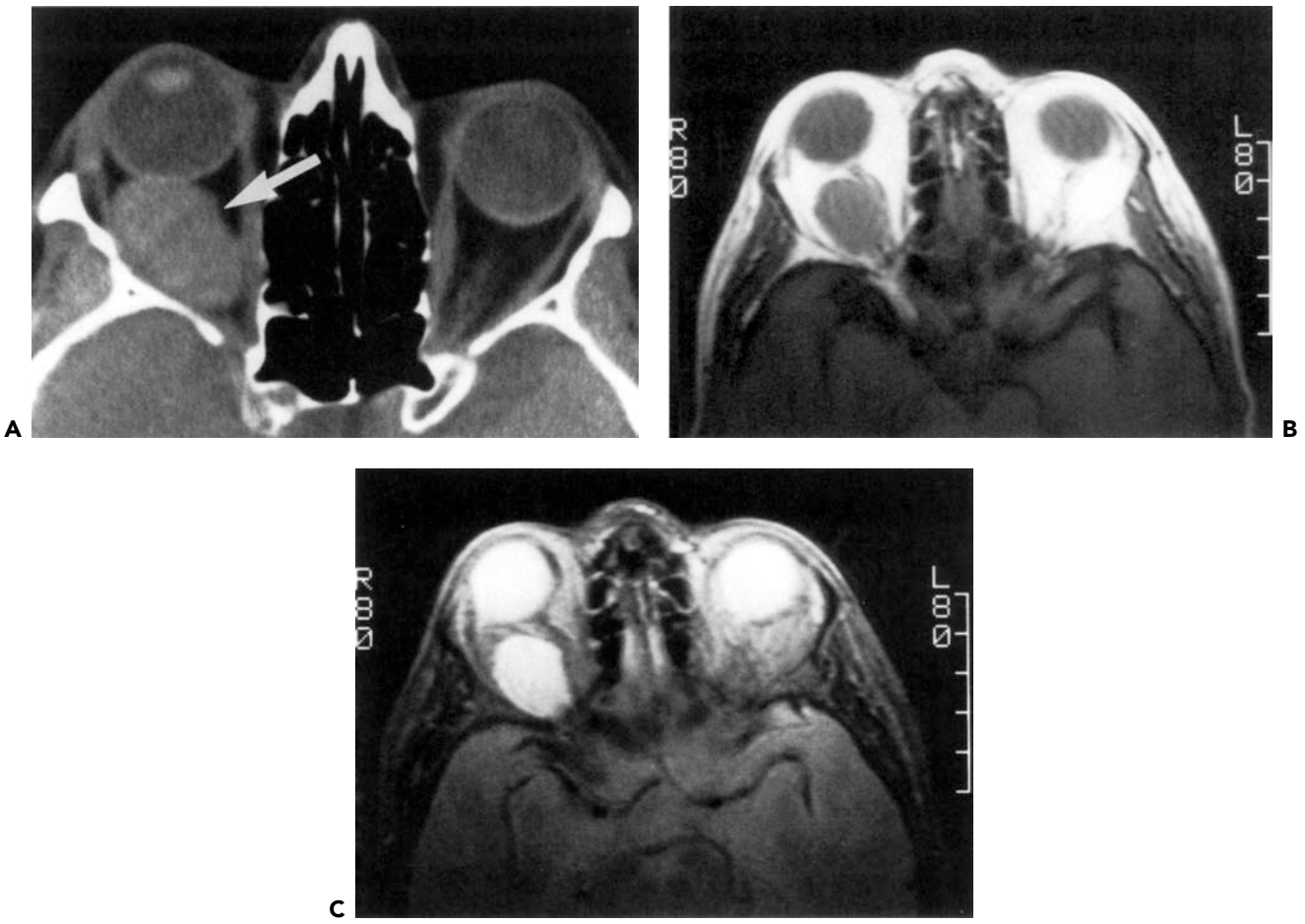


Figure 10.11 **A:** Axial computed tomography scan of a 51-year-old woman with an oval, well-circumscribed mass (*arrow*) in the retrobulbar space of right orbit causing proptosis. The mass is approximately 3 cm in greatest dimension and there appears to be a slight expansion of the orbital apex suggesting a tumor of long duration. Proptosis of 4 mm that was first noted 2 weeks previously. This underscores the difficulty of judging the inception of tumor growth on the basis of the patient's history. The relationship of the mass to the optic nerve was not clear. Therefore a magnetic resonance scan also was suggested to aid in the differential of optic nerve sheath meningioma, cavernous hemangioma, and neurilemmoma. **B:** Magnetic resonance, T_1-weighted sequence of the same tumor. The lesion is hypointense to the surrounding orbital fat, isointense with the nearby medial rectus muscle, and hyperintense to the vitreous. The optic nerve is separate from and displaced medially by the mass. This rules out optic nerve sheath meningioma. **C:** T_2-weighted sequence showing hyperintense mass and adjacent optic nerve in more detail. Surgically verified cavernous hemangioma.

The configuration, homogeneity, and circumscription of cavernous hemangioma are also well delineated on MRI (Char et al., 1985). The imaging response of the lesion on short and long signal sequences is illustrated in Figure 10.11. This figure also emphasizes the value of MRI in outlining the course of the optic nerve where it is obscured by the hyperdensity of the tumor on CT scan. Regardless of the imaging method employed, the scans also tell the clinician whether the lesion is intraconal or extraconal. Imaging was available for all the 21 patients just been added to our series. Only two patients had extraconal tumors (one above the superior rectus and the other in the inferior temporal quadrant).

Pathology

This neoplasm is the classical, encapsulated tumor of the orbit. The capsule, which is made up of fibrous tissue, is thick enough to provide a firm contour for the tumor, yet sufficiently compressible to permit firm but gentle dissection without rupture. The tumors vary in color from red to reddish blue to purple. They are almost always larger than the eye in their longest diameter (see Fig. 10.13). They may be round, oval, oblong, or even pyramidal in shape, and some portion of a larger retrobulbar tumor will often have a cone-like contour because its surfaces have been molded by contact with the posterior bony orbit.

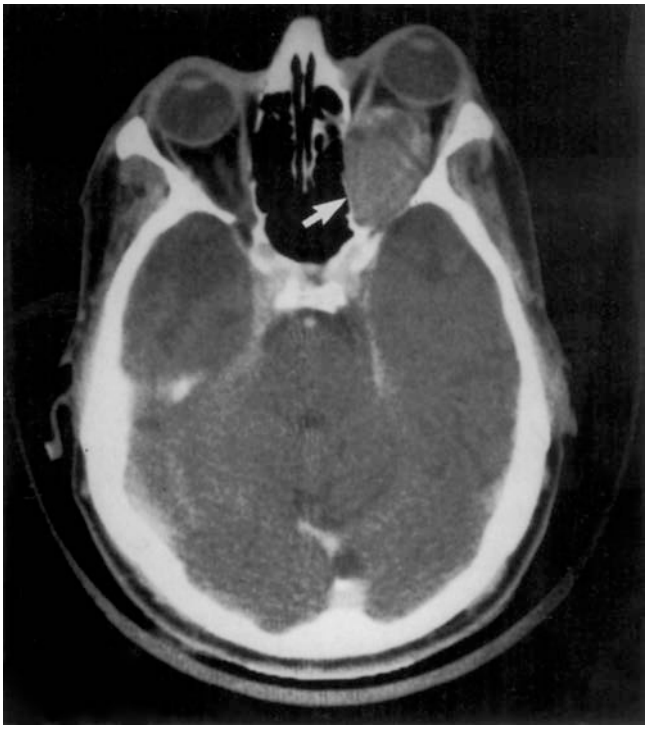


Figure 10.12 Axial computed tomography scan of a large retrobulbar cavernous hemangioma (*arrow*) that completely fills the apex of the left orbit.

The lesions usually have a smooth surface but occasionally will be bosselated. These bosselations may represent areas where the tomor is expanding into the host environs.

When bisected, the tumor has a sponge-like consistency (see Fig. 10.14), which reflects the numerous ectatic spaces that comprise the main components of the tumor. The large spaces are lined with flattened but not particularly attenuated endothelial cells. The lumens usually contain clumps of erythrocytes showing varying degrees of stasis, intraluminal thrombosis, fibroblastic replacement, and vascularized endothelial buds from the surrounding wall (see Fig. 10.15). A mantle of spindle-like cells of varying thickness encompasses the cavernous-like spaces. These smooth muscle-type cells may merge imperceptibly into the surrounding interstitium or collect into small bundles.

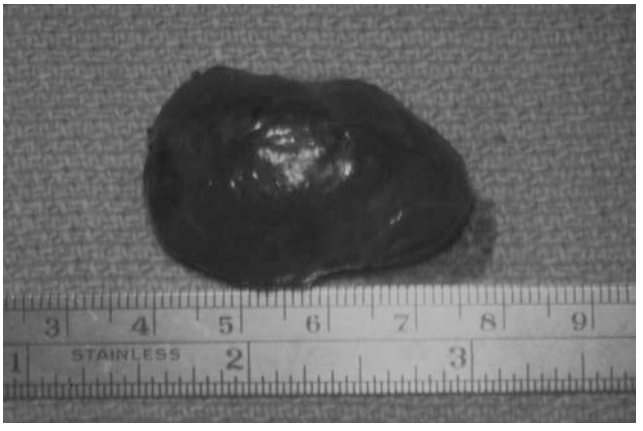


Figure 10.13 Dusky red, smooth-surfaced cavernous hemangioma measuring 35 × 25 × 20 mm that had caused reduced vision for 13 years and proptosis for 6 years in a 40-year-old woman. The pyramidal contour of the portion of the tumor (to the right) suggests molding by the bony contour of the posterior orbit.

Figure 10.14 Cavernous hemangioma: Dilated, blood-filled channels impart a sponge-like appearance to the tumor. Compare to Figure 10.17.

The interstitium of the tumor may show small collections of fat, myxomatous foci, and zones of intralesional hemorrhage. A few inflammatory cells and macrophages may be seen in the latter areas. Foci of lymphocytes are absent or sparse in contrast to a lymphangioma where multiple foci of lymphocytes are present. The interstitial fibrous tissue component is not particularly prominent except in tumors of large size. Neither is the interstitium heavily vascularized as in capillary hemangioma.

If a large expanse of tumor is studied microscopically, lobular collections of capillary-size channels will be discovered. These capillary subunits, for years, have reinforced

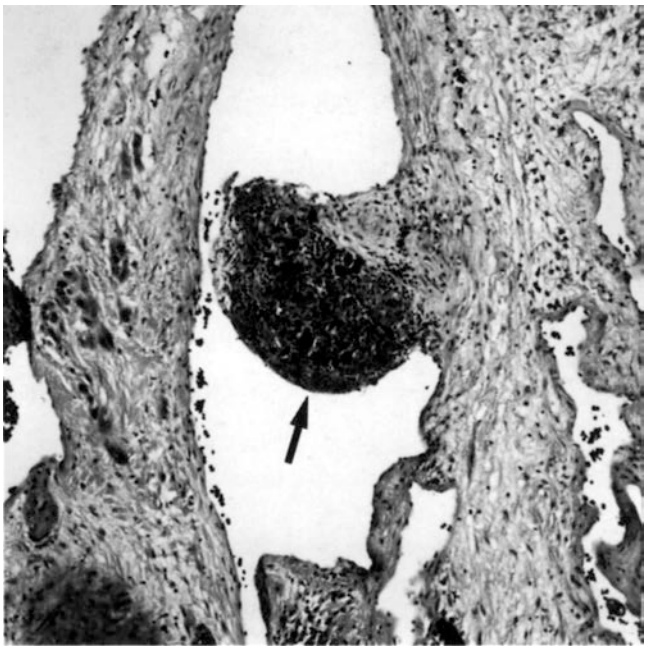


Figure 10.15 Cavernous hemangioma: Showing a thrombus (*arrow*) along the wall of a thick-walled vascular channel (×100).

the basis for considering cavernous and capillary hemangiomas as coexistent or related tumors. If the latter, it was assumed that the cavernous type evolved from a preexisting capillary progenitor of many years' duration. However, Harris and Jakobiec (1978) suspect these capillary nests are the immature, growth-sustaining portion of the tumor, the capillary channels gradually enlarging and acquiring a mantle of smooth muscle cells. It would be interesting to learn whether these capillary-like patches are correlated in size or location with the bosselations observed on the surface of some tumors.

Treatment and Prognosis

The surgical removal of this neoplasm is usually by some modification of a lateral orbitotomy except for those in the medial portion of the orbit or deep within the orbital apex. Those in the medial orbit may be removed by some variation of an anteromedial orbitotomy if they are located in the anterior orbit, or combining this orbitotomy with an ethmoidectomy and/or lateral orbitotomy if the tumor is tucked away in the posteromedial orbit near the optic nerve. A craniotomy is usually required to reach the orbital apex. The tumor is readily identified by its color, although a hemangiopericytoma may be a "look-alike." Slow, meticulous dissection with cotton-tip applicators has significantly increased the frequency of intact removal in recent years. The tumor tends to soften with surgical manipulation, which facilitates dissection along the masked surface of the tumor. Alternatively, a large bore needle can be used to aspirate some of the blood from the tumor, which softens it thereby facilitating its removal. Exceptionally, when located near the orbital apex, the tumor can be "cored-out" with a carbon dioxide laser and the sides folded in upon themselves.

The cryoprobe is another device that has contributed to an intact removal. It can be applied to the exposed surface of the tumor as a traction device, thereby eliminating the need for forceps and tenacula. The cryoprobe also expedites the final delivery of the slippery tumor, which, otherwise, tends to twist and roll away from the grasp of the surgeon. There is a tendency of younger surgeons to overuse the tractive effect of the cryoprobe, resulting in irregular tears along the surface of the mass.

Most deliveries of tumor are relatively bloodless. The venous bleeding that pools in the cavity that is created by the removal of the tumor can be stanched by packing with cotton pledgets or gauze squares for a few minutes. Drains are not necessary.

Our object is always the intact removal of tumor without incisional biopsy. The effect on the preoperative proptosis is most striking, and the patient's acceptance of the postoperative result is gratifying. Seventy nine percent of our 81 tumors were removed intact over the 40-year period of study. This percentage would be higher if only the past 15 years were analyzed.

Our follow-up data is sparse chiefly because we seldom see or hear from distant patients who have had intact removal. On correspondence with some of these patients, their reply is, "getting along fine," although no details are included regarding their visual status. Even so, we realize there are a certain number of patients with residual refractive errors, choroidal folds, pallor of the optic disk, afferent pupillary defects, visual loss >20/80, and strabismus that were not improved no matter how the tumor was removed.

Incomplete removal can, but does not always, result in regrowth of tumor. Three of our patients had undergone several surgeries for recurrent tumor at the time of our initial surgery. Two of our patients whose tumors were not removed intact are known to have regrowth of tumor. The course of one of these patients is most interesting and was reported by Henderson et al. (1990). The tumor regrowth has been followed up by observation and CT scan imaging for 18 years with eventual regression of proptosis and spontaneous partial involution of the retrobulbar mass.

HEMANGIOPERICYTOMA

In the time depth of the several editions of this text, the hemangiopericytoma has come of age. Its separation from hemangioendothelioma almost 50 years ago (Stout and Murray, 1942) is no longer debated, and the pericyte or a precursor cell is now universally accepted as the cell of origin. This cell and its relationship to capillary-size vessels has been widely studied by light and electron

microscopy. Because of this relationship, the tumor's ubiquitous distribution is now explained. This diversity also extends to its wide age distribution, although cases in infants and children remain a distinct minority (Boyle et al., 1985; Kapoor et al., 1978). Several publications in the 1970s (Jakobiec et al., 1974; Henderson and Farrow, 1978) also helped to define the clinical characteristics of the tumor primary in the orbit.

Once thought to be predominantly a benign tumor, it is now feared because of its infrequent but definite malignant behavior, particularly if, at the initial surgery, it has been incompletely resected. Also, it is now established that, contrary to the behavior of most neoplasms with malignant potential, several decades may pass between benign and malignant phases of the initial neoplasm, and between a benign recurrent tumor and its malignant transformation. However, one feature of hemangiopericytoma that has remained elusive throughout the nearly five-decade period of study is the difficulty in correlating histopathologic appearance with its clinical behavior.

Incidence

Our current survey of orbital tumors (Table 3.3) includes 24 cases of hemangiopericytoma (18 primary, 5 secondary, 1 metastatic). The 24 cases represent an incidence of 1.3% of the total 1,795 tumors, and considering the small size of the sample, it is a steadfast ratio compared with the 1.7% incidence in the 1978 series. In our current series, the primary hemangiopericytomas comprise 2.7% of the total 672 primary tumors.

The sex incidence (Table 3.3) favors men in a ratio of 1:2:1. In a larger series (30 cases) of hemangiopericytomas studied by Croxatto and Font (1982), the male:female ratio was 2:1. The male predominance in both series differs from our statement in the second edition of this text that the tumor was seen more often in females. A larger number of cases will need to be surveyed to settle the question of sex prevalence. In our series the right orbit was affected more often than the left orbit in a ratio of 2:1, whereas there was essentially equal orbital involvement in the Croxatto and Font series.

The age distribution of these tumors in adults was similar to cavernous hemangioma, namely, 66% (16 out of 24) were seen in the fourth, fifth, and sixth decades. There was no significant difference in the age distribution of the primary versus secondary tumors. We have not observed the hemangiopericytoma in infants and children as have Croxatto and Font who reported two of the five cases recorded in the literature.

Clinical Features

What has already been said about the clinical presentation of cavernous hemangioma is equally applicable to hemangiopericytoma primary in the orbit. Therefore, it seems more relevant to note the few differences in the symptomatology of the two tumors rather than repeat the dissertation of the prior subchapter. In 25% of our primary orbital hemangiopericytomas, some telangiectasia or vascular tortuosity was present in the adnexal tissues overlying the palpable mass in the anterior orbit. This reddish purple suffusion proved to be an external marker of an underlying hemangiopericytoma and probably reflects the inherent vascularity of the supporting tissues as compared to cavernous hemangioma.

Several reports in the literature suggest that the duration of symptoms prior to presentation was shorter with hemangiopericytoma when compared to cavernous hemangioma. On the contrary, we did not note any such discrepancy in the mean longevity of symptoms in the two lesions.

In regard to *secondary orbital hemangiopericytoma*, our five patients are too few to recognize a pattern of symptomatology. In general, most hemangiopericytomas of this type originate in the nasal cavity, extend into the ethmoid sinus, and invade the medial orbit through the ethmoid plate. Initially, these patients have some degree of nasal obstruction, epistaxis, and a visible intranasal mass. The presenting pattern is not specific for hemangiopericytoma except that epistaxis may be much more alarming when compared to other neoplasms of the nasal cavity. The initial episode of bleeding was so severe in one of our patients that hospitalization and surgical intervention were necessary to secure hemostasis. In the main, the behavioral pattern of the secondary hemangiopericytoma is essentially the same as the primary type. They differ chiefly in the difficulty of surgically eradicating the secondary type once recurrence has occurred.

At this point we should mention the unusual case of a hemangiopericytoma of the sheath of the intraorbital optic nerve reported by Boniuk et al. (1985), apparently the only case of this type in the literature. This was a 61-year-old man (April 1981) whose vision had decreased from 20/20 to light perception in the right eye over a 4-month period. An afferent pupillary defect also was present in the affected eye. Skull x-rays were normal and the CT scan did not show any enlargement of optic nerve. The diagnosis was indeterminate. In December 1983, a repeat CT scan revealed a fusiform expansion of the intraorbital portion of the right optic nerve. A 20 mm segment of the nerve was excised and revealed an intradural hemangiopericytoma compressing the atrophic nerve against the dura.

Mention should also be made of one case in our series with *bilateral orbital metastasis* that may be unique. The patient was a 19-year-old woman who presented with a mass in the upper nasal quadrant of the *right orbit*. *A* hemangiopericytoma had been removed from the left costal area 9 months previously. Two months prior to presentation metastasis had appeared in the lung. Three months after presentation a mass appeared along the medial wall of the *left orbit*. Radiotherapy brought some temporary relief, but the patient expired 6 months after presentation with multiple metastases.

Imaging Aspects

The configuration, density, and signal intensity of hemangiopericytoma on CT scan and MRI are essentially the same as described for cavernous hemangioma, except that greater emphasis is placed on the contrast enhancement properties of hemangiopericytoma. However, we have already pointed out the capriciousness of contrast enhancement in the preoperative differential diagnosis of suspected vascular tumors of the orbit in adults. Once the circumscribed tumor is imaged, more concern should be given to the intact removal of the mass. If this is accomplished, the degree of its enhancement becomes irrelevant.

The true vascularity of hemangiopericytoma is best revealed by angiography, but this invasive procedure is not usually done in the planned operation of a circumscribed, presumed vascular neoplasm. Prominent enhancement, though, might suggest a Doppler ultrasound study (Davies et al., 2002). However, it is important to know the tumors supporting arterial supply if an operation is contemplated for a noncircumscribed tumor recurrence, particularly for any extension into the intracranial vault. Such information is mandatory for successful hemostasis of those recurrent tumors that are capable of life-threatening hemorrhage. The CT scan features of a large recurring secondary hemangiopericytoma are illustrated in Figure 10.16.

These lesions accessible to A-mode echography will show a more solid consistency than cavernous hemangioma.

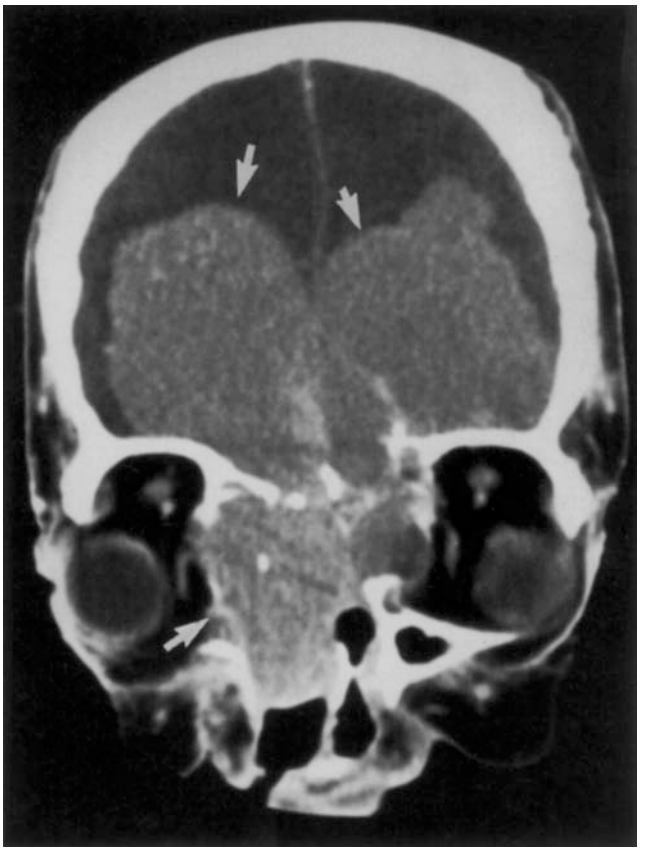


Figure 10.16 Coronal computed tomography scan of huge, enhancing, recurrent hemangiopericytoma (*arrows*) with bilateral involvement of ethmoid sinuses, orbits, and frontal lobes in a 60-year-old man. A highly vascular tumor was first removed from right nasal fossa, including exenteration of right ethmoid sinuses, 16 years previously. Surgical removal of two subsequent recurrences 12 years and 3 years ago. This lesion was considered inoperable because patient would not consent to probable need of blood transfusion during surgery. Patient still living 2 years after this scan.

Pathology

Grossly, the hemangiopericytoma has, in general, the same color, configuration, and circumscription of cavernous hemangioma. When bisected, however, the hemangiopericytoma is a more solid tumor (see Fig. 10.17). In the orbit, the hemangiopericytoma may show a more knobby surface when compared to the more smooth-surfaced cavernous hemangioma, although this is not a constant finding.

Most of the hemangiopericytomas have a thin pseudocapsule that contrasts with the layered capsule of the cavernous hemangioma. The malignant varieties may show a frankly infiltrative interface with the host tissue.

The chief microscopic feature of this neoplasm is the uniformity of the cellular and vascular pattern together with the reticulin framework that surrounds the individual pericyte. The pericyte has ill-defined borders, a moderate amount of cytoplasm, and round-to-oval nuclei. Most commonly the cell is plump, but spindle-shaped cells are also seen. These cells are usually closely apposed, but in focal spindle-cell areas the cells are arranged diffusely and never in bundles or fascicles, which help to distinguish this neoplasm from other spindle-cell tumors (see Figs. 10.18–10.22). The number of mitotic figures that are present is helpful in distinguishing the benign from the malignant forms. In other parts of the body, most benign tumors have fewer than two to three mitotic figures per 10 high-power fields. More than four mitotic figures per 10 high-power fields are seen with rapidly growing tumors that are capable of recurrence of metastases. In their study of orbital tumors, Croxatto and Font counted the number of mitotic figures per 40 high-power fields, and found that in the benign group of tumors, mitotic figures numbered four in the borderline group 14, and the malignant tumors averaged 35 mitotic figures per 40 high-power fields. Other histopathologic features that were considered were the degree of cellularity and nuclear atypia.

The closely apposed pericytes lie between vascular channels, which form a ramifying network; typically, the sinusoidal vessels have a "staghorn" configuration. These channels are lined by a single row of flattened endothelial cells, and surrounding each vascular channel is a basal lamina that extends to surround each individual pericyte. The amount of reticulin varies from one tumor to another. On occasion, foci of degeneration are present together

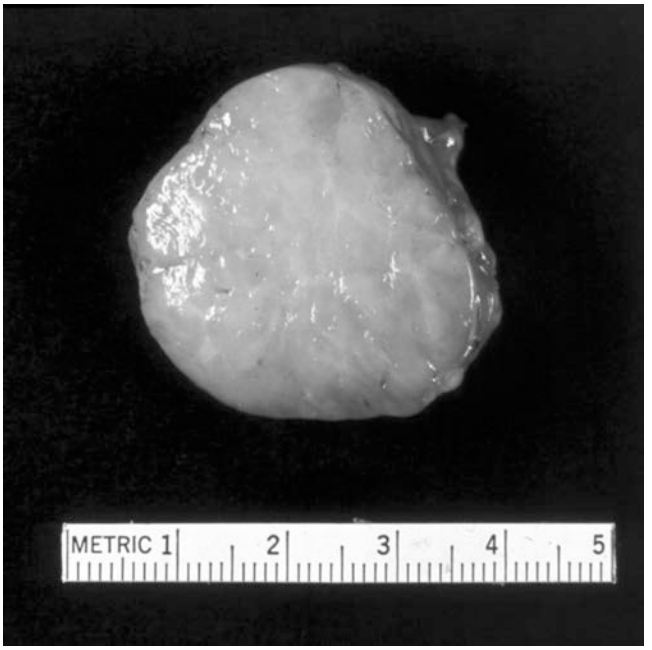


Figure 10.17 Bisected, well-circumscribed hemangiopericytoma measuring 32 mm in longest meridian removed from 54-year-old man with 12 mm proptosis and vision of 20/80 in affected eye. Note solid consistency of tumor as compared to Figure 10.14.

with mucoid material. A lipomatous variant with mature adipocytes occupying 25% to 75% of the tumor has also been described. Although the trunk and extremities are the most frequent location, there have been two cases reported in the orbit (Davies et al., 2002; Guillou et al., 2000). The clinical behavior of this variant is "benign" after 48 months and 77 months of follow-up.

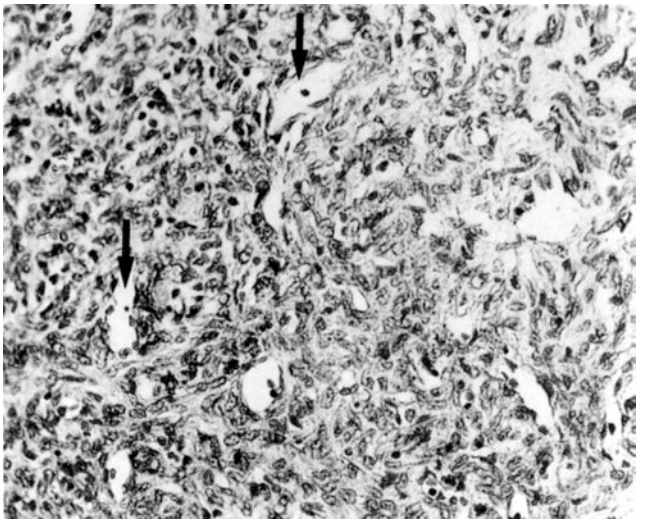


Figure 10.18 Benign hemangiopericytoma: Plump cells with oval nuclei and indistinct cytoplasm surround sinusoidal (*arrows*) channels lined by flattened endothelium (×250).

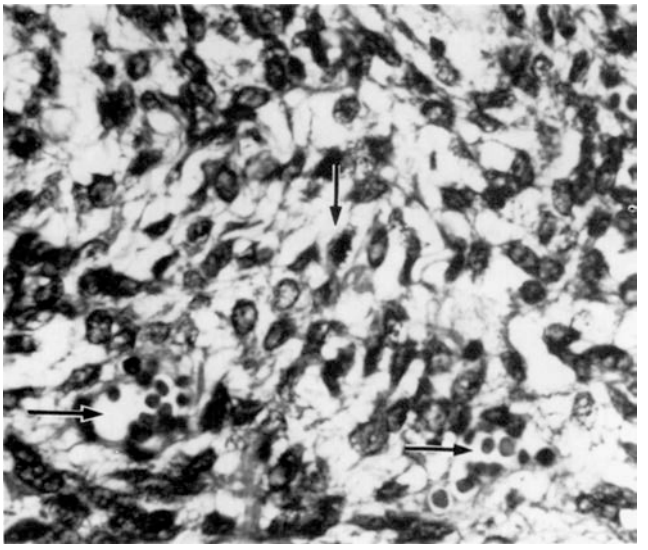


Figure 10.19 Borderline hemangiopericytoma: Plump spindle-shape cells with oval and round vesicular nuclei containing a single nucleolus surround compressed vascular spaces (*horizontal arrows*) containing erythrocytes. Occasional mitotic figures (*vertical arrow*) were noted in this specimen (×640).

The histologic appearance is suggestive of solitary fibrous tumor. Goldsmith et al. (2001) have suggested that solitary fibrous tumors and hemangiopericytomas are not distinct pathologic entities but rather exist along a morphologic and immunohistochemical spectrum.

On the basis of these criteria, the primary hemangiopericytomas of our series were classified as benign (seven cases), borderline (eight cases), and malignant (three cases). In the

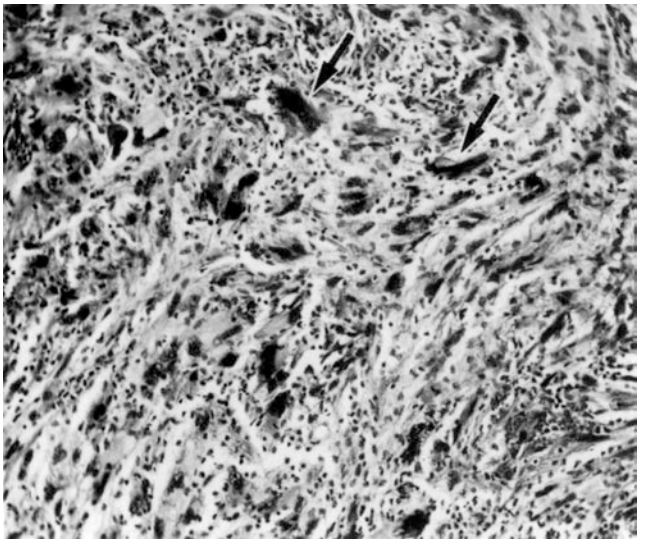


Figure 10.20 Malignant hemangiopericytoma: Highly anaplastic tumor with bizarre, pleomorphic, hyperchromatic cells (*arrows*) recurring 9 years after incomplete excision supplemented by radiotherapy. Cellular features suggest fibrosarcoma, probably radiation induced (×160).

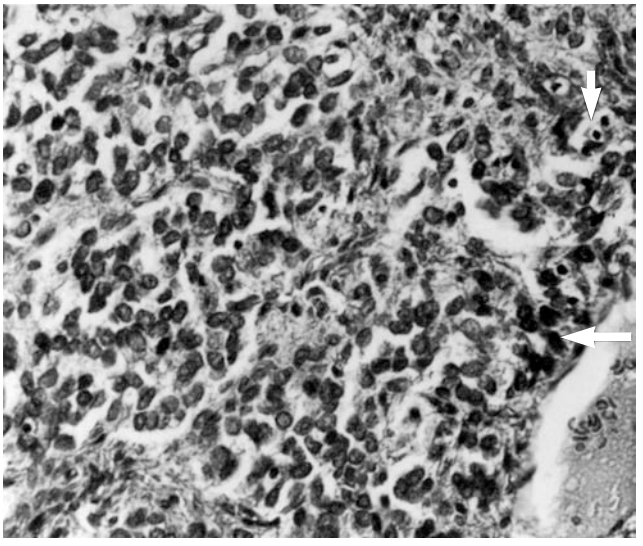


Figure 10.21 Malignant hemangiopericytoma: Pleomorphic cells with hyperchromatic nuclei (*horizontal arrow*) surround occult (*vertical arrow*) vascular channels (×400).

secondary type, one of these cases was benign, two were borderline, and two were malignant. In the one case that was metastatic in a woman who was 19 years old at the time of presentation, the primary focus of tumor was in the soft tissues of the left rib cage.

The hemangiopericytoma belongs to the large group of soft tissue tumors, which are of mesenchymal cell origin. Immunohistochemistry may aid in distinguishing this tumor from other vascular neoplasms. The endothelial cell reacts with factor VIII–related antigen and/or *Ulex europaeus* I lectin, neither of which stains the pericyte. The pericyte is

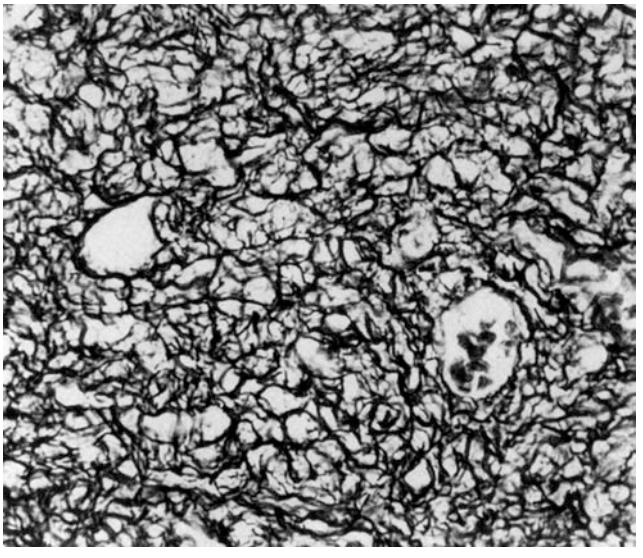


Figure 10.22 Hemangiopericytoma: Network of black-staining reticulin fibers demonstrate that proliferation of cells is peripheral to the two vascular channels in section (reticulin stain; ×405).

actin and vimentin positive. Rarely, smooth muscle myosin is demonstrated (Rootman, 1988). A negative S-100 protein reaction in mesenchymal tumors distinguishes them from tumors of neurogenic origin.

Ultrastructural studies have established the tumor cell as the pericyte. The nuclei appear ovoid or large and round, and the relatively electron lucent cytoplasm has elongated processes and contains sparse cytoplasmic organelles that include rough surface endoplasmic reticulum with few ribosomes, mitochondria, and small numbers of intermediate microfilaments (Jakobiec and Jones, 1979). The most conspicuous feature is the presence of pinocytotic vesicles. Also distinctive is the basal lamina, which separates individual cells and also separates them from endothelial cells. The lamina may be continuous or discontinuous. Desmosomes are poorly developed and rare.

Treatment and Prognosis

If the tumor is truly removed intact without any preliminary fine-needle biopsy or exploratory incisions of any kind, the patient is probably cured unless the lesion proves histologically malignant at the initial surgery. With any other type of surgical removal, although grossly complete, the patient is at risk for recurrence. However, factors such as size of residual tumor, orbital location, age of patient, histopathologic type (except frankly malignant tumors), and the possibility of recurrence are not known. Neither can we say that all patients with an incompletely removed tumor will positively have recurrence. Finally, the interval between incomplete removal and recurrence may be so very long (many years) that it is very difficult to collect meaningful data about any of the factors mentioned in the preceding text. Rice et al. (1989), for example, reported a recurrence 33 years after incomplete removal of tumor in a 56-year-old woman. In the case reported by Panda et al. (1984), the first recurrence occurred 22 years after incomplete excision. It is our clinical impression that radiotherapy of an incompletely removed tumor tends to suppress regrowth of tumor, but it is not curative. However, such patients may be at greater risk for malignant transformation of tumor than patients not receiving radiotherapy. The risk of malignant transformation also may be related to the amount of radiotherapy.

The management of a primary tumor that is histopathologically malignant at the time of initial surgery, although completely removed, is exenteration of the orbit. This may be followed by radiotherapy for its potential suppressive effect on metastasis or local recurrence.

In the management of recurrent tumors, there are several options. If the recurrent tumor appears well circumscribed on CT scan, if it is located in an easily accessible area of the orbit, and its original histopathologic classification is benign or borderline, another attempt may be made to remove the lesion intact. Setzkorn et al. (1987) describe a 23-year-old patient with two recurrences following

local excision. A third local excision was followed by radiation therapy. There was no recurrence after 7 1/2 years of follow-up. If histopathologic study of the specimen reveals no significant increase in the degree of nuclear atypia or number of mitotic figures when compared to the original specimen and the tumor margins are clear, further surgery may be deferred. Even so, if one or more of these conditions are not fulfilled, radical surgery followed up by radiotherapy offers the least risk for further tumor recurrence. Adjunctive chemotherapy has not been used in a sufficient number of patients to judge its effectiveness.

As already noted, most of the hemangiopericytomas in our series were either benign or borderline type, histopathologically. We are not aware of any deaths in this group if the lesion was initially removed intact. Of the 24 patients with primary or secondary tumors, six are dead either from metastasis or extension into the intracranial vault, a mortality of 25%. In all the six patients, the initial removal of tumor was incomplete. In two of the six patients, the tumor was initially considered benign, for two patients the classification was borderline type, and two patients were frankly malignant at presentation. However, we are suspicious that overuse of radiotherapy in two patients played some part in the malignant transformation of the lesions.

Follow-up studies were available for 27 patients of the Croxatto and Font series. Four of these patients died as a result of metastatic disease, a mortality of 15%. The difference in mortality between their series and ours might be due to a longer follow-up in our study, a mean duration of 12.7 years as compared to a mean duration of 5.5 years in their study. In our remaining 16 patients, there has been recurrent tumor in four patients (25%). Croxatto and Font noted a 30% recurrence in their follow-up series.

This data is essentially a continuum of the conclusions reached in our second edition and closely approximates the analysis of Croxatto and Font. Therefore, *we continue to believe that prognosis and clinical behavior of orbital hemangiopericytoma cannot be predicated on the present histopathologic classification*.

Aware of a search for a more reliable indicator of prognosis, Larson and Campbell (1987) undertook a flowcytometry analysis of nuclear DNA content of 12 hemangiopericytomas. Prior studies by others had shown the ploidy patterns of renal carcinoma and pheochromocytoma to be of prognostic value. Subsequently, the usefulness of DNA analysis has been extended to the prognosis of prostatic and thyroid carcinoma. Larson and Campbell found normal diploid DNA patterns in all 12 cases. Therefore, a satisfactory technical method for determining clinical behavior and prognosis of orbital hemangiopericytoma remains elusive.

In conclusion, *the adequacy of surgical removal of tumor at the initial orbitotomy may be the major determinant in the frequency of recurrence and the patient's ultimate life span*.

HEMANGIOBLASTOMA

This is a benign vascular neoplasm, principally of capillary-size vessels. It occurs most commonly in young and middle-aged adults and affects men more often than women (Amador, 1988). Its principal location is the cerebellum. Here it comprises 1% to 2.5% of all intracranial neoplasms.

The tumor usually occurs as an isolated lesion but 15% to 20% may be multiple (Nerad et al., 1988). When multiple, features of the von Hippel-Lindau syndrome also are the rule. This syndrome includes a variable combination of "angiomas" of the retina, cerebellum, and spinal cord; pancreatic and renal cysts; cellular skin nevi; and renal cell carcinoma. Some of the cases of multiple hemangioblastoma also are familial.

A supratentorial location of the hemangioblastoma, such as the optic nerve, is considered rare. A single case report of a hemangioblastoma involving the medial rectus muscle was published by Cockerham et al. (2003). A 73-year-old woman noted slowly progressive proptosis over a 5-year period with limited abduction. An encapsulated tumor was removed from the anterior portion of the muscle but the posterior portion of the muscle was diffusely infiltrated. There was no family history of von Hippel-Lindau disease and the patient had multiple small vascular liver masses and a 1 cm enhancing mass within the frontal lobe. The patient declined further evaluation of these masses. Case reports of hemangioblastoma involving the intraorbital optic nerve include those of Schneider (1942); Eckstein et al. (1981); Lauten et al. (1981); In et al. (1982); Nerad et al. (1988) and Hotta et al. (1989). The mean age of these six patients at time of diagnosis was 27 years (range, 15 to 39 years). The left orbit was involved in five of the six patients, and female-to-male incidence was 4:2. In two of the six patients, the intracranial optic nerve was also involved. Three (50%) of the six patients had features of von Hippel-Lindau syndrome also. One of the latter cases was also familial. In a case reported by Stefani and Rothmund (1974), the tumor was confined to the prechiasmal, right intracranial optic nerve. The tumor in this case was found at an autopsy of a 65-year-old man, 23 years after the onset of visual loss followed by slowly progressive optic nerve atrophy.

A familial-type hemangioblastoma involving the intracranial-intracanalicular portion of the right optic nerve has also been observed at the Mayo Clinic. This is the case of a 35-year-old woman who was seen in December 1990 because of slowly progressive visual loss of the right eye of 2 months' duration. An afferent pupillary defect was present on the right side, and a superior altitudinal defect was present in the right visual field. Visual acuity of the right eye was 20/400. A small retinal angioma-like mass was seen adjacent to the right optic disk that was found to be unchanged in size when compared to a photograph taken in 1984. There was no proptosis of the right eye. No abnormality was present in the left eye.

The CT scan showed a 1 cm densely enhancing mass in the region of the right ophthalmic artery with expansion of the right optic canal, suggesting either an ophthalmic artery aneurysm or a possible tuberculum meningioma. The interpretation of an MRI of the same area favored the latter diagnosis.

In April 1984, past history revealed a left suboccipital craniectomy and total excision of two nodules of cerebellar hemangioblastoma. Two weeks later, a right total adrenalectomy was performed for a solitary encapsulated pheochromocytoma. In September 1989, the patient had undergone a left lower pole nephrectomy and enucleation of a mass at the junction of the upper and middle third of the left kidney. Both lesions were renal cell carcinomas. The patient's father was also known to have features of von Hippel-Lindau syndrome.

For the lesion in the right optic nerve, the patient underwent a right frontal craniotomy with removal of the posterior aspect of the right optic foramen in January 1991. A tumor within the optic nerve was enucleated in pieces using the operating microscope. The pathology report was a hemangioblastoma in pieces aggregating $1 \times 0.7 \times 0.7$ cm.

In June 1991, the visual acuity of the right eye was counting fingers, a small residual isle of vision was still present in the inferior nasal quadrant of the right visual field, and the optic nerve showed moderate pallor.

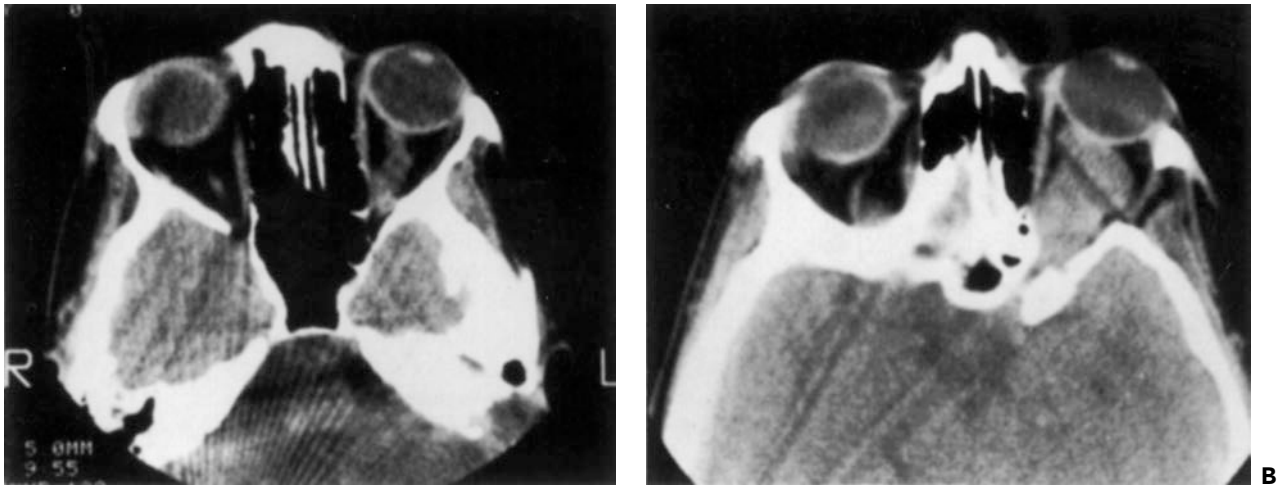
In June 1992, a repeat MRI did not reveal any residual or recurrent tumor in the right optic nerve but did show new, small enhancing nodules throughout the cerebellum, presumably hemangioblastoma.

The clinical presentation of the intraorbital optic nerve tumors, roughly in the order of the sequence of symptoms, is visual loss (rapid or slow), edema or pallor of the optic disk, an afferent pupillary defect in the affected eye, and slowly progressive proptosis. The proptosis is disproportionately mild in degree in relation to the marked visual loss. In a child or an adolescent, this pattern would suggest a slow-growing optic nerve glioma. In an adult, this symptomatology resembles a meningioma near the lesser wing of the sphenoid bone.

The imaging modes utilized in some of the reported cases were optic canal tomography, angiography, and CT scan. Optic canal tomography will show an enlargement of the optic foramen if the tumor also involves the intracanalicular optic nerve. Angiography will show a highly vascular tumor with a dense homogeneous stain and early venous drainage. CT scan (see Fig. 10.23) shows a homogeneous mass that is hyperdense to vitreous, isodense with brain, and hypodense when compared to adjacent extraocular muscle. None of these imaging characteristics is necessarily specific for hemangioblastoma. In the future, MRI should provide a major advance in differential diagnosis of this tumor.

Grossly, the tumor is yellow or reddish brown. In the optic nerve, the tumor is usually a soft solid lesion intrinsic in the nerve substance rather than arising from the optic nerve sheaths (see Fig. 10.24). The tumor may also be cystic, particularly in the cerebellum. It is the compression of the nerve by the enlarging mass that accounts for the early visual loss of affected patients.

Low-power light microscopy shows a profusion of capillary-size vessels of variable size and configuration. The capillary constituents of the tumor may be more clearly demonstrated by a reticulin stain. A higher magnification shows the two principal cellular components of the tumor. One includes the endothelial cells lining the vascular channels with their supporting pericytes. The others are



A B

Figure 10.23 **A:** Computed tomography axial scan showing enlargement of left optic nerve in a 23-year-old woman with a swollen left optic disk. Incisional biopsy revealed a hemangioblastoma. **B:** Axial scan 16 months later shows tumor filling posterior left orbit. There was no optic canal enlargement. Tumor and optic nerve subsequently excised en bloc. (From Nerad JA, Kersten RC, Anderson RL. Hemangioblastoma of the optic nerve. *Ophthalmology*. 1988;95:398–402, with permission.)

Figure 10.24 Hemangioblastoma of optic nerve: Nerve (*N*) is compressed and replaced by tumor (*below*); dura (*D*) above (×16). (Courtesy of R Folberg, MD, University of Iowa, Iowa City.)

groups of large polyhedral cells with vacuolated foamy (lipid containing) cytoplasm and bland nuclei. The lipid material stains brightly with oil red O. The latter cells are considered specific for the neoplasm.

If the tumor is well demarcated within the optic nerve, such as in the Mayo Clinic case (*supra vide*), an effort may be made to enucleate the lesion by microscopic techniques, sparing the surrounding nerve. The frequency of recurrence after incomplete excision is not known.

Once the tumor is removed the physician should search for other manifestations of von Hippel-Lindau syndrome and follow up the patient carefully for any future lethal manifestations such as cerebellar hemangioblastoma and renal carcinoma (Hardwig and Robertson, 1984).

ANGIOSARCOMA (MALIGNANT HEMANGIOENDOTHELIOMA)

We have used the two most common names for this particular tumor in our title to accommodate those who think of this lesion in terms of either one but not both of the names mentioned above. Enzinger and Weiss (1988) prefer *hemangioendothelioma* for a neoplasm of lesser (borderline or intermediate) malignancy than angiosarcoma. Tumors that are highly anaplastic and therefore difficult to define have resulted in a wide spectrum of nomenclature that includes *malignant hemangiopericytoma*, *Kaposi's sarcoma*, and *malignant lymphangiosarcoma*. We prefer to use the term *angiosarcoma* for this tumor entity, which is so rare in the orbit. In the literature, this tumor is frequently cited as comprising only 1% of all sarcomas of soft tissue of the entire body. Its orbital incidence is considered to be only 3% of the above 1%. This emphasizes the rarity of the tumor in this location.

Because it is so rare, we would be hard put to round up the orbital cases scattered throughout the literature. Thankfully, Hufnagel et al. (1987) have accomplished this task. Their review is the most extensive and comprehensive up to the present. Our discourse on this orbital tumor, therefore, is chiefly a summary of their review along with a discussion of three additional case reports, one primary to the orbit (Siddens et al., 1999), one secondary (Lopes et al., 1999) and one metastatic (Burnstine et al., 1996). We have not encountered a case of orbital angiosarcoma in the time span of our tumor survey.

One of the chief problems with angiosarcoma is recognition of the disease entity. The lesion is a malignant neoplasm of endothelial cells (Ordonez and Batsakis, 1984), although it can be confused with several other entities including sclerosing rhabdomyosarcoma and angiomatoid melanoma just to name two. It is a very aggressive tumor with a propensity for early local recurrence, lymph node metastasis, and diffuse hematogenous spread. Hufnagel et al. located 14 previously reported, well-documented, orbital cases and added one of their own. Tumors of the ocular adnexa and other related neoplasms such as malignant hemangiopericytoma were excluded from their list. This list is reproduced in Figure 10.25. It tabulates the salient ophthalmologic features of each reported case. It covers the subject more adeptly than a discourse of several hundred words, which otherwise would be required.

Clinically, the lesion was more common in the pediatric age-group. It was more frequent in the anterosuperior orbit and was associated with swelling of the upper eyelid. In such cases, it was difficult to separate tumors limited to the eyelid from those with an orbital extension. The margins of these tumors were not well defined. There is no sex predilection. The major difference between pediatric and adult groups was the frequent, rapid, fatal outcome in the latter group. The case of Messmer et al. (1983) had the unusual presentation of painful ophthalmoplegia, sensory defects along the first and second divisions of the fifth cranial nerve, and slowly progressive proptosis. In children who show aggressive growth or rapid onset of an ostensible lymphangioma, an angiosarcoma may prove to be the underlying neoplasm (Royer et al., 1969). Here, we should also note a case of angiosarcoma of the breast that metastasized to many sites, including the orbit (Jakobiec and Jones, 1979). Another breast angiosarcoma metastasized to the orbit resembling a cavernous hemangioma although at the time of surgery the inferior and medial rectus muscles were infiltrated (Burnstine et al., 1999). Despite postoperative radiation therapy, the residual tumor progressed and since there was still no evidence of other metastatic disease, an

Author	Age	Sex	Duration, Signs, and Symptoms	Tumor Location	Size	Treatment	Last Follow-up
Adult group							
Stout (1943) Case 12	40 yr	F	2 yr, swelling upper eyelids, proptosis, ophthalmoplegia	L, medial orbit, apex to base	2 cm	Excision	6 yr, local recurrence
Mortada (1961) Case 2	30 yr	F	4 mo, swelling upper eyelid, proptosis	R, superior orbit	3.5 × 3 cm	Excision	14 mo, alive and well
Sekimoto et al (1971)	47 yr	M	NS, proptosis	R, posterior orbit with extension through superior orbital fissure	NS	Exenteration	6 yr, alive with tumor, brain metastases
Messmer et al (1983)	66 yr	M	1 yr, Tolosa-Hunt syndrome	L, orbital apex and superior orbital fissure	2 × 1 × 0.5 cm	En bloc resection, radiation therapy	NS
Current article (1986)	37 yr	F	2 yr, swelling upper eyelid, blepharoptosis	R, medial and anterior orbit	3 × 1.5 × 1 cm	Exenteration, radiation therapy	1.5 yr, alive and well
Pediatric group							
Carelli and Cangelosi (1948)	11 yr	F	2 mo, swelling upper eyelid ptosis	R, anterior and superior orbit	NS	Excision, radiation therapy	2.5 yr, alive and well
Mortada (1961) Case 1	5 mo	M	5 mo, swelling upper eyelid, ptosis	L, medial and anterior orbit	NS	Excision	NS
Kano and Ota (1966)	17 yr	M	9 mo, ptosis	L, anterior orbit	1.2 × 0.6 cm	Exenteration	4 yr, local recurrence
Cernea et al (1968)	3 yr	F	3 mo, swelling upper eyelid, ptosis	L, medial and superior orbit	NS	Excision	NS
Royer et al (1969)	4 mo	M	3 mo, swelling upper eyelid with subconjunctival mass	L, medial and superior orbit	NS	Excision, radiation therapy	3 yr, died of tumor, first recurrence after 2 yr
Mortada (1969) Case 2	16 yr	F	1 mo, ptosis	R, massive orbital involvement	NS	Exenteration radiation therapy	6 mo, died of tumor (liver metastases)
Tsuda and Takaku (1970)	14 days	NS	2 wk, ptosis	R, posterior orbit	5 × 3 × 3 cm	Exenteration	5 mo, alive with local recurrence, brain metastases
Diallo and Moliva (1970)	2 yr	M	10 days, exophthalmos, ophthalmoplegia, preauricular adenopathy	R, NS	NS	Exenteration, chemotherapy	6 mo, alive with local recurrence, brain metastases
Treheux et al (1975)	8 yr	M	3 mo, exophthalmos	R, medial and posterior orbit	NS	Exenteration, chemotherapy, radiation therapy	6 wk, alive with tumor, local recurrence, massive extension in maxillary sinus
Nath et al (1977) Case 2	2 yr	F	3 mo, ptosis	NS	2 × 1 cm	Exenteration	NS

F = female; M = male; NS = not specified; L = left; R = right.

Figure 10.25 Orbital angiosarcoma: A review of the literature (Reproduced from Hufnagel T, Ma L, Kuo TT. Orbital angiosarcoma with subconjunctival presentation. *Ophthalmology*. 1987;94:72–77, with permission.)

exenteration was performed. Evidence of metastases did develop 4 months later followed shortly thereafter by death.

Among the case reports, there are several where the lesion was imaged by CT scan. However, there was nothing specific that would differentiate the image of angiosarcoma from other enhancing vascular masses. The secondary orbital angiosarcoma described by Lopes et al. (1999) was a lytic lesion within the greater wing of the sphenoid bone. Pain was not a symptom in this presentation as opposed to the usual presence of pain with a soft tissue tumor. With 16 months of follow-up, there has been no evidence of local or distant disease following radical surgery with exenteration.

These lesions are commonly an angry red in color with poorly delineated or invasive margins, all befitting a malignant vascular neoplasm. Microscopically, three patterns are usually described, although these are not always clear-cut (see Figs. 10.26 and 10.27). The *angiomatous type* is characterized by congeries of dilated vascular channels lined by intensely staining, pleomorphic endothelial cells. The cells tend to proliferate in intravascular clumps, which fill the lumen and distort the contour of the vascular space partially. In the *spindle-cell pattern*, the vascular spaces are anastomosing and have a less recognizable endothelial lining. The basement membrane material surrounding these channels may be incomplete. The spindle cells form a loose, sponge-like network interspersed with circular or oval collections of cells in a pseudoluminal arrangement mimicking a true vascular channel. The *undifferentiated type* is composed of pleomorphic, polygonal-shaped, mitotically active cells proliferating in a papillary fashion. Some cells with an eosinophilic cytoplasm suggest an epithelioid metaplasia. Special stains for reticulin and elastin such as van Gieson's stain may help in defining the vascular nature of the undifferentiated type.

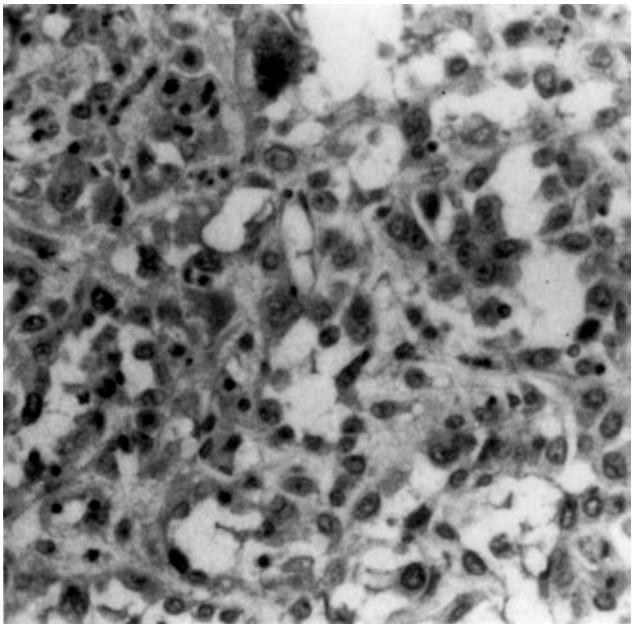


Figure 10.26 Angiosarcoma: Vascular channels lined by hyperplastic, pleomorphic endothelial cells. Specimen is from the liver (×375). (From Ashley DJB. *Evan's histological appearance of tumours*. 4th ed. Edinburgh: Churchill Livingstone; 1990. p 95, with permission.)

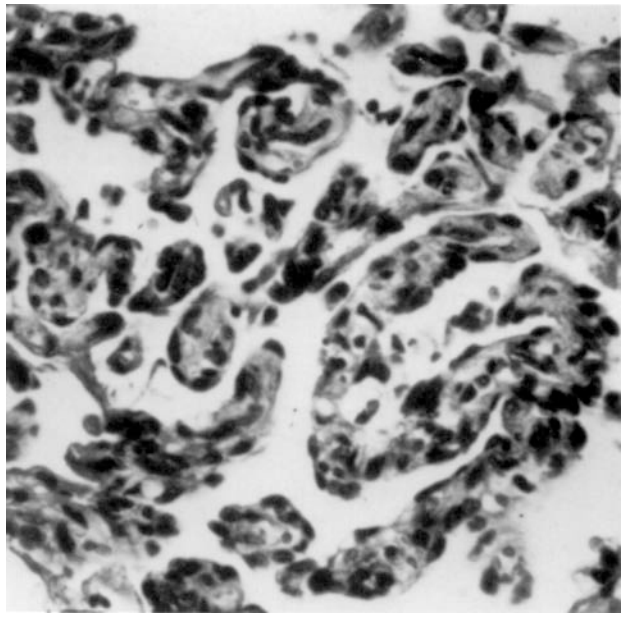


Figure 10.27 Angiosarcoma: Typical papillary complex of vascular channels lined by pyknotic malignant cells (×400). (From Azar HA. *Pathology of human neoplasms*. New York: Raven Press; 1988, p 200, with permission.)

Ultrastructurally, in the better differentiated tumors, the cells display the features of normal endothelium, namely, tight intercellular junctions, pinocytotic vesicles, occasional cytofilaments, and a partial investing basal lamina along the antiluminal border. Although Weibel-Palade bodies are characteristic of normal endothelium, they are present in only small numbers in angiosarcoma. Immunohistochemically, the usual marker for endothelial cells, namely, factor VIII-AG, varies from cell to cell and tumor to tumor. *Ulex europaeus* I lectin is more sensitive in recognizing endothelial differentiation but less specific as it also binds with a number of epithelial tumors.

Because of their invasive margins and aggressive behavior, local excision of the tumor seldom provides lasting relief. Perhaps this is one of the factors contributing to the very poor prognosis of tumors in the apical area of the orbit. Exenteration of the orbit soon after initial diagnosis is probably the preferable management to thwart recurrence and metastasis. Siddens et al. (1999) did manage an anterior orbital lesion around the medial canthus without an exenteration and at 6-year follow-up there was no evidence of recurrent disease. A glance at Figure 10.25 confirms the lethal potential of the tumor. Only a few of the listed patients are living and well. Radiotherapy may be used as a last resort if the patient refuses radical surgery.

INTRAVASCULAR PAPILLARY ENDOTHELIAL HYPERPLASIA

Here we will discuss the first of two tumors classified as *vascular hyperplasia*. Initially, this tumor was regarded as a neoplasm of endothelial cells and named *hémangio-endothélioma végétant intravasculare* by Masson (1923). Subsequent investigators believed that the tumor represented an unusually exuberant proliferation of vascular endothelium as a response to the organization of a thrombus rather than a neoplasm (Font et al., 1983). This seems an appropriate point to discuss this reparative lesion because of it being frequently confused with the preceding angiosarcoma.

The eyelid is a more frequent location of intravascular papillary endothelial hyperplasia (IPEH) (Werner et al., 1997) and in the orbit it is even more infrequent than the rare angiosarcoma. There are six well-documented orbital cases of IPEH in the literature. One of these was about a 20-year-old woman reported by Weber and Babel (1981). The three men described by Font et al. were 41, 55, and 51 years of age, respectively. A 63-year-old woman had a tumor located in an orbital vascular malformation as part of a limited Sturge-Weber syndrome (Hofeldt et al., 1979) and the sixth case was associated with bilateral orbital varices (Shields et al., 1999).

In all six cases the reparative process involved a vein. So the lesion grossly showed hues of purple, blue, and black. This differs from the bright red color of the angiosarcoma. The wall of the vein, in fact, is the circumscribed wall of the lesion. However, in the case reported by Weber and Babel, part of the wall was breached. The unencapsulated portion of the mass was infiltrative, eroded the lateral wall of the orbit, and extended into the temporalis fossa of the patient. This trait of bone resorption is remindful of the behavior of the organizing hematoma of the orbital frontal region discussed in Chapter 4. The organizing hematoma shares the infiltrative and progressive self-perpetuating mannerisms of IPEH described by Weber and Babel; both lesions represent a reaction to blood products. The organizing hematoma is a response to extravascular blood and IPEH represents a reaction to an intravascular thrombus.

It is the location of the mass within a vascular lumen that is a useful point in distinguishing the tumor from angiosarcoma.

With light microscopy, the low-power appearance of IPEH resembles angiosarcoma. In both lesions, there are intraluminal endothelial cells that proliferate in sheets, fronds, trabeculae, or in a papillary manner. However, in a high-power view of IPEH, the endothelial cells are uniform in staining and configuration and lack mitotic activity. Other features such as fibrin deposition, degree of collagenization, and the inflammatory cell component depend upon the age of the thrombus. Ultrastructurally, the basic features are those of well-differentiated endothelial cells with abundant micropinocytotic vesicles, tight junctions, and occasional intracytoplasmic Weibel-Palade bodies.

The triggering event of venous thrombosis tends to make the onset of proptosis rather sudden. Even so, this is not a dependable differential in the tumor's clinical presentation, because patients with angiosarcoma may also have a fairly rapid onset. On CT scan, these lesions do not show any pattern that would differentiate them from other well-circumscribed, enhancing orbital masses.

Local excision of the thrombosed vein seems sufficient. Font et al. did not observe any recurrence of tumor in their three cases over a follow-up interval of 37 to 57 months.

ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA

This lesion, like the preceding intravascular papillary endothelial hyperplasia, has been considered a benign neoplasm of vascular structures and has been confused with angiosarcoma (Jakobiec and Font, 1986). In a like manner, subsequent study has suggested that angiolymphoid hyperplasia is a reparative process or an inflammatory lesion rather than a neoplasm. We have had no experience with this lesion in the orbit, but on the basis of the descriptive literature, we would not consider it a neoplasm. Even so, angiosarcoma, intravascular papillary endothelial hyperplasia, and angiolymphoid hyperplasia share a common feature of an abnormal proliferation of endothelial cells. These considerations prompt us to discuss angiolymphoid hyperplasia at this point—while the characteristics of the two preceding tumors are fresh in mind—rather than relegating the discussion on the lesion to a later chapter on idiopathic inflammatory lesions (pseudotumors).

Historically, Kimura's name has been associated with what is now considered a clinical entity. Kimura et al. (1948) described a benign disorder manifested clinically by single or multiple, inflammatory, angiomatous papules or nodules involving, primarily, the skin of the face and scalp that were associated with blood eosinophilia and lymphadenopathy peculiar to Orientals. Later, when the entity's racial and geographical distribution was expanded, differing names were proposed as a substitute for *Kimura disease*. Also, clinical features that were believed appropriate by subsequent investigators were added or subtracted from the original description. The present name *angiolymphoid hyperplasia with eosinophilia* was proposed by Wells and Whimster (1969). Although the cause of the tumor remains unclear and its classification is not settled, we are mainly interested in its orbital manifestations.

The report of Hidayat et al. (1983) best summarizes the tumor's present orbital status. In their review of eight patients, the orbit was involved in five. An orbital case previously reported by Bastad and Pettersen (1982) was included in Hidayat et al's list of five cases. The list comprised four men and one woman with an

age range of 38 to 57 years. Interestingly, in two men the orbital lesion was attached to the periorbita near the superior orbital rim. In four of the patients, where the presenting symptomatology was known, proptosis was present. Subsequently, Smith et al. (1988) reported a 64-year-old man whose tumor was thought to be an orbital recurrence of an intraocular melanoma that was enucleated 10 years previously. Instead, an angiolymphoid hyperplasia was found adjacent to the polymethyl methacrylate orbital implant. Most of the above mentioned patients did not have peripheral eosinophilia. Another case, that of Dr. Paul Ocken of Warren, New Jersey, was a 55-year-old woman with proptosis and massive soft tissue involvement of the right orbit, which was illustrated in Shield's text (1989). Other than the histopathologic findings, no further details of this case were stated. Total cases are still too few in number to judge any common pattern of imaging by CT scan. Another term, *epithelioid hemangioma*, was introduced in 1983 to describe a usual benign condition of endothelial cell proliferation (Enzinger and Weiss, 1983). While many features of this condition overlap with Kimura disease, the following points of distinction were noted by McEachren et al. (2000). Kimura disease occurs almost exclusively among Asian men, presents as lymphadenopathy with or without an inflammatory mass, and is almost always accompanied by increased serum immunoglobulin E and blood eosinophilia. The lesions themselves generally range in size from 3 to 10 cm, and there may be an associated nephrotic syndrome. Histopathologically, there are dense lymphoid aggregates with prominent germinal centers with adjacent thin-walled postcapillary venules and prominent eosinophilia in the inflammatory infiltrate. Epithelioid hemangioma occurs in all races, has smaller lesions and is less likely to be associated with impaired renal function or show systemic hematologic changes. The main distinguishing feature between these two entities is the histopathologic nature of the vascular changes. The attenuated endothelial cells of Kimura disease are pale and lack both dense hyaline cytoplasm and cytoplasmic vacuoles, and the muscular layer is not involved. Interstitial fibrosis is usually insignificant. The prognosis of epithelioid hemangioma is good and recurrence after surgical excision is approximately 33% although spontaneous regression has occurred. In the two cases of McEachren, one recurred after surgery and the other did not.

Grossly, the tumors have been described as red, tan-brown, and brown. Most of them are said to be circumscribed, but Hidayat et al. described two orbital cases with an inflammatory infiltrate extending into the adjacent orbital fat. The basic histopathologic feature is a rather exuberant proliferation of small vascular channels lined by enlarged endothelial cells that may form cell clusters extending into the luminal space. In some vessels, the lining cells have an epithelial appearance. In some specimens, medium-sized arteries show fragmentation of their internal elastic membrane and destruction of the smooth muscle cells in their medial layer. Serial sections show intramural neovascularization. Interspersed among the proliferating vessels is a dense infiltrate primarily of eosinophils with varying number of lymphocytes, mast cells, histiocytes, and plasma cells. It is this infiltrate that differentiates this lesion from angiosarcoma. None of the lesions are mitotically active.

The preferred treatment is complete excision. There are no recurrences reported among the few orbital cases so managed.

ANGIOMYOMA (VASCULAR LEIOMYOMA)

Stout (1937) introduced the term *vascular leiomyoma* to describe a smooth muscle tumor with a prominent vascular component that occurs in situations other than the skin. Within the orbit, this benign solid tumor probably arises from the walls of small orbital veins. In the older literature, this tumor was called a *venous hemangioma* or a *hemangioleiomyoma*. Such terms emphasized its vascular rather than smooth muscle origin.

The tumor is equally as rare as several of the other vascular tumors mentioned in this chapter. Sanborn et al. (1979) counted 12 cases up to the time of their report. Only a few additional cases have been reported. Most of these tumors occur in an age range of 5 to 45 years of age and have no sex predilection. Our single case (Henderson and Harrison, 1970) was that of a 9-year-old girl. We have encountered no other cases since. Most recently Gündüz et al. (2004) reviewed the reported leiomyomas but none were reported as "vascular."

In general, the presenting clinical picture of this neoplasm is a slowly progressive proptosis or displacement of the eye of several months' to several years' duration. As a rule, there is negligible interference with ocular functions unless the mass is located near the back wall of the eye or on an extraocular muscle. The tumor may occur anywhere in the orbital space. Some patients may note intermittent episodes of pain or discomfort, a feature not common to other benign tumors of slow growth. Such discomfort, if present, is attributed to the vascular makeup of the lesion. In our single patient there was intermittent enlargement of the orbital mass associated with exercise. The imaging pattern by CT scan has not been well studied, other than that the lesion appears well circumscribed. Some tumors, usually of longer duration, may show some calcification. The latter may be the delayed result of brief episodes of intralesional hemorrhage.

Histopathologically, there are two principal patterns Lattes, 1981. In one, there are compact bundles and fascicles of spindle cells separated by minimal columns of interstitial collagen. Thin streamers of reticulin tend to run parallel to the spindle-cell fascicles. When the spindle-cell bundles are cut in cross section, obliquely, as well as in parallel

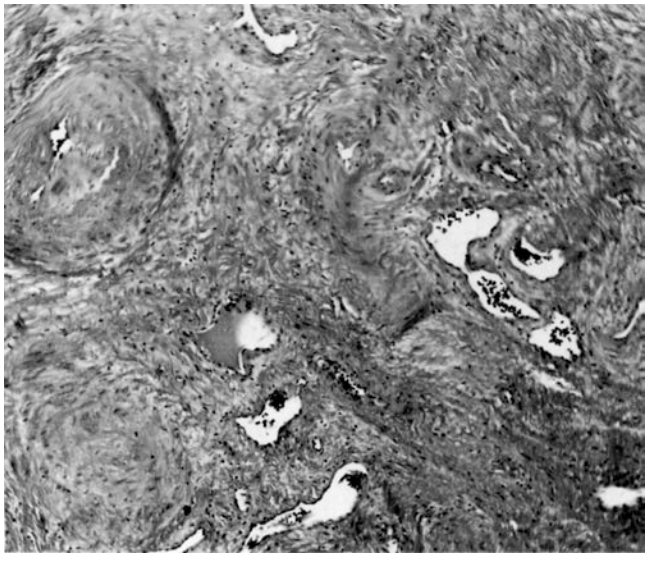


Figure 10.28 Angiomyoma: Principal tissue is smooth muscle, apparently arising from outer muscular coats of prominent, thick-walled vascular channels. The interlacing bundles (*lower left*) suggest the storiform pattern of fibrous histiocytoma (×60).

rows, the tumor has an interlacing appearance suggestive of the storiform pattern of fibrous histiocytoma. Thin-walled, empty, small vascular spaces are sparsely scattered throughout these compact cellular areas.

In the other type, vascular channels are more prominent, and smooth muscle cells show a looser arrangement. The interstitial collagen is more prominent, and the reticulin tends to spiral and curl around the cells in a more irregular arrangement, suggestive of hemangiopericytoma. Here and there, the cells will stream and swirl away from a thick-walled vascular channel.

The nuclei are rod- or cigar-shaped, vesicular, with small, single nucleoli and may show some degree of palisading. The cytoplasm is slightly eosinophilic and contains the fine, discrete myofibrils that are the diagnostic features of this tumor. In both cellular patterns there may be small loci of a myxomatous stroma and calcium deposition. Figures 10.28 and 10.29 illustrate some of these features.

If the thin myofilaments cannot be demonstrated with suitable stains, ultrastructural study is necessary. Here, the cytoplasmic myofilaments will be seen in addition to fusiform dense bodies (probably modified Z-bands), micropinocytic vesicles along the cell membrane, a well-defined basal membrane, and a few cell junctions.

Grossly, the tumors may have a gray to gray-tan color and be partially lobulated.

The preferred management is complete excision of the tumor. Although the lesion is encapsulated, it tends to attach to nearby structures such as periorbita, extraocular muscle sheaths, optic nerve sheath, and the superior orbital fissure. This trait differs from the usual isolated, benign, encapsulated orbital tumor and may interfere with an intact removal of the vascular leiomyoma. The tumor tends to recur, which emphasizes the importance of complete excision. A 31-year-old woman reported by Jakobiec et al. (1975) experienced two recurrences in the 13-year period following initial orbitotomy. One recurrence was treated with radiotherapy. Intracranial extension occurred 2 years after final exenteration. Complete excision was performed in our single case. There was no recurrence over a 10-year follow-up. Radiotherapy is not recommended, because the tumors tend to be radioresistant.

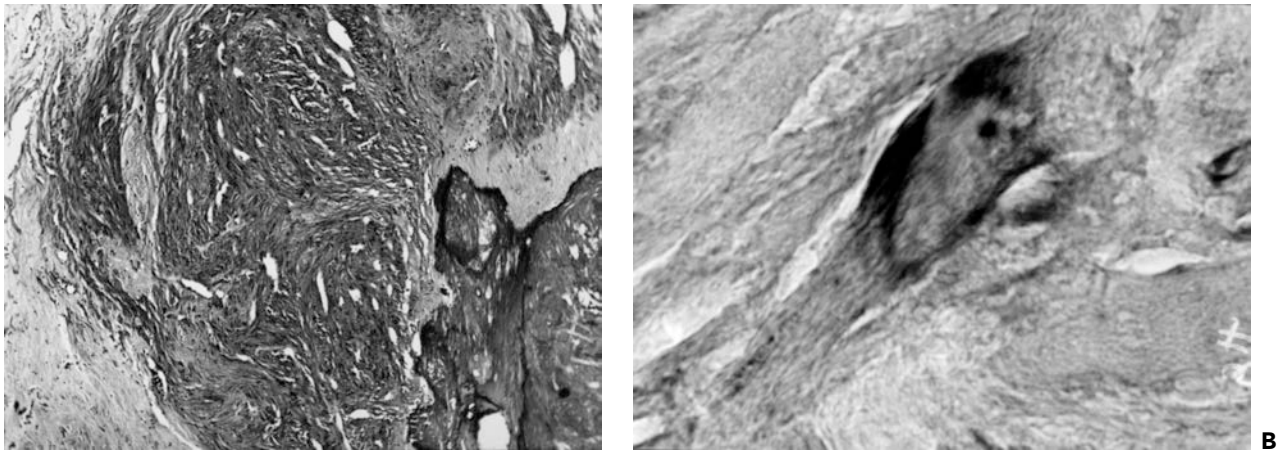


Figure 10.29 Angiomyoma. **A**: Interlacing bundles of smooth muscle cells stream from wall of irregular vascular spaces lined by endothelium; the lighter staining areas are connective tissue; the darker, calcification (×55). **B**: Fine, discrete, longitudinal striations (myofibrils) in section of myoma (phosphotungstic acid and hematoxylin; ×1,200). (From Henderson JW, Harrison EG. Vascular leiomyoma of the orbit: Report of a case. *Trans Am Acad Ophthalmol Otolarygol*. 1970;74:970–974, by permission of the American Academy of Ophthalmology and Otolaryngology.)

LYMPHANGIOMA

In the past decade or so, some studies have suggested that lymphangioma may be related to venous malformations or represent a modified form of orbital varix. Nevertheless, we include lymphangioma in this chapter because, not infrequently, there is a significant admixture of blood capillaries in the tissue specimen. However, in such cases, the clinical behavior is that of a lymphangioma rather than a capillary hemangioma. This warrants its consideration as an entity separate from other related hemangiomas. This confusion, on a morphologic basis, was addressed by Harris (1999) wherein he suggested that orbital venous anomalies, specifically lymphangiomas, be reclassified on the basis of their hemodynamic relationships. This is meant to emphasize features most germane to their management. They can be grouped into categories with no flow, venous flow and arterial flow lesions.

Technically it is benign but sometimes so cantankerous in behavior and so perverse to management that a less bland designation would be more appropriate. It may occur in the eyelid, pop up in the conjunctival fornix, appear on the epibulbar surface of the eye, or conceal itself in the orbit, either as a single lesion or a diffuse tumor in a combination of these sites. Its orbital presence is most frustrating to the ophthalmologist who must manage such an affair, and its conjunctival and epibulbar location is cosmetically disabling to the patient or a parent. The question of whether lymphangioma is a neoplasm, a choristoma, or a mixture of both is not settled.

Incidence

Incidence statistics relating to orbital lymphangiomas are variable because of the inclusion of lesions in the ocular adnexa in the analysis. Our own series is subject to this discrepancy because in 9 of our total 27 lymphangiomas an adnexal lesion was present that seemed to be an extension of a larger orbital tumor. The remaining 18 cases were all localized to the orbit. Twenty-six of the 27 cases underwent surgical excision and histopathologic study of the orbital mass; the remaining patient had excision of tissue from the temporalis area that was contiguous with the orbital lesion. None of our 27 cases were operated for cosmetic correction of an adnexal lesion.

Our 27 cases constitute 1.5% of our series total of 1,795 orbital tumors (Table 3.3) and represent 4% (27 out of 672) of the primary tumors of our series. The sex incidence is nearly equal, 13 men and 14 women. The right orbit was affected in 12 cases and the left orbit in 15 cases. Fifty-two percent (14 out of 27) of the lymphangiomas occurred in the first decade, and 85% (23 out of 27) occurred in the first three decades. The age range at time of presentation ranged from 8 months to 71 years. Only four patients were older than 28 years of age.

This age range, however, is subject to misinterpretation. It does not necessarily approximate the age at onset. One of our patients who presented with proptosis of 4 mm at the age of 33 years illustrates this discrepancy. The proptosis had been present only for 3 weeks and was associated with headache around the affected right eye. The vision in this eye had always been poor. This amblyopia was attributed to a prominence of the eye in infancy. The prominent eye eventually receded. Surgical intervention at the age of 33 years revealed a multiloculated tumor in the retrobulbar space that contained a so-called "chocolate cyst." The mass was partially excised resulting in relief of headache and proptosis. Our 71-year-old male patient had first noted a prominent eye at the age of 61 years. Over the ensuing 10 years, it gradually progressed and we had been following it up for 3 years prior to surgery. Another patient aged 28 years, with 6 mm of proptosis was said to have had a prominent eye since the age of 3 years; such cases suggest that incidence data would be more valid if the age of onset could be accurately pinpointed.

Another series that is of comparable size to ours in the recent literature is that of Rootman et al. (1986). In 18 patients with lymphangiomas of the orbit and adnexal structures, six occurred posterior to the orbital septum. The age range of the latter was from birth to the age of 34 years. Another comparable series is that of the 19 cases reported by Iliff and Green (1979). The age at *onset of proptosis* ranged from birth to 59 years of age. This series differed from ours in the prevalence of the tumor in women in a ratio of 3:1. Fourteen cases involved the right orbit and five cases the left.

Clinical Features

The symptomatology of lymphangioma parallels that of capillary hemangioma in infants. Features common to both are similarities in color and consistency, a tendency of the tumor to fluctuate in size with changes in posture or straining, displacement of the eye in a vertical or horizontal meridian, some degree of ocular motility impairment, the presence of multicentric lesions, and poorly defined swellings of the eyelids and upper cheek on the side of the tumor.

However, there are several differences. With hemangioma, "strawberry" marks may be found in the scalp, neck, face, and upper trunk. With lymphangioma, there are vascular tumors of the soft tissues of the cheek, forehead, and bridge of nose; straw-colored cysts on the epibulbar surface of the eye and the conjunctival fornix; and mucous membrane of the roof of the mouth (see Fig. 10.30). Also, with lymphangioma there may be intermittent and transient swelling of the orbital mass associated with episodes of upper respiratory infection. These patients are often given antibiotics for a presumed cellulitis.

Although both tumors may reach considerable size in early life, the course of the hemangioma is much more rapid

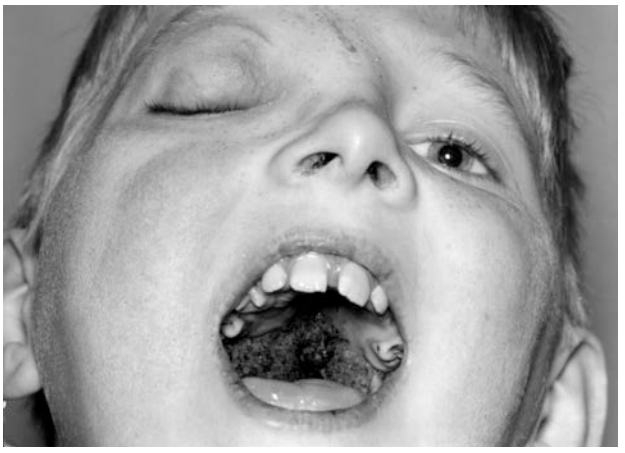


Figure 10.30 Lymphangioma: Tumor in roof of mouth associated with lymphangioma involving right upper eyelid, forehead, and orbit in a 2-year-old boy with symptomatology since birth.

and florid. We have already noted how the rapidly growing hemangioma may push itself out of the orbit rather than cause proptosis of the eye. The growth of a lymphangioma may also reach an extreme degree but is less rapid than hemangioma and is associated with proptosis more often. Consequently, the infant with an orbital hemangioma has a more alarming course and is usually seen in consultation before 6 months of age. Conversely, a lymphangioma that has been present since birth may dawdle in growth, so an ophthalmologist may not see the patient until the latter part of the first year or after. Figure 10.31 illustrates the slower evolution of such a lymphangioma that was first evaluated at the age of 18 months. In general, patients with lymphangioma do not seem to suffer the degree of visual disability that occurs with hemangioma of similar size.

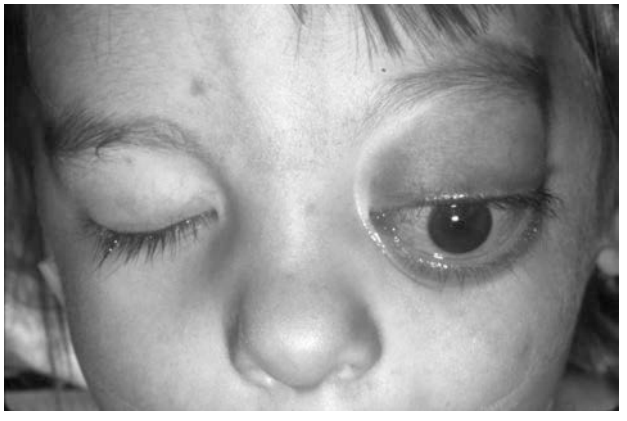


Figure 10.31 Lymphangioma: Bluish red discoloration of left upper eyelid associated with marked proptosis and displacement of left eye due to a slowly expanding orbital mass of 1-year duration in an 18-month-old girl. The appearance is similar to an orbital rhabdomyosarcoma in the same age-group except this tumor has a much more rapid evolution than lymphangioma.

Pain does not seem to be a prominent feature in the evolution of these tumors in young people. However, pain is a manifestation of and a clue to a sudden intralesional hemorrhage. In such cases, the pain or headache is severe and coincides with the formation of a so-called hemorrhagic "chocolate cyst" (Eiferman and Gushard, 1986). In our experience, these intralesional hemorrhages occur more often in an older child or an adolescent, wherein an orbital mass either has long been known but not diagnosed or has been subject to one or more surgical excisions. These sudden, severe hemorrhagic episodes seem more prevalent in retrobulbar tumors than in those located in the anterior orbit or adnexa. If these patients with severe pain and proptosis can be examined further, a reduced visual acuity associated with an afferent pupillary defect will be noted; and ophthalmoscopy may reveal choroidal folds and/or some edema of the optic disk.

The surprising discovery of orbital lymphangiomas in adults over 30 years of age lends credence to the belief that lymphangiomas do not spontaneously regress. It is puzzling how these usually aggressive tumors may remain occult for so long a time. In the pre-CT scan era, one of our patients, a 46-year-old woman, had developed a slowly progressive proptosis of her left eye over a 4-year period associated with almost daily headache around the affected orbit. An asymmetric Graves orbitopathy was thought to be the basis for her 4-year problem. With a lateral orbitotomy, a dark red, encapsulated tumor measuring 23 mm in its longest diameter was completely removed from the retrobulbar space. This lymphangioma was partially attached to optic nerve sheath just posterior to the eyeball. Dryden et al. (1985) encountered a 31-year-old man with severe pain in the left orbit of 12 hours' duration associated with 5 mm of proptosis. CT scan showed a retrobulbar, well-circumscribed, isodense mass. On surgical removal the tumor proved to be a lymphangioma. On the basis of preoperative imaging, two of our adult lymphangiomas were initially believed to have cavernous hemangiomas. In our 71-year-old male patient (see Fig. 10.32), at the time of surgery, a typical purple lesion was encountered and initially it was possible to dissect around the lesion. The plane of dissection was more difficult to follow along the deep aspect. Histopathologically, it was a lymphangioma with cavernous differentiation. Selva et al., 2001 noted similar findings.

In the earlier years of our study, we were under the impression that growth of lymphangioma tended to slack off by the age of 30 years. We assumed that the tumor became less active. In retrospect, this arrest may be due to slow encapsulation of tumor by the host with a resultant barrier to further tumor expansion.

Pathology

With low-power magnification, the lymphangioma is principally a collection of variable-sized, bloodless channels,

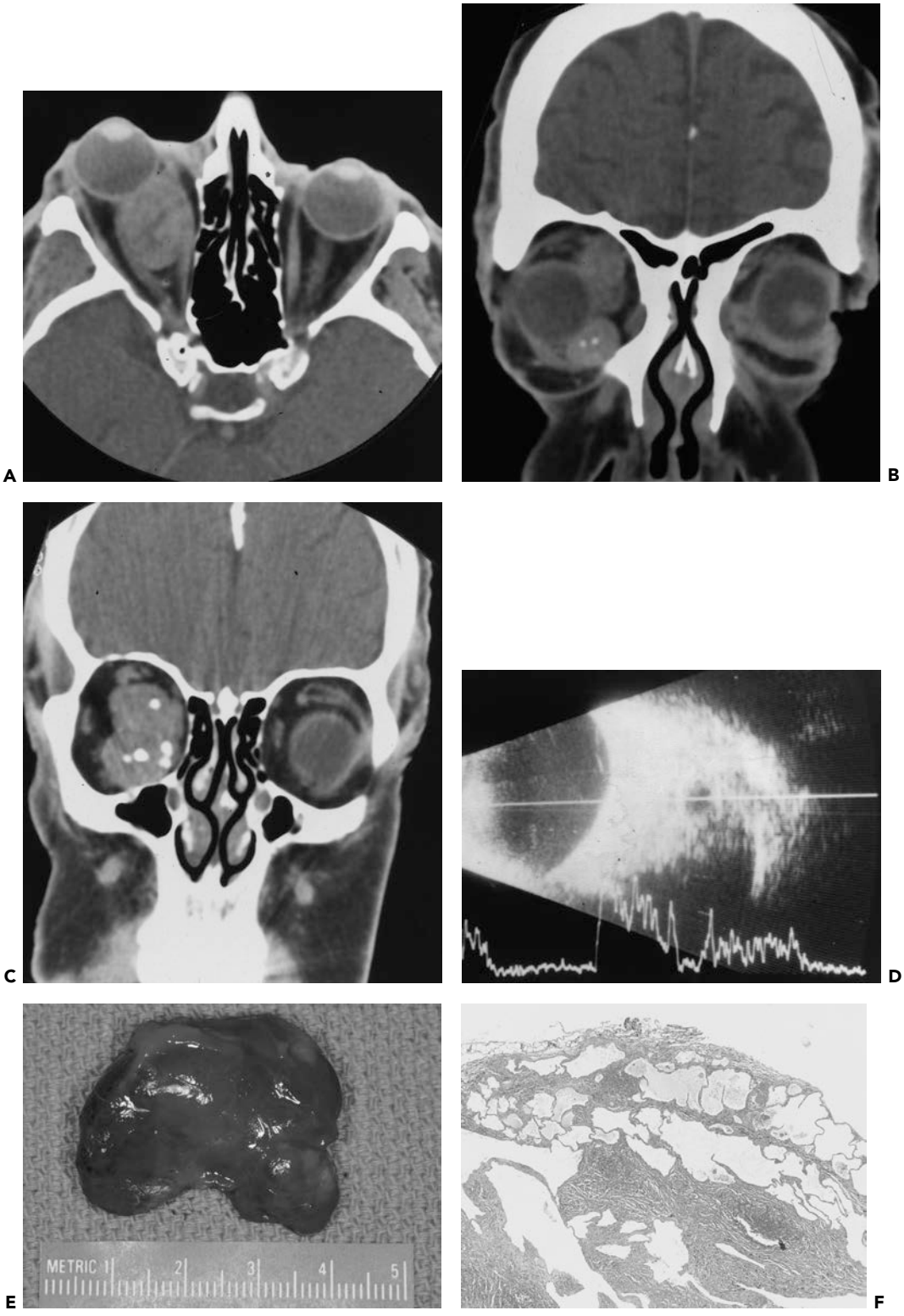


Figure 10.32 Axial computed tomography scan **(A)** in a 71-year-old male with cavernous-type lymphangioma reveals intraconal mass displacing optic nerve laterally. Mass appears well demarcated but has some ''lucent'' areas within the mass. Coronal computed tomography scan **(B)** and **(C)** show large medial mass with intralesional calcium phleboliths. Mass appears to have cystic component especially noted on anterior image **(C)**. B-scan ultrasonography **(D)** shows one of many small cysts within the lesion. A-scan vector through the cyst shows anechoic area. Gross specimen removed intact **(E)** resembles cavernous hemangioma. Microscopic image **(F)** reveals typical lymphangioma with solid and cystic component. The tumor is composed of multiple endothelial lined channels of various size and contour. Among the channels there are collections of lymphocytes in clusters.

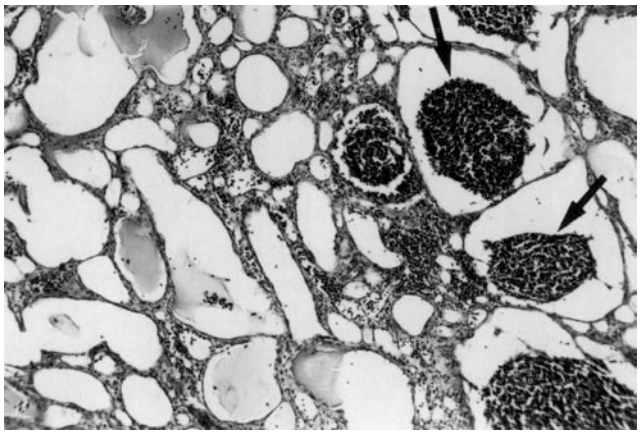


Figure 10.33 Cavernous-type lymphangioma. Vascular spaces are lined by flattened endothelial cells, some of which contain amorphous-appearing lymph. Clumps of lymphocytes (*arrows*) invaginate the thin-walled lymph channels (×100).

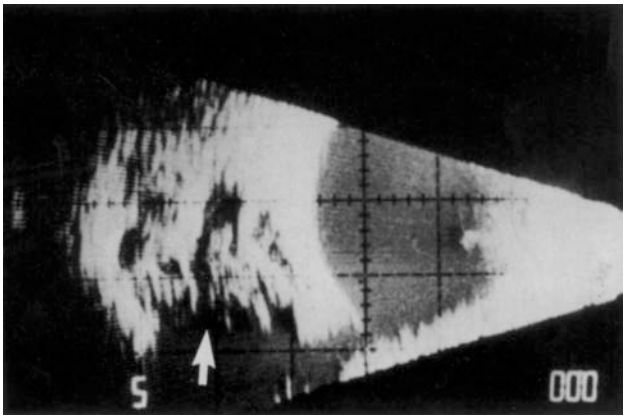


Figure 10.34 B-scan ultrasonogram of diffusely infiltrating orbital lymphangioma (*arrow*) containing multiple fluid-filled cysts. (From Haik BG, Ellsworth RM: Pediatric orbital tumors. In *Pediatric ophthalmology and strabismus. Trans new orleans acad ophthalmol.* New York: Raven Press; 1986:89–109, with permission.)

which, according to size or contour, are described as capillary, cavernous, or cystic, depending on the dominant pattern. All these channels are lined with a single layer of benign, somewhat attenuated, endothelium. With higher magnification the small, irregularly contoured spaces appear delicate. The walls of the cavernous and cystic spaces are more structured, and the spaces are patulous. Some of the small and medium-sized channels may appear empty, but most of them will contain a faint pink staining, amorphous collection of lymph. Lymphoid aggregates that have invaginated the thin wall of the lymph spaces may appear as intraluminal nodules (see Fig. 10.33). These nests of lymphocytes will also be seen in the stroma of the tumor. The larger cyst-like spaces may contain erythrocytes or blood breakdown products, which are residues of prior intralesional hemorrhage.

In tumors of recent origin, the stromal framework is delicate, sparse, and reasonably acellular. In older tumors, and particularly those that have been subject to surgical trauma, the stroma is thicker, contains aggregates of lymphocytes, and shows variable degrees of fibrosis. Most of the lymphangiomas are unencapsulated, infiltrating tumors, but, in long-standing cases or in adults, the lesion may be encapsulated.

Ultrastructurally, lymphangiomas differ from capillary hemangiomas in showing endothelial gaps in their channels, fragmented basal lamina, and absence of mural pericytes.

There are no reports, to our knowledge, of malignant transformation of an orbital lymphangioma.

Imaging Aspects

The characteristics of lymphangioma, which principally determine their imaging pattern, are the tendency to expand beyond the usual fascial planes and compartments of the orbit, a scanty interstitial tissue, and numerous vascular channels of variable size. With ultrasonography they show good sound transmission with numerous anechoic spaces corresponding to medium and large-sized vascular channels (see Fig. 10.34).

Its noncompartmentalized growth is well seen with CT scan, but the sponge-like structure of the tumor is less well imaged than with ultrasonography. The lesions show little or no enhancement with contrast, which differs from capillary hemangioma in the same age-group. The degree of enhancement of a lymphangioma may be proportional to its age, the content of admixed capillaries, and the number of intralesional hemorrhages and surgical manipulations to which it has been subjected. The large, cystic spaces in some multiloculated tumors may show some rim enhancement (see Fig. 10.35). An older lesion may show a spot of calcium or even a phlebolith.

The heterogeneous pattern of lymphangioma is evident with MRI (see Fig. 10.36). The lymph-containing spaces tend to be hypointense. However, if there has been recent hemorrhage into one of the cystic spaces, this will be hyperintense on T_1-weighted sequence because of the paramagnetic properties of blood breakdown products (Saint-Louis et al., 1986) and there may also be visible fluid–fluid levels (Kazim et al., 1992). In large aggressive lymphangiomas where surgery is almost mandatory and excessive bleeding is a likely accompaniment, MRI can show the tumor's blood supply. Such vessels will show a flow-void artifact, which appears as dark tubular or serpiginous structures against the high intensity of the background tumor or orbital reticulum (Bond et al., 1992; Haik et al., 1987).

Enlargement of the orbit is often noted, but this is not specific for lymphangioma. Many other expanding orbital tumors in infancy and childhood will show this picture.

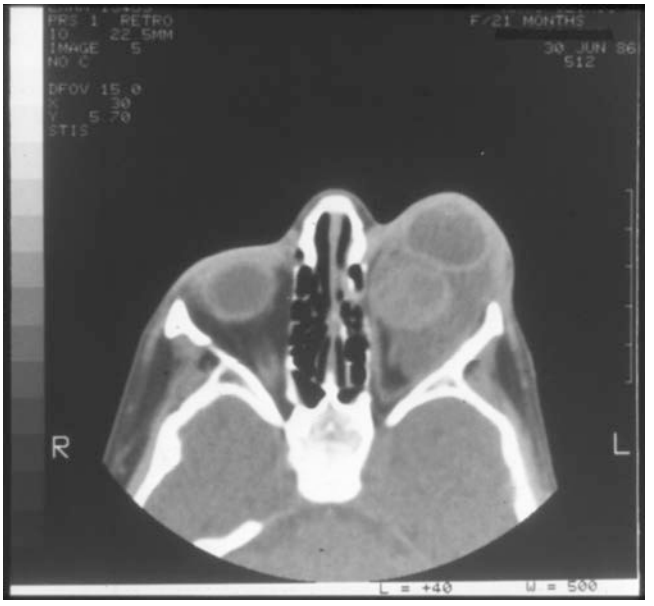


Figure 10.35 Axial computed tomography scan of patient in Figure 10.31. A large lymphangioma of mixed density fills the superoposterior portion of left orbit causing medial and inferior displacement of optic nerve. The tumor showed little enhancement with contrast.

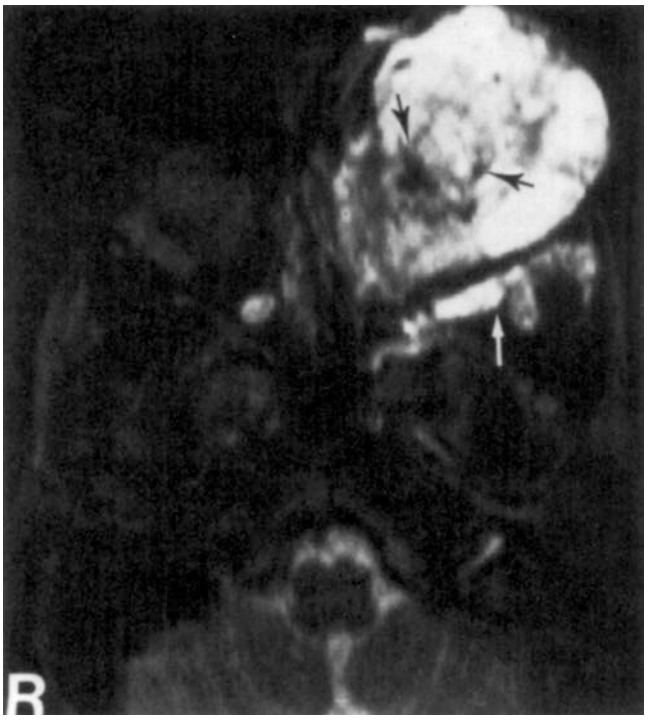


Figure 10.36 Axial magnetic resonance image at TR=2,000 and TE=90 of large heterogeneous lymphangioma filling left orbit. Stromal spaces are hypointense (*black arrows*). Infratemporal fossa component (*white arrow*). (From Saint-Louis LA, Haik BG, Amster JL. Magnetic resonance imaging of the orbit and optic pathways. *Int Ophthalmol Clin.* 1986;26(3):169–185, with permission.)

Treatment and Prognosis

Fourteen (52%) of our 27 patients were followed up for a period of 8 years or longer. The mean duration of observation of these 14 patients was 18 years. This follow-up mean is probably the longest in the literature considering the size of the sample. Analysis of this cohort provides considerable insight into what may or may not happen to patients with orbital lymphangioma over the long term.

Perhaps, one of the most important observations concerning lymphangiomas is their association with noncontiguous intracranial vascular anomalies. Katz et al. (1998) described seven of 25 patients (28%) with orbital lymphangiomas with intracranial vascular anomalies, one of whom sustained an intracranial hemorrhage. Diffuse orbital lesions with superficial and deep components, orbital bony expansion, intraconal and extraconal components, and involvement of the superior orbital fissure were common in affected individuals. This was the case with two of our patients. The first was a 3-year-old girl who was born with obvious orbital and forehead swelling that was progressive. The ipsilateral palate was also involved. Investigations led to the discovery of a Vein of Galen aneurysm for which she underwent numerous invasive procedures. The forehead and orbit were debulked and the intracranial disease did not require any additional treatment. The second patient was an 8-month-old girl who was also born with a swollen orbit in association with a forehead mass. In addition to lymphangioma being present on the ipsilateral palate, there was also lymphangioma in the cavernous sinus and middle cranial fossa. Kasabach-Merritt syndrome with intracerebral hemorrhage has also been reported (Vachharajani and Paes, 2002).

A brief summary of the clinical course of several of these patients illustrate the variables in the behavior and management of this tumor better than a drawn out, detailed report of all cases. A 17-year-old girl with a retrobulbar lymphangioma underwent successive excisions of tumor at 2 months, 3 years, 6 years, 8 years, 9 years, and 17 years of age. Vision in the affected eye was 20/70 at the time of the last surgery. A complete removal of the lesion was not accomplished by the six surgeries in 17 years. It was anticipated that this patient would continue to have regrowth of tumor in the future. This case illustrates the persevering regrowth of tumor throughout infancy, childhood, and adolescence with a discouraging prognosis in adulthood.

A second case was a 19-year-old girl who had undergone two surgeries for an orbital lymphangioma by the age of 3 years. At the age of 12 years, there was only 2 mm of residual proptosis but a 3 mm downward displacement of the affected eye secondary to masses in the superior conjunctival fornix and upper eyelid. Vision was 20/60 in the affected eye. Five surgeries followed in the next 7 years to excise the tumor in the ocular adnexa and repair

surgical sequelae such as corneal scarring, symblepharon, and strabismus. This case illustrates the relative arrest of an orbital lesion in childhood but the harassing morbidity consequent to the cosmesis of adolescence. The prognosis for the latter is poor.

A third example was a 28-year-old man with slowly progressive proptosis of left eye over a 25-year period. The proptosis of the affected eye was 6 mm. A retrobulbar lymphangioma was partially excised. Eighteen years later there was no apparent regrowth, and the vision was 20/25 in the left eye. This case illustrates an unusually benign course.

A fourth example is that of a 4-year-old boy who had a "swollen eye" during the previous 6 months and had a 2-day history of sudden onset of more swelling with pain. The vision was normal and 3 mm proptosis was present. The proptosis increased to 7 mm with Valsalva maneuver.

Neuroimaging showed a diffuse intraconal and extraconal mass that surrounded the optic nerve. B-scan ultrasonography displayed cysts typical of a lymphangioma. Surgical therapy was deferred and over the ensuing 3 years, there were three similar episodes that resolved spontaneously. At the age of 11 years, he had another sudden onset of pain, proptosis and loss of vision. Because of a severe winter storm, therapy was delayed for a day at which time vision was light perception with an afferent papillary defect, 6 mm proptosis and evidence of a central retinal artery occlusion. Debulking surgery was performed with no return of vision although the pain was relieved. Numerous chocolate cysts were encountered and drainage of bright red blood was also experienced. Intraoperative bleeding was extensive as predicted by the changes associated with the Valsalva maneuver. There have been no further recurrences after 8 years of follow-up.

The last case was that of an 18-month-old girl who developed 8 mm of proptosis over a 7-month period. A retrobulbar lymphangioma was partially excised. Four months later, a second surgical procedure was required for sudden extreme proptosis. Proptosis persisted to such a degree that by the age of 3 years the affected eye was enucleated because of corneal decompensation secondary to exposure. Further orbital tumor was removed at this time. This case illustrates the aggressive behavior of a lymphangioma in infancy with an outcome exactly opposite to the preceding case.

These five cases illustrate the extremes of benign and aggressive types of lymphangiomas, the arrest of an orbital lesion but perseverance of the adnexal tumors, and the nagging morbidity of an orbital lesion from childhood well into early adulthood. These cases underline the inconsistencies in the tumor's behavior and underscore our inability to make specific recommendations regarding treatment.

Inasmuch as radiotherapy, implantation of radon, and intralesional injections of various drugs and chemicals have not proved effective in a limited number of cases, therapeutic options are limited to the type, time, and extent of surgical intercession. The following generalities apply to this knotty problem.

1. Any therapeutic intervention must be tempered by the amount of tumor that can be debulked, vaporized, or excised without doing harm to the functionally important structures in the orbit.
2. It is better to do too little rather than too much at any given therapeutic stage.
3. Therapy in infancy and childhood is preferably deferred until school age except in extreme degrees of proptosis or when the visual axis is obscured by a ptotic upper eyelid.
4. The older the patient is at the time of therapy, the less the frequency of intralesional hemorrhage ("chocolate cyst") and longer the interval before recurrence.
5. Abrupt intralesional hemorrhage associated with painful, severe proptosis is best managed conservatively unless an afferent pupillary defect or a marked ophthalmoplegia is present. These factors have probably more significance and reliability than visual acuity measurement.
6. Cosmetic surgery is probably best deferred to adolescence or adulthood.
7. Surgical excision seems best suited for well-delineated lymphangiomas in the retrobulbar space and inferior orbit.
8. Large, diffuse lymphangiomas are probably best managed with the carbon dioxide laser or the YAG contact laser in staged sequences (Kennerdell et al., 1986).
9. Cryotherapy seems to be a popular method for the handling of cystic lymphangiomas in the conjunctival fornix and epibulbar surface of the eye, but the resulting scar tissue may outweigh the putative benefits of such therapy.
10. Multiple management procedures of whatever types may cure a minority of cases of lymphangioma but leave in their wake a new problem, namely, how many surgeries will be required to remove the scar?
11. None of the above may be of value if the sole reason for therapy is the insistence of a parent or guardian that "something must be done now, not later," to effect a cure (Wilson et al., 1989).

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Vascular Malformations 11

Any orbital vascular problem, especially the arteriovenous (AV) communication engenders a good deal of anxiety not only on the part of the patient and the referring physician but also the orbital specialist. The thought of uncontrolled bleeding, be it vigorous or even just a persistent ooze, is not appealing to anyone at any level of training. The tumefactions discussed in this chapter are a heterogeneous group of "abnormalities," "anomalies," "aberrations," "dilatations," "enlargements," and "intercommunications" of established vascular channels that we elect to lump together simply as *malformations*. They are composed, either entirely or in part, of arteries and veins of variable size and in various combinations. We will restrict our discussion to those malformations of nontraumatic origin that may be primarily intraorbital or located in an adjoining space, where their size may alter the dynamics of the orbital vascular circulation. Whether primary or secondary in anatomic type, they produce proptosis or an orbital symptomatology that must be considered in the differential diagnosis of orbital tumors. We once again reference the work of Harris (1999) and Rootman (2003) in the consideration of orbital vascular disease. Rather than discuss morphology, we will classify these tumefactions on the basis of their hemodynamic properties because this is germane to patient management. The classification has three primary categories: No flow, venous flow or arterial flow. The no flow lesion is typified by the lymphangioma; the venous flow lesion is typified by the orbital varix (both distensible and nondistensible variety); and the lesion with arterial flow is typified by the AV malformations or arteriolized veins distal to them.

The nontraumatic malformations comprise 4% (72 out of 1,795) of our total tumor series (Chapter 3). Most are secondary in type and make up 7.6% (56 out of 732) of the group of secondary tumors. They are the fourth most common secondary orbital tumor. There is a strong preponderance among women, outnumbering men in a ratio of 4:1. They occur in all age-groups, but the majority, 68% (49 out of 72), are clustered in individuals over 50 years of age. A future survey of this type, predictably, will show an increase in the number of vascular malformations relative to the total tumors because of the diagnostic capabilities of the newer imaging methods, particularly magnetic resonance imaging (MRI).

ORBITAL ANEURYSM

In this subchapter, we reserve the term *aneurysm* for a vascular dilatation, the makeup of which is entirely arterial. In the orbit, such an aneurysm would involve the intraorbital portion of the ophthalmic artery or one of its branches. Over 40 years ago, the literature was rife with reports of orbital aneurysm, in which diagnosis was chiefly based on clinical findings. In retrospect, many such cases were a mixture of arteries and veins. The advent of angiography differentiated the several types of vascular dilatations. Later, improvements in surgical techniques encouraged exploration and excision of these lesions, further narrowing the diagnosis of aneurysm to only a very few histopathologically proved cases.

In the 1980 edition of our text, this situation was reviewed in some detail. We summarized the cases in the literature in English language, which were confirmed by angiography or surgical exploration, and added three of our own. We estimated that the total of well-studied cases of orbital aneurysm did not exceed 16, including some in the literature in foreign languages, which were not annotated by us. This underscores the rarity of this lesion in the orbit.

We have not seen a new case but there have been three case reports of aneurysms of the ophthalmic artery in the orbital apex in the literature in English language since 1971 (Ogawa et al., 1992; Kikuchi and Kowada, 1994; Ernemann et al., 2002). One of these was in association with a dural AV malformation of the anterior fossa skull base and the authors speculated whether the hemodynamic stress of the fistula had played a role in the genesis of the aneurysm (Kikuchi and Kowada, 1994). Those well-studied cases from the literature that we annotated in the 1980 edition are referenced at the end of this chapter for the interest of new readers who would not have access to the 1980 text, because it has long been out of print.

The three cases from the Mayo survey were all women aged 26, 31, and 63 years, all with the involvement of the right orbit. Diagnosis was made by angiography. The feeding vessel of one aneurysm was surgically ligated with only partial relief of orbital symptomatology; one case was surgically deferred because of left-sided seizures following angiography and was subsequently lost to follow-up; and the third case underwent management of the aneurysm elsewhere.

In the clinical assessment of a case of presumed aneurysm, it is important to keep in mind that the location (orbital or nonorbital) of the aneurysm along the ophthalmic artery may determine the presenting symptomatology. The intraorbital aneurysm is basically a mass lesion chiefly characterized by proptosis. Beyond this symptom, the clinical picture is not well standardized. Ancillary findings are bloodshot eye, impairment of ocular motility, pain or headache on the affected side, pulsation of eye, and subjective or objective bruit. These ancillary signs and symptoms vary in number, severity, and combinations.

The nonorbital aneurysms are located either in the extreme proximal intracranial portion of the artery or in its intracanalicular course. In both, the presenting picture includes visual loss, visual field defects, pallor or atrophy of the optic disk, deep orbital pain, and neurogenic type motility paresis, but no proptosis. In the rare instances in which the entire artery is involved, there may be combinations of both of the above clinical presentations but, more often, the picture is that of the nonorbital aneurysm.

The past management of these lesions included temporary surgical compression, clipping, embolization, ligatures, excision, and conservative observation. The choice depended on the severity of symptoms and the size of the aneurysm.

ARTERIOVENOUS COMMUNICATIONS

Most of the vascular malformations affecting the orbit are due to some abnormal communication between arteries and veins. The most common of these AV communications result from an abnormal flow of blood directly into the cavernous sinus from a defect in the intracavernous segment of the internal carotid artery or indirectly through intervening branches of the internal carotid or external carotid arteries. We will discuss this group first. A discussion of the less common AV communications not based on an arterial communication with the cavernous sinus will follow. In both subgroups, the mechanism of the orbital tumefaction is secondary to a rise in the orbital venous pressure. As noted earlier, we will exclude those cases in which the malformation is due to trauma and will dwell only on those cases of spontaneous type of unknown origin.

Carotid-Cavernous Fistula

Terminology and Classification

Fistula is a term that has long been associated with the high-pressure flow of arterial blood into the cavernous sinus resulting from trauma. Fistula connotes a cleft or break in the feeding artery and is also a suitable term for the direct, spontaneous carotid-cavernous communication. *Dural shunt*, currently, is a popular designation that emphasizes the participation of a plexus of small meningeal vessels in the carotid-cavernous intercommunication, with the understanding that the carotid artery, as it passes through the cavernous sinus, is intact.

Barrow et al. (1985), in an effort to standardize a system for judging symptomatology, management, and prognosis, proposed a classification based on angiographic findings rather than the hemodynamic properties of the carotid-cavernous fistulas. They divided them into four types: Type A, a direct high-flow "shunt" between internal carotid artery and cavernous sinus (there is a defect within the intracavernous carotid artery); type B, an indirect communication involving meningeal branches of internal carotid; type C, an indirect communication involving meningeal branches of external carotid; and type D, an indirect communication involving branches of both internal and external carotid artery systems. The "direct" or the type A defect is associated with an intracavernous sinus carotid artery defect and is synonymous with the carotid-cavernous fistula or the "high-flow" fistula. The indirect fistulas are the types B, C, and D. The intracavernous carotid artery, by definition, is intact. These are the so-called dural fistulas or the "low-flow" shunts. We shall refer to this classification later. This can be further classified as whether the onset was traumatic or spontaneous. The traumatic fistula is primarily the concern of the neurosurgeon, but the spontaneous type is usually seen initially by the ophthalmologist.

Incidence

Fifty-one of our patients are classified in the spontaneous category. Forty-three are women; eight are men, a ratio of approximately 5.4 to 1. The age range is 31 to 84 years with a mean of 62.5 years. Seventy-six percent (39 out of 51) of the cases were clustered in a 24-year age span of 48 through 72 years. The right orbit was involved in 27 cases, the left orbit in 19 cases, and bilateral orbital involvement was present in five patients. Incidence data based on other publications are scant because these reports include a mix of traumatic and spontaneous cases. Two other surveys, each reporting ten cases of spontaneous dural shunts, are those of Newton and Hoyt (1970) and Grove (1984). Both publications cite the prevalence of the fistula in women and the concentration of cases in the sixth and seventh decades of their life span.

Clinical Features

No other tumefactions of the orbit are associated with such a variety of symptoms and signs as the carotid-cavernous fistulas

TABLE 11.1
PRINCIPAL PRESENTING FEATURES OF 51 PATIENTS WITH SPONTANEOUS CAROTID-CAVERNOUS FISTULAS IN ORDER OF DECREASING FREQUENCY: MAYO CLINIC 1948–1995

Symptoms and Signs	Number	Percent
Red eye (epibulbar vascular dilatation, bloodshot eye, subconjunctival hemorrhage)	47	92
Proptosis (3 mm or more)	41	80
Ocular motility impairment	32	63
Headache or orbital pain	29	57
Bruit or head noise	24	47
Swelling, puffiness, fullness of eyelids	23	45
Secondary glaucoma	19	37
Ophthalmoscopy (retinal vein engorgement, retinopathy of carotid insufficiency, optic disk edema, optic disk pallor)	18	35
Pulsation	8	16
Visual acuity <20/30	11	22

with secondary orbital manifestations. There is no single feature that will always appear in all cases. Neither will all the clinical features be present in any given case. For the purpose of analysis, we have divided the presenting manifestations of our patients into ten principal subgroups. These are summarized in Table 11.1.

Redness and congestion of the eye owing to dilation and tortuosity of the epibulbar venous plexus are the most common and striking features of these fistulas with secondary orbital manifestations. The plexus of corkscrew vessels extends directly to the limbus of the eye and has a brighter red hue than an average vein. The plexus of vessels is often more prominent on one sector of the globe than another (see Fig. 11.1). The tissue spaces between the dilated vessels tend to retain their normal color unless chemosis supervenes. Patients usually refer to their eye as bloodshot. Occasionally, this increase in epibulbar venous pressure is manifest only as a chronic subconjunctival hemorrhage.

Second in frequency is proptosis of the eye. Usually the proptosis is straightforward, but, with time, downward displacement occurs owing to persistent engorgement of the superior ophthalmic vein. The proptosis averaged 4.9 mm with a range of 3 to 9 mm in our group of patients. One patient had a sudden and dramatic increase in proptosis noted in association with a probable thrombosis of the superior ophthalmic vein (*vida infra*).

Some degree of impairment of ocular motility with diplopia was the third most frequent presenting manifestation. It was mild in degree in approximately half of the 32 patients with an ocular motility disorder and consisted of a limitation of gaze in all directions. This milder disability probably was due to the bulk effect of the suffused orbital tissues on ocular rotations. Such patients likely would show some enlargement of the extraocular muscles and an enlarged superior ophthalmic vein on computed tomography (CT) scan. In another 30% of these patients, the impairment was more severe owing to a sixth cranial nerve palsy. Bilateral sixth cranial nerve paresis also was a common accompaniment of bilateral orbital tumefactions. The remaining 20% of patients had severe ophthalmoplegia, secondary to pressure on both the third and sixth cranial nerves in their intracavernous course.

Headache, deep orbital pain, bruit, and head noise occurred in only 48% of the total series but were distressing

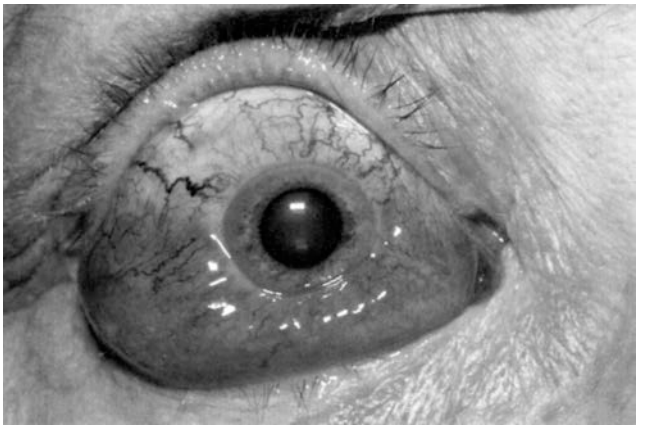

Figure 11.1 Spontaneous indirect carotid-cavernous fistula: Dilated, corkscrew veins on the superior surface of right eye with marked chemosis inferiorly of 1 week duration in a 64-year-old woman who had noted a swishing head noise. Angiography showed a low-flow fistula supplied by terminal branches of the internal maxillary artery, and inferior hypophyseal and dorsal meningeal branches of internal carotid artery. Orbital process underwent resolution following angiography with full recovery over subsequent 16 months. (Courtesy Bartley GB, M.D., Rochester, MN.)

and noteworthy features of the anamnesis when present. The head noise was described as buzzing, pounding, blowing, swishing, or simply "strange," and often was lateralized to the ipsilateral ear. The bruit, when present, had no localizing significance. Interestingly, the patient, described in the subsequent text, had a sudden cessation of her bruit in association with thrombosis of the superior ophthalmic vein (SOV) and cavernous sinus. Two patients had orbital pain prior to diagnosis of indirect shunts that responded to prednisone. Facial pain is well described in association with direct and indirect fistulas (Brazis et al., 1994; Sugano et al., 2003; Jensen et al., 2004)

Eyelid manifestations such as fullness, puffiness, drooping, and swelling did not contribute significantly to diagnosis although present in 45% of total cases. Inability to elevate a nonswollen lid was indicative of a partial third nerve palsy.

Curiously, the 37% incidence of secondary glaucoma is much lower than we anticipated. Studies on smaller but similar series of carotid-cavernous fistulas that have been published by ophthalmologists tend to emphasize secondary glaucoma as one of the three main manifestations (Keltner, 1987). The latter may reflect the ocular rather than orbital orientation of such studies. In roughly 50% of our series of 19 patients with secondary glaucoma, the elevation of intraocular pressure was mild to moderate in degree and was controlled with medical therapy. In the other 50%, the intraocular pressure was high, recalcitrant to medical measures, and was a motivating factor to pursue surgical management of the fistula. Glaucoma surgery alone was not an effective control in our limited experience with one patient. The secondary glaucoma was unilateral except in one patient with bilateral orbital findings.

Pulsation of the eye, which in an earlier era was considered the most obvious and frequent sign of a fistula, was present in only 16% of the total series. It tended to be present in those patients with the higher blood volume communications, which resulted in a greater degree of proptosis, although this relationship was not absolute. Often, its presence was one of the major determinants on which therapeutic surgical intervention was based.

Considering the complex symptomatology and the prevalent proptosis of significant degree, we were surprised that only 11 patients (22%) presented with a visual acuity <20/30. A central scotoma was present in three of the eight patients, reflecting the altered vascular dynamics of the optic nerve associated with the increased intraorbital pressure. These three patients were the only ones with a visual acuity of 20/200 or less. Prior to availability of the now routine endovascular techniques, a 59-year-old woman had a left indirect type B fistula with drainage through the contralateral SOV. Externally, both eyes were quite red and chemotic. Visual acuity was 20/50 right eye and 20/40 left eye. Each fundus displayed superficial retinal hemorrhages and deep round retinal hemorrhages consistent with marked venous obstruction. Bilateral disk edema and cystoid macular edema were also present. The cavernous sinus was explored and the fistula was repaired. Postoperative follow-up was limited but the left eye remained the same whereas the right eye vision dropped to 20/400 secondary to a central retinal vein occlusion. Another patient, a 49-year-old woman, was seen for further evaluation of a one-week history of visual loss, which was a presumed exacerbation of her well established Graves ophthalmopathy. Visual acuity was 20/60 in the right eye with a mild afferent papillary defect (the left eye was amblyopic); 6 mm proptosis was recorded; and corkscrew vessels going to the limbus were present. The right optic disk was mildly swollen (see Fig. 11.2A and B). CT scanning showed enlarged extraocular muscles in the right eye, greater than in the left eye, (Fig. 11.2C) consistent with a diagnosis of Graves ophthalmopathy, but the right SOV was enlarged (Fig. 11.2D). There was not felt to be enough extraocular muscle enlargement to support a diagnosis of Graves optic neuropathy so the plan was to proceed with an angiogram that revealed an indirect right carotid-cavernous sinus fistula that was being fed by both meningohypophyseal arteries and branches from the right internal maxillary artery. The lesion could not be completely treated with endovascular techniques. When she returned 3 weeks later, the visual acuity had dropped to 5/200, and she reported numerous episodes of no-light-perception vision lasting up to 30 minutes. The right cavernous sinus was explored and packed. Postoperatively, she was asymptomatic and the visual acuity improved although she has a hypesthetic cornea. Final visual acuity was 20/25 with 13 months of follow-up. In general, ophthalmoscopic findings did not play a major role in the patients' disabilities, other than those with central scotomas. It is intriguing that eyes of these 50- to 80-year-old individuals can withstand the rise of intraorbital pressure attendant to this entity with so little impairment of vision, unlike the higher incidence of visual impairment associated with a similar event in infants with capillary hemangioma.

Another interesting finding was the absence of a palpable mass in all 38 patients. Neither was the orbital swelling exacerbated by the Valsalva maneuver, although some patients noted a difference in symptoms with changes in posture or head position.

A further study of our data revealed that patients presented with an average of five of the diagnostic groups listed in Table 11.1. This underscores the heterogeneous mix of orbital symptoms and signs associated with spontaneous fistulas. We also analyzed our patients in terms of the angiographic classification of Barrow, which was described earlier. A type A communication was present in 9 patients, type B in 12 patients, type C in 2 patients, and type D in 24 patients. In four patients who underwent angiography in the 1960s, the feeder arteries were not detailed. No correlation was found between the angiographic classification and the number or character

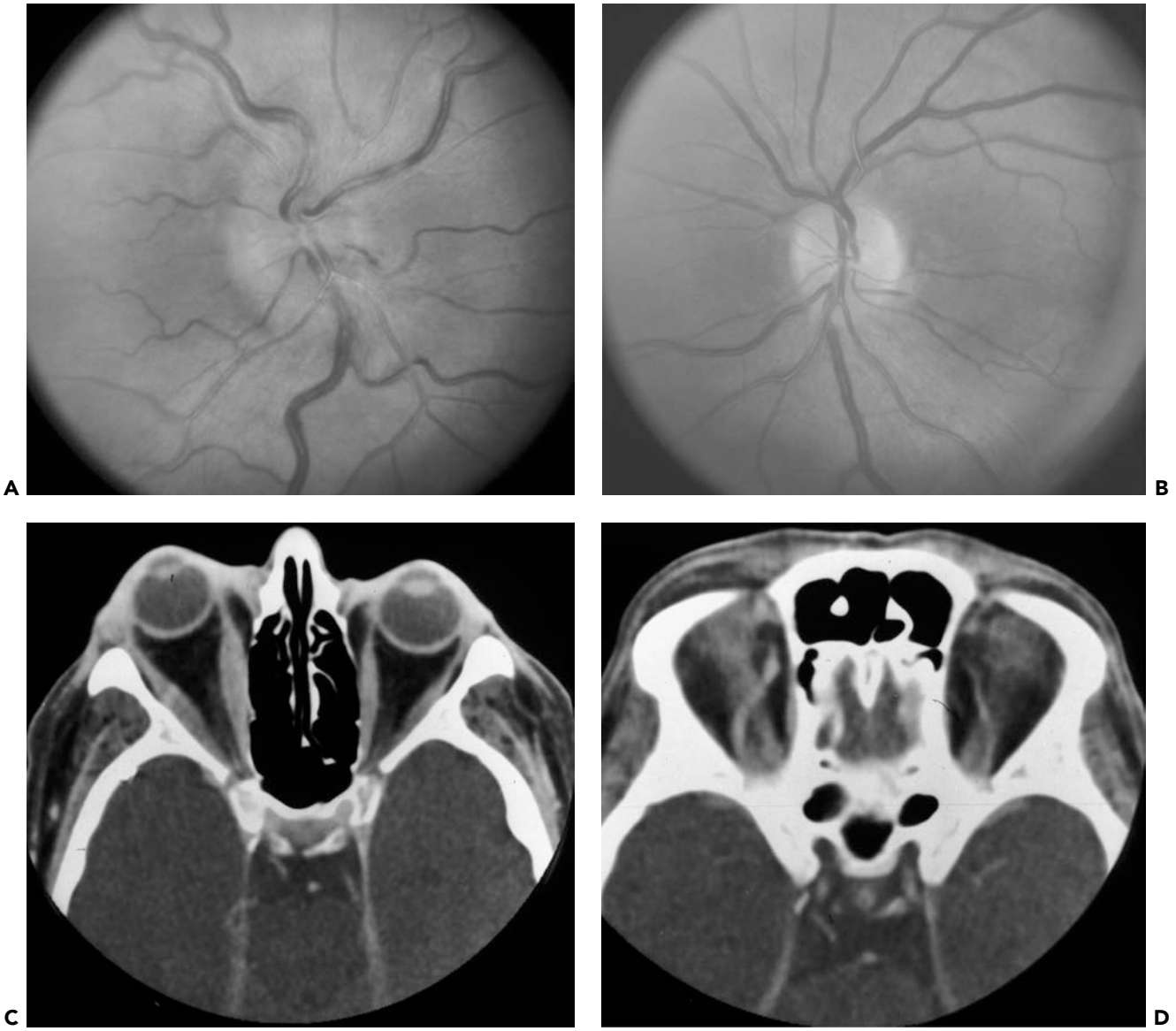

Figure 11.2 Indirect carotid-cavernous fistula in a 49-year-old woman. Disk edema right eye **(A)** is obvious compared to normal left optic disk **(B)**. Axial computed tomography scan **(C)** shows fusiform enlargement of medial and lateral rectus muscles, right eye greater than left eye. Morphology of enlargement is consistent with patient's known Graves ophthalmopathy. There is not enough apical compression to produce optic neuropathy/disk edema. Axial computed tomography scan **(D)**, higher view demonstrates asymmetry with right superior ophthalmic vein enlarged.

of the diagnostic groups in Table 11.1. This suggests that factors other than the arterial components of the vascular communication may play a part in the degree of orbital engorgement and clinical presentation.

The duration of symptoms prior to presentation usually extended over a period of months in 45 of our 51 patients. The average duration was 6.4 months with a range of 0.5 to 36 months. The median of the duration curve was 5.1 months. There was a noticeable trend toward earlier diagnosis in the last 10 years, most likely reflective of wider availability of neuroimaging and endovascular therapy. The onset of the orbital problem was commonly associated with some noticeable or startling event, such as headache or pain in the affected orbit associated with vomiting, sudden appearance of diplopia, red eye, or head noise. In this respect, these fistulas differ from other orbital tumors—except some metastatic carcinomas—in the more prominent delineation of their onset. In one patient, symptoms of right-sided face pain, blepharoptosis, and bruit commenced 3 days before physician evaluation.

Another event peculiar to this disorder is the tendency of some patients to have a severe exacerbation of symptoms

before undergoing clinical improvement. This paradox of "getting worse before getting better" was ascribed to a thrombosis of the SOV by Sergott et al. (1987). They reported three cases of this "dural-cavernous malformation." Their cases were angiographically proved in women in the 70 plus age range. The first case initially was thought to have either a low-flow or early thrombosis through the SOV. When symptoms worsened, a repeat imaging by MRI demonstrated evolution of the thrombosis. Within 19 days of this event, her signs and symptoms improved. In their second case, the orbital manifestations increased in severity 1 month after onset. A second arteriogram disclosed a thrombosis of the SOV. This was quickly followed by fever and a clinical picture suggestive of orbital cellulitis, but blood cultures were negative. The patient was treated with antibiotics. Thirty-five days later the problem had resolved. Their third case involved a sudden increase in a preexisting proptosis. Angiography and MRI demonstrated thrombosis of SOV and the patient improved spontaneously within 16 days.

We have seen this paradoxical symptomatology in three patients of our series. In one, a 77-year-old woman, the sudden thrombosis of the SOV was angiographically demonstrated 4 months after embolization of the external carotid supply to a dural fistula. In the other patient, a 64-year-old woman, the thrombosis and exacerbation of the orbital disorder immediately followed diagnostic angiography. The last case was quite dramatic. An 84-year-old woman had spontaneous onset of a "carotid-cavernous sinus fistula" 1 month prior to evaluation. There was 4 mm proptosis and the eye was injected with minimal chemosis. A dull ache was present. Visual acuity was 20/60, the intraocular pressure was 21 (the fellow eye was 20/25 with intraocular pressure of 11), 4 mm proptosis was present and there was mild sixth nerve paresis. No specific therapy was given, and then one day prior to evaluation she noted an abrupt worsening of the proptosis, chemosis, reduced visual acuity and marked orbital pain (see Figs. 11.3A and B). The bruit that had been present was now gone. Visual acuity was 20/400 with a mild afferent papillary defect. The lids were minimally swollen and ecchymotic whereas the globe was quite injected with minimal chemosis. The globe was "fixed" and 9 mm proptosis was present. The anterior chamber was very shallow although the intraocular pressure was 23. Massive choroidal effusions were present with evidence of a central retinal vein occlusion with disk edema. An angiogram suggested that an intracavernous carotid artery aneurysm had ruptured and spontaneously thrombosed as there was no flow within the right SOV, cavernous sinus or inferior petrosal sinus. An incidental 5 mm internal carotid artery aneurysm was noted within the left cavernous sinus. No specific therapy was given and within 1 week there was marked clinical improvement. One month later, visual acuity was 20/40, the intraocular pressure was 11, and the choroidal effusions had resolved although there was still evidence of a mild central retinal vein occlusion.

One last feature of importance is the rare presentation of younger women with the symptomatology of carotid-cavernous fistula. In these 20- and 30-year-old women, a pregnancy is likely the triggering mechanism. Upon completion of the pregnancy, the orbital manifestations subside only to recur if a second pregnancy occurs. Such recurrences may be so severe that an early termination of pregnancy may be necessary.

Imaging Aspects

Most attention, in the past, has been given to the display of the carotid-cavernous sinus fistula because of its traumatic

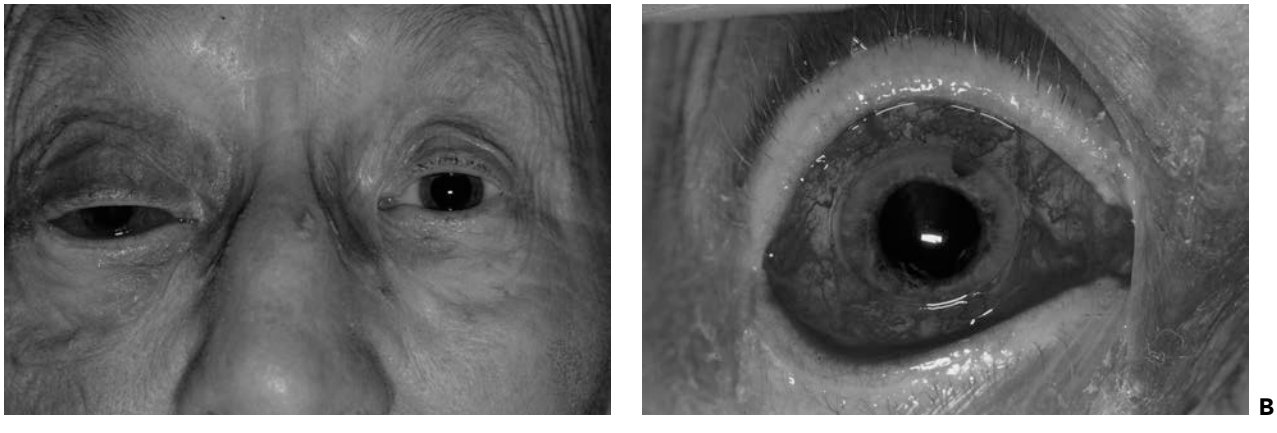

Figure 11.3 Spontaneous direct carotid-cavernous fistula with subsequent spontaneous thrombosis. An 84-year-old woman with rupture of intracavernous carotid artery aneurysm. The lesion underwent spontaneous thrombosis of cavernous sinus, superior ophthalmic vein and inferior petrosal sinus commensurate with pain and clinical deterioration. Proptosis of 9 mm was present and globe was immobile **(A)**. Arterialized episcleral vessels coming to limbus. Note shadow of choroidal effusions temporally and nasally **(B)**.

origin, high morbidity, guarded prognosis, and tricky management. The "Johnny-come-lately" spontaneous type has received less attention. In the latter, ultrasonography will show the dilated SOV and the enlarged extraocular muscles that usually occur, but echographic findings and clinical assessment are not always in agreement (Phelps et al., 1982). CT scan also shows the enlarged veins and the swollen muscles in the orbit (see Fig. 11.4A). The coronal scan is particularly useful in demonstrating the symmetrical thickening of the extraocular muscles unlike the asymmetric enlargement of extraocular muscles of Graves orbitopathy although this is not a constant finding. Some observers comment that CT scan will show a bulging of the cavernous sinus, which, if present, is a helpful ancillary finding. Although echography, CT scan, and MR angiography are supportive of a carotid-cavernous intercommunication, neither technique demonstrates the actual location of the fistulous tract.

Although MRI is proving useful in the evaluation of carotid-cavernous vascular disorders, angiography is still the premier choice for the accurate study of carotid-cavernous fistulas. The relationship and location of the small meningeal vessels communicating with the cavernous sinus are best delineated by selective (separate) injection of the internal and external carotid arterial systems with supplementary subtraction display. Otherwise, some of the smaller caliber communications may not be visualized. Even in the latter event, selective angiography will visualize the dilated venous channels that drain the communication. The importance of injecting the internal and external carotid arteries separately was driven home by the finding of an indirect left carotid-cavernous fistula with drainage through the right SOV. The patient had the clinical findings of a right-sided fistula but only an outside angiogram performed on the right carotid artery was normal. The answer was

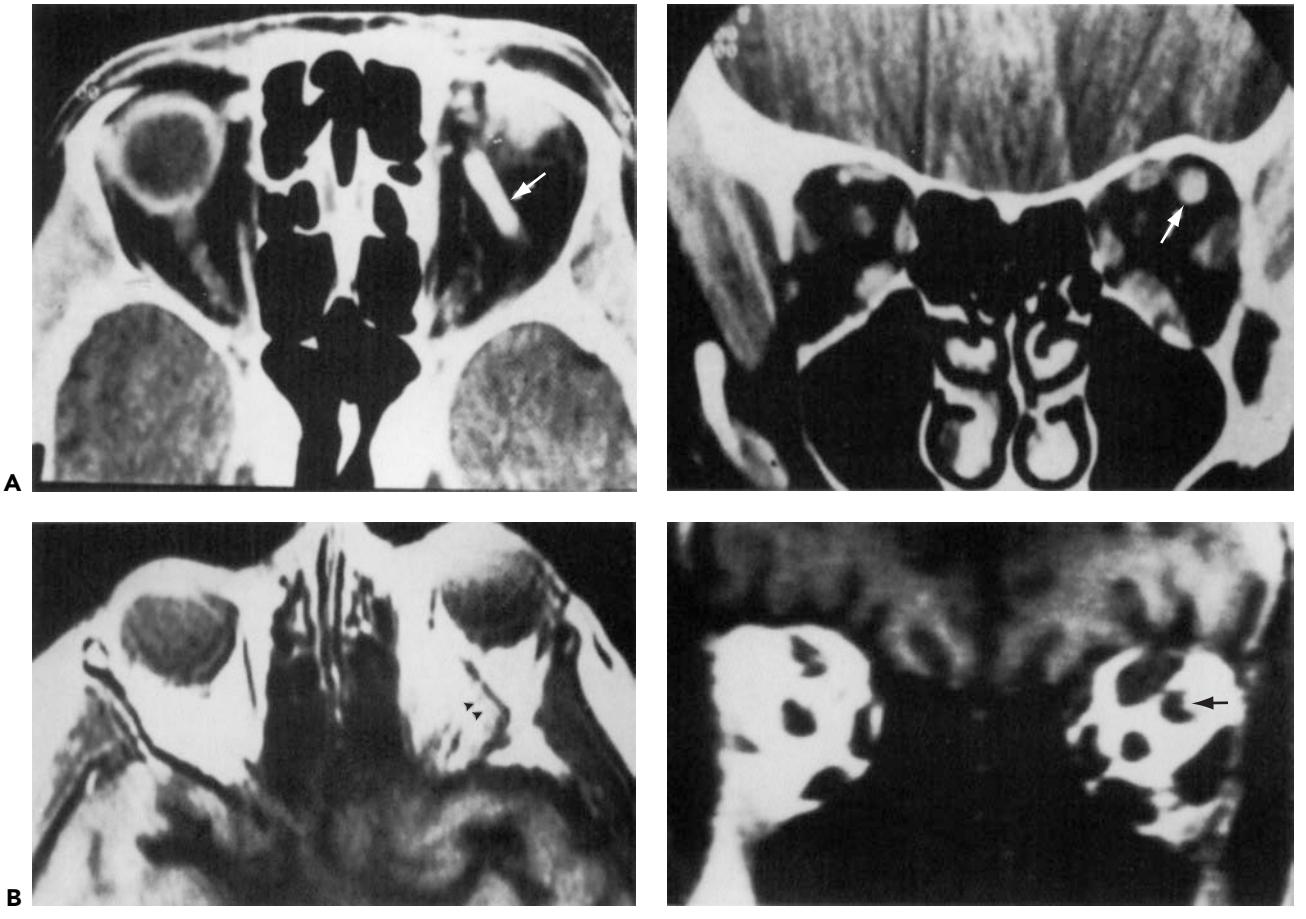

Figure 11.4 A: Contrast-enhanced computed tomography scans axial (*left*) and coronal (*right*) showing enlargement of extraocular muscles and markedly dilated left superior ophthalmic vein (*arrows*) of a 72-year-old woman with an angiographically proved dural-cavernous communication. **B:** Magnetic resonance T_1-weighted axial (*left*) and coronal (*right*) images of left superior ophthalmic vein in the same patient. The hyperintense signal (*arrowheads*, *left*, and *arrow*, *right*) represents the thrombosed vein. The adjacent black area is chemical shift artifact. (From Sergott RC, Grossman RI, Savino PJ, et al. The syndrome of paradoxical worsening of dural-cavernous sinus arteriovenous malformations. *Ophthalmology*. 1987;94:205–212, courtesy of *Ophthalmology*.)

revealed when the left internal carotid artery was injected.

The present role of MRI is ancillary to arteriography. MRI can serially assess the evolution of thrombosis of the draining venous channel, which may occur either during the clinical course or following therapeutic embolization. In either case, MRI replaces the need for a second angiogram that once was necessary in the follow-up evaluation of the patient. Normally, with MRI there is an absence of signal "flow void" from patent venous channels. When thrombosis occurs, the flow void of the affected venous channel will be replaced by a signal of some intensity, the latter being proportional to the degree of thrombosis (Fig. 11.4B). In the stage of recanalization of a thrombus, the reverse of this signal sequence will occur (Macchi et al., 1986).

The recent development of color Doppler imaging of the orbit may also play an increasing role in both diagnosis and tracking of low-flow fistulas. Flaherty et al. (1991) describe their experience with this modality in two patients with this type of vascular malformation.

Treatment and Prognosis

Those clinicians who have written on this subject generally tend to defer surgical intervention so long as the patient is not severely symptomatic. This reasoning is based on the known tendency of some fistulas to undergo spontaneous resolution (Kupersmith et al., 1988; Keltner et al., 1987; Guthoff and Jorgensen, 1987). DeKeizer (2003) published a large series of both traumatic and spontaneous carotid-cavernous fistulas. There were 38 patients with dural-based lesions managed conservatively and 60% spontaneously resolved.

It is somewhat difficult to accurately assess whether or not the fistula has completely resolved, in part related to the heterogeneity of orbital and other clinical features. Focal thrombosis modifies the flow's direction and possibly some of the manifestations. Clinical changes may or may not parallel angiographic changes. The most accurate answer then would depend on results of conventional angiography, which is not practical in all instances.

In terms of management, the ophthalmologist plays an important role. The untreated patient must be watched for signs of visual deterioration, which may signal the need for therapeutic intervention. Likewise, a secondary glaucoma requires regular assessment. We may be amiss in assuming these potential complications will be closely followed when the patient either is returned to the referring physician or the care of a new physician in a distant city. The ophthalmologist also must assist the management team in determining the need for surgical intervention. *The status or severity of the ophthalmic manifestations should be a major factor in this question of treatment*. The nub of the matter is, "Will the visual status of the patient, postoperatively, be worse than the patient's preoperative status?" This is a sticky question, but who may be as qualified as a neuro-ophthalmologist to judge this parameter? A more subtle clinical feature that may be pointed out to the ophthalmologist by family members is a mental status change. We saw this in one of our traumatic fistulas with posteriorly directed venous drainage that produced cortical venous hypertension with secondary mental status changes. In addition, cortical venous hypertension is a risk factor for intracranial hemorrhages.

The objective assessment of the patient's head noise probably is the most difficult aspect of this complex problem of treatment versus no treatment. Often the patient's concern about this problem tips the scales in favor of treatment.

If the initial diagnosis is based on such things as clinical presentation, CT scan, or MRI, but the suspected fistula has not been accurately localized, angiography may serve as both a diagnostic aid and a therapeutic solution. It is intriguing, but reasonable, that some tiny, low-flow dehiscences between the carotid arterial and cavernous venous trunks are closed by this maneuver. Although other treatment aspects go beyond the scope of this discourse, there are several options to consider. If observation with hopes of spontaneous resolution is not realistic, an endovascular approach may be considered (Hilal and Michelsen, 1975). For direct fistulas, the optimum treatment involves an endoarterial approach to the cavernous sinus, and a detachable balloon is introduced into the fistula and inflated until the fistula is closed. Most direct fistulas can be treated with minimal morbidity using this technique. Approximately 30% of patients can have a transient ocular motor paresis. For indirect fistulas, arterial embolization may not be realistic because multiple small branches from the internal and external carotid artery may be involved. If the intercommunication has already been pinpointed by prior angiography, embolization of the external carotid artery branches supplying the fistula is a frequent second choice. If necessary, this may be supplemented by ligature of a major branch to the fistula such as the internal maxillary or middle meningeal arteries. There is a reluctance to therapeutically tackle the internal carotid artery's role in these entities, unless severe symptoms persist in spite of the measures just mentioned. Whether to reduce the participation of the internal carotid arterial trunk by balloon occlusion, ligation, embolization, or trapping procedures must depend on the experience and preference of the neurosurgical and neuroradiology team involved in the surgery.

Use of the venous approach is another consideration although one of the risks attendant with venous embolization is the possibility of changing the venous drainage from a benign pattern to a more aggressive one with cortical vein involvement (Roy and Raymond, 1997). Hanneken et al. (1989) have circumvented the risks and problems attendant to an approach through the internal carotid arterial trunk by embolizing the venous side of the intercommunication. They uncover the SOV in the anterior orbit on

the affected side, unkink the course of the vessel by dissection, enter the vein by needle puncture, insert and thread a balloon-tipped catheter into the cavernous sinus by fluoroscopic control, and inflate the balloon until closure of the communication is verified by angiography. This approach was used successfully in three patients with spontaneous fistulas. Further successful experience has been recorded with this technique (Baldauf et al., 2004; Quiñones et al., 1997; Goldberg et al., 1996) although an unsuccessful attempt with subsequent ligation of the SOV led to sudden thrombosis with subsequent visual loss and neovascular glaucoma (Gupta et al., 1997).

Twenty of our 51 cases were subject to surgery because of persistence of headache or bruit, marked proptosis or pulsation of the eye, severe chemosis, third cranial nerve paresis, visual decrease, or recalcitrant secondary glaucoma. Since the introduction of endovascular techniques, there have been only two patients who underwent exploration and packing of the cavernous sinus. The patients who did undergo surgery with packing did have various degrees of corneal anesthesia but did well overall.

The utilization of the Gamma Knife offers another treatment option. We reported results from 20 patients with indirect carotid-cavernous sinus fistulas (seven of whom are included in the most recent portion of our tumor survey) treated with Gamma Knife alone ($n = 7$) or Gamma Knife plus embolization ($n = 13$) (Pollock et al., 1999). In this series, 19 of 20 patients improved their clinical symptoms and 14 of 15 patients had total ($n = 13$) or near total ($n = 1$) obliteration of their fistulas. Treatment with radiosurgery was done before embolization so that the entire fistula was visualized and treated. Radiation-induced fistula obliteration occurs months to years after the procedure, although many do obliterate within the first few months. For patients with cortical venous drainage or who are quite symptomatic, rapid symptom relief or protection against hemorrhage is afforded by endoarterial embolization during the latency period before radiation-induced obliteration occurs.

Arteriovenous Aneurysm

Here we will continue our review but in a summary fashion of the nontraumatic AV communications affecting the orbit other than those of the preceding subchapter. AV aneurysm is the term widely used for this diverse collection of vascular malformations. This diagnosis should be reserved for those situations in which both arterial and venous components are verified either by surgical exploration or angiography. Those cases of orbital AV aneurysm in the older literature associated with carotid-cavernous fistula and dural carotid-cavernous shunts should be excluded.

There are three types of nontraumatic, orbital AV aneurysms.

1. A primary type involving the soft tissue of the orbit with or without some extension into the eyelids
2. A secondary type associated with an intracranial AV aneurysm other than in a carotid-cavernous location
3. An AV aneurysm that is but one part of a multifocal, systemic vascular anomaly

None of these categories include a sufficient number of cases to warrant their review in separate subchapters.

In respect to their genesis, the primary type probably arises from a preexisting vascular hamartoma in the orbit, and multiple hamartomas probably are the predecessors of the multifocal AV aneurysm. Those orbital AV aneurysms associated with intracranial vascular malformations are but a reflection of the altered hemodynamics induced by the primary lesion.

All three types share to some degree a diverse collection of signs and symptoms including proptosis, red eye, pain, headache, visual impairment, diplopia, head noise, bruit, pulsation of the eye, swelling of eyelids, extraocular muscle paresis, retinal venous engorgement and tortuosity, and secondary glaucoma. However, there is no standard clinical pattern that will differentiate one category of AV aneurysm from another. These lesions often have some cutaneous manifestation that resembles a hemangioma or lymphangioma. A biopsy of these lesions may be misleading, because the deeper AV aneurysm remains unrecognized. Only angiography will delineate the basic disorder in such cases. In the near future, MR study may take the place of angiography in the diagnosis of some cases. CT scan and ultrasonography also can suggest the vascular makeup of such a mass but do not show accurately the arterial and venous components of the vascular anomaly.

Grossly, these lesions may be suspected by the bluish tinge of the tissues overlying the malformation. Also, there may be a palpable thrill. When surgically explored, the lesions consist of a tangled convolution of tortuous vessels. Histopathologically, these vascular channels vary in caliber, thickness, and structure, a mixture of thin-walled veins intermingled with thick-walled arteries. Some vessels may show features of both an artery and a vein with, in addition, an incomplete internal elastic lamina. The age or duration of the lesion may be guessed by the degree of interstitial fibrosis. In cases with a profuse arterial supply and a disproportionately small venous return, an exuberant proliferation of endothelial cells and capillary-like channels may occur. Reticulin stains will help delineate the basement membrane-type material surrounding such proliferations. In a case described by Howard et al. (1983), such an endothelial proliferation comprised 50% of the bulk of the malformation.

Primary Type

The spontaneous AV aneurysm primary in the orbit is the least common of the three types. Several cases reported in the literature seem to fit our restricted definition of this entity. One of these, a 19-year-old man, was initially described by Michelsen et al. (1978) and reviewed

again with follow-up data by Howard et al. (1983). This patient had noted progressive proptosis of right eye and swelling of right upper eyelid over a several-year period. A palpable mass was present in the superotemporal orbit. On orbitotomy a diffuse vascular tumor was encountered. An incisional biopsy proved to be an AV aneurysm. Selective internal carotid and external carotid arteriography demonstrated an arterial supply from branches of the internal maxillary and ophthalmic arteries. The lesion was embolized with silastic liquid through the terminal branches of the internal maxillary artery with prompt resolution of orbital swelling. Proptosis recurred 4 years later. At this time the major portion of the tumor was resected. Histopathologic study confirmed an AV aneurysm.

The case of Murali et al. (1981) was that of a 53-year-old man with a 2-year history of swelling of the right eye. A bruit was present. Arteriography showed an AV aneurysm that was supplied by a large ophthalmic artery and ethmoidal branches of the maxillary artery. Outflow channels were the superior and inferior divisions of the ophthalmic vein. This lesion underwent spontaneous thrombosis with resolution of symptoms.

A case of Wolter et al. (1972) should also be mentioned. A *nevus flammeus* was first noted on the right face of a 4-year-old boy. This lesion increased in size and coloration during childhood. Swelling of the right upper eyelid was first noted at the age of 31 years. Within a year, the swollen eyelid began to pulsate, and the patient noted a buzzing sound in the affected orbit. At the age of 33 years, arteriography revealed an AV aneurysm in the superoanterior orbit. At the age of 36 years, a painful, throbbing mass in the superior orbit prompted surgical removal of a lesion consisting of large and small vascular channels as well as blood-filled vascular spaces. Some clinicians, understandably, might consider this case an incomplete Sturge-Weber syndrome rather than an orbital AV aneurysm.

A 29-year-old woman from our series might or might not be another example of an orbital AV aneurysm. A sudden, painful proptosis and "swelling" of the left eye occurred 2 weeks after delivery of a normal child. The symptoms responded to prednisone therapy. Twenty-two months later, there was recurrence of proptosis associated with a red eye. CT scan showed a mass in the posterior left orbit. The mass did not increase in size with Valsalva maneuver. A vascular mass containing a hemorrhagic cyst was partially removed. Histopathologic diagnosis was a mass of vascular channels consistent with an AV malformation. Inasmuch as arteriography was not performed, we could not exclude the possibility that the mass represented the residual feeding and draining channels of a prior carotid-cavernous fistula associated with her prior pregnancy.

Multiple Type

In our series of AV aneurysms, the multiple type was most common. This group has several features in common. The vascular anomaly is either evident at birth or appears early in life. In the latter subtype, a cutaneous red spot or a subcutaneous mass with a bluish overtone may look deceptively innocent or benign. These spots and lumps soon enlarge, heralding the trait of progression so frequent in these multiple vascular malformations. Eventually this leads to a distressing morbidity in almost all patients and, in some, a guarded prognosis. A brief summary of our cases illustrates the gamut of symptoms, signs, morbidity, and location of the lesions.

Case 1

A 73-year-old man stated that a vascular malformation of the left cheek and oral cavity was first diagnosed at the age of 4 years. By the age of 10 years, he had undergone two surgical procedures to halt the progressive increase in the size of the malformations. Slowly, progressive proptosis of left eye commenced at the age of 26 years. At the age of 34 years, radiotherapy was administered to the left face because of continued hypertrophy. By the age of 56 years, the proptosis had been replaced by a slight enophthalmos, but episodes of proptosis and pain occurred when the patient's head was in a dependent position. Vision was 20/20 in the red left eye. Retinal veins were engorged, but there was no aneurysmal tortuosity. Selective angiography showed AV aneurysms in the left orbit, left pterygoid fossa, and left pharynx. Thereafter, the progressive features of the several vascular loci "simmered down." At the age of 73 years, CT scan showed some evidence of calcification of the left SOV. The Krahn exophthalmometer measurements were equal in the two eyes. Vision was 20/40 in the affected eye. Engorgement of the retinal veins in the left eye was still present. There was no aneurysmal involvement of the brain.

Case 2

At birth, a telangiectatic coloration covered the entire left side of this patient's body from scalp to toe. The telangiectasia increased in volume and intensity during childhood, particularly in the head and neck area. At the age of 16 years, a lymphangiomatous-like lesion was removed from the floor of the mouth. At the age of 35 years, reddish blue discoloration and pulsation of left eye was noted, but there was no bruit. Ophthalmoscopy of left eye showed no significant abnormality. Visual acuity was not impaired. Selective angiography revealed AV anomaly involving left orbit and left pterygoid fossa with major arterial supply from the occipital artery and external carotid system. There was no involvement of the internal carotid system. Ligation of the external carotid and left facial arteries was performed without significant symptomatic benefit. By the age of 40 years, proptosis had increased to 12 mm. A medial and lateral tarsorrhaphy was performed to protect the protruding, pulsating left eye. Repeat angiography showed additional involvement of the thyrocervical, vertebral, subclavian, occipital, and ophthalmic arteries on the left side. A transcranial surgical procedure was next performed

in an effort to reduce the size of the intracranial vascular malformation but was unsuccessful. At the age of 51 years, proptosis of the right eye appeared, which was secondary to the shunting of blood from the left-sided intracranial AV aneurysm into the right cavernous venous system. At the age of 56 years, an embolization procedure was considered, but after consultation at several surgical centers, the vascular anomaly was considered inoperable.

Case 3

At birth, a mass was noted in the right upper eyelid of this girl. Because of progressive enlargement, the mass was partially excised at the age of 6 months. At surgery, the mass was found to extend into the anterior orbit. Histopathologic diagnosis was vascular hamartoma. At the age of 7 months, swelling and tenderness commenced in the right cheek. At the age of 15 months, the hamartoma of the check was excised. At this time, a 2-mm proptosis of the right eye was first noted, but eyesight did not seem impaired. Ophthalmoscopic examination was negative. At the age of 28 months, CT scan showed a mass of enlarged tortuous vessels in the right orbit, but there was no intracranial extension. Also, tiny, salmon-colored cysts appeared on the surface of the eye associated with transient episodes of hemorrhage. At the age of 5 years, a soft compressible mass appeared anterior to the right ear. At this time, CT scan did not show significant change in the orbital mass, although proptosis had increased to 4 mm. A vascular malformation was also discovered in the cerebellum. This drained into a large vein that passed anteriorly into the right cavernous sinus. Over the next 2 years, there was little change in the patient's status. At the age of 7 years, vision in the affected eye was 20/40.

Case 4

At birth, a red spot was present on this boy's left forehead. This red spot enlarged and gradually became a purplish red mass involving both the forehead and eyelid. Downward displacement of the left eye soon followed. At the age of 5 years, angiography showed an AV malformation of the left scalp, forehead, eyelid, and left orbit that was supplied by branches of the superior temporal and internal maxillary arteries associated with enlargement of the left frontal and lacrimal arteries. Vision in the left eye was 20/20. A ligation of the external carotid artery was performed, and a radical excision of the malformation of the forehead and scalp was covered with a skin graft. Histopathologic examination of the excised tissue confirmed the diagnosis of AV aneurysm. Nevertheless, the malformation in the periorbital area continued to enlarge and began to pulsate. At the age of 11 years, another excision was performed on a vascular tumor involving the right upper lid, supraorbital ridge, and roof of left orbit. Vision of left eye was still 20/20.

We have not encountered a patient with the Wyburn-Mason syndrome and an AV aneurysm of the orbit. Miller (1988) has referenced the known cases and refereed which should or should not be included in the unilateral retinocephalic vascular malformation syndrome.

Secondary Type

The AV malformations of the brain occasionally show protrusion of the eye early in their clinical course, which necessitates a differential consideration from the preceding vascular disorders that affect the orbit. The intracranial malformation seems to arise from a hamartoma and, in this sense, is also congenital. However, in most patients, signs and symptoms do not appear until the second or third decade and not infrequently seem associated with puberty. In this respect, they differ from the multiple AV aneurysms that manifest early in life and the spontaneous carotid-cavernous communications that are predominant in older individuals.

Most patients first seek consultation because of some sign or symptom such as headache, subjective bruit, seizures, and various neurologic deficits. This suggests some intracranial disorder. The malformation may be so small as to be barely visible on neuroimaging or so large as to be life threatening. They are also quite unpredictable in their rate of progression. In general, they are single lesions and vary in location. The majority are supratentorial. Symptomatology often reflects their effect on blood circulation to neighboring areas of the brain rather than their precise location. It is this factor that accounts for their orbital manifestations, although the lesion is located some distance from the orbit. In essence, the orbit is a passive victim of an abnormal shunting of blood through the cavernous sinus-ophthalmic vein outlet. There is no AV aneurysm in the orbit, per se.

Two cases in our series illustrate some of the usual and unusual features of these vascular malformations.

Case 1

A 21-year-old man presented with a history of vomiting over a 3-week period not associated with nausea. He had had occipital headaches of increasing severity over a 2-year period, which were aggravated by coughing and physical activity. Visual acuity was 20/20, ophthalmoscopy showed bilateral papilledema, but there was no proptosis. A bruit was heard over the parietal area. Vertebral and carotid arteriography showed large bilateral anomalous vessels extending upward from the cervical area into the intracranial vault associated with abnormalities in the branches of the occipital artery. A cerebellar decompression was performed with the removal of the arch of the foramen magnum. At the age of 23 years, bilateral proptosis was evident with pulsation and epibulbar venous engorgement of the right eye. Krahn exophthalmometer measurement was right eye 29 mm and left eye 24 mm. Bruit was still present. Vomiting had decreased to approximately one episode per week. His headache was no worse. By the age of 28 years, proptosis had increased and vision was 20/50 right eye and 20/20 left eye. Krahn measurement was

36 mm right eye and 27 mm left eye. An incongruous left hemianopsia was found. The patient was also having some movement incoordination. Arteriography now showed an additional anomalous vessel in the right mastoid area supplied by the external carotid trunk. The jugular vein on the right side was enlarged and carried arterial blood. A ligation of the right common carotid and left external carotid arteries was performed. When last seen at the age of 32 years, he was again having severe headaches and frequent vomiting. Proptosis measured 40 mm right eye and 30 mm left side. There was marked bilateral dilatation of retinal veins. The significant change on arteriography was a large saccular aneurysm of the vein of Galen.

Case 2

A 12-year-old girl presented with a 2-year history of occipital pain and occasional numbness of left arm and hand. A mild hydrocephalus was present. Arteriography showed a small AV aneurysm in the right occipital area of high-flow type that emptied into an enlarged sigmoid sinus. Five months later a bruit was noted. At the age of 14 years, the bruit was worse, and 2 mm of proptosis of the right eye was present. Retinal vessels of the right eye were engorged. Eleven months later, proptosis of right eye was 5 mm, and pulsation had now commenced. A convulsive disorder also had appeared. At the age of 15 years, arteriography showed an additional massive vascular anomaly in the right parietotemporal area supplied by a huge middle meningeal artery. The severity of the convulsive disorder rapidly increased, and the patient died 3 1/2 years after initial consultation.

Three additional cases from the literature should be mentioned. A man (age not stated) reported by Forman et al. (1975) also had bilateral proptosis with pulsation of one eye from a large midline frontal lobe AV aneurysm that impinged on the roof of both orbits. Malzone and Gonyea (1973) discussed two cases. One, a 50-year-old man, had bilateral proptosis secondary to a large AV malformation in the left temporal lobe. The other patient had a large lesion in the left cerebral hemisphere with contralateral proptosis.

Treatment

It is evident that there is no single management plan that can cover the many exigencies of these AV aneurysms. For the rarer primary type, a partial embolization should be considered first, particularly if branches of the external carotid artery trunk participate in the arterial supply. Later, if necessary, the malformation may be excised or ligated (Gross and Hornblass, 1989), depending on its orbital location, the remaining arterial supply, and the visual status of the patient. In general, all the arterial components of these malformations must be addressed, otherwise the lesion will return.

In respect to the multiple type, there is a trend to remove the malformations around the head and face although they are still small. This seems far better than waiting to see if the malformation will undergo remission when the patient reaches maturity, as was the common practice 20 to 30 years ago. Of course, earlier management will not prevent the subsequent appearance of other aneurysms in adjacent areas if that is the lesion's tendency.

Management of the secondary type is out of the domain of the ophthalmologist. Here, the indications for surgery are based on neurologic parameters rather than the status of the eye or orbit.

ORBITAL VARIX

Varix is a tumor comprising abnormally large veins. It may be a single vessel with saccular or segmental dilatations or a tangled plexus of venous channels. From a historical perspective, Lloyd et al. (1971) classified this tumor into two types, *primary* and *secondary*. The primary varix represented a congenital venous malformation. The secondary type, also called *acquired*, may be caused by orbital trauma or retention of an orbital foreign body. The secondary varix also was attributed to extraorbital lesions such as carotid-cavernous fistula, carotid-cavernous communications, and AV aneurysms of the brain. In the latter three variants, the venous tumor is but a dilatation of normal orbital venous channels, which reflect the altered hemodynamics of the orbit induced by the extraorbital lesion. Such secondary types are not true malformations as were the congenital varices. These secondary types might more appropriately be designated according to the primary extraorbital lesion with which they are associated. Rootman and Graeb (1988) have classified these tumors into distensible and nondistensible types, which roughly correspond to the above primary and secondary groups. Earlier, the diagnosis of varix was based chiefly on clinical findings. When imaging techniques such as venography, ultrasonography and its various modifications, CT scan, and MRI were discovered, the occult varix became real. A significant increase in the literature of varix corresponded to the application of these diagnostic advances to the orbit. The term *varix* gradually was stretched to its broadest meaning by the clinicians who now could visualize venous dilatations. Therefore a clinician's report of a thrombosed orbital vein would be regarded as a varix by another clinician. Or, a clinician might discuss varix and enlarged orbital veins in the same report, suggesting that a diagnosis of varix was based only on the relative size of one channel as compared to another. What one clinician may suspect is an orbital venous dilatation secondary to an extraorbital AV communication in a 60-year-old individual might be regarded as spontaneous, acquired orbital varix by another observer. Another report might detail the surgical removal of a "thin-walled" vein, but the histopathologic report would describe the specimen as composed of "thick-walled" channels, and so on. In short, what is a dilated vein as contrasted to a varix? Therefore, we may be approaching

an era in which the term *varix* will become as meaningless as the present overused term *orbital pseudotumor*. We fully agree with the classification proposed by Harris (1999) which emphasizes the hemodynamic qualities of the lesion rather than the morphologic features. Varices (lesions with venous flow) can be the so-called "distensible" or "nondistensible" and their features will be discussed below.

Clinical Features

The congenital venous malformation of the orbit is the classic varix. Its genesis is probably a vascular hamartoma, its makeup is entirely venous, and its sex incidence is equal. If a large series of proved cases were surveyed, the right and left orbits probably would show equal involvement. It is almost always unilateral. A case of bilateral involvement, which was thought to be posttraumatic, has been reported by Safran et al. (1984). Another case with bilateral involvement was reported by Shields et al. (1999). An 80-year-old woman experienced slow progressive proptosis of the right eye over 6 months. The examination recorded 5 mm proptosis and there were no changes with Valsalva maneuvers. Imaging revealed bilateral orbital masses. The right mass was intraconal and displaced the optic nerve superiorly. Intracranial extension was also present. The left orbit had a more irregular appearance and was located in the deep superior nasal orbit. When the right mass was removed, it was consistent with a thrombosed varix that was associated with intravascular papillary endothelial hyperplasia. The varix is usually manifest in infancy or early childhood, but its appearance may be delayed until the later part of the first decade or the early part of the second decade. Often in infancy or childhood, other vascular stigmas are noted in the face, forehead, eyelids, and buccal cavity. Later, venous engorgement may develop in the conjunctiva or an eyelid of the affected eye, or in the subcutaneous tissue of the abdomen or extremities. The epibulbar venous engorgement does not have the reddish purple color or the corkscrew configuration of vessels such as described earlier with carotid-cavernous fistulas.

A transient and evanescent proptosis is the principal sign of an orbital varix. This "now you see it, now you don't" phenomena is called *intermittent exophthalmos*. In children, this intermittent exophthalmos is easily induced by crying or straining. In the early stages, the proptosis also may be induced by movements of the head to a dependent position or triggered by some maneuver that increases the orbital vascular pressure. In older children or adolescents, the transient proptosis can be induced by pressure over the jugular vein, by forced expiration with the mouth and nose closed (Valsalva maneuver) or by putting the head into a dependent position. By this age, the patient has learned to demonstrate the striking bulging of the eye almost at will or by *command*. Waller et al. (1989) have emphasized the latter sign in the differential diagnosis of true varix from other venous lesions simulating varix. If pulsation is noted, there may be an unsuspected extraorbital or intraorbital vascular component associated with the malformation. Or, it may be noticed if the varix is a large one, situated posteriorly and associated with a dysplasia or defect in the bony partition between the orbit and intracranial space. At these various stages, the disorder is painless. Variations on this theme were reported in association with other cranial defects and encephaloceles (Islam et al., 2004). This can be very problematic for the patient and the clinician especially for defects near the cribriform. The authors described one patient with an inferior nasal varix and a midline encephalocele that had enlarged enough to obstruct normal antral drainage causing an infective sinusitis that had spread to the central nervous system.

However, the degree of progression is unpredictable. In time, the periods of proptosis gradually become more prolonged, and the eye recedes even more slowly. In the resting stage, enophthalmus eventually appears, which is attributed to atrophy of the orbital fat. By the latter part of the second decade or sometime in the third decade, either some pain is associated with the intermittent proptosis or the orbital disorder becomes such a nuisance that the patient returns for surgical relief. If the varix also involves the upper eyelid, young adults may seek some type of cosmetic relief.

In general, the course of this lesion is benign, but children with varix are subject to orbital hemorrhage from trauma. Nontraumatic, spontaneous orbital hemorrhage in childhood associated with an acute bulging eye is probably due to the "chocolate cyst" of lymphangioma rather than varix.

Reports of nontraumatic acquired varix in adults, which were assumed to be primary in the orbit, are those of the following: Brismar and Brismar (1977); Bonavolonta and Sammartino (1981); Shields et al. (1984); and Bullock et al. (1989). Selective arteriography was not done in any of these cases, so an associated AV lesion in the pterygoid fossa, at the base of the skull, or in the area of the superior orbital fissure could not be ruled out. The two cases of Bullock et al. were men aged 38 and 75 years. In both cases, the onset was of short duration, acute in degree, and diagnosed by CT scan. Blood clots were surgically removed from each patient's lesion. In retrospect, the acute onset probably corresponded to thrombosis of the affected vein rather than the duration of the assumed varix. The case of Shields et al. was that of a 33-year-old woman with a 2-year history of fullness of the affected orbit and a 6-month history of intermittent exophthalmos. The diagnosis of orbital varix was based on an orbital mass that, on CT scan, showed an increase in the size with the Valsalva maneuver. In a review of eight cases of thrombosis of the orbital veins and cavernous sinus, Brismar and Brismar (1977) noted two women, aged 56 years and 63 years, in whom phlebography showed irregular widening of the SOV anterior to a complete occlusion in the posterior portion

of the orbit. Bonavolonta and Sammartino reported a 29-year-old woman with an enlarging orbital mass of 5 years' duration, which, on jugular compression, produced a copious transudation of blood-tinged tears. A varix at the junction of the superior orbital vein with the angular vein was surgically removed. A thrombosed orbital varix was also to blame for a 45-year-old man with left eye proptosis and gradual loss of vision over an 18-month period (Menon et al., 2004). There had been no trauma or any positional changes. Vision in the left eye was no light perception. Imaging had shown an apparent varix just lateral to a dilated SOV. A recent clinical change prompted reimaging, which now demonstrated enlargement of the lesion and a normalization of the SOV. Extensive blood loss was encountered at surgery and the histopathologic examination was supportive of a thrombosed varix. It is this author's speculation, but one might wonder if this represented a diverticulum of the SOV.

The cases of two of our patients were very similar to the above cases described by Bullock et al. (1989). One was a 59-year-old man with acute pain and swelling of right eye of 5 days' duration. The vision was not affected, but there was 4 mm of proptosis and moderate impairment of motility in all directions of gaze of the affected eye. CT scan showed a smooth enhancing mass at the apex of the right orbit. Dark, clotted blood was evacuated from a dilated vein through an anterolateral orbitotomy. The second case was a 78-year-old woman who, 5 weeks before admission, had had sudden proptosis, chemosis, subconjunctival hemorrhage, and diplopia of left eye associated with a subjective bruit. The acute features had gradually subsided but, on presentation, a residual mass remained in the superonasal quadrant of the left orbit. Through a superonasal anterior orbitotomy a dilated vein was exposed, which, upon dissection, ruptured with release of old partially clotted blood. In both of these cases, the blood clot represented a partially thrombosed vein. We suspect these cases of acquired varix were probably secondary to a preceding, mild, relatively asymptomatic carotid-cavernous communication. Another one of our cases, a 68-year-old woman, awoke with painful proptosis on the right (see Fig. 11.5A). There had been no previous history of positional proptosis. Visual acuity right eye was 20/40 with normal pupils. The eyelids were ecchymotic, there was 5 mm proptosis, and ductions were limited. The orbit was tight but not firm. Admission MRI showed an apparent hemorrhage into and around the right lateral rectus muscle. She returned 1 month later with a normal clinical examination (Fig. 11.5B). CT scanning with (Fig. 11.5C) and without (Fig. 11.5D) Valsalva maneuver clearly demonstrates an enlarging lesion consistent with a varix. The lesion was readily apparent on the coronal CT (Fig. 11.5E).

The symptomatology of secondary orbital varix is essentially that of the primary vascular lesion with which it is associated and was detailed in the preceding subchapter.

Imaging Aspects

In the era prior to the present imaging methods, plain film radiography was a confirmatory supplement to the clinical diagnosis of congenital varix. Such clues as phlebolith formation, an enlarged orbit, a widening of the superior orbital fissure, and venous lakes or vascular markings in the ipsilateral frontal bone were often found.

Later, CT scan and ultrasonography supplanted venography as the principal imaging methods for confirmatory diagnosis because of their noninvasive qualities. CT scan will depict the tortuous and dilated structure of the congenital varix, which readily enlarges with either jugular compression or the Valsalva effect. A varicose enlargement of the superior or inferior orbital vein also will show a similar response, but the image will not have the tortuous, plexiform pattern of the congenital varix (see Fig. 11.6). In both types, the venous mass enhances homogeneously with contrast material unless thrombosis has occurred. As alluded to in the preceding text, a recurring theme in the clinical presentation is the "now you see it, and now you don't" concept. This also pertains to the radiographic evaluation. We have seen on numerous occasions patients purported to have an orbital tumor come in with virtually normal MRIs. We have also seen virtually normal axial CT scan evaluations but the coronal view has a large mass to the point where we wondered if the scans belonged to the same patient (note unimpressive axial scan in Fig. 11.5B) when compared to coronal view in Figure 11.5D. The reason for the difference in CT scan images relates to an inadvertent Valsalva maneuver for the direct coronal views. The patient is repositioned on the stomach with the neck extended for the coronal view while the axial view is done with the patient supine and relaxed. The MRI is done completely with the patient supine although the computer reformats all the images so no "inadvertent" Valsalva maneuver would ever be performed.

If the venous lesion is large enough in the resting state to be seen with echography, it will appear as an anechoic void with a negative Doppler analysis. Echography also nicely illustrates the expansion of the mass with the Valsalva maneuver. Color Doppler flow imaging has greatly improved the echographic display of a varix (Erickson et al., 1989; Lich et al., 1990). Both para-ocular (through closed eyelids) and transocular (direct contact between transducer and eye) techniques are used. One color code can be assigned to the retrograde flow of blood toward the transducer when the intraorbital pressure is increased. When maximum distension of the varix is reached, color Doppler flow ceases. Another color can be assigned to the antegrade flow of blood when the Valsalva maneuver is released. This provides a permanent, colorful, photographic display of the size and flow volume of the venous mass.

In the use of MRI, Osborn et al. (1986) found that a varix was best delineated on the T_1 weighted spin echo (SE) 40/5,000 and SE 40/1,000 sequences, because it had a much lower signal intensity than the surrounding orbital

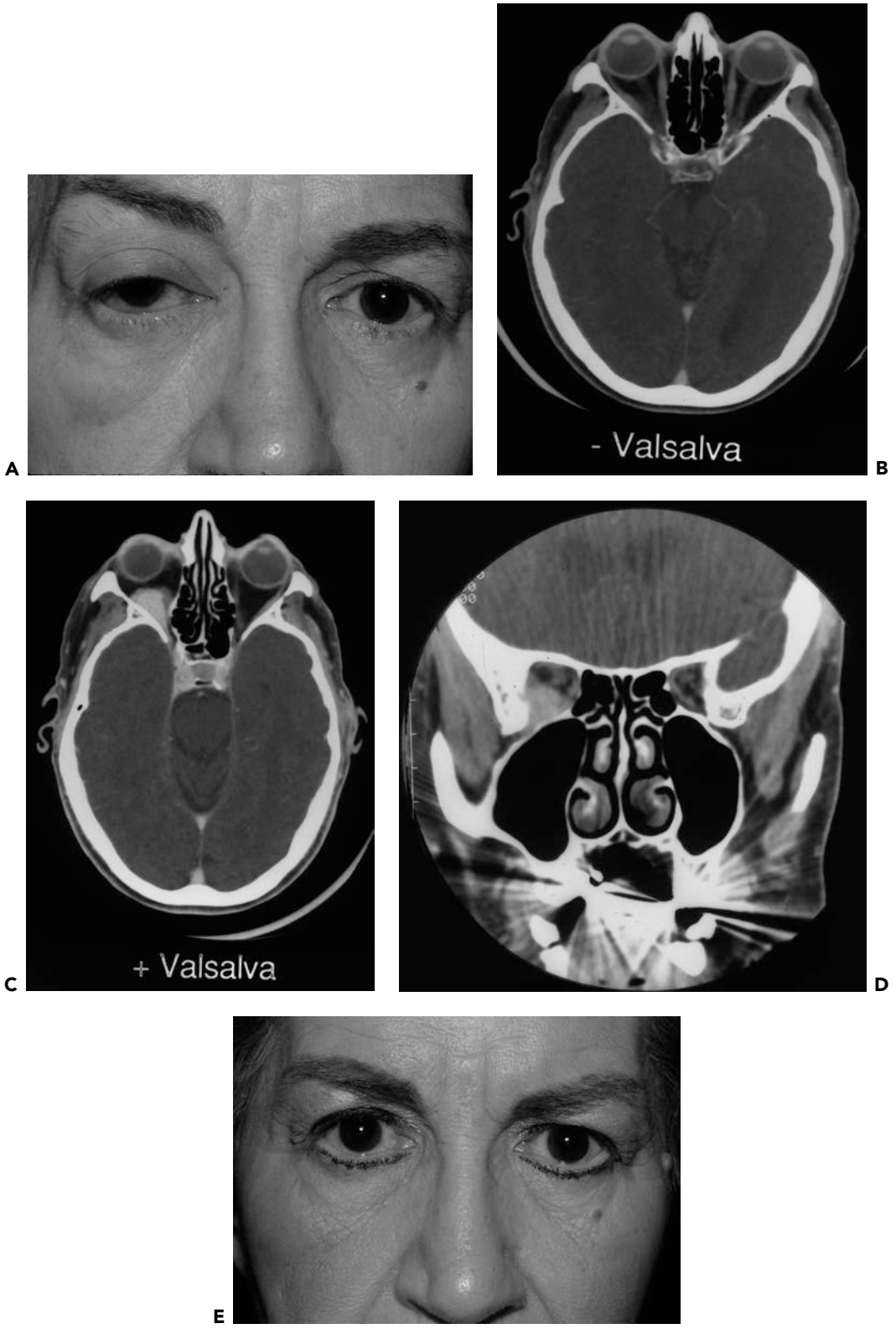

Figure 11.5 Orbital varix with acute hemorrhage. **A:** A 68-year-old female with sudden onset of pain and proptosis. Note the ecchymotic eyelids. **B:** Axial computed tomography scan before Valsalva maneuver shows minimal enlargement of right lateral rectus muscle belly and ill-defined density in the posterior lateral apex. **C:** Axial computed tomography after Valsalva maneuver is associated with enlargement of the varix, which is now clearly evident. **D:** Coronal computed tomography shows an enhancing infiltrative lesion in the posterior, inferior, lateral portion of the orbit. The apparent extension toward the inferior orbital fissure is typical of some varices. **E:** Normal clinical appearance 1 month later.

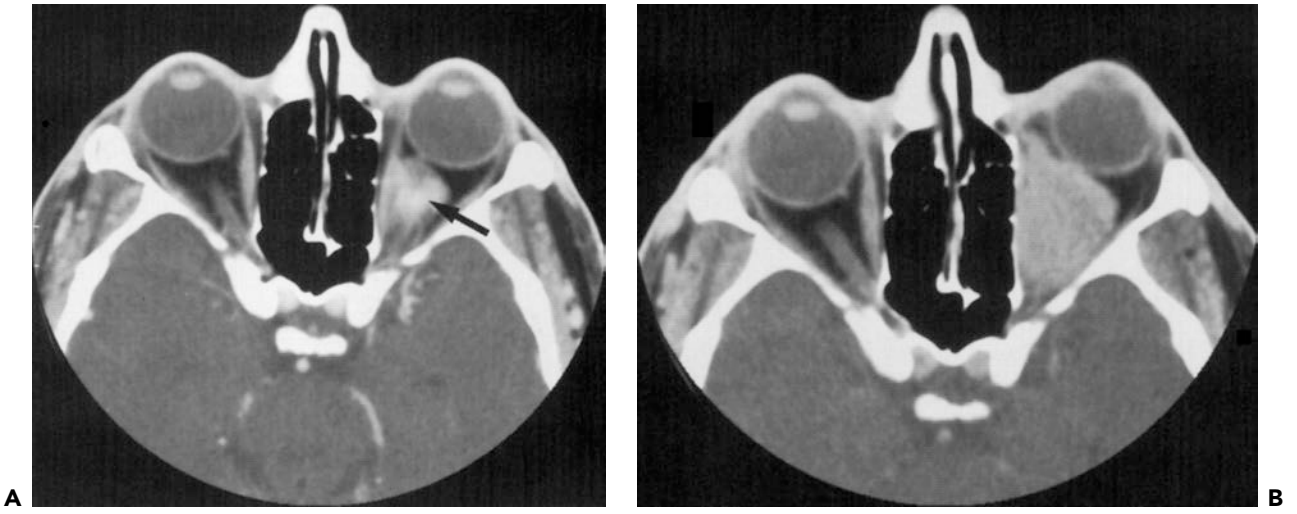

Figure 11.6 Acquired varix: A 48-year-old man with a 6-month history of discomfort and prominence of left eye when ''bending over.'' No proptosis in the upright position. Computed tomography **(A)** shows a homogeneous, enhancing, irregularly contoured, hyperdense mass (*arrow*) in left orbit inferior to optic nerve. **B:** The mass increases by half its volume with the Valsalva maneuver.

fat. The high intensity of the signal of orbital fat partially obscured the varix when it was not distended.

Although the diagnostic role of venography has largely been replaced by CT, MR, and echography, it is still an important adjunct of surgical management of the varix if surgical removal is necessary. The extent and ramifications of the varix will show to better advantage with venography than with the other imaging methods.

Pathology

Microscopically, under low-power magnification, the congenital varix will consist of a plexiform mass of vascular channels with walls of varying thickness, whereas the tissue from an acquired varix more likely will be a single enlarged vein. The congenital varix likely has been present for some years before it reaches the stage of histopathologic study. Hence, this lesion will reflect the passage of time in the thickening of the walls of the veins, the presence of interstitial fibrosis, an infiltration of chronic inflammatory cells, variable degrees of thrombosis, and intraluminal calcification (phleboliths) (see Fig. 11.7). In the acquired varix, on the other hand, recent laminated thrombus will be the dominant feature. The thrombus may be in various stages of organization, such as was described for the organizing hematoma (Chapter 4), and may show evidence of recanalization. In both types of varix, the Masson trichrome stain will help identify the smooth muscle content of the venous wall.

Therapy

In general, a conservative approach to the therapy of varix, of whatever type, is the rule. In the symptomatic varix, surgical management is undertaken if the intermittent proptosis becomes a cosmetic liability or a source of nagging discomfort. Rarely does this varix lead to visual loss or extreme pain, unless there is spontaneous intraorbital hemorrhage or unexpected thrombosis. Sudden thrombosis of a varix, typically in an elderly adult, associated with

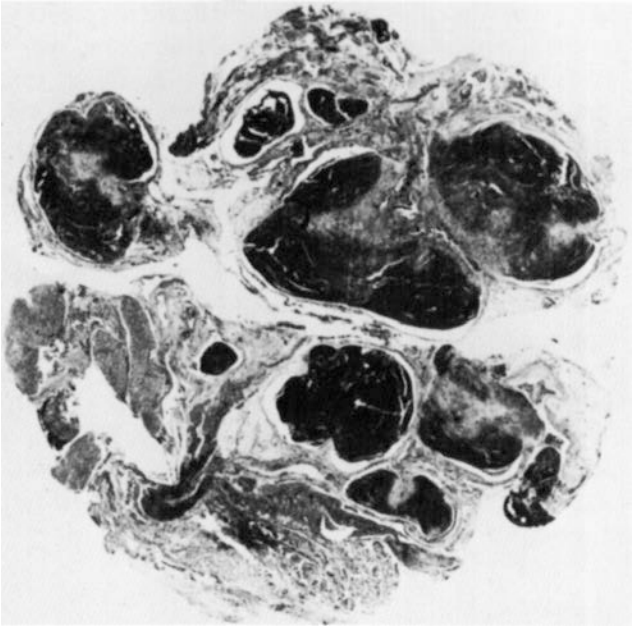

Figure 11.7 Varix: A cluster of ectatic venous channels (×6). (From Jakobiec FA, Font RL. Vascular tumors and malformations. In: Spencer WH, ed. *Ophthalmic pathology. An atlas and textbook*, Vol. 3. Philadelphia, PA: WB Saunders; 1986:2544, by permission, WB Saunders.)

visual impairment and an acute rise in intraorbital pressure, is the compelling factor in surgical intervention in these patients.

The principal risk in surgical intervention is, of course, uncontrolled hemorrhage. Currently, hypotensive anesthesia helps to lessen this problem. Even so, some bleeding tends to complicate the meticulous dissection that is necessary if removal of varix is the intended goal. Also, bleeding tends to obscure the fine branches of the motor nerves to the extraocular muscles, which may inadvertently be cut, resulting in some degree of blepharoptosis or ophthalmoplegia. In cases of unsatisfactory hemostasis, postoperative bleeding into the orbital reticulum may pose a threat to vision. The use of intraoperative venography with intralesional cyanoacrylate glue embolization followed by excision of the resultant cast was described by Lacey et al. (1999). Fluoroscopic imaging was used in the operating room to confirm needle placement within the lesion and to facilitate manual occlusion of the venous outflow. Cyanoacrylate glue was then injected into the lesion followed by excision. The glue-casted lesion can then be manipulated to facilitate its removal. This technique also minimizes blood loss. In one of their patients in whom the cast was initially left in place, orbital inflammation ensued 6 weeks later. Excision of the glue-cast had an associated foreign body response and thereafter the authors recommended glue-cast excision for all patients.

In one of our cases of congenital varix, the lesion was approached through a frontotemporal craniotomy. Under direct view, the anterior and posterior extent of the lesion was ligated, and the mass of dilated vessels removed in toto. Two months after surgery, the patient's pain was totally alleviated, but marked blepharoptosis and complete sixth nerve palsy were present. Another one of our patients, a 29-year-old man had a 5-year history of progressive positional proptosis with escalating pain. He also underwent a similar craniotomy with clipping and excision of his right orbital lesion. He had paresis of the inferior division of III, which persisted for 9 months. He is currently asymptomatic with 8 years of follow-up. Vascular clips were applied to the proximal extent of the varix with excision of the mass anterior to the clips by Rathbun et al. (1970) and Beyer et al. (1985). Beyer believed that hemostasis was more secure with clips than with ligatures or surgical cautery. He pointed out that ligatures tend to slip or come loose, and the cautery tends to rupture the vessel with subsequent necrosis in the area adjacent to the cautery.

In the varices of adults associated with thrombosis and acute proptosis, incision of the affected vessel and extirpation of the blood clot is usually sufficient to relieve the subjective morbidity. In the three cases of this type reported by Bullock et al. (1989), the remainder of the lesion was left undisturbed except for the use of the cautery to obtain hemostasis. Handa and Mori (1968) and Ward (1987) recommend electrothrombosis after surgical exposure of the venous mass or dilated vein. Thrombosis is induced by the intraluminal insertion of a suitable-size needle connected to an anodal current.

The surgeon who does this surgical procedure for the first time should keep in mind that a varix often is in a collapsed state when the patient is supine. This can be a real hindrance to the discovery and dissection of a varix, particularly in the posterior orbit. In such a case, surgical management of the lesion is greatly enhanced by the application of jugular compression, placing the patient in the Trendelenburg position, or having the anesthesiologist increase the intrathoracic pressure. Conservative therapy with expectant observation remains paramount in our practice unless clinical events dictate otherwise. As Lacey et al. (1999) stated, the development of a biodegradable intravascular sclerosant/thrombosant holds promise for obviating surgery in these challenging orbital lesions.

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Orbital Aneurysm

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Malignant Melanoma

12

The update of the manuscript written on the subject of malignant melanoma for the third edition of Orbital Tumors (1994) was largely based on a publication of Lorenz Zimmerman (1986). Zimmerman had long been interested in the ophthalmologic aspects of malignant melanoma. His tome on the subject contained 124 references of which 26% (34/124) have the name of Zimmerman as author or coauthor. This 29-page report included heterogeneous information on the subject written before 1986 and combined it with his own research. The result was the most factual information on the subject up to 1986. Our 40-year (1948 to 1987) review of the site of origin, age, sex, treatment, and follow-up of the 43 patients seen at Mayo Clinic is reprinted in Table 12.1.

In this chapter, we will try to update the information on the management, course, prognosis, and so on of malignant melanoma, which has evolved since our third edition. Our chief interest is the primary orbital melanoma but also includes pertinent data concerning cases with orbital extension from the uveal tract, paranasal sinuses, epibulbar and conjunctival surfaces, adnexal structures of the eyelid and face, and metastatic tumor.

PRIMARY TUMOR

In the present timeframe of our update review (1988 to 1997), we have not encountered a primary orbital malignant melanoma. Probably, the most informative publication in this period is that of Tellada et al. (1996). They studied 21 cases from the file at the Armed Forces Institute of Pathology. The mean age at diagnosis was 42 years (range 15 to 84 years). There was an associated intraorbital blue nevus (see Figs. 12.1 and 12.2) in 19 patients (90%), and in 10 patients (47.5%) there was some form of congenital melanosis. All patients were of the white race. The male-to-female ratio was approximately 3:1 (16 men, 5 women). Histopathologically, 11 (52%) tumors were of the mixed cell type and 10 (48%) were spindle cell tumors. Risk factors for poor prognosis in their series were associated with mixed cell type histology and high mitotic content. They conclude that primary orbital melanomas are similar to uveal melanomas with respect to prognostic indicators.

Single case reports in the literature during the current period are: Loffler and Witschel (1989) (M 27); Rice and Brown (1990) (F 17); Shields et al. (1993) (M 70); Ijiri et al. 2000 (F 5). Two tumors of the above group originated from a cellular blue nevus. The other two were thought to be *de novo*. In none of the four cases was there any accessory pigmentation in the orbital soft tissues. Histologically, two tumors were of the spindle cell type; one was a mixed epithelioid–spindle cell tumor, and one was predominantly epithelioid type. At the time of presentation, two of these cases were thought to have an orbital vascular tumor. In one of the latter, the orbital mass had the imaging characteristics of a varix. In the 5-year-old child, repeated episodes of subconjunctival hemorrhage were noted.

SECONDARY TUMORS FROM AN INTRAOCULAR SOURCE

In the third edition of this text, and as noted in the preceding text, we listed 23 patients with an orbital extension from an intraocular malignant melanoma. We tabulated the age, sex, treatment, and follow-up of these patients over the 40-year period from 1948 to 1987. In all but three of these cases, an enucleation or evisceration of one eye had previously been performed. Such patients were aware their eye contained either a *tumor* or a *malignant melanoma*. In these cases, the suspicions of both patient and physician for recurrent tumor were confirmed. Most of these patients sought consultation because of the need for frequent adjustments of their prosthesis over a period of several months. An occasional patient also noted some discoloration of his/her eye socket. Rarely, the initial manifestation of orbital recurrence was associated with swelling of the eyelids and orbital pain, a likely indication of hemorrhage or necrosis within the neoplasm. In all these patients, an orbital mass other than an orbital implant was palpable. The age range of these patients was 16 to 84 years; the average age was 60.6, and the follow-up range

TABLE 12.1
ORBITAL MALIGNANT MELANOMA: SITE OF ORIGIN, AGE, SEX, TREATMENT, AND FOLLOW-UP, 1948–1987

	Age	Sex	Treatment	Status	Follow-up
Primary (N = 4)					
Orbit	13	Male	Complete excision	L + W	29 y
Orbit	34	Female	Complete excision	L + W	8 y
Orbit	49	Male	Partial excision	Dcd	22 m
Orbit	62	Female	Partial excision	Dcd	9 m
Secondary (N = 35)					
Eye	16	Male	Excision and radiotherapy	L + W	20 y
Eye	29	Female	Radiotherapy	Dcd	10 m
Eye	42	Male	Exenteration	Dcd	4 y
Eye	46	Male	Exenteration	L + M	2 y
Eye	48	Female	Exenteration	Dcd	4 y
Eye	53	Male	Exenteration	Dcd*	62 m
Eye	54	Male	Exenteration	Dcd	14 m
Eye	57	Female	Exenteration	Dcd	3 y
Eye	59	Male	Exenteration	Dcd*	14 y
Eye	62	Female	Exenteration	Dcd	67 m
Eye	64	Female	Exenteration	Dcd	6 m
Eye	67	Female	Exenteration	L	33 m
Eye	67	Male	Radiotherapy and partial excision	L + T	2 y
Eye	67	Female	Subtotal exenteration and radiotherapy	Dcd*	91 m
Eye	67	Female	Exenteration and radiotherapy	Dcd	18 m
Eye	68	Female	Exenteration	Dcd	7 m
Eye	69	Male	Exenteration	Dcd	3 m
Eye	69	Female	Exenteration	Dcd	14 m
Eye	69	Female	Exenteration	Dcd	15 m
Eye	76	Male	Radiotherapy	Dcd	Cause?
Eye	80	Male	Partial excision	Dcd*	4 y
Eye	82	Male	Biopsy	L + M	21 m
Eye	84	Female	Exenteration	Dcd	Cause?
Antrum	45	Female	Electrocoagulation	Dcd	1 y
Antrum	50	Male	Exenteration	—	No follow-up
Antrum	62	Female	Exenteration	Dcd	15 m
Nasal cavity	62	Male	Exenteration	Dcd	20 m
Ethmoid sinus	63	Male	Radium implants	Dcd	14 m
Epibulbar	48	Male	Biopsy	—	No follow-up
Caruncle	50	Male	Exenteration	Dcd	1 y
Conjunctiva	52	Male	Partial excision and radiotherapy	Dcd	62 m
Conjunctiva	71	Male	Radiotherapy and subtotal exenteration	Dcd	9 y
Conjunctiva	80	Male	Subtotal exenteration	Dcd	22 m cause?
Eyelid	77	Male	Multiple excision radiotherapy and exenteration	Dcd*	14 m
Upper face	68	Male	Radical extirpations, radiotherapy, and chemotherapy	Dcd	11 y
Metastatic (N = 4)					
Back	36	Male	Incomplete excision, radiotherapy, and chemotherapy	Dcd	5 m
Back	64	Male	Biopsy	Dcd	2 m
Groin	69	Female	Radiotherapy and biopsy	Dcd	22 m
Nasal septum	92	Male	Exenteration	Dcd	20 m

L + W, living without known recurrence or metastasis; Dcd, death from tumor; Dcd*, death from cause other than tumor; L + M, living with metastasis; L, living but no data concerning status of tumor; L + T, living with tumor at original site; Cause?, cause of death not known.

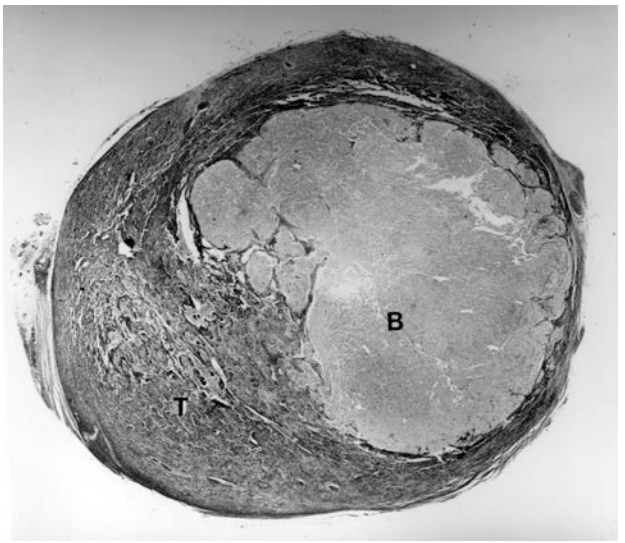

Figure 12.1 A well-circumscribed tumor consisting of pigmented epithelioid malignant melanoma (T) arising from an amelanotic cellular blue nevus in a 13-year-old male (B) (×5). This patient was living without tumor recurrence 29 years later.

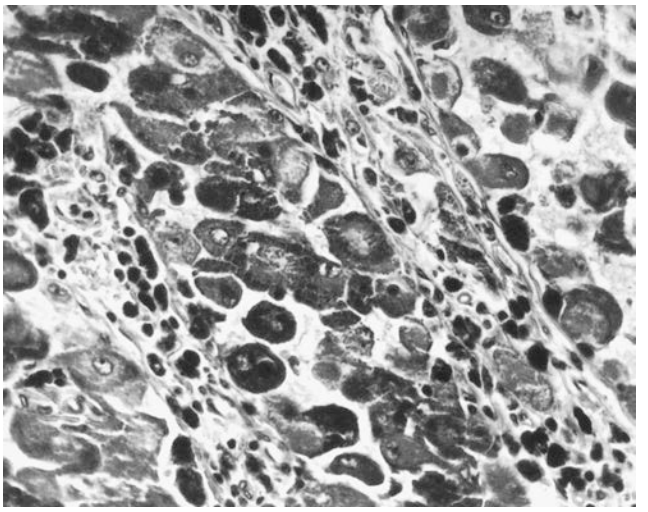

Figure 12.2 Section (melanotic zone T) showing epithelioid cells. Note the round, granular, rather uniform melanosomes (×385). Compare to Figure 12.6.

was 3 months to 20 years. The sex ratio was 12 women and 11 men. We now add six cases to this group of secondary melanomas seen in the last decade (1988 to 1997) of our 50-year statistical survey. These included two men, ages 50 and 65, and four women, ages 74, 75, 81, and 85. Follow-up time for this group of six patients was too short to make any statement concerning the effect of treatment on prognosis.

Some additional cases of orbital extension of intraocular melanoma in the literature in the present timeframe (1988 to 1997) of our review, including authors, sex and age of patients, are: Sallet et al. (1993), 41-year-old man; Liarikos et al. (2000), nine patients; Sambuelli et al. (2001), 75-year-old man; and Mittica et al. (2003), a 61-year-old woman. All were managed by exenteration of the orbit. The patients of Liarikos et al., also received radiotherapy and chemotherapy.

A large randomized North American clinical trial by the Collaborative Ocular Melanoma Study (COMS) was inaugurated in 1986 and concluded on July 31, 1998. The study included nearly 9,000 patients with choroidal melanoma evaluated at 53 COMS clinical centers in the United States and Canada. They now recommend enucleation of eyes containing large intraocular tumors >8 mm in thickness and/or >16 mm in longest base diameter (Robertson, 2003). However, not all patients so treated will have an extraocular extension.

What should be done if extraocular extension is present? In a study published prior (1986) to the COMS survey, Pach et al. (1986) analyzed 46 patients with follow-up data of 1 to 23.5 years collected from the Mayo Clinic (between 1911 and May 1982) with extraocular extension of a choroidal melanoma. They found that all patients who underwent exenteration developed metastasis and died. They concluded that exenteration was of little value other than local palliation. They further suggested that adjunctive radiation should be considered if the tumor extension has been surgically transected, but it is not necessary in cases where extraocular extension has not been transected.

Later, Hykin et al. (1990) treated ten cases in which an extraocular extension was transected at time of enucleation with external beam radiation. Only one patient experienced an orbital recurrence in the timeframe of their follow-up observation.

For cases in which brachytherapy has been considered for a given tumor and it is discovered there is an extraocular extension that is relatively small (<3 mm in thickness), it may be reasonable to proceed with brachytherapy and place the radioactive plaque on top of the extraocular extension with the expectation the treatment will be unassociated with an orbital recurrence (Koranyi et al., 2000).

Ultrasonography is the preferred scanning procedure to reveal a small, unsuspected extraocular extension of uveal melanoma (see Figs. 12.3A–C and 12.4).

SECONDARY TUMOR FROM NASAL CAVITY OR PARANASAL SINUS

Five of our patients had this type of tumor (Table 12.1). The clinical feature common to all five was evidence of orbital invasion or destruction demonstrated by roentgenography or computed tomography. Accessory signs of orbital invasion were a palpable mass, upward or lateral displacement of one eye, or swelling of soft tissues at the medial canthus. In two of the patients, orbital invasion was present at the time of initial diagnosis of paranasal sinus tumor. In three

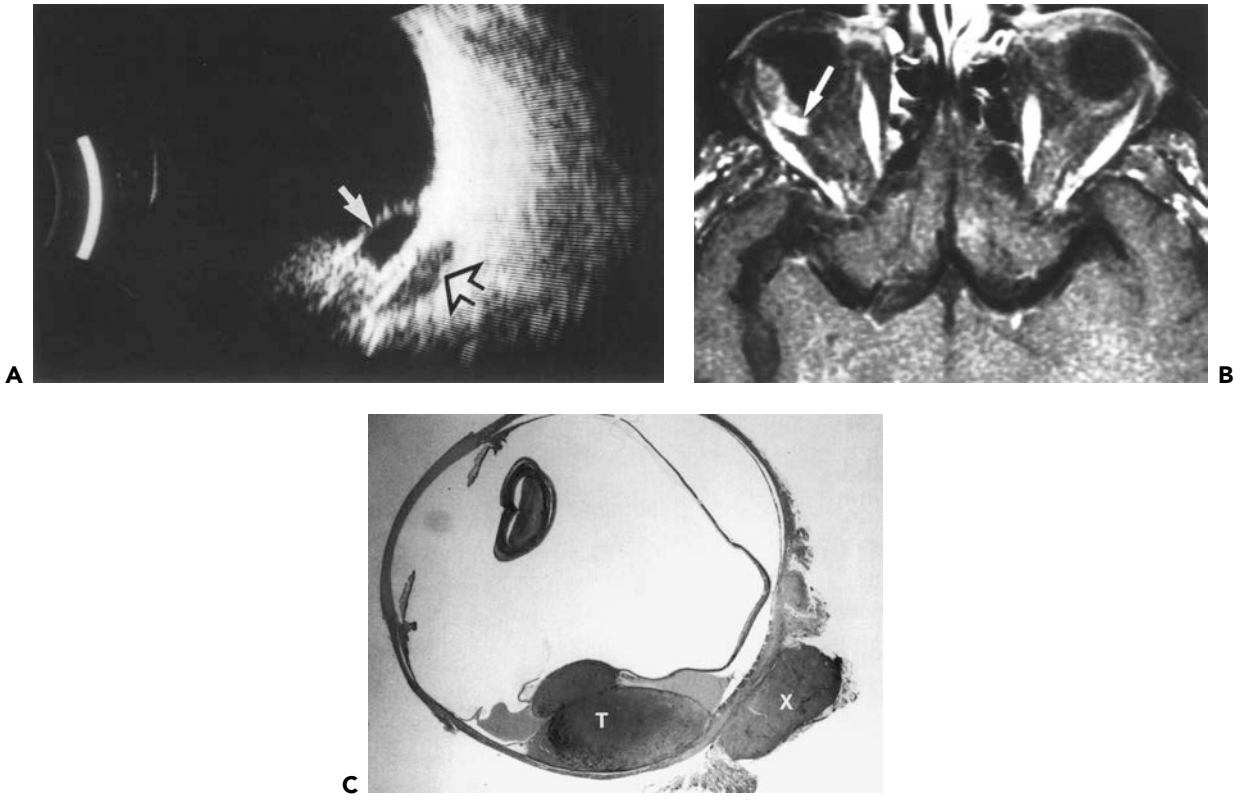

Figure 12.3 **A:** Scan ultrasonogram shows intraocular tumor (*arrow*) and extrascleral extension (*arrowhead*) **B:** Gadolinium-enhanced T_1-weighted magnetic resonance imaging (MRI) with fat-suppression technique shows intraocular mass (*arrow*) with tail-like extrascleral extension medially toward optic nerve. There was decreased signal with T_2-weighting, a characteristic compatible with malignant melanoma. **C:** Gross specimen showing intraocular tumor (T) with extrascleral extension (X) correlating with ultrasonogram and MRI. (All photos courtesy of DM Robertson, Rochester, Minnesota.)

patients, several surgical procedures had been performed for recurrent tumors before orbital extension occurred. The overall symptomatology of this small group was not specific for malignant melanoma and differed little from that of patients with other malignancies in this area such as adenocarcinoma.

SECONDARY TUMOR FROM OCULODERMAL MELANOSIS, EYELID, AND CONJUNCTIVAL MELANOMA

The term *oculodermal melanosis* or "melanoma" designates cutaneous tumors arising from the "dendritic melanocyte." This can occur in association with oral, intranasal, and leptomeningeal melanocytosis. The histomorphology of this cell differs from that of the melanocyte of neuronal crest origin associated with the primary orbitae and the intraocular melanoma with orbital extension. (vida infra, "Pathology"). Here, we will discuss the malignant melanomas which appear in the skin of the upper face and adjoining lower eyelid, the temple, the upper eyelid and eyebrow, the conjunctiva, and caruncle which prove to have orbital extension (see Fig. 12.5).

It is the melanotic spot, nodule, or a flat cluster of cells, which initially appears on any of the above anatomic areas in an adult, which is of most concern as a possible malignant melanoma. In contrast, melanotic spots in similar areas in children are usually benign. The latter may not become malignant unless there is some change in the size or color of the lesion as adolescence or adulthood approaches. At the time of its first appearance in adults, we do not know of any fool-proof way to determine, only on a clinical basis, whether the lesion is benign, a precursor of malignancy (acquired melanosis), or frankly malignant; unless there is rapid enlargement of the melanotic cluster. Only biopsy with histopathologic study of the section will provide an answer to this question (see Fig. 12.6). Some lesions, particularly, may be relatively amelanotic.

Over a period of years, we have seen a small number of patients who presented with secondary orbital extension. We have noted that many years may elapse from the time a pigmented lesion is first discovered on the surface of

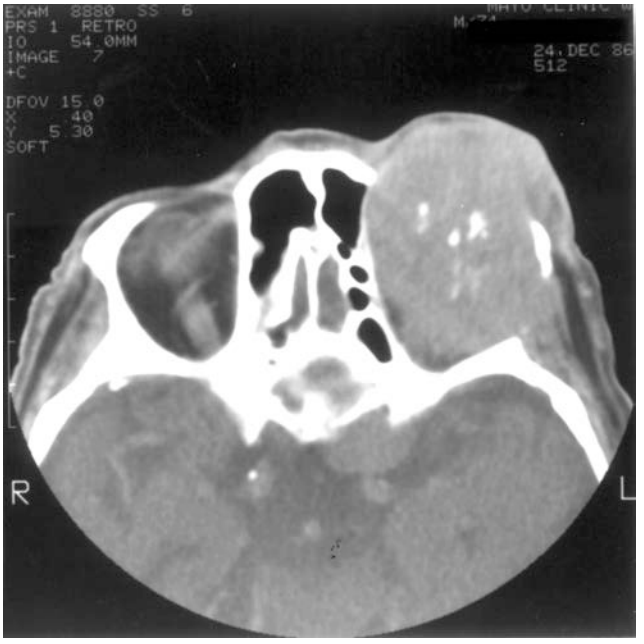

Figure 12.4 Axial computed tomography scan shows huge, homogeneous mass across orbital floor with calcific-like densities that has produced pressure remodeling of medial and lateral orbital walls. This mass was the presenting feature of an 82-year-old man who had a blind left eye of 22 years' duration.

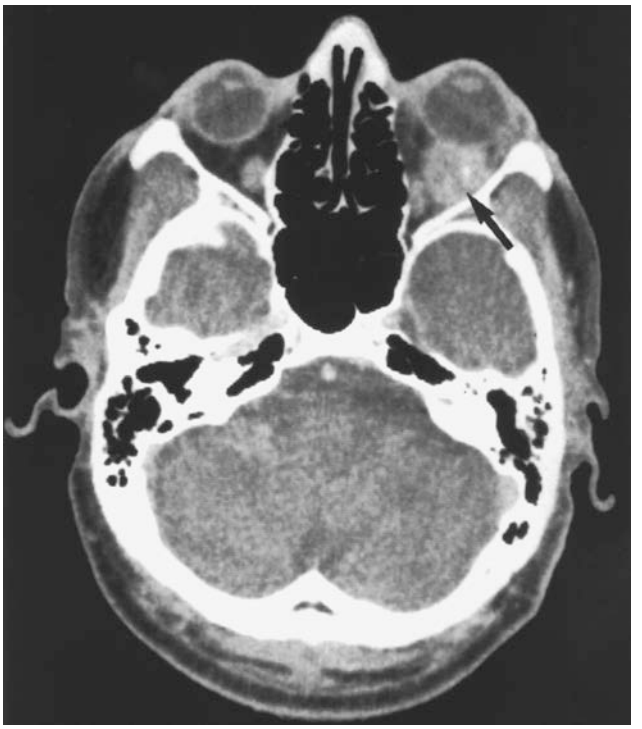

Figure 12.5 Axial computed tomography scan showing multilobulated, retrobulbar enhancing mass (*arrow*) in left orbit secondary to an acquired melanosis of conjunctiva in a 52-year-old man. Slight decrease of vision and 4 mm proptosis of 4 months' duration were the only symptoms. This case illustrates the rapid progression, size, and depth of orbital infiltration from an innocuous-appearing source.

the eye or periorbital skin until the reality of an orbital extension is manifest. In the meantime, the lesion may wax and wane, and a long time may pass before a biopsy definitely establishes a malignant transformation. In one of our patients, 7 years passed before a diagnosis of malignancy of an epibulbar lesion was established, and another interval of 14 years elapsed before orbital extension. In another patient, the original lesion was thought to have been present 35 years before malignancy was established and another 5 years before orbital extension occurred. Overall, these patients seem to survive longer both before and after orbital extension than patients with secondary melanomas from an intraocular source. The oculocutaneous neoplasm is the only one prone to lymphatic spread. This is usually manifested by enlargement of the preauricular or submandibular nodes on the side of the tumor.

In the early decades of the last half century, complete surgical resection was the recommended management of an initial area of oculodermal melanosis. This was assumed to be the best way to affect a cure. With a further decade or so of follow-up, some, but not all cases had recurrences. The recurrence would either appear at the site of the surgical melanosis or pop up somewhere else on the periorbital skin or surface of the eye. A histopathologic examination of the recurrent tumor showed "atypical melanocytes," such as would be present in a superficial spreading malignant melanoma. The recurrence appearing in areas other than the original site also showed evidence of pagetoid spread of melanotic cells. The surgical extirpation of the *acquired melanosis with atypia* recurrence becomes the first of a continuum of surgical resections of recurrences over a period of subsequent months or years. Each surgery of this series sacrifices more tissue. Finally, what has become a malignant melanoma reaches the tissues of the retrobulbar orbit.

At this point in time, exenteration of the orbital contents, with or without adjunctive laser ablation, cryotherapy, chemotherapy, or radiation, is performed in the hope of eradicating the neoplasm. In our experience, all of these patients died of their malignancy, and the final surgical ventures are, in my opinion, *exercises in futility*. If, at the time of orbital extension, pain is a major concern of the patient, an enucleation of the eye can be performed, but an orbital exenteration can be avoided. This will eliminate the patient having a large hole in his/her skull during the interval of survival. Small doses of palliative radiotherapy may be given until death intervenes. We have included recent references describing desmoplastic spindle cell melanoma involving the eyelids/orbit (Dithmar et al., 1999; Ellis et al., 1994) along with periorbital cellular blue nevus with orbitopalpebral and intracranial melanoma (Gunduz et al., 1998) and a large series of exenteration for conjunctival melanoma (Paridaens et al., 1994).

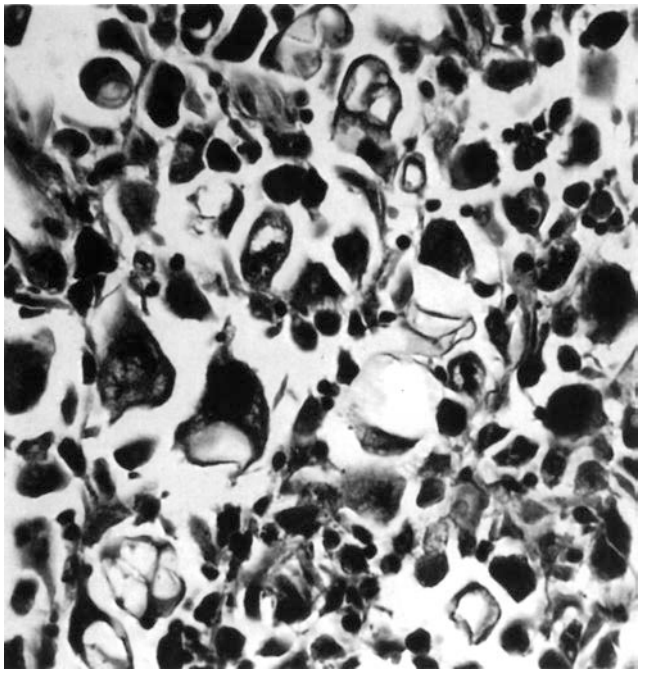

Figure 12.6 Recurrent epithelioid tumor 5 years after enucleation of eye for epibulbar melanoma. Note the pleomorphism of cells. The melanosomes are coarse and irregular in contour (×325).

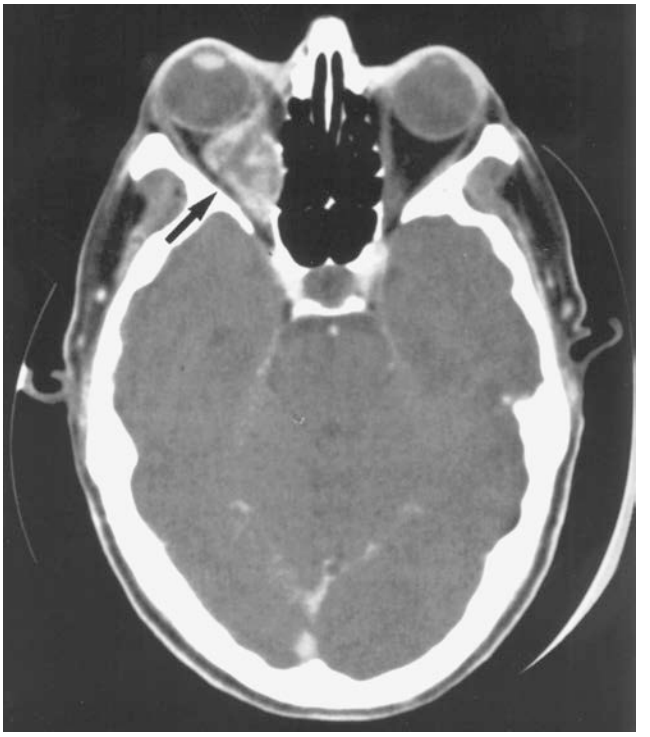

Figure 12.7 Metastatic malignant melanoma. Axial computed tomography scan of 64-year-old man showing right proptosis associated with a slightly enhancing, inhomogeneous mass in the posteromedial orbit (*arrow*), that surrounds or even be intrinsic within the medial rectus muscle and displaces the optic nerve laterally. Patient had widespread skeletal metastases from a malignant melanoma in the left flank that had been excised 3 years earlier. The extraocular muscles are a common site for orbital metastatic disease.

METASTATIC TUMOR TO THE ORBIT

The site of origin of a malignant melanoma metastatic to the orbit may be anywhere in the skeletal system but occurs most often from the skin of the back. Also, a metastasis from an intraocular source, either before or after enucleation is frequently reported. Sometimes, the primary is very small and tucked away in some unusual place (i.e., the scalp, underneath the fingernail or toenail). Usually, when extension to the orbit is discovered, metastasis to other anatomic sites has already occurred. In general, orbital metastasis is a late event. Local treatment of the orbital metastasis by any method is lacking. There is no systemic remedy (see Fig. 12.7).

Pathology

The malignant melanocyte is the cell common to the several types of malignant melanoma noted in the preceding text. However, the cellular pattern differs somewhat dependent on the site of origin of the tumor. The primary orbital melanoma is usually a mixture of epithelioid and spindle cells, but either of these cell types may predominate in any given case. A tumor containing a high proportion of epithelioid cells is the more malignant form (Spencer, 1996). The cells stain positively for S-100 protein and antimelanoma specific antibody. The granular melanosomes of the epithelioid cells are round and uniform. All these histologic features pretty much recapitulate the histology of the uveal melanoma. In the primary orbital melanoma, satellite specks of flat brown melanosis are usually absent. If present, the nests of pigment are elevated, nodular, and dark representing a multifocal or pagetoid spread of the malignant lesion. These pigment clusters differ from the brown pigment flecks associated with an orbital spread of an oculodermal malignant melanoma.

The histopathology of the *orbital extension of an oculodermal melanosis* is much more complex. The histologic patterns may include nests and nodules of melanocytes in the basilar layer of the epithelium with or without extension into the substantia propria. The tissue specimen may show a random distribution of melanocytes or a pagetoid spread. Cell types include dendritic cells, epithelioid cells, and polyhedral cells with small, round nuclei and scant cytoplasm. The cells' melanosomes are coarse and irregular in contour, a distinct difference from the melanosomes of intraocular origin.

At the present time, a careful study of the melanin pigmentation at the original site or recurrent tumor is thought to be the chief means for determining whether the lesion is benign or malignant. If the hyperplasia of

the melanocytes does not show any atypia, the lesion is benign and will probably remain so in future recurrences, although this prediction is not absolute. The nuclei of these cells are small, dark, and surrounded by a clear halo. The cells lack nucleoli, and the nuclear shape is regular. In contrast, the cells with *atypia* have abundant cytoplasm (epithelioid cells) and variation in nuclear size and shape. The degree of malignancy may increase with the number of recurrences, particularly in adults. If these changes are found in a melanotic spot in a child, the tumor is probably a *junctional nevus*. Immunohistochemical stains have not added prognostic histologic information (Fuchs et al., 1989).

The tumor *metastatic* to the orbit is predominantly epithelioid in type. The cells are larger and more bizarre in size and shape than the preceding tumor. Some of these tumors may be so undifferentiated that staining with S-100 marker is equivocal or absent. However, the absence of reactivity to cytokeratins and common leucocyte antigens will suggest the diagnosis of malignant melanoma in such equivocal cases.

SUMMARY

Perhaps! At some future time, oncologists may conclude that a primary malignant melanoma of the orbit is curable, providing it is well circumscribed and is surgically removed intact and there are no flat, brown patches of melanosis in the adjoining orbital fat. Alas, for all of the other types of orbital malignant melanoma (noted in the preceding text), I believe the tumor is lethal, if they do not die of some other disorder during the short or longer interval after treatment. At present, the literature devotes much space to survival of the patient on the basis of the type of treatment administered. By and large, this data is meaningless. I believe survival is based on the efficacy of the patient's immune system, that is, its ability to suppress the concealed melanocytes these patients harbor. With aging, this suppressive effect lessens, eventually allowing melanosis or a malignant clone of melanoma to reappear. We agree with Robertson (2003) that, at present, what is needed is some way to either *modify* the patient's immune *system or discover a more potent systemic remedy, or a combination of both.*

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Hematopoietic Tumors 13

In this chapter, we will discuss a select group from a wide array of hematopoietic neoplasms that, in their extranodal, extralymphatic, intravascular, and extramedullary forms, often affect the soft tissues of the orbit. This select group includes the non-Hodgkin lymphomas, the myelogenous tumors, and Hodgkin lymphomas. Also, we will add a brief discussion of the non-neoplastic lymphoid hyperplasia that, if the antigen stimulus responsible for the hyperplasia does not subside, may become malignant. Likewise, amyloidosis (AL), as it affects the orbit, is included because this protein dyscrasia is sometimes associated with a malignant clone of plasma cells.

CLASSIFICATION

Classification of these tumors, which is important for their diagnosis by the pathologist and for an estimate of their prognosis by the clinician, has been an integral component of the prior editions of this text. Starting with the decade of the 1940s and continuing through 1993, hematopoietic tumors were the subject of numerous classifications such as: Rappaport, Dorfman, Kiel, Lukes and Collins, World Health Organization (WHO) (1982), British National Lymphoma Investigation, Working Formulation, Revised European American Lymphoma (REAL), and non-Hodgkin Lymphoma Pathologic Project. However, there was considerable duplication inherent among the classification and the goal of a single worldwide classification encompassing the advances in diagnostic histopathology, genetic features, management, and survival of patients with hematopoietic tumors remained elusive. Accordingly, the WHO, in 1995, launched a project to provide "*the first, true worldwide consensus classification of haematologic malignancies*" that would include standardized nomenclature for the study and definition of the tumors' clinical oncology, and multicenter therapy trials and comparative studies in different countries. They solicited proposals and advice from hematopathologists, geneticists, and clinicians. The classification project was completed in 2001 with their publication, Pathology and Genetics of Tumors of Haematopoietic and Lymphoid Tissues. This publication "stratifies neoplasms primarily according to lineage: Myeloid, lymphoid, histiocytic/dendritic cell and mast cell. Within each category, distinct diseases are defined according to a combination of morphology, immunophenotype, genetic features, and clinical syndromes." In the latter category, a total of 75 distinct entities are listed. The group of mature B-cell neoplasms contains the largest (16) number of subtitles. The group of myelodysplastic/myeloproliferative disease and the group of immunodeficiency associated lymphoproliferative disorders each have the fewest (four) entities. The nomenclature for each entity reflects the editors' best estimate of its lineage and stage of differentiation. Overall, this *new* classification seems very complex and may require several years before its practical value is proved. We are yet to convert the 175 hematopoietic tumors in our 50-year collection to the WHO classification.

MATURE B-CELL NEOPLASMS

The title of this section was chosen by the WHO for the largest family of neoplasms within the wide array of hematopoietic tumors (see Table 13.1).

In the list (Table 13.1), we will first discuss the lymphomas that are known to involve the orbit, either as a localized tumor or part of the systemic disease. In prior editions of this text, these tumors were called *non-Hodgkin lymphomas*.

Non-Hodgkin Lymphoma

All of these tumors, despite the implication of benignity by the suffix "*oma*," are malignant, with varying degrees of morbidity and mortality. These neoplasms do not, necessarily, have a cell of origin but are thought to be clonal proliferations of B cells at various stages of differentiation.

Incidence

These lymphomas are the most common malignant neoplasms associated with orbital involvement. In our 50-year collection, there are 175 lymphomas comprising 9.7% (175 out of 1,795) of the total tumors. Eighty-seven tumors,

TABLE 13.1
WORLD HEALTH ORGANIZATION CLASSIFICATION

Mature B-Cell Neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone lymphoma
Hairy cell leukemia
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone B-cell lymphoma
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary effusion lymphoma
Burkitt lymphoma/leukemia

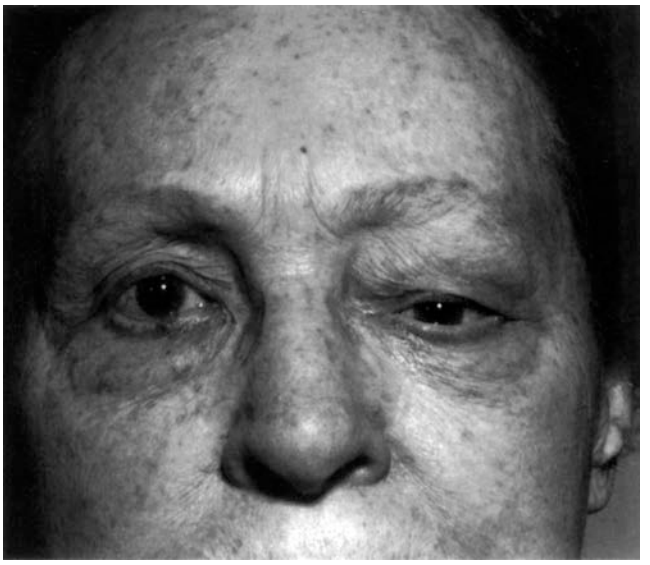

Figure 13.1 Lymphoma: A common presentation is a painless, unilateral swelling of an upper eyelid in an elderly individual. The droopy left upper eyelid of this patient conceals a slight downward displacement and minimal proptosis of the left eye.

4.8% of total tumors, were an extranodal manifestation of multifocal disease; 82 tumors, 4.5% of total tumors, were localized to the orbit; and six neoplasms (secondary type) invaded the orbit from a nasal, paranasal sinus, or conjunctival source—mucosa-associated lymphoid tumors (MALT). Almost all lymphomas with orbital involvement occur after the fourth decade. Only seven patients overall were <40 years of age. There was a slight preponderance of males (94) over females (81). Bilateral orbital involvement is relatively more frequent in the multifocal group. This incidence data does not apply to Burkitt lymphoma and large B-cell lymphoma because they occur more frequently in children.

Clinical Features

In patients with unifocal orbital lymphomas, the single most common presenting sign is either eyelid-related or some protrusion or change in the position of the eye. Less common presenting signs in order of frequency are a visible mass, diplopia, epiphora, redness of the affected eye, and a foreign body sensation. The principal sign is a painless puffiness, swelling, or edema of an eyelid on the affected side. If an upper eyelid is affected, it may be ''droopy'' (see Fig. 13.1). Seldom is the affected eyelid red or congested in appearance. These eyelid manifestations seem related to the juxtaposition of a mass either in the anterior orbit just behind the orbital septum or in the conjunctival fornix. A mass in the conjunctival fornix will have a smooth surface and a distinctive red-salmon color (see Fig. 13.2).

Proptosis, if present, is seldom marked in degrees. Approximately 70% of patients will have 6 mm or less of proptosis on the affected side. Approximately 10% of patients may have no proptosis. Others may have only a slight displacement of the eye without forward protrusion, which reflects the presence of a mass in the far forward region of the orbital space.

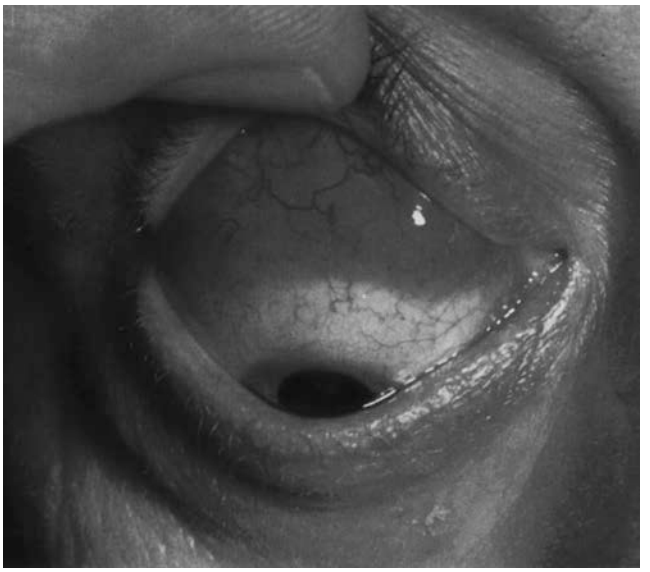

Figure 13.2 Lymphoma: A reddish salmon-colored mass was found on the surface of the right eye upon elevation of the upper eyelid of a 52-year-old man who had noted a slight prominence of the eye of 3 months' duration. The mass was a forward extension of another palpable mass in the anterosuperior orbit. The pattern of blood vessels on the surface of the mass, its color, and tendency of tumor to adapt to the curvature of the eyeball are quite distinctive of lymphoma.

The onset of the disease is insidious, and the mean duration of the presenting complaint in our series was 10 months (range 1 to 48 months). Most patients will have two or more of the aforementioned signs and symptoms at presentation. Other than the color and contour of a mass in the conjunctival fornix, if present, the presenting features are not specifically relative to other orbital tumors in adults (see Fig. 13.3A).

None of the other major orbital tumors of adults are so often associated with a palpable mass as these lymphomatous tumors. This reflects the tendency of these soft tumors to extend along fascial planes of the anterior orbit, extraocular muscles, and surface of the eyeball, rather than forming an isolated circumscribed mass in the posterior orbit. In this sense, the tumors tend to conform to the space in which they grow. In the inferior orbit, where there is less fascial restraint to expansion, the tumors may feel "shoddy," "corded," "nodular," or even "rubbery." In the superior orbit, where they may lie just behind the orbital septum, the mass is firm and less easily defined. Approximately 83% of our patients had a palpable mass.

The tumors may grow in any area of the orbit. In two of our patients, the tumors could be palpated in all four orbital quadrants. In general, these tumors localize in the superior orbit in a ratio of 2:1 over other combined orbital sites. The superior nasal and superior temporal quadrants are equally affected. In the superior nasal quadrant, the tumors are prone to cluster around the trochlea.

Other manifestations of these lesions such as significant visual loss, afferent pupillary defect, papilledema, and choroidal folds were seldom encountered. When present, these signs and symptoms usually indicate a lymphomatous tumor that has been unable to escape the more rigid fascial restraints at the orbital apex.

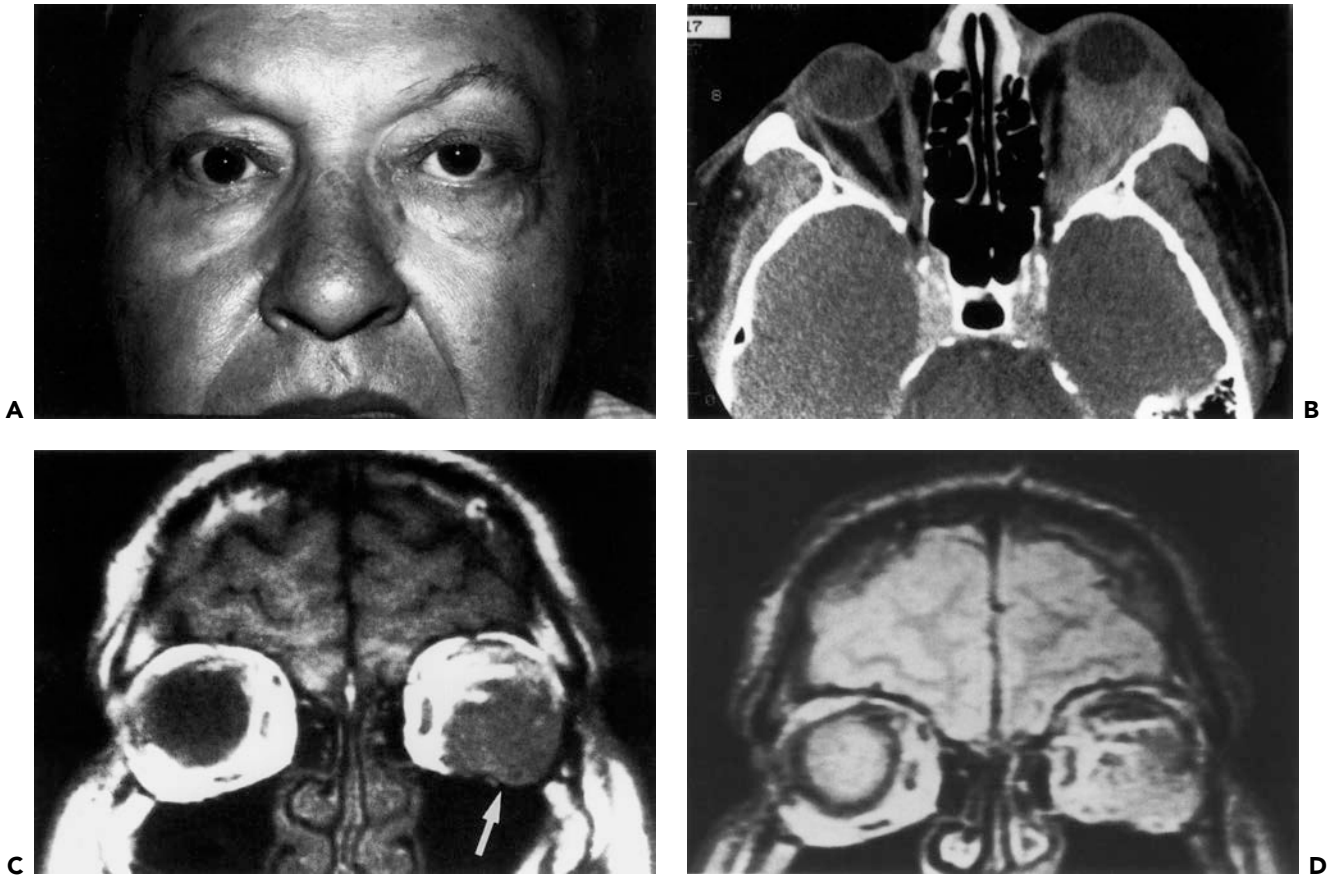

Figure 13.3 Lymphoma: **A:** A 61-year-old man with swelling of the temporal portion of the left upper and lower eyelids and slight upward displacement of the left eye. The edematous eyelids conceal a salmon-colored flat contoured mass overlying the left lateral rectus muscle and a purplish discoloration of the inferotemporal conjunctival fornix. **B:** Axial computed tomography scan showing the left orbit almost completely filled by a slightly enhancing homogeneous mass. The large size of the mass is disproportionate to the minimal objective findings in (**A**), a discrepancy not seen in most orbital tumors of adults. **C:** Magnetic resonance T_1-weighted coronal scan of the same patient showing a homogeneous hypointense mass (*arrow*) relative to the signal intensity of orbital fat. **D:** The lesion as seen on the spin-echo sequence.

Patients with either known or unsuspected *multifocal disease* differ little from those with unifocal orbital lymphoma in their orbital presentation.

Imaging Aspects

With computed tomography (CT) scan, the tumors are relatively high-density masses that show definite but mild contrast enhancement and are not associated with bone erosion unless they are located in the peripheral orbital space, the lacrimal gland, or are of the secondary type. The lesions are usually homogeneous, and the imaging shadow has a soft putty-like appearance. However, these features of the scan are nonspecific. A clinical aspect is the tendency of the lesion to extend along fascial planes and contour around solid structures such as the eyeball and intraorbital optic nerve. In areas where the mass pushes against soft tissue structures of greater density, the border of the lesion appears circumscribed; where there is little resistance to expansion, the border of the mass looks fuzzy. If the lesion is limited to the peripheral orbital space, its border may appear angulated. Another interesting facet involves the patients with minimal proptosis who have a large bulky mass that fills the entire orbital space (Fig. 13.3B). This disproportion between orbital mass and displacement of the eye is due to the soft consistency of the tumor. Study of the lesion with magnetic resonance imaging (MRI) usually shows a hypointense mass relative to orbital fat and an isointense mass relative to brain (Fig. 13.3C and D) on T_1-weighted sequence.

Iridium 111, a γ-ray emitter, can be used for radioimmunoscintigraphy as a surrogate of yttrium 90 monoclonal antibody, a β-ray emitter .

Pathology

The gross appearance of extranodal, unifocal orbital lymphomas gives no clue about their morphologic or immunotyping status. In color, the orbital tumors are some shade of gray, gray blue, tan, or reddish gray, which helps delineate the lesion from the surrounding yellow-hued orbital fat. Some observers have also described the tumors as purplish or maroon and likened this to the color of a cavernous hemangioma. In consistency, they are soft and friable but not necrotic. Although slightly lobulated, the lesions are reasonably compact when situated in the anterior orbit. Their surface is slightly circumscribed where the tumor abuts the orbital septum or is confined by a fascial partition. The posterior border of such a lesion, however, is less structured, infiltrative, and ill defined. They are reasonably avascular-appearing tumors until touched or manipulated. Then the surgeon is aware of the vascularity of their interlobular septae. When the tumors extend into the conjunctival fornices, their color changes to a reddish tan or salmon hue, and their smooth surface is covered by a visible vascular arcade. With low-magnification light microscopy, the tumors are hypercellular and stromal components are either absent or sparse. Two types of B-cell neoplasms comprised most of the unifocal, orbital lymphomas in our 50-year study. These were *the small lymphocytic lymphoma and the follicular lymphoma*. Occasionally, a third type was encountered, the *mantle cell lymphoma*. The first two are considered low-grade (indolent) neoplasms, whereas the mantle cell lymphoma is now known to be more aggressive (Looi et al., 2005). The small lymphocytic lymphomas are a diffuse proliferation of lymphocytes of nearly normal size with a scanty cytoplasm, round or dark nuclei, coarsely clumped nuclear chromatic, and inconspicuous nucleoli interspersed in a sparse stroma (see Figs. 13.4 and 13.5).

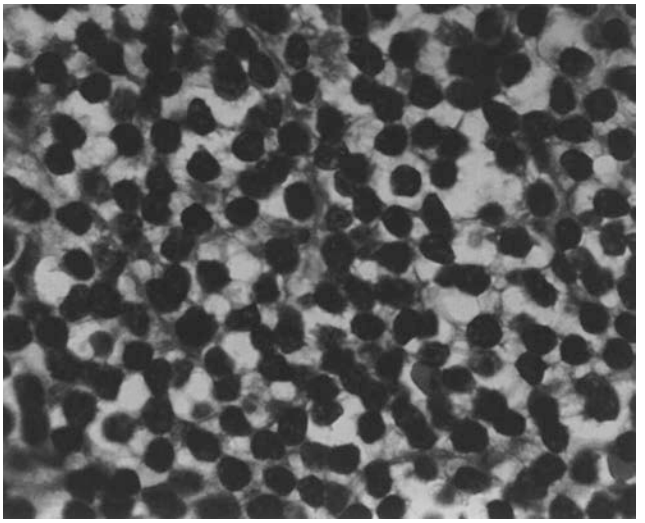

Figure 13.4 Lymphoma: Small lymphocytic diffuse type showing a uniform population of round and oval cells with regular nuclear outlines and scanty cytoplasm within a delicate stroma (×800).

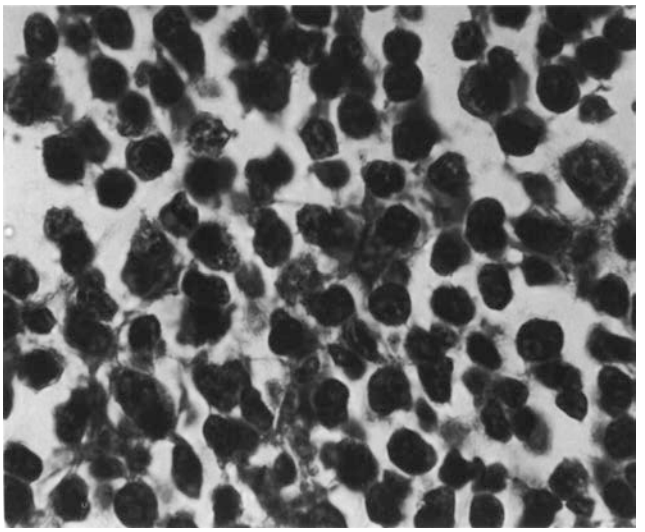

Figure 13.5 Lymphoma: Mixed type showing a population of small and large cells with differing amounts of nuclear chromatin and cytoplasm (×800).

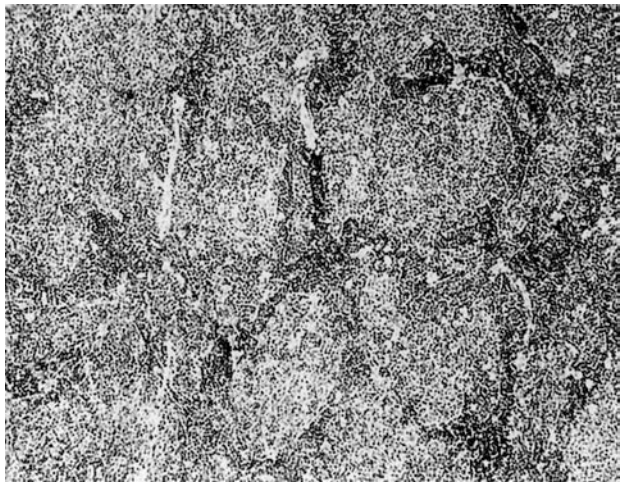

Figure 13.6 Follicular lymphoma: Ill-defined follicles without a clear distinction between mantle zones and follicular center zones. In both zones, the same monoclonal, cleaved cells are present (×100). (From Spencer WH. Follicular lymphoma. *Ophthalmic Pathology*. 1996;4:2710.)

In the *follicular* lymphoma, the germinal center with its surrounding zone of small lymphocytes (normal follicle) is replaced by a collection of small monoclonal lymphocytes with cleaved (infolded) nuclei. In the *mantle cell* lymphoma, the architecture of the follicle is preserved, but the periphery consists of monoclonal, small lymphocytes (see Figs. 13.6, 13.7, and 13.8).

Immunophenotypes

This staining modality is a useful diagnostic adjunct to differentiate benign lymphoid hyperplasias from lymphomas and, in addition, to separate some lymphoma types from one another. In general, the B-cell lymphomas of this section are positive for surface immunoglobin M (IgM), IgM and IgD, CD5, CD19, CD20, CD22, CD79a, CD23, CD43, CD11c, and as a rule, are negative for CD10, cyclin D1, and CD76b. CD23 and cyclin D1 are useful in distinguishing the leukemic and soft tissue phases of small cell lymphoma from mantle cell lymphoma. Rare cases of mantle cell lymphoma may partially express CD23; therefore, cyclin D1 should be assessed in lymphomas that are CD^+ and CD^- (WHO classification).

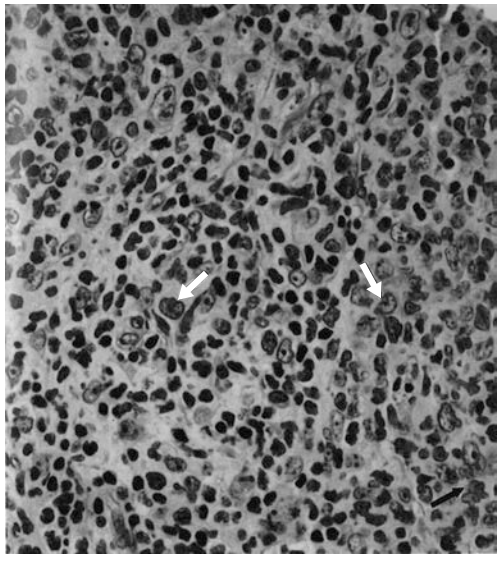

Figure 13.7 Lymphoma: A diffuse proliferation of predominantly small lymphoid cells which show (*arrows*) marked nuclear angulation and indentation (cleaved cells) (×640).

Figure 13.8 Mantle cell lymphoma: Small neoplastic cells proliferate as large, expanded mantles around residual benign germinal centers (×80).

Management and Course

Esik et al. (1996) published a retrospective review of experience at a single institution with 37 patients having "primary," *orbital* lymphoma treated with three modalities: Radiotherapy (17 cases), surgery alone (13 cases), and chemotherapy (7 cases). Patients were followed up with a mean and median of 7.6 and 6.2 years. There were 34 low-grade tumors; *small lymphatic lymphoma, follicular lymphoma, and mantle cell lymphoma*. The remaining three were higher grade lymphomas. Only patients with low-grade tumors were analyzed for effectiveness of treatment, recurrence, and survival.

Briefly, a summary of their conclusions were:

1. Radiotherapy in a relatively low dose (30 Gy) has the most decisive impact on the tumor when administered as the initial treatment. There was complete remission of the lymphoma over a 10-year period.

2. There was a high relapse rate in patients after surgery alone. Radiotherapy, at the time of relapse, was given to bring about remission.
3. Initial treatment with multiagent chemotherapy showed only a very slow, and sometimes no effect. It was difficult to achieve complete remission, even when radiotherapy was also given. Survival may be worse after initial chemotherapy (even with salvage radiotherapy) than with initial radiotherapy.

For intermediate and high-grade lymphomas, chemotherapy in combination with radiation therapy was shown to be more effective than chemotherapy alone (Miller et al., 1998). Subsequently, advances in biotechnology have led to the creation of a biologically active, unlabeled anti-CD20 chimeric (murine-human) antibody called *rituximab*. This is the first monoclonal antibody licensed (November 1997) by the Food and Drug Administration after review of multi-institutional, pivotal study of 166 patients confirmed its antitumor activity in the treatment of relapsed, low-grade lymphomas, particularly follicular lymphomas. The target for this antibody is the CD antigen. This antigen, on the surface of the cell, is present in >90% (Leget and Czuczman, 1998) of the family of B-cell lymphomas of our present regard.

We found only one report of the use of rituximab for low-grade lymphoma of the orbit (Esmaeli et al., 2002). Three patients received intravenous rituximab 375 mg per m^2 weekly for 4 weeks. The patients had nearly complete resolution of the orbital lymphoma in a follow-up time from 6 to 22 months (mean 14.5 months). The most common adverse effect is B-cell depletion. The authors believe targeted immunotherapy may offer several advantages, in the future, over conventional chemotherapy or external beam radiotherapy in the treatment of orbital lymphomas.

Most hematopoietic malignant neoplasms are radiosensitive, particularly the lymphomas. Iodine 131-radiolabeled antibody has been used in the past for relapses of low-grade lymphoma and initial therapy of high-grade malignant tumors. More recently, the β-emitting isotope yttrium 90 has received favorable reviews for its effectiveness, as an alternative to iodine 131, in the management of lymphomas. Yttrium 90 emits β rays that are five times as energetic as those from iodine 131 (Press et al., 1999). Also yttrium 90 emits very few γ particles and has a favorable half-life of 2.5 days. It is used on an outpatient basis. Anti-CD20 antibodies radiolabeled with iodine 131 and yttrium 90 administered at nonablative doses yield remission in 75% to 80% of cases, including 35% to 40% complete remissions (Kaminski et al., 1993). ''Higher-dose radio-immunotherapy combined with stem cell transplantation also induces responses in >85% of patients, most of whom achieve complete remission. Encouraging trials have also been conducted with antibodies targeting other B-cell antigens, including immunoglobulin isotopes CD22'' (Press, 1999).

Summary

Immunotherapy is still so new, the agents recommended for therapy so diverse, a sizable collection of cases of a particular type of lymphoma and its response to therapy so small, follow-up periods so short, that neither a standardized protocol for therapy nor an estimate of survival has evolved. Reports of immunotherapy for localized orbital lymphoma are very few.

In our long association with a collection of consecutive, pathologically-proved cases of orbital tumors, radiation has been the mainstay of initial therapy for lymphomas localized to the orbit. Stafford et al. (2001) attempted an update of patients treated from 1971 to 1987, inclusive, as well as a longer follow-up on Mayo patients described by Minehan et al. (1991) Their analysis was limited to 46 patients, 45 with *low-grade* and 1 patient with *intermediate-grade* histologic findings based on the working formulation and, later, the REAL classification. This cohort, if converted to the present WHO classification, would consist of 29 extranodal marginal zone B-cell lymphomas of MALT, 11 small lymphatic lymphoma, and 6 follicular lymphomas. About half of this total was localized to the orbit; the remainder involved conjunctiva and lacrimal gland.

Radiation doses ranged between 15 and 53.8 Gy (median 27.5 Gy). Acute complications occurred in half of the patients but resolved by the first follow-up visit. Conjunctivitis was the principal acute complication. Severe complications occurred in four patients, that is, cataract, sicca syndrome, keratitis, and mild radiation retinopathy. No late complications occurred with doses <35 Gy. Lens-blocking techniques did not seem to have any significant effect on the reduction of cataract in patients aged 68 years or older.

The 5- and 10-year rates of survival were 69% and 40%, respectively, for the entire cohort of patients. The authors believe control of local orbital lymphoma is possible with moderate-dose radiation therapy in tumors of low histologic grade, including MALT lymphomas. As of 2004, radiotherapy is still the preferred modality for the initial management of orbital lymphomas. The radiation dosage has been reduced to 25 Gy at the Mayo Clinic in an effort to further minimize post-radiation complications to the eye. An occasion appropriate for the use of rituximab has not occurred in these patients, although rituximab is used for the treatment of some types of systemic lymphoma.

Burkitt Lymphoma

This is a high-grade B-cell neoplasm. It is usually found in the pediatric population. Many pediatricians consider the tumor as the most aggressive malignancy in this age-group. It exists in endemic, sporadic, and human immunodeficiency subtypes. The endemic type is better known as the *African* subtype. Names for the sporadic form are: *North American type, nonendemic Burkitt lymphoma, and non-African Burkitt lymphoma*. It usually presents as a multifocal neoplasm; although rarely, it may apparently

be localized to one anatomic site such as the orbit. The histopathology of the tumor is the same regardless of its geographical location.

Clinical Features

The *African* neoplasm is virtually always associated with the (herpes-like) Epstein-Barr virus (EBV). Positive titers are found in over 90% of cases (Davi et al., 1998). It is diagnosed at an average age of 9 years (Banthia et al., 2003). These children present with a rapidly growing mass (see Figs. 13.9 and 13.10) in the maxilla or mandible. The maxilla is affected more often than the mandible in a ratio of approximately 2:1. As the tumor expands, the teeth on the affected side become loose; there is odontalgia, paresthesias of the cheek, sore throat, enlarged cervical nodes, fever, and secondary orbital encroachment. In the meantime, an enlarging abdominal mass may go unnoticed. If the disease goes untreated, soon there is invasion of bone marrow, dissemination to the lungs and the central nervous system, and extension of tumor into the posterior orbit. Ocular motility disturbances and palsies of cranial nerves III and VI are late manifestations of either orbital or brain involvement.

The sporadic type is more heterogeneous, and an association with EBV is less often detected. Also, there is more frequent initial presentation of abdominal and mediastinal masses and lymph node and bone marrow involvement. The disease tends to occur in an older age-group than in the endemic African type, and jaw involvement is seen in only a minority of cases (12%) according to the American Burkitt Lymphoma Registry (Yih et al., 1990).

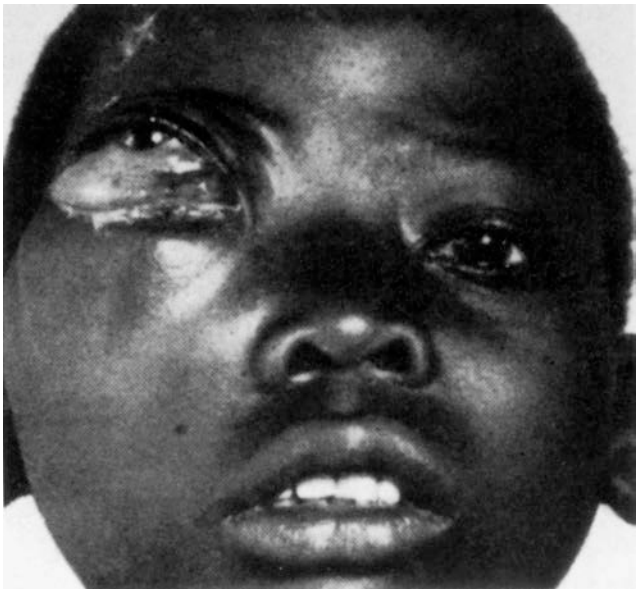

Figure 13.9 Burkitt lymphoma: One of the 38 African children described by Dr. Denis Burkitt with an evolving sarcoma of the jaw. The tumor originated in the right maxilla of a 10-year-old boy and extended into the orbit. The tumor did not arise in relation to the teeth. (From Burkitt D. A sarcoma involving the jaws in African children. *Br J Surg.* 1958;46(197):218–223. By permission of the publisher Butterworth-Heinemann, Ltd.)

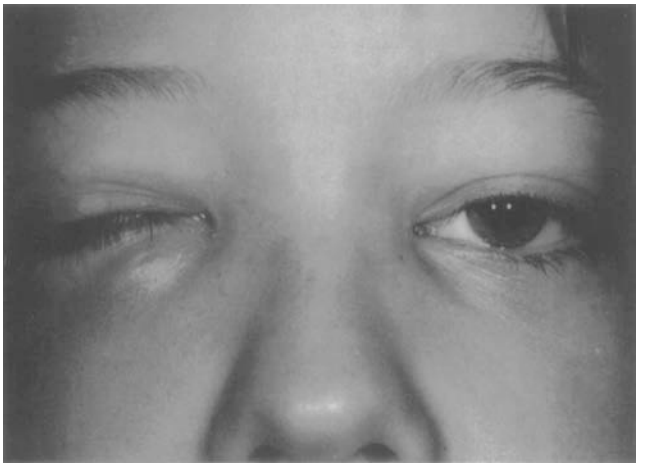

Figure 13.10 A 9-year-old boy whose assumed orbital ''cellulitis'' was unresponsive to a month's course of antibiotics. A computed tomography scan then revealed a mass in the inferonasal orbit that, on biopsy through the medial portion of the right lower lid, proved to be a Burkitt lymphoma. The patient died 2 months later. (Courtesy JD Bullock, Dayton, Ohio.)

Weisenthal et al. (1995) reported a 16-year-old girl with a rapid development of a conjunctival mass 6 weeks after an illness associated with a positive Monospot test. CT scan showed extension into the anterior orbit. Evidence of EBV infection was *not* found in the tumor cells but the EBV-encoded nuclear RNA was present in the surrounding adenoid tissue. The patient was treated with combined chemotherapy and was disease free 4 1/2 years after diagnosis.

Edelstein et al. (1997) describe a 26-month-old boy who developed oral thrush associated with painless swelling of the right eyelid, 10-mm proptosis, a diffuse orbital mass, and both maxillary sinuses. Abdominal CT scan showed involvement of the kidney, pancreas, and liver. Bone marrow biopsy disclosed a neoplastic clone of cells bearing the t(8;14) translocation. This patient received six cycles of combined chemotherapy with complete regression of both orbital and systemic manifestations in 8 months.

Another sporadic case is the 6-year-old girl with progressive right facial and orbital swelling with loss of vision in the right eye (Banthia et al., 2003). MRI revealed an orbital mass, maxillary tumor, and hard palate involvement. An extensive physical examination did not reveal systemic disease. Immunogenetic analysis revealed cells bearing the t(8;14) translocation. The patient was still undergoing chemotherapy at the time of their publication.

In our third edition (1994), we described five cases of sporadic Burkitt lymphoma. We will not redescribe these cases but will list the authors of these cases in our references (1978 to 1990) at the end of this chapter (Blakemore et al., 1983; Kielar, 1978; Trese et al., 1980; Zak et al., 1982).

Burkitt lymphoma also occurs in patients with acquired immunodeficiency syndrome (AIDS). This form of the tumor is similar to the preceding clinical type except for a higher initial presentation with central nervous system disease. A case of this type with unilateral orbital involvement was the 22-year-old man with a positive Epstein-Barr antigen titer, an elevated cytomegalovirus immunoglobulin titer, and inversion of the T-cell helper-to-suppressor ratio. On CT scan, the right globe was displaced by a large enhancing orbital mass (Brooks et al., 1984).

The imaging characteristics of these neoplasms by CT scan and MRI are essentially the same as described for the preceding non-Hodgkin lymphoma.

Histopathology and Immunocytology

The histopathologic pattern is a proliferation of small, closely packed lymphocytes interspersed with phagocytic histiocytes, which has been likened to a "starry sky" (see Fig. 13.11). The small lymphocytes have uniform oval or round nuclei with distinct nuclear membranes and contain one to several distinct basophilic nucleoli. Each cell has a rim of amphophilic cytoplasm. Mitotic figures are frequent. In contrast, the macrophages are very large with an abundant clear cytoplasm containing speckles of cellular debris. The intercellular reticulin network is delicate and sparse.

Immunocytochemical marker studies are positive for antibodies to leukocyte common antigen, B-cell lineage markers including C19, CD20, CD22, CD74, CD79a, and CD10. Also expressed are cell surface immunoglobulin heavy chains—most commonly IgM and either κ or λ light chains (Freedman and Nadler, 1991). Histiocyte markers KD-1 (CD68) stain the macrophages.

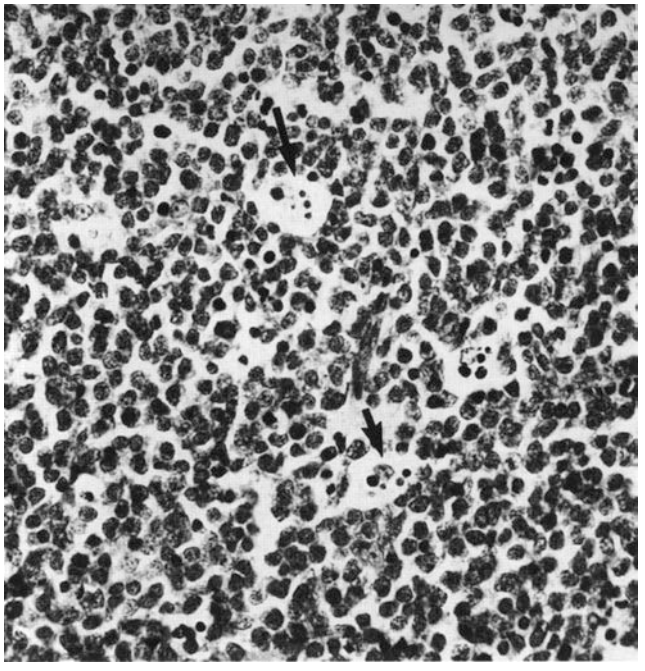

Figure 13.11 Burkitt lymphoma: Starry-sky appearance is due to large, pale histiocytic cells scattered among closely packed, small lymphocytes (×400). Some histiocytes contain phagocytosed nuclear material in their cytoplasm (*arrows*).

Treatment

The primary therapeutic modality for Burkitt lymphoma is *chemotherapy*. The neoplastic cells are highly sensitive to cytotoxic agents (Banthia et al., 2003). Most chemotherapy regimens are cyclophosphamide based. A combination of multiple agents with different mechanisms of action maximizes dose intensity and decreases the chance of drug resistance. Patients with Burkitt lymphoma limited to the head and neck have a 90% long-term survival when treated with multiple-agent chemotherapy regimens. Patients with involvement of bone marrow, brain, and HIV fare less well (Link et al., 1990). The central nervous system is a common site of relapse of disease.

Extranodal Marginal Zone B-Cell Lymphoma (WHO Classification)

This neoplasm is a relatively new member of the lymphoma family, considering the known, multidecade association of other small cell lymphomas with orbital involvement. Isaacson and Wright (1983) thought these neoplasms should be a separate entity from other small cell lymphomas because their origin was *not* in a lymph node but in the follicular lymphatic aggregates (Peyer patches) of the gastrointestinal tract—therefore, the name, *extranodal*. The authors proposed the term *MALT*.

Within a year, the concept of MALT lymphomas extended to extranodal sites other than gut (Banks and Isaacson, 1999). Soon after, the neoplastic element was identified as the B cell (memory cell) in the marginal zone surrounding the reactive (benign), antigen-processing center of the lymphoid follicle. Antigen dependence is still considered to be an important factor in the pathogenesis of the neoplasm. In brief, these neoplasms differ in morphology, immunophenotype, and clinical course from other small cell lymphomas.

Our interest is chiefly the MALT lymphoma of the extranodal lymphoid tissue of the conjunctival submucosa or the nonlymphatic reticulum in the posterior orbit. The incidence of the tumor in these two sites is not known because they are either lumped together with the incidence of head and neck lymphomas, or combined in a discussion of extraocular MALT lymphomas. Most MALT lymphomas occur in adults with a median age of 61 and a slight female preponderance (male:female ratio 1:1.2) (Jaffe et al., 2001). The conjunctival neoplasms are, by far, more common than orbital lymphoma.

Because the consistency of the MALT lymphoma is so soft and its growth so indolent that many months may pass before the patient is aware of the minimal, painless proptosis. CT scan will confirm the presence of an orbital

mass, but the image display is no different than the CT scan analysis of other small cell lymphomas of the orbit. The conjunctival tumor will be evident over a less number of months. Usually, the tumor will present as a painless, soft, reddish mass in one of the fornices of the conjunctiva. The literature has noted a delay in initial diagnosis because of the clinicians' presumption that patients had some type of conjunctivitis. Other mistaken initial diagnoses include cicatricial entropion of unknown etiology, recurrent trichiasis, cicatricial pemphigoid, sebaceous carcinoma, and contact lens intolerance.

If, at the time of presentation, the lymphoma is primary in the orbit, several authors believe that bone marrow may also be affected. However, other authors do not support this assessment. Nevertheless, there is general accord that foci of tumor are more often associated with MALT tumor of the orbit when compared to tumor in the gastrointestinal tract. If, in the course of either conjunctival or orbital tumors, there is dissemination of tumor, it likely will spread to another extranodal site.

With light microscopy, the follicle components of the tumorous, polyclonal, benign lymphoid hyperplasia and MALT tumor are similar in appearance. Immunohistochemistry is helpful in the differentiation of the two lesions. The benign tumor will stain for different immunoglobulin light and heavy chains. The neoplastic cells of a MALT lymphoma are B cells that are negative for CD5, CD10, and cyclin D1.

In the histopathology of the MALT lymphoma, the cells infiltrate around the reactive B-cell follicles, external to a preserved follicle mantle, in a marginal zone distribution. These marginal zone B cells have small- to medium-sized, slightly irregular nuclei with moderately dispersed chromatin and inconspicuous nucleoli. The cells have relatively abundant, pale cytoplasm. Alternatively, the marginal zone cells may more closely resemble small lymphocytes (see Fig. 13.12A, B, and C) (Jaffe et al., 2001).

Hardman-Lea et al. (1994) have noted that, in the absence of systemic disease, a MALT lymphoma of conjunctival origin may be so innocuous that observation alone is sufficient. Two of their five patients were observed, with no local or systemic treatment. One patient was followed up for 30 months and the other for 12 months. Neither showed evidence of either local progression or

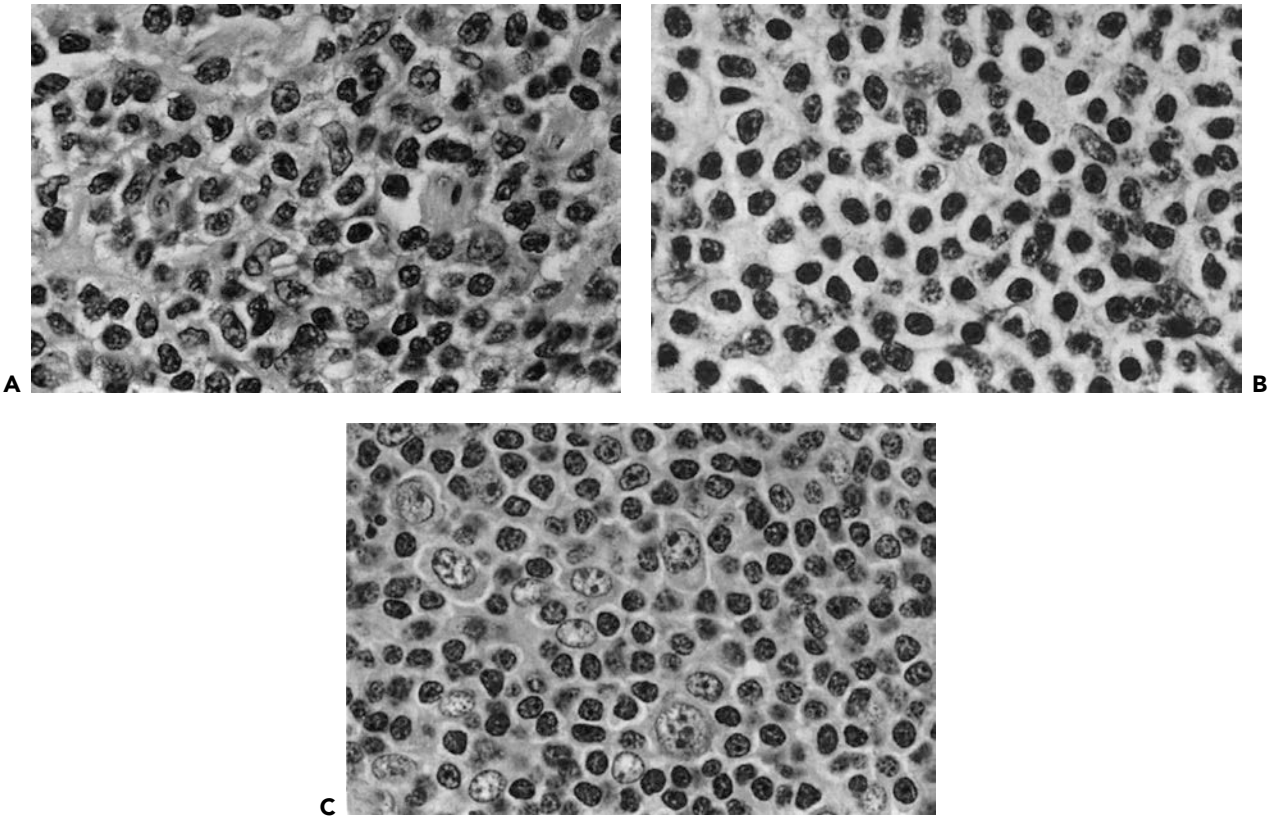

Figure 13.12 Morphologic spectrum of MALT lymphoma cells. **A:** Neoplastic marginal zone B cells with nuclei resembling follicle center centrocytes but with more abundant cytoplasm. **B:** The cells have abundant pale staining cytoplasm leading to a monocytoid appearance. **C:** The cells resemble small lymphocytes associated with larger transformed lymphoblasts. Magnification not stated. (From Jaffe ES, Harris NL, Stein H. *World Health Classification of Tumors.* Lyon: IARC Press; 2001:158.)

systemic dissemination. Thereby, the patients were spared some of the morbidity of radiotherapy. Likewise, a large, bulky MALT lymphoma that is either a cosmetic nuisance or interfering with ocular rotation can be surgically debulked. Radiotherapy may be reserved for the lymphomas that, over a passage of many months or several years, undergo a more malignant transformation of a large-cell clone. The MALT lymphoma of the orbit is said to be more aggressive than a conjunctival neoplasm. Low-dose radiotherapy is the initial, preferred treatment.

Lymphoid Hyperplasia

Synonyms: *Pseudolymphoma, borderline lesions, atypical hyperplasia, reactive lymphoid hyperplasia* (*RLH*), *benign lymphoid hyperplasia,* and *inflammatory pseudotumor*. The reason for discussing this tumor, at this point, is that the presentation, clinical signs and symptoms, age distribution, and imaging aspect are very similar to those of the small cell and, particularly, the follicular lymphoma of our prior regard.

In the distant past, this lymphoproliferative lesion was an enigma in diagnosis, that is, was it truly a benign process or was it a low-grade lymphoma? In the 1970s, it was discovered that lymphocytes are divisible into subpopulations of B cells and T cells (phenotypes). The next step in differential diagnosis was recognition that lymphoid tumors could be subdivided into polyclonal types (a mixture of B cells and T cells) and monoclonal types (consisting principally of one subpopulation of lymphocytes). Subsequently, with each succeeding decade, refinements in differential diagnosis have come about, principally, in the study of the immunohistochemical characteristics of lymphomas and non-lymphomas.

The germinal center of the follicle of lymphoid hyperplasia contains a mixture of large lymphoblasts, tingible body macrophages (cells that have accumulated cellular and nuclear debris from mitotic activity), plasma cells, histiocytes, and a rare eosinophil. These follicles tend to be irregular in shape and highly active mitotically (Spencer, 1996) (see Figs. 13.13, 13.14, and 13.15). In short, the follicles are busy processing antigen required by some unknown humoral agent. The follicles are surrounded by a mantle of mature lymphocytes. This conglomerate of cells and its antigen-producing properties is given the name ''*reactive*.'' Reactive should not be confused with the term *inflammatory*. The latter is applied to orbital pseudotumor. The pseudotumor has a high content of fibrous tissue when compared to the scant stroma of lymphoid hyperplasia and lymphoma. Lymphoid hyperplasia may be either systemic or localized to a site, such as the orbit, that is devoid of lymphoid tissue.

The monoclonal or polyclonal characteristics of a lymphoid lesion can be predicted by determining the ratio of B cells to T cells. Immunohistochemistry of lymphoid hyperplasia will show a percentage T-cell infiltrate varying between 42% and 65% (mean 5.7%) (Coupland et al., 1998). The B-cell component varies between 15% and 47%. Furthermore, immunohistochemistry showed polyclonality for κ and λ light chains. Immunophenotyping for B cells is positive with CD20 and CD22, the T cells show positive staining with CD2 and CD5.

Figure 13.13 Lymphoid hyperplasia: The follicular types contain larger reactive germinal centers (upper left) with a polymorphous cell population including mitotic figures and tangible body macrophages, which are surrounded by a dense collection of small lymphocytes, large blood vessels, and, in this specimen, residual lacrimal gland acini ($\times$100). (From McNally L, Jakobiec FA, Knowles DM. Clinical, morphologic, and molecular genetic analysis of bilateral ocular adnexal lymphoid neoplasms in 17 patients. Am J Ophthalmol. 1987;103:555–568.)

Coupland et al. (1998) published a retrospective review of 112 lymphoproliferative lesions of the ocular adnexa. This included 12 cases of RLH, 99 cases of lymphoma, and one case was indeterminate because of insufficient biopsy material. The RLH lesions were located as follows: Two in the eyelid, three in conjunctiva, and seven in the orbit. In the total of 111 cases, the ratio of RLH to lymphoma is roughly 11:89. This data may differ from several similar analyses published over 15 years ago when differential diagnosis of the two entities was less refined. The authors' median follow-up on their cases of RLH was 31.3 months. In this interval, none of these cases developed either localized or systemic manifestations of lymphoma. There were no bilateral cases. Neither was there any dissemination of the lymphoid hyperplasia cases.

All of our 11 cases of lymphoid hyperplasia in our 50-year study were initially seen elsewhere. All patients had had steroid treatment on the basis of an assumed diagnosis,

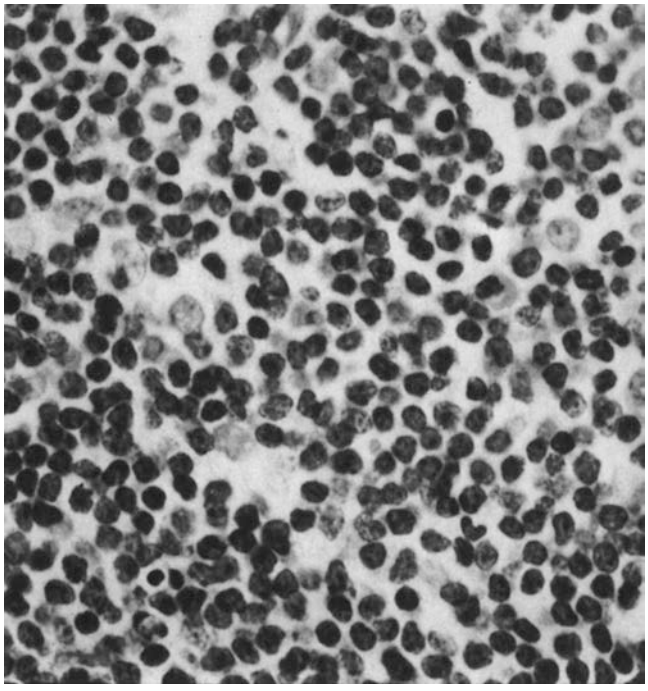

Figure 13.14 Lymphoid hyperplasia: A diffuse proliferation of small lymphocytes admixed with occasional plasma cells, immunoblasts, and histiocytes. The subtle cellular polymorphism differs from the monomorphous pattern of lymphocytes in the diffuse small lymphocytic lymphoma (×500). (From Knowles DM, Jakobiec FA. Malignant lymphomas and lymphoid hyperplasias that occur in the ocular Adnexa (orbit, conjunctiva and eyelids). In: Knowles DM, ed. *Neoplastic Hematopathology*. Baltimore, MD: Williams & Wilkins,1992:1009–1046.

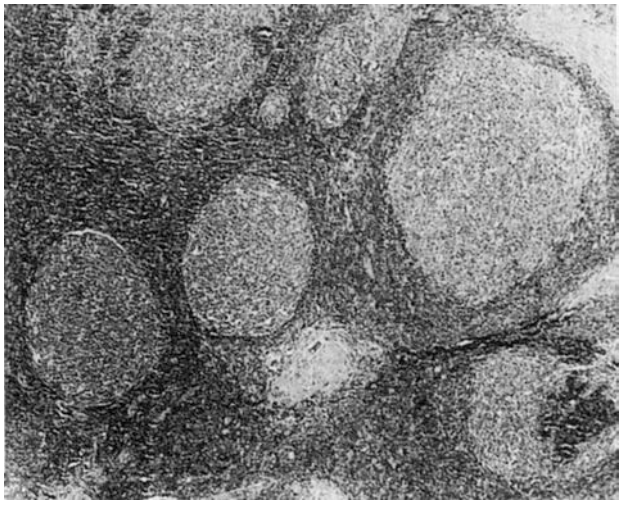

Figure 13.15 Lymphoid hyperplasia: Note the variable size of the lymphoid follicles (×45). (From Spencer WH. *Ophthalmic pathology*, Vol. 4, 4th ed. Philadelphia, PA: WB Saunders; 1996:2703.)

based solely on clinical signs and symptoms of inflammatory pseudotumor. None of these patients had orbital biopsy or imaging studies. Steroid therapy was ineffective. Here at Mayo Clinic, all cases were diagnosed as lymphoid hyperplasia based on biopsy and immunohistochemical staining (κ and light chain polyclonality).

After biopsy, ten patients were managed either with radiotherapy or simple observation. In three of the ten patients, the orbital mass was partially debulked at the time of biopsy. In terms of functional improvement of the eye, postoperatively, the response was so complete that no further treatment was recommended except observation. One patient had no recurrence at the time of death six months later from an unrelated cause. The other two patients were followed up for 2 years and 6 years, respectively, without recurrence. However, the ptosis of the upper eyelid in none of the three patients disappeared.

An additional four patients were initially treated with radiotherapy. Two of these patients had a complete response including reduction of proptosis, reduction of lid edema, and restoration of normal ocular motility. One received 1,990 cGy with a follow-up of 6 months. The other patient received 3,060 cGy with follow-up of $2\frac{1}{2}$ years. The remaining two patients, of the original four, were each given 20 Gy of radiation but had only partial response over a follow-up period of 6 months and 1 year, respectively. There was no follow-up on three of the ten treated patients.

The number of ten cases is too small, the treatment modalities too fragmented, and follow-up too short to make any objective conclusions as to preferred treatment and the period of remission without recurrence.

Early in the decades of our study of these hyperplasias, retrospectively, we wrongly assumed that surgical debulking of the tumor would do more harm than good, in respect to gaining normal function of the eye. On our final analysis, we were pleasantly surprised that, in selected patients, the tumor could be debulked, without postoperative dysfunction of the eye. Orbital residues of the tumor would disappear without any subsequent treatment. Another oddity is three bilateral cases. None of our ten cases developed disseminated disease to our knowledge.

The 11th patient will be discussed separately because the course and management of the disease are different from the other ten cases. The salient features of this case follow:

December 9, 1997: A 40-year-old man presented with a slowly progressive, painless drooping of right upper eyelid of one year's duration. Right eye proptosis of 5 mm. CT scan showed an enlarged lacrimal gland.

December 10, 1997: Biopsy of lacrimal gland with resultant diagnosis of RLH.

January 12, 1998 to January 23, 1998: Radiotherapy 2,000 cGy in ten fractions.

April 20, 1998: Eyelid swelling gradually decreasing.

January 25, 1999: Proptosis persists.

March 19, 1999: Another biopsy of lacrimal gland. Hyperplasia still present but shows some fibrosis.

April 26, 1999: An enlarged inguinal lymph node is biopsied. Diagnosis: Lymphoid hyperplasia.

May 14, 1999: A new therapeutic agent, *rituximab* (an anti-CD20 monoclonal antibody), is started (Leget and Czuczman, 1998) (Coiffier et al., 1998). The recommended dosage was 375 mg/m^2/infusion, given weekly for 4 weeks.
June 4, 1999: Rituximab course completed.
August 23, 1999: Proptosis disappeared.
October 13, 1999: Recurrence.
October 21, 1999: Second course of rituximab.
November 18, 1999: Third course of rituximab resulting in remission.
January 18, 2000: Fourth course of rituximab completed.

Unfortunately, we have no further follow-up. Subsequent patients with orbital lymphoid hyperplasia have responded well to rituximab infusions, but the requirement for retreatment seems to be the rule.

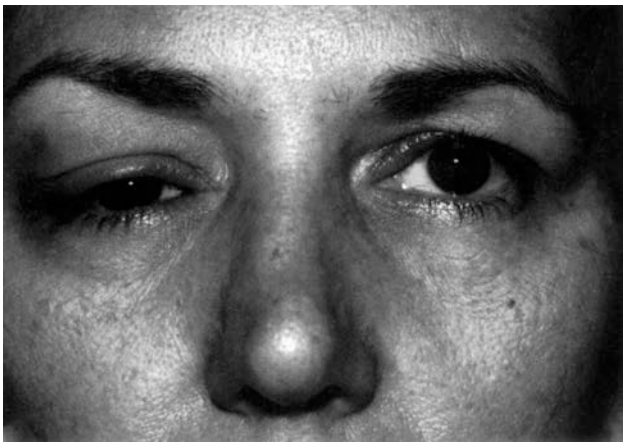

Figure 13.16 Plasmacytoma: A 44-year-old woman with slight downward displacement of right eye and drooping of right upper eyelid from a palpable mass in superotemporal orbital quadrant.

Plasma Cell Neoplasms

These neoplasms arise from an expansion of a single clone of immunoglobulins secreting, terminally differentiated, end-stage B cells (de Smet and Rootman, 1987 and Jaffe et al., 2001). These monoclonal proliferations of plasma cells or plasmacytoid lymphocytes have a common component, normally, the secretion of a single homogeneous IgM. This immunoglobulin is present in serum and/or urine, detected by protein electrophoresis. Neoplasms with these characteristics are designated by the broad term, *monoclonal gammopathies* which includes many clinicopathologic variants. Most of these variants present with manifestations of systemic disease. Only a few present as a solitary focus in the orbit, or the orbit may be the initial manifestation of systemic disease. We will direct our discussion to those neoplasms with orbital manifestations.

Solitary Plasmacytoma of Orbital Bone

This tumor is a collection of neoplastic cells localized in one bone. It is considered a low level of malignancy (Aboud et al., 1995). In the orbit, these tumors usually arise from the marrow of either the zygomatic, frontal, or sphenoid bone. We have only two patients of this type in our 50-year collection of orbital tumors: One man, aged 72, and one woman, aged 44 (see Fig. 13.16). Both patients presented with a unilateral, droopy, swollen, upper eyelid associated with a downward displacement of the eye of <6 weeks' duration. In one patient, CT scan imaging showed erosion of the bony roof and lateral orbital wall (see Fig. 13.17). In the other patient, the bony mass extended across the roof of both upper orbital quadrants. If an M-protein is found in the serum or urine, it usually disappears after local treatment.

Many authors believe that orbital involvement is often the presenting feature of an eventual multiple myeloma. Indeed, this event was fatal in the female patient, 16 months after initial diagnosis. Adkins et al. (1996) noted a similar occurrence. Orbital pain is seldom present in these patients. Most patients are responsive to radiotherapy, but this is not absolute. According to Kyle and Bayrd (1976), at 10 years, approximately 35% of patients appear to be cured, although 55% develop plasma cell myeloma, and 10% have either local recurrence, or another solitary plasmacytoma develops.

Extraosseous Plasmacytoma (WHO Classification)

Synonym: *Solitary extramedullary plasmacytoma*.

This extraosseous, malignant neoplasm of plasma cells is usually (80%) located in the upper respiratory tract (oropharynx, nasopharynx, sinuses, and larynx) (Alexiou

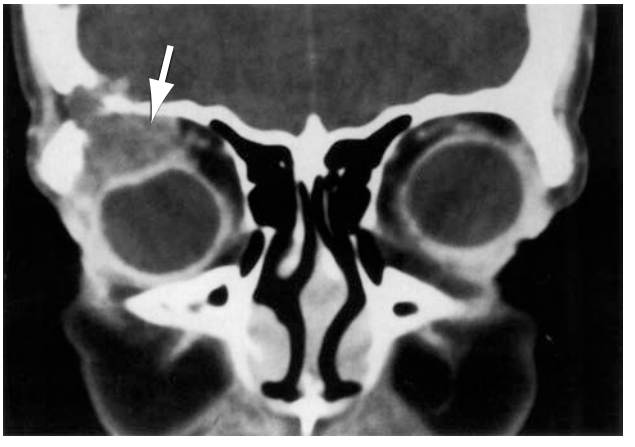

Figure 13.17 Plasma cell myeloma: Computed tomography scan of a 44-year-old woman shows a relatively homogeneous mass in superotemporal orbit (*arrow*) associated with destruction of bone and extension of mass into orbit, anterior cranial and temporal fossa which includes the superior wall of the eye. Several punched out, lucent, lytic lesions also were present in the calvarium (not shown).

et al., 1999). Less often, it may present in one of many other sites. The conjunctiva and the soft tissue of the orbit may be one of these rare sites of involvement, either as a primary site or secondary to extension of a tumor in the upper respiratory tract. The tumor is most common in the 7th and 8th decades. The male to female ratio is 2:1.

Its orbital presentation includes a unilateral, painless swelling or drooping of the upper eyelid with minimal, if any, displacement of the eye and, on orbital imaging, there will be a large homogeneous, non-encapsulated mass, with mild enhancement that tends to mold to the surface of the eyeball. The disproportion between the large size of the orbital mass and the minimal disruption of the position of the eye is strongly suggestive of some type of lymphoma. Other tests should be performed such as bone marrow aspirate, serum and urine electrophoresis, alkaline phosphate level, skeletal bone imagery, and scintigraphy of the head and neck area to rule out plasma cell (multiple) myeloma.

Over the 50+ years of our study, radiotherapy has been the favored management of these neoplasms. The initial dose ranges from 30 Gy to 40 Gy, administered in fractions over a period of several weeks, with the expectancy that regression of tumor will occur. Uceda-Montanes et al. (2000) describe a 71-year-old male patient who responded to radiation therapy and remains disease free with a 9-month follow-up. Subsequently, if regression does not occur, and the neoplasm has not disseminated, many authors perform surgical removal of the mass supplemented with additional radiotherapy. However, we are reluctant to give further radiotherapy. Instead, we would perform an exenteration of the orbit. The development of plasma cell myeloma occurs in approximately 15% of cases (Alexiou, 1999).

Ezra et al. (1995) report a similar experience with a 41-year-old man who was initially treated with 5 Gy radiotherapy to the left orbit. The treatment was not effective. Proptosis was still present. Additional radiotherapy was started but after another 20 Gy, severe periorbital edema developed and further radiation was abandoned. Then an orbital exenteration was performed. A similar course was described by Sen et al. (2003) for a 50-year-old man who ultimately underwent exenteration. One year later, there was no local or systemic recurrence. In the past, the use of chemotherapy in the management of this neoplasm has been equivocal.

The morphology of the tumor is similar to the osseous plasmacytoma of the preceding section. Both the osseous and extraosseous lesions have immunophenotype and genetic features similar to those of plasma cell myeloma (see next section).

Plasma Cell Myeloma (WHO Classification)

Synonyms: *Multiple myeloma, myelomatosis.*

This is a multifocal, monoclonal neoplasm of plasma cells of B-cell type. The source of the neoplasm is the bone marrow of skeletal bone. From here, it produces lytic lesions in other bones, is associated with a leukemic stage, is characterized by a serum monoclonal protein, infiltrates in various organs and deposits abnormal immunoglobulin chains in other tissues. Bone pain, hypercalcemia, and anemia are other clinical features. It comprises approximately 15% of all hematologic neoplasms. The median age at diagnosis is 68 years in males and 70 years in females (Devesa et al., 1987). In the analysis of Kyle et al. (2003) of 1,027 patients, 59% were men, 41% women and the median age was 66 years. An exceptional case involving a 19-year-old woman has been reported (Levin et al., 1977).

Orbital involvement by this neoplasm is usually unilateral and is quite rare. Ockrim et al. (2000) describe a 75-year-old man with bilateral orbital soft tissue involvement. Howling et al. (1998) estimates <50 cases are in the world literature. In a series of 2,000 patients, Allen and Straatsma (1961) noted only five patients. The neoplasm may affect the orbit in several ways. The classic variant (Kyle and Bayrd, 1976) is the appearance of a soft tissue mass in the retrobulbar, orbital space sometime after diagnosis of systemic disease (see Fig. 13.18). The resulting proptosis is painless.

If the neoplasm locates in the apex of the orbit, some compression of the optic nerve occurs, resulting in visual loss and some pain on movement of the eye. Over time, some lysis of bone around the optic foramen will appear.

A second variant at the time of diagnosis is a unilateral proptosis with lysis of the walls of the orbit. The walls of the medial, lateral, and superior bones are so thin, their surface is easily dissolved by lysis allowing extrusion of the tumor into the retrobulbar tissues. On a CT scan,

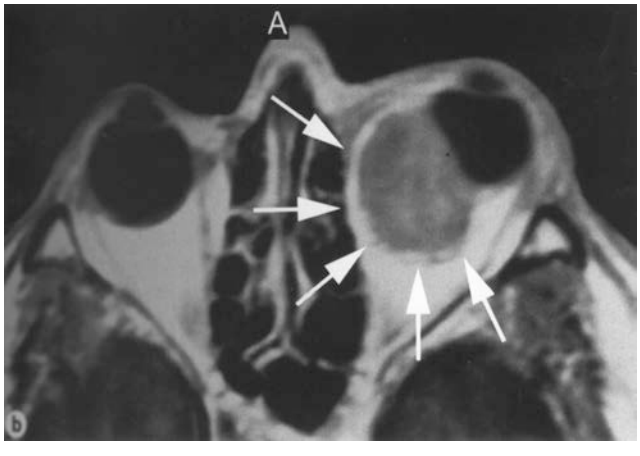

Figure 13.18 Plasma cell myeloma: Magnetic resonance imaging of a 60-year-old man shows a mass with homogeneous contrast enhancement in the mediobasal part of left orbit (T_1-weighted image) that compresses the eyeball. Ten months earlier, the patient had been treated for multiple myeloma with remission. (From Kottler UB, Cursiefen C, Holbach LM. Orbital involvement in multiple myeloma: First sign of insufficient chemotherapy. *Ophthalmologica.* 2003;217(1):76–78.)

the homogeneous tumor appears to be attached to the underlying bone (Fig. 13.17).

Also, there are cases in which, on imaging, the neoplasm may appear as the initial deposit of a recurrence, as well as patients who have completed treatment, are asymptomatic, but have residual orbital deposits.

In addition to bone pain, hypercalcemia and anemia, the diagnosis includes one or more of the following: Weight loss, fatigue, lytic lesions in bone, and an elevated erythrocyte sedimentation rate. A monoclonal light chain (Bence-Jones protein) is found in the serum of 15% of patients and in the urine of 75% of patients. An IgM is found in the serum or urine in 99% of patients. Also, there is a reduction of >50% in the normal Ig serum value in most patients (Salmon and Cassady, 1988). Leukemia, if present, is no longer considered a separate entity. In the WHO classification, this dyscrasia is part of the basic plasma cell myeloma.

In Table 13.2, Kyle et al. (2003) list the initial treatment of 1,027 patients who were seen over the period January 1, 1985, to December 31, 1991.

TABLE 13.2
INITIAL TREATMENT OF PLASMA CELL MYELOMA IN 1,027 PATIENTS

Treatment	No. (%) of Patients
Conventional-dose chemotherapy	
Melphalan + prednisone	577 (56)
Combination alkylating agents	177 (17)
VAD	70 (7)
Radiation	38 (4)
Corticosteroids	8 (1)
Other	13 (1)
Unknown	46 (4)
High-dose chemotherapy with stem cell transplantation	98 (10)

VAD, vincristine, doxorubicin (Adriamycin), dexamethasone.

The median survival of patients treated with oral melphalan and prednisone was 31 months (577 patients). The corresponding median survival for patients treated with all other regimens was 38 months (450 patients). Other studies since 1998, Barlogie et al. (1999), Desikan et al. (2000), report much better survival, but they represent highly selected patients undergoing one or more autologous bone marrow transplantations. However, bone marrow transplantation is not an option for patients older than 70 years of age and for patients with serious comorbid illness (Rajkumar et al., 2002). Newer drugs that seem to have a salutary effect on advanced or relapsing plasma cell myeloma are: Thalidomide (Barlogie et al., 2001), Velcade PS-341, and CC5013 (Richardson et al., 2002).

The plasma cell in this myelomatous disorder is a differentiated form of the B lymphocyte. Microscopically, differentiation is evident in terms of an eccentrically placed nucleus with clumping of nuclear chromatin at the nuclear membrane (clock-face pattern). The cytoplasm has a dusky hue because of the presence of cytoplasmic proteins and immunoglobulin (see Fig. 13.19A and B) (Spencer, 1996). The cells are subdivided into units by delicate connective tissue septae. The methyl-green-pyronine stain

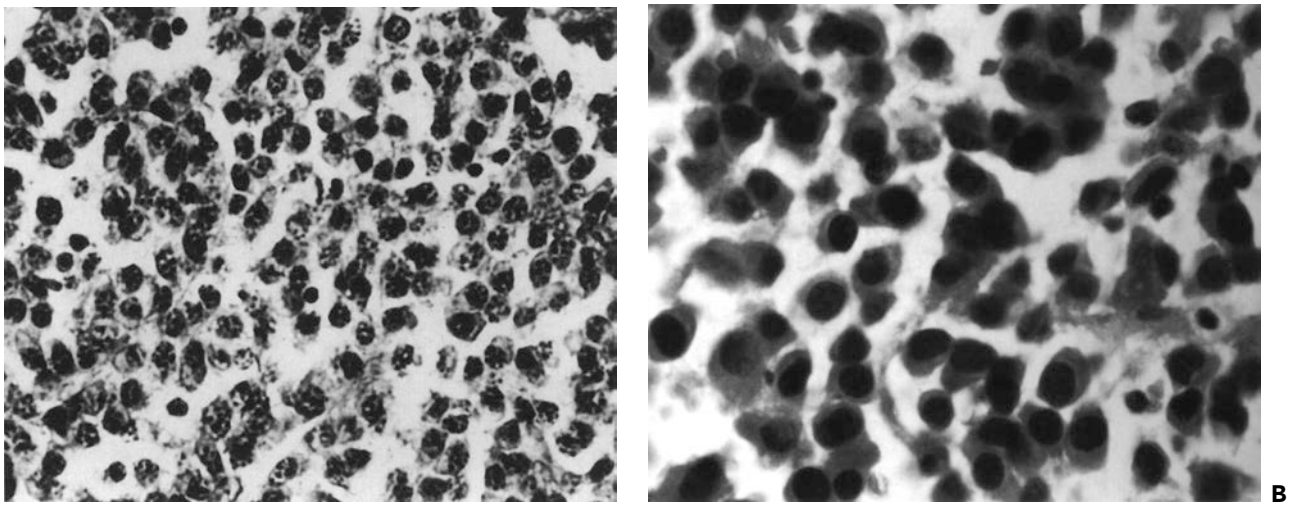

Figure 13.19 Histopathology of plasmacytoma: **A:** A well-differentiated tumor consists of sheets of uniform plasma cells with typical round eccentric nuclei and ''cartwheel'' clumping of chromatin. A fine connective tissue stroma subdivides cells into small units (×250). **B:** A more undifferentiated tumor with less uniformity in cell size and nuclear configuration. Some nuclei show slight grooving and irregularity in contour (×800).

for cytoplasmic ribonucleic acid is helpful in recognizing poorly differentiated myelomatous disorders from undifferentiated carcinomas.

AMYLOIDOSIS

This disorder is a deposition of a fibrillary protein (*amyloid*) in various organs and bone resulting in organ failure and bone destruction. Amyloidosis is classified into four major types based on the type of the fibrillary protein. Our interest is the *primary* AL type composed of an immunoglobulin light chain that is secreted by monoclonal plasma cell myeloma tumors. The AL type may affect the orbit either as a localized tumor or be part of a systemic AL. Among myeloma patients, approximately 15% have or will develop primary AL (Kyle and Gertz, 1990).

Primary AL of the orbit is very rare. Our 50-year collection of orbital tumors includes only three cases of the localized tumor—one of the three later developed systemic disease. The ages of the three patients at the time of presentation were 50, 57, and 64 years. The age range of patients with localized orbital AL, in the literature is approximately 40 to 80 years with a female to male ratio of 3:1. Pasternak et al. (1996) referenced nine authors who, collectively, had reported 23 cases of localized orbital AL in the period 1979 through 1994. Five patients of this group had bilateral tumors. Most of the 23 had tumors in the anterior orbit. Pasternak et al., added two cases—one bilateral and one unilateral. The latter was in the inferior orbit and associated with thickening (amyloid deposit) of the lower eyelid. Murdoch et al. (1996) reported six cases of localized orbital AL located in the superior orbit, mainly near the lacrimal gland.

It is common for patients with localized orbital AL to present with a "droopy" upper eyelid due to amyloid deposition in the subcutaneous tissue. The duration of eyelid swelling varies from 3 to 12 years with a median of $2\frac{1}{2}$ years. The long interval of symptoms is associated with the indolent character of a low-grade plasma cell myeloma. Frequently, the thickened, ptotic eyelid will have a pink or reddish discoloration due to ecchymosis resulting from rubbing the eyelid. This is a sure sign of systemic AL, if it is not already known. Some patients present with a painless, slowly progressive proptosis indicating a mass in the retrobulbar space. If there is some impairment of visual acuity, the tumor is probably adjacent to the orbital apex.

Less frequent are patients who present either with a pink or red mass in the medial or lateral conjunctival fornix. These masses are a source of recurrent hemorrhage and represent a forward extension of a localized orbital AL. Such was the case of a 46-year-old woman with recurring epibulbar hemorrhages of one year duration. She was first seen in March 1999 (see Fig. 13.20A). Arrangement was made to excise the red mass six hours later. When she returned, she had experienced another hemorrhage (Fig. 13.20B). The mass and its orbital extension were excised. The histopathologic diagnosis was *amyloid* deposition. A patient with orbital AL may also present with an acute glaucoma. Such was the case of Vella et al. (2002) with proptosis and a throbbing headache of nine months' duration. The orbital mass was debulked with relief of the glaucoma. Villafruela-Guemes et al. (2003) also reported a 71-year-old man with AL of one orbit who presented with tortuous episcleral vessels, 7-mm proptosis, glaucoma, and only light perception in the eye. Glaucoma is also frequently present in patients with the familial type of AL.

Systemically, amyloid deposition may occur in the heart (congestive failure), liver (hepatomegaly), kidney (nephrotic syndrome), gut (malabsorption), tongue (macroglossia), bone (lysis), and blood vessels (bleeding).

The *polymerase chain reaction* analysis will definitely establish the monoclonal plasma (myeloma) cell as the

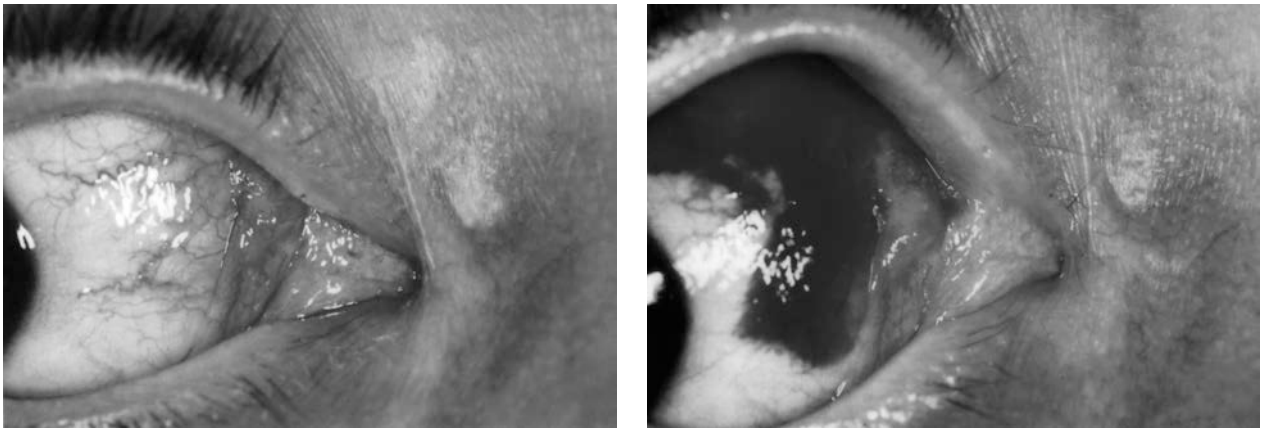

Figure 13.20 **A:** Subconjunctival amyloid. **B:** Recurrent hemorrhage. (Courtesy G. B. Bartley, Rochester, MN.)

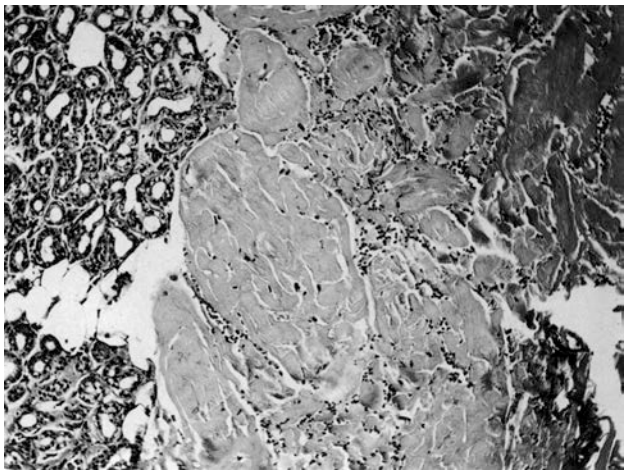

Figure 13.21 Amyloidosis: Orbital tissue from the region of the lacrimal gland (center) is massively infiltrated by eosinophils, hyalin, and acellular material (Hematoxylin and eosin ×100).

origin of the specific amyloid type associated with localized orbital AL (Pasternak et al., 1996).

Grossly, amyloid is an amorphous substance with a pale yellow color and a waxy consistency. The surface of a conjunctival deposit may have a darker red color than the salmon color of a lymphoma. Orbital deposits of amyloid may be firm, rubbery, glassy, or gritty, whereas amyloid in the eyelids has a more waxy consistency. The waxy deposit bleeds easily when touched.

Histologically, the amyloid looks pink with hematoxylin and eosin stain. The acellular aggregates may be found in adipose tissue, walls of small blood vessels, extraocular muscle, and lacrimal gland. The most widely used stain is Congo red, which imparts an orange-pink tint to the amyloid deposit. Such tissue, when viewed by polarization microscopy, will show an apple-green birefringence that is the *sine qua non* of the diagnosis of AL. Amyloid also fluoresces with some of the fluorochrome substances, but the reaction is not as specific or as reliable as the birefringence with Congo red.

Some amyloid deposits incite very little reactive response in the host tissue. Other cases may show a granulomatous foreign body response with multinucleated histiocytes partially rimming the amyloid deposit and surrounded by an overlay of lymphocytes and plasma cells of varying density (see Figs. 13.21 and 13.22A and B).

CT scan will show an enhancing, poorly defined mass with areas of calcification. The mass tends to mold or conform to lacrimal gland, eyeball, or optic nerve. One case of localized lacrimal gland AL had calcium within the lacrimal gland and the glands conformed to the shape of the globe (Conlon et al., 1991). If an extraocular muscle is involved, its contour is either irregular or thickened. The tendon of the muscle is also infiltrated with tumor.

The localized and systemic forms of AL are progressive disorders. As of 2005, there is no cure. The aim of treatment is to prolong survival. In recent years, the localized tumor has been treated with radiotherapy, chemotherapy, or surgical removal. Pasternak et al. (1996) treated one orbit, of a bilateral case, with 3,000 cGy. The dosage of the radiotherapy given to the other orbit is not stated. Vella et al., treated their case with 15 courses of a melphalan combination. The AL involved the extraocular muscles in the case of Villafruela-Guemes et al. Only an incomplete removal was performed. The tumor continued to progress. Six years later, a palliative debulking of recurrent tumor was necessary to alleviate the pain associated with a 7-mm proptosis. All these treatments result in temporary remission of symptoms, but eventually, there was recurrence. The interval between treatment and recurrence varies. The interval after recurrence (with or without treatment) also varies. Ultimately, AL is fatal.

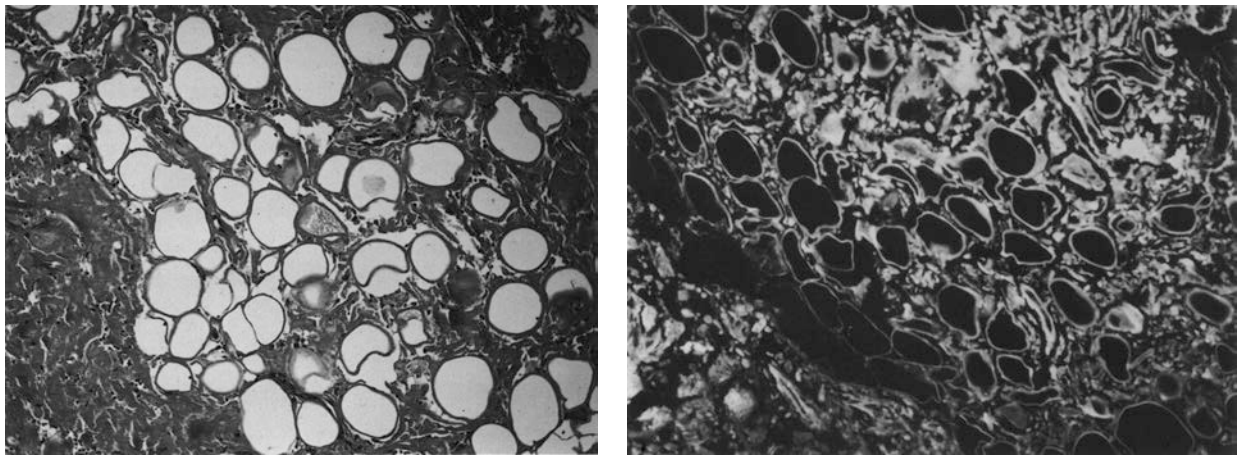

Figure 13.22 Amyloidosis: **A:** A distinctive feature is the deposit of amyloid around fat cells, ''*amyloid rings*'' (Hematoxylin and eosin ×100). **B:** When treated with thioflavine T, amyloid deposits bind the fluorchrome substance and show bright fluorescence in ultraviolet light (×100).

HODGKIN LYMPHOMA

Synonym: *Hodgkin disease*.

Samuel Wilks (1865) at Guys Hospital, London, in the second of two papers on the enlargement of lymphatic glands and spleen, recalled the observation of Thomas Hodgkin (1832), a prior worker at Guys Hospital, of a patient with a similar disorder. Wilks suggested the name Hodgkin disease. For over 100 years, there has been controversy as to the origin of one of the two cells (Reed-Sternberg) which are the diagnostic features of this neoplasm. One component is a large mononucleated cell, but the derivation of the multinucleated, Reed-Sternberg cell remained a puzzle. The Reed-Sternberg is now known to be a lymphoid cell (Haluska et al., 1994), most often of B-cell type. Jaffe et al. (2001) believe Hodgkin tumor should be called a ''*lymphoma.*''

Hodgkin lymphoma is divided into two disease entities: A nodular lymphocytic predominant type and a classical type. The classical version accounts for 93% of all Hodgkin lymphomas and is the subtype most often associated with orbital involvement. We will confine our discussion to this type.

In 1989, in one of the weekly case discussions of the New England Journal of Medicine, (*N Engl J Med*, 1989) Jakobiec made a thorough review of previous surveys of intraorbital tumors over a 10-year period, as well as single case reports of orbital HL in the literature but found only two cases of orbital HL. These were Fratkin et al. (1978) and Patel and Rootman (1983). Subsequently, there are five more case reports. These are Park and Goins (1993), Sahjpaul et al. (1996), Radner et al. (1997), Gross et al. (1998), and Klapper et al. (1999). All were males, age range 11 to 88 years.

The symptomatology is usually a progressive, painless, proptosis of one or both eyes of short duration without significant visual impairment. If the tumor is located in the anterior superior orbit, there will be blepharoptosis, displacement of the eye, and some impairment of ocular motility. These masses are palpable but not tender. All patients will have some systemic manifestation of HL, most often a cervical lymphadenopathy. CT scan will show a homogeneous, contrast-enhancing, multilobular or unilobular, soft tissue mass in the superior orbit (see Fig. 13.23).

HL is a progressive disorder. In an orbital specimen, at any given time, the change in the histopathologic cellular pattern will reflect the stage of the increasing malignancy. There are four stages as follows:

1. Lymphocytic and/or histiocytic predominance (diffuse or nodular forms)
2. Nodular sclerosis
3. Mixed cellularity
4. Lymphocytic depletion (diffuse fibrosis and reticular types)

In the early stage, there is a minority of large, mononuclear, neoplastic cells with scant cytoplasm intermingled with a larger array of non-neoplastic small lymphocytes, polyclonal plasma cells, dendritic histiocytes, eosinophils, neutrophils, and macrophages. At this stage, it may be difficult to find the diagnostic, multinucleated Reed-Sternberg (HRS) cell (see Figs. 13.24 and 13.25).

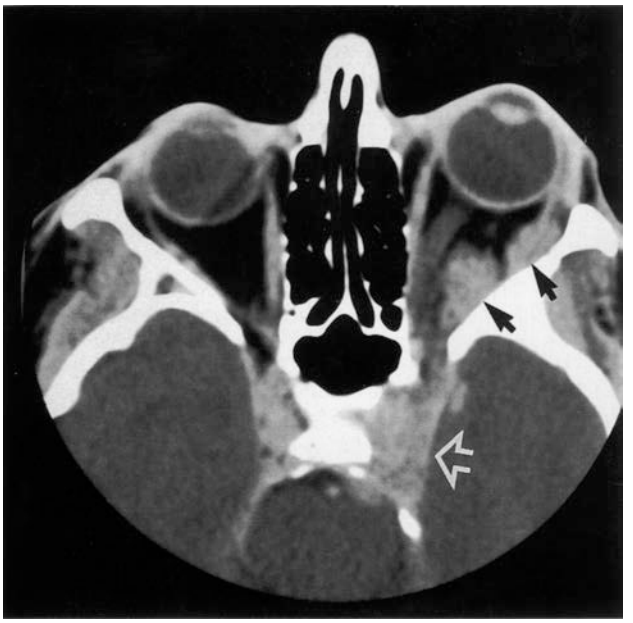

Figure 13.23 Hodgkin lymphoma: Computed tomography scan shows slightly enhancing, homogeneous, multilobulated (*upper arrows*) mass occupying lateral and apical orbit with intracranial extension (*lower arrow head*) and medial displacement of optic nerves.

At the next stage, fibroblasts appear with deposition of collagen bands. The Reed-Sternberg cells increase in number. There is a lesser number of small non-neoplastic lymphocytes. The larger neoplastic Hodgkin cells tend to clump together in cellular aggregates. These cells frequently show retraction of the cytoplasmic membrane, giving them a lacunar appearance. Some necrotic zones also appear in these cellular aggregates (see Fig. 13.26).

In the mixed-cellularity stage, interstitial fibrosis is evident. The tissue specimen consists of a mixture of cells, which vary greatly in type (see Fig. 13.27). The histiocytes show epithelial differentiation and may form granuloma-like clusters. The Reed-Sternberg cell can be distinguished from surrounding lymphocytes by its prominent red-staining nucleoli.

In the final stage, the non-neoplastic lymphocytes are depleted and replaced by large Hodgkin cells and Reed-Sternberg cells in a fibrillary matrix (see Figs. 13.28 and 13.29).

With immunophenotype staining, the Reed-Sternberg cells are present in nearly all cases and are positive for CD15 in approximately 75% to 85% of cases. They are negative for CD45 and macrophage-specific markers. The large, mononuclear, neoplastic Hodgkin cell will stain positive for B-cell specific activator protein (see Fig. 13.30).

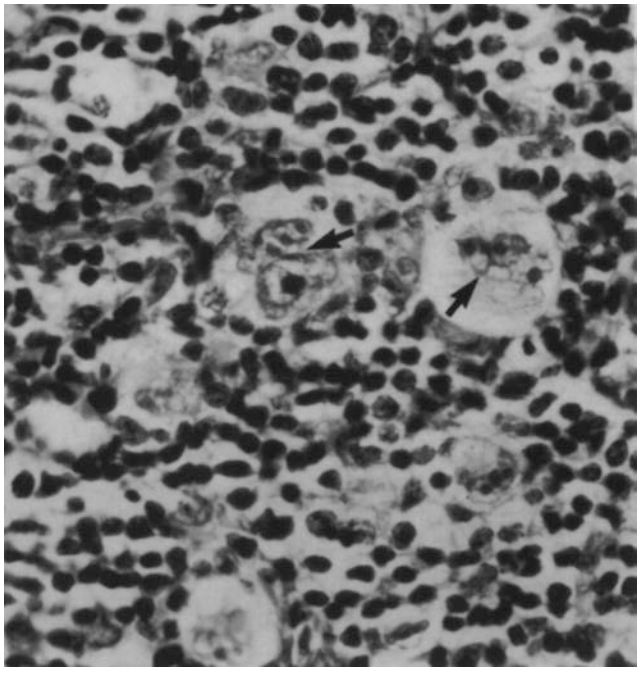

Figure 13.24 Hodgkin lymphoma: Early stage, showing several, large, binucleated Reed-Sternberg cells (*arrows*) against a background of small lymphocytes (×480).

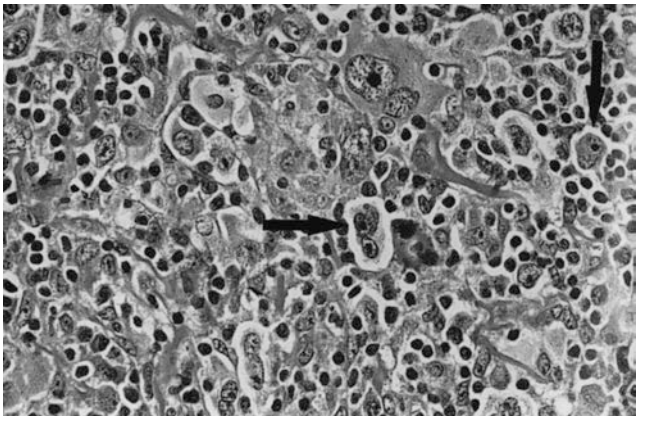

Figure 13.26 Nodular sclerosis subtype of classic Hodgkin lymphoma. Several lacunar cells (*arrow head present*). (Reproduced from Jaffe ES, Harris NL, Stein H. *World Health Classification of Tumors.* Lyon: IARC Press; 2001:244–253.)

At the time of writing this (2005), there is no standard treatment of HL. Radiation therapy seems to be the favored treatment for localized disease. In systemic disease, polychemotherapy with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) and/or doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is considered the treatment of choice (Reuss et al., 1996). Remission of the disease usually follows treatment, but its length varies widely. Patients treated during the early stages of disease have a much better prognosis than those treated in the late stages of HL. Because of the lack of *long-term* follow-up, there are no firm statistics of either survival or cure.

Few ophthalmologists are aware that Graves ophthalmopathy may be a sequela in some patients who previously received mantle radiotherapy to their neck for HL. Mortimer et al. (1986) studied 66 patients who had been so treated. Five (9%) developed Graves ophthalmopathy. They conclude that impaired thyroid function develops within 6 years of mantle irradiation, but once apparent, remains stable. In a review of 437 patients (Loeffler et al., 1988) who received similar mantle irradiation, seven (1%) developed Graves ophthalmopathy. The actuarial risk of developing the ophthalmopathy at 10 years following therapy was 3.3% in female patients and 1% in male patients in this study. The patient of Belfiore et al. (1995) suffered more serious sequelae from treatment. Five years after radiation and

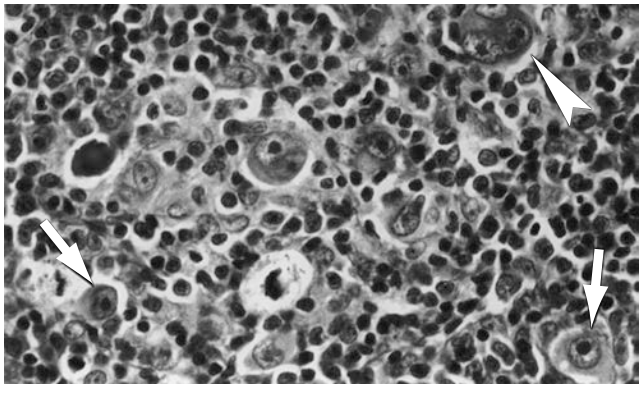

Figure 13.25 Classical Hodgkin lymphoma: Uninucleated Hodgkin cells (*arrows*) and a multinucleated Reed-Sternberg cell (*arrow head*) are seen in a cellular background of eosinophils. (Reproduced from Jaffe ES, Harris NL, Stein H. *World Health Classification of Tumors.* Lyon: IARC Press; 2001:244–253.)

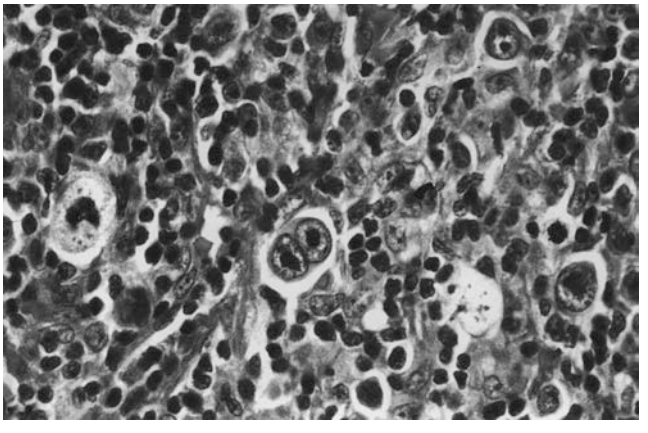

Figure 13.27 Mixed cellular infiltrate: Showing a typical Reed-Sternberg cell (center) admixed with lymphocytes, macrophages, and eosinophils. (Reproduced from Jaffe ES, Harris NL, Stein H. *World Health Classification of Tumors.* Lyon: IARC Press; 2001:244–253.)

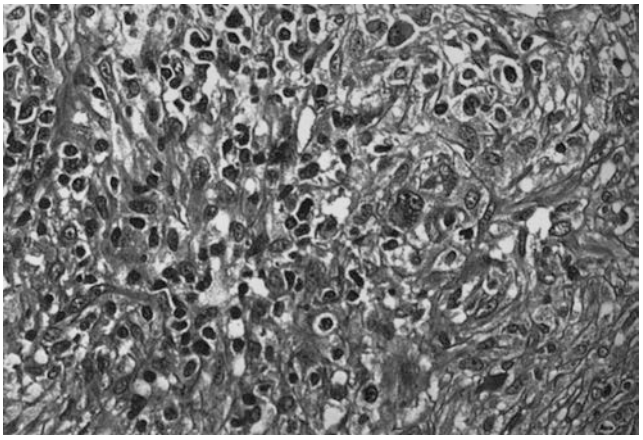

Figure 13.28 Lymphocyte depleted subtype: Many bizarre, large and small Reed-Sternberg cells in a fibrillary matrix. (Reproduced from Jaffe ES, Harris NL, Stein H. *World Health Classification of Tumors*. Lyon: IARC Press; 2001:244–253.)

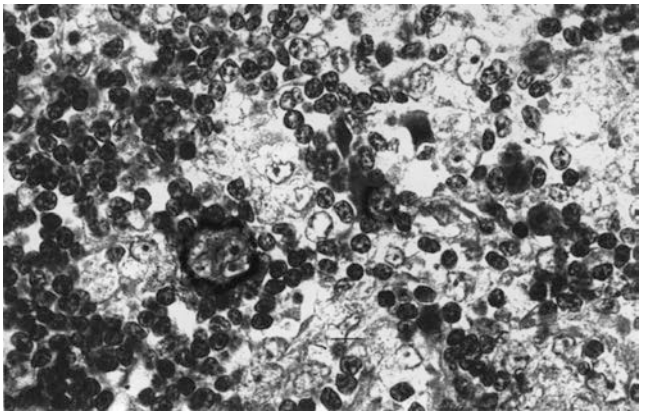

Figure 13.30 Immunostaining: Mixed-cellularity stage. CD30 negative histiocytes with pronounced epithelioid differentiation forming clusters. The CD immunostaining highlights the Reed-Sternberg cell (left center). (Reproduced from Jaffe ES, Harris NL, Stein H. *World Health Classification of Tumors*. Lyon: IARC Press; 2001:244–253.)

adjunctive chemotherapy for HL, Graves ophthalmopathy and papillary thyroid occurred.

MYELOID SARCOMA (WHO CLASSIFICATION)

Synonyms: *Chloroma, extramedullary myeloid tumor, granulocytic sarcoma*.

This is a malignant neoplasm of precursor myeloid cells, which may also occur in soft tissue sites. Its association with acute myelogenous leukemia (AML) has long been known. The tumor may precede, occur concurrently, or appear during a remission stage of the leukemia. It may also appear after allogeneic bone marrow transplantation (Bekassy et al., 1996). Alas, it may manifest in the absence of leukemia. In the older literature, the neoplasm was named *Chloroma* because of the greenish hue of fresh tissue specimens. The content of the pigment, myeloperoxidase, is responsible for its color. The color is not constant and tends to fade on exposure to air.

The neoplasm may occur in all age-groups, but young patients are preferentially affected. In the pediatric population, 75% of cases are under 10 years of age (Bulas et al., 1995). In a study of seven patients with orbital involvement, a mean age of 8.8 years was noted (Stockl et al., 1997). Some authors believe there is no sex predilection, but other authors note a male to female ratio of 3:2. The orbit is a frequent site for a focal, soft tissue tumor (see Fig. 13.31).

There are several types of acute myeloblastic leukemia. The *myoblastic* (precursor myeloid cells) type tends to occur in young patients. Since 1990, there are several case reports

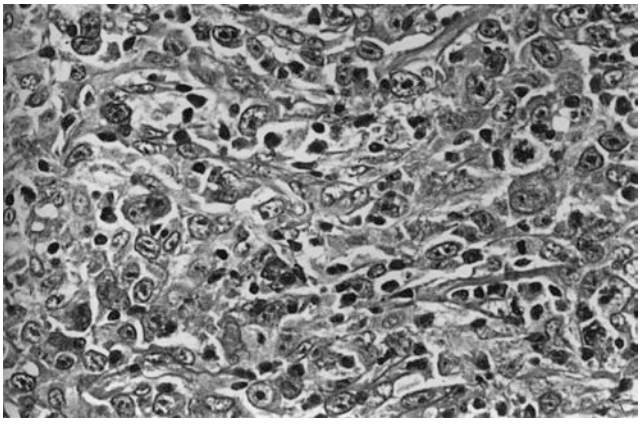

Figure 13.29 Lymphocytic depleted subtype: Many Hodgkin cells with relatively few admixed lymphocytes. (Reproduced from Jaffe ES, Harris NL, Stein H. *World Health Classification of Tumors*. Lyon: IARC Press; 2001:244–253.)

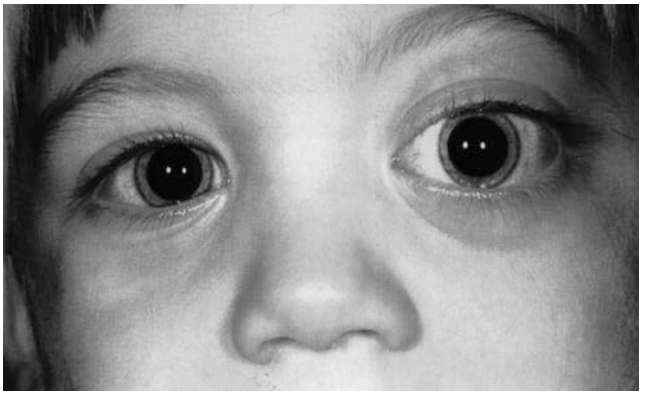

Figure 13.31 Granulocytic sarcoma: Proptosis and displacement of left eye with discoloration of eyelid of 3 weeks' duration in 22-month-old boy. (Courtesy of JD Bullock, MD, Dayton, Ohio.)

in this age-group that presented with an orbital mass that on biopsy and histopathologic examination, proved to have either a localized myeloid sarcoma that preceded an AML or concurrent orbital neoplasm and leukemia. Banna et al. (1991) described four cases of the preceding type. Stockl et al. (1997) noted a 9-year-old boy with orbital myeloid sarcoma who developed leukemia 11 months later. Bulas et al. (1995) reported a 3-year-old boy and Soker et al. (2003) a 10-year-old boy with orbital presentation of simultaneous myeloid sarcoma and AML. A 25-year-old man (Bhattacharjee et al., 2003) and a 72-year-old man (Brock et al., 2001) each had an orbital extramedullary myeloid sarcoma.

The presenting features of the orbital neoplasm in the above patients included: Proptosis, restriction of ocular motility, displacement, pain, epiphora of the eye, swelling, and discoloration of the eyelids. The duration of symptoms and signs before presentation was short—1 1/2 months.

On CT scan, the orbital mass is well delineated, will show enlargement of extraocular muscles, molding around structures such as the eyeball and lacrimal gland. Bone destruction is seldom seen. T_1-weighted MRI will be hypointense to isointense compared to gray matter. On T_2-weighted imaging, the tumor is isointense to intermediate intense (Stein-Wexler et al., 2003).

The myoblasts in tissue sections of the tumor stain positive with Sudan black and the enzymes myeloperoxidase, lysozyme, and chloracetate esterase. These cells also express myeloid-associated antigens: CD13, CD33, CD117, and myeloperoxidase.

Cytogenic analysis of tissue specimens is also a diagnostic determinant. Chromosomal translocation t(8:21) (q22:q22) is specific for this neoplasm (Lasudry and Heimann, 2000)

Histopathologically, most cells are undifferentiated, small, and round. The nuclei may be vesicular with prominent nucleoli or may be irregular in contour with small nucleoli and delicate chromatin. The cytoplasm harbors the eosinophilic granules that contain myeloperoxidase that stains reddish brown with the Leder stains (see Fig. 13.32). In the leukemic phase, Auer rods may be seen in the peripheral blood smears (see Fig. 13.33).

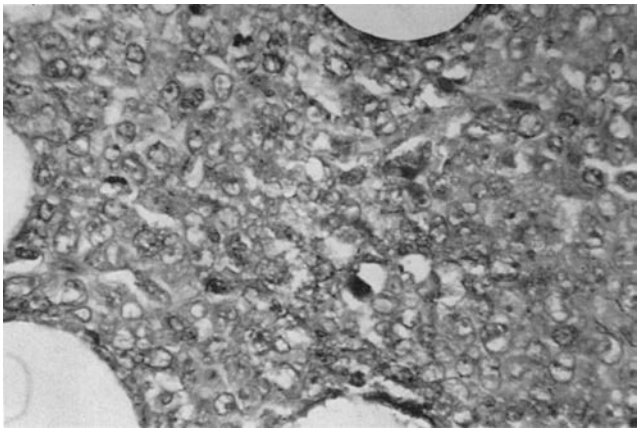

Figure 13.32 Myeloid sarcoma: Leder stain shows reddish brown reaction of differentiating granulocytes (×400). (Courtesy of JD Bullock, M.D., Dayton, Ohio.)

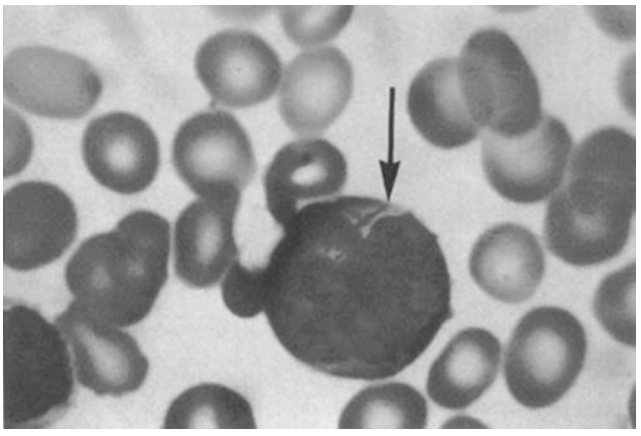

Figure 13.33 Myeloid sarcoma, leukemia phase: Peripheral blood smear reveals myoblastic cells with an occasional Auer rod (*arrow*) present in the cytoplasm, thereby confirming the diagnosis. Giemsa stain ×100 (AFIP negative). (From Spencer WH. *Ophthalmic pathology*, Vol. 4, 4th ed. Philadelphia, PA: WB Saunders; 1996:2738.)

Bhattacharjee et al. (2003) treated a 25-year-old male patient with chemotherapy. The regimen consisted of daunorubicin, cytosine arabinoside, and mitoxantrone over a period of three cycles with regression of proptosis. The patient was asymptomatic without recurrence or leukemia at 18 months' follow-up. Hung et al. (2002) treated a 3-year-old girl with chemotherapy followed by allogeneic bone marrow transplantation. She is disease free at 19 months' follow-up. Some physicians have combined chemotherapy and radiotherapy. In these situations, Ohta et al. (2003) believe chemotherapy is the more effective agent for stabilizing the neoplastic process and inducing remission. Also, there is a general belief that an isolated myeloid sarcoma, without any evidence of leukemia treated with radiotherapy, may have a prolonged survival.

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Histiocytic Disorders

14

This chapter includes non-neoplastic disorders featuring proliferations of histiocytes that may occur in any soft tissue or bony component of the body. Clinical entities of this group are Langerhans cell histiocytosis (LCH), sinus histiocytosis with massive lymphadenopathy (SHML), juvenile xanthogranuloma (JX), Erdheim-Chester (EC) disease, and sarcoidosis.

LANGERHANS CELL HISTIOCYTOSIS

This entity includes three subtypes, the usually solitary *eosinophilic granuloma of bone*, the disseminated *Schüller-Christian syndrome*, and the disseminated fatal variety *Letterer-Siwe disease*, Unni (1996) seems reasonably sure that eosinophilic granuloma and Schüller-Christian syndrome represent stages of the same disease process, but it is possible that Letterer-Siwe disease is caused by a variety of conditions.

Incidence

In early literature, LCH was usually considered a disorder chiefly confined to children. However, Howarth et al. (1999) analyzed 314 Mayo Clinic patients with histologically proved LCH over a 50-year period. Forty-two percent ($n = 131$) were <20 years of age. Five patients (1.6%) had orbital proptosis. The period of this study was between 1946 and 1996, an interval almost the same as our 1948 to 1997 survey of orbital tumors. The most common sites of involvement were the calvarium, spine, and proximal femur.

Our 50-year survey of orbital LCH included 12 patients, 0.6% of the total 1,795 orbital tumors. In the orbital group, there were two unifocal, six multifocal, and four secondary tumors. The male to female ratio was 9:3. Seven patients on this list were 3 years or less of age. The two oldest patients were 17 years old. The Schüller-Christian syndrome and the unifocal eosinophilic granuloma most often affect children and young adults. The disseminated Letterer-Siwe usually affects very young children but can also occur in adults.

Clinical Features

Of most interest to the reader are the cases in which orbital symptoms alone, or associated with multifocal symptomatology, are the presenting features of the disorder. Some combination of unilateral proptosis and swelling of the lateral portion of the upper or lower eyelid is the most frequent initial symptom in these cases (see Fig. 14.1). These symptoms usually evolve over a period of 1 to 6 months. In general, the shorter the interval, the younger the child. In tiny tots, an accompanying redness and tenderness of the adnexal soft tissues suggests subacute cellulitis. Such cases are usually first treated with an antibiotic. In adolescents, tenderness is often absent. In such cases, onset is more protracted and the patient may not be brought for consultation until a reddish-brown or reddish-blue pustule-like lesion appears in the upper lid fold or the crease of the lower eyelid corresponding to the inferior orbital rim (see Fig. 14.2). Finally, when the child or adolescent does not respond to antibiotic therapy or conservative observation, computed tomography (CT) scan of the orbit reveals the defect in orbital bone. In our small series, the frequency of involvement of the zygomatic bone was nearly as great as that of the frontal bone.

In patients with multifocal disease, the presenting pattern is less specific. Here, we are often dealing with patients showing lytic defects of the sella turcica and sphenoid bone secondary to retro-orbital or orbital apex involvement. Such patients may show some measure of visual loss, afferent pupillary defects, painful ophthalmoplegia, sensory loss secondary to trigeminal nerve disease, otitis media, and stomatitis. Two of our patients developed the infrequently seen Schüller-Christian syndrome consisting of osteolytic lesions, diabetes insipidus, and exophthalmos.

In other interesting cases of LCH in recent literature, Kramer et al. (1997) reported three female children, aged 24, 24, and 21 months, respectively, in Nogales, Arizona, with involvement of the sphenoid bone and lateral orbit by tumor. The authors calculated an incidence rate of 40 per million, which is approximately 26 times the expected rate ($P = 0.0001$). This cluster of cases may imply that LCH may be a sentinel disease for unusual environmental exposure.

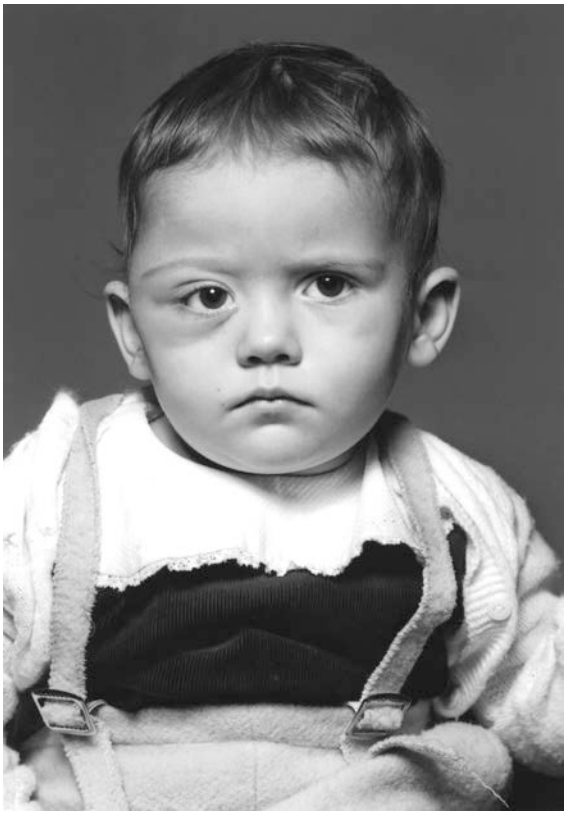

Figure 14.1 Langerhans cell histiocytosis: Swelling of the right upper face with downward and inward displacement of the eye secondary to lytic defects in the zygoma and lateral wall of orbit with extension of soft tissue component into the orbital cavity. This 2-year-old child eventually died from disseminated disease.

MacCumber et al. (1990) observed an adult patient who developed the chronic, diffuse type of tumor without osseous lesions over a 7-year period. An autopsy showed tumor spread to the dura, sagittal sinus, pericardium, *both orbits*, sella turcica, sclera, optic nerve, and choroid. Stromberg et al. (1995) noted a 16-year-old boy with a biopsy-proved mass in the sphenoid sinus that secondarily produced destruction of the lateral wall of the sinus and orbital invasion.

Imaging Aspects

CT scan appearance is quite distinct. In the early stages, the lesion appears as a sharply delineated, radiolucent area of expanding bone. When the soft tissue component of the lesion breaks through the thinned-out cortex, the osseous defect has a dished-out, somewhat moth-eaten appearance (see Fig. 14.3). The bony lesion may be solitary in the orbit, or the calvarium will show other lytic defects (*geographic skull*). The soft tissue component usually shows some contrast enhancement. These bony defects heal if the child does not succumb to the systemic and visceral manifestations of the disease. In the healing process,

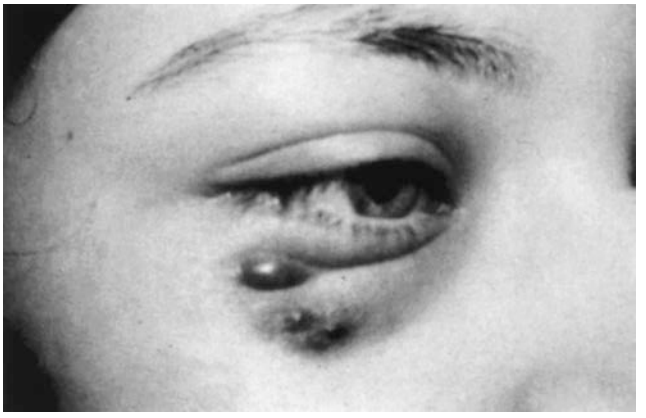

Figure 14.2 Nasal displacement of eye by Langerhans cell histiocytosis. The right lower eyelid had a reddish discoloration with fluctuant, purple, ecchymotic areas in the subcutaneous tissue that waxed and waned over a period of 1 month because of recurrent hemorrhage from underlying tumor. The tumor involved the inferolateral orbital wall with encroachment of a tender and indurated mass into orbital cavity. This 17-year-old girl was treated with irradiation.

the affected bone may undergo sclerosis with ultimate reduction in the overall size of the orbit. This accounts for the residual prominence of the eyes of some children whose localized disease has been arrested. This sclerosis occurs in both treated and untreated patients.

Pathology

Grossly, these tumors have been described as tan gray, tan yellow, yellowish red, and white in color. The hues of red probably reflect the vascularity of the lesion. The yellow

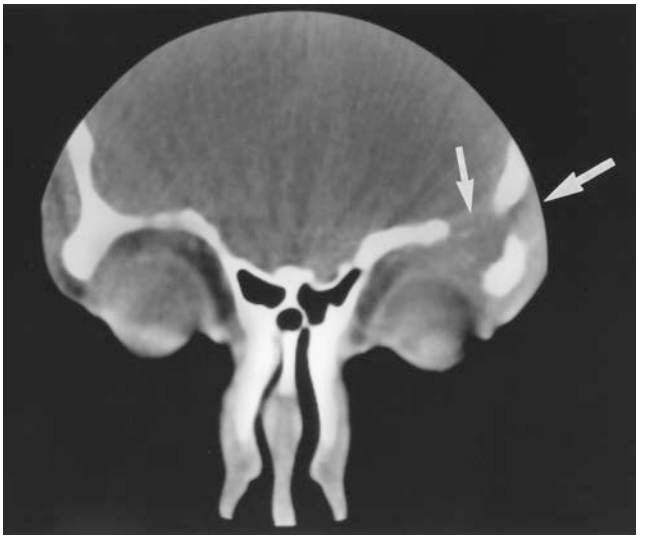

Figure 14.3 Coronal computed tomography scan shows lytic defects (*arrows*) in the left supraorbital ridge and orbital roof with slightly enhancing soft tissue extension into the orbit and adjacent anterior cranial fossa of a 16-year-old boy.

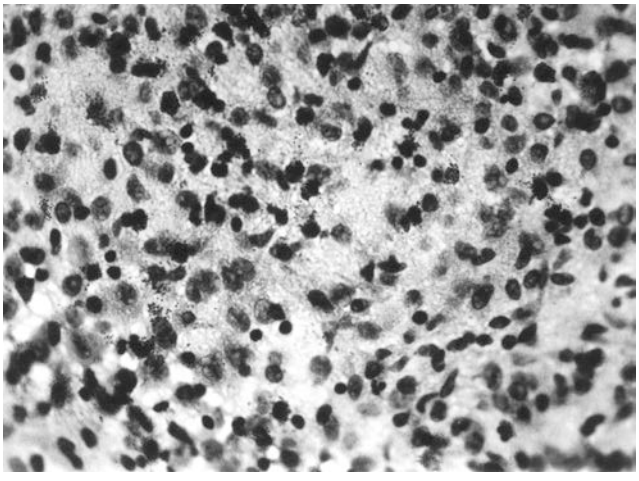

Figure 14.4 An admixture of histiocytes with ill-defined cell boundaries and finely vacuolated cytoplasm, and eosinophiles (×400).

color probably indicates the amount of lipid accumulation in the lesion. The lesions are soft, friable, and often hemorrhagic.

The cellular component common to the localized, diffuse, and disseminated forms of LCH is the histiocyte. These histiocytes are usually arranged in loose sheets; have ill-defined cytoplasmic boundaries; have a pale, slightly foamy cytoplasm; and contain an oval or indented nucleus (see Fig. 14.4). Occasionally, the histiocytes have a focal arrangement and are completely surrounded by an abundance of eosinophiles. Inflammatory cells such as lymphocytes, plasma cells, and neutrophils are less in number. Multinucleated giant cells are frequent (see Fig. 14.5A and B). The histiocytes stain positive for S-100 protein and vimentin. The cell membrane receptors stain with T-6 monoclonal antibodies. Ultrastructurally, cytoplasmic inclusions, *Birbeck granules*, may be present in about 50% of cases.

Management and Course

Our small cohort of patients, mostly children ($n = 12$, age range 1 to 17 years) received three initial types of therapy over the 50-year period of study. Six patients, with focal lytic defects in the calvarium and skeletal bone, including the orbit, were treated only with irradiation. Three of these patients died 6 months to 3 years after therapy. The other three patients were alive 7, 14, and 29 years after initial treatment. Three of the patients had only lytic defects limited to the orbit. These patients underwent surgical removal of the soft tissue component of the tumor followed by irradiation. All are living 3, 6, and 28 years after treatment. One patient, a 17-year-old boy, received irradiation and andirine (surinamine) therapy and was living 15 years later. Two of our patients were lost to follow-up. There were no clues, initially, that we could use to predict which patients would or would not die except, possibly, the fewer the lytic spots treated, the longer the survival.

In the time interval of our tumor study, other treatments of LCH in the literature were surgery, irradiation,

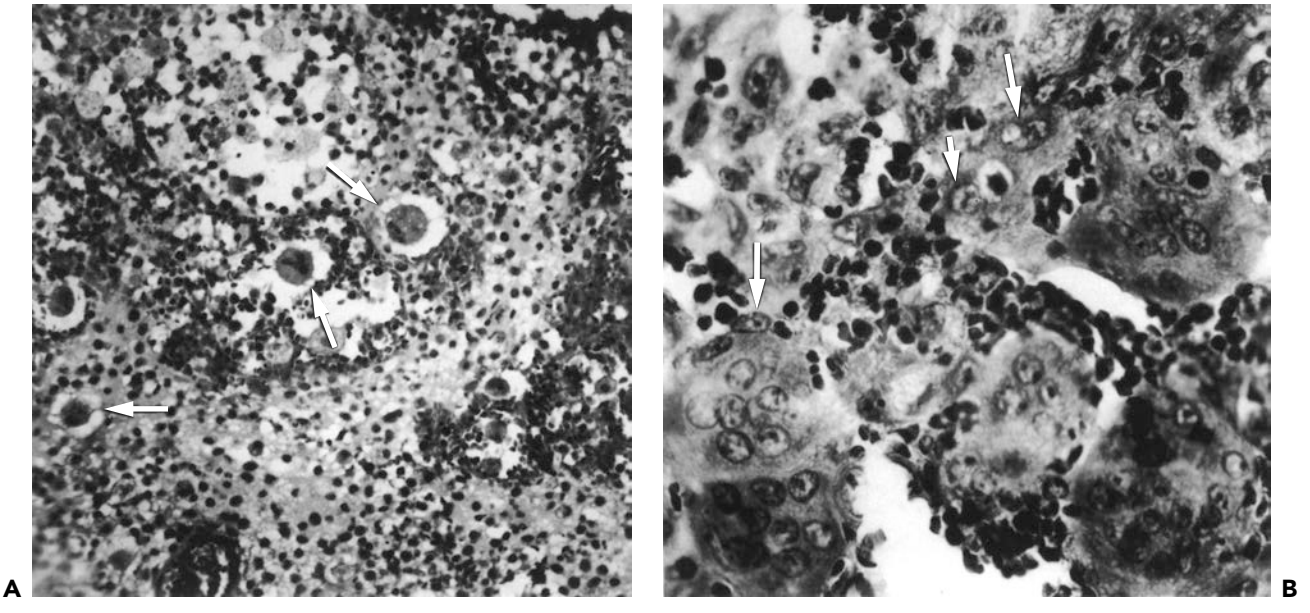

Figure 14.5 Histopathology **A:** Shows numerous histiocytes with pale cytoplasm (*arrows*) (×250). **B:** An admixture of histiocytes with folded or indented nucleus membranes (*arrows*), multinucleated giant cells, eosinophiles, and lymphocytes (×400). Both specimens from a 17-year-old girl with unifocal, orbital bone disease.

and chemotherapy alone or in some combination, oral corticosteroids, intralesional injection of corticosteroids, low-dose radiotherapy, bone marrow transplantation, antibody therapy, intramuscular injections of an extract of thymus gland (a T-cell suppressor), and simple observation. We are not aware of any published protocol for the therapy of LCH, derived from a grouped medical center study. With the passage of time, we are more hesitant to recommend radiotherapy for young children. Instead, we favor a more conservative therapy, one of the above, as the initial remedy for LCH limited to the orbit.

Recently, a relatively new treatment looms on the horizon in treating disseminated LCH. This is a purine nucleoside analog, 2-chlorodeoxy-adenosine (2-CDA). Several reports of this drug have appeared in the literature since 1993. A more recent report is that of Pardanani et al. (2003). They treated five patients between December 1994 and January 2001. The age range of patients was 19 to 81 years. Median follow-up after initiation of treatment was 33 months. In one patient, the drug was used as frontline therapy and as salvage therapy for the other patients. Complete response was achieved in three patients and a partial response in the other two patients. The drug is a potent immunosuppressive and needs "*to be studied prospectively*."

Eosinophilia is a major component in the orbital lesions of patients with LCH. When the eosinophil degranulates, it releases a major basic protein, indicating an *effector* role in the pathogenesis of this disease (Trocme and Aldave, 1994).

SINUS HISTIOCYTOSIS

The disorder received its first name, *SHML*, and its stature as a clinicopathologic entity, chiefly through the publications of Rosai and Dorfman (1969, 1972). The disease consists of a proliferation of benign histiocytes with an admixture of lymphocytes chiefly in sinusoidal spaces of the cervical lymph nodes, resulting in their enlargement. Subsequently, it was noted that some histologically proved cases in extranodal sites had little or no cervical lymph node enlargement, which suggested that the original name was no longer appropriate. Consequently, the name was shortened to sinus histiocytosis (SH). The etiology of the disorder is not known.

Incidence

The primary locus of the disorder is massive and is a uni- or bilateral cervical lymphadenopathy. All ages may be affected, but there is a strong predilection for children. Extranodal sites are not uncommon and may be observed in about 43% of cases (Foucar et al., 1990). In the skull, the nasal fossa and paranasal sinuses are the most common extranodal sites. The orbit and central nervous system are both less common sites for manifestations of the tumor. Of the 423 patients in the SH registry, 36 (8%) had some evidence of orbital involvement (Resnick et al., 1996). Including all loci of the disorder, there is a mean age of presentation of approximately 20 years with a slight male predominance of 58%. We have not encountered a patient with SH in our 50-year file of orbital tumors.

Clinical Features

The cardinal feature of orbital presentation is a slow, painless, proptosis of one or both eyes over a period of several months. Associated signs and symptoms may include fever, leukocytosis, elevated sedimentation rate, hypergammaglobinemia, transient visual loss, and blindness. Blindness occurred in two 12-year-old patients of Remadi et al. (1996) because of massive tumors in the retrobulbar space that exerted such pressure and pain on the eye as to warrant enucleation. Other authors who have reported cases of orbital involvement in the literature in the past 15 years are Resnick et al. (a 38-year-old man), Burton et al. (a 2-year-old girl), Brau et al. (1995) (a 5-year-old boy), and Salmon and Duffield (1989) (a 12-year-old girl). Cases of bilateral orbital involvement are also reported. Optic nerves are rarely involved except by orbital compression from a massive tumor.

Imaging Aspects

The orbital image of this soft tissue mass with CT scan shows a homogeneously enhancing mass with a density and contour likened to lymphoma (see Fig. 14.6A). With magnetic resonance (Fig. 14.6B), the tumor is isointense to gray matter on all sequences (Burton et al., 1989). With increasing bulk, the orbital lesion may cause expansion of the foramina and fissures into adjacent paranasal sinuses or intracranial cavity, but bone destruction is seldom seen.

Pathology

Grossly, this tumor is whitish gray, firm, and usually adherent to surrounding orbital structures. However, the histology of the lesion is its most distinctive feature. Cytoplasmic vacuoles within the macrophage contain T-cell lymphocytes and other inflammatory cells—a phenomenon known as *emperipolesis* (see Fig. 14.7A). The outline of some cells is indistinct, but the nuclei are oval or round with regular outlines. The histiocytes stain positively with S-100 protein but do not contain the cytoplasmic organelle (Birbeck granules) peculiar to the Langerhans histiocyte. Fibrosis is a common component of most tissue specimens (Fig. 14.7B) and probably represents the natural course to involution.

Management and Prognosis

According to Foucar et al. (1990), >400 cases have been reported and are included in an SHML registry, allowing

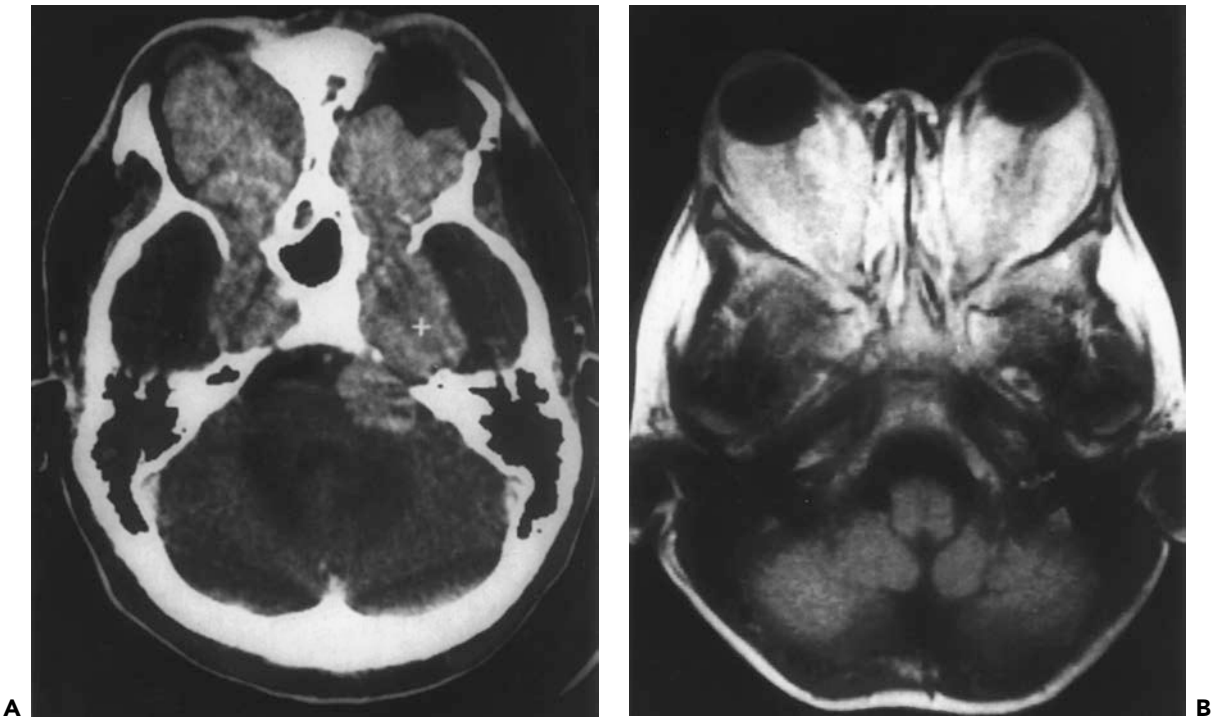

Figure 14.6 Sinus histiocytosis. **A:** Computed tomography scan with contrast shows enhancing bilateral soft tissue masses with intracranial extension. There is no bone destruction. **B:** Magnetic resonance imaging: Another case showing the nasal fossa and orbital spaces occupied by expansive processes causing marked proptosis. (From Remadi S, Anagnostopoulou ID, Jlidi R, et al. Extranodal Rosai-Dorfman disease in childhood. *Pathol Res Pract.* 1996;192:1007–1015, with permission.)

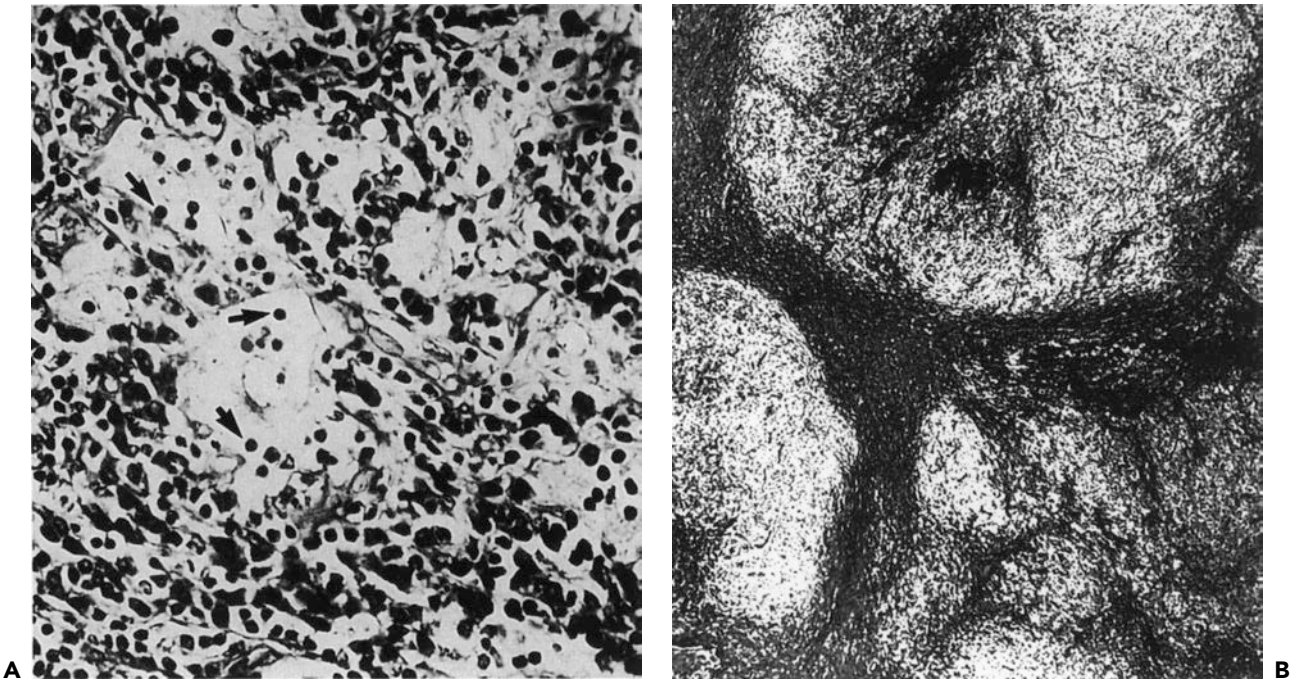

Figure 14.7 Sinus histiocytosis **A:** Large histiocytes with pale vesicular nuclei are interspersed in a lymphoplasmacytoid infiltrate. Numerous mature lymphocytes (*arrows*) are engulfed in the cytoplasm of the histiocytes (×350). **B:** Orbital mass consisting of well-defined lobules of histiocytes and focal collections of lymphocytes separated by broad fibrous septa (×25). (From Friendly DS, Font RL, Rao NA. Orbital involvement in 'sinus' histiocytosis. A report of four cases. *Arch Ophthalmol.* 1977;95(11):2006–2011, Copyright, American Medical Association, with permission.)

for some comment on the natural history of the disease. Of 238 patients followed up with the disease for at least 1 year, 49 had a complete spontaneous remission, 165 have had stable disease, and three have had notable progression of disease; 4 patients died free from the disease, and 34 patients died with or of Rosai-Dorfman disease. The group of patients with progressive disease was noted to have a very high incidence of immunologic abnormalities and tended to have multiple nodal and extranodal sites of involvement. Almost all patients who died of the disease had a widely disseminated nodal disease. Involvement of the kidneys, lower respiratory tract, and liver carried a particularly grave prognosis.

The authors also noted that one in six patients with orbital disease will have no other manifestation of the disease. Therapies including steroids, antibiotics, and radiotherapy have been used for progressive disease, but their putative effect has not engendered much enthusiasm. We would be reluctant to use radiotherapy for the orbital disease in children. In brief, there is no specific treatment for these orbital cases except surgical debulking or excision where the tumor is so massive in the orbit as to cause pain or extreme proptosis.

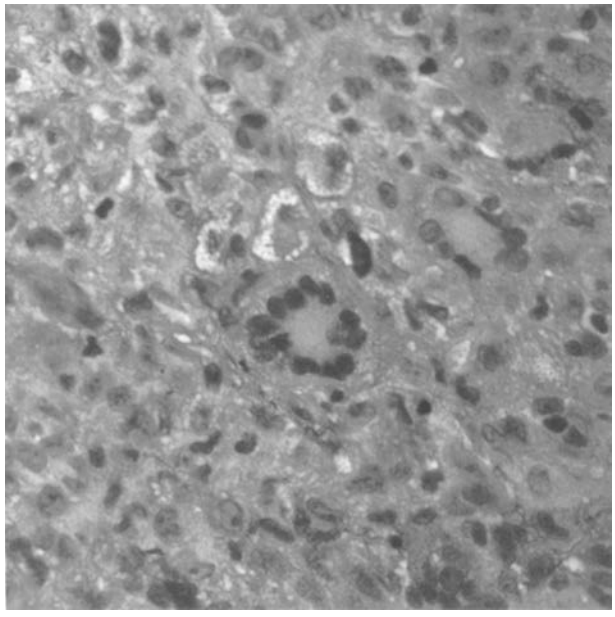

Figure 14.8 Juvenile xanthogranuloma showing foamy histiocytes and Touton giant cell (center) (×640).

JUVENILE XANTHOGRANULOMA

Juvenile xanthogranuloma (JX) is a benign disorder chiefly of the skin of infants and children characterized by smooth, rounded nodules or papules of red, yellow-orange, or brown color. Single lesions tend to involve the scalp, face, and neck; multiple lesions tend to be distributed over the head, trunk, and extremities (Sonoda et al., 1985). The lesions most commonly are <1 cm in size, rarely exceeding 4 cm (Campbell et al., 1988). In ophthalmology, it is best known for its occurrence in the iris where, in the course of its growth, it may produce recurrent episodes of hyphema and result in secondary glaucoma if not recognized.

In the third edition of this text (1994), we referenced seven cases of orbital involvement, all of whom were <10 months of age at presentation; (Zimmerman, 1965; Gaynes and Cohen, 1967; Shields et al., 1990). Five of the patients in this list were reported by Zimmerman, four of whom had no skin involvement. Borrego and Hidayat (1996) reported a 5-month-old boy who presented with a large brownish mass on the superomedial surface of the eyeball. It was attached to the anterior portions of the superior and medial recti muscles. It was also a solitary JX with no cutaneous manifestations.

Proptosis or swelling of an eyelid for 1 week to 2 months is the usual presenting sign of orbital disease. The disorder has also been observed at birth. The tumor may be located anywhere in the orbit and a minority of cases may show some erosion of the adjacent bone. In the case of Shields et al. (1990), CT scan showed an ill-defined, homogenous mass with minimal contrast enhancement.

Histopathologically, a distinctive marker is the multinucleated Touton giant cell (see Fig. 14.8) (Spencer, 1996). In this cell, "multiple nuclei are aggregated as a circle in the middle of the cell, enclosing a central, intensely eosinophilic cytoplasm, whereas the outer cytoplasm between the nuclei and cell membrane is more frothy and vacuolated" (Spencer). A variable number of lymphocytes, plasma cells, and occasionally eosinophils may be scattered among mononucleated, spindled, and vacuolated histiocytes. Electron microscopy will not show Langerhans granules. In general, mitoses are rare or absent. Immunohistochemistry will be positive for HAM 56, HHF 35, and vimentin. There will be inconsistent labeling for lysozyme, α_1 antichymotrypsin, and antitrypsin. Most lesions stain negative for S-100 protein.

Management

There are several options for the treatment of the common, solitary orbital JX in young children.

1. Watchful observation while waiting for spontaneous resolution.
2. Surgical debulking if necessary for marked proptosis or excision of large brown lesions on the surface of the eyeball.
3. Oral corticosteroids to supplement recovery.

In the literature, radiotherapy also is recommended, but we do not believe the benefits of radiotherapy outweigh its long-term risks.

ADULT ORBITAL XANTHOGRANULOMA

Adult orbital xanthogranuloma (AOX) is a xanthogranulomatous proliferation occurring in adults that is not associated with other organ involvement or dermatologic manifestations (Nasr et al., 1991). On a clinical basis, we believe it is an entity distinct from other histiocytic disorders discussed in this chapter. In addition to the case reported by Nasr et al., another report, that of Rouhiainen et al. (1992) has come to our attention.

The patient of Nasr et al. was a 38-year-old woman with painless, progressive bilateral proptosis of 16 years' duration. The patient of Rouhiainen et al. was a 45-year-old woman who presented with a soft, palpable mass in the left upper eyelid beneath the orbital rim, but there was no proptosis. Over the next 8 months, the mass on the left side became solid and was associated with pain. Finally, 16 months after presentation, the right orbit was involved. In both these cases, a systemic workup was negative including lipid profiles. CT scans on both cases confirmed the presence of orbital lesions. The CT scan on the Nasr et al., patient showed a nonhomogeneous mass with uniform contrast enhancement. Biopsy was performed in each case and showed a histopathologic xanthogranulomatous proliferation. Each case had a dramatic response to oral corticosteroids. However, in the patient of Nasr et al., proptosis recurred after a 3-week remission. The dose of prednisone was increased and tapered over a period of several weeks, followed by a 6-month remission. The bilateral disease process again recurred. The patient was given a low dose of radiation therapy (1,500 rads) combined with another course of oral cortisone. At the time of the authors' report, the patient had experienced a total remission of 3 years.

The initial disease in the left orbit was also treated with an oral corticosteroid with partial remission. Two months later, when the right orbit was affected, prednisone was again administered. The symptoms diminished slightly, and therapy was discontinued. Nearly a year later, there was a marked exacerbation of the mass on the left side. Nineteen months after initial presentation, the left orbital tumor was subtotally extirpated. At the time of the authors' report, the patient continued to have orbital pain, but the patient refused further corticoid therapy.

Histopathologically, AOX consists predominantly of sheets of xanthoma cells. Xanthoma cells are histiocytes that imbibe cholesterol, although abnormalities of the peripheral blood are generally not found (Spencer, 1996). The histiocytes are intermixed with mononuclear cells such as plasma cells and lymphocytes associated with some degree of fibrosis. This suggests some abnormality in metabolism wherein histiocytes imbibe excessive amounts of lipid that cannot be processed. The xanthoma cells have small, centrally positioned nuclei and abundant pale cytoplasm. Touton giant cells also are present.

Where does AOX fit in the gamut of histiocytic disorders? First, it should not be considered an adult variant of JX. Aside from the age difference, AOX is a bilateral orbital disorder without well-documented systemic manifestations; JX is a unilateral orbital disorder that may be associated occasionally with cutaneous lesions. More important, the histopathology of the histiocytes differs in the two diseases.

Indeed, AOX is more closely related to the EC disorder (next section) than to JX. In past years, several authors have alluded to AOX as an orbital variant of the EC complex *syndrome*. This allusion was based on the fact that the histopathologic patterns of these two proliferative disorders are *identical*. Otherwise, they have little in common. It is possible that some of the cases reported in past years as a variant of EC disorder were similar to the entity reported by Nasr et al., in the preceding text.

If, in the future, AOX is accepted as a clinical entity rather than as an orbital variant of the EC complex, it no longer would be necessary to include EC as a disorder affecting the orbit. However, it is likely that reports will continue to appear in the literature wherein the author will discuss the *periorbital* manifestations of EC but include the misleading word, *orbital*, in the title of the article.

NECROBIOTIC XANTHOGRANULOMA

This is the last histiocytic disorder we will discuss in this chapter that includes Touton giant cells in its histopathologic make-up. The initial publication about this histoproliferative disorder was that of Kossard and Winkelmann (1980). Their definition of necrobiotic xanthogranuloma NX was "a proliferation of *multiple, xanthomatous plaques and subcutaneous nodules that had a predilection for the periorbital area, flexures, and trunk that showed a combination of xanthogranulomatous nodules with necrosis*." All eight patients in their report had an accompanying dysproteinuria, which was associated with monoclonal IgG paraprotein. It is the collagen necrobiosis that distinguishes NX from other histiocytic disorders that include Touton giant cells in their histopathologic pattern.

The periorbital manifestations, usually, are confined to eyelids and, most often, are the features that bring the patient to the attention of the physician. These lesions resemble the soft, movable xanthomas, but those of NX are almost always indurated and prone to superficial ulceration. Sometimes, yellow plaques occur on the sclera of the underlying eye. Among the original eight patients of Kossard and Winkelmann, their case 3 also had proptosis.

Soon, other reports of NX appeared in the literature. Codere et al. (1983) reported a 56-year-old woman with moderate restriction of left eye in all fields of gaze. Orbital echography showed a mild thickening of the medial and lateral recti muscles of the left eye, and lateral rectus muscle,

right eye. No orbital biopsy was performed. In retrospect, we believe these changes were an inflammatory response (edema) to rock hard masses palpable on the surface of adjacent periocular bone.

Next was the analysis of 16 patients (seven men and nine women) with NX by Robertson and Winkelmann (1984). Two of these patients were listed as having orbital involvement on the basis of palpation of indurated lesions of the overlying eyelids that seemed to extend postseptally into the orbit. We would have to regard this orbital extension as *presumed*. Bullock et al. (1986) reported a 57-year-old woman with bilateral periorbital swelling. The masses were biopsied with a diagnosis commensurate with NX. CT scans showed bilateral, periorbital soft tissue masses. However, there was neither proptosis, displacement of the eyes, nor ocular motility impairment. Several authors have listed the patient of Bullock et al. as an example of orbital involvement, but we believe their statements were misleading. Next was the case, a 63-year-old woman reported by Char et al. (1987), who presented with proptosis and limitation of gaze in one eye. On surgical exploration of the orbit, a yellow mass was found in the palpebral lobe of the lacrimal, which, on histiocytic study, was an NX. The orbital findings were probably a secondary inflammatory response.

Several reports appeared in 1991 and 1992, for example, Cornblath et al. (1992), Luck et al. (1992), and Plotnick et al. (1991). Case 3 of four cases of Cornblath et al., on biopsy proved to be "a nonspecific inflammation." The case of Luck et al. was quite different. A 41-year-old woman presented with proptosis, displacement of the eye, and restriction of ocular rotations. CT scan showed an extensive, soft tissue mass encircling the eye, which, on histopathologic study, was an example of NX. The case of Plotnick et al. was a disseminated case of NX associated with multiple myeloma but with no orbital lesion.

At this point in time, we have found only one proved case (Luck et al.) of NX; all the other cases in the preceding text are *presumptive*. Jakobiec et al. (1993) reported six individuals who had eyelid and orbital lesions with histopathologic features that closely mimicked those exhibited in biopsy specimens from patients with EC disease, but *did not have* the typical systemic associations. They compared the findings in these patients with other histiocytic proliferative, *especially necrobiotic, xanthogranuloma*. They detailed three clinical histories typifying the clinical findings, behavior, and treatment shared by the six cases. Their cases 1, 3, and 5 were selected for closer analysis shared by the six cases.

Of the three representative cases in the preceding text, case 1 was the only one to develop severe bilateral proptosis (Krahn, R31, L32) over the period of the authors' observation. Orbital CT scans disclosed bilateral, diffuse, symmetric enlargement of the rectus muscles. However, there was *no mass* lesion such as was noted in the biopsy-proved case of Luck et al. Biopsy of a mass in the right temple *showed* a typical xanthogranuloma but no necrobiosis of any of the tissue components. From an orbital standpoint, the histiocytic process was *not NX*. The bilaterality and the reactive edema of the recti muscles are remindful of the entity described in the preceding section namely, *AOX*. In the summary of their publication the authors say, "Our patients' eyelid and intraorbital lesions were extensively evaluated with sequential biopsies, and no evidence of necrobiosis was ever discovered." We conclude that none of the six patients had NX of the orbit.

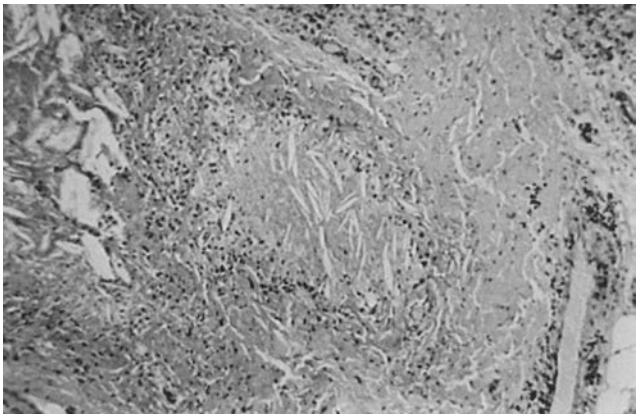

Figure 14.9 Necrobiotic xanthogranuloma. Well-formed granuloma (center) with central necrosis, palisading, xanthomatous histiocytes (left), and peripheral necrobiotic collagen (right) (periodic acid-Schiff ×100). (From Bullock JD, Bartley GB, Campbell RJ, et al. Necrobiotic xanthogranuloma with paraproteinemia: Case report and a pathogenetic theory. *Tran Am Opth Soc.* 1986;84:342–354, with permission.)

The patient of Luck et al., with the well-documented orbital xanthogranuloma was treated with chlorambucil, 4 mg daily. On a review 6 weeks later, the ocular movements were again full, and the proptosis had resolved. The histopathology of NX is illustrated in Figure 14.9.

SARCOID AND SARCOIDOSIS

These two granulomatous tumefactions have identical histopathologic patterns. They differ in clinical features and course. Orbital involvement may occur with either one. Sarcoidosis is a multisystem disorder that may affect any tissue system or organ except the adrenal gland (Spencer, 1996). Sarcoid is a single focus of granulomatous disease usually involving one orbit that, for some unknown reason, does not (with few exceptions) develop systemic manifestations. In this section, it is not our goal to include all that has been published about the disease since the first histopathologic description in 1899 but to update literature and changing concepts, if any, since 1988.

Pathology

Grossly, these tumors are yellow to yellow-white, firm in composition, and infiltrative. In our dozen or so cases,

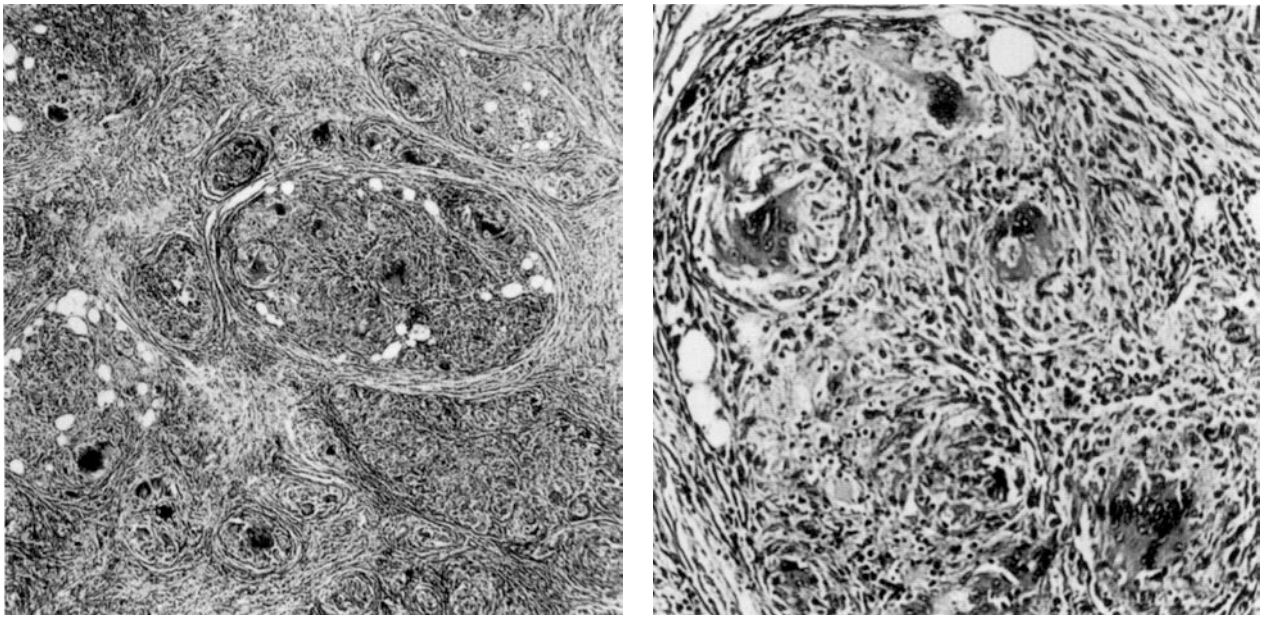

Figure 14.10 Epithelial cell granuloma. **A:** Numerous small noncaseating granulomas with intervening bands of fibrous tissue (×35). **B:** Details of granuloma showing epithelioid cells. Langerhans giant cells, and mononuclear cell infiltrates surrounded by fibrous tissue septa (×130). The specimen is from the lacrimal gland fossa of a 70-year-old woman.

most lesions were located in three areas. The tumor could arc just beneath the superior orbital rim from lateral to medial side between the periorbits and levator–superior rectus complex and be palpable through the upper lid. In these cases, the compression of the levator complex was responsible for the *''puffiness'' and ''drooping''* of the upper lid, a sign first noted by the patient at onset. Or, a similar band of tumor would stretch across the lower orbit like a sling. The third favorite location was the lacrimal gland. The three locations were approximately equal in frequency.

Histopathologically, the predominant unit is the noncaseating epithelioid granuloma (see Fig. 14.10). The precursor of the epithelioid is the morphologically altered histiocytes. Two patterns may be seen. One type is a nodular pattern of variable-sized granulomas containing epithelioid histiocytes with slightly foamy cytoplasm surrounded by dense connective tissue. Other cells such as mononuclear inflammatory cells are sparse. In the second group, there is heavy infiltration of lymphocytes in the supportive tissue with cuffing of the granulomas. Necrosis within the granuloma is absent (Satorre et al., 1991).

Incidence

Incidence data, including age, race, type of granulomatous involvement, and laterality of the orbital process, in the literature is mostly based on only a small sample of cases, such as our own. Faller et al. (1995) states that orbital involvement among patients with *sarcoidosis* is chiefly noted in women over 50 years of age. Sharma and Dostanic (1995) estimated the frequency of lacrimal gland involvement in *sarcoidosis* to be approximately 5% to 15% of patients. Raskin et al. (1995) reported five patients (three men, two women) with the solitary type of *sarcoid*. Their mean age was 36 years. In a larger sample, Satorre et al. (1991) noted seven patients with *sarcoid*, mean age 64 years and six patients with orbital involvement associated with *sarcoidosis*, mean age of 50.8 years.

Our 50-year tumor survey (see Chapter 3) included 15 patients with the diagnosis of sarcoid or sarcoidosis. Two of the patients were excluded from an objective analysis of incidence data. One of these, a case of presumed solitary sarcoid, did not undergo a physical examination, so we do not know whether the patient did or did not have sarcoidosis. In the other patient, exclusion was based on the development of malignant lymphoma soon after our diagnosis of sarcoid. We think the granulomatous process represented a preliminary disturbance in the patient's immune system prior to the development of a malignancy. This association of granulomatous type disorder with subsequent malignancy has been noted by other authors.

In the remaining 13 patients, there were seven cases of limited orbital *sarcoid* and six patients with sarcoidosis. Among the patients with sarcoid, there was only one male. The mean age of the total group was 65.4 years. All cases were unilateral. The *sarcoidosis* group of six patients also included only one male. The mean age of this group was 61.6 years. This sample suggests that *sarcoid and sarcoidosis* are predominantly diseases of *women* (*n* in a ratio of 11:2); the *age range* of the two entities *is not*

significantly different, and the orbital manifestation of the granulomatous disorder is predominantly *unilateral*.

Clinical Features

In a paragraph of the preceding text, we noted the usual presentation is a puffy or droopy upper or lower eyelid associated with a painless, palpable mass in the anterior orbit or lacrimal gland fossa, with or without some degree of proptosis (depending on the size and duration of the mass), and little or no disturbance of vision aside from some degree of diplopia. One patient from our series with sarcoidosis had a painful mass on palpation. However, if the patient presents with a significant loss of vision, an afferent pupillary defect, and color vision abnormality, in addition to other abnormalities noted in the preceding text, a concealed granulomatous involvement of the orbital portion of the optic nerve is likely.

Diagnosis of systemic sarcoidosis is based on some combination of an elevated sedimentation rate and angiotensin converting enzyme, hilar and mediastinal lymphadenopathies on CT scanning, some hypercalcemia (absent with optic nerve involvement), and anergy to the skin tuberculin test. A decrease in visual acuity may also indicate a uveitis, the most common sign of ocular involvement in sarcoidosis. The isolated sarcoid does not show the above systemic disturbances.

Imaging Aspects

CT scans will confirm the location, size, and full extent of the palpable masses in the anterior orbit. In addition, some cases may show enlargement of some of the extraocular muscles. Most importantly, scanning may reveal an unsuspected involvement of the orbital portion of the optic nerve that has not produced any ocular dysfunction. If MRI is necessary, it will reveal the T_1-weighted image isotense to muscle and T_2-weighted sequence hypotense. All defects show enhancement. Bone destruction is not present unless a granulomatous lesion along with intracranial portion of the sphenoid bone shows erosion of bone accompanying extension of the mass into the posterior orbit through the superior orbital fissure.

Management

Almost all the isolated orbital *sarcoid* cases reported in the literature have been responsive to a single course of oral corticosteroids or intralesional injections. Recurrence after some months is unusual but can be treated again, likely, with apparently permanent resolution. Treatment of the orbital *sarcoidosis* is more tedious in some cases showing repeated recurrences over a period of several years. Some such cases undergo fibrosis after repeated courses of corticosteroids. A surgical debulking of the granulomatous mass may be necessary.

Course

The course of *sarcoidosis*, with or without orbital involvement is unpredictable. Death seems related to the extent of the disseminated foci of disease and the organ systems involved. We do not know what kind or the amount of drugs prescribed for such victims. One of our patients with orbital manifestations died 6 years later with widely disseminated sarcoidosis.

The prognosis of patients with isolated orbital *sarcoid* is quite the opposite. We have four patients who have lived 8, 12, 14, *and* 24 *years* after initial diagnosis without recurrence or further therapy. When we cared for some patients 40 or 50 years ago, we wondered when they would develop systemic disease. It never happened! Another surprise! The sarcoid in one of our patients spontaneously resolved.

CONCLUSION

The long life of patients who are living and well, without recurrent localized tumor or systemic spread, is still generally unknown to authors who write about sarcoid and sarcoidosis. It reinforces our belief that sarcoid and sarcoidosis of the orbit are different clinical entities. Although they have identical histopathologic features, the immunochemistry of orbital tissue of sarcoid seems able to suppress the immune derangement that caused the original lesion. In sarcoidosis, this suppression factor in the involved tissue is absent.

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15 Primary Epithelial Neoplasms

This chapter includes a host of epithelial neoplasms of various histologic types, which, with rare exceptions, arise from the functional components of the lacrimal gland. One exception in the Mayo Clinic series of orbital tumors is noted later. The factor common to these intrinsic lesions is a variable degree of proliferation of cellular derivatives of the secretory or ductal epithelium. Nonepithelial tumors that may be primary in the lacrimal gland including non-Hodgkin lymphomas, cavernous hemangioma, hemangiopericytoma, inflammatory tumor with or without vasculitis, Wegener granulomatosis, sarcoid, and sarcoidosis will be mentioned only as one or they may all go into the differential diagnosis from the epithelial group of tumors. The number and histologic type of the primary and secondary epithelial neoplasms in the Mayo Clinic series are listed in Table 15.1.

Before discussing the individual tumor subtypes, consideration should be given to those clinical and radiologic correlates that are either common to the group as a whole or provide preoperative characterization of a particular tumor subtype. A feature common to all the lacrimal gland neoplasms is a firm enlargement of the lacrimal gland that indents the surface of the contiguous eye resulting in a downward and inward displacement of the eye associated with some degree of proptosis. The larger the tumor, which is a factor of its duration, the greater the malpositioning of the eye. This malposition may reach an extreme degree in many cases of long duration, but may also be seen with slowly expanding orbitofrontal hematocele of bone (Fig. 1.1 and Fig. 4.18). None of the nonepithelial lesions of the lacrimal gland listed earlier produce the degree of downward displacement of the eye that is seen with the intrinsic neoplasms. The mass effect of the tumor also causes some mechanical limitation of ocular movement in the direction of the lesion.

If the neoplasm expands anteriorly, medially, or inferiorly, the mass is always palpable. If the tumor expands into the roof of the orbit or posteriorly toward the orbital apex, its palpation may be minimal in degree or absent. However, this dictum is not specific to the intrinsic neoplasms and may also apply to other neoplasms and non-neoplastic lesions in the same location.

All the lacrimal gland tumors may be associated with some degree of pain, discomfort, pressure sensation, or be entirely pain free throughout their progressive course. Although the malignant tumors are more often associated with pain in their clinical course when compared to the benign tumors, this is not a reliable basis for a preoperative differentiation between the benignity or the malignancy of the lesion. The presence of pain, especially when the eyelids are erythematous and swollen, may even be a manifestation of an inflammatory, vasculitic, or granulomatous lesion in the same location.

The literature uniformly implies that the duration of symptoms at the time of presentation plays a key role in predicting a malignant or benign neoplasm. A shorter period of symptoms (<1 year) is said to be representative of a malignant lesion, and a longer period is characteristic of a benign mass. This rule does not take into consideration the highly variable factor of how observant patients are of their ocular disability and how they react to it. One type of patient may present after a 1-month interval of "pressure sensation" over the eye and prove to have a benign mixed tumor. Another patient may be aware of the displacement of one eye but tolerate the problem for some years before presenting with a mass that proves to be malignant. Extreme examples of malignant tumors (adenoid cystic carcinomas) associated with long intervals of symptomatology include reports of 25 years (case 3 of Portis et al., 1985), 30 years (Waller et al., 1973), and 60 years (Shields et al., 1987), 20 years (Byers et al., 1975), 18 years (Wright, 1982), and 18 years (Jakobiec, 1987). These case reports, which are contrary to the general rule, are largely overlooked in discussions of the subject. In our experience, *the duration of*

TABLE 15.1
NUMBER AND HISTOLOGIC TYPE OF PRIMARY AND SECONDARY EPITHELIAL NEOPLASMS OF THE LACRIMAL GLAND: MAYO CLINIC SERIES 1948–1997[a]

Histologic Types	Number	Percentage
Adenoid cystic carcinoma	29	35
Benign mixed tumor	26	31
Malignant mixed tumor	16	19
Adenocarcinoma	7	8
Mucoepidermoid carcinoma	2	2.5
Squamous cell carcinoma	2	2.5
Apocrine carcinoma	1	1
Total	83	

[a]Total number of orbital tumors in series 1795.

symptoms is too variable and subjective to serve as a dependable guide to diagnosis.

The specificity of radiologic features in the preoperative differential diagnosis of malignant versus benign lesions is also overstated (Lemke et al., 1996) and (Mafee et al., 1999). Changes in the bone contiguous to the tumor may occur in both types. Likewise, calcific-like densities in the soft tissue are nonspecific. Although the tumor conforms to all the credos of the preliminary diagnosis, and none of the above exceptions exist, there is a 50:50 chance that a working diagnosis will be wrong when the true identity of the tumor is established. In the realm of changes in the bone contiguous to the tumor, the lytic destruction (as opposed to compression erosion) of bone is the only positive feature that may differentiate a malignant from a benign process. Eleven of 16 nonrecurrent adenoid cystic carcinomas in our Mayo series were initially radiographically negative for changes in bone. Only 3 of 16 cases showed a malignant type of bone destruction. An atypical feature was noted by Rootman and Dolman (1988) in two children aged 11 and 14. The authors believed the invasive features of adenoid cystic carcinoma were not evident in the computed tomography (CT) scans of these patients because of the tendency of the more pliable bone in this age-group to undergo expansion rather than invasion. Nevertheless, the absence of the invasive features of bone in these two cases is compatible with our finding (*vide supra*)that 68% (11 out of 16) of nonrecurrent adenoid cystic carcinomas were radiographically negative for changes in bone. Also Wharton and O'Donnell (1999) report an atypical case in a 65-year-old woman with a long history of right hypoglobus with sudden exacerbation of symptoms. CT scan showed a round, well-defined lesion in the fossa of the lacrimal gland with a hypotense extension suggestive of malignancy. The lesion was excised revealing a hemorrhage within a pleomorphic adenoma.

With these preliminary inconsistencies in mind, the surgical and histologic identification of the lacrimal gland mass remain the only means for correct diagnosis. The anterolateral surgical route (Mourier et al., 1994) is useful for this identification process.

Ordinarily, when the surgeon is confronted with an unknown type of tumor, incisional biopsy and frozen tissue study will determine whether the lesion should be removed or allowed to remain in the orbit. However, such an approach to an unknown type of tumor in the lacrimal gland fossa would be a hazard to the patient should the mass prove to be a benign mixed tumor. This lesion is notorious for seeding into the operation site when handled in such a manner. The consequence is a high rate of multiple recurrence throughout the lifetime of the patient with a chance of malignant transformation of the recurrent tumor at some later date. Surgeons who are acquainted with the color and configuration of the benign mixed tumor, therefore, will strive for an "intact," "complete," or "total" removal of such a tumor without a preliminary biopsy. For surgeons not well acquainted with the gross appearance of tumors in this area, it would be advisable to completely remove all encapsulated or well-circumscribed masses without incisional biopsy, although the mass proves not to be a benign mixed tumor. An alternative is the "protective" incisional biopsy. Here the lesion is dissected from its bed except for a remaining

TABLE 15.2
INCIDENCE OF PRIMARY EPITHELIAL NEOPLASMS OF LACRIMAL GLAND: SERIES OF OVER 50 CASES

		Percentage Distribution by Type of Neoplasm			
Authors	Number of Cases	Benign Mixed	Malignant Mixed	Adenocystic Carcinoma	Adenocarcinomas
Mayo (1948–1997)	83	26	16	29	7
Wright (1968–1981)	54	30 (56%)	3 (6%)	11 (20%)	10 (18%)
Ashton (1975) (25 years)	54	30 (55%)	2 (4%)	13 (24%)	None

Other carcinomas included in the above calculations are Mayo series (5) and Ashton (9).

pedicle of lacrimal gland, rotated laterally out of the orbital space, stabilized by a narrow gauze-strip wrap around the pedicle, and incised outside the orbital space. Subsequently, the pedicle can be severed and the tumor removed, or the biopsy incision closed and the mass returned to the orbital space depending on the outcome of the frozen tissue examination. Infiltrative and malignant tumors can be safely diagnosed, without fear of seeding, by this method of biopsy.

The Mayo series of primary, *consecutive*, neoplasms are listed in Table 15.2 with a comparison to other reported series of comparable size.

The total patients in the 50-year Mayo series is 1,795. The total of lacrimal gland tumors, of all types, is 118. Of these 118 cases, 70% (83 out of 118) are primary epithelial neoplasms. The remaining 30% are a variety of other tumor types. Ni and Ma (1995) made a retrospective study of 1,921 orbital tumors from the Eye Pathology of Shanghai Medical University. The author found 32% (138 out of 1,921) malignant lacrimal gland tumors and 13% (150 out of 1,921) benign mixed tumors. The total of these two subtypes is 288 cases, a total of 15% of all patients.

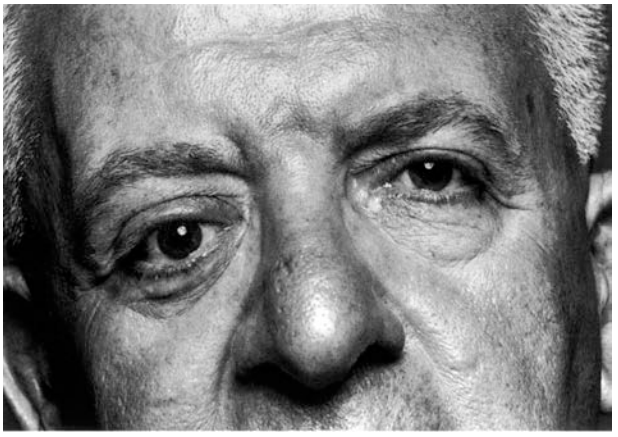


Figure 15.1 Benign mixed tumor: A 65-year-old man with prominence and downward displacement of the right eye of 6 months' duration.

BENIGN MIXED TUMOR (PLEOMORPHIC ADENOMA)

The term *mixed tumor* is a carryover from an earlier era when the histogenesis of the neoplasm was considered a mixture of epithelial and mesodermal elements. Later, the World Health Organization proposed the name *pleomorphic adenoma*, but the older name still persists in many publications.

Incidence

The age range of our 26 patients in the Mayo series is 16 to 81 years, with an average age of 41.8 years. There are 15 males and 11 females. There are two adolescents in the Mayo series, a 16-year-old boy and a 17-year-old girl. The tumor has been reported in children, a 7-year-old boy (McPherson, 1966), a 6-year-old boy (Faktorovich et al., 1996) and an adolescent 16-year-old girl (Tsunoda et al., 1994).

Clinical Features

In 50% of patients, the initial presenting sign is a painless, unilateral, slowly progressive proptosis associated with *downward and inward displacement* of one eye (see Fig. 15.1). In the other 50% of patients, a *drooping of the upper eyelid* is a presenting sign. Other symptoms or signs include a change in the refractive error induced by the pressure of the tumor on the eye, diplopia, or an ocular motility disturbance upon the superotemporal movement of the affected eye, an orbital "pressure" sensation, and puffiness of the upper eyelid. A palpable mass in the superotemporal orbital quadrant was present in 88% of our patients on initial examination. In the three patients without a palpable mass, the tumor had extended posteriorly instead of the usual upward, forward, or downward expansion of tumor. The mass is usually not tender. The palpable mass represents only a small part of the total volume of the tumor (the "tip of the iceberg"). Almost all mixed tumors are larger than 2 cm when uncovered surgically. In recurrent tumors, multiple nodules may be palpable in areas of the orbit and adnexa rather than the superior temporal quadrant.

Choroidal folds may also be noted at the time of the initial presentation depending on the size of the neoplasm. A rare condition that may also produce an inward and downward displacement of the eye is a hematocele of the lateral portion of the orbitofrontal bone plate.

A less common clinical aspect of this neoplasm is its presentation as a mass in the palpebral lobe of the lacrimal gland (Parks and Glover, 1990: four cases; Murphy and Rodrigues, 1974: two cases; Auran et al., 1988). The age range of these seven cases, 23 to 69 years, parallels the age span of patients with orbital lobe involvement. The palpebral lobe masses were approximately 10 × 10 mm in size when first seen, nontender, freely moveable, and did not present into the superior conjunctival fornix when the upper lid was everted. A tumor of the palpebral lobe does not produce proptosis because it is exterior to the orbital space. Vangveeravong et al. (1996) reported six tumors arising in the palpebral lobe of the lacrimal gland. Three of these were pleomorphic adenomas.

Several unusual manifestations of benign mixed tumors have been reported in the recent literature. Christie et al. (1995) excised a well-circumscribed mass from the lacrimal gland fossa of the right orbit of a 57-year-old woman. The mass proved to be a combination of a small benign mixed tumor and a large ductal cyst, *dacryops*, of the lacrimal gland. Guerra et al. (2000) described a huge, tender, well-defined

globular mass ($8 \times 5 \times 4.5$ cm size) protruding from the superolateral left upper eyelid that concealed a blind eye for 6 years in a 24-year-old man. The mass was completely excised and proved to be a *giant* pleomorphic adenoma of the lacrimal gland.

Imaging Aspects

With CT scan and magnetic resonance imaging (MRI), benign mixed tumors are either round or oval, smooth, well-defined, and show mild to moderate enhancement. Some long-standing tumors show lobulations (bosselations) and scattered radiolucent areas (cystic-like degeneration). The presence or absence of calcific-like densities is not of diagnostic significance. Indentation of the contiguous surface of the eye is a frequent supplementary feature in those tumors showing posterior expansion (see Fig. 15.2).

The proximity of the initial focus of tumor to bone, its direction of expansion (superiorly or laterally), and tumor size (its duration) are the factors that determine the presence of radiographic changes in bone. In order of frequency, the bony changes are fossa formation (pressure erosion), increased bone density (reactive sclerosis), and bone destruction. Forty-four percent (11 out of 25) of our patients showed some degree of bony involvement. One of our cases showed a 1 cm defect in the orbital roof (see Fig. 15.3). A similar-sized defect was noted in the orbital roof of a patient reported by Hornblass et al. (1981). MRI shows long T_1 and long T_2 signal characteristics, but some tumors may be heterogeneous on T_2-weighted imaging. The size and position of the orbital mass and the presence or absence of bone defects are the important imaging features the surgeon needs to know when planning his surgical approach.

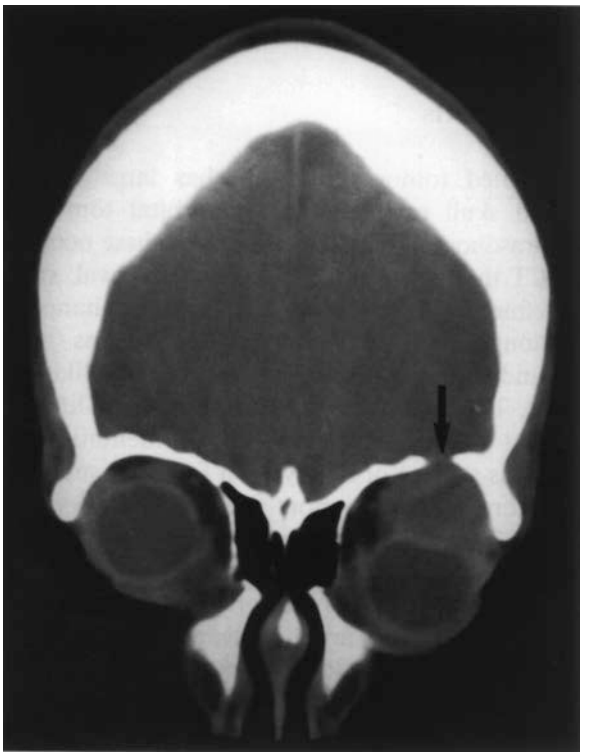


Figure 15.3 Benign mixed tumor: A coronal computer tomography (CT) scan without contrast of a 45-year-old woman shows a large, round, well-circumscribed mass indenting the left eye and pushing it downward. Note the erosion of the orbital roof (*arrow*) that was conformed on subsequent orbitotomy.

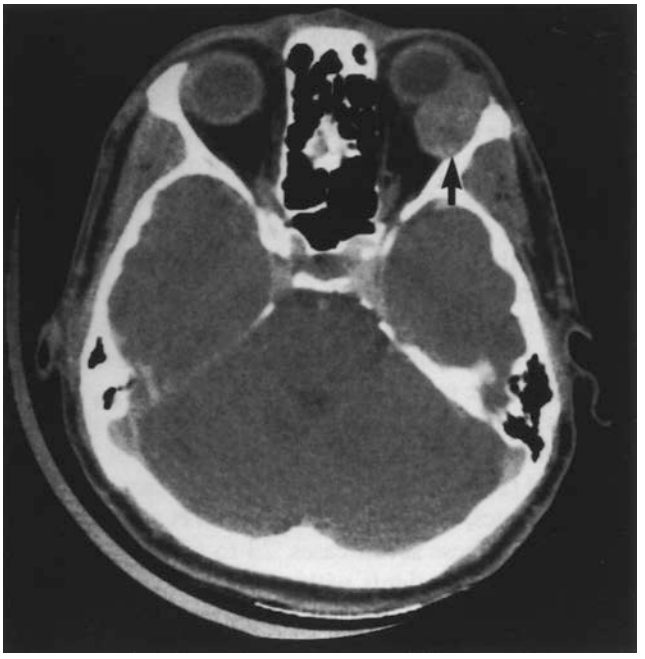


Figure 15.2 Benign mixed tumor: A 30-year-old man was found to have proptosis of the left eye on routine refraction. Axial computer tomography (CT) scan shows a well-defined, oval, slightly enhancing mass containing scattered, faint radiolucencies that is attached to or is part of the posterior portion of the left lacrimal gland (*arrow*). There is some compression erosion of the lateral orbit wall.

Pathology

Grossly, the tumor is grayish-white, unilobular, slightly bosselated, and well delineated by a thin pseudocapsule (compression capsule) (see Fig. 15.4). When sectioned, the specimen is less solid than suggested by its surface, consisting of lobules of different density, separated by scanty connective tissue septa and scattered areas of cyst-like degeneration and focal hemorrhage. Under low-power magnification, the tumor consists of alternating areas of myxoid tissue, cellular islands of epithelial cells interspersed with ductal structures, hyaline cartilage, and bands of fibrous tissue (see Figs. 15.5 and 15.6). Small nests of tumor may also be seen outside the pseudocapsule intermingled with normal lacrimal tissue, the latter remaining attached to the tumor during its excision.

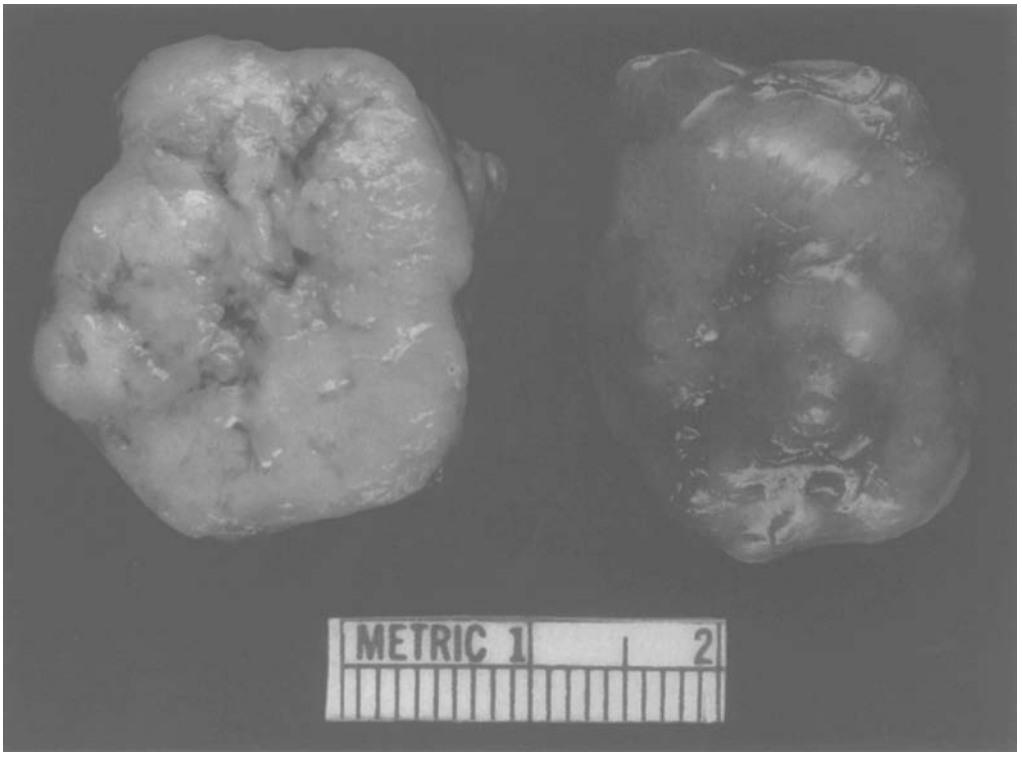


Figure 15.4 Benign mixed tumor. Right: Surface of tumor is circumscribed and slightly bosselated. Left: Cut surface is lobulated and variegated in appearance.

The epithelial cells consist of anastomosing ducts composed of two layers of cells. The basally located cells show the features of myoepithelial cells and may be cuboidal or spindle shaped. These cells merge into the stroma and undergo metaplasia to form the mesodermal-like elements (see Fig. 15.7). The lining epithelial cells are cuboid or even columnar. The central lumen of the ductal structure is either empty or contains mucous material that is characterized by its high content of neutral glycoprotein. This contrasts with the mucin of the stroma, which is a highly sulfated glycosaminoglycan. On occasion, keratin may be produced by the lining cells (see Fig. 15.8). In long-standing tumors, zones of cyst-like degeneration and hemorrhagic necrosis are also seen. Some pleomorphic adenomas are extremely cellular, and with recurrences, the tumor becomes increasingly cellular (see Fig. 15.9). These tumor cells are either round or spindle shaped, and the extreme cellularity may cause confusion with malignant tumors. The rarity of mitotic figures in the absence of necrosis is helpful in differentiating the tumor from a truly malignant neoplasm.

Immunohistochemistry

Grossniklaus et al. (1990) studied the immunohistochemical features of six benign and six malignant mixed tumors. They found that both types displayed similar ductal and myoepithelial characteristics. This underlies the belief that most malignant mixed tumors arise in a prior benign mixed tumor. The immunohistopathologic features indicated that the ductal epithelium of the normal lacrimal gland develops into the epithelial component of both benign and malignant mixed tumors of the lacrimal gland. Additionally, some of the myoepithelial cells of the normal lacrimal duct complex could be identified in the stromal component of both benign and malignant mixed tumors of the lacrimal gland.

Management and Course

The management of this tumor is complete removal, preferably with an intact capsule. In addition, a rim of the normal lacrimal gland surrounding the lesion should be included in the extirpation. The latter supplement will minimize any tumor seeding from the microscopic extension of the tumor into or through the compression capsule. This capsule, although thin, is, in the main, the most effective barrier to the escape of neoplastic elements into normal gland or orbital soft tissue. Because the capsule of the tumor is frequently fused laterally to the periorbita, we recommend that adjacent periorbita be included in the excision. The anterolateral orbitotomy is the preferred approach to best accomplish these goals.

Sixty percent of our patient cohort was managed in this manner. Follow-up data on all these patients were available with one exception. This exception was a patient

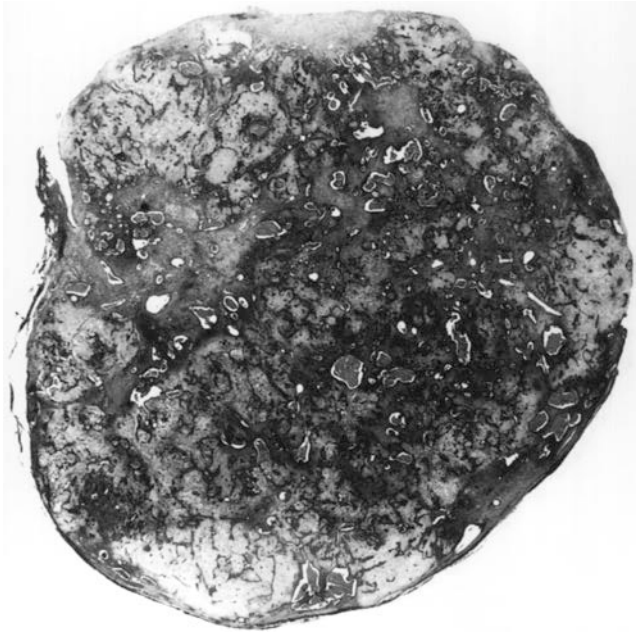


Figure 15.5 Benign mixed tumor: A mixture of myxoid tissue, islands of epithelial cells interspersed with tubular structures, hyaline cartilage, and fibrous tissue surrounded by a thin compression capsule (×3).

who was living 7 years after an intact removal of tumor, but no information was available concerning the presence or absence of the recurrence of neoplasm. The remaining 15 patients were free of recurrence with a mean follow-up of 9.7 years (range 3 to 21 years).

One patient with a 3-year follow-up, and two patients each followed for 10 years died from causes unrelated to their previous benign mixed tumor.

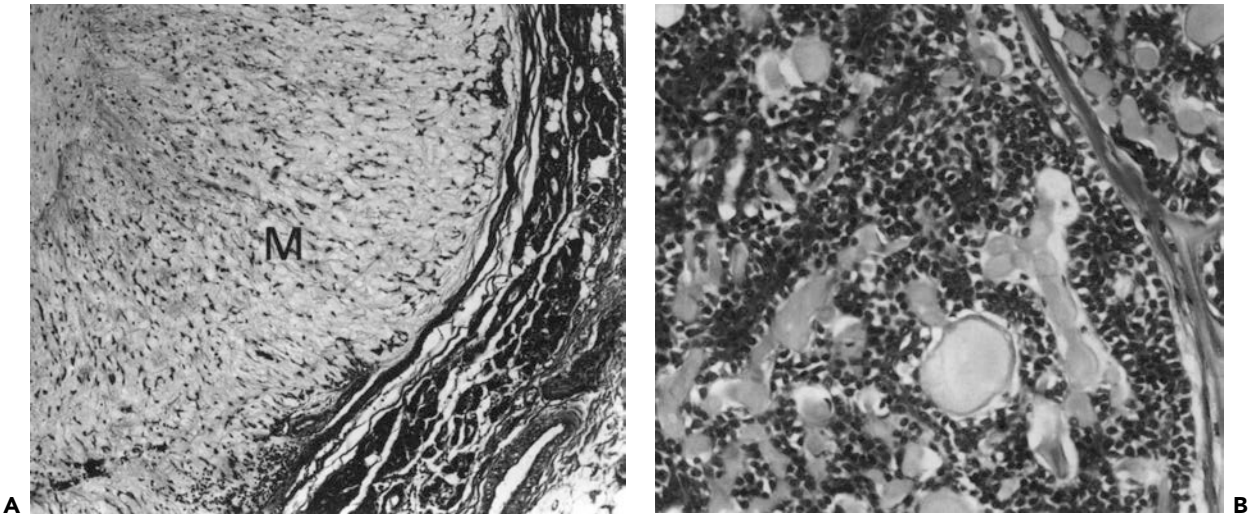
Four other patients did not have an intact removal of the tumor upon initial surgery at the Mayo Clinic. In two of these four patients, the capsule of the tumor ruptured near the completion of extirpation with escape of liquid contents into the surgical field. These patients have been followed up for 9 and 10 years, respectively, without local recurrence. In a third patient of this group, the tumor was so necrotic that only a piecemeal, but thorough, excision was accomplished. This patient was without recurrence of tumor for 8 years after surgery. In the fourth patient of this group, a guarded incisional biopsy was performed. When frozen tissue examination revealed a benign mixed tumor, the incisional breach of the capsule of the tumor was closed, followed up by an excision of the tumor without gross spillage of tumoral contents. There was no recurrence of the tumor at the 15-year follow-up.

Tang et al. (1997) reviewed 42 cases of benign mixed tumors which were followed up postoperatively, the follow-up periods ranging from 0.5 to 17 years. Thirty-four cases had no recurrence or malignant change, and eight cases had recurrences. Of the cases with recurrence, seven had several surgeries because of incomplete removal at the time of initial surgery. For successful surgery, they emphasized the need for complete removal of the tumor at the time of initial surgery and to avoid *incisional or aspiration biopsy* prior to surgery.

In summary, *the surgeon who makes the initial surgical approach has the best chance to cure the patient by complete intact removal of the tumor*.

MALIGNANT MIXED TUMOR

The lesion combines clinical and histologic features of pleomorphic adenoma and carcinoma of the lacrimal



A B

Figure 15.6 Benign mixed tumor. **A:** A pseudocapsule is sandwiched between the myxoid connective tissue component of the tumor (M) and the compressed lacrimal gland (right) (×50). **B:** Epithelial component shows tubules with a double row of epithelial cells (×250).

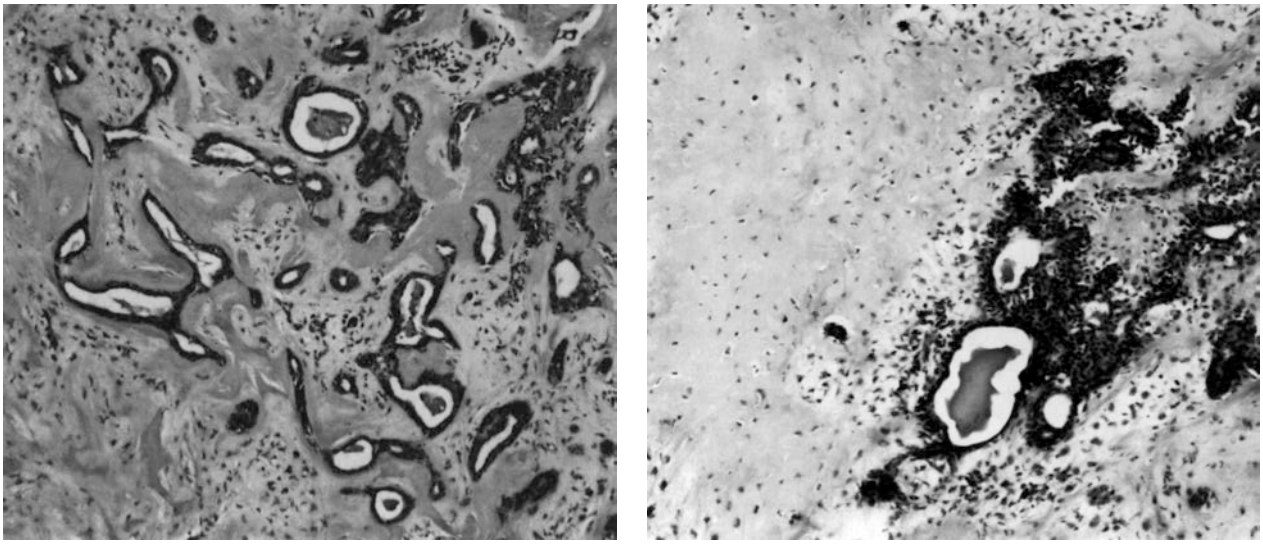


Figure 15.7 Benign mixed tumor. **A:** A mixture of epithelial cells, tubular and ductal elements, and spindle-shaped cells streaming into a hyaline intercellular matrix (×80). **B:** Hyaline cartilage may be one of the tissue components of intercellular matrix (×80).

gland. Its size, configuration, and clinical presentation may mimic the benign mixed tumor, but its course is comparable to carcinoma. Historically, the malignant mixed tumor was separated from other neoplasms in the lacrimal gland fossa 50 years ago (Forrest, 1954).

Incidence

Of the total 83 neoplasms of the lacrimal gland listed in the Mayo series in the preceding text, 16 (19%) are malignant mixed tumors. Eleven of the 16 were primary tumors. There are six men and five women, in an age range of 29 to 79 years, with an average of 46 years. In the literature of the past decade, Font et al. (1998) noted that 7 (17%) of 41 epithelial neoplasms were malignant mixed tumors and Ni and Ma (1994) noted that 9% of 272 primary epithelial lacrimal gland tumors were malignant mixed tumors. Fifty percent of our Mayo series presented with a recurrence of a benign mixed tumor that had undergone a malignant transformation by the time of our examination.

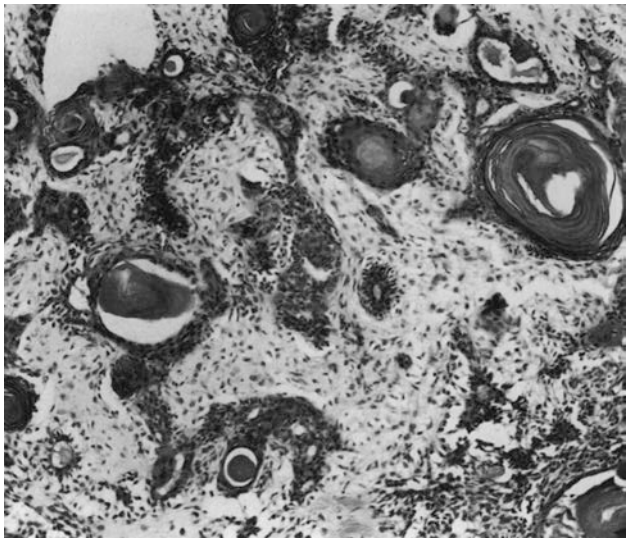


Figure 15.8 Benign mixed tumor: In epithelial zones, lumens may be filled with swirls of keratin owing to the squamous metaplasia of lining epithelium (×80).

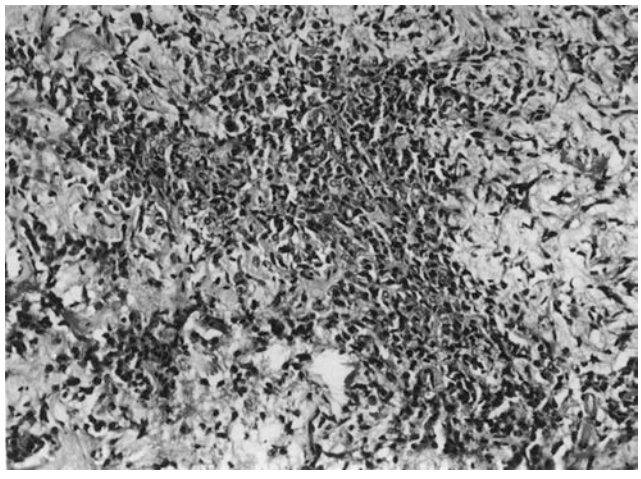


Figure 15.9 Benign mixed tumor: This specimen is the second recurrence of a tumor that was incompletely removed 11 years previously. With each recurrence, such a tumor becomes increasingly cellular and clinically more aggressive in growth. Recurrent cellular tumors are worrisome because of potential malignant transformation (×160).

Clinical Features

The presenting patterns of the primary mixed tumors in our series were of three types. In the first type, the prior symptomatology was very short, 5 months or less, and the tumor proved to be malignant at the time of initial excision. Three of our patients of this type had high-grade carcinomatous change. It is likely these tumors were malignant at or near the time of onset and could be considered *de novo* in type.

The second pattern was the patient whose original benign mixed tumor was not removed intact but was malignant at the first or second recurrence several years later.

The third pattern was the patient who was known to have had a slowly progressive, painless, downward and inward displacement of one eye over a period of several decades who presented with swelling of the upper lid, a palpable mass, and pain of short duration (usually several weeks). On initial orbitotomy in such cases, the lacrimal gland neoplasm proved to be a malignant mixed tumor superimposed on a benign mixed tumor. This last pattern suggests that *the natural course of an undisturbed mixed tumor is a malignant transformation*. A variant of this third pattern was the patient in our series who was found to have successive foci of metastatic adenocarcinoma in the thoracic vertebra, ilium, and scapula over a 4-year period, before the discovery of the primary source in a malignant mixed tumor of the lacrimal gland. Photographs of this patient documented the slow evaluation of this lacrimal gland tumor over a 35-year period.

These variable patterns of presentation again emphasize the fallacy of a stereotyped temporal factor in a presumptive preoperative diagnosis of benignity or malignancy.

Imaging Aspects

Only one patient in our series of malignant mixed tumors was imaged in the time frame of the CT scan. All the others were studied by standard orbital roentgenography. With the CT scan, a malignant mixed tumor may appear as a heterogeneous enhancing mass with expansion and invasion of the orbital roof. The interesting mass reported by Font et al. (1990) displayed an ill-defined nodule, centrally, with translucent zones peripherally of dense white tissue. The central area corresponded to the original benign mixed tumor whereas the more uniform peripheral density corresponded to a rim of invasive carcinoma. If the gross specimen of a malignant mixed tumor pictured in Figure 15.10 had been studied by the CT scan, its image might have shown features similar to the case of Font et al.

Pathology

The gross appearance of a malignant mixed tumor may be deceptively similar to a benign mixed tumor, but upon sectioning, the benign and malignant components are readily discernible (Fig. 15.10). In others, the carcinomatous component may be attached to and arising from the benign mixed tumor, giving the mass a bilobed appearance (see Fig. 15.11). In still others, the carcinomatous feature may be only focal in type, and will require extensive sampling of the tissue for its discovery.

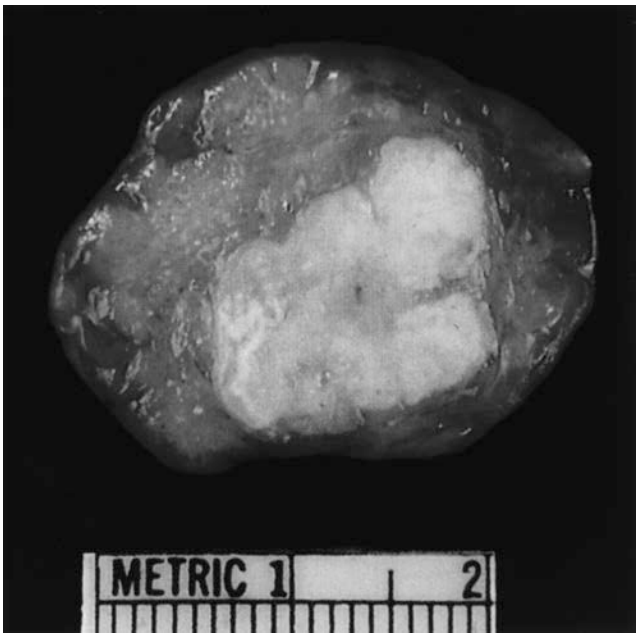


Figure 15.10 Malignant mixed tumor: Outer portion of specimen is highly malignant adenocarcinoma surrounding a central benign mixed tumor.

Malignant mixed tumors are usually classified according to their malignant components although such a subclassification does not seem to have any significant clinical relevance. Almost all are highly malignant neoplasms. Although some tumors show a mixture of malignant subtypes, one malignant type usually predominates. Our series of cases showed three of these subtypes: Adenocarcinoma, squamous cell carcinoma, and spindle cell sarcoma. The adenoid cystic carcinoma subtype was not encountered in our series. Our series of 11 malignant mixed tumors is too small to further classify the malignant subtypes according to incidence of sex, as was done by Font and Gamel (1978) in their survey of a larger series of cases. These authors noted that men are more often affected by adenocarcinoma subtypes, whereas women are more frequently affected by the adenoid cystic carcinoma subtype.

In the adenocarcinoma subtype, the lumens of the tubular structures are irregular in shape and variable in size, and the surrounding epithelium becomes multilayered (see Fig. 15.12). The individual cells and their nuclei vary in size, and staining characteristics and mitotic figures are present.

In the tumors showing squamous cell differentiation, the epithelial cells tend to grow in nests (see Fig. 15.13). In

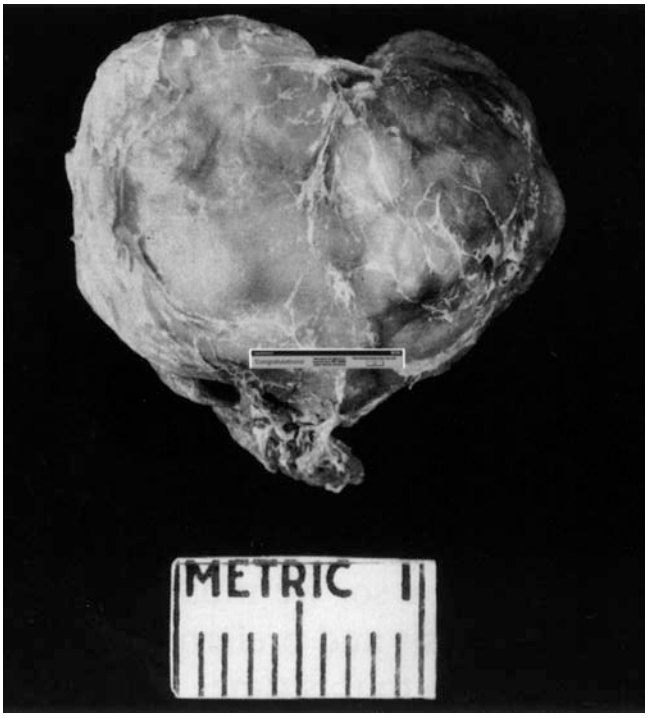


Figure 15.11 Malignant mixed tumor: Large, bilobed, well-circumscribed tumor consisting of an adenocarcinoma attached to and arising from a mixed tumor.

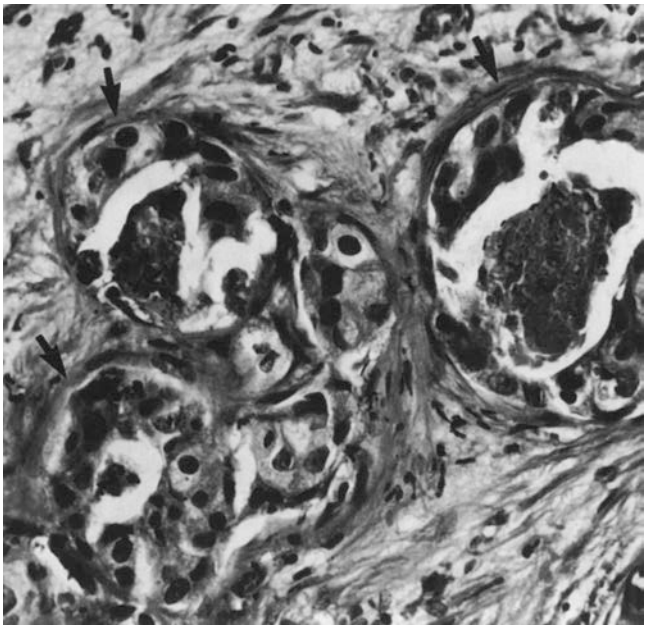


Figure 15.12 Malignant mixed tumor: The malignant component is adenocarcinoma (*arrows*) (×400).

some areas, the lumen of the ductal element is obliterated by proliferating cells; in other areas, a lumen is still visible, but the wall of the duct is irregularly thickened by the unequal growth of adjacent epithelial cells. The nuclei tend to retain their oval contours but enlarge to several times their usual size. An occasional giant cell containing two nuclei may be encountered.

The sarcomatous variant shows interlacing bundles of closely packed cells with very pleomorphic, dark-staining nuclei (see Fig. 15.14).

The adenoid cystic subtype may show any of the several cellular patterns associated with the pure adenoid cystic carcinoma (*vide infra*), but the "Swiss cheese" pattern usually predominates.

Immunohistochemistry

The immunohistochemical features of benign and malignant mixed tumors are discussed in the preceding text. A more recent analysis of a specimen from a malignant mixed tumor is that of Lauer et al., 1997. Tumor sections expressed cytokeratin but were negative for muscle-specific actin, vimentin, and glial fibrillary acidic protein.

Management and Course

In our 50-year association with orbital tumors at Mayo, surgical ablation of the malignant mixed tumor has been the preferred management. In the early decades, the initial surgical approach was an anterior orbitotomy. This was soon replaced by the lateral orbitotomy in the succeeding decade. A wider approach evolved next, the anterolateral orbitotomy. At the present moment, orbitofacial and orbitocraniotomy approaches are the preferred procedures to eradicate this malignant neoplasm.

In our 1994 edition, we reviewed all surgical procedures from 1948 through 1987. Of the total 15 patients, 14 eventually died of tumor recurrence. However, among the deceased, survival was surprisingly long, 22, 25, 28, 27, 41, and 66 years, respectively, of six patients.

Alas, in the past decade, we have not found any sizable review of surgical cases of malignant mixed tumor in the literature which can be analyzed for mortality and survival data, and compared to the surgical results of prior decades. Surgical procedures for the eradication of this neoplasm at Mayo also belong in this category.

The object of the present day, a more radical, surgical approach, is to remove the neoplasm with preservation of the eye, if at all possible. The neoplasm should be removed with its underlying periorbita. The question of bone removal, other than to gain access to the tumor is moot. These tumors seem to prefer to spread along and through the soft tissue components of the orbit, but not the marrow channels of the temporal and sphenoid bones. If the bulk of the tumor is in the posterior orbit, the tumor reaches the intracranial vault by perineural spread. If the mass is pushing forward into or through the orbital septum, the tumor finds its way into the periorbital lymphatics with involvement of the preauricular, submandibular

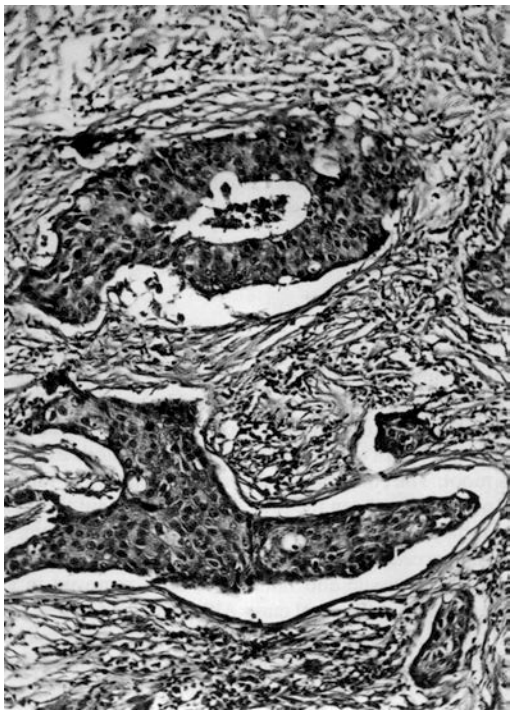


Figure 15.13 Malignant mixed tumor: The malignant component is squamous cell carcinoma (×100).

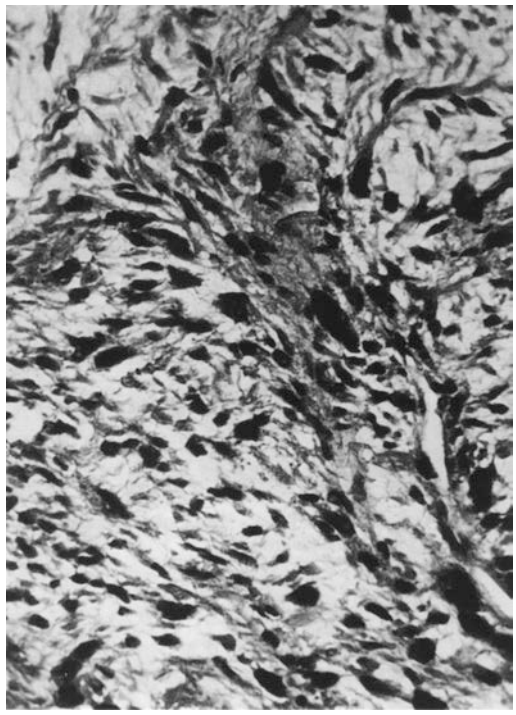


Figure 15.14 Malignant mixed tumor: The malignant component is highly anaplastic spindle cell sarcoma (×285).

lymph nodes. If the surgical removal is not successful and recurrence of the tumor evolves, exenteration will be necessary. We believe radiotherapy is of questionable value in neoplasms with a major component of epithelial cells. Radiotherapy can be used only as a palliative measure for recurrent tumors associated with pain.

ADENOID CYSTIC CARCINOMA

This is the most common, primary, malignant, epithelial neoplasm of the lacrimal gland. Its older name, *cylindroma*, is seldom used in the present-day literature.

Incidence

There are 30 of these neoplasms in the total 1,795 tumors in our 50-year (1948 to 1997) collection, an incidence of 1.6%. Our 30 cases comprise 4.4% of the primary tumors in our survey. The neoplasms age range at the time of the initial visit to Mayo is 12 to 77 years, with a mean of 46.3 years. Twenty-two of 30 cases were clustered equally in the fourth, fifth, sixth, and seventh decades. Sex incidence was nearly equal—17 men, 13 women. From this data, we can assume this neoplasm principally occurs in adults. However, in our third edition of this text (1994), we referenced those publications that reported adenoid cystic carcinoma in five children, aged 9, 11, 12 (two), and 14 (one). In the preparation of this current manuscript, we have discovered additional references to the occurrence of the neoplasm in children. These are: Lorenz et al. (1982), a 12-year-old child, a 6-year-old reported by Galliani et al. (1993), and more importantly, a review of 11 patients, 18 years or younger, from the files of the Armed Forces of Pathology (Washington, DC) by Tellado et al. (1997). The age range of the latter group was 6.5 to 18 years of age. We should be ware that the neoplasm is now known in the first two age decades. This definitely widens the age range of this tumor. In reporting the incidence of adenoid cystic carcinoma, henceforth, we could simply say the neoplasm occurs in all age decades, first through eighth decade.

Clinical Features

The principal presenting features of adenoid cystic carcinoma are as follows: A palpable mass in the superotemporal quadrant of the orbit, downward displacement of the eye, some degree of proptosis, and no impairment of visual acuity, all with or without some association with pain. Ophthalmologists continue to partake in discussions of how to differentiate, preoperatively, benign mixed tumors and adenoid cystic carcinomas on the basis of presenting features. These opinions are usually based on the assumed frequency of a palpable mass, some apparently miniscule in the degree of displacement of the eye, and the time interval (short or long) of the presenting symptoms and signs.

Overlooked in the conclusions of these physicians is that several other nonepithelial tumors also occur in

the lacrimal gland fossa such as dacryadenitis, vasculitic and nonvasculitis inflammatory tumors, sarcoidosis, and non-Hodgkin lymphoma, all of which may mimic the preoperative presenting profile of either benign mixed tumor or adenoid cystic carcinoma. The inclusion of all of these into the mix of differential diagnosis reduces the efficacy of preoperative assessment of the presenting pattern of any one tumor.

Metastasis of a primary orbital adenoid cystic carcinoma does not often occur. Nakamura and Miyachi (1999) reported a 55-year-old woman who presented with a rapidly erupting, small, red, dome-shaped nodule on the upper lid that was a metastasis of a lacrimal gland adenoid cystic carcinoma that had, 2 years earlier, undergone *subtotal* resection followed by radiotherapy.

Imaging Aspects

Attempts to construct a preoperative radiographic profile specific for orbital adenoid cystic carcinoma have been nearly as inconsistent as diagnostic imaging profiles founded on clinical features at the time of presentation. In our series of lacrimal gland tumors, calcific densities, necrosis, and nodularity have been noted in both benign and malignant lesions. Likewise, the diagnostic imaging nuances and the consistency of the soft tissue masses are equally ambiguous. In the realm of bone changes, cystic destruction, as opposed to compression erosion, of the bone is the only positive feature that may differentiate a malignant from a benign process. Even so, most of our nonrecurrent adenoid cystic carcinomas did not show imaging changes of bone involvement at the time of initial presentation. One adenoid cystic carcinoma showed compression erosion rather than lytic destruction of bone (see Fig. 15.15) that could easily be construed as an imaging feature of a benign tumor.

Pathology

The gross appearance of adenoid cystic carcinoma and adenocarcinoma are similar with respect to color (grayish-white or grayish-purple) and circumscription but lack of encapsulation. Each tumor may be unilobular or bilobed in contour.

The latter factors add to the difficulty of differential diagnosis of these neoplasms without CT imaging. The cellular components of adenoid cystic carcinoma may be small, hyperchromatic, and basaloid types, with scant cytoplasm. Whatever the pattern of proliferation, the demarcation between cell clusters and supporting stroma is sharp and distinct, a feature not seen in mixed tumors. There are five histopathologic types: Cribriform (Swiss cheese), solid (basaloid), sclerosing, comedocarcinomatous, and tubular (ductal), roughly in order of frequency (see Fig. 15.16).

All or several of these patterns may be present in any given tumor but, as a rule, one pattern predominates.

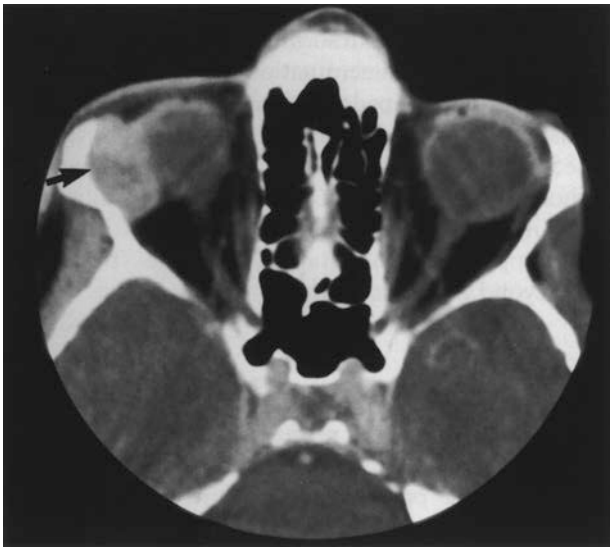


Figure 15.15 Adenoid cystic carcinoma: Axial computed tomography (CT) scan showing a well-defined, oval, slightly heterogeneous mass with some rim enhancement (*arrow*) associated with compression erosion of adjacent bone in a 41-year-old man who had a downward displacement of the right eye of 3 years' duration (compare to Fig. 15.2A) benign tumor. The long duration of the lesion and the CT scan image suggested a benign mixed tumor of the lacrimal gland, but the tumor proved to be an adenoid cystic carcinoma on histopathologic study.

Management and Course

In the mid 1940s, one of the authors (JWH) assumed responsibility for the care of patients with orbital disorders as a supplement to the role of comprehensive ophthalmic surgeon. This led to the initiation of the study of consecutive, pathologically proved orbital tumors in 1948. At that time, and continuing up to the present, our initial goal has been to complete surgical removal of adenoid cystic carcinoma.

However, in the early years of the 1930s, surgical removal of the neoplasm was not attempted. Instead, a biopsy of the tumor through a transseptal incision was performed. Once the pathologic verification of an adenoid cystic carcinoma was made, the orbit was treated with irradiation. Radiotherapy was a popular remedy for other orbital disorders because it was effective in reducing the size of the orbital mass, the function of the eye was preserved, and the complexities of the orbital Kroenlein operation were avoided. In general, radiotherapy was thought to be a very efficient cure for adenoid cystic carcinoma. Alas, after an interval of 8 to 10 years, from the time of initial radiotherapy, these patients returned with an even more malignant version, a spindle cell sarcoma, than the surgical grade of the original tumor. This was a deadly surprise because this was our first encounter with the long-term, unknown effects of orbital radiotherapy.

By the 1940s, we were aware that radiotherapy was useless in effecting a "*cure*" of the adenoid cystic malignancy.

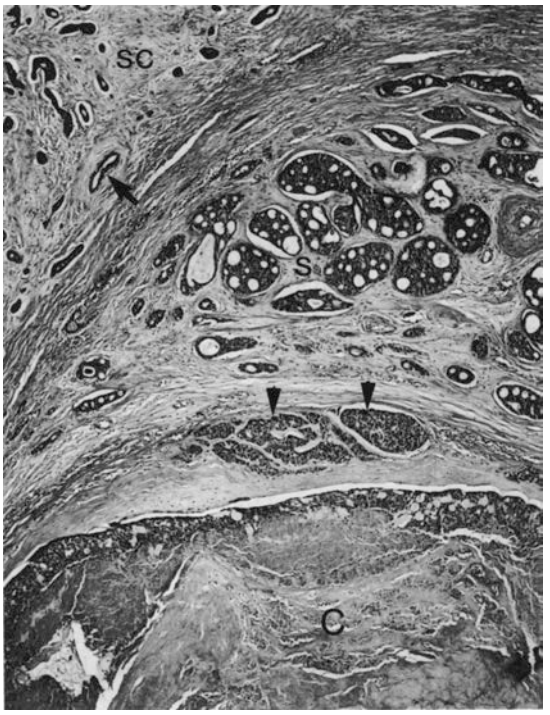


Figure 15.16 Adenoid cystic carcinoma: Showing the five histologic patterns—basaloid (*arrowheads*), comedocarcinomatous (C), cribriform (S), sclerosing (SC), and tubular (*arrow*) (×64).

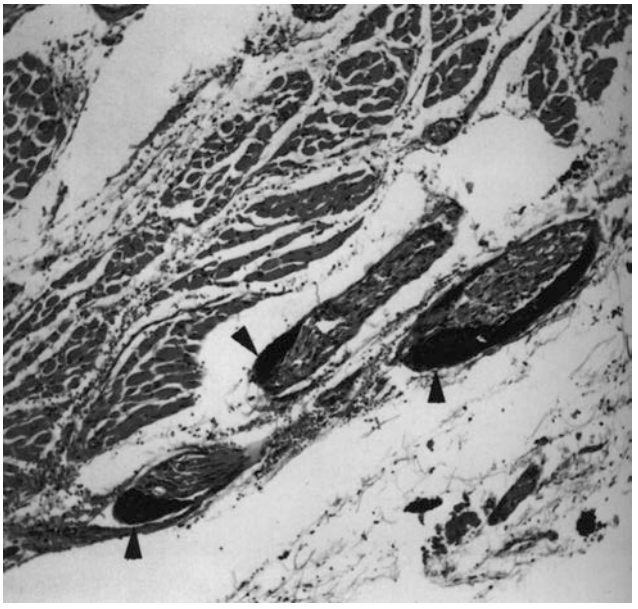


Figure 15.17 Adenoid cystic carcinoma: Showing perineural invasion of tumor cells (*arrowheads*) (×100).

In the early 1950s, the Stryker bone saw was invented. This instrument was a big improvement in fashioning the bone flap of the Kroenlein operation when compared to the prior use of the hammer and chisel. Accordingly, we returned to the anterolateral orbitotomy for most operations on the lacrimal gland. This approach provided good exposure of the gland. The adenoid cystic carcinoma could be completely removed with the underlying periorbita, and the eye could be retained in the orbit. Most adenoid cystic carcinomas are low-grade malignancies, are circumscribed to some degree, and the neoplasm can be removed *intact*. We emphasized the word "*intact*" to warn the surgeon not to break the thin compression capsule either by biopsy or piecemeal removal of tumor. At this point in time an intact removal of the neoplasm, without bone involvement, would probably be a cure, that is, there would be nothing left of the tumor to recur, so we assumed.

A surgical procedure of this type for the removal of an adenoid cystic carcinoma was performed in February 1951. Two years later, much to our chagrin, the neoplasm recurred. We suspected that the recurrence was due to the microscopic foci of malignant cells in the orbital soft tissues (see Fig. 15.17) or the marrow of underlying bone (see Fig. 15.18) which were beyond the perimeter of the original surgical eradication.

We then reasoned that a total exenteration with the removal of the bone flap (although imaging techniques did not reveal any bone involvement) would eliminate all routes of escape. We were wrong. One patient who underwent this surgical approach in June 1957 developed the first of a number of recurrences in April 1959 and finally died of tumor. Another patient operated on in September 1962, using the same surgical procedure, developed metastasis in April 1964. With each succeeding decade, surgeons working in this field have removed more and more bone from the upper face and skull base but a long-term follow-up on many patients treated in the past decade is not sufficient to warrant an objective analysis of either mortality or survival.

In the 1950s, 1960s, and 1970s, most patients first seen at Mayo had already had a biopsy of the mass or an incomplete removal. Surgical procedures, whatever type, on these patients may bring temporary relief, but the course of the neoplasm is fatal. Radiotherapy, in modest dosage, may bring relief of pain.

Several reports of the treatment of orbital adenoid carcinoma with adjunctive chemotherapy have appeared in the literature since our last edition. These are Meldrum et al. (1998) and Tse and Neff (2000). These publications introduce the concept of intra-arterial chemotherapy as a supplement to present surgical therapies. The thrust of the chemotherapy is to eliminate the perivascular invasion that, theoretically, is present early in the course of the malignancy. A *preoperative* treatment regimen of two cycles of intra-arterial cisplatin and intradoxorubicin is administered through the external carotid artery to shrink the tumor and make it more surgically manageable. Tumor shrinkage occurred in two of their first patients, verified by CT scan. After a short interval, orbital exenteration, postoperative radiation, and further intravenous chemotherapy

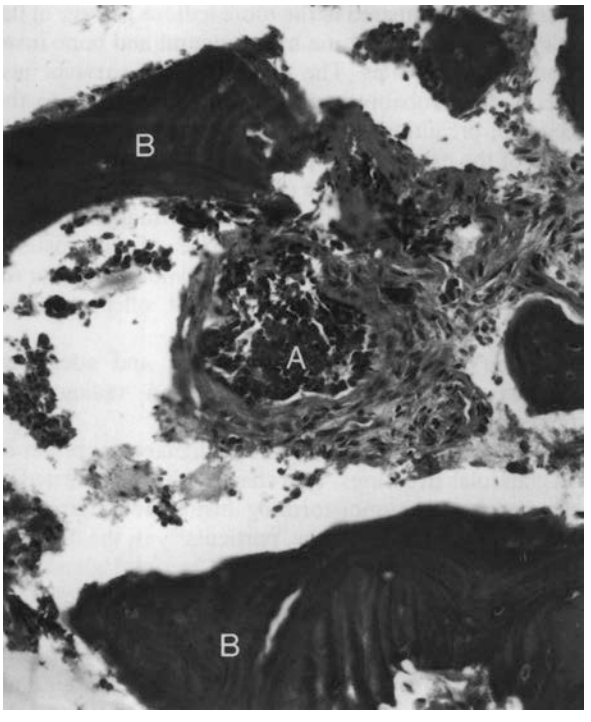


Figure 15.18 Adenoid cystic carcinoma: Invasion of tumor (A) into the orbital bone (B) in a 34-year-old woman 6 weeks after the onset of unilateral proptosis. Both metastasis to lung and intracranial extension were present at death 4 years later.

were performed. These two patients were tumor free 14 and 12.5 years at the time of the latter report.

Lee et al. (1985) and several other publications have studied the five histologic variants of adenoid cystic carcinoma to determine if histology influences survival. In adults, the results seem rather mixed. However, the longer survival of children is attributed to the predominance of the glandular—Swiss cheese histologic pattern-type.

ADENOCARCINOMA

Adenocarcinoma is the basic malignant neoplasm of all glandular structures. In the lacrimal gland, it differs from the preceding adenoid cystic carcinoma. Adenocarcinoma has a decidedly different histologic pattern, is more predominant in men, occurs in a more restricted age range, is less common in the orbit, metastasizes earlier, and is associated with a shorter patient survival time when compared to adenoid cystic carcinoma. The total adenocarcinomas primary in the lacrimal gland in the Mayo series is seven. This total is too small to calculate any meaningful incidence data. The age range of the patients was 38 to 61 years with a mean of 47.8 years. The mean age of patients with adenocarcinoma and adenoid cystic carcinoma is almost the same. All seven of the adenocarcinomas were men.

The follow-up observation of our patients with adenocarcinoma tends to bear out the very malignant nature of the tumor. Follow-up data are available in five of the seven primary orbital adenocarcinomas. All seven patients underwent what was considered a radical surgical excision of their tumor. Four patients died of metastatic tumor with a mean survival of 10.5 months. A fifth patient experienced a recurrence 1 year later that required further study, but died 5 years after presentation with metastatic tumor. Our oldest patient died of heart block 3 months after initial surgery. The only survivor is a 51-year-old man with a grade 3 adenocarcinoma that was incompletely removed at the initial operation elsewhere. One month later, an exenteration was performed at Mayo, also with removal of the lateral bony wall. Eighteen months later, an excision of the preauricular lymph nodes combined with a total parotidectomy and radial neck dissection was carried out for the lymphatic spread of the neoplasm. The patient was living without local recurrence or metastasis of tumor 19 years after initial surgery.

The shorter survival of the patients with adenocarcinoma is probably related to the early dissemination of the neoplasm through the lymphatic network of the nasal cavity, paranasal sinuses, face, eyelids, and lacrimal gland when compared to the more tedious passage of the adenoid cystic carcinoma by perineural and bone invasion in similar sites. The one long-term survivor just mentioned probably had subclinical metastasis to the cervical, preauricular, and parotid lymph nodes at the time of the exenteration procedure. Our experience with this small group of adenocarcinomas suggests that a *monobloc craniofacial orbitectomy combined with regional lymph node dissection* might offer a longer survival rate, provided there is no metastatic disease at the time of diagnosis. Primary adenoid cystic carcinoma and adenocarcinoma have a similar clinical and radiographic presentation (see Figs. 15.19 and 15.20). This characteristic is reflected in the tumor-forming histologic pattern and mucous-producing tendency of the neoplasm (see Fig. 15.21), particularly in the differentiated forms of the lesion. In the adenocarcinoma, the lumen (tubular) formation contrasts with the pseudolumenal pattern of adenoid cystic carcinoma, the tubular-like structures of the latter containing hyalinized matrix material. The mucin content of the adenocarcinoma may be demonstrated with mucicarmine and Alcian blue stains. The undifferentiated type of adenocarcinoma does not show these features. The proliferating cells of an adenocarcinoma are pleomorphic, mitotically active, irregularly layered in the tubular structures, and arranged in sheets or cords in extralumenal areas.

Khalil and Arthurs (2000) call our attention to a recently recognized entity that should be included in the differential diagnosis of lacrimal gland tumors. They report a lacrimal gland tumor that was incompletely removed from a 36-year-old woman in 1988 that was diagnosed as "*solid basaloid adenoid cystic carcinoma*." Soon thereafter, an exenteration of the orbit was performed. In *1999*, upon

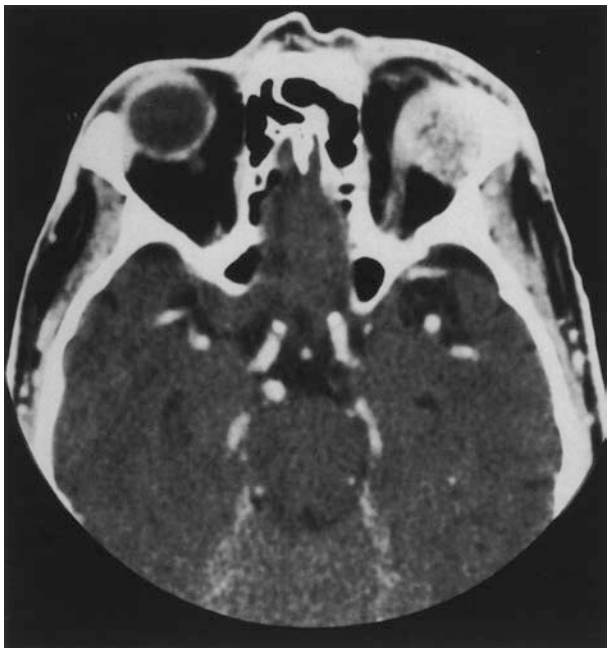


Figure 15.19 Adenocarcinoma: Axial computed tomography (CT) scan showing a smoothly marginated, speckled, round mass in the lacrimal gland fossa of a 60-year-old man.

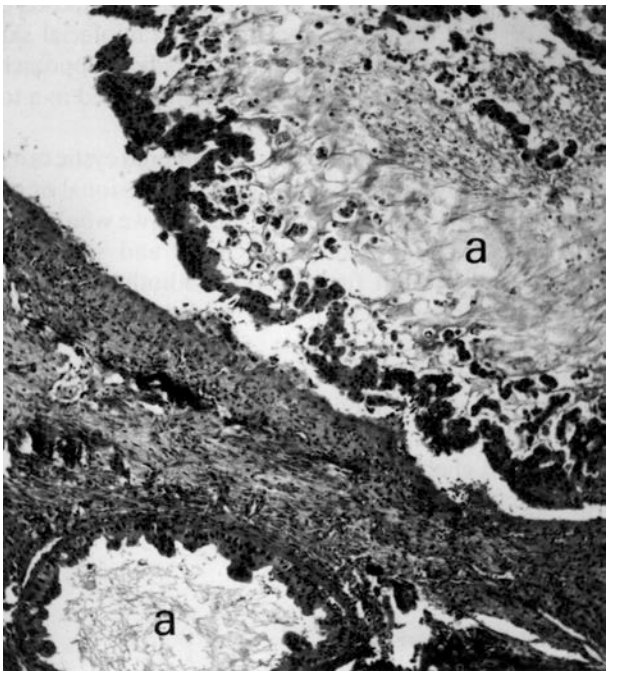


Figure 15.21 Adenocarcinoma: Mucous-producing tumor (a) primary in the lacrimal gland of a 60-year-old man (×100).

a review of the initial histopathology, the diagnosis was changed to "*basal cell adenocarcinoma*." The latter neoplasm has a negative stain for Alcian blue and a negative reaction to smooth muscle actin. The patient is still alive 10 years after exenteration. The recognition of this apparent new tumor entity may account for some of the mixed opinions in the literature of the past that the basaloid pattern of an adenoid cystic carcinoma had a good prognosis. The pathologist viewing such tissue specimens may, unknowingly, have been looking at basal cell adenocarcinoma.

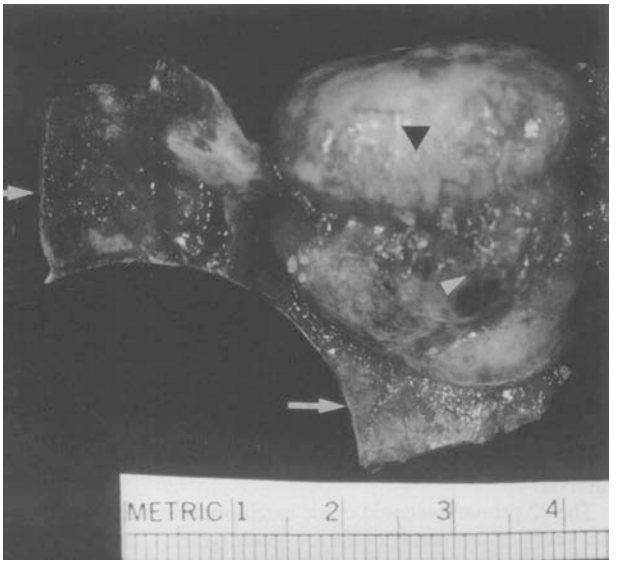


Figure 15.20 Adenocarcinoma: En bloc specimen of slightly bilobed tumor showing malignant component (*lower arrowhead*) of lacrimal gland (*upper arrowhead*) attached to the inner surface of the lateral orbital wall (*horizontal arrows*).

Heaps et al. (1993) retrospectively studied 13 cases, including the follow-up data, of primary adenocarcinoma of the lacrimal gland to determine which of the currently used methods were most effective in treating this tumor. The authors acquired these cases by a request of help from 22 surgeons or pathologists worldwide. Eight of the cases were managed by a combination of exenteration and radiotherapy. Four cases were managed by radiotherapy alone. One case had only an exenteration. Based on the results of this study, the authors ascertain that primary adenocarcinoma of the lacrimal gland is not inevitably fatal, and should be treated with exenteration and adjuvant radiotherapy as soon as a histologic diagnosis is established. A *shorter* duration of symptoms before treatment appeared to decrease the chance of metastases and increased the chance of long-term survival. We are in full accord with the authors' conclusions.

Nasu et al. (1998) report an adenocarcinoma of a lacrimal gland duct in a 67-year-old man and their patient was alive at 2 years followup despite recurrence in the subdural space.

ACINIC CELL CARCINOMA

Acinic cell carcinoma is a less known, less frequent carcinoma, affecting the major and minor salivary glands. It occurs most commonly in the parotid gland. This tumor

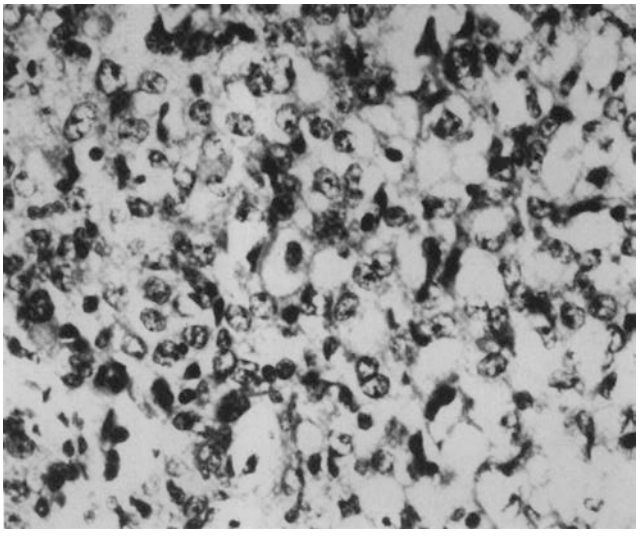


Figure 15.22 Acinic cell carcinoma: Showing solid pattern of growth of a mixture of medium-sized cells with basophilic granular cytoplasm and large cells with optically clear cytoplasm (×430). (From De Rosa G, Zeppa P, Tranfa F, et al. Acinic cell carcinoma arising in a lacrimal gland. First case report. *Cancer*. 1986; 57(10):1988–1991, with permission of JB Lippincott.)

may represent a neoplasm of multipotential duct cells which have mainly differentiated into granulated serous cells, the presence of which are required to make the diagnosis (Perzin and LiVolsi, 1979). The only case reported in the English literature primarily affecting the lacrimal gland is that of De Rosa et al. (1986). This was a 57-year-old woman with painless proptosis caused by a hard mass in the right lacrimal fossa. A thinly encapsulated mass was removed intact through a lateral orbitotomy. On sectioning, the mass consisted of a large cystic portion and a smaller subcapsular area of a whitish spongy tissue. Histologically, the spongy tissue showed a solid acinic growth pattern with microcystic spaces containing material of a mucoid character. About 20% of the cells had clear cytoplasm, and the remainder had a granular, basophilic cytoplasm (see Fig. 15.22). The basophilia of the latter cells differentiated the neoplasm from clear-cell adenomas and low-grade mucoepidermoid carcinomas. There was no perineural or vascular invasion. The patient of De Rosa et al. was followed up for 30 months without local recurrence of tumor. Complete removal of the neoplasm is necessary because of its tendency to recur after long periods. No additional cases of lacrimal gland involvement have been reported.

SQUAMOUS CELL CARCINOMA

Earlier in this chapter, squamous cell carcinoma was noted as one of several, malignant, histologic components of malignant mixed tumors of the lacrimal gland. The squamous cell component was present in 2 of the 11 malignant mixed tumors primary in the gland. There are two additional squamous cell carcinomas which seem to be primary (*de novo*) in the orbit in our 50-year tumor survey.

One case was a 43-year-old man who presented with 4 mm of right proptosis that developed over a 4-month period in 1948. There was no pain. A mass was palpable in the superotemporal orbital quadrant. A tumor of the lacrimal gland was partially removed through a transfrontal approach. On pathologic examination, the tumor was a grade 3 squamous cell carcinoma without mixed tumor features. The patient was treated with radium plaque therapy, 9,600 mg hours. Five months later, a right preauricular mass was palpated. An additional radium plaque application of 8,400 mg hours was given to the right face. The patient's condition was unchanged when lost to follow-up 7 months after initial admission. The other patient is the *exception* noted in the initial paragraph of this chapter. This is a 61-year-old man who presented in November 1949 with aching and downward displacement of the left eye of 5 months' duration. A mass was palpable in the *superonasal* orbital quadrant. Through an anterior orbitotomy, a hard mass 1 cm in size was removed that was attached to a smaller fibrocystic mass that contained a straw-colored fluid. On pathologic examination, the hard mass was a grade 2 squamous cell carcinoma, but the histogenesis of the fibrocystic component was unclear.

Two years later, the patient returned with a recurrence of the mass in the *superonasal* quadrant. The left eye was divergent, slightly enophthalmic, with marked restriction of ocular motility. An exenteration was performed. The orbital specimen again showed a grade 2 squamous cell carcinoma. There was no local recurrence or metastasis of the carcinoma in a follow-up of 5 years.

What could be the origin of a squamous cell carcinoma in this odd orbital location? The region could have been an ectopic lacrimal gland or an ectopic respiratory cyst that underwent malignant transformation.

The histopathology of squamous cell carcinoma is described in Chapter 16.

MUCOEPIDERMOID CARCINOMA

This malignant neoplasm is slow-growing and indolent in character. The main histopathologic features are a mixture of epidermoid and mucous-secreting cells. The multimorphic makeup of the cellular components of these tumors accounts for variations in their histopathologic grading (these features are discussed in more detail in the next chapter).

In one of the cases from our Mayo file, a 59-year-old woman presented with a painless, progressive proptosis of one eye of 7 years' duration. This long interval suggested a benign mixed tumor of the lacrimal gland. The circumscribed tumor was removed in one piece through the

transfrontal route. However, in the course of handling the tumor, leakage of liquid contents occurred from the mass. Histopathologically, the tumor was low-grade (grade 1) of the differentiated type. Five months later, an exenteration was performed for recurrence. This specimen of tumor was a grade 3 degree of anaplasia. The patient died 12 years after initial diagnosis from intracranial extension.

In a second case, an 81-year-old woman presented with a painless, unilateral mass in the lacrimal gland fossa of 3 years' duration. A CT scan showed pressure erosion of bone underlying the mass. An en bloc excision of tumor was performed. The carcinoma showed grade 2 differentiation. The patient was alive without recurrence or metastasis 4 years and 11 months later.

In one of two cases reported by Wagoner et al. (1982), a highly anaplastic tumor in a 72-year-old woman was initially managed by exenteration, combined with removal of frontal bone and postoperative radiotherapy. The patient was alive without recurrence or metastasis 4 years later.

Paulino and Huvos (1999) note three cases of mucoepidermoid carcinoma among a total series of 19 malignant tumors of the lacrimal gland.

Regardless of the degree of histopathologic differentiation (low or high grade) of these neoplasms, we believe it safest to advise exenteration of all cases. Radiotherapy may be reserved for recurrence.

Levin et al. (1991) reported a 62-year-old woman with a mucoepidermoid carcinoma of the lacrimal gland with oncocytic features (*vide infra*) that arose in the wall of a chronic cyst, which had been present for more than 40 years. The mass was removed *in toto*. There was no follow-up stated. The authors thought the origin of the tumor was a malignant transformation within a preexisting benign cyst.

ONCOCYTOMA

Two terms, *oncocytoma* and *oxyphil adenoma*, are used interchangeably to designate this infrequent neoplasm in the area of the eye and orbit. The name, oncocytoma, refers to the large size of the cell when compared to columnar and cuboidal cells usually present in glandular tumors. Oxyphil refers to the acidophilic staining properties of the cell. Oncocytes may be found in mucous membranes such as the caruncle, conjunctiva, lacrimal sac, accessory glands of the oral cavity, pharynx, trachea, esophagus, thyroid, parathyroid, and lacrimal glands, and along the intestinal tract (Pecorella and Garner, 1997). Oncocytes seem to increase in number with age. We have seen oncocytomas in the caruncle but not in the lacrimal gland. In an adnexal location, the tumors are usually benign and even cystic in some cases. Gonnering and Sonneland (1987) report a malignant oncocytoma of the plica semilunaris with orbital extension. However, in the lacrimal gland, malignant oncocytomas have been reported by Biggs and Font (1977) in an 81-year-old woman, by Dorello (1961) in a 59-year-old man, and by Reidel et al. (1983) in a 58-year-old man. In the two last-named cases, there was also an intracranial extension of the tumor. Case reports of benign oncocytoma of the lacrimal gland include two cases in Radnt (1939), two cases in Reidel et al. (1983), and in Beskid and Zarzycka (1959). The tumor is rare in children.

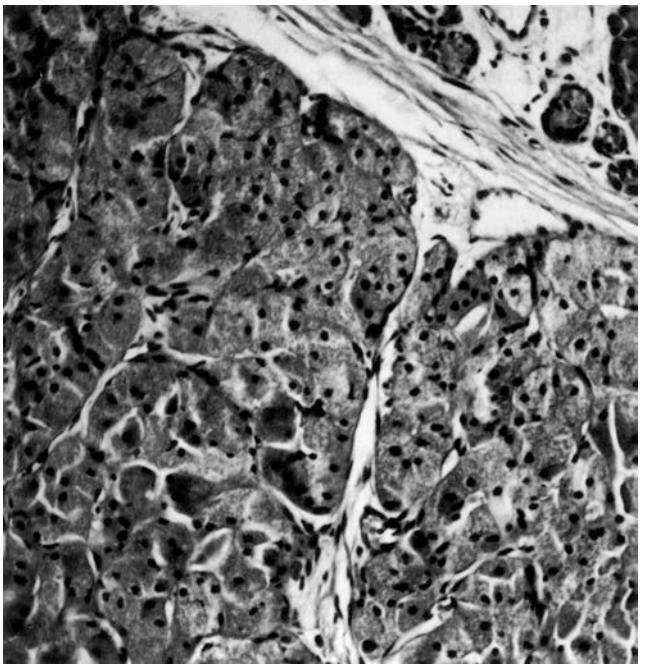


Figure 15.23 Oncocytoma: Benign neoplasm having large cells with abundant eosinophilic cytoplasm, this section is from a tumor of the parotid gland (×155).

The benign oncocytoma may have a glandular pattern or proliferate in nests or sheets of cells with only a sparse stroma. The tumors are a composite of large, uniform polyhedral cells, with an abundant, granular, eosinophilic cytoplasm, and small, dark eosinophilic cells with hyperchromatic nuclei (see Fig. 15.23). Mitoses are rare. If cystic spaces are present, the eosinophilic content stains with alcian blue and shows a positive, periodic acid-Schiff reaction. In malignant oncocytomas, the cells lose their uniformity and the nuclei are pleomorphic and hyperchromatic. Mitoses are also present.

These tumors should be totally removed by an anterolateral orbitectomy.

SPINDLE CELL MYOEPITHELIOMA

Heathcote et al. (1990) described this neoplasm in a middle-aged woman (see Fig. 15.24). At this time, the tumor was considered very rare. Subsequently, several authors have reported case studies of the neoplasm which have added further information about the lesion. The case reports of the benign spindle cell myoepithelioma

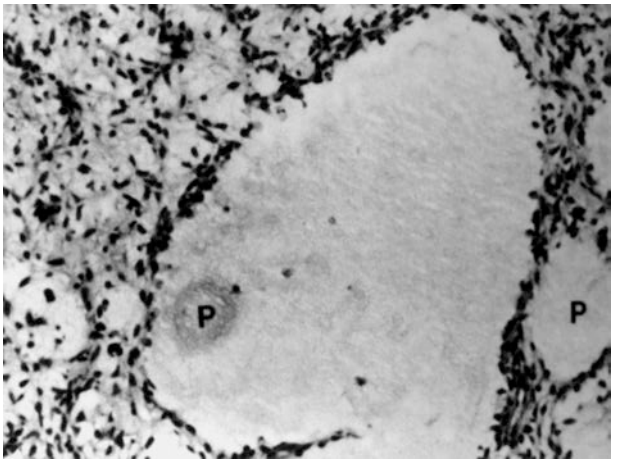


Figure 15.24 Myoepithelioma: Showing spindle cells in a loose matrix with the focal accumulation (P) of myxoid material (×300). (From Heathcote JG, Hurwitz JJ, Dardick I. A spindle-cell myoepithelioma of the lacrimal gland. *Arch Ophthalmol*. 1990; 108(8):1135–1139, copyright American Medical Association.)

of the lacrimal gland include a 23-year-old woman (Font and Garner, 1992), a 76-year-old woman (Grossniklaus et al., 1997), and a 40-year-old man (Rootman, 1988). A malignant spindle cell carcinoma in a 63-year-old man was described by Ostrowski et al., 1994. The tumors may be monomorphic or arise as within a pleomorphic adenoma (benign mixed tumor).

The benign neoplasm mimics the presenting features of the benign mixed tumor of the lacrimal gland, that is, a slow, painless proptosis and lacrimal gland palpable mass of long duration. The malignant form has a much shorter presentation, a few months. With CT scan, both histopathologic types show a well-circumscribed mass. The malignant type may show foci of calcification.

The neoplasms are encapsulated. Although the tumors are predominantly composed of spindle cells, there may be a lesser mixture of cuboidal cells. The nuclei are round or elongated, and the cytoplasm is eosinophilic. An epithelial *clear* cell is present in the myoepithelial carcinoma. The cells in sheets or trabeculae are interspersed in a loose, vascularized, myxoid stroma. Mitotic figures are rare. Immunohistochemical staining shows focal positivity for smooth muscle actin, vimentin, and glial fibrillary acidic protein.

The benign tumors may be totally removed with their underlying periorbita. However, a neoplasm with a large acetabular component may be very fragile and ruptures easily if it is not handled carefully. The clear-cell epithelial-myoepithelial carcinoma should be managed by exenteration.

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16 Secondary Epithelial Neoplasms

The secondary epithelial neoplasms encroach upon the orbit from contiguous sites such as the nasal cavity and paranasal sinuses; lacrimal sac; caruncle; parotid gland; external surface of the eye; and skin of the forehead, eyelids, and temple.

Features common to the secondary epithelial neoplasms are their variable presentation, radiologic evidence of bone destruction, and a slow relentless course. They are difficult to eradicate by the present treatment modalities, have a high rate of recurrence, and a discouraging death rate. Their presentation varies according to where they enter the orbit. If the tumor invades the anterior orbit either from an adjacent paranasal sinus or from the surface of the eyelids or face, there is usually a palpable mass or fullness of the cheek or medial canthal area, an upward or lateral displacement of the eye, epiphora, and a mass effect influencing ocular motility. If the tumor enters the posterior orbit, there may be pain or numbness over the superficial branches of the trigeminal and facial nerves, visual loss, papilledema, afferent pupillary disturbance, and ophthalmoplegia.

Neoplasms of this type from the Mayo Clinic Series, 1,795 consecutive cases (1948 to 1997), are listed according to their histopathologic type and order of frequency in Table 16.1.

As a group, these neoplasms are three times more frequent (252:80) in the orbit as the primary epithelial neoplasms discussed in Chapter 15. These secondary tumors comprise 14% of the total of 1,795 tumors studied by us over a 50-year period. In past years, the literature contained several reports wherein the incidence of secondary tumors was based on large patient cohorts. These reports were not comparable to our own because their analyses were not limited to epithelial neoplasms.

SQUAMOUS CELL CARCINOMA

This is the most frequent carcinoma (133 cases) in the total of 1,795 consecutive, histopathologically proved orbital tumors. Secondary squamous cell carcinomas, alone, constitute 6.8% (122 of 1,795 tumors) of the total tumors. 'Table 16.2 illustrates the primary source of the secondary neoplasms at the time of orbital invasion, as also the sex ratio and mean age of the patients.

Patients with lesions on the eyelids, eyebrow, or surface of the eye and an obstruction along the nasolacrimal excretory duct were usually first seen by an ophthalmologist. Ulcerative and nodular lesions of the cheeks, nose, forehead, and temple were usually first diagnosed by the patients' family physician.

Patients whose carcinoma, on subsequent examination, would prove to have an origin in the ethmoidal sinus would present with some combination of displacement of the eye, unilateral proptosis, pain, and a palpable mass suggesting an orbital tumor. However, only a small minority of the large number of carcinomas in the maxillary sinus and nasal passage presented as an orbital disorder.

The presenting signs and symptoms of paranasal sinus and nasal carcinomas were chiefly rhinologic in nature. In order of decreasing frequency, these included a mass or swelling of the cheek, pain or paresthesia of the face, a mass along the alveolar ridge of the maxilla, a sore gum, numbness of the face, nasal mass, history of polypectomies, epistaxis, nasal obstruction, and orbital apex syndrome. Some combination of two or more of these findings was present in all patients. The orbital manifestations of proptosis, displacement of the eye, and diplopia with or without a palpable orbital mass would follow at some variable interval after the onset (see Fig. 16.1).

The orbital manifestations of the few cases of nasopharyngeal carcinoma were those of the orbital apex syndrome (papilledema, trigeminal nerve paresthesias or anesthesia, optic disk pallor, ophthalmoplegia, afferent pupillary defect, and severe visual loss) indicating an extension of the tumor along the base of the skull.

Orbital extension from neoplasms of the adnexal tissues and lacrimal sac was more straightforward. These patients usually had a history of multiple surgical procedures on

TABLE 16.1
SECONDARY EPITHELIAL NEOPLASMS MAYO CLINIC SERIES, 1948 TO 1997

Histologic Type	Number
Squamous cell carcinoma	122
Basal cell carcinoma	52
Adenoid cystic carcinoma	34
Adenocarcinoma	18
Sebaceous carcinoma	10
Transitional cell carcinoma	6
Malignant mixed tumor	5
Undifferentiated carcinoma	4
Benign mixed tumor	1

a nodular or ulcerative mass, which finally invaded the contiguous orbit. A hard mass would be palpable along the affected orbital rim, and the motility of the eye would be increasingly impaired (see Fig. 16.2). These patients did not have the pain and discomfort associated with squamous cell carcinoma in other orbital sites unless the lesion was well advanced.

In the Mayo Clinic Series, *squamous cell carcinoma of the lower eyelid is nearly as frequent as the lesion in the upper eyelid*.

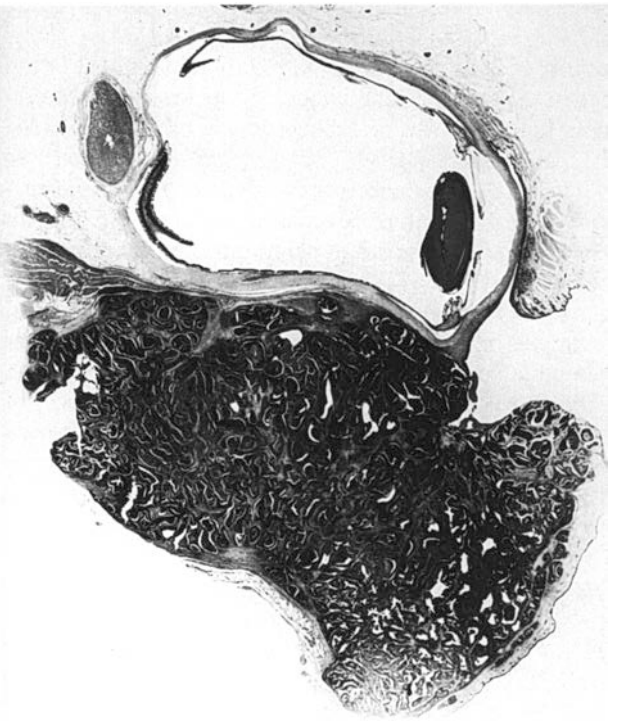

Figure 16.1 Gross specimen of a squamous cell carcinoma of the maxillary sinus showing massive, secondary invasion of inferior orbit from a 67-year-old man with 3 months' swelling of left upper face and 1 month epiphora (×2½).

Imaging Aspects

Both magnetic resonance imaging (MRI) and computed tomography (CT) scan are useful in the diagnosis and management of these neoplasms when orbital invasion occurs. MRI is considered the imaging modality of choice for soft tissue definition and CT scan is best for revealing the location and extent of bone destruction, which is invariably present. The lesions are usually homogeneous, highly attenuated in character, and enhance to some degree (see Fig. 16.3). Physicians working in this field for long have been hopeful these imaging modes would be helpful in determining the presence and degree of perineural spread.

TABLE 16.2
SECONDARY ORBITAL SQUAMOUS CELL CARCINOMAS MAYO CLINIC SERIES, 1948 TO 1997

Primary Source	Number	Male:Female Ratio	Mean Age
Paranasal sinuses	(69)	46:23	60
Maxillary sinuses	52		
Ethmoid sinuses	13		
Frontal sinuses	4		
Skin of the ocular adnexa	(26)	22:4	61.8
Eyelid	10		
Eyebrow and forehead	7		
Temple	5		
Face	4		
Nasal cavity and nasopharynx	(15)	13:2	60.4
Epibulbar and lacrimal sac	(12)	10:2	52.1
Total	122	91:31	

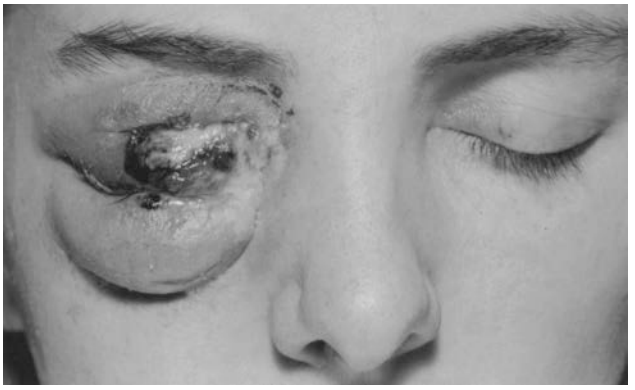

Figure 16.2 A 23-year-old woman with nodular and ulcerating lesions at the medial portion of the right upper and lower eyelids from a squamous cell carcinoma with secondary extension into the orbit. Several months earlier, an ''infection'' at the medial canthus had been treated by a dacryocystotomy. Origin of the lesion was the lacrimal sac. Secondary orbital squamous cell carcinoma, an extension from a lower eyelid.

Nemzek et al. (1998) reported a sensitivity of 95% for MRI detection of perineural spread but only a 63% sensitivity for mapping the entire extent of the process. Contrarily, despite a clinical suspicion of perineural spread, de Keizer et al. (1997) did not find either imaging method helpful in determining nerve extension. Preoperative detection of insidious but not clinically visible perineural spread is almost always a component of secondary orbital squamous cell carcinoma. The image display of perineural spread is an enlarged or expanded cord-like structure extending outward from the periphery of the mass lesion (Veness and Biankin, 2000), as it may be a solitary structure appearing on an image plane beyond the carcinomatous mass.

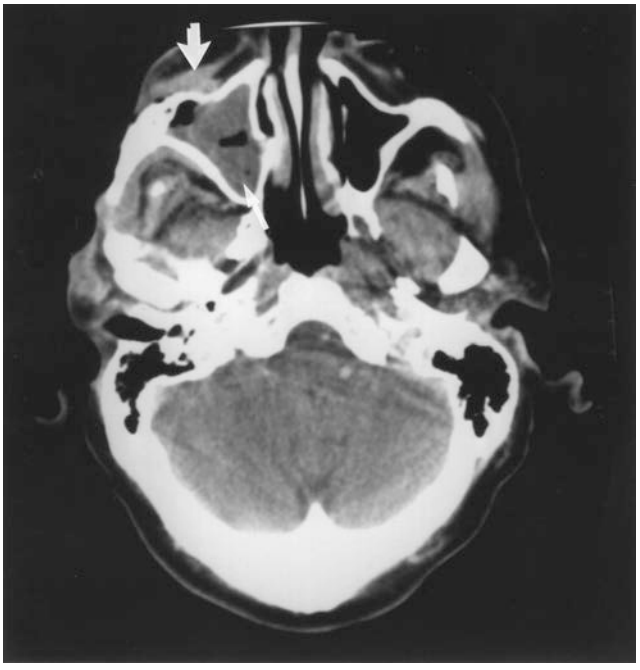

Figure 16.3 Squamous cell carcinoma: Axial computed tomography (CT) scan shows homogeneous mass occupying right maxillary sinus (*lower arrow*) with extension into right cheek (*upper arrow*) of a 59-year-old man. Subsequent maxillectomy also showed extension into right orbit, although this was not evident on preoperative scan.

Pathology

In a small zone around the anterior nares, squamous epithelium is normally arranged in a pavement-like pattern similar to that of skin. Elsewhere in the upper respiratory passages, squamous epithelium has undergone functional modification into a pseudostratified, sometimes ciliated, epithelium. The histologic pattern of this epithelium is, however, alike everywhere, but it varies according to the functional purposes of the specific anatomic sites. In the mucous membranes of the sinuses and anterior nasal cavity, the epithelium is ciliated and less stratified than in skin but it still possesses some characteristics of keratinization of skin. In the more posterior recesses of the nasal cavity, the epithelium becomes more columnar with little or no keratinization. This histologic pattern is frequently referred to as a transitional type of epithelium. In the nasopharynx, the epithelium becomes but a loose and thin layer of squamous cells covering a predominantly lymphocytic-adenoid type of stroma. Such an arrangement is usually termed a *lympho-epithelial type of respiratory epithelium*. Lower down the respiratory passages, squamous cell surfaces show further changes that make possible their identification with a specific anatomic area when tissue specimens are examined microscopically. The carcinomas, in their growth, reflect these nuances in cellular morphology, but basically, all of them represent malignant squamous metaplasia.

Squamous cell carcinomas of the maxillary sinus and nasal passages vary significantly in the degree of cellular differentiation. In general, the poorly differentiated and anaplastic types are more common than the highly keratinizing types (see Fig. 16.4). As the neoplasm becomes more anaplastic, the prickle type cell may take on a spindle shape in some of the higher-grade malignancies. The latter cellular patterns resemble the histologic picture of some sarcomas. The cellular boundaries of these proliferating cells also become less distinct, and mitosis and hyperchromatism are observed, as with all malignancies. Foci of degeneration may appear in the highly undifferentiated tumors, giving them a pseudoglandular appearance.

It might be expected that the more malignant types of squamous cell carcinomas would be the ones that would finally reach the orbit. Among the cases in the Mayo Clinic Series, this was not always so with those tumors from the nasal cavity. Of the 52 carcinomas originating in the maxillary antrum, the malignancy was, in all the 52, either

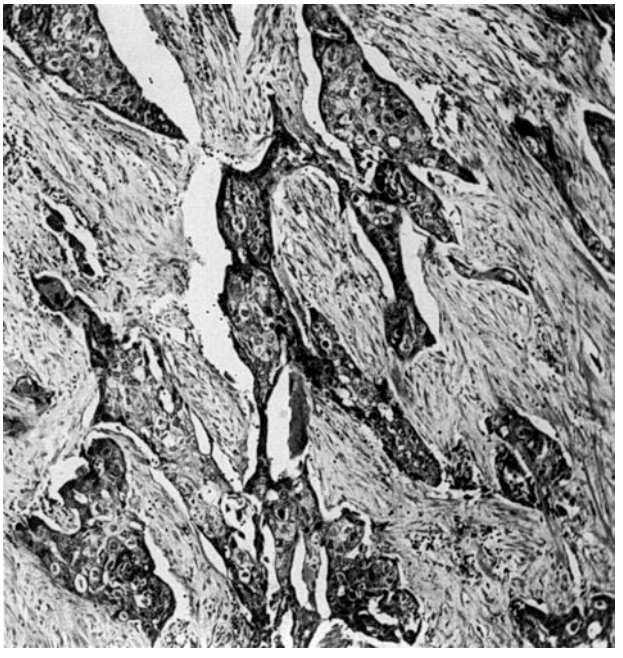

Figure 16.4 Squamous cell carcinoma orbital infiltration by highly anaplastic squamous cells with little evidence of keratin production in a 53-year-old man (×100).

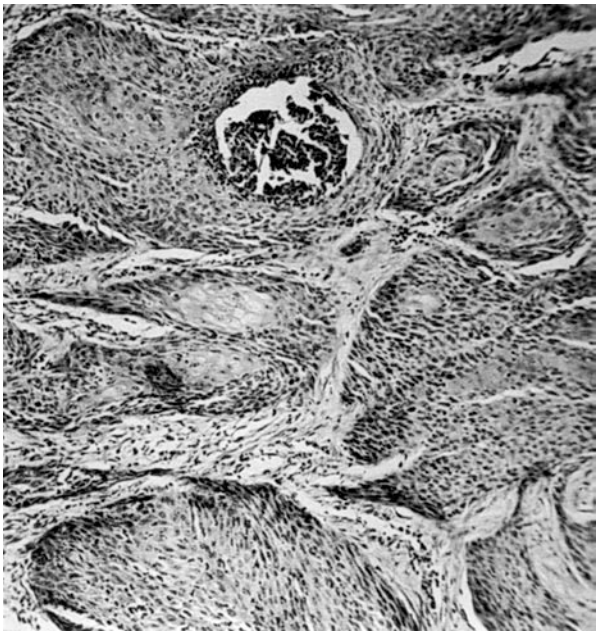

Figure 16.5 Squamous cell carcinoma. A papillary cell differentiated neoplasm resembling normal epidermis along the floor of the nasal cavity with extension into the area of the lacrimal sac and orbital floor of a 38-year-old man (×85).

grade 3 or 4. Of the squamous cell carcinomas arising in the nasal cavity, there was a nearly equal distribution among grade 2, grade 3, and grade 4 anaplastic types.

The histopathologic features of the secondary neoplasms arising in the skin of the face, eyelids, temple, and eyebrow were similar to those of squamous cell carcinomas elsewhere in the integument (see Fig. 16.5). They were more differentiated tumors and their course was more prolonged than other carcinomas, and only one case had malignancy of grade 4 degree.

Management and Course

The behavior of squamous cell carcinomas with secondary orbital extension is notable for their perversive spread, their refractory response to irradiation, and their high recurrence rate, even with what is considered a major surgical ablation of both soft tissue tumor and the bone involved. In general, prognosis has been related to the degree of malignancy; the more undifferentiated the tumor, the worse the prognosis. These carcinomas possess potentialities for local invasive growth as well as distant metastatic spread. In many tumors of grade 4 showing a malignant degree of undifferentiation, the prognosis is almost hopeless. Prognosis is also influenced to a lesser extent by other factors. With secondary carcinomas arising from the maxillary antrum, for example, the eventual outcome may be influenced by their size and extent at the time of discovery. Some of these carcinomas are not discovered until they have invaded the orbit and by this time they will be almost beyond the boundaries of a radical dissection. For those carcinomas that invade the orbit from adjacent integumentary structures, prognosis may be altered by the completeness of the initial surgical treatment; once the tumor has recurred owing to incomplete excision, the opportunity to eradicate the tumor by subsequent treatment is proportionately limited.

In the several disorders we have dealt with of this vicious neoplasm, the *goal* of successful treatment—and possible cure—has been the total surgical eradication of the tumor. With recurrence of the neoplasm, it was evident that *incomplete excision* was the rule. The culprit in this fallacy probably has been the insidious, unsuspected, extension of the carcinoma by perineural spread (see Fig. 16.6). Even present refinements in imaging methods cannot always detect this spread.

In the 1940s and 1950s, we advised exenteration of the orbit in people showing early stage, orbital invasion. This, sometimes, was considered *too harsh*. However, later, recurrent tumor would be surgically discovered in the former epicenter of the lesion along the side away from the orbit. A somewhat similar situation evolved when Mohs surgery, several decades ago, became popular for lesions around the face and periorbital adnexae. When a lesion was removed and the margins were negative for carcinoma cells, it was assumed that a complete excision had been performed. Alas! This technique was not infallible. Recurrences were later related to *skip* foci of cells along the nerve.

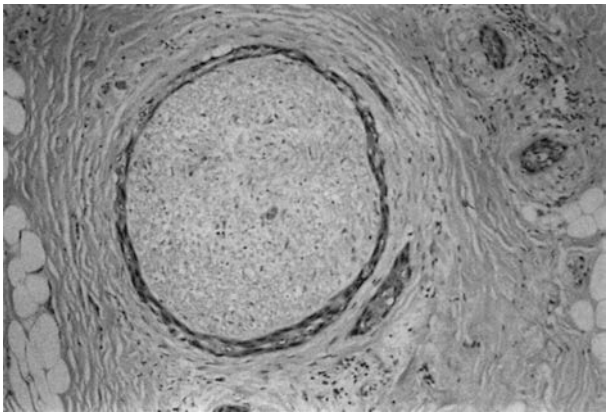

Figure 16.6 Histopathologic section of a branch of the facial nerve surrounded by a thin cuff of squamous cell carcinoma (×150). (From McNab AA, Francis IC, Benger R, et al. Perineural spread of cutaneous squamous cell carcinoma via the orbit. Clinical features and outcome in 21 cases. *Ophthalmology*. 1997;104:1457–14620.)

Conclusions

1. Orbital invasion should be considered an advanced stage of secondary carcinomatous disease.
2. Most patients die of their disease.
3. Of the several subgroups studied, those carcinomas arising on the surfaces of the eye, ocular appendages, and eyelids are associated with the smaller percentage of tumor-related deaths. This may be attributed to earlier discovery, easier access of the lesion to ablative surgery, and a lesser degree of histologic anaplasia.
4. The survival, in years, of patients with tumor-related deaths in the preceding subgroup is about twice that of patients whose carcinomas were primarily in the paranasal sinuses and nasal cavity. However, the percentage of tumor-related mortality in these two subgroups is comparable.
5. Most secondary orbital carcinomas will have some degree of bone involvement. The full extent of bone destruction may not be radiographically or grossly evident.
6. Occult bone involvement should be considered in the planning of the extent of surgical resection.
7. Orbital exenteration combined either with local removal of bone, orbitectomy, maxillectomy, or orbitocranial–facial resection is the present treatment of choice. These management options should be performed by a multidisciplinary surgical team.
8. No universal controlled study has been performed on a large series of patients regarding the effectiveness of Gamma Knife ablation, adjunctive radiotherapy, or chemotherapy.
9. In a hypothetical situation of two patients with secondary carcinomas in a similar location with similar extent and the same degree of tumor anaplasia, and equal access of the lesion to surgical removal, the *presence* or *absence* of perineural invasion of tumor beyond the margin of surgical removal may be the factor that determines the death of one patient and the survival of the other.

BASAL CELL CARCINOMA

The eyelids, side of the nose, upper face, and forehead are common sites for orbital, invasive, basal cell carcinomas. Certain features of the skin in these areas—its thin texture, glandular appendages, and exposure to direct sunlight—make it susceptible to these tumors.

A carcinoma in the area of the medial canthus, in particular, is apt to extend into the orbit because of discontinuity of the orbital septum in this area. Also, a surgeon's reluctance to extirpate the lacrimal drainage system at initial tumor removal may contribute to increased incidence of a secondary orbital extension (Rootman, 1988).

The basal cell carcinomas primarily in the skin of the upper face and periorbital area have often been analyzed in the literature in terms of their frequency, age range, and sex distribution. The tumor is frequently lumped with squamous cell carcinoma in such analysis because the two tumors occur in the same anatomic sites. However, with reference to orbital invasion, a sizable series of basal cell carcinomas are seldom surveyed as a separate subject.

Incidence

In our 50-year tumor survey (see Table 3.3), there are 52 secondary basal cell carcinomas (2.9% of the total 1,795 orbital tumors and 7% of the total 735 secondary orbital tumors). The primary sites of these neoplasms are listed in Table 16.3. Eighty-six percent (45/52) of our patients had recurrent tumor at the time of initial presentation. Often, the duration of symptoms was so long or multiple surgical procedures so numerous that the patients forgot such data. The mean age at the time of presentation was 64 years

TABLE 16.3
SITE OF ORIGIN OF SECONDARY ORBITAL BASAL CELL CARCINOMAS MAYO CLINIC SERIES (1948 TO 1997) (*n* = 52)

Lower eyelid	(*n* = 12)
Cheek	(*n* = 10)
Medial canthus	(*n* = 10)
Upper and lower eyelids	(*n* = 7)
Upper eyelid	(*n* = 5)
Forehead and eyebrow	(*n* = 4)
Temple	(*n* = 3)
Palate	(*n* = 1)

(range 28 to 88 years). The male-to-female ratio was 34:18. The right orbit was affected in 31 patients, the left orbit in 19 patients, and 2 patients had bilateral orbital disease.

Clinical Features

This type of neoplasm is a master of disguise. In the early stages of growth, the tumor may be a round, elevated, smooth nodule with a shiny surface. In the upper eyelid and eyebrow, it may be warty. Or it may be a sinuous, elongated, superficial, or a lumpy ulceration along the margin of the lower eyelid. Sometimes the tumor is elevated and nodular but with a scaly center surrounded by a rolled border. Lastly, the tumor may be nothing more than an innocent-looking indurated plaque.

However, by the time orbital invasion occurs, these singular aspects tend to merge into an ugly, dirty-looking ulcer with an elevated irregular edge that is covered by a smelly crusted exudate. The surrounding tissues become progressively indurated as the lesion penetrates deeper into the soft tissue. Very advanced lesions may bleed easily, undergo partial necrosis, or show a fistula between the orbital cavity and nose.

The clue to orbital invasion is a *fixation of the ulcerated lesion to the underlying rim or surface of the bony orbit*. At this stage, the surrounding soft tissues usually show a mild inflammatory response characterized by redness and swelling of tissues or chemosis of adjacent conjunctiva. Pain is not a common accompaniment of early orbital invasion. Only 2 of our 40 cases noted pain at the time of presentation.

Gradually, the tumor becomes rooted to the orbicularis oculi muscle of both the upper and the lower eyelids, the canthal tendons, and the extraocular muscle nearest to the advancing border of the lesion. This results in fixation and immobility of the eyelids and a tethering effect on ocular motility (see Fig. 16.7). Later, the eye becomes immobile and "frozen," corneal desiccation and perforation occurs, and the vision is lost. Seven of our patients had a visual acuity of hand movements or less in the affected eye at the time of presentation.

Once the neoplasm gains access to the periorbita and soft tissues of the orbital cavity, it tends to expand in a circular fashion in preference to a deeper penetration. Eradication may be possible at this stage provided there is no bone involvement.

Imaging Aspects

The most common areas of early orbital extension, by this neoplasm, are the medial and lateral canthi. A CT scan will show the posterior extent of the soft tissue mass along the inner face of the medial or lateral wall of the orbit, and there may be no bone destruction (see Figs. 16.8 and 16.9). Even so, upon palpation, the anterior orbital rim may have some irregularity indicating minimal bone involvement at this stage. Neuro-imaging is of critical importance in revealing the posterior extent of a recurrent neoplasm that has deeper involvement of orbital tissue. Bone destruction, if present, will also be evident by CT scan. T_1 contrast–enhanced, fat-suppressed MRI will show the makeup of the mass and enhancement of the dura if early intracranial expansion is present (Selva et al., 2003).

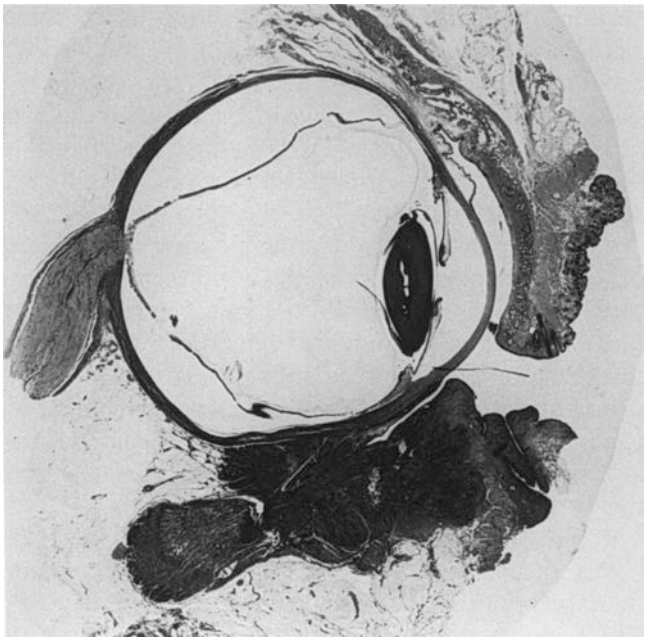

Figure 16.7 Secondary basal cell carcinoma. Gross specimen showing marked involvement of lower eyelid, which was fixed to inferior orbital rim. Specimen removed by orbital exenteration ($\times 2\frac{1}{2}$).

Pathology

Histopathologically, the cells of the tumor are small with hyperchromatic nuclei and little cytoplasm. They are arranged in nests and irregular islands (see Fig. 16.10), at the periphery of which the nuclei may show a palisaded appearance (see Fig. 16.11). Once the tumor invades the orbital tissue, the palisading may be lost. Sclerosis between the tumor cells may be a feature giving the appearance of the morphea form of basal cell carcinoma (see Fig. 16.12). On occasion, squamoid differentiation may occur with keratin formation. Infiltrating sebaceous gland carcinoma of the orbit may also take on a basaloid appearance and be confused with basal cell carcinoma.

Management

Our concern is not the primary lesion localized to the skin but the eradication of an invasive carcinoma that, in most cases, has previously been unsuccessfully removed or treated by one or a combination of several modalities. With orbital involvement, the choice narrows to the method that

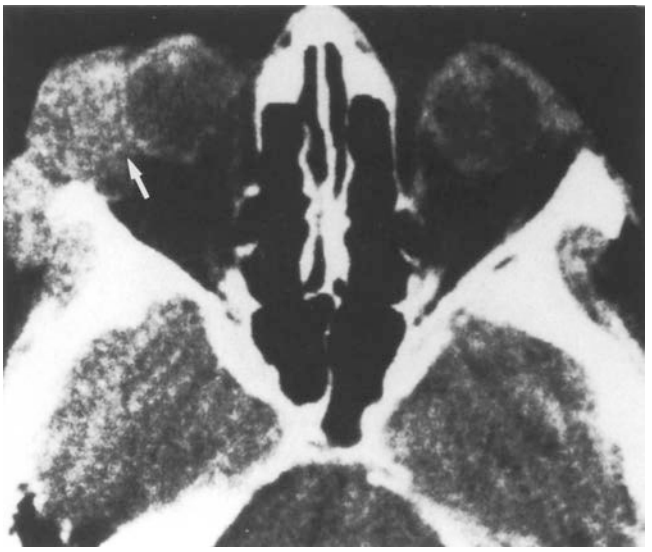

Figure 16.8 Axial computed tomography (CT) scan showing bone destruction of the right lateral orbital rim and wall (*arrow*) by a secondary basal carcinoma. Soft tissue mass is adjacent to the eyeball and extends posteriorly into the soft tissues of the temple.

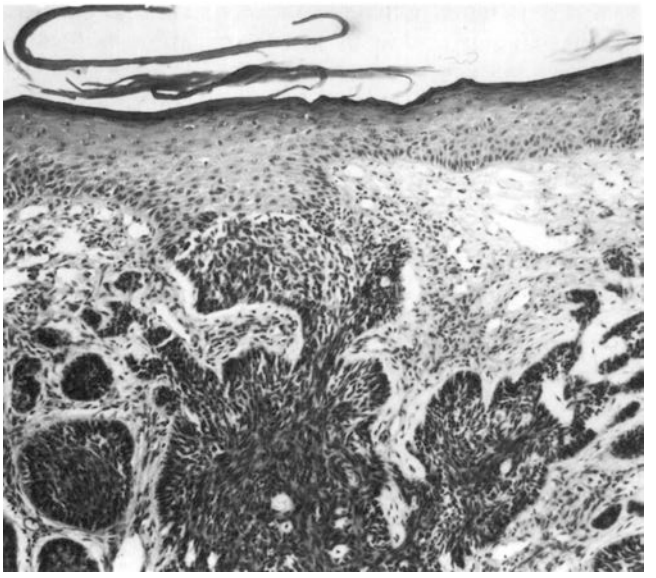

Figure 16.10 Secondary basal carcinoma. Small, prismatic cells resemble basal layer of epidermis, indicating an origin of neoplasm from skin (×100).

will encompass the widespread extent of the lesion once and for all. Many publications have been devoted to a search for this elusive surgical or medical nirvana.

In selecting an appropriate treatment, three considerations prevail. The first consideration is the large size of the lesion. The diameter of most of these ulcerating carcinomas is between 40 and 60 mm in at least one meridian. This technical factor hinders the application of treatment modalities such as radiotherapy, cryotherapy, Mohs microscopic dissection technique, and chemosurgery.

A second consideration is the recurrent nature of most secondary basal cell carcinomas. Such tumors show an increasing degree of histologic aggressiveness, which lessens the lesions' response to topical or intralesional agents when compared to an otherwise favorable response of a carcinoma in its primary site.

The third consideration is the presence of bone invasion. Systemic chemotherapy, for example, is less efficacious in these situations when compared to its effectiveness upon soft tissue diseases.

At present, surgical ablation of tumor seems to offer the best chance of overcoming these barriers provided the

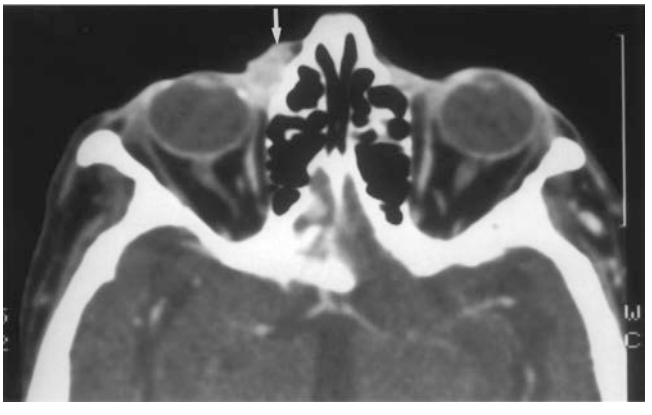

Figure 16.9 Axial computed tomography (CT) scan shows a basal cell carcinoma (*arrow*) in the right inferomedial canthus area that extends posteriorly into the medial rectus muscle in an 88-year-old woman. No bone destruction. Primary tumor had previously been excised by Mohs technique.

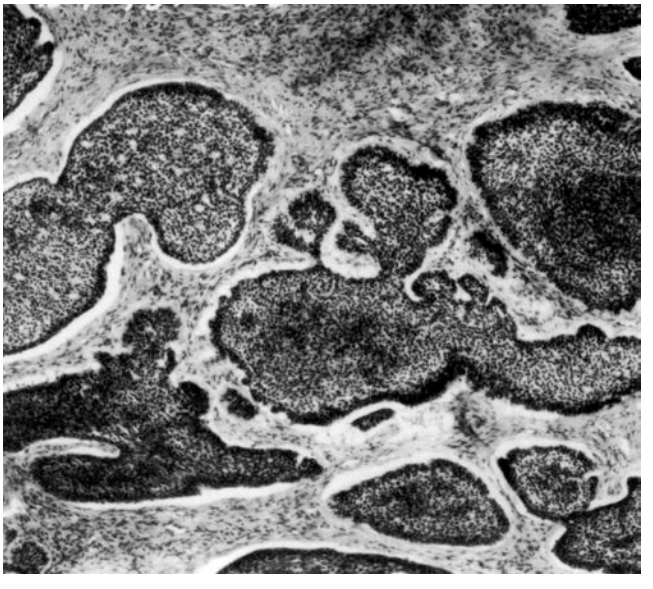

Figure 16.11 Secondary basal carcinoma: Cells are arranged in large clusters bounded peripherally by palisade-like layer (×65).

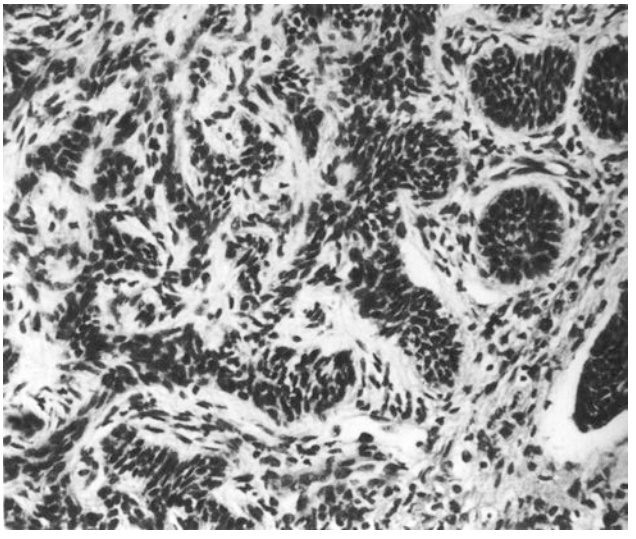

Figure 16.12 Secondary basal cell carcinoma. Morphea-type showing cords and islands of cells with fibrous stroma invading orbital tissues (×250).

neoplasm is in a surgically appropriate area of the orbit, upper face, or cranium.

Total exenteration of orbital contents, including all periorbita, may provide a cure in those cases without bone involvement. For those cases with neoplastic invasion of the inferior orbit from a primary source in the lower eyelid, maxillectomy combined with an orbital exenteration may be sufficient. For the malignant invasion of the upper bony orbit, a monobloc orbitocraniectomy combined with an exenteration of soft tissue would be the procedure of initial choice.

These procedures involving removal of bone are usually done by a team of two or more of the surgical specialties who operate in those anatomic sites.

If there is recurrence of tumor, further removal of bone, if possible, is necessary. However, there is a limit to bone removal if tumor has recurred in the skull base. Here, radiation is administered as a palliative measure. Many other surgeons, however, use radiotherapy in recurrences.

In the earlier years (1940s and 1950s) of our orbital tumor study, we performed only a simple, total orbital exenteration procedure. However, there were some unexplained recurrences. At the time of surgery, a few cases had tiny, shallow facets of irregular bone along the orbital rim. We assumed these irregularities represented a remodeling (pressure effects of bone). In retrospect, these irregular areas might have been shallow erosions of bone from invasive tumor, which harbored a nidus of tumor that was the reason for the recurrence.

Course

Traditionally, secondary basal cell carcinoma is an indolent neoplasm. Therefore, long-term observation of these patients is required to learn the final outcome of the disease. In addition, many patients are in an advanced age-group and may succumb to other disorders before the basal cell neoplasm has run its course. Other variables include patients who become indifferent to their recurrent disease, who miss their appointments for follow-up consultation, or drift away to the care of other physicians. Whatever the reason, follow-up data are more erratic with this disease than with any other orbital tumor referred to in this text.

In our series, follow-up was available in six of seven patients whose orbital invasive neoplasm was treated for the first time while under our care. There were two patients with tumor-related deaths 34 and 80 months, respectively, after diagnosis. One of the deceased patients was too debilitated to be treated other than by radiotherapy. The other tumor-related death was initially treated by orbital exenteration with supplementary radiotherapy. One of the four survivors underwent enucleation of the eye combined with a maxillectomy and was living without recurrence 23 months later. However, we consider this patient still at risk for recurrent tumor. A second survivor underwent an orbitocraniectomy with preservation of the eye but experienced further invasion of tumor into soft tissues of the affected orbit 2 years after initial surgery. The recurrence was treated by further removal of orbital bone combined with orbital exenteration. Two additional years have passed without recurrence, but again, we believe the patient is still at risk for recurrence of tumor. One of the two remaining survivors underwent an enucleation of the eye combined with an orbitomaxillectomy. Over 9 years have passed without recurrence. This tumor-free survival probably represents a cure. The last referred patient was treated by an orbitomaxillectomy combined with an orbital exenteration and has been tumor free for 69 months.

However, among the patients with recurrent tumor on their initial visit, the outcome is more dismal. In the 40-year survey, 1948 to 1987 (Table 3.1), 33 of the 40 had recurrent tumor. We have some follow-up on 22 of the 33 patients. Eleven of the 22 died of tumor over a range of 1 to 18 years (mean 6.5 years). In the same period, three patients with recurrent tumor died from other causes.

The cohort of 12 patients (Table 16.3) observed over the past decade, 1988 to 1997, have not been analyzed for survival and mortality data. We believe the time interval is too brief for *long-term* values.

ADENOID CYSTIC CARCINOMA

It is usually a surprise to many physicians in their initial contact with orbital tumors that secondary adenoid cystic carcinoma is more frequent than the primary type, with a ratio of 34:30 based on our 50-year collection of consecutive, pathologically proved tumors. The incidence of the secondary tumors is 1.9% (34/1,795) of total tumors in the Mayo Clinic Series and 4.7% (34:732) of the

secondary orbital tumors in our list. The *female-to-male* ratio is 19:16. Of the 34 adenoid cystic carcinomas, only one case showed bilateral orbital involvement. The mean age of these patients is 53.4 years at the time of orbital invasion. This is higher than the mean of 49.6 years of patients with *primary* adenoid cystic carcinoma. The difference in the mean age of the two groups reflects the time required for the secondary tumor to reach the orbit from its primary site, and a later diagnosis of the secondary tumor that may be concealed in an extraorbital location when compared to a more obvious primary tumor palpable in the lacrimal gland.

Clinical Features

The initial location of the secondary adenoid cystic carcinomas in the Mayo Series was known in 33 patients of the Mayo Series. These were maxillary sinuses (15 cases), nasal passage (7), ethmoid sinus (6), oral cavity (3), and lacrimal sac (1) and parotid gland (1).

The presentation of the secondary tumor includes a combination of two or more of the symptoms or signs such as paresthesia, anesthesia, pain in the distribution of the trigeminal nerve, "fullness" of the cheek, a mass in the oral cavity or nasal passage, epistaxis, nasal obstruction, epiphora secondary to an obstructive process along the nasolacrimal duct, upward or superolateral displacement of the eye, an afferent pupillary defect, rapidly progressive visual loss, papilledema, a parotid gland mass, blepharoptosis, or trouble with a tooth extraction (Osguthorpe, 1994).

A CT scan will outline the size and extent of the mass and show the degree of bone destruction. On MRI, the soft tissue mass will be isotense, but if bone cortex is involved, the marrow content will show bright intensity. T_2-weighted image shows hyperintense signal in Figure 16.13.

The histopathology of adenoid cystic carcinoma was described in Chapter 15. Primary and secondary neoplasms are similar in their histologic features. Figure 16.14 shows an orbital exenteration specimen harboring a secondary tumor from an adenoid cystic carcinoma of the adjoining ethmoid sinus.

Management and Course

Here, we will attempt to update the reader about the recent advances, principally surgical, which are directed to the eradication of the secondary carcinomas extending into or from the orbit from paranasal sinuses, nasal passages, intracranial vault, ocular adnexa, and face, since the last edition of this text. We again reviewed the literature of the 1990s up to 2004 including some reports.

We note that in this time interval there are the usual number of publications by authors who describe either a more convenient approach or an improved method for removal of neoplasm and affected bone. Complete

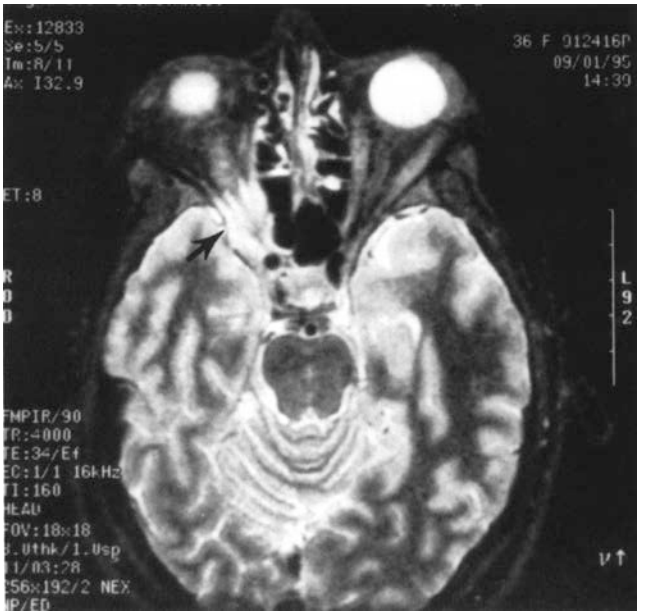

Figure 16.13 Secondary adenoid cystic carcinoma. Magnetic resonance imaging (MRI) (axial view): T_2-weighted image shows hyperintense signal intensity in the right orbital apex (*arrow*) and along the adjoining optic nerve sheath. (From Lee AG, Phillips PH, Newman NJ, et al. Neuro-ophthalmologic manifestations of adenoid cystic carcinoma. *J Neuroophthalmol.* 1997;17:184.)

eradication of the affected bone has been the principle surgical therapeutic mainstay for over 50 years. The ostectomies performed in and around the orbit, both in volume and extent of bone removed, are now very complex. The reader may wonder how much more bone can be removed to assure surgical success. The answer is "very little." The bone at the skull base is considered unresectable. All of the above literature on this subject has been mostly concerned

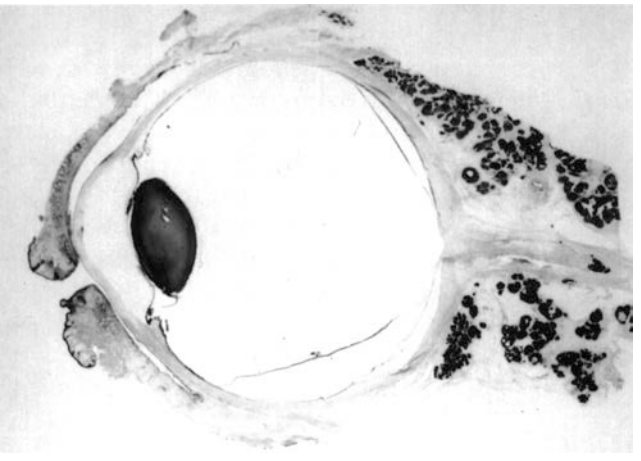

Figure 16.14 Secondary adenoid cystic carcinoma. The retrobulbar tissue of an orbital exenteration specimen is infiltrated with clusters of cells from a primary site in an adjacent ethmoid sinus. Surprisingly, the orbital tissue shows little reactive inflammatory response.

with refinements in the major surgical approaches over the last 25 years.

The one new procedure that may be useful in this field is the widespread use of the "Gamma Knife" in the late 1980s and mid 1990s. For residual neoplasms involving the skull base, particularly in the areas of the cavernous sinus, Gamma Knife radiotherapy is now used as a supplement to bone removal and might evolve into a substitute for bone removal. However, the time interval over which it has been used is too short to provide an objective assessment of its effect on survival or mortality rates.

The literature of the 1990s also contained occasional reviews of a cohort of patients upon which the author based an estimate of the incidence of survival and mortality of secondary adenoid cystic carcinomas. One of the most recent ones, at the time of this writing, is the publication of Naficy et al. (1999). The authors have compared the efficacy of radiotherapy alone versus its use as an adjuvant treatment to surgical resection in 17 patients with histologically confirmed adenoid cystic carcinomas arising from the paranasal sinuses. No patients were treated by surgical resection alone. Their follow-up averaged 6 years.

Ten of 17 patients (59%) underwent a combination of surgical resection followed by external beam radiation therapy. Nine of these patients had some type of maxillectomy, and the one remaining patient underwent a total maxillectomy and orbital exenteration. The dose of postoperative radiation ranged from 4,500 to 7,000 cGy. Radiation therapy was the sole modality in 5/17 (29%) of patients (4,500 to 7,000 cGy). A curative resection was not attempted because they all were deemed unresectable. Two patients with advanced local disease refused any form of treatment and died 4 and 5 years respectively after diagnosis.

The 6-year survival for the combined surgery and radiotherapy group was 73% compared to 50% for radiotherapy alone. The overall local recurrence rate was 70%, and metastasis occurred in 18% of the patients. The study concluded that "*complete resection of the tumor with the widest margin possible offers the best hope for long-term disease-free survival*."

The above review of Naficy et al., prompted us to study the 34 secondary adenoid cystic carcinomas, which we have collected over a period of 50 years, which might show changes in survival and mortality rates over this period of time. Among the malignant neoplasms occurring in and around the orbit, adenoid cystic carcinoma, probably, is the slowest growing. In a study of adenoid cystic carcinomas primary in the lacrimal gland (Henderson, 1987), I noted that some patients have a survival period of 10 to 15 years after surgical removal, only to die later with tumor recurrence. Long-term follow-up is therefore necessary for accurate analysis of survival and mortality. Therefore, through correspondence, I have tried to track the course of the secondary neoplasm in each of our 34 patients. This has provided the long-term preferred follow-up.

We divided our cohort of patients into two main groups: 15 patients in the first 25-year study (1948 to 1972) (see Table 16.4), and 19 patients in the second 25-year period (1973 to 1997) (see Table 16.5). Each 25-year group was further subdivided into one class of patients who underwent their initial surgery at Mayo for the newly discovered extension of the neoplasm into the orbit, and a second class of patients with recurrent tumors. The latter class usually had had a conglomerate of surgical remedies including the herald Mohs surgical procedure, which had failed to halt recurrences.

TABLE 16.4
ADENOID CYSTIC CARCINOMA WITH SECONDARY ORBITAL EXTENSION MAYO CLINIC SERIES 1948 TO 1972 (*n* = 15)

Initial Surgery			Recurrent Tumor		
Patient	**Follow-up (y)**	**Treatment**	**Patient**	**Follow-up (y)**	**Treatment**
		Died of Tumor			
ME	(9)	D, R, E	RB	(1)	E, D
TP	(1)	S, R	MS	(1/2)	P
EM	(19)	S, X, R	WH	(7)	B, R, C
EV	(8)	S, D, E, R	TH	(1/2)	S
DL	(2)	S, R, P			
TM	(19)	S, R, B, C			
FK	(7)	S, B, X, R			
MT	(5)	R, C			
GH	(1/2)	S			
AH	(1)	X			
JR	(9)	S, B, R			

B, ostectomy; C, chemotherapy; D, surgical diathermy; E, enucleation of eye; P, palliation; R, radiotherapy; S, excision of primary tumor and/or secondary tumor; X, orbital exenteration.

In this table, a letter symbol designates the surgical and nonsurgical remedy applied at Mayo. The number in parentheses after the patients' code designation indicates the follow-up (in years) after the patient was first seen at Mayo Clinic.

In the first 25-year period (Table 16.4), all patients died of tumor regardless of recurrent or now recurrent tumor when first seen at Mayo. Among the 11 patients in the nonrecurrent group, death averaged 7.2 years with a range of 6 months to 19 years. It is interesting to note that there are two patients in each group surviving 19 years. It is obvious that patients who underwent surgery at the time of initial discovery of orbital extension live much longer than patients with prior recurrence. We might also conclude from this 25-year sample that secondary adenoid carcinoma is always lethal.

In the second 25-year study group of 19 patients (Table 16.5), there is one patient for whom the cause of death is not known. Among the remaining 18 patients, 12 have died of tumor, one case was inoperable, and one patient was living with metastasis. All 14 cases should be considered fatal (14/18, 77%). In the seven patients in whom tumor was treated at time of presentation, fatality ranged from 1 to 8 years with a mean of 4.42 years of survival. In the recurrent tumor group of five patients, four patients died in a year or less, but one patient lived a surprising 10 years before death. Among the remaining patients in the overall cohort, two patients are living with recurrent tumor 8 and 21 years after surgery at Mayo. It is likely these two cases will be fatal in the future. Another two patients are living *without* recurrence 2 and 4 years after surgery, but this brief survival is meaningless for the calculation of survival and mortality rates.

If we combine the two 25-year protocols, we find that 85% (29:34) have died of tumor. If we were to continue our follow-up of the patients in the 1973 to 1997 group, I suspect we would find that all patients with secondary, orbital adenoid cystic carcinoma would die of tumor unless they die of some other cause. In brief, this neoplasm is *lethal*.

ADENOCARCINOMA

Adenocarcinomas and adenoid cystic carcinomas are similar in several respects, that is, their presentation, their inevitable recurrence (once removed), radiosensitivity but not radiocurable, medical and surgical efforts to ablate the neoplasms, high fatality ratio, the same age range (*adenocarcinoma 16 to 84 years; mean 53 years*) (*adenoid cystic carcinomas 31 to 82 years, mean 53.4 years*), and secondary

TABLE 16.5
ADENOID CYSTIC CARCINOMA WITH SECONDARY ORBITAL EXTENSION MAYO CLINIC SERIES 1973 TO 1997 (*n* = 19)

Initial Surgery			Recurrent Tumor		
Patient	**Follow-up (y)**	**Treatment**	**Patient**	**Follow-up (y)**	**Treatment**
		Died of Tumor			
KC	(8)	S	BC	(1)	R
AL	(5)	R, S, B	LP	(1/2)	S, R
CS	(3)	S, R, C	LM	(1/2)	S, C
FH	(2)	C, R, S	DS	(1/2)	Refused treatment
BG	(7)	S, R	JA	(10)	X
KO	(5)	R, S, B, X			
AO	(1)	S, B, X			
		Living, No Recurrence			
JE	(4)	R, S, B	WC	(2)	S, B
		Living with Metastasis			
LB	(3)	S, B, R			
		Inoperable			
IK		S, B, R	No follow-up		
		Living with Recurrence			
JM	(21)	S, B	MO	(8)	S, B, X
		Cause of Death Not Known			
CD	(1/2)	S, B			

B, ostectomy; C, chemotherapy; D, surgical diathermy; E, enucleation of eye; R, radiotherapy; P, palliation; S, excision of primary tumor and/or secondary tumor; X, exenteration of orbit.

orbital tumors outnumber primary orbital neoplasms (*adenocarcinoma 18*:*8*, *adenoid cystic carcinomas 34*:*30*). The most frequent site of origin of these two neoplasms is the maxillary sinus. However, the two secondary neoplasms differ in their sex ratios; the males predominate in the adenocarcinomas 12:6, whereas the sex ratio is nearly equal, 33 males:32 females. Histopathologically, the adenocarcinoma is a more malignant aggressive tumor than the indolent adenoid cystic lesion (Svane-Knudsen et al., 1998). Among the neoplasms in which the grading classification was stated, there were 9 of 16 adenocarcinomas (grades 3 and 4), and 25 of 26 adenoid cystic carcinomas (grades 1 and 2). Patients with the aggressive adenocarcinoma have a shorter life span than patients with adenoid cystic carcinoma. Our cohort of 11 patients with secondary adenocarcinoma died of tumor over a range of 4 months to 6 years, mean 20 months compared to 11 patients of the nonrecurrent adenoid cystic group who died 7.2 years, and the patients in the recurrent tumor group who died 4.42 years after the first medical or surgical treatment at Mayo.

The two neoplasms also differ with respect to an early metastasis to regional lymph nodes, liver, and lungs, by the adenocarcinoma. Metastasis of an adenoid cystic carcinoma occurred very late in the course of the tumor, but an equal number of deaths occurred from perineural spread into the intracranial vault.

TRANSITIONAL CELL CARCINOMA

Although this neoplasm is dignified by a classification based on cell morphology, its orbital presentation and clinical features are those of the preceding tumors, particularly the squamous cell carcinoma. A common substrate for both squamous cell carcinoma and transitional carcinoma is the nasal inverted papilloma (Elner et al., 1993; Bajaj and Pushker, 2002). However, by the time orbital extension occurs, there is nothing specific about this neoplasm that would suggest its histopathologic identity.

We have seen only six patients with this type of secondary carcinoma over the 50-year period of our study. Their age range was 26 to 74 years with a mean of 56 years. The primary site of origin was the nasal cavity with one exception, that is, a posterior ethmoid sinus. These are highly anaplastic tumors; five of the neoplasms were histopathologically grade 4. One tumor was not graded. Survival of five patients ranged from 1 month to 36 months (mean 19.2 months) from the time of initial ablative surgery at Mayo. A sixth patient survived a miraculous 10 years.

MIXED TUMOR

This neoplasm is an uncommon secondary orbital tumor. Six cases were encountered in our 50-year collection of orbital tumors. One of these was a benign mixed tumor. This was a 47-year-old man who presented with a hard mass in the inferonasal quadrant of the right orbit. Fifteen years earlier, a tumor had been incompletely removed from the juncture of the right check and lateral side of the nose. An *en bloc* removal subsequently showed the origin of the tumor in the lateral nasal wall with extension into the maxillary and ethmoid sinuses and the orbit. In a 9-year follow-up, there was no recurrence of tumor.

The remaining five cases were malignant mixed tumors. All five were males. In four of the five patients, the malignant mixed tumor had reached the orbit from a source in the hard palate (two cases), nasal cavity, and parotid gland, respectively. Their ages at time of presentation were 20, 33, 55, and 57 years. Orbital symptoms were displacement of one eye in a direction opposite to the area of orbital presentation (inferiorly or medially), diplopia, and visual loss.

Three of these four cases underwent extensive bone removal, removal of eye, and dissection of regional lymph nodes but to no avail. The remaining case with a neoplasm arising in the nasal cavity underwent a partial excision of the tumor when an extension into the intracranial vault was discovered. The operation was terminated. All patients died of metastasis within a period of 12 to 43 months after their surgery at Mayo.

There is very little literature, in recent years, on the subject of secondary orbital extension of either benign or malignant mixed tumors.

SEBACEOUS CELL CARCINOMA

This is a carcinoma that may occur in sebaceous glands other than in the periorbital area, and its origin in the sebaceous glandular appendages of the eyelids cannot always be pinpointed with certainty. For this reason, we prefer the generic term *sebaceous cell carcinoma* to the time-honored name *meibomian gland carcinoma* for the title of this section.

The presentation, diagnosis, and management of the sebaceous cell carcinoma primary in the ocular adnexal tissues (usually the eyelids) are widely covered in the literature. We have selected additional references, since our last edition, that we believe are most germane to this type of carcinoma, including Nelson et al. (1995), Alessi et al. (1997), Zurcher et al. (1998), Sinard (1999), Chao et al. (2001), Shields et al. (2002), and Font and Rishi (2003). We have omitted articles reporting only one or two cases.

In its primary site, the neoplasm usually invades the tissues of the eyelid, tarsal plate, conjunctiva, caruncle, and so on, with eventual extension into regional lymph nodes and/or orbit. Once in the orbit, it is prone to recurrence and metastasis, and is fatal. The incidence of orbital invasion varies widely among publications dealing with this aspect of the tumor.

In our 50-year collection of tumors (Table 3.3), there are ten cases; five cases each of females and males. The age range of this cohort at the time of orbital invasion was 45 to 92 years, with a mean age of 63.2 for men and a mean age of 77.6 for women. The primary sites of the carcinomas were upper eyelid (six cases), lower eyelid (three cases), and the caruncle (one case). The histopathologic degree of malignancy was grade 4 (five cases), grade 3 (three cases), and grade 2 (two cases).

Neuroimaging can demonstrate orbital invasion (see Figs. 16.15 and 16.16). We also scan the parotid gland and neck to examine for lymphadenopathy. Six patients had orbital extension of their carcinoma at initial presentation and underwent their first surgical procedure at Mayo. The other four patients presented with recurrent tumors. Five of the six patients who had their first surgery at Mayo underwent what was considered an ablative surgical procedure. All had an exenteration of the orbit besides neck dissection of involved lymph nodes in two patients and an additional craniofacial reaction for extension of tumor into frontal and ethmoid sinuses. The sixth patient underwent only an orbital debulking procedure for palliative relief of pain. In the latter case, the extension of the tumor beyond the orbit was considered inoperable. Four of six patients were dead in a mean of 2.7 years. Five patients were alive without recurrence 1 year after ablative surgery. The 1-year follow-up on these latter two patients is too short for meaningful analysis.

We have a follow-up on two of the four patients who had ablative surgery for recurrent tumor. One of the two had radiotherapy followed by surgical resection of the neoplasm but died 5 years later with widespread metastasis. The other patient underwent only an orbital exenteration but is living and well 15 years later. We consider this a cure for this type of carcinoma.

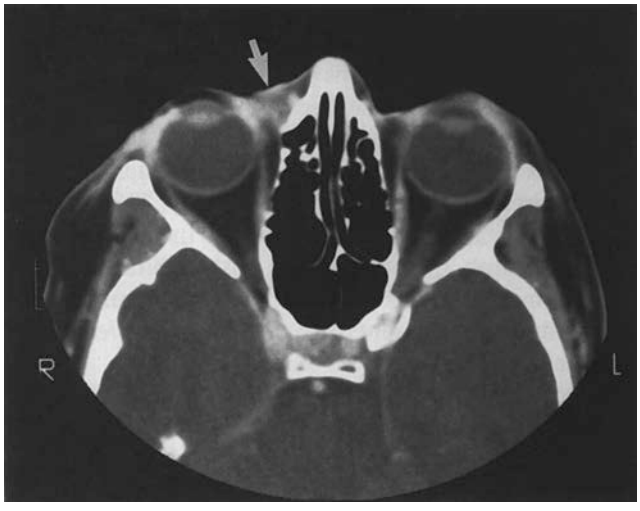

Figure 16.15 Sebaceous gland carcinoma. Axial computed tomography (CT) scan shows enhancing, homogeneous soft tissue mass (*arrow*) with posterior extension along right anteromedial orbital wall. Primary tumor excised from right caruncle 3 years earlier. (Compare with Fig. 16.9.)

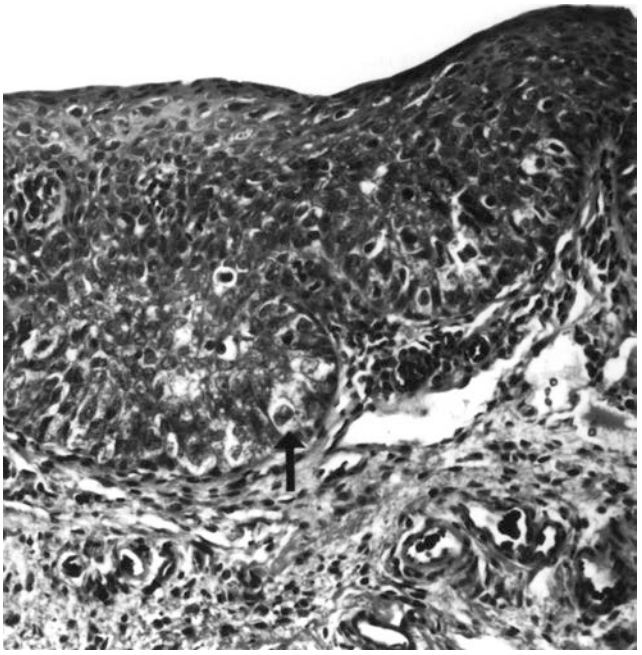

Figure 16.16 Tissue from an eyelid shows pagetoid cells (*arrow*) in the epithelium associated with an underlying sebaceous gland carcinoma (×100).

Yen et al. (2000) recommend radiation therapy as an alternative therapy for patients who refuse surgery. This modality was used on two patients, each with a neoplasm of an eyelid. One patient received 69 Gy of combined superficial and megavoltage irradiation to an eyelid. The second patient received 59-megavoltage electron beam irradiation to an eyelid. In both the cases, the tumor responded to radiation therapy. However, one patient died of myocardial infarction 39 months after treatment. The second patient is without clinical evidence of tumor 46 months after treatment. The authors conclude that radiotherapy with an appropriate delivery system is effective as a *curative* treatment for eyelid sebaceous cell carcinoma.

Epithelial neoplasms, in general, are radiosensitive over a short span of time. The patient described in the preceding text will eventually have a recurrence over a longer period of time. When this occurs, the tumor will have a higher degree of malignancy, which will be fatal. Epithelial neoplasms are *not radiocurable*.

MUCOEPIDERMOID CARCINOMA

In the head and neck area, the usual loci of the primary mucoepidermoid carcinoma are the parotid, submandibular, lacrimal, and minor salivary glands. Less often, it may arise from the mucoid surfaces of the oral cavity, nasal passages, paranasal sinuses, and ocular adnexal structures such

as the eyelid and conjunctiva. The neoplasm is a variant of squamous cell carcinoma. These two neoplasms have a similar histopathology and location in extraorbital sites. Orbital invasion covers a wide age range from the second through the seventh decade. Each of the three secondary neoplasms in our 50-year collection of orbital tumors had an unusual site of origin, two of them illustrate the neoplasms' resistance to treatment and inexorable spread, and one case seemed responsive to radical surgical ablation.

The first patient was a 16-year-old girl who had a soft tissue mucoepidermoid tumor of 1 year's duration resected from the surface of the *left* hard palate. Subsequently, the tumor extended through bone into the alveolar ridge and maxillary antrum. Next, it extended over the midline into the *right* maxilla and antrum. The tumor then spread into the right orbit, soft palate, pharynx, and lymph nodes on each side of the neck. The tumor reached the right orbit approximately 49 years after the initial operation. In the meantime, she had undergone approximately 18 major surgical procedures including removal of recurrent soft tissue masses and both the upper jaws, bilateral neck dissections, a parotidectomy, removal of the floor and medial wall of right orbit, as well as irradiation and radium implants. She died of extension into the sphenoid sinus with erosion of the internal carotid artery at age 71. During this long age interval, the degree of malignancy increased from grade 1 to grade 4 intensity. In retrospect, the total dose of radiotherapy administered to the patient may have been a factor in the unrelenting increase in the malignancy of the neoplasm.

In a second case, a 34-year-old woman presented with a fungating, bleeding mass protruding from the floor of the right orbit (see Fig. 16.17), nodules of a recurrent tumor along the left orbital rim, and pulmonary metastasis. One year earlier, a right maxillectomy had been performed for grade 3 mucoepidermoid carcinoma of the right maxillary sinus. The patient died of tumor 16 months after the initial surgery.

In the third patient, a 38-year-old woman, a nodule of grade 1 mucoepidermoid carcinoma was fortuitously discovered at the mucocutaneous junction of the right medial canthus during the course of a surgical face-lift. Three months later, a radical excision of soft tissues and the underlying bone of the right orbit was performed for the invasive neoplasm. The patient is living without local recurrence or metastasis of tumor 7 years later.

The histopathology of this neoplasm consists of an admixture of epidermoid and mucous-secreting cells arranged in patterns of cords and islands (see Fig. 16.18). The mucous-secreting elements have clear vacuolated cytoplasm and eccentric nuclei (signet ring cells). These cells, as well as cystoid spaces that may be present in the specimen, react positively to mucicarmine and Alcian blue stains and the periodic acid-Schiff reaction. The mucous-secreting elements are prominent in the well-differentiated (grade 1) neoplasms, whereas the epidermoid cells predominate in the less-differentiated (grade 3) neoplasms.

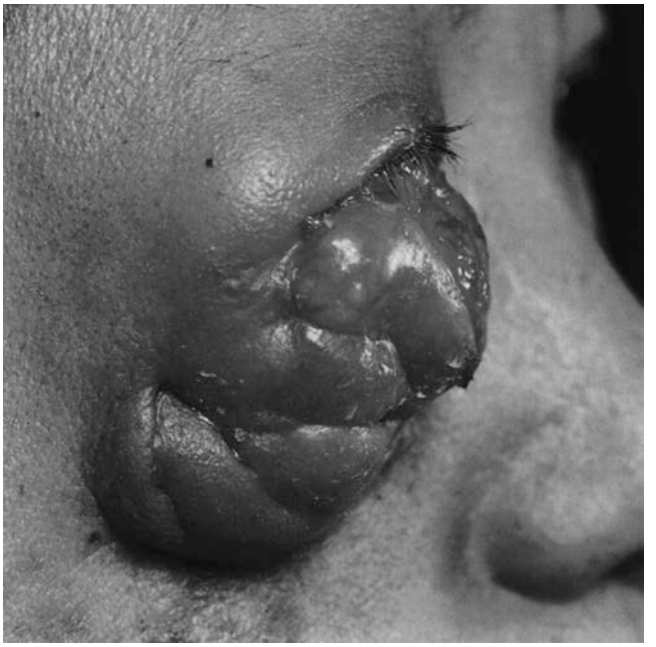

Figure 16.17 Secondary mucoepidermoid carcinoma. A 34-year-old woman presented with a fungating, bleeding mass protruding from the right orbital floor secondary to primary tumor in the maxillary sinus that had been removed by a maxillectomy 1 year earlier. At presentation, there also was tumor extension to the left orbit and pulmonary metastasis.

The histologic grade of the tumor is considered a factor in its prognosis, at least in the major salivary glands. However, in the orbital and periorbital area, we believe all mucoepidermoid carcinomas should be considered treacherous

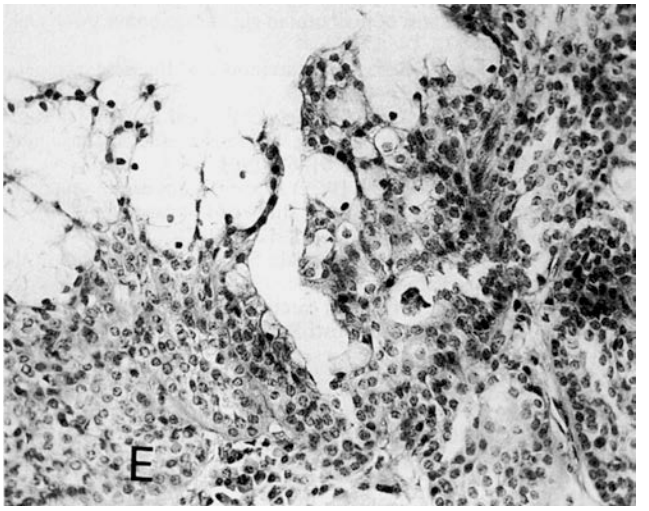

Figure 16.18 Mucoepidermoid carcinoma neoplasm is a mixture of mucous-secreting goblet cells (above) and epidermoid cells (below) (E) (×200).

neoplasms irrespective of the histologic grade. In these areas, prognosis seems more related to the promptness and totality of surgical excision.

The term mucoepidermoid carcinoma is often used synonymously with *adenosquamous carcinoma*. The latter is of cutaneous origin (Johnson et al., 2001). It is controversial whether these two tumors are identical on the basis of histologic criteria or are separate entities on the basis of clinical course.

SWEAT GLAND CARCINOMA

This title designates a small group of adenocarcinoma of eccrine and apocrine types that arise in the dermis of the lower eyelid, which, if left untreated or incompletely removed, may eventually disseminate through regional lymph nodes or secondarily invade the orbit. The primary tumors are quite rare and orbital invasion is even more so. The terminology includes mucinous *eccrine* sweat gland carcinoma, mucinous a*pocrine* sweat gland carcinoma, and microcystic adnexal carcinoma. The primary tumor in the eyelid presents as a solitary slow-growing, painless, dome-shaped firm mass that seems so innocuous that a year or so may elapse before the patient seeks consultation (Duffy et al., 1999). The tumor reaches the orbit by subcutaneous invasion and perineural spread.

Orbital invasion was a definite component in the cases reported by Stout and Cooley (1951); Grizzard et al. (1976); and Khalil et al. (1980). The histopathology of these carcinomas is essentially the same regardless of terminology (see Fig. 16.19). Prognosis may be more dependent on the histopathologic grade of malignancy rather than on the tumor type. A well-differentiated neoplasm may invade the orbit before regional lymph node dissemination, whereas the reverse sequence occurs with poorly differentiated lesions.

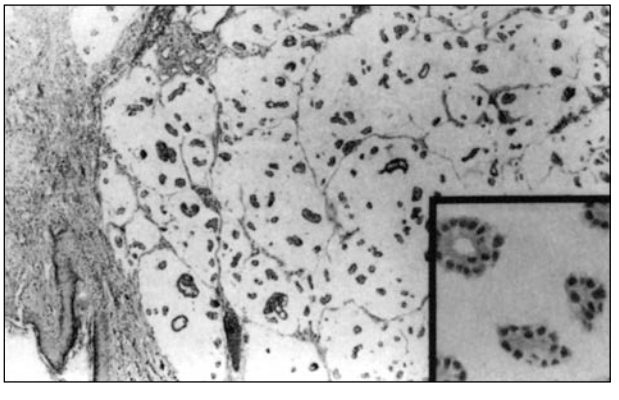

Figure 16.19 Mucinous adenocarcinoma of eccrine origin showing islets of tumor cells in the sea of mucin (hematoxylin and eosin ×40). (Inset) High magnification (×400) showing tubular lumen. (From Sudesh R, Siddique S, Pace L. Primary eyelid mucinous adenocarcinoma of eccrine origin. *Ophthalmic Surg Lasers*. 1999; 30:394–395.)

A recurrent, invasive sweat gland carcinoma is best treated by radical removal of periorbital appendages combined with orbital exenteration. This might eradicate the neoplasm provided lymphatic spread has not already occurred.

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Metastatic Carcinomas

17

CLINICAL FEATURES

Over the time interval of our study of orbital tumors, 1948 to the present, I am impressed by the proliferation of publications describing carcinomas (chiefly adenocarcinomas) metastatic to the orbit from distant sites, either before or after the primary origin of the tumor is recognized. Included in these publications are a plethora of reports describing only one, or not more than two, patients whose presentation, clinical features, and course differ little from printed material at some prior time. This latter trait was noted in all of our prior editions. We will not reference these numerous case reports unless they contain some information other than the "norm."

There are 78 metastatic carcinomas of the above type in our 50-year collection of orbital tumors. This is 4.3% (78 out of 1,795) of our total tumors. There were 27 men and 51 women. The predominance of women is due to the frequency of metastases from breast carcinomas. However, if the 37 breast carcinomas are excluded from the calculation, the remaining metastatic carcinomas occur predominantly in men in a ratio approximating 2:1 (32 men and 15 women). In the time interval of our study (1948 to 1997), we have referenced 15 sites of origin of these metastatic carcinomas including prostate, urinary bladder, intestine, breast, gallbladder, adrenal gland, lung, thyroid, pancreas, liver, thymus gland, kidney, cervix, urachus, and ovary.

Blepharoptosis of the upper eyelid associated with diplopia, due to a definite impairment of ocular motility, are the initial signs and symptoms at the time of presentation of these carcinomas. These features emphasize the frequent lodgement of the itinerant neoplasm in or adjacent to the extraocular muscles. Because of their excellent blood supply, these muscles are a logical location for hematogenous metastasis. Proptosis soon follows, but it is relatively slight (2 or 3 mm) compared to the marked disturbances of motility.

At this stage, pain or headache is absent in about half the cases. If pain is present, it is probably indicative of bone destruction. The pain is nagging in character. If pain is associated with visual loss, it is probably due to a tumor in the orbital apex, compressing the optic nerve, or retrobulbar space. Other signs and symptoms such as pulsation of the eye, enophthalmos, afferent pupillary defect, numbness, or paresthesia, and epiphora are infrequent.

Computed tomography (CT) scan and magnetic resonance imaging will show the size, location, and composition of the neoplasm but are not particularly helpful in differentiating the site of origin of the neoplasm. However, there are some features common to all metastatic carcinomas to the orbit. They all show some degree of enhancement; areas of necrosis may appear as hypodense, and it is unusual to see calcification or cystoid changes.

CARCINOMA OF THE BREAST

Of the adenocarcinomas in our 50-year collection, metastasis from the breast is the most common, occurring in 49.3% (39 out of 75) of the total metastases. In four of the women, the metastasis to the orbit was bilateral. The average age of these patients at the time of orbital presentation was 58.9 years. An additional four patients developed bilateral orbital metastasis in the course of the disease. Therefore, 21.6% (8 out of 37) of the total patients had bilateral metastasis some time in the course of the disease.

Breast carcinoma is noted for the time lapse between recognition of the primary tumor and its metastasis. Excluding the four patients in whom the primary carcinoma was not recognized until orbital presentation, there are 33 patients in the Mayo Clinic series for whom the interval from diagnosis of the primary lesion and orbital metastasis is known. In this subgroup, the mean was 5.9 years, and the median was 4 years (range 3 months to 27 years). In a similar analysis of ten patients (Bullock and Yanes, 1980) with orbital metastasis from breast carcinoma, the interval averaged 6.5 years (range 2 to 15.3 years).

In this same field, Reeves et al. (2002) report a case with an unusual twist. At 50 years of age, the patient had a uterine metastasis of unknown origin. Eleven years later, she presented with an orbital metastasis of breast origin. A retrospective analysis of the uterine metastasis and orbital metastasis showed they were identical, but

the carcinoma in the breast was not palpable over the interim 11 years. Eight years after her orbital presentation, a resection of a metastatic adenocarcinoma of the colon was performed which proved to be another metastasis of the lobular carcinoma of the breast. In the case of Saitoh et al. (1997) the patient had a metastasis to both eyelid and orbit 8 years after mastectomy for breast carcinoma.

In four of our patients, *enophthalmos* rather than exophthalmos was the clue to an orbital metastasis, usually a scirrhous type of an adenocarcinoma.

The carcinoma infiltrates the extraocular muscles. The muscles undergo fibrosis, atrophy of the surrounding orbital fat occurs, and ocular motility becomes so limited that the affected eye becomes *fixed and frozen* in forward gaze. The eye is so immobile that diplopia may not be present in some cases. One of these four patients thought one of her eyes was too prominent, a *pseudoproptosis*, (see Fig. 17.1) and was not aware of the enophthalmos of the other eye. Smith et al. (2001) report a sad case of a tethered, sunken eye in a 76-year-old woman heralding a widespread metastasis of a breast carcinoma. Eight years previously, she had had the primary carcinoma treated by wide excision, radical radiotherapy to the breast, axilla, and supraclavicular lymph nodes; and tamoxifen 20 mg daily for 2 years. Alas, the heroic therapy given to the patient was all of no avail.

Enophthalmos associated with metastatic scirrhous adenocarcinoma from the bladder and intestinal tract also occurs (*vide infra*).

Chandran and Lee (1998) report an interesting case of a 38-year-old woman with a history of breast carcinoma who developed increasing levels of tumor marker CA 15.3. Ten months later, visual loss, diplopia, and blepharoptosis occurred in one eye due to a metastatic adenocarcinoma in the right cavernous sinus and superior orbital fissures. She was treated with surgery and radiotherapy and did well. The authors think that physicians should be aware of the significance of increasing levels of tumor markers as a precursor sign of possible metastasis.

Sekundo and Vogel (1997) report an intriguing case of a 54-year-old woman with a metastatic orbital carcinoma from the breast. Unlike the primary tumor, the metastatic tumor was repeatedly negative for estrogen and progesterone receptor markers. Because the primary tumor was positive for these hormone receptors, the patient was treated by chemotherapy and tamoxifen. The follow-up supported a favorable effect of this adjuvant hormone therapy.

CT scan (see Figs. 17.2 and 17.3) shows several nonspecific features of metastatic breast carcinoma.

The histopathology of adenocarcinoma of the breast varies. Some may be differentiated into papillary-like growths that remain confined to intraductal, glandular units. Others may appear as a straightforward mucinous type of carcinoma. Still others show a histiocytoid pattern with the cells interspersed in a fibrous tissue stroma. The histiocytoid cells have atypical hyperchromatic nuclei and cytoplasmic, mucin-positive vacuoles. However, by the time the neoplasm has reached the orbit, the original features of the tumor have been replaced by undifferentiated, anaplastic cells that may show a "single-file" infiltration of orbital fat or densely packed cellular lobules of neoplasm. All of the neoplasms in the Mayo Clinic series except

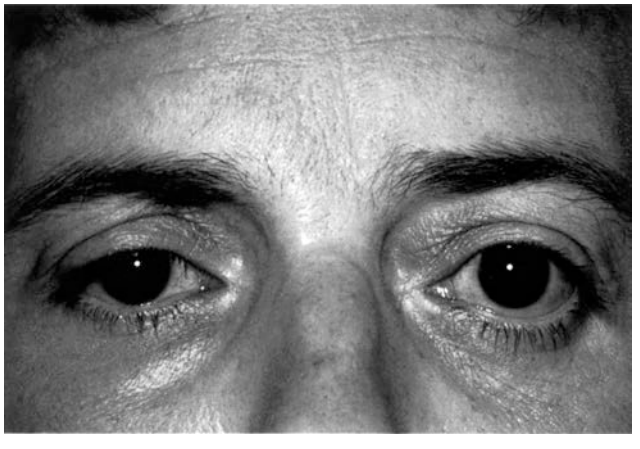

Figure 17.1 Metastatic adenocarcinoma (breast): A 45-year-old woman presented with prominence of left eye of 3 months' duration. However, the abnormal findings were in the right eye consisting of marked limitation of upward ocular rotation, blepharoptosis owing to partial paralysis of levator palpebrae superioris, and enophthalmos of 5 mm. These were the first manifestations of metastasis from carcinoma of the breast removed 4 years previously.

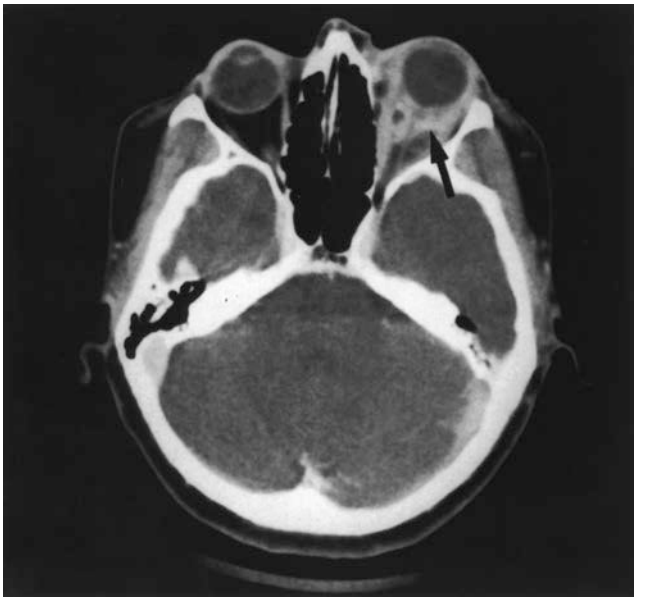

Figure 17.2 Metastatic orbital carcinoma from the breast: Axial computed tomography scan shows irregularly contoured, infiltrative, enhancing retrobulbar mass with marked thickening of sclera (*arrow*) in a 50-year-old woman. No bone involvement.

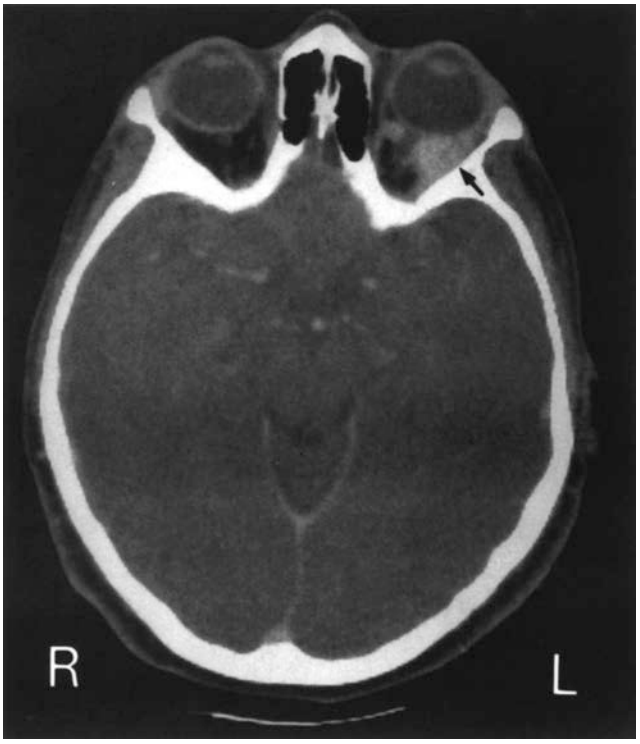

Figure 17.3 Metastatic orbital carcinoma: Axial computed tomography scan shows a large, enhancing, infiltrating mass in the left lateral orbit intimately related to the lateral rectus muscle (*arrow*). The absence of proptosis was unusual considering the size of the mass. This lesion was the presenting sign of a latent carcinoma of the breast in a 59-year-old woman.

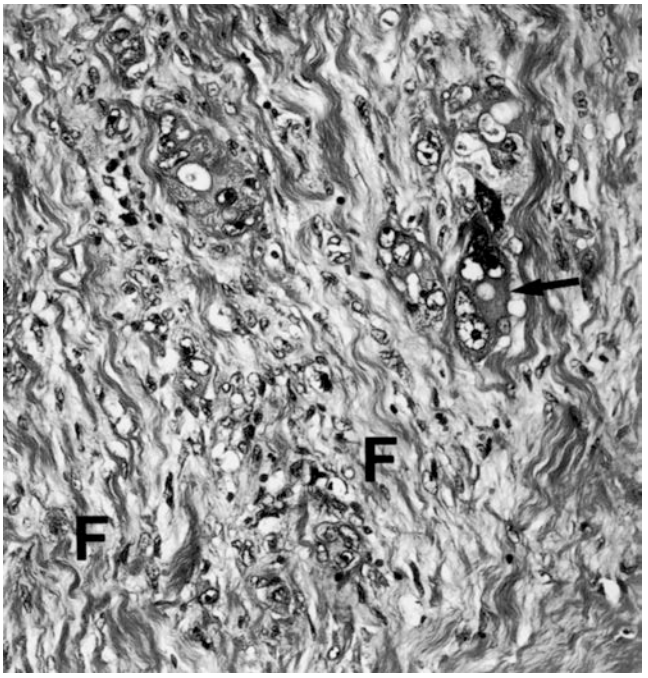

Figure 17.4 Metastatic adenocarcinoma (breast): Metastatic tumor cells (*arrow*) with fibrosis (F) (×250).

two were anaplastic (grade 3 or grade 4) neoplasms (see Fig. 17.4).

Of our total 37 patients, 30 patients have died of their tumor, four patients are living with tumor, one patient was lost to follow-up, and in two patients the cause of death is not known. The average survival from the time of orbital metastasis was 31 months with a median of 19 months (range 1 to 116 months). On this basis, orbital metastasis can be considered an omen of doom.

Three of the four living patients have survived only 68 months, 15 months, and 13 months, respectively, from the time of orbital metastasis. In the fourth living patient, diagnosis of the primary carcinoma and its orbital metastasis was concurrent. This patient has survived 76 months from diagnosis. The interval of survival from the time of orbital metastasis in these four patients is still in the risk interval of death from tumor based on the course of the 30 patients with tumor-related deaths.

The survival data given above do not support the concept of surgical removal of an orbital metastasis although it is an initial and apparently isolated focus of disease. Unmanageable pain may be the only reason for surgical intercession. The best management option is probably orbital radiotherapy for its palliative effect. Patients whose tumor shows a positive estrogen receptor assay may also be responsive to hormone therapy with increased survival when compared to tumors with a negative estrogen receptor assay.

In the past decade, an antiestrogenic agent, *tamoxifen*, has come into widespread use as a systemic adjuvant therapeutic agent for postmenopausal women with breast carcinoma. It is most effective on adenocarcinoma, which has a positive estrogen receptor assay. Controlled studies, over a 10-year period, have provided patients with a longer, nonrecurrence survival interval when compared to patients treated prior to tamoxifen therapy.

CARCINOMA OF THE LUNG

This neoplasm is second to carcinoma of the breast in the frequency of metastasis to the orbit. However, in respect to metastasis, the carcinoma of the lung differs in its predilection for men, occurs at a younger age (age range 34 to 80 years, average 51), and is more aggressive than the breast carcinoma. Dissemination from the lung may occur so early in the tumor's growth that a metastatic focus may precede the discovery of the primary neoplasm. In 6 of 11 cases in the Mayo Clinic series, orbital metastasis was the initial symptom of the silent primary in the lung.

The orbital presentation usually is more fulminant than most of the metastatic tumors in this chapter. Rapidly evolving proptosis is usually the predominant presenting sign. In 7 of 11 patients, orbital symptoms and signs were 3 months or less in duration at the time of presentation.

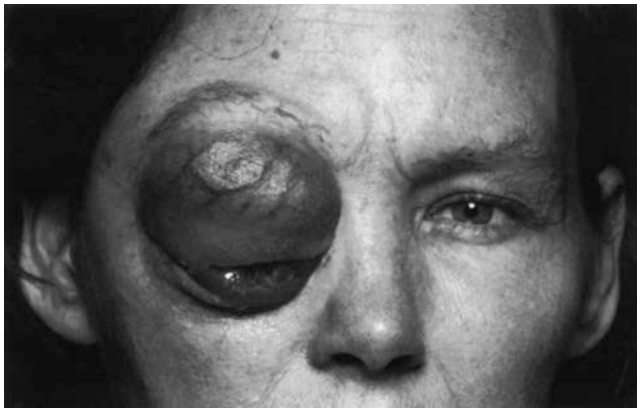

Figure 17.5 Metastatic carcinoma (lung): Rapidly progressive proptosis of the right eye over a period of 1 month and complete loss of vision in the affected eye of 3 weeks' duration in a 39-year-old woman from a metastatic small cell carcinoma of the lung. A hard mass was palpable across the superior quadrants of the right orbit. This illustrates the rapid and aggressive metastasis of many carcinomas of the lower respiratory tract. The patient died 2 weeks after this photograph was taken.

In the remaining four patients, the longest interval before presentation was 6 months. In one patient, a unilateral proptosis of 10 mm developed over a 3-month period. The orbital manifestations may appear so acute in some cases that the patient is treated for an acute inflammatory process (see Fig. 17.5). Spaide et al. (1989) also reported a patient of this type. Another patient presented with bilateral orbital masses but proptosis of only one eye. Neither enophthalmos nor the "frozen" fixed eyes are seen with metastasis of lung carcinomas as against metastatic breast carcinomas.

Carcinoma of the lung is an inclusive term for several histologic types regardless of their specific site. The three principal cytologic types are adenocarcinoma, squamous cell carcinoma (see Fig. 17.6), and undifferentiated carcinoma (see Fig. 17.7). The undifferentiated type is also called *small cell*. In 11 cases of the Mayo Clinic series, there were five adenocarcinomas, four small cell, and two squamous cell types. Each of these cell types responds differently to current chemotherapeutic regimens (*vide infra*).

Life expectancy in 7 of our 11 patients was nearly as short as the temporal aspects of their presentation. Death occurred from 1 to 26 months after orbital presentation. The mean was 9 months. No follow-up data were available in the remaining four patients. Radiotherapy and the chemotherapy programs in use at the time these patients were first seen were of no avail. However, none of these patients were treated in a time frame corresponding with recent programs of combined chemotherapy (*vide infra*).

DeLeo et al. (1979), working with immunized mice, produced an antigen, which they thought was associated with malignant transformation, and termed *p*53. Gradually, it was recognized that cancer patients developed antibodies to this tumor suppressor antigen. Currently, these antibodies are almost exclusively associated with a diagnosis of cancer (Campling and El-Deiny, 2003).

The latter authors have extensively studied and reviewed the literature pertaining to the possible role of gene p53 in

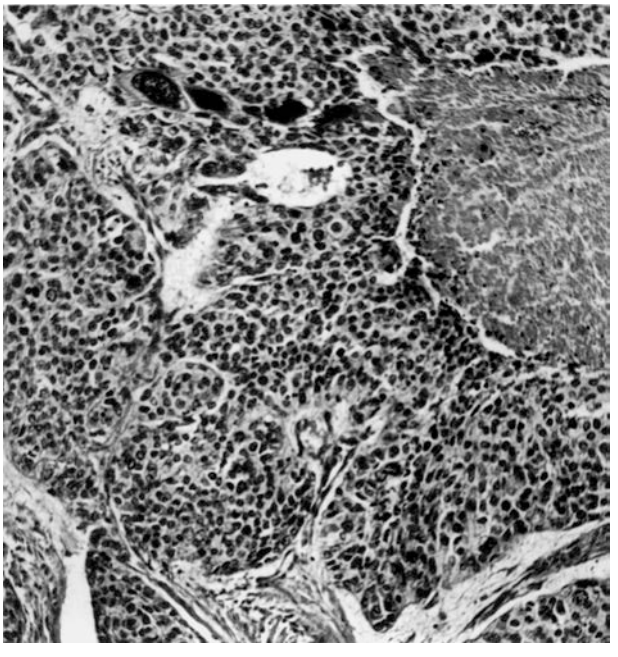

Figure 17.6 Metastatic lung carcinoma: Neoplasm is squamous cell in type (×110).

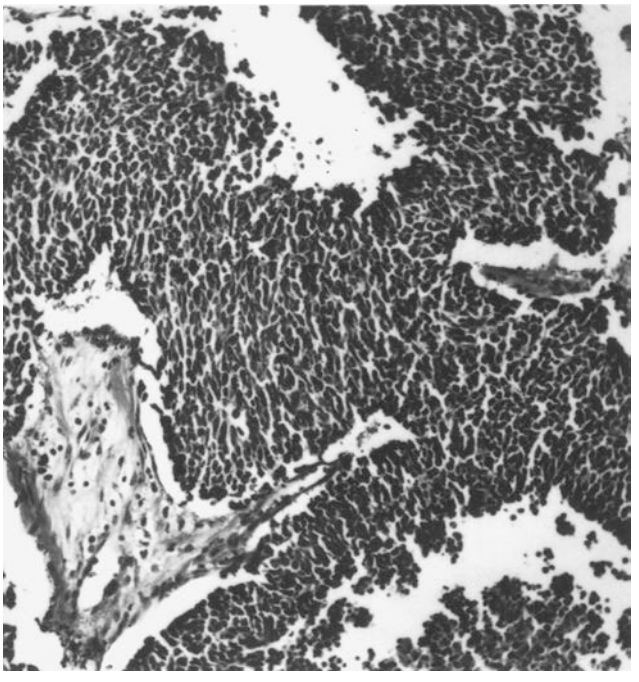

Figure 17.7 Metastatic carcinoma (lung), small cell (oat cell) type: Sheets of small cells resemble an undifferentiated retinoblastoma (×100).

the diagnosis, management, and prognosis of lung cancers. The following generalities are taken from their publication.

1. In 1989, a study of 30 lung cancer cell lines indicated that p53 was frequently mutated or inactivated in all major types of lung cancer (Takahashi et al., 1989).
2. The frequency of p53 mutations is highest in squamous cell carcinoma and lowest in adenocarcinomas among non-small cell lung cancer (NSCLC) surgical samples.
3. A study of patients with alterations in p53 by immunohistochemistry or molecular analysis has not been completed, and the effect on prognosis is still not definitely settled. However, most of the evidence indicates that alterations in p53 are associated with a poor prognosis in NSCLC patients.
4. The presence of p53 antibodies in a person without a diagnosis of cancer should prompt a search for a primary tumor.
5. Chemotherapy is the major modality of treatment of small cell lung cancer (SCLC) and plays a significant role in treatment of locally advanced NSCLC as well as palliative therapy of metastatic NSCLC.
6. SCLC usually responds dramatically to chemotherapy and radiotherapy but frequently recurs and is resistant to further treatment (Murren et al., 2001).
7. Although NSCLC tumors often respond to chemotherapy and radiation, the responses are usually not as dramatic as for SCLC (Ginsberg et al., 2001).

CARCINOMA OF THE PROSTATE GLAND

This carcinoma is third in frequency of metastasis to the orbit. Metastases occur in 70% to 90% of patients with prostatic cancer (Boldt and Nerad, 1988). The route of metastasis to the orbit is either through the lung or the prevertebral venous plexus.

Patients with orbital metastasis are older than patients with other types of metastatic carcinoma. The age range of our seven patients was 61 to 85 years of age with a mean of 68.8 years. This figure is closely akin to the mean age, 70.1 years, reported by Boldt and Nerad in a larger series of prostatic carcinomas. The mean age of our patients is a decade older than the mean age, 58.9 years, of our group of patients with breast carcinoma.

Prostatic carcinoma also differs, in some respects, from other metastatic carcinomas in its orbital presentation. In addition to the usual signs and symptoms of proptosis, impairment of ocular motility, and visual loss, the patient will frequently have weight loss, nocturia, and pain. The latter is caused by orbital bone metastasis. Two of our patients also had jaundice, a sign of widespread metastasis. The prostate specific antigen level also will be markedly elevated.

Prostatic carcinoma also has a tendency to metastasize to orbital bone more often than soft tissues. The lesion in bone may be osteolytic or osteoblastic in type, more often the latter. The osteoblastic type may simulate the imaging features of a meningioma, particularly when the greater wing of the sphenoid bone is affected (see Fig. 17.8).

Green et al., 1995, describe a case with bilateral orbital metastasis. Histopathologically, the tumor is an adenocarcinoma but may vary widely from a poorly differentiated to a well-differentiated neoplasm (see Fig. 17.9). The neoplasms have variable cellular patterns including cords, islands, cribriform arrangements of pseudoglandular or glandular patterns with or without intracytoplasmic vacuoles of mucin and some degree of desmoplasia. The tumor cells show nuclear enlargement, contour irregularity, hyperchromasia, and prominent nucleoli. Numerous mitoses may vary according to the degree of differentiation.

Raghavan (2003) includes a subset of eight pages on hormone therapy for prostate cancer. Raghavan has reviewed the literature and analyzed numerous group studies, which have searched for therapies adjuvant to the conventional radical prostatectomy and/or orchiectomy combined with radiotherapy, which might prolong the survival of patients with prostatic carcinoma.

Raghavan notes that the cure rate of early stage carcinoma by conventional local treatment (radical radiotherapy, radical prostatectomy) is <40%. However, 20% to 25% of new cases have advanced degree of carcinoma at the time of presentation. Orbital metastasis would be

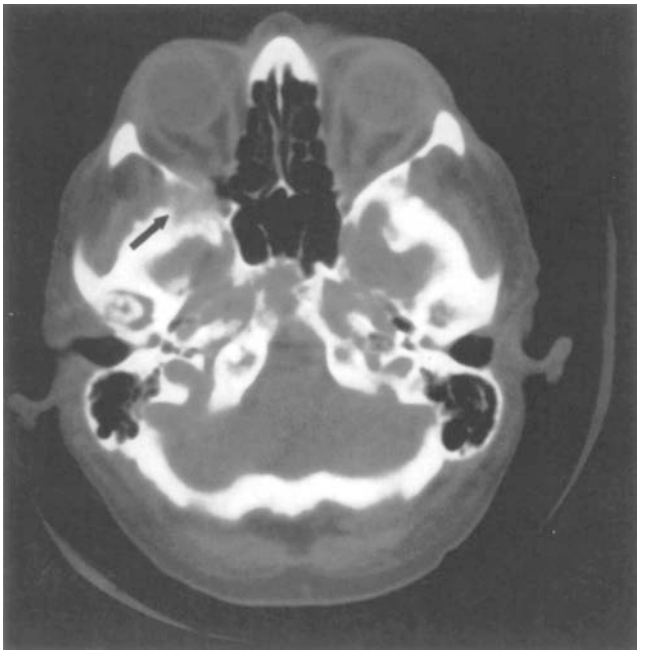

Figure 17.8 Metastatic orbital carcinoma from the prostate gland: Axial computed tomography scan shows an enhancing destructive lesion of the greater wing of the right sphenoid bone (*arrow*) that extends anteriorly into the orbit and posteriorly into the middle fossa of a 63-year-old man. There is slight proptosis of the right eye.

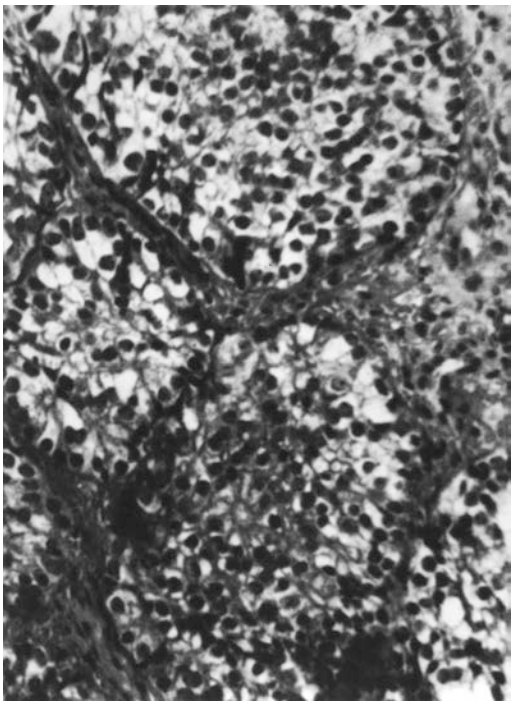

Figure 17.9 Metastatic carcinoma (prostate): Showing nests of well-differentiated cells (×400). (From Carriere VM, Karcioglu ZA, Apple DJ, et al. A case of prostate carcinoma with bilateral orbital metastases and the review of the literature. *Ophthalmology*. 1982;89(4):402–406, with permission.)

considered an advanced degree. Many other authors have noted that patients with advanced carcinoma are less responsive to therapy when compared to patients with early discovery of the neoplasms. This fact is attributed to the heterogeneity of the neoplasm. In brief, not all prostatic carcinomas are alike.

According to Raghavan, various authors, over the past 15 years, have demonstrated "coincidental" subpopulations of cells with classical adenocarcinomatous features intermingled with cells that exhibit neuroendocrine differentiation, features of small cell undifferentiated carcinoma, and even cells that actually represent transitional cell carcinoma. It, therefore, has seemed unlikely that any one procedure would control these disparate cell populations, at least in the setting of advanced disease. "The possible role of genetics in this confused puzzle is still to be resolved."

Therefore, most oncologists now direct combination therapy to patients with early stage disease. For patients with metastasis, therapy, at best is only palliative.

CARCINOMA OF THE KIDNEY (HYPERNEPHROMA)

This carcinoma is the most common neoplasm of the kidney in adults. It is interesting to observe the unpredictable course of this lesion when compared to the more predictable behavior of the preceding neoplasms in this chapter. The renal cell tumor is basically an adenocarcinoma.

In our 50-year series of consecutive orbital tumors, there are six men, age range 46 to 80 years with a mean of 61.5 years. Most authors have noted a male predominance. Parnes et al. (1993) state the neoplasm "typically" occurs in men between the ages of 30 and 60 years. Nevertheless, Clinton-Thomas and Robinson (1956) reported the tumor in a 10-year-old girl.

Some cases have an unusual twist in the interval of years between either the recognition or treatment of the primary tumor and the first metastasis. In the case of Kindermann et al. (1981), orbital metastasis did not occur until 15 years after nephrectomy. In the case of Mezer et al. (1997), this interval was 7 years. Metastatic lesions have occurred 10 to 20 years after removal of the primary tumor, Woody and Geeraets (1966). The most frequent sites of metastasis are lung, liver, and bone. Orbital metastasis is less frequent but, when and if it occurs it is an ominous sign. In cases where the orbit is the initial sign of metastatic disease, 25% to 30% of cases will have multiple metastases and widespread disease, the latter remaining asymptomatic. Metastases in three of our six patients were unusual in that both brain and orbit were involved simultaneously.

Contrary to a diffuse pattern of metastasis in most other carcinomas, the renal cell carcinoma is a circumscribed, solitary, soft tissue mass with or without bone involvement. If there is no bone destruction, the retro-orbital carcinoma may be relatively asymptomatic. However, if the lesion is also osteolytic, the patient will have pain.

The soft tissue type metastasis, on CT scan, will probably appear as a well-circumscribed, homogenous mass. The metastasis associated with bone destruction will appear infiltrative, with less homogeneity (see Fig. 17.10).

The neoplasm is a type of adenocarcinoma arising either from renal tubules or from islets of nephrogenic tissue that have persisted in the renal cortex. The tumor cells are large and round with a clear vacuolated cytoplasm (see Fig. 17.11).

The cells proliferate in sheets, cords, or tube-like structures, which are compartmentalized by delicate collagen septae. There are relatively few vessels. Nuclei are vesicular, round to oval, with pleomorphism and relatively frequent mitoses. A pseudocapsule may surround the solitary, solid metastatic tumor.

All six patients in the Mayo Clinic series died of tumor on an average of 51 months (range 28 to 97 months) from the diagnosis of the primary tumor and an average of 25 months (range 1 to 97 months) from the time of orbital metastasis. Only one of these patients had a circumscribed, soft tissue metastasis without bone involvement. This mass was removed intact but had no effect on survival. All other patients had cases of bone destruction. The soft tissue component of the metastasis was simply debulked.

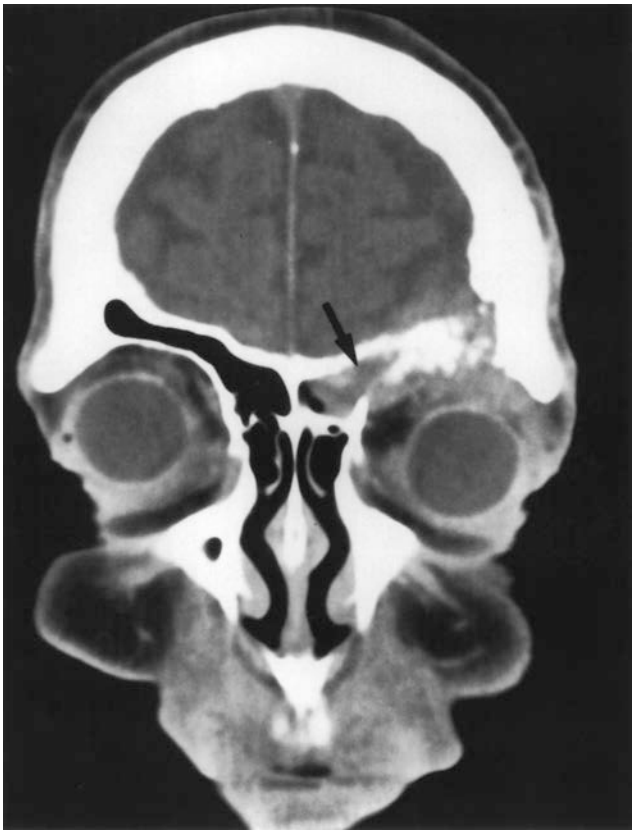

Figure 17.10 Metastatic carcinoma (renal cell): Coronal computed tomography scan shows soft tissue mass in the left superior orbit with extension into left frontal sinus (*arrow*) and irregular destruction of orbital roof.

We have found in the literature a remarkable description of a 50-year-old man (Bersani et al., 1994) whose management included many of the *unpredictable* features of this neoplasm noted in the prior paragraphs. A summary follows:

1. (1973) Patient had nephrectomy for renal cell carcinoma.
2. (1982) Lobectomy for lung metastasis.
3. (1984) Brain metastasis. Received radiotherapy.
4. (1986) Radiotherapy for mouth metastasis.
5. (1986) Lumpectomy for spine metastasis.
6. (1988) Patient presents with unilateral proptosis.
7. (1989) Brain metastasis. Received radiotherapy.
8. (1992) In remission. Patient gainfully employed, no activity restrictions.

In the 1980s, extensive use of systemic chemotherapy, in various protocols, evolved as an adjuvant therapy to conventional remedies, surgery, and radiation, with the hopes it would reduce recurrent rates of the carcinoma. However, a review of the publications on this treatment modality, including 2,120 patients treated with various protocols, indicated very poor results (Yagoda, 1989).

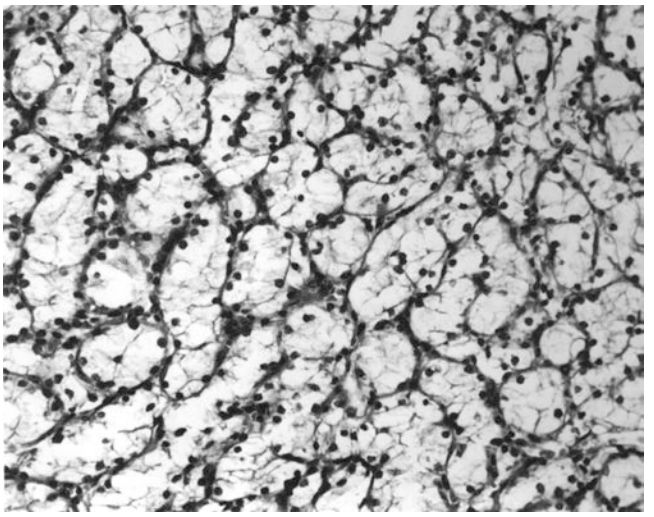

Figure 17.11 Metastatic carcinoma (renal cell): Clear-cell type of adenocarcinoma (×205).

Interest in adjuvant therapies continued into the 1990s utilizing the therapeutic potential of radio-labeled (Iodine-131), monoclonal antibody (G250), Interferon, cytokines, and gene therapy (Northway et al., 2001). At the time of this writing, 2003, the local administration of interleukin-2 (IL-2) has received the most attention for the therapy of the advanced renal cell carcinoma. The rationale for local administration is to expose tumor tissue and surrounding lymph nodes to therapeutic levels without the toxicity of systemic administration. The use of pulmonary IL-2 delivery to perform local cytokine therapy for pulmonary metastatic growth is being used in several cancer centers with encouraging results. Good tolerance has been confirmed. The drug is delivered through nebulizer (Huland et al., 2001).

CARCINOMA OF THE ALIMENTARY TRACT

The principal metastatic carcinoma of the alimentary tract is adenocarcinoma of the stomach and colon. In the first half of the twentieth century, adenocarcinoma of the stomach was the most common cause of cancer-related deaths in the first half of the century, but its incidence fell dramatically in the century's latter half. There has been no adequate explanation for this change. The decrease in gastric carcinoma has been offset or equalized by a more recent emergence of adenocarcinoma of the gastroesophageal juncture (Collins et al., 1999; Kelsen et al., 2002, and Lekse et al., 2003). Therefore, the overall incidence of these adenocarcinomas has remained relatively static over a long period of time. Actually, any discussion of the orbital consequences of these adenocarcinomas must be based on a negligible number of cases.

Orbital metastasis is predominantly to the extraocular muscles. Only one, several or all muscles may be affected. Metastasis may be unilateral or bilateral (Capone and Slamovits, 1990; Clerici et al., 2001). The metastasis may infiltrate the entire muscle bundle or, on exploratory orbitotomy, the ophthalmologist may find nodular clumps of neoplasia within the sheath of the muscle (Patrinely et al., 1989). Figure 17.12 illustrates a woman with bilateral metastases. All extraocular muscles were so infiltrated with metastases that the eyes were immobile.

Most of these adenocarcinomas are notorious for being relatively asymptomatic in their primary locus in the bowel. So much so that orbital metastasis may be the presenting feature of the neoplasm. Furthermore, the orbital metastasis is likely but one of occult metastases to other sites, particularly to the liver and celiac lymph nodes.

The five cases from our 50-year file of orbital tumors illustrates several of the above features. There were three women and two men, age range 59 to 69 (mean 64.8 years). In all five, the orbit was the presenting feature of the occult malignancy. The primary site of the adenocarcinoma was the sigmoid and stomach, each two cases, and the colon in the fifth case. All cases showed widespread metastases to other sites including both soft tissue components of the tumor and osteolytic bone destruction. A CT scan of one of the cases is depicted in Figure 17.13. The orbital mass is unhomogenous but not specific for this type of carcinoma.

Four of the patients were treated with radiotherapy alone or a combination of radiotherapy and chemotherapy but to no avail. These four patients died of tumor dissemination with an average of 46 months (range 6 to 96 months) from the time of discovery of the primary tumor and 23 months (range 1 to 59 months) from the time of orbital presentation. The delay in the discovery of the primary tumor is thought to be a factor in the tumor's poor prognosis. If the tumor is not discovered until the first recurrence or metastasis, it is likely the patient will have such an array of multiple sites of metastases, which defeats

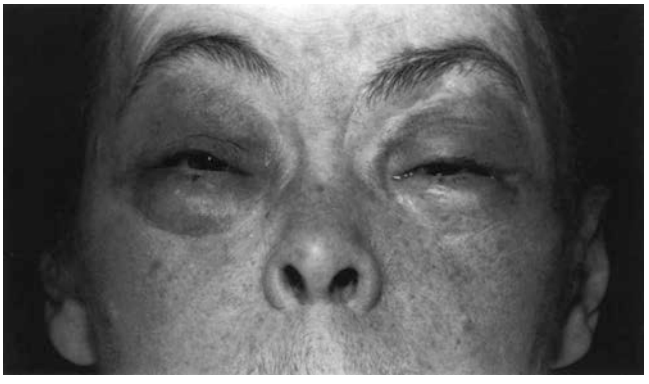

Figure 17.12 Metastatic carcinoma (stomach, scirrhous type): Initial signs of otherwise hidden carcinoma were bilateral enophthalmos, blepharoptosis, and ophthalmoplegia due to diffuse infiltration of both orbits; no diplopia because eyes were so immobile.

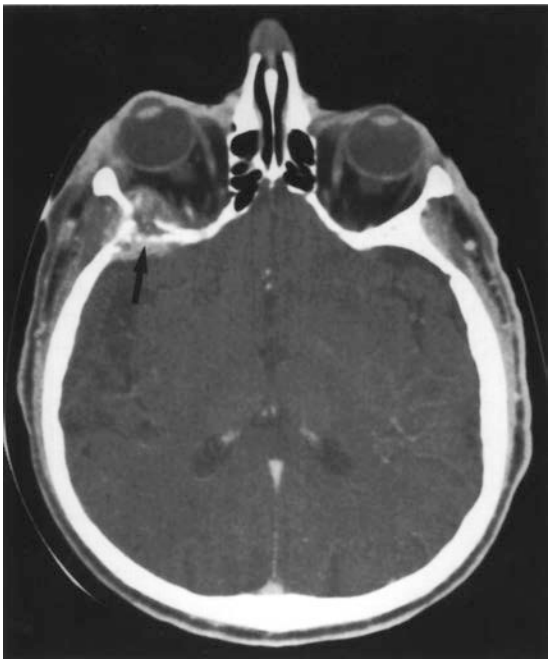

Figure 17.13 Metastatic carcinoma (colon): Axial computed tomography scan shows an enhancing mass in the right posterolateral orbit (*arrow*) that extends intracranially and causes destruction of the adjacent sphenoid bone and proptosis of the right eye.

therapy. There is little the physician can offer such patients other than palliative management.

These neoplasms arise from glandular structures lining the alimentary tract. Some may show differentiation into acinar structures and papillary patterns with or without mucus-secreting components. In others, spheroidal cell forms predominate in which the cell nucleus is pushed to one side (signet ring type). Metastases are usually associated with the elevation of carcinoembryonic enzyme levels (see Fig. 17.14).

In the 1990s, if a patient presented with an abdominal complaint that, on exploratory surgery, proved to be a gastric carcinoma and a thorough examination of the patient did not reveal apparent metastasis, the conventional treatment for the primary tumor was at least a partial gastrectomy with en bloc dissection of nearby lymph nodes. However, if postresection examination showed node positivity, overall survival was, at best, 30% (Macdonald et al., 1995) (Hermans et al., 1993). When the latter patients (node positive) died, it was speculated their tumor recurrence arose from unresected microscopic metastases present at the time of surgical resection. Such patients were considered likely candidates for postresection adjuvant chemotherapy. However, the adjuvant cytotoxic chemotherapy, alone, was of no proven value.

Subsequently, the United States Intergroup Study proposed that the use of a combination of 5FU (fluorinated pyrimidine, a radiation sensitizer) with leucovorin plus radiation, would be useful therapy in a controlled study

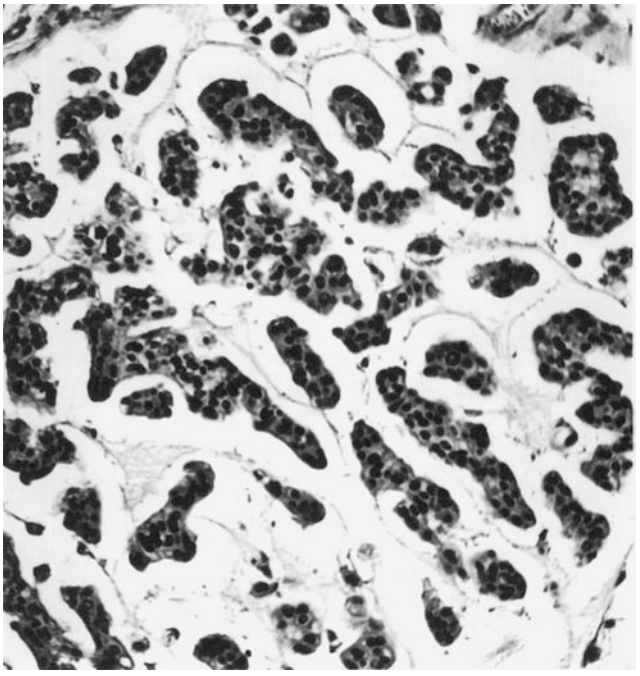

Figure 17.14 Metastatic carcinoma (stomach): Papillary and mucus-producing adenocarcinoma (×120).

(Kelsen et al., 2002). The study enrolled 556 patients in 7 years of accrual (Macdonald et al., 2000). The disease-free and overall survival rates have improved by the use of this combined modality when compared to the 205 patients in the observation arm of the study.

CARCINOMA OF THE THYROID GLAND

Metastasis to the orbit from the thyroid gland is less frequent than the preceding carcinomas in this chapter. In the Mayo Series of orbital tumors, there are 104 metastatic adenocarcinomas from multiple sources. Four of these ($4 \div 104 = 3.8\%$) were from the thyroid gland. There is general agreement that women are affected more than men, mostly in the fifth and six decades with a mean of 55 to 58 years of age. soft tissue metastasis is more common to the lung and brain and bone metastasis to the femur, pelvis, and sternum than orbital metastasis.

Datum is also skewed by the tendency of ophthalmologists to report cases wherein the orbital metastasis is the presenting manifestation of a thyroid cancer rather than reporting a routine case of metastasis following treatment of a primary carcinoma in the thyroid gland. Cases reported in the update literature wherein the presenting feature of an occult thyroid gland carcinoma was the orbit are Moisseiev et al. (1988); Friedman et al. (1990); Bernstein-Lipschitz et al. (1990), and Daumerie et al. (2000). The signs and symptoms of orbital metastasis varies with the site of lodgment. If the adenocarcinoma is confined to the retrobulbar space, there will be painless proptosis to a small degree. If the metastasis lodges against an orbital wall, there will be a greater degree of proptosis associated with bone destruction. The metastasis may lodge in an extraocular muscle or muscles producing varying degrees of immobility of the eye.

Once the metastatic orbital lesion has been surgically identified and studied histologically, the finding of the tumor's primary source may be likened to a Sherlock Holmes vignette. A case in point is the patient reported by Oberman and colleagues (1969). This 57-year-old woman had undergone two craniotomies in a period of several years for what was thought to be, histologically, a chromophobe adenoma. At the time of the second operation, this tumor had invaded the orbit. This unusual behavior of a chromophobe adenoma led to further sleuthing and retrospective discovery of a well-differentiated medullary carcinoma in the tissue of a thyroid gland that had been resected 3 years previously.

The case of Hornblass et al. (1987) was similar. Discovery of a metastatic lesion led to a second review of thyroid tissue that had been resected 6 years prior to orbitotomy. This revealed a papillary thyroid carcinoma that was initially overlooked.

Figures 17.15A and 17.15B illustrate the magnetic resonance imaging features of a 42-year-old woman with a metastatic Hurthle cell carcinoma.

With respect to their course, some thyroid neoplasms are as indolent and slow in growth as are prostatic carcinomas; others disseminate as rapidly as do small cell carcinomas of the lung. In the course of metastasis, the thyroid carcinoma attacks bone, but the effect is osteolytic rather than osteoblastic. Almost all clinicians who have encountered these tumors in the orbit have commented on their marked vascularity, and pulsation of the eye has been noted at the time of orbital presentation in a few cases.

Adenocarcinomas of the thyroid gland are a complex lot in regard to their histologic types, their problems in the histologic separation of some benign subtypes from clinically well-differentiated carcinomas, and their unpredictable course. Histopathologically, these neoplasms are divided into papillary, follicular, oxyphil (Hurthle cell), medullary, epidermoid (squamous cell), and undifferentiated types. Two or more of these histologic types may occur in the same tumor. All of these histologic types, singly or in combination, are capable of metastasis. Approximately 80% of thyroid malignancies originate from the follicular cell (thyroglobulin and thyroxine secretions) line, 5% from para-follicular cells (calcitonin secreting), and 15% from miscellaneous cell origin. The metastatic follicular tumor (see Fig. 17.16) consists of differentiated, closely packed follicles, which are filled with an eosinophilic colloid-like material. A few mitoses may be seen. Adenocarcinomas from sites other than the thyroid gland do not secrete thyroglobulin. Therefore, positive staining for thyroglobulin

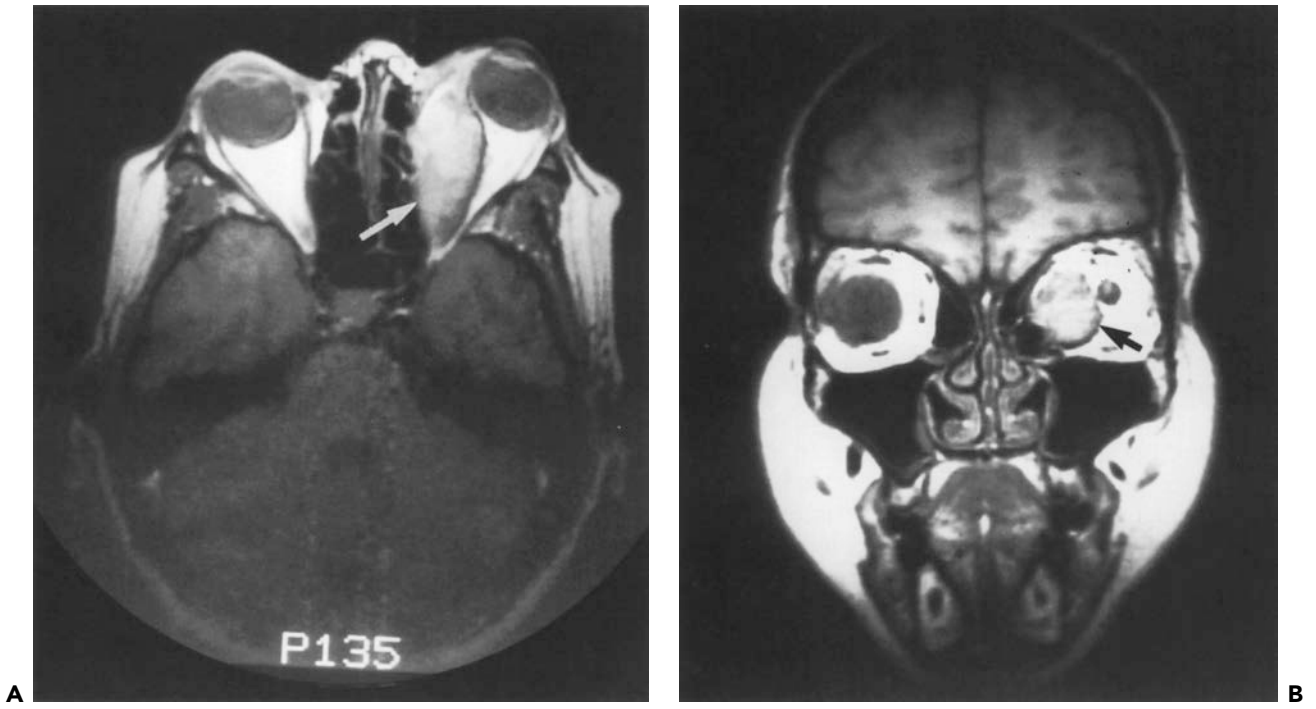

Figure 17.15 Metastatic orbital carcinoma from the thyroid gland: **(A)** Axial and **(B)** coronal magnetic resonance T_1-weighted sequences of large mass filling the medial portion of the left orbit (*arrows*) with lateral displacement of left optic nerve and marked distortion of the left eye in a 42-year-old woman.

is pathognomic for thyroid derived carcinoma. However, some undifferentiated types and neoplasms that have undergone a great deal of fibrosis may have lost their secretory function.

At the present time, Clark, 2000, says, "There is considerable clinical and laboratory evidence supporting the use of L-thyroxine to suppress serum thyroid stimulating hormone levels in patients with thyroid cancer. This therapy is effective and palliative for most but not all patients. Further studies are necessary to determine which tumors will respond and to what level the thyroid stimulating hormone needs to be suppressed. Until such information is available, it seems advisable to give enough thyroid hormone to suppress thyroid stimulating hormone for virtually all patients who have had thyroid cancer."

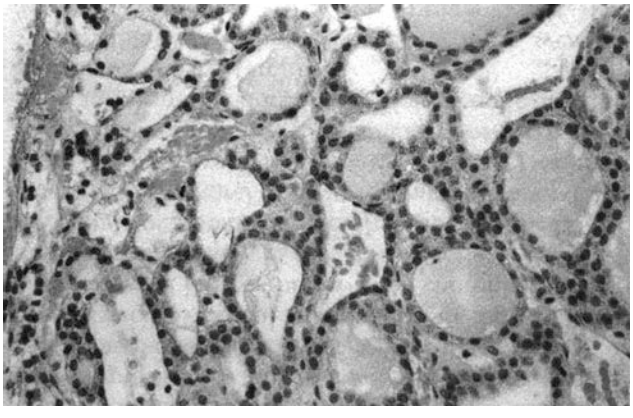

Figure 17.16 Histopathology: A metastatic orbital, follicular thyroid carcinoma (hematoxylin and eosin, ×50). The colloid-like material will stain positive for thyroglobulin (From: Daumerie C, De Potter P, Godfraind C, et al. Orbital metastasis as primary manifestation of thyroid carcinoma. *Thyroid*. 2000;10(2):190; Figure 2.)

CARCINOID

Carcinoid, meaning *carcinoma-like*, is a neoplasm of the enterochromaffin secreting cells of the gastrointestinal tract from the stomach to the rectum, and similar cells located in the bronchus, biliary systems, pancreas, ovaries, and thyroid (Godwin, 1975). Carcinoids are not adenocarcinomas but belong to the neuroendocrine group of tumors. The precursor of the enterochromaffin cells is the embryonic primitive endoderm (Rush et al., 1980).

The carcinoid at its primary site is considered benign but if it metastasizes, it is considered malignant. If, in its course, the neoplasm enlarges to a size of 2 cm in diameter or greater, metastasis occurs 80% of the time (Moertel et al., 1961). The most common site of metastasis is the liver. Mesentery, brain, and bone are less often involved. The carcinoid of the gastrointestinal tract also tends to metastasize to the orbit whereas those tumors from the

bronchus tend to metastasize to the uveal tract of the eye (Shetlar et al., 1990).

All authors writing on this subject state that metastasis to the orbit is uncommon. Many of these authors cite the actual number of cases of orbital metastasis reported in the literature up to the time of their publication. Whatever number is stated, it is probably incorrect because the author or authors have not fully accessed the literature on the subject. I would estimate at this time (December 2003), that there are at least a total of 35 cases. Orbital metastasis is more common in women, female to male ratio is about 2:1, and the age of onset of the orbital metastasis is about 60 years of age. The unilateral-bilateral ratio of orbital occurrence is about 3:1.

Orbital metastasis may become manifest before the primary tumor is discovered. Several cases of this type are reported in the literature. Nida et al. (1992) reported an orbital metastasis in a 62-year-old man that was followed by a 9-year interval before the primary carcinoid was found in the lung. El-Toukhy et al. (1996) noted an interval of 6 years between the orbital metastasis and the discovery of the primary carcinoid in the ileum. Another instance of a long latency period was the 71-year-old woman with slowly progressive proptosis of the right eye of 11 years' duration reported by Zimmerman et al. (1983). The affected eye of this patient had been blind for 4 years at the time of presentation. Histologically, the orbital mass was a carcinoid, and the orbit was exenterated. However, this patient did not show any other evidence of metastatic disease. This case was followed 15 years without local recurrence or metastasis of tumor and without any evidence of another primary lesion (Shields, 1989). In view of the patient's advanced age, it is possible the primary carcinoid underwent some degree of involution following surgical removal of the sole metastasis. A reverse latency from the time of removal and the orbital metastasis, also has been reported. In most of these cases, during the latency interval, metastasis to the liver already has occurred but has been asymptomatic. The orbital metastasis in these cases is but an indicator of widespread, forthcoming fatal disease.

A metastatic deposit to the orbit may lodge either in the retrobulbar soft tissue or in one or several of the extraocular muscles. In the retrobulbar soft tissue, the metastasis behaves like a soft tissue, space-occupying tumor producing variable degrees of proptosis or displacement of the eye. There is no pain. If the mass locates in the superior quadrants of the orbit, there will be some drooping of the upper eyelid. If the metastasis lodges in an extraocular muscle, there will be some degree of extraocular muscle dysfunction causing diplopia and some discomfort on ocular rotation.

If metastasis to the liver also is present, the patient may have ophthalmic manifestations of the *carcinoid syndrome* which include conjunctival injection, intravascular sludging, and perivascular pigment clumping. Systemic manifestations of the syndrome are a marked rise in blood pressure, when the tumor is palpated or surgically manipulated; and episodic flushing, asthma, diarrhea, and edema of the lower extremities. Release of serotonin and other vaso-amines is responsible for this syndrome. Urinalysis may or may not show an elevated level of 5-hydroxyindole acetic acid. A positive value is more prone to occur with liver metastasis.

A metastasis into the soft tissue quadrant of the orbit will appear as a well-delineated mass, usually with homogenous consistency, with or without well-demarcated borders on CT scan. Well-demarcated tumors tend to have some rim enhancement, whereas an "infiltrative" tumor has a fuzzy outline (see Fig. 17.17). Metastases to extraocular muscles tend to be infiltrative. With magnetic resonance imaging, the T_1 signal is isotense but is of decreased signal intensity on T_2-weighted images. Hanson et al. (1998) state that carcinoid tumors have an affinity for uptake of iodine-131 meta-iodobenzylguanidine (MIBG). An abnormal uptake of this agent by an orbital mass is indicative of an orbital carcinoid.

Grossly, these tumors are firm and yellowish or gray-white (Rodrigues and Shields, 1978). On fixation in formaldehyde, cytoplasmic granules may reduce certain silver or chrome salts demonstrating the argentaffin or chromaffin features. Carcinoid tumors of gastrointestinal origin are usually both argentaffin and argyrophilic positive, whereas bronchial carcinoids are argyrophilic positive but argentaffin negative.

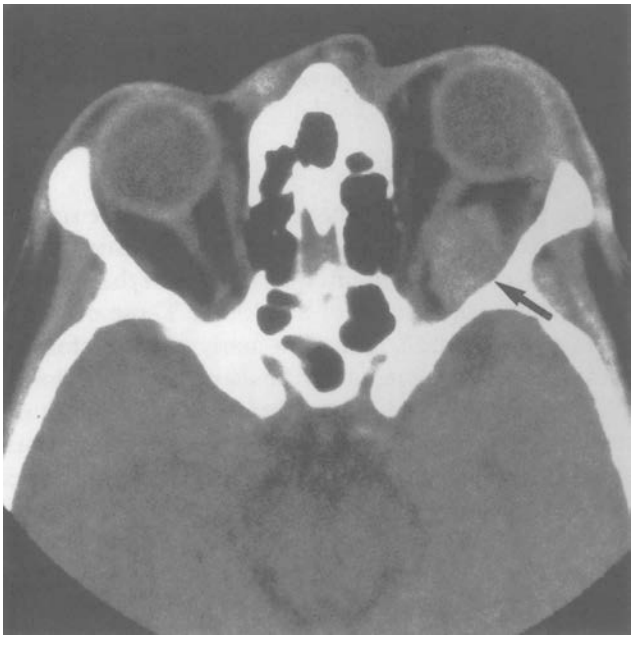

Figure 17.17 Metastatic carcinoid: Axial computed tomography scan shows a homogenous delineated mass (*arrow*) with a slightly fuzzy border in the posterolateral left orbit in a 51-year-old woman. On surgical exploration, the mass was unencapsulated. Note the slight bowing of the optic nerve.

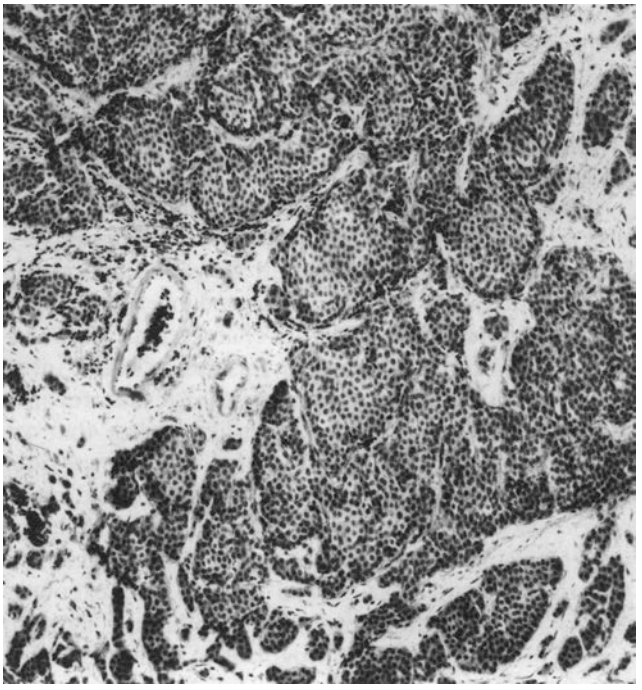

Figure 17.18 Metastatic carcinoid: Well-defined nests of carcinoid cells infiltrate fibrous connective tissue of orbit (×160).

Histologically, the small cells with round or oval hyperchromatic nuclei may be arranged in one or a mixture of several patterns. In the usual pattern, the cells are arranged in solid nests with well-defined connective tissue septae (see Fig. 17.18), or the cells may be arranged in interanastomosing cords and strands. A third pattern is a rosette-like configuration. At a higher magnification, both light and dark staining cells are evident. In many of the nest-like cellular patterns, the light cells with clear cytoplasm tend to be located centrally, whereas the dark cells are located along the periphery of the lobule. Other specimens may show only a haphazard admixture of light and dark cells. In a study of 15 carcinoid tumors from the orbit, choroid, and iris, Riddle et al. (1982) found an average of 3.6 mitotic figures in 50 high-power fields.

It has long been appreciated that carcinoid does not show the usual histologic criteria of malignancy (anaplasia and frequency of mitoses) (Godwin, 1975). Instead, malignancy is determined by incidence of local invasion and extent of the primary tumor. These factors tend to correlate with the size of the lesion.

Positive immunochemical reactivity to chromogranin-A, cytokeratin, neuron-specific enolase, and synaptophysin in the absence of reactivity for S-100 and HM 8–45 is most consistent with the diagnosis of metastatic carcinoid.

If orbital metastasis occurs in a patient whose primary carcinoid was removed at some prior time, imaging studies should search for the number, size, and location of other possible metastases. CT scan can now be augmented by the use of the radiopharmaceutical MIBG, described in the preceding text, which will provide a more precise search for small tumor deposits in some obscure spot that would not be revealed by the CT scan. If the orbital mass is circumscribed and located in the retrobulbar space, and imaging scans do not reveal another metastatic deposit, except a small patch or two of lymph nodes in some other surgically accessible spaces, the orbital mass, as well as any lymph nodes should be completely excised. Such a patient likely will have some interval of survival although the length of survival cannot be predicated. However, it is the best chance for an ultimate cure. One patient with orbital metastasis from a carcinoid tumor of the ileum survived 9 years after orbital exenteration and 11 years after initial bowel resection (Font and Ferry, 1976). Orbital exenteration is an alternative surgical option for a patient with metastatis to one or more extraocular muscles.

If the imaging modes of a patient with orbital metastasis show asymptomatic metastases to the liver, lung, bone, or abdominal lymph nodes, heroic orbital surgery is futile. These patients have end-stage disease.

This dictum also applies to patients wherein orbital metastasis is the presenting sign of a carcinoid tumor which has remained asymptomatic in reference to its primary course and metastasis to the liver. Such patients can be given palliative radiotherapy. The use of radiotherapy as a definitive treatment is controversial. For palliative effect, Khaw et al. (2001) recommended a dose in the region of 30 Gy. All four patients in the 50-year Mayo collection with metastatic orbital neoplasms had widespread metastases when first seen. All died from carcinoid spread.

OTHER METASTATIC CARCINOMAS

The site of origin of carcinomas—usually adenocarcinomas—metastatic to orbit other than listed in this chapter include adrenal gland (Bartley et al., 2001; Burch, 1932), bile duct (Bullock and Straughen, 1981), urinary bladder (Fynn-Thompson et al., 2003; Hugkulstone et al, 1994; Prats et al., 1989; Scott and Williams, 1995; Krauss et al., 1982), gallbladder (Misra et al., 2002), liver (Font et al., 1998; Schwab et al., 1994; Phanthumchinda and Hemachuda, 1992), ovary (Bomanji et al., 1990), parotid gland (Saxena et al., 1975), pancreas (Geetha et al., 1998; Gotwald et al., 2000; Sniderman, 1942; Van Buskirk, 1959), salivary glands (Thomas et al., 1995), testes (Ballinger and Wesley, 1984; Leyson, 1974; Mann, 1967; Rush et al., 1981; Taylor et al., 1978), thymus (Stockl et al., 1997), urachus (Giordano, 1995), and cervix (Lee et al., 1997). We have had little or no personal experience with most of these carcinomas, and the literature is very sparse. We do not believe we can write an objective view of any in this list. However, we will append what literature we have collected on each neoplasm over a 50-year period, which may be helpful to a physician who reports a case and will need some reference to start a search of the literature.

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Meningioma

18

If the reader were to think of just one tumor type that would cross multiple specialty lines it would probably be the meningioma. The meningioma is a very important tumor in the fields of ophthalmology, neuro-ophthalmology, neurosurgery, and head and neck surgery because of its frequency, its destructive effect on vision, the difficulties associated with its surgical eradication, its persistent course, and its sometimes fatal termination.

A major event in the study of this tumor, since the third edition of this text was published, has been the availability of neuroimaging in all major hospital/medical centers for the demonstration of this tumor. This has made possible the visualization of the soft-tissue component of the tumor that was previously unseen by standard orbital radiography. This provided earlier diagnosis of meningioma when compared to imaging methods used before. Imaging of the tumor has been further refined by the use of magnetic resonance and the subsequent clinical use of the contrast agent gadoliniumdiethylene triamine pentacetic acid. The latter further increased the diagnostic yield. Surgeons kept pace with these advances in diagnosis by providing more extensive surgical exposures and using microsurgical techniques for the removal of the tumor, particularly those meningiomas along the skull base. More recently steroid receptors have been identified on the meningioma cell that may have implications for hormone therapy of these tumors. Finally, the use of the Gamma Knife (stereotactic radiosurgery) offers another therapeutic option for the management of selected meningiomas.

As has been the practice in the previous editions of this text, we are chiefly concerned with meningiomas that by reason of proptosis, imaging characteristics, or the findings uncovered at the time of surgery were known to have encroached upon the orbital cavity. This includes those tumors that seem to arise within the orbit (*primary type*) and those that extend into the orbit from an intracranial source (*secondary type*). The primary group may be subdivided into those tumors arising within *the sheath of the intraorbital portion of the optic nerve* and those arising elsewhere in the orbit, particularly along the *orbital face of the greater wing of the sphenoid bone*. In the latter, the position of the meningioma is almost exclusively intraorbital. The secondary tumors with orbital encroachment usually arise from *the sphenoid ridge, the basofrontal region*, the area around *the sella*, or *extracranial sites* such as the paranasal sinuses. In general, the source of any given meningioma can be judged by the tumor's principal blood supply. In cases where the meningioma arises along a cranio-orbital junction, such as the optic canal or superior orbital fissure, the tumor is tabulated in the "secondary" group.

INCIDENCE

The importance of meningioma in orbital oncology is underlined by the 178 cases with orbital involvement in our 50-year survey (Table 3.3). They constitute 9.9% of our total of 1,795 orbital tumors. Meningioma is the fourth most common primary orbital tumor and the third most common secondary orbital tumor (Table 3.3). According to the classification noted in the preceding text, 64 (36.0%) are primary in the orbit and 114 (64.0%) are the secondary type. Of the 64 of the primary type, 30 (47%) are of optic nerve sheath origin. The remaining of the primary type arise from the orbital surface of the sphenoid bone and encroach on the intraorbital space by a combination of hyperostosis of affected bone and expansion of soft-tissue tumor.

In bygone years, orbital meningioma was almost always considered a disease of adults. Younger patients who also presented with monocular visual loss followed by unilateral proptosis were assumed to have an optic nerve glioma, based on age selectivity of the two tumors. Over time an increasing number of cases of orbital meningioma have been recorded in children. When Walsh (1970) first reported a series of seven pediatric optic nerve sheath meningiomas, he commented that the tumors were "aggressive." Karp et al. (1974), reflecting the Armed Forces of Pathology experience with 10 patients, believed these tumors were highly invasive but not malignant. Wright et al. (1989), commented that four of the six children studied already had intracranial extension at the time of surgical excision. The patients described and the period of this article predate high-resolution neuroimaging, and subtle degrees of intracranial extension were not detected

prior to surgery but the point remains that most had intracranial extension. The case of Cibis et al. (1985) is of particular interest. This was a 13-year-old girl with intraocular extension of an optic nerve sheath meningioma who had had visual symptoms since 2 years of age. Initially, the patient was assumed to have an optic nerve glioma. This patient also had neurofibromatosis type-2 (NF-2). The Mayo Clinic series included five patients (two girls, three boys) who were 18 years or less of age (range 5.8 to 18 years). In our patients, the histopathology was benign but described as invasive. A recurring theme amongst all the reports is the frequency of NF-2. Of Walsh's 7 patients, at least 2 had NF-2, whereas 2 of Karp's 10 patients, 1 of Wright's 6 patients, and 3 of the 5 patients from Mayo had NF-2. One of the Mayo patients is shown in Figure 18.1. Some of the data in the older literature concerning childhood meningioma might be challenged, because meningeal hyperplasia secondary to an underlying optic nerve glioma was sometimes erroneously diagnosed as meningioma. Despite this disclaimer, it is apparent that orbital meningioma can arise in children and should be considered in the differential diagnosis of the more common optic nerve glioma. Also, the presence of an optic nerve sheath meningioma in a child should call to mind the possibility of an underlying NF-2.

Secondary orbital meningiomas, specifically the sphenoid wing meningioma, can also occur in the pediatric population. We have seen four patients, all boys with this meningioma. The age range was 5.5 to 15.6 years. All were of meningothelial type and one invaded the bone and the others invaded orbital fat. One patient had neurofibromatosis type-1 (NF-1) and another had NF-2. Right lower lid swelling was noticed in a 5-year-old boy in 1985. Biopsy through anterior orbitotomy revealed meningothelial meningioma. A more definitive craniotomy was done 2 months later. From 1986 through 1991 he had three recurrences, all treated by craniotomy. When we examined him in 1992, he had no light perception in the right eye, had a frozen, enophthalmic globe, and a palpable mass along the lateral inferior orbital rim. He was treated with another craniotomy, an exenteration, a rectus abdominus free flap and 5,000 cGy external beam radiation therapy. To date (2004) he has not had a recurrence.

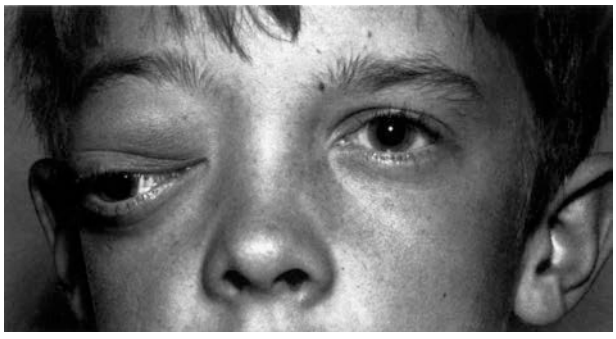

Figure 18.1 Recurrent meningioma: A 13-year-old boy with proptosis of right eye commencing at age 10 years. First craniotomy for removal of intraorbital meningioma was at age 12. Two additional craniotomies and one orbitotomy were performed over the next 2 years. At age 21 recurrent orbital tumor and proptosis of right eye gave the patient a gargoyled appearance. However, visual acuity in the affected eye was still 20/40. No further follow-up until age 35 when patient was seen elsewhere. Clinical diagnosis at this time was bilateral hearing loss secondary to acoustic neurinomas. The visual acuity was not measured. Computed tomography scan showed probable meningioma of right orbit, lesser wing of sphenoid bone, and frontal convexity, left cavernous sinus, and anterior falx.

The prevalence of meningiomas in women is well known. In the Mayo Clinic series, 72% (129/178) are women, a female-to-male ratio approximating 3:1. Five of the 33 men are clustered in the first and second age decades.

The tumor's prevalence in women suggests some hormonal association. Indeed, several recent studies document *the presence of receptors for estrogen, progesterone, and somatostatin in meningioma cells* (Halper et al., 1989; Cahill et al., 1984; Tilzer et al., 1982; Huisman et al., 1991; Arena et al., 2004). Specific receptors for progesterone were found in 76% of 70 meningiomas studied by Lesch and Fahlbusch (1986). This is consistent with the observed progression of meningiomas during pregnancy and breast-feeding. Such cases associated with pregnancy are frequently reported in the literature. Wan et al. (1990) reviewed this subject and reported three patients whose symptoms were exacerbated during pregnancy. Estrogen receptors are found less consistently and tend to be present in men.

Schrell et al. (1990) have a different view. They examined 50 human cerebral meningiomas and concluded that estrogenic and progestrogenic targets are of negligible significance. They inferred that female sex steroids are not primarily involved in the proliferative rate of these tumors and are of limited value as markers for adjuvant medical therapy.

The most recent work with RU-486 (mifepristone) is currently unpublished data (Gruenberg et al.). Their data on 18 patients suggests that there is no clinical effect in 33%, slows down progression in another 33%, and leads to a slight decrease in tumor volume with visual field improvement in the remaining 33% (Sadun A., *unpublished data, personal communication*, 2004).

The discrepancy amongst the reports of both estrogen and progesterone receptors may be related to differences in laboratory techniques. Nevertheless, meningiomas can be clearly conceived as targets of hormonal action on their receptor types, but the hormonal effects have still to be defined in detail (Schrell, 1992). Schrell also concluded that meningioma is, indeed, a tumor of endocrinologic interest but is not an endocrine tumor.

Somatostatin receptors have been detected in virtually all human meningiomas (Koper et al., 1992; Huisman et al., 1991). The effects of hormonal manipulation have been controversial and currently there are no therapeutic applications related to this receptor (Cavalla and Schiffer, 2001; Arena et al., 2004).

At one time the age distribution of orbital meningiomas was thought to be bimodal, with one age peak in the first two decades and the other peak in the 40 to 50 age range (Karp et al., 1974; Eggers et al., 1976). With the advent of computed tomography (CT) scan and magnetic resonance imaging (MRI) it is now apparent that *orbital meningiomas may occur at any age*. Table 3.4 shows a broad age distribution at the time of surgical diagnosis of both primary and secondary meningiomas. Eighty-seven percent (154/178) of cases were concentrated in the fourth through seventh decade. The age range of the 64 primary meningiomas was 6 months to 83 years with a median age of 40 years. The age range of the 114 secondary meningiomas was 4 months to 75 years with a median age of 52 years. The slightly greater prevalence of primary meningiomas in the younger age range is consistent with other surveys of meningioma in the literature.

In the total 178 patients in our study core, the laterality ratio is 78:56, right to left orbit. Bilateral orbital meningiomas were present in three patients at the time of presentation. In several additional patients the disease became bilateral during the course of their long survival.

NF was recorded in three patients with primary orbital meningiomas (NF-2) and two patients with secondary orbital meningiomas (one NF-1 and one NF-2).

In the 8-year period (1980–1987) since the third edition of this text, 505 intracranial meningiomas without orbital invasion were surgically verified at the Mayo Clinic. In this same interval of time, 41 meningiomas with orbital involvement were identified. The ratio of intracranial meningiomas to orbital meningiomas in the 8-year interval, therefore, is 505:41 (roughly 12:1). The grand total of all meningiomas is the sum of these two groups or 546 cases. The incidence of primary orbital meningiomas (nine cases) relative to total meningiomas then becomes 1.6%. The incidence of orbital meningiomas (both primary and secondary types) relative to all meningiomas is 7.5%.

We have not attempted a specific comparison of incidence data of the present Mayo Clinic series, which consists of consecutive cases with pathologic verification, with other surveys of meningioma in the literature. Most other series of meningiomas differ from ours in size, the data in some is based on a combined sample of proved and assumed cases of meningioma, others include only selected clinical cases, and in still others the data is based on cases selected from a file of pathologic specimens. Such comparisons, which were attempted in the previous two editions, give inconsistent conclusions, not unlike a comparison of oranges and apples.

CLINICAL FEATURES

The presenting symptoms and signs associated with meningiomas, either originating in or encroaching on the orbit, are numerous and diverse; they include the gamut of *proptosis*, a *decrease of visual acuity* of 20/40 or less, *pallor of the optic disk*, detection or awareness of *a visual field defect*, *passive edema of the eyelid*, *disturbance of ocular motility*, *papilledema*, *headaches or orbital pain*, *a visible or palpable mass*, *opticociliary* (*chorioretinal*) *shunt vessels*, *paralytic blepharoptosis*, and *seizures*, roughly in the order of their frequency. Other symptoms or signs, such as chemosis and afferent pupillary defects, are secondary to the size of the orbital mass or the degree of visual loss, respectively. Most patients usually have a minimum of three of the above signs or symptoms at the time of presentation. However, none of these signs or symptoms is specific for meningioma. The degree or frequency of any of these clinical features depends on the duration of the meningioma and its location.

Although unilateral proptosis is the most frequent presenting sign, it is neither present nor is it always the initial clinical feature in all cases. Some degree of visual impairment often preceded proptosis in the anamnesis of the patient. The amount of proptosis was greater in primary orbital meningiomas than with meningiomas secondarily encroaching on the orbit.

Impairment of visual acuity (20/40 or less) paralleled proptosis in its diverse degree. Some patients noted only a visual blur of one eye that could only be defined by demonstrating a depression of the visual field by perimetry. A few patients described visual obscurations that were gaze evoked, indicating a large mass in the orbital apex that was compressing the optic nerve. Of more serious note were patients whose vision in the affected eye was reduced to light perception, light projection, or no light perception at the time of presentation. The prevalence of such a serious visual loss was slightly greater in the secondary orbital meningiomas when compared to primary orbital meningiomas.

Pallor of the optic disk of the affected eye, the fourth most common clinical feature, was equally prevalent in the primary and secondary orbital meningiomas. Its presence at the time of the patient's presentation indicates that the meningioma either had been present longer or was greater in extent than the patient suspected.

Visual field loss is another clinical feature that varies widely in extent. From an initial, overall depression, the visual field may progress through a dense arcuate defect, a central scotoma associated with an irregular peripheral contraction, a bizarre irregular altitudinal defect, to a complete loss of central field associated with a few peripheral islands of remaining vision. Such a visual field loss in the affected eye, when associated with a hyperostosis of the sphenoid bone, was a positive indication for an exploratory surgical procedure in the years before the present neuroradiologic imaging modes.

Boggy edema of the eyelids, usually more marked in the lower eyelid, is a peculiar manifestation of some long-standing meningiomas and occurs more often with this lesion than any other orbital tumor of similar duration

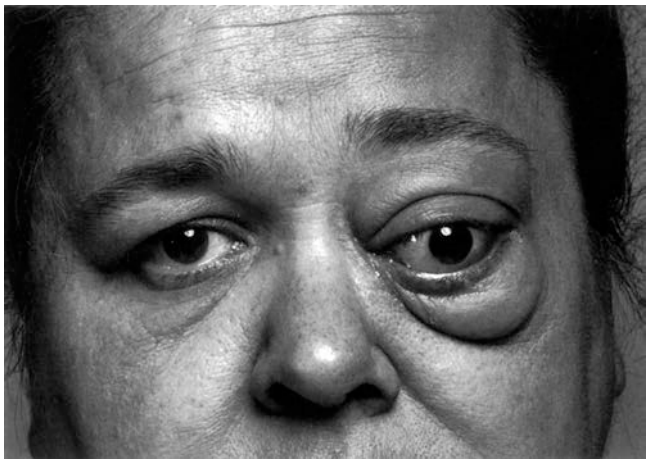

Figure 18.2 Intraorbital meningioma: A 49-year-old woman with marked edema of left eyelid and proptosis of approximately 6 years' duration. Vision of left eye reduced to counting fingers.

or size. The affected lid is pale and soft, and the swelling resembles the puffiness of the eyelids seen with myxedema in women of the same age-group (see Fig. 18.2). It occurs in both the primary and secondary types of orbital meningioma. It is puzzling why edema of the eyelids occurs in some orbital meningiomas but not in other meningiomas of equal size or location. The cause of the edema is not known, although it is commonly assumed to be secondary to a stasis of venous flow through the exit channels of the orbit. In some cases, intravascular clumps of meningioma may be responsible for the edema (see Fig. 18.3).

A derangement of motility of the affected eye may be secondary to the mechanical effect of a bulky orbital mass, to an infiltration of the extraocular muscle by a meningioma that has escaped from the dural sheath of the intraorbital optic nerve, or to an entrapment of the III, IV, or VI cranial nerves by a tumor invading the superior orbital fissure or the area of the cavernous sinus. As a rule the subjective or objective importance of the motility disturbance is overshadowed by other clinical manifestations of meningioma at the time of presentation.

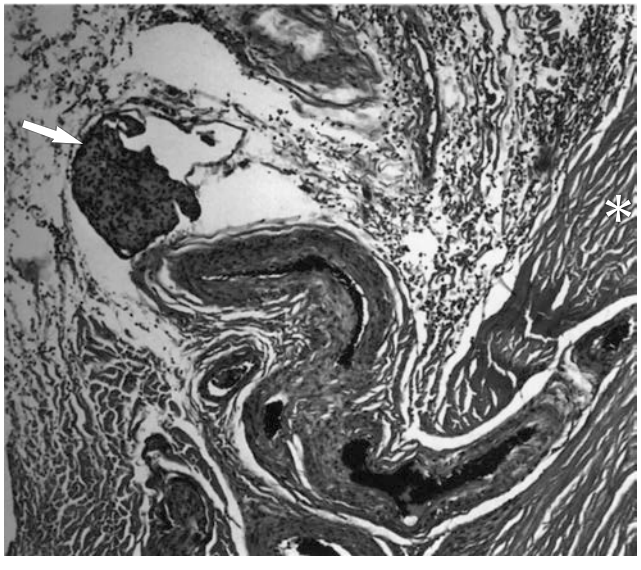

Figure 18.3 Meningioma: Clump of tumor within vessel wall (*arrow*). *Asterisk* designates sclera (×100).

The presence of papilledema at the time of the patient's presentation is of interest, because it occurs much more frequently in primary orbital meningioma when compared to a percent prevalency in the secondary type of meningioma.

Fortunately, orbital pain or nagging headaches are an infrequent manifestation of meningioma at the time of presentation. However, when present, it is of major concern to the patient and is the major reason for the patient's seeking consultation. This clinical manifestation does not seem to have any specific localizing significance.

The meningiomas with which we are concerned are, with few exceptions, residents of the posterior orbit. Seldom will the mass be palpable in the anterior portion of the orbit unless the tumor has reached considerable size. However, in a minority of cases the mass may be present in the temporal fossa. Here the mass is smooth, not tender, and may give the area of the temple a "fullness" or domed appearance. These masses are the result of a slow lateral expansion of a meningioma of the greater wing of the sphenoid bone. A mass in the temporal fossa is very suggestive of a meningioma because there is no other orbital tumor that so frequently presents in this manner in an adult.

A type of presentation not mentioned in the preceding discussion is the intraocular meningioma. This tumor represents the less common, anterior extension of a meningioma of the sheath of the intraorbital optic nerve. This route of extension is very infrequent, and when it occurs, the case frequently is reported in the literature. Such was the situation in one case of the Mayo Clinic series that was reported by Henderson and Campbell (1977).

Briefly, this case was a 70-year-old woman whose sightless, anesthetic, proptosed eye was enucleated in 1976. The retrobulbar space was filled with a poorly circumscribed cellular meningothelial meningioma. Apart from a very pale optic disk, the posterior pole of the enucleated eye appeared normal. However, microscopy revealed focal meningiomatous invasion of the sclera and a tumor nodule within the choroid. Seventeen additional cases of intraglobal extension of a meningioma were also referenced in the publication. Earlier we cited a subsequent case of intraocular extension of a meningioma in a 13-year-old girl (Cibis et al., 1985).

Bilaterality was noted in five female patients with secondary meningiomas who first presented at Mayo Clinic for evaluation. Their ages were 18, 62, 65, 68, and 76 years. All patients had bilateral pallor of the optic disks. All had experienced slowly progressive visual loss. Several of the elderly patients had experienced visual loss over a period of several

decades, but the cause of the visual loss was not detected by standard roentgenography. Diagnosis finally was made by the CT scan of the 1970s. The intracranial origins of the tumor were usually the surface of the lesser wing of the sphenoid bone. One tumor originated from the falx, and one tumor arose from the greater wing of the sphenoid bone.

A few additional remarks are appropriate concerning the clinical aspects of those patients with an exacerbation of meningioma during *pregnancy*. Initially, in the first few months of pregnancy, such patients will note some unilateral blurring of vision associated with headache. A diagnosis of unilateral retrobulbar optic neuritis might be considered at this stage. However, this innocuous onset quickly gives way to a rapid decline in vision in the affected eye with pallor of the optic disk. This leads to a discovery by neuroimaging of an enhancing mass somewhere along the course of the optic nerve, with or without hyperostosis of the bone, which is suggestive of meningioma. Usually, an effort is made to manage these patients conservatively until the pregnancy is successfully completed. Intervention, either surgical or with radiation therapy is deferred unless the loss of vision is very rapid and severe.

In some patients the symptoms may improve and the meningioma stabilizes after delivery. Surgical resection of the presumed meningioma may then be postponed. In such cases the meningioma may recur with increased severity during a subsequent pregnancy.

In terms of counseling a patient with a meningioma regarding pregnancy, management issues are not clear in the literature. Wan et al. (1990) did mention that management of pregnant patients with meningioma should be tailored to the individual, and we would agree with this. In general, although we do not discourage pregnancy or breast-feeding, patients should be apprised of the potential risks.

At this point, we will digress and consider several selected cases from the Mayo Clinic series that either have some interesting clinical features or illustrate the diverse nature of meningiomas.

The first case illustrates the tribulation of a woman with relentless, progressive meningioma. The patient was 31 years of age when a diagnosis of meningioma of the left sphenoid bone was made. The first partial excision of the tumor was performed at age 35, followed by a second partial resection at age 41. Severe progressive proptosis developed postoperatively necessitating a left tarsorrhaphy at age 45 to protect the bulging eye. By age 48, the left eye was blind and the tumor involved the entire left face and orbit below the eyebrow (see Fig. 18.4A). Surgical removal of the highly vascular tumor included an orbital exenteration. By age 58, recurrent meningioma involved the left orbit, left paranasal sinus, middle and anterior intracranial fossae, and parasellar region (see Fig. 18.4B). A fourth major resection was performed including a left orbitectomy. In the next 13 months the intracranial portion of the tumor nearly doubled in size, and a palliative surgical procedure was performed to relieve the patient's pain. Encroachment on the right optic nerve soon followed, and the patient was blind in the remaining eye at the time of her tumor-related death at age 62, after 31 years of pain and suffering.

A similar case was that of a 47-year-old man with an intracranial, orbital, and facial meningioma who died from intracranial progression of his tumor. This case differed slightly from the patient discussed earlier in that only three major craniofacial surgical procedures were performed before death at age 60, 13 years after onset. He also was totally blind before death.

Less commonly the course of a meningioma is predominantly *extracranial.* Such was the case of a 36-year-old

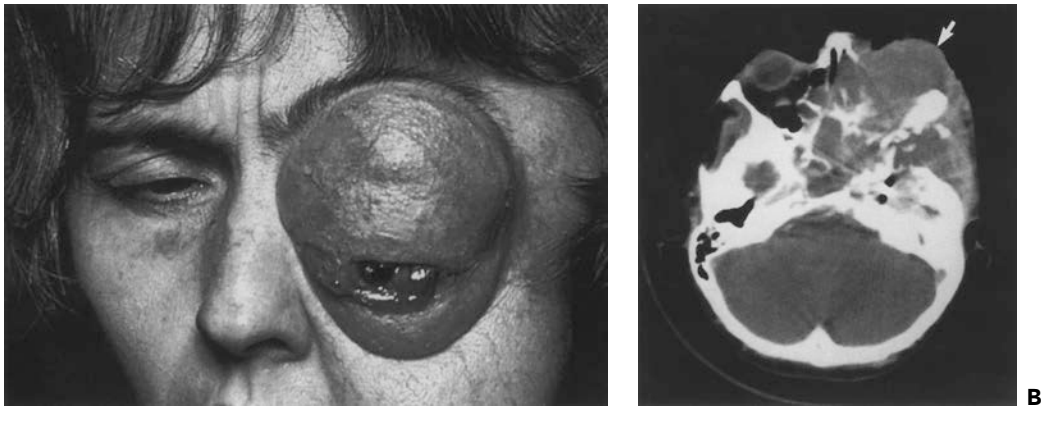

Figure 18.4 **A:** Recurrent meningioma. A 48-year-old woman who had had two previous resections of a sphenoid wing meningioma 12 and 6 years prior to this photo. A left lateral tarsorrhaphy had been performed at the age of 45 to protect the bulging, displaced eye. The left eye was blind. The tumor involves the face below the left eyebrow, and there is also a bulging mass in the left temple. The left orbit was exenterated in the course of a third surgical resection of the tumor. **B:** Axial computed tomography scan 10 years later shows recurrent tumor (*arrow*) involving left orbit, paranasal sinuses, middle, and anterior intracranial fossae, temporalis fossa, and parasellar region.

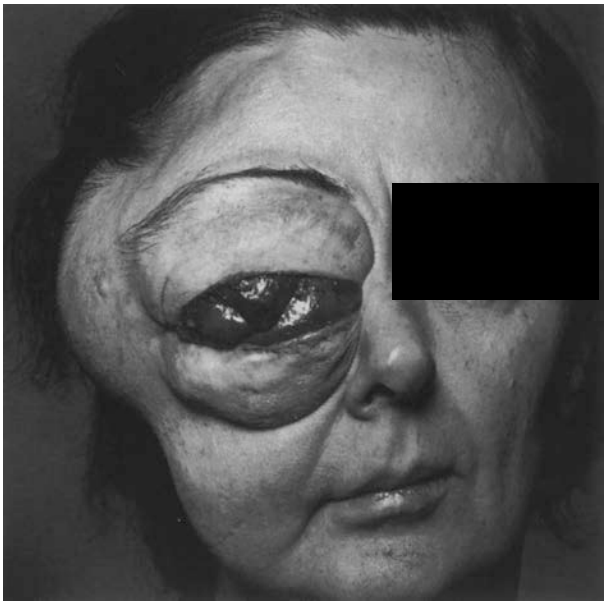

Figure 18.5 Meningioma: A 51-year-old lady with a marked craniofacial deformity from a recurrent tumor originating on the orbital surface of the greater wing of the sphenoid bone. The patient had very little pain. Two prior surgical resections of the tumor in its 15-year evolution.

woman who underwent a surgical resection of a meningioma with orbital encroachment originating from the orbital surface of the sphenoid bone. A second craniotomy was performed a year later for a spheno-orbital recurrence. Continued proptosis of the right eye became so extreme that the right eye was enucleated at age 39. By the age of 51, hyperostosis of the greater wing of the sphenoid bone had extended into the orbit, frontal bone, maxilla, and palate causing a marked craniofacial deformity (see Fig. 18.5). All the teeth in the right upper jaw were loose. The entire tumor was removed by an external surgical approach except for some residual tumor around the right superior orbital fissure. The patient was then lost to follow-up until she was 64 years of age. At this time her home physician reported spread of the hyperostosis into the right middle ear.

Other examples of extracranial spread are those meningiomas that present as a sinonasal mass. This was the situation in a 36-year-old woman whose initial complaint was a swelling of the left face and a sinus-like headache. The swelling suggested a malignancy of the left maxillary sinus. Surgical exploration revealed a meningioma arising from the sphenoid bone. Most of the intracranial portion of the tumor was removed. Within a year the meningioma had spread to the subtemporal fossa, nasal cavity, nasopharynx, posterior orbit, and ethmoid sinus, all on the left side. Another surgical resection was performed. By age 42, the recurrent meningioma had extended into the middle intracranial fossa, orbit, infratemporal and parapharyngeal spaces, lateral portion of the cavernous sinus, and completely filled the maxillary sinus, again on the left side. Nevertheless, the visual acuity was still 20/20 right eye and 20/30 left eye. The tumor was considered inoperable.

The most unusual case in the Mayo Clinic series was a woman who underwent a resection of a parasagittal

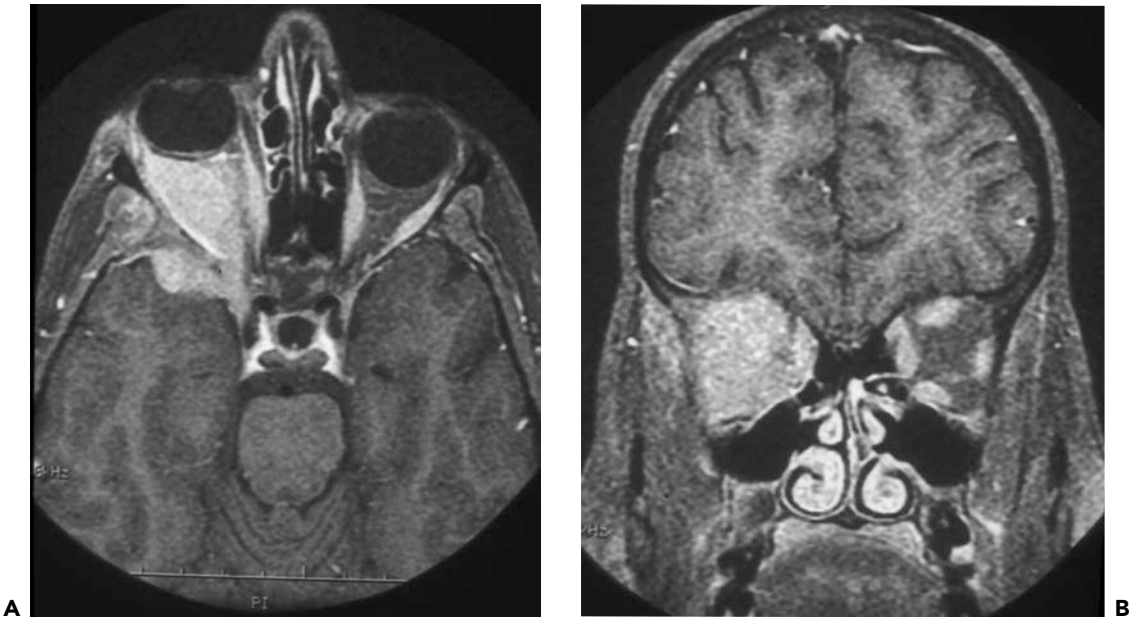

Figure 18.6 A radiation-induced meningioma. Radiation-induced sphenoid wing meningioma. Axial **(A)** and coronal **(B)** magnetic resonance imaging following gadolinium contrast demonstrates infiltrating mass filling the right orbit and displacing the optic nerve medially. The mass has an intracranial component in the cavernous sinus and middle cranial fossa.

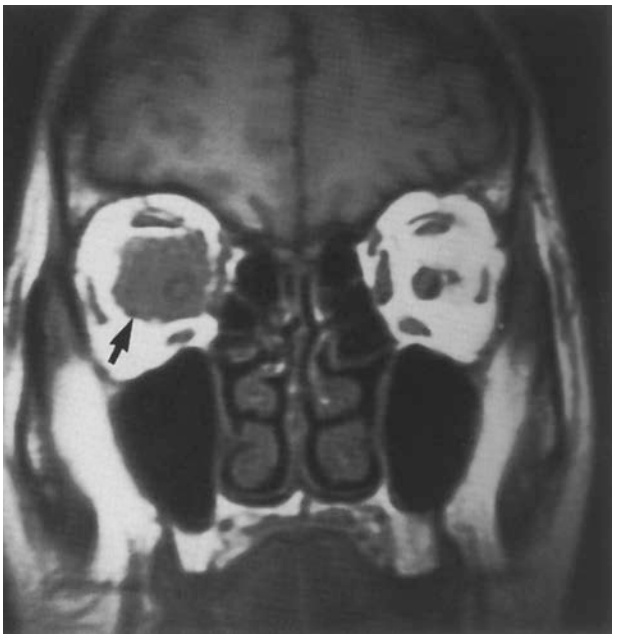

Figure 18.7 Optic nerve sheath meningioma. Meningioma: Coronal magnetic resonance T_1-weighted scan shows a large mass (*arrow*) completely surrounding the right intraorbital nerve in a 55-year-old woman. The nerve itself is not enlarged. There was no intracranial extension. Vision in the proptosed (8 mm) right eye was 20/30.

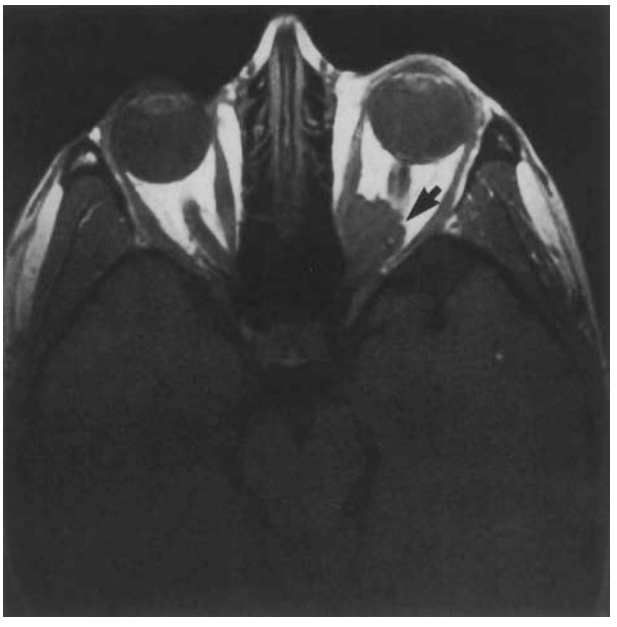

Figure 18.8 Meningioma: Axial magnetic resonance imaging T_1-weighted scan shows mass (*arrow*) with an irregular border in the apex of the left orbit with some extension into the optic canal in a 33-year-old woman. The mass displaces the optic nerve downward and laterally. Vision in the left eye was 20/20. The mass was adherent to the optic nerve when subtotally removed through a frontal craniotomy. The vision was still 20/20 in the left eye 11 months postoperatively.

meningioma at age 31. Over the next 13 years she underwent four additional craniotomies for recurrent meningioma with supplementary radiotherapy in the last year of her life. With each successive surgical procedure, the meningioma, histopathologically, became more cellular with frequent mitoses. At autopsy, at age 44, metastasis was found in the second lumbar vertebra.

A 21-year-old man was seen in 1998 with an atypical, radiation-induced meningioma. Since he was seen after the

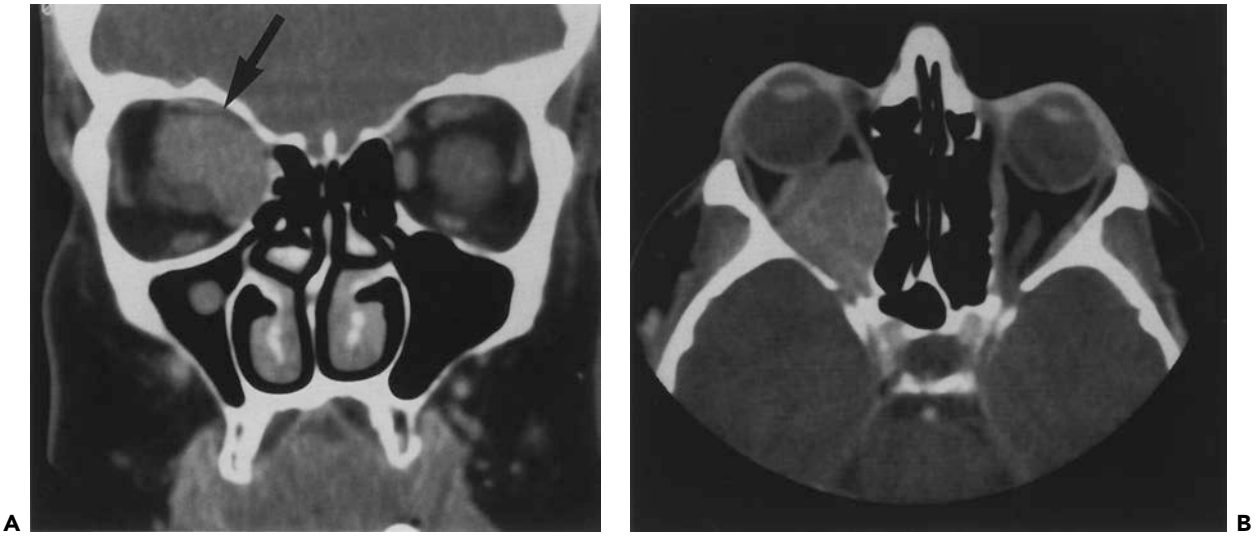

Figure 18.9 Meningioma: Axial and coronal scans show a large, homogeneous, enhancing mass in **(A)** the superomedial (*arrow*) and **(B)** apical portions of the right orbit with some expansion of the orbital roof and medial wall in a 49-year-old woman with ''fuzzy'' vision of 6 months' duration. A preoperative diagnosis of cavernous hemangioma was considered. At orbitotomy, the well-vascularized, purple, circumscribed tumor simulated a cavernous hemangioma.

defined tumor series interval, he is not included in the series itself but his case is instructive and will be detailed here. Acute lymphocytic leukemia was diagnosed at age two. He was treated with chemotherapy and radiotherapy of 2,000 cGy to the brain. Twenty months later an additional 3,000 cGy were given to the brain for a central nervous system relapse and he remained disease free. In 1998, he developed right proptosis over 2 weeks. Neuroimaging showed a mass along the sphenoid bone (see Fig. 18.6A and 18.6B). Incisional biopsy demonstrated a meningothelial meningioma. One month later a gross total removal was accomplished through craniotomy/orbitotomy. Approximately 8 months later a large middle cranial fossa recurrence with extension into the sphenoid sinus was treated with another debulking craniotomy. Histopathologic evaluation now showed necrosis and atypia. An additional 5,000 cGy external beam radiation therapy was given and the tumor mass continued to grow. Palliative Gamma Knife radiosurgery (33 cGy) was given to the middle fossa tumor. The tumor continued to grow and low dose interferon was given for its antiangiogenesis properties. He died of disease progression 2 months later, which was 3 years after initial manifestation. This case is included in a series of eight radiation-induced orbital meningiomas seen at Mayo Clinic (Jew et al., 2001). These eight patients had a mean age of 42 years (range, 21 to 70 years), and a mean latency interval from radiation to detection of meningioma of 26 years (range, 3 to 54 years). Five of the tumors recurred at a mean interval of 3 years (range, 9 months to 9 years) and three of the patients had atypical histology.

IMAGING ASPECTS

In the past decade, CT scan and MRI have become the mainstay in the preoperative investigation and the posttreatment observation of patients with suspected meningioma. In this time interval technical advances and improvements have occurred every few years that have brought the imaging of meningioma to a high state of diagnostic accuracy. These advances include better surface-coils, use of reformatted imaging, shortening of imaging time, reduction in chemical shift artifact, contrast enhancement, fat-suppression techniques, higher strength magnets, and machines capable of increasingly higher resolution scanning.

At the time of writing this text, MRI is the favored mode for the study of intraorbital optic nerve sheath meningiomas and nonoptic meningiomas with orbital encroachment. The forte of MRI is the delineation of the intracanalicular portion of the optic nerve and the chiasmal extension or intracranial spread of meningiomas. MRI also delineates whether the enlarged optic nerve sheath complex is from an enlarged optic nerve itself or an expanded optic nerve sheath with a preserved optic nerve within it. CT scan provides a good evaluation of intraorbital anatomy and shows well the contrast between the normal soft-tissue of the orbit and the enhancing features of both soft-tissue meningioma and hyperostotic bone. Intralesional calcium is also seen well with CT scan. MRI improves the study of the intracanalicular and intracranial portions of the optic nerve by eliminating bony artifact. When combined with gadolinium contrast enhancement and chemical shift fat-suppression techniques, MRI delineates the hyperintense meningioma well against the isointense brain on T_1-weighted sequences. This is of great value when considering the possible intracranial extension of an orbital meningioma. In delineating the configuration of these intraorbital meningiomas, both axial and coronal views are recommended. We now feel that MRI is the imaging technique of choice for any optic nerve lesion. MRI also shows the soft-tissue meningeal component to better advantage than CT scan.

Most of the positive features and a few of the pitfalls of the imaging of orbital meningiomas are shown in Figures 18.7 through 18.11. These facets of the imaging of meningiomas are reviewed in the recent publications of Alper and Sherman (1989), Azar-Kia et al. (1987), Hendrix et al. (1990), Rothfus et al. (1984), Tien et al. (1991), and Zimmerman et al. (1990). More recently, Saeed et al. (2003) reported a series of 88 patients with optic nerve sheath meningiomas. Neuroimaging existed for 74 of these patients. Tubular expansion of the optic nerve was the most common morphologic feature seen in 46 out of 74

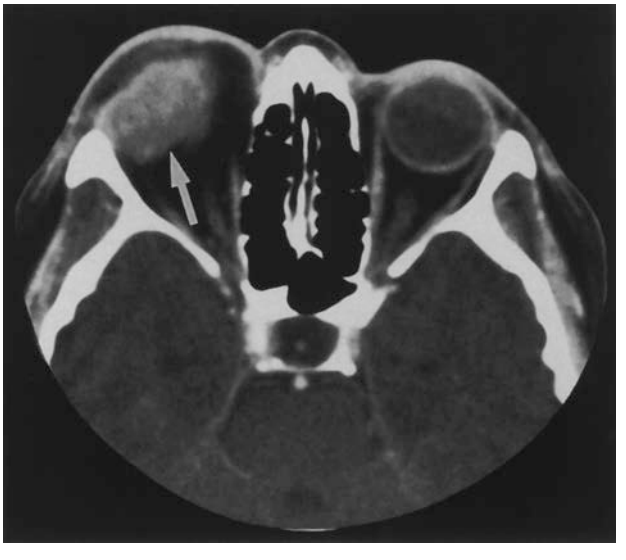

Figure 18.10 Meningioma: Axial computed tomography scan shows an enhancing mass (*arrow*) with irregular densities (calcium) in the right superolateral orbit that displaces the right eye inferiorly and medially in a 65-year-old woman. The presenting clinical features were those of a lacrimal gland tumor. On orbitotomy the mass was localized to the peripheral orbital space and its point of origin was the orbital roof. Bone invasion also was present but was not radiographically evident. Calcium deposition is usually a late development in the course of meningioma.

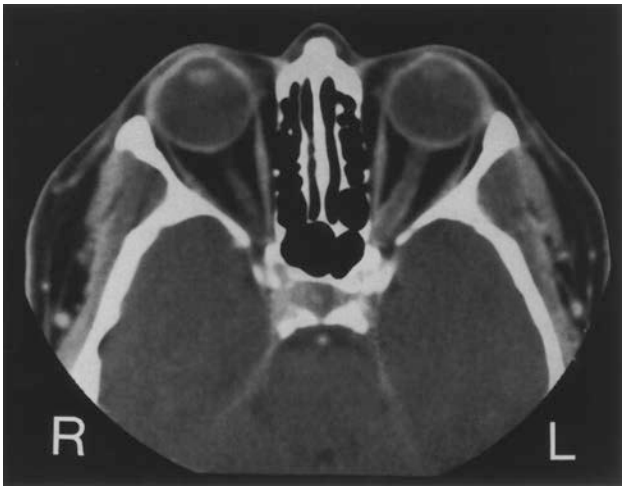

Figure 18.11 Suspected meningioma: Axial computed tomography scan shows thickening of left orbital optic nerve from mid portion to optic foramen with linear (tram-track) enhancement of its sheath surrounding the linear low-density image of the nerve in a 50-year-old woman. Vision was 20/20 in the left eye (compare with Figure 19.5). (Courtesy of GS Forbes, MD, Rochester, MN.)

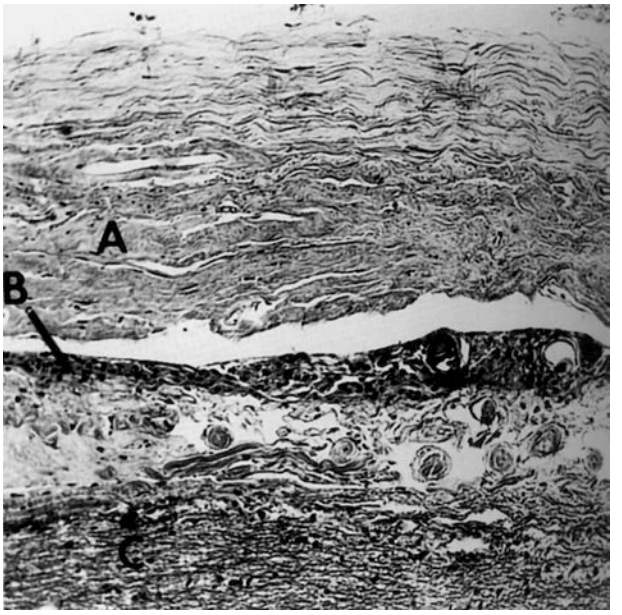

Figure 18.12 Meningioma: Longitudinal section through normal optic nerve and sheath illustrating clumping of arachnoid cells into a ''cap.'' Dura, **(A)** arachnoid cluster with psammoma bodies, **(B)** optic nerve, widened subdural space is an artifact **(C)** (×90). (From Craig WM, Gogela U. Intraorbital meningiomas: A clinicopathologic study. *Am J Ophthalmol*. 1949;32:1663–1680. Copyright by the Ophthalmic Publishing Company.)

(62%), optic nerve calcification was noted in 23 out of 74 (31%) and intracranial extension was present in 21 out of 74 (28%) of their patients. Intracanalicular meningiomas still provide diagnostic troubles. A delay in diagnosis is common and a high index of suspicion is still required, even with high-resolution MRI with gadolinium contrast material (Jackson et al., 2003)

No longer is catheter *angiography* as necessary in the diagnosis of meningioma when compared to the years before the use of CT scan and MRI. Still, in very large or extensive meningiomas, it plays an important role in the preoperative assessment of the source and extent of the tumor's blood supply if preoperative embolization is a consideration. Also in cases of tumor invasion into the cavernous sinus, angiography shows the relationship of the meningioma to the internal carotid artery.

PATHOLOGY

The meninges, from which the meningioma arises, vary in origin according to the level of the central neural axis. The primary meninges arise from condensation of primitive mesenchyme that surrounds the neural tube. Elements from the neural crest also may be incorporated. The leptomeninges, which consist of arachnoid and pia mater, are closely linked within the optic nerve sheath and the arachnoid, the source of the meningioma, is loosely attached to the dura. Those tumors that are primary arise from the arachnoid cells (see Fig. 18.12) that cover the optic nerve or from ectopic nests of cells within the orbital tissues. Secondary meningiomas arise from the cells of the arachnoid granulations associated with the major venous sinuses of the cranium. Some meningiomas may arise from pial cells or fibroblasts of the dura that lie within the orbital tissues. However, the tumor is predominantly of the meningotheliomatous type, suggesting that most arise from arachnoid cells. Fibrous trabeculae and blood vessels are not usually as prominent as in their intracranial counterparts.

Initially, primary orbital meningiomas tend to compress the optic nerve, but ultimately the dura is invaded and the tumor extends into the orbital contents (see Figs. 18.13 and 18.14). Intraocular extension of the primary meningioma is rare, and this may occur through the penetrating ciliary vessels or directly through the sclera (Henderson and Campbell, 1977; Cibis et al., 1985).

The tumors are usually firm in consistency, smooth in contour, and are either yellow-tan or gray–white. Tumors with a profuse blood supply have a purplish hue, not unlike an orbital cavernous hemangioma. On cut section the tumor has a gristly composition. Tumors of long duration may show areas of calcification interspersed with areas of cyst-like degeneration. The en plaque meningioma along the orbital surface of the sphenoid bone is associated with gross hyperostosis of the affected bone (see Fig. 18.15). The bony thickening is associated with clumps of tumor cells within the medullary spaces. On occasion localized thickening of bone, particularly if it is the inner table, is unassociated with tumor invasion and may be due to a tendency of the dura to become detached from the skull.

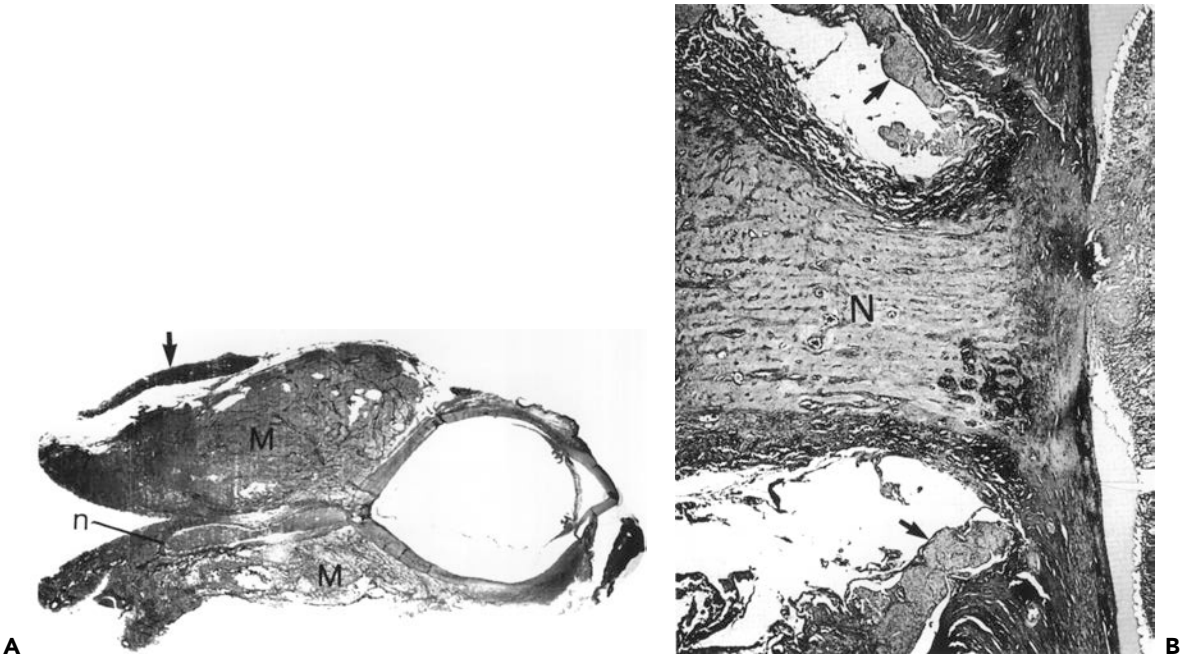

Figure 18.13 **A:** Meningioma: Surgical specimen showing intraorbital optic nerve (n) encased by meningioma (M) that is encroaching on extraocular muscle (*arrow*) (×4). **B:** Another case showing primary meningioma (*arrows*) surrounding optic nerve (N) (×40).

The World Health Organization (WHO) has grouped meningiomas into two broad categories: Meningiomas with low risk of recurrence and aggressive growth and meningiomas with greater likelihood of recurrence and/or aggressive behavior (Louis et al., 2000). The former group has nine different subtypes but the more common types encountered in the orbit are meningothelial (syncitil), transitional, and fibroblastic. The meningotheliomatous type is the one most commonly found within the orbit. The polygonal cells are arranged in sheets and have a stringy

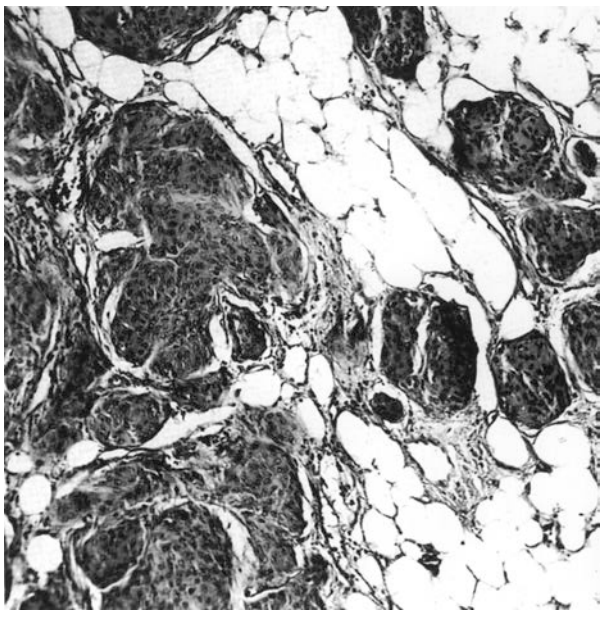

Figure 18.14 Meningioma: The intraorbital tumor has breached its dural covering and infiltrates orbital fat (×90).

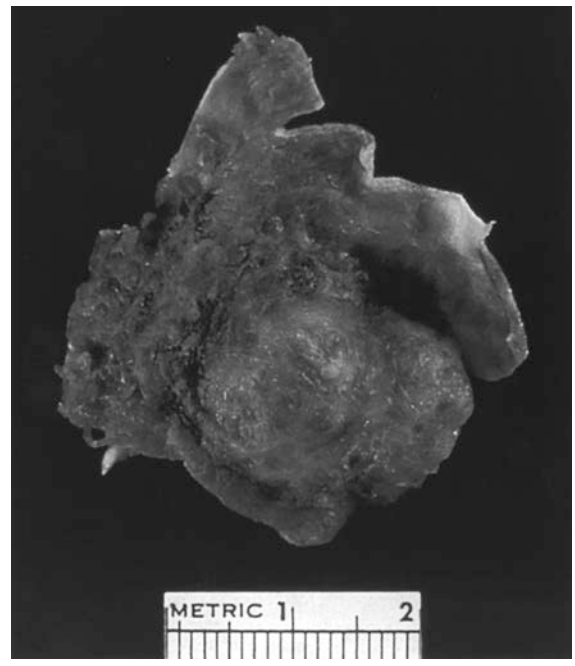

Figure 18.15 Meningioma: Gross specimen shows marked hyperostosis of greater wing of sphenoid bone (left), lateral wall of orbit (upper right), and globular mass (below) of meningothelial cells from a 33-year-old woman.

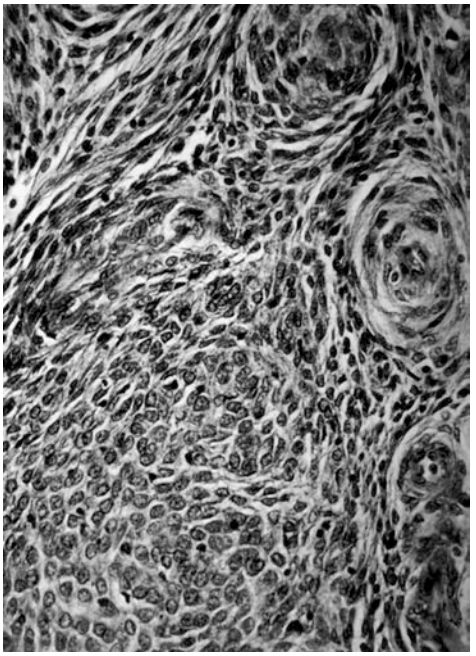

Figure 18.16 Meningioma: Lobules and whorls of meningothelial cells are separated by thin, vascularized, fibrous septae (×160).

cytoplasm and large spheroidal centrally placed nuclei that show little chromatin (see Figs. 18.16 and 18.17). Psammoma bodies (see Fig. 18.18) are infrequently found except in those tumors that involve the optic canal (*personal observation*). The transitional form of meningioma may also be found within the orbit. In this type, whorls of cells are closely wrapped around each other, and a small blood

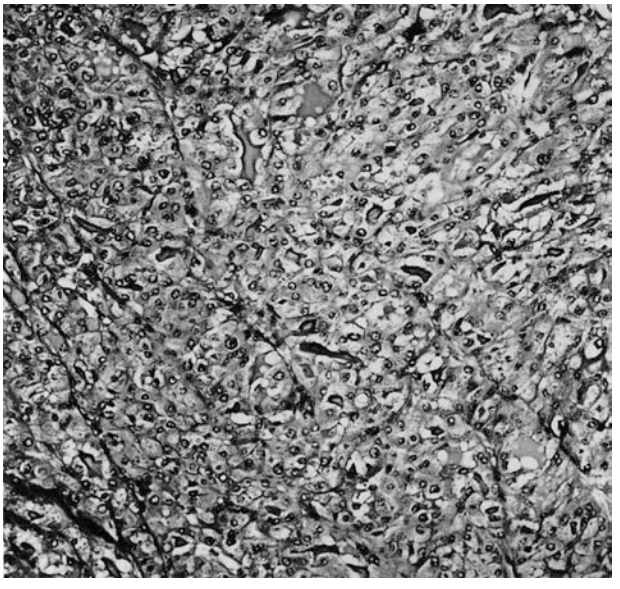

Figure 18.17 Meningioma: In this specimen the cell boundaries are indistinct, and the nuclei have a vacuolated, washed-out (Orphan Annie eyes) appearance (×160).

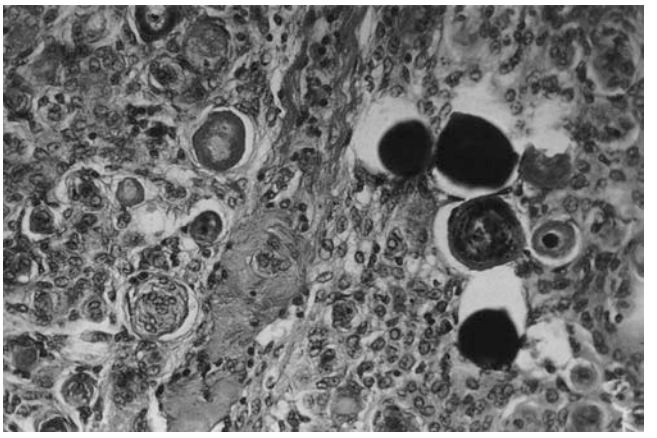

Figure 18.18 Meningioma: The central core of whorls of meningothelial cells hyalinize and calcify to form psammoma bodies (×90).

vessel is often found in the center of the whorl. Conversion of these whorls into psammoma bodies may occur. Mitoses are rare except in the more aggressive cellular tumor (see Fig. 18.19).

Immunohistochemical studies have shown the expression of both epithelial and mesenchymal markers. All types of meningiomas stain positive for vimentin (intermediate-sized filaments) and, in addition, are positive with various classes of cytokeratins and polyvalent anti-keratin sera (Holden et al., 1987). Artlich and Schmidt (1990) undertook a study of 77 cases to further define the immunohistochemical features of meningioma subtypes and to determine if the findings supported the prevalent histologic subdivision. Positive staining for vimentin was present in 97%; neuron-specific enolase, 88%; S-100 protein, 60%; epithelial membrane antigen, 53%; and cytokeratin, 20%. For meningiomas of all types, the

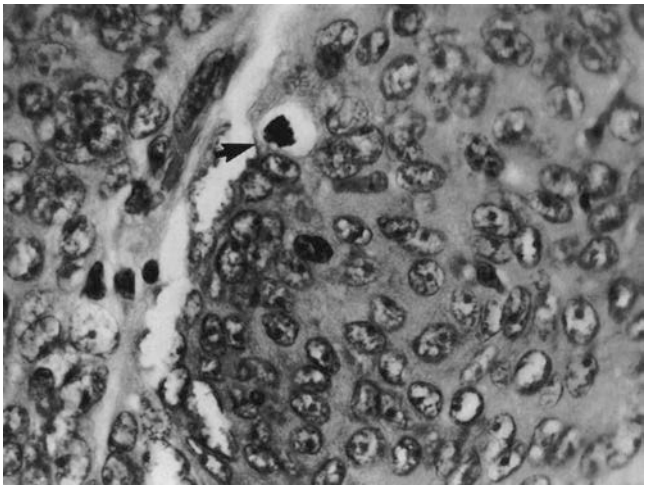

Figure 18.19 Meningioma: A mitotic figure is present (*arrow*) in this specimen from a 10-year-old boy (×600).

S-100 protein shows a highly variable reaction. It is the coexpression of desmosomal and vimentin proteins that characterize the meningothelial cell.

Meningiomas with greater likelihood to recur and/or aggressive behavior are uncommon in general and distinctly uncommon in the orbit. The atypical meningioma is a frequently seen radiation-induced meningioma (Jew et al., *vida supra*). Lamszus et al. (2000) noted that vascular endothelial growth factor (VEGF) was detected in statistically higher levels in malignant meningiomas than in benign meningiomas. This may be a potential therapeutic opportunity in the future. Huisman et al. (1991) noted that aggressive tumors tend to have less numbers of progesterone receptors than benign tumors.

MANAGEMENT AND PROGNOSIS

In the 50-year Mayo Clinic series, surgical removal of the meningioma has been the paramount method of management. Over this time interval, surgery maintains its prominent role in the management of sphenoid wing meningiomas. Radiotherapy, however, has been utilized more commonly as a postoperative adjunct to delay recurrences. Peele et al. (1996) showed no recurrences over the brief follow-up interval, 4.2 years for primary tumors and 3.5 years for recurrent tumors. One of their patients did suffer an ipsilateral anterior ischemic optic neuropathy 6 months after radiation therapy. One of our sphenoid wing meningioma patients, who received postoperative radiation therapy, experiences middle cerebral artery ischemia presumably related to post-radiation atherosclerotic changes (see Fig. 18.20). Radiation therapy is associated with premature atherosclerosis in the radiation field (Cheng et al., 2004; Sharabi et al., 2003) among other complications and this should be considered in the discussion with the patient.

Radiation therapy, however, has supplanted surgery as primary therapy for optic nerve sheath meningiomas (Capo and Kupersmith, 1991; Turbin et al., 2002; Saeed et al., 2003).

The premise for such an approach is to preserve vision. In such cases surgery is deferred until the clinical course or imaging features of the case indicate an extension of tumor toward vital structures in the intracranial vault.

In the period of the above study, the removal of meningioma as completely as possible has been the goal of management. This was considered the best means of minimizing regrowth of tumor, prolonging survival, and preventing death of the patient. In general, the factor of survival has subsumed preservation of vision as the preferred objective of management except in cases with bilateral involvement of optic nerves.

In determining the indications for any given treatment of orbital meningioma, whether it is surgery, surgery combined with irradiation, irradiation alone, or simple observation and judging the effectiveness of the selection, many factors must be taken into consideration. The major considerations are listed below.

Location of Tumor

The accessibility of the lesion is a major factor in its management. Orbital meningiomas differ in this respect not only from each other but also from intracranial meningiomas. High on the list of a favorable location is the intraorbital optic nerve sheath meningioma. At the opposite, unfavorable extreme is the meningioma arising from the lesser wing of the sphenoid bone and encroaching on the orbit through the superior orbital fissure/optic canal. The surgical removal of the former is much easier than excision of the latter. It follows that the probable survival of the patient with the optic nerve sheath tumor will be longer when compared to the patient with the tumor traversing the superior orbital fissure. However, if prognosis is based on the factor of visual preservation rather than the length of survival, both tumors are equally bad. The accessibility of meningiomas encroaching on the orbit from the lateral portion of the orbital surface of the greater wing of the sphenoid bone lies somewhere between the two preceding subtypes, but chances of some preservation of vision is better compared to the other two tumor locations.

Size and Extent of Tumor

These factors are subtypes of tumor location. A tiny optic nerve sheath meningioma located just anterior to the optic foramen with equivocal extension along the optic canal poses a greater threat of chiasmal involvement than larger tumors located either in the anterior optic nerve sheath or protruding from the orbital face of the sphenoid bone. Early removal of the tiny tumor would take precedence over the larger tumors because of proximity to the chiasm. In contrast, the surgeon would be less hesitant in removing a large tumor along the orbital face of the sphenoid bone or occupying the sheath of the orbital optic nerve compared to a tiny tumor located in the area of the cavernous sinus with extension into the orbit.

Age of Patient

There is general agreement and good clinical support for the assumption that meningiomas in the age-groups younger than 20 years are more aggressive than tumors in patients of middle age and older. In spite of these comments, there have not been any reports of tumors with "aggressive" histopathology. Despite this, however, there is still anecdotal support for earlier surgical intervention in the young compared to the older patients with meningiomas of similar size and location.

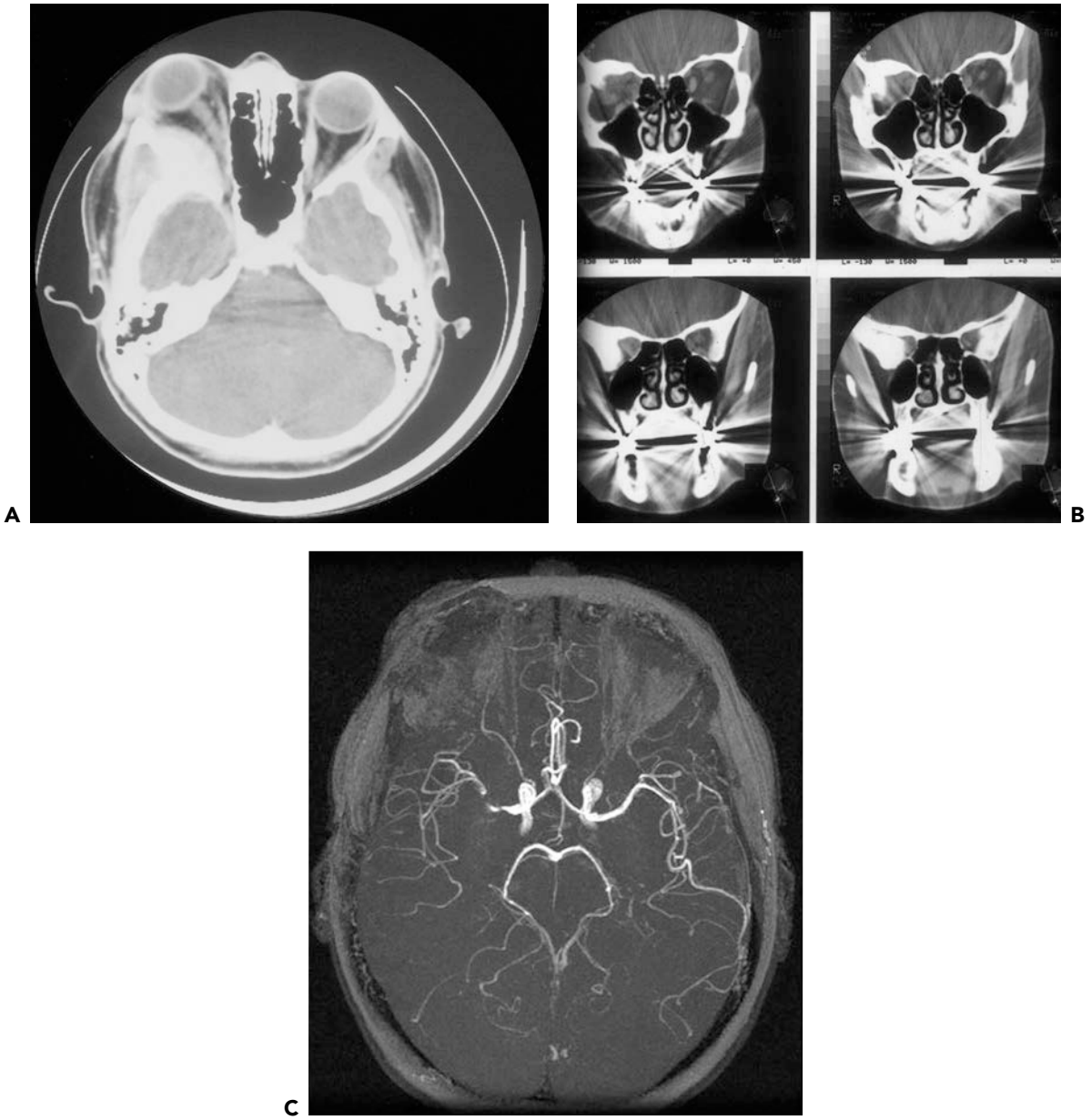

Figure 18.20 Sphenoid wing meningioma treated with surgery and postoperative radiation therapy. The salient features of this case follows. A 39-year-old woman with right sphenoid wing meningioma presented with slowly progressive visual loss (20/60) in the right eye. A proptosis of 11 mm was present. **A:** axial computed tomography scan and **(B)** coronal CT scan show hyperostosis of the sphenoid bone with an enlarged lateral rectus muscle and medial deviation of optic nerve. The temporalis muscle is probably infiltrated. Following craniotomy and optic canal decompression, the visual acuity improved to 20/20. Ten years later clinical and radiographic recurrence was noted. Another craniotomy was performed followed by radiotherapy (5,000 cGy) to the right orbit. Two years later patient returned with right hemisphere transient ischemic attacks. A magnetic resonance angiogram **(C)** showed narrowing in the right M1 segment, which was felt to be due to radiation effect. Symptoms resolved after anticoagulation.

Period of Tumor Study

Much of the meaningful data concerning patient's survival, mortality, loss of vision, and so on, in the literature are based on patients who were diagnosed and treated prior to the use of CT scan and MRI. These imaging modes have made it possible for an earlier diagnosis and treatment of meningioma, ergo a better prognosis. Therefore, many of the statistical conclusions in the present-day literature are not applicable to the present-day patient with meningioma.

Our 50-year Mayo Clinic series of 178 patients is an example of these conflicts. In general, those patients

who initially underwent surgical resection of meningiomas before the advent of CT scan and MRI had larger and more extensive tumors when compared to present-day patients who have had the advantage of earlier diagnosis through computer-assisted imaging. Therefore, survival and mortality analysis of the total 178 patients would not reflect the prognosis of the recent patients.

Length of Follow-up Observation

In general, most orbital meningiomas of whatever subtypes have a prolonged course. In many of these patients, there are several recurrences associated with multiple surgical procedures. Therefore, a long period of follow-up extending over many years is necessary to obtain a factual grasp of the patient's ultimate outcome. No longer is a 5-year follow-up relevant to the study of these tumors as was customary over a decade ago. Any publication comparing the success or failure of differing therapies with <5-year follow-up should be viewed with some skepticism. Follow-up periods longer than 5 years of the present-day patients are complicated by two problems. One problem is the well-known difficulties inherent in keeping tabs on most patients over such a long period. The other problem peculiar to the present-day patient is that CT scan and MRI have not been in routine use long enough to collect a sizable group of cases with the necessary follow-up of 10 years or longer.

Size of Sample

The number of consecutive cases of orbital meningioma that will serve as a base for reasonable and factual analysis has not been standardized. Furthermore, analytic objectivity is best served if the orbital meningiomas are only considered in terms of their primary or secondary subtypes. A sample of 20 or more primary orbital meningiomas and 30 or more secondary types with a follow-up of 10 or more years might be a good starting point for evaluating the effectiveness of recent management options. The collection of such a series of cases will require further time.

Histologic Subtypes

Almost all orbital meningiomas are meningothelial in character. Therefore, the several histologic subtypes of meningioma with the exception of atypical or malignant histopathology should not be a factor in the survival or mortality of patients with orbital involvement.

Other Judgment Factors

A minority of meningiomas that have ostensibly been completely removed recur, and a majority of meningiomas that have been incompletely excised regrow. Some physicians judge recurrence or regrowth of the tumor on the basis of the patient's increasing neurologic deficits. Others regard the increasing signal densities of CT scan or the increasing signal intensities of MRI as the best indicator of tumor recurrence or regrowth. We already have mentioned progressive visual acuity decrease and visual field defects as sensitive indicators of recurrent or regrowing meningiomas located in close proximity to the optic nerve. However, none of these tests is specific as proved by surgical reexploration of some cases only to find there is no active residual tumor. In such circumstances the progressing neurologic, imaging, and visual defects are but late sequelae of ischemia, necrosis, or fibrosis of either the brain or optic nerve resulting from previous surgery or radiation therapy. Surgical confirmation is the only factual basis for judging the incidence of recurrence or regrowth of meningioma.

A deficiency inherent in almost all statistical surveys of management modes is the lack of well-matched controls. Ideally, this would involve a series of untreated patients. Data are not necessarily factual in the published surveys, which include cases diagnosed on the basis of their clinical aspects rather than histopathologic study.

Mayo Clinic Series

This series has some of the omissions cited in the preceding text. Nevertheless, a more uniform subset of 81 cases is worthy of analysis in reference to the course and management of meningioma. All cases of the subset are based on a histologic study, the sample size is large considering the period (December 1974 through December 1997) of the study, all cases were initially processed with the aid of CT scan or MRI, the median follow-up was longer than 5 years, all cases were treated surgically, and the cases are analyzed according to their orbital subtypes (primary or secondary).

The subset consists of 35 primary and 46 secondary orbital meningiomas. The range of follow-up in the primary subgroup is 12 to 132 months with a median of 72 months. All patients were living at the time of last follow-up. In all but one patient the meningioma arose from the optic nerve sheath. In the one exception the origin of the tumor was the orbital face of the lateral portion of the greater wing of the sphenoid. This one patient still had 20/25 vision in the eye of the affected orbit following subtotal removal of the meningioma. In the remaining 12 optic nerve sheath meningiomas, the tumor was debulked or subtotally removed in nine patients, and the orbital optic nerve was totally removed in the remaining three patients. Two of the patients who underwent subtotal removal of their optic nerve sheath meningioma had 20/25 vision of the affected eye postoperatively. The remainder of the subtotal resection group had no light perception in the affected eye postoperatively. In the nine patients with subtotal resection of tumor, three patients each have had one further surgical resection for regrowth of their meningiomas.

In the 46 patients with secondary orbital meningioma, three patients were lost to follow-up shortly after surgical

removal of the tumor. Another patient died from further intracranial extension of a sphenoid wing-middle fossa meningioma 21 months after the first of two subtotal resections of the tumor. The follow-up range of the remaining 25 patients is 9 to 192 months with a median of 68 months. Eight (32%) of the 25 living patients have had a total of 11 additional surgical resections for regrowth of the tumor during the follow-up period. Only seven (28%) of the 25 patients had 20/200 or less vision in the affected eye at the time of the last follow-up. In general, the mortality of the secondary group is worse, but the visual outcome is better when compared to the primary orbital meningiomas.

In the past decade, the literature reflects an increased interest in radiotherapy as the primary agent for the management of both orbital and intracranial meningiomas (Smith et al., 1981; Kennerdell et al., 1988; Kupersmith et al., 1987; Peele et al., 1996; Turbin et al., 2002; Saeed et al., 2003). These publications are, in general, favorably impressed with the results of irradiation in selected cases, but these reports are marred by some of the omissions in statistical analysis mentioned in the preceding text.

None of the above series of Mayo Clinic patients managed in the 1974 to 1997 interval received radiation therapy either as the initial or the only therapy. Its principal role has been adjunctive to surgical resection in patients whose initial tumors were mitotically active, in tumors showing aggressive growth following gross removal, in residual tumors located in inoperable areas at the base of the brain, and in patients in whom further surgery is not advisable or appropriate. In these occasional situations, the mean total radiotherapy was in the range of 5,000 to 5,500 cGy.

In an early paragraph of this chapter we mentioned the future use of stereotactic radiotherapy. Such management may be useful for residual intracranial meningiomas located in inoperable areas along the base of the skull. The prospect of using Gamma Knife radiosurgery for orbital tumors or an exophytic optic nerve sheath tumor in the apex is probably not feasible. Technical problems might not allow treatment of an orbital lesion unless the patient's skull is small, and furthermore, treatment of a lesion adjacent to the optic nerve would probably be associated with vision loss that could be minimized by fractionating the treatment course.

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19 Inflammatory Orbital Pseudotumors

In this chapter, we will discuss the orbital manifestations of a group of clinical entities, which, for many years, were lumped together as pseudotumors. These entities are idiopathic orbital inflammation, idiopathic sclerosing inflammation, Tolosa-Hunt syndrome, multifocal fibrosclerosis, vasculitis, and Wegener granulomatosis. Birch-Hirschfeld (1930), in the period 1905 to 1909, coined the term, *pseudotumor*, to describe inflammatory swellings of the orbital contents that produced proptosis and, thereby, mimicked neoplastic disorders. A reader may now assume that the term, pseudotumor, would be obsolete. However, a recent publication (1999) pertaining to the orbit includes bacterial infection, fungal infections, sarcoidosis, Erdheim-Chester disease, Sjögren syndrome, and Wegener granulomatosis under the rubric, pseudotumor.

IDIOPATHIC ORBITAL INFLAMMATION[1]

This idiopathic orbital inflammatory process has also been called *nonspecific orbital inflammation*, *idiopathic inflammatory pseudotumor*, and *nonvasculitic inflammatory tumor*. It was separated from the conglomerate of pseudotumors by several authors in the 1960s and 1970s, and is now recognized as a clinical entity.

This entity has been known for over 50 years, but its cause remains elusive. The inflammatory orbital mass is probably a cell-mediated and humeral response to a primary immunopathologic dysfunction, but the antigen is unknown. Farrow (1973), who studied the tissue specimens of our early cases, thought the histopathology was remindful of the Arthus type of hypersensitivity reaction.

[1] This term is used by Spencer (1996) and several other authors for this group of inflammatory orbital tumors. It replaces the designation, nonvasculitic inflammatory tumor, used in our third edition (1994).

Incidence

It is difficult to accurately assess this factor on the basis of a review of the literature. First, there is a lack of a universal definition. The question of just what constitutes inflammatory tumor is highly subjective, sometimes depending on an author's predetermined notion of what its clinical presentation should be. Of greater concern is the number of case studies in the literature that are not proven by histologic study. It is disappointing to review an article with an attractive title only to find that all or most case reports are based on an assumed diagnosis. This is particularly applicable to the published reports in the pediatric and radiology literatures. Our knowledge of this lesion would be better served if such reports would base their clinical data on the surgically proven cases, even though the number of patients is small. We prefer not to reference those many reports in the literature that are not based on factual data.

In our 50-year list of orbital tumors, there are 83 patients with idiopathic orbital inflammation, an incidence of 4.6% (83/1795) of total tumors. The real incidence is probably higher because a sizable number of presumed orbital cases are never biopsied. There were 40 males and 43 females. The age range of males is 2 to 89 years with an average age of 42.3 years and a median of 44 years. The greatest concentration (16 cases) of patients is in the fourth and fifth decades at the time of presentation. The age range of female patients is 7 to 79 years with an average age of 49.6 years and a median age of 44 years. The greatest concentration (12 cases) of patients is in the fifth and sixth decades at the time of presentation. Among the overall group of 83 patients, there are 7 with bilateral involvement, age range 2 to 68 years, 5 males and 2 females. Among the 83 patients, there were only 7 (ages 2 to 18 years) children.

The bulk of the literature addresses idiopathic orbital inflammation in adults. The latest review of this inflammatory tumor in children is that by Berger et al., 1996.

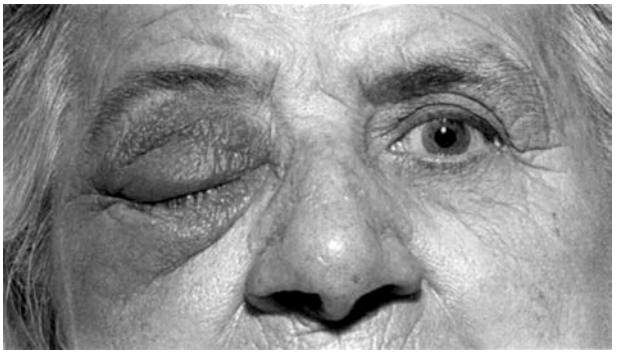


Figure 19.1 Idiopathic orbital inflammation: A 76-year-old woman with right-sided blepharoptosis, edema, and erythema of eyelids, and frontal headache of 2 months' duration owing to a lesion in the posterior orbit. Other findings were chemosis, proptosis, ophthalmoplegia, and a visual acuity limited to recognition of hand movements by the affected eye. A subtotal removal of the inflammatory lesion was performed. The patient was followed up for 87 months. The inflammatory process subsided without further treatment, but the eye remained sightless, blepharoptosis was complete, there was very little ocular motility, and optic atrophy developed.

Clinical Features

The idiopathic inflammatory tumor has a relatively short and aggressive onset. In our Mayo series, the duration of symptoms averaged about 5 months. This tumor, among all those described in this text, is unusual in its tendency to locate in any orbital anatomical site and affect any of the tissues within the orbital confines including the extraocular muscles, lacrimal gland (dacryoadenitis), orbital fat, the connective tissue of Tenon capsule, trochlea, the outer dural sheath of the optic nerve, and periorbita. As a rule, some combination of two of these tissue elements is affected at any given time. Rarely are all orbital tissues involved, and the eye immobile. A unilateral orbital lesion, while under treatment or observation, may become bilateral.

The signs and symptoms voiced by the patient at the time of presentation are numerous such as swelling of the upper lid, a palpable mass in the anterior orbit with or without tenderness, axial protrusion of the eye, extraocular motility impairment, pain associated with an orbital mass, drooping of upper eyelid, a red eye, erythema of the upper eyelid, and visual loss $>20/200$. Usually, there is a combination of two clinical features. Vision is not impaired unless there is hyperemia or pallor of the optic disk. None of these clinical features is present in all cases (see Fig. 19.1).

Imaging Aspects

The imaging display, usually computed tomography (CT), of idiopathic orbital inflammation may be nearly as diverse as its presenting symptomatology. Any orbital structure may be involved, alone, or in combination. However, regardless of location, the lesions all tend to enhance after contrast administration and show irregular margins. In their various orbital sites, the lesions are rather distinctive, but their features are not necessarily specific to inflammatory tumor.

The lacrimal gland is a frequent location of the tumor. Here, the tough capsule of the gland tends to delimit the lesion, giving the tumor a circumscribed appearance that strongly suggests an intrinsic neoplasm. More often, the configuration of the lesion will show wisps of inflammatory tissue extending outward along the fascial planes between the lacrimal gland and the eyeball.

When located in an extraocular muscle, the inflammatory lesion also may be partially delimited by the muscle sheath but less so than a lesion in the lacrimal gland. The lesion in muscle tends to spread linearly, seldom producing the bulk that is associated with the edema of Graves orbitopathy. In addition, the inflammatory tumor may involve the lateral rectus muscle or the tendinous attachment of the extraocular muscle, features not seen with Graves orbitopathy.

In the apex of the orbit, the lesion tends to extend forward like a fan, closely resembling the configuration of some meningiomas. However, the forward border of the inflammatory lesion is more irregular than in meningioma owing to tufts and threads of tissue extending out into the fascial planes of the retrobulbar space. A metastatic carcinoma may also show the same features.

A variant of the apical lesion is the perineural infiltration of the sheath of the orbital optic nerve. The linear hyperdensity of the sheath infiltration contrasts with the hypodensity of the optic nerve core, giving the CT image a "tram-track" appearance. Again, an optic nerve meningioma may produce a similar imaging sign.

A peculiar tendency of the inflammatory tumor is to encompass the posterior wall of the eyeball by an infiltration of Tenon capsule and sclera. This produces a distinctive thickening and enhancement of the scleral ring. In addition, the infiltrating tumor may extend haphazardly into the retrobulbar tissues. These imaging features may also be seen with metastatic carcinoma, orbital cellulitis, and the scleritis associated with rheumatoid arthritis.

Last, the inflammatory process may be so intense and diffuse that it fills the entire retrobulbar space with "wall-to-wall" tumor, a feature also seen in Wegener granulomatosis (WG). Figures 19.2 to 19.7 show many of the differing features of CT imaging.

In the past decade or so, there has been a steady stream of publications wherein authors state a biopsy is no longer necessary to establish the diagnosis of idiopathic orbital inflammation. We have selected several quotations from the literature pertaining to this trend such as: "*In the majority of pseudotumor cases, the diagnosis can be ascertained on the basis of the clinical information and the CT findings.*" "*The constellation of clinical findings and the results of diagnostic and laboratory tests exclude the need for a diagnostic orbital biopsy in the majority of cases.*" "*Because in most instances, the diagnosis of orbital pseudotumor can be made clinically together with*

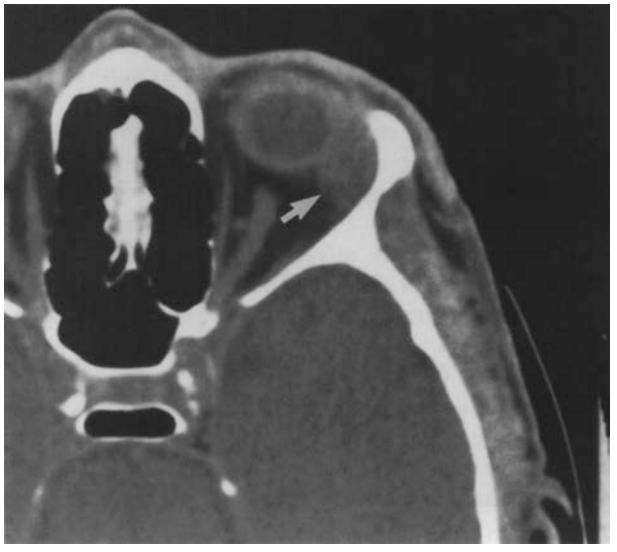


Figure 19.2 Idiopathic orbital inflammation: Axial computed tomography scan without contrast shows enlargement of the left lacrimal gland by a circumscribed homogeneous mass (*arrow*) in a 59-year-old man. However, the anterior and posterior borders of the lesion are not sharp.

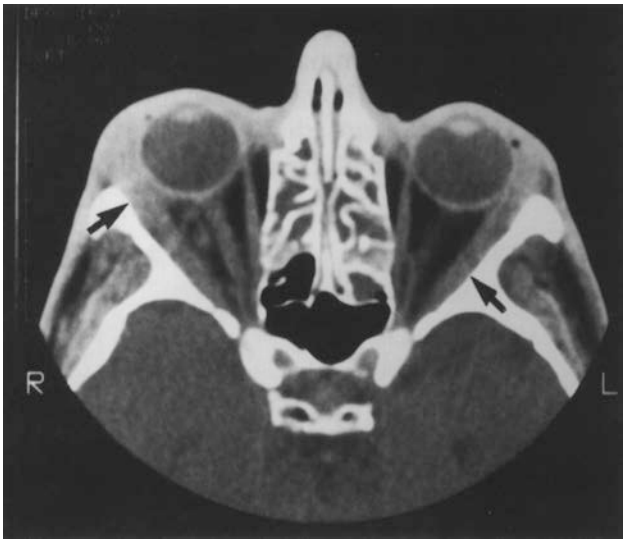


Figure 19.3 Idiopathic orbital inflammation: Presenting features in a 29-year-old man were bilateral swelling of the eyelids, palpable masses in each lacrimal gland fossa, and proptosis, more on the right side. Axial computed tomography scan shows thickening of the entire length of the lateral recti muscles by enhancing, infiltrative lesions (*arrows*). Surgically proved diagnosis on the right side. Postoperative radiotherapy was administered to right orbit. Two years later, exacerbation of disease occurred in the left orbit. Biopsy of left orbital lesion showed inflammatory tumor. In contrast, isolated involvement of lateral recti muscles in Graves orbitopathy is very rare.

ancillary ultrasonographic and radiographic studies.'' We do not believe any of these statements are factual. The imagery of CT is not specific for idiopathic orbital inflammation and can also be seen with many other orbital disorders, as noted in prior paragraphs. Actually, the reports of presumed orbital inflammation simply clutter up the literature and continue to thwart efforts to more specifically define idiopathic orbital inflammation as a separate clinical entity. Perhaps, it would be better not to accept cases for publication that are not proven by biopsy.

Pathology

Grossly, the color of the lesion is usually tan, gray, or yellow. Occasionally, the yellowish lesion may appear a bit pink, indicating a very vascular makeup. The tumors are said to be ''gritty,'' ''rubbery,'' ''firm,'' or ''hard.''

I believe the best description of the complicated histopathology of this tumor, in the literature, is that by Spencer (1996) in his publication. The following summary is quoted directly from his text. ''Edema and a polymorphic, light, inflammatory infiltrate at the early stages of the disease are highly characteristic; the infiltrating cells include lymphocytes, plasma cells, eosinophils with degranulation, and less often, polymorphonuclear leukocytes. Especially in children, whose orbital biopsies exhibit a heavy eosinophilic infiltrate, there may be an elevated absolute count of eosinophils in the peripheral blood.

As the disease progresses and fibrosis is laid down, the inflammatory cells become more widely separated by tracts of collagen, which radiate outward from the fibrous tissue septa and blood vessels into the orbital fat. The connective tissues of the muscles thicken, and hyperplasia of the periacinar and periductal connective tissues of the lacrimal gland will be observed. With progressive fibrosis, extraocular muscle degeneration occurs; the secretory acinar units of the lacrimal gland are obliterated, leading to blind-duct proliferation or hyperplasia. Once the acini of the lacrimal gland have been destroyed, they do not redifferentiate. Widely separated lymphoid follicles with germinal centers are frequently seen in the chronic stage of idiopathic orbital inflammation; this feature, combined with the presence of eosinophils, helps distinguish idiopathic orbital inflammation from thyroid-related orbitopathy. Compared to orbital lymphoid tumors, there is far more fibrosis in these tumors, and the lymphoid elements are widely separated; in other words, there is no diffuse, sheet-like hyperplasia of lymphocytes as is characteristic of the comparatively stroma-free lymphoid tumors of the orbit. Furthermore, lymphoid tumors of the orbit do not exhibit acute inflammatory signs and are generally unifocal masses rather than the diffuse or multifocal processes represented by idiopathic orbital inflammations.

Evidence of perivascular lymphocytic cuffing in idiopathic orbital inflammatory pseudotumor is frequent, and occasionally eosinophils may be admixed. Such cuffing represents diapedesis of blood-borne cells into the immediate adventitial area of the capillaries or postcapillary venules; this finding, therefore, does not constitute true vasculitis.''

Another interesting finding in some of the biopsies of orbital inflammatory pseudotumor is necrosis of the orbital

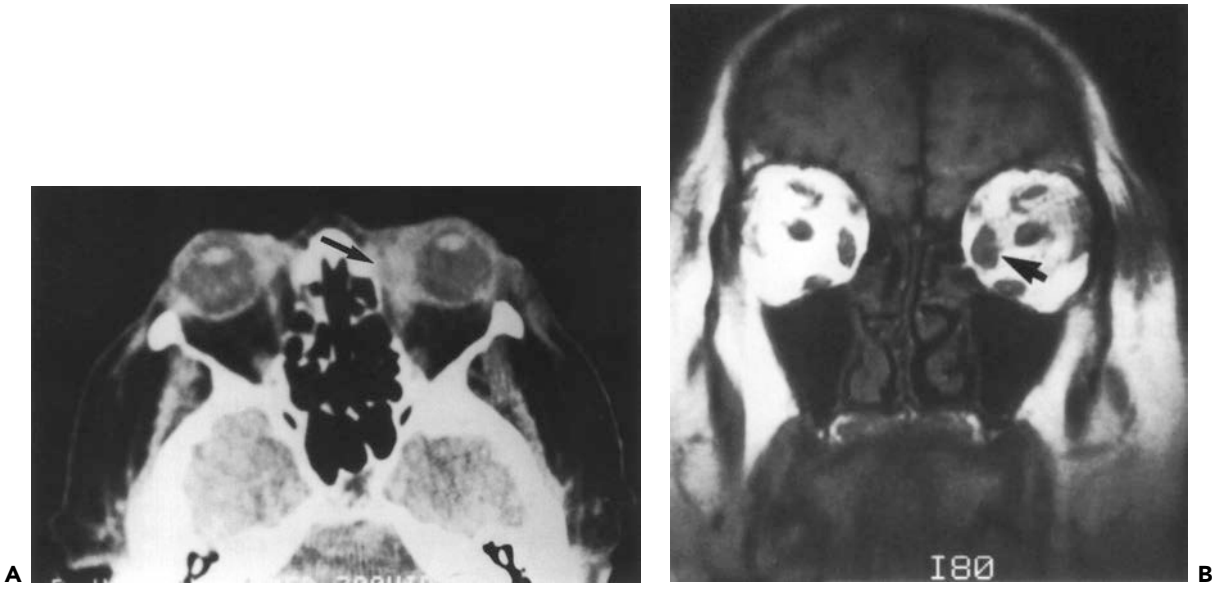


Figure 19.4 Idiopathic orbital inflammation: **A:** Axial computed tomography scan shows thickening and irregularity of anterior portion of left medial rectus muscle (*arrow*) by an infiltrating, enhancing lesion in a 67-year-old patient with pain and limited abduction of left eye. In contrast, Graves orbitopathy usually does not involve the tendinous attachment of the muscle to the globe. **B:** Coronal magnetic resonance T_1-weighted scan shows enlargement of left medial rectus muscle (*arrow*).

fat, with a multinucleated foreign body giant cell response to the released lipid.

Figures 19.8 to 19.12 from the file of Mayo patients illustrate some of the salient histopathologic features.

In the study of large specimens of tissues of this inflammatory tumor removed at the time of biopsy, Farrow, in the mid 1960s, noted that intensity of the inflammatory response varied from the periphery to the center of the specimen. The inflammatory response was acute at the periphery of the specimen merging gradually into the subacute phase, and at the center of the specimen, to a chronic stage of fibrosis. The end-stage of this inflammatory process, in cases in which exenteration of the orbit was performed for relief of pain, was an eyeball encased by a mass of fibrosis and dense connective tumor that contained shrunken aggregates of lymphocytes (see Fig. 19.13). However, most biopsy tissue specimens did not show the full range of acute to chronic inflammatory stages. Instead, the inflammatory process sometimes lingered at an acute or subacute stage, or the disease process clinically came to a halt, with or without treatment, without showing features of advanced fibrosis. We found no correlation of the degree of inflammation with other clinical features of idiopathic orbital inflammation.

Alper, a retired ophthalmologist from Washington, DC (quoted by Jakobiec et al., 1984) studied a fresh surgical specimen from an orbit with this inflammatory tumor and found a predominance of B-cell lymphocytes producing the immunoglobulin that was found in the orbital tissue. If circulating immune complexes are responsible for some of these pathophysiologic changes in orbital tissues, in the manner of an Arthus reaction, these immune complexes may also be multifocal and occur in extraorbital sites such as those noted in the next section.

Immunostaining was also performed on some cases of idiopathic inflammatory tumor from our collection of cases seen in the 1990s. Most tissue specimens showed a more advanced stage of the progressive inflammatory process, that is, a subacute inflammatory stage admixed with bands of fibrous tissue replacing the stromal cellular elements, and other specimens showing a more advanced stage consisting of residual lymphoid follicles with germinal centers entrapped in a dense mass of fibrous connective tissue. All tissues, regardless of their inflammatory stage, were encompassed predominantly by B cells showing polyclonality of both κ and λ light chains. A rim of T-cell lymphocytes with predominant subsets of T cells encircled the follicle-like aggregates in the cases studied.

The presence of eosinophils in tissue specimens of idiopathic orbital inflammatory tumor has been known for many years. Noguchi et al. (1991) conducted a controlled study wherein eosinophil infiltration and extracellular major basic protein deposition were evident in all tissue specimens. The eosinophil granule is composed of several toxic cationic proteins (Gleich and Adolphson, 1986). Noguchi et al. also noted that extracellular major basic protein deposition predominated over intact eosinophil infiltration, especially in areas of fibrous connective tissue. In fact, intact eosinophils were not observed in areas of dense fibrosis. This suggests that degranulation of the

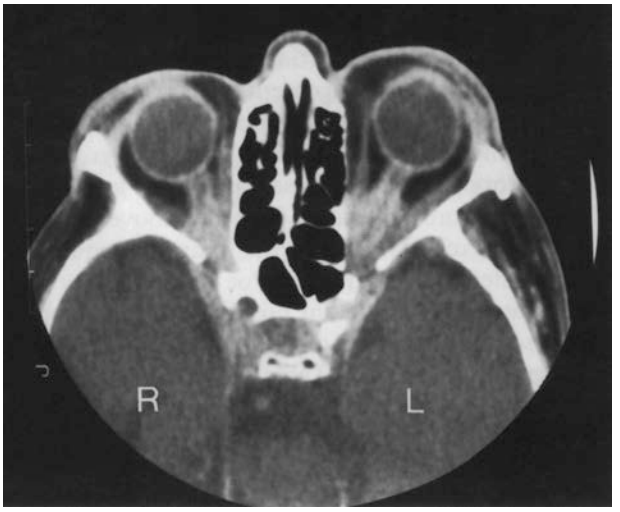


Figure 19.5 Idiopathic orbital inflammation: Bilateral, total loss of vision over a period of 1 year in a 68-year-old man. Initial, bilateral temporal artery biopsies were negative for arteritis. Axial orbital computed tomography scan shows enhancing, infiltrative masses in the apex of both orbits with extension into the adjacent cavernous sinuses. Note the ''tram-track''—like enhancement of optic nerve sheath, particularly on the left side. This imaging feature may also be seen in optic nerve meningioma (compare with Fig. 18.11). Surgically proved diagnosis of inflammatory lesion on the left side.

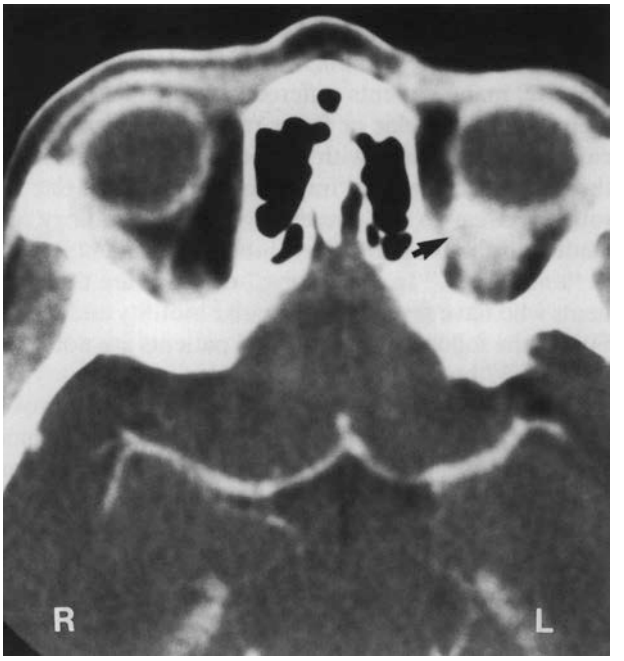


Figure 19.6 Idiopathic orbital inflammation: Axial computed tomography (CT) scan shows an enhancing mass (*arrow*) with an irregular border encasing the posterior wall of the eyeball, obscures the ocular optic nerve junction, and extends posteriorly along the left optic nerve in a 44-year-old woman. The same process is present along the lateral wall of the right orbit.

eosinophil and release of the toxic granule proteins is the major factor that contributes to fibrosis. This activation of fibrosis by extracellular deposition of eosinophil major basic protein is also seen in patients with end-stage WG and some inflammatory lesions with a major component of vasculitis.

Management and Course

A detriment to an objective discussion of the management of this benign inflammatory tumor is lack of knowledge of the natural, untreated course of the disorder. Most of our cases were treated in some manner, but the duration of the inflammatory disease varied widely. A second problem is formulating a controlled management protocol that would include all the variables in the clinical features of the tumor: Does the tumor differ in children versus adults (considering the wide age range in adults, 21 to 89 years of age)? Can we assume the immune system is the same in individuals at these age extremes? Does the intensity of the inflammatory process differ or does it affect individual structures in the orbit (muscle, lacrimal gland, fat, dural sheath of the optic nerve, etc.) in the same way? Will it recognize differing stages of the inflammatory process (acute, subacute, or chronic)? Can it require a long follow-up (5 years) so as to include many cases that respond favorably to initial therapy with a period of assumed arrest, only to have the inflammatory process recur some months later? This is a statistical dilemma.

Table 19.1 is reproduced from our third edition published in 1994. The table lists the management and follow-up of 45 patients in the 40-year period 1948 to 1987. The size of the group of patients studied and length of follow-up time were probably unique in the literature over the 40-year period. We kept track of these 45 patients over the 40-year period and found the disease subsided in this period of observation.

The list includes nine categories of management, which, for the most part, were based on favorable reports in the literature and our own experience in any given year. There was no standard protocol. Resolution was judged by the disappearance of proptosis, eyelid swelling, and erythema, and pain, or headache. Although the orbital disease became inactive, many patients suffered permanent sequelae. If there were no sequelae or fewer residual signs of the disease when compared with presenting symptomatology, the patient was listed as ''improved.'' If the sequelae were roughly equal to the presenting symptomatology, excluding the above signs of resolution, the patient was listed as ''unchanged.'' In the ''worse'' category were those patients who had severe loss of both ocular motility and vision.

The patients who showed the best percentage of improvement, considering the size of the sample, were those managed either by a combination of biopsy and steroid therapy or complete excision. Complete excision of the lesion was the preferred treatment in the 1950s and 1960s, before steroid therapy came into general use. Total excision was possible if the tumor was located in the anterior orbit. Those tumors located just behind the orbital

TABLE 19.1
IDIOPATHIC INFLAMMATORY TUMOR (N = 44) (1948–1987): MANAGEMENT AND RESIDUAL STATUS OF PATIENTS WITH A LIMITED COURSE

	Result				Follow-up (months)		
Management	**Cases**	**Improved**	**Unchanged**	**Worse**	**Range**	**Mean**	**Median**
Subtotal excision (debulking)	11	1	7	3	3–336	—	50
Biopsy and steroids	7	6	1	—	5–51	19	—
Subtotal excision and radiotherapy	6	2	4	—	29–192	—	67
Complete excision	5	4	—	1	5–59	52	—
Subtotal excision, steroids, and radiotherapy	5	1	2	2	5–39	26	—
Subtotal excision and steroids	4	2	1	1	4–64	31	—
Biopsy and radiotherapy	4	2	2	—	14–120	—	30
Biopsy only	2	—	2	—	15–55	—	—

septum, in particular, were often lobulated, circumscribed, and shelled out with careful dissection. This brought about immediate relief of proptosis and lid swelling, and these patients had no sequela. It is possible that complete excision also ablated the antigenic focus responsible for the tumor. In the one patient with visual loss, in this category, who got worse with treatment, the lesion was located in the orbital apex and was thought to be an optic nerve glioma. Accordingly, the orbital optic nerve was removed.

Biopsy supplemented with steroid therapy also brought early resolution of the inflammatory process and was particularly efficacious in patients having pain or headache. Biopsy and steroid therapy in the 6 patients showing improvement were effective regardless of the age of the patient, the orbital location, or the histologic stage of the lesion.

In less surgically accessible orbital locations, a debulking procedure (subtotal, partial, or incomplete excision) was about the only management we could offer the patient in the 1950s and 1960s. Approximately 25% (11/45) of the patients are in this group. The inflammatory tumors in these cases were less circumscribed and more infiltrative than the above cases that were totally excised. Later,

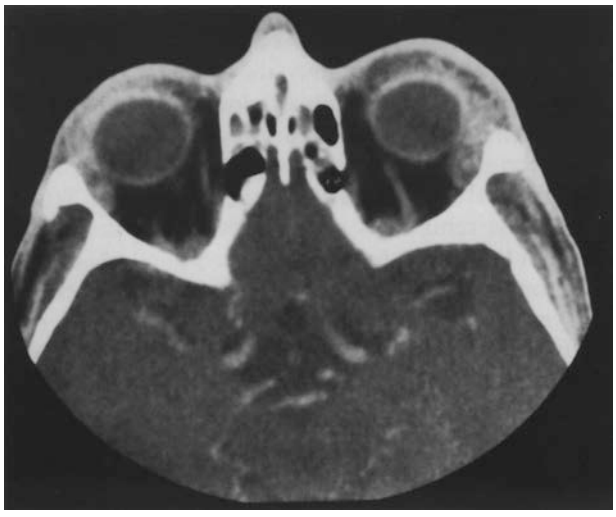


Figure 19.7 Idiopathic orbital inflammation: Axial computed tomography scan shows bilateral, diffuse, nonhomogeneous, enhancing lesions involving soft tissues of the superior orbits and lacrimal glands in a 39-year-old man. There is also some scleral enhancement.

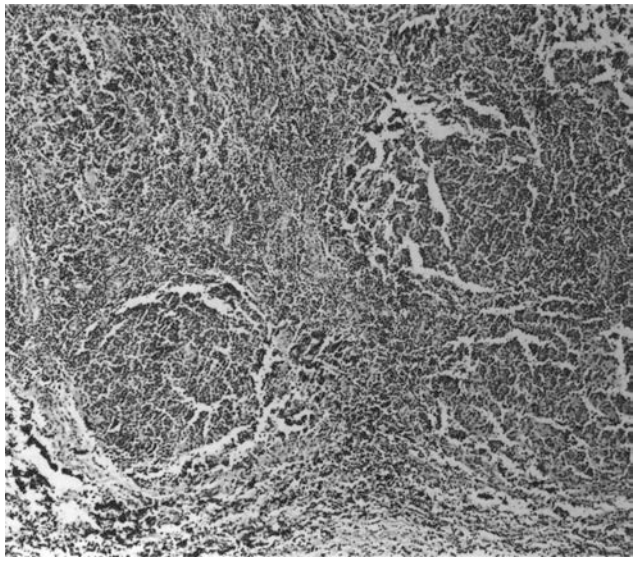


Figure 19.8 Idiopathic orbital inflammation: Diffuse, predominantly lymphocytic infiltration of orbital tissue with rounded cellular aggregates (×64).

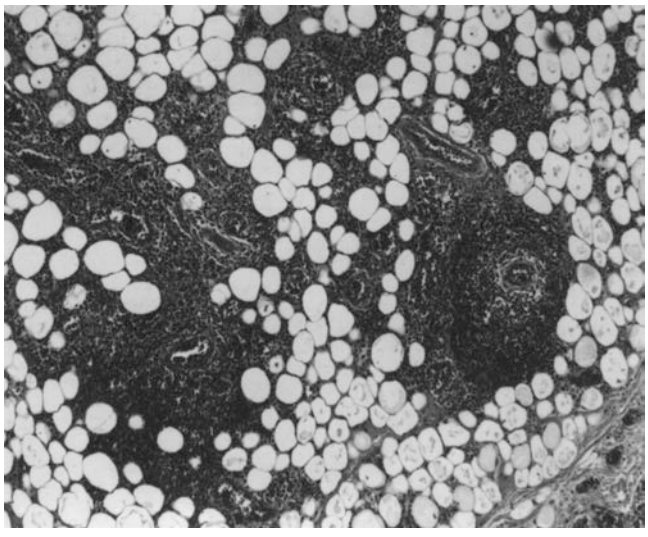


Figure 19.9 Idiopathic orbital inflammation: Dense infiltration of lymphocytes into orbital fat with marked vascular proliferation and some perivascular cellular cuffs. Fibrous tissue trabeculae lower right (×64).

in the temporal sequence of patients, steroid therapy and/or radiotherapy were added in an effort to quiet the postoperative reaction and hurry resolution of some of these cases. Overall, in the several groups of patients whose management option included subtotal excision, the sequelae were more severe when compared to other patient subgroups that did not include the surgical debulking option. In retrospect, it is possible that incomplete removal of the orbital inflammatory focus only reactivated the immune response that was responsible for the initial lesion. The intensity of the inflammatory response and the orbital location of the tumor were also probable factors in the less favorable resolution of the disease in these patients.

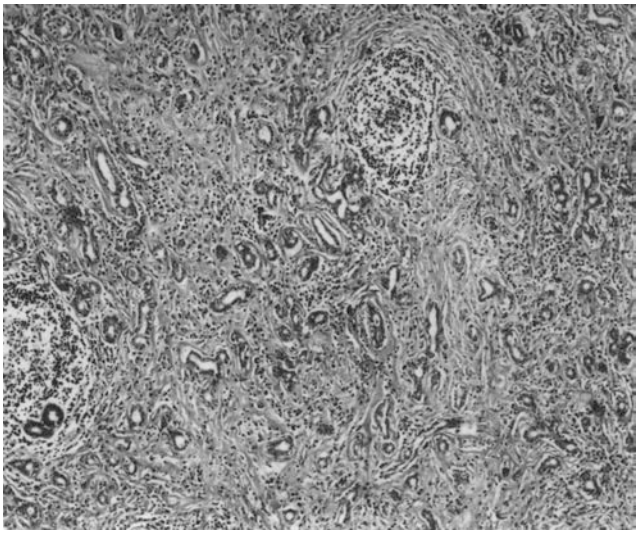


Figure 19.10 Idiopathic orbital inflammation: Fibrous tissue replacement of lacrimal gland components. Note focal lymphoid aggregates upper right and lower left (×64).

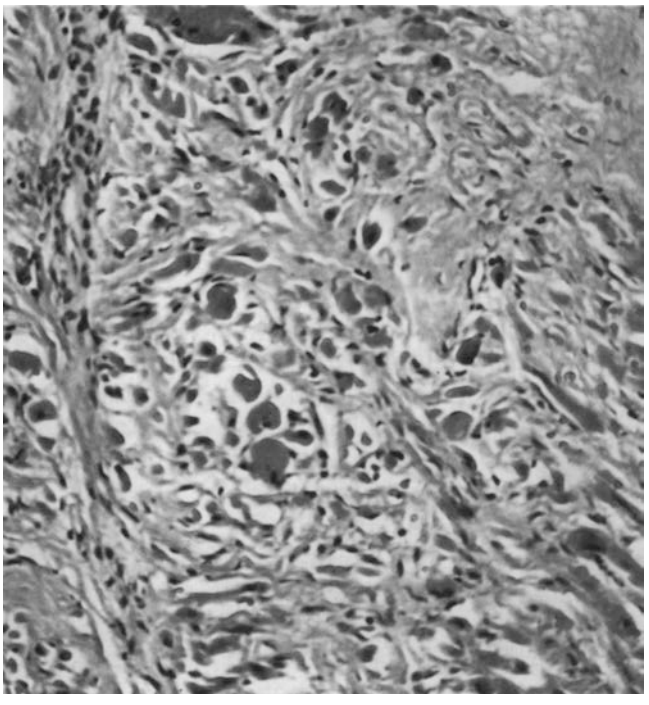


Figure 19.11 Idiopathic orbital inflammation: The inflammatory lesion shows a marked desmoplastic reaction involving an extraocular muscle of a 5-year-old boy (×160).

The worst sequelae encountered in patients with an unfavorable resolution of the disease included blindness, total ophthalmoplegia, complete blepharoptosis, and phthisis bulbi on the side of the affected orbit.

The two patients who were managed only by biopsy are of interest. In both cases, the presenting features of the disorder were mild, and it was decided to withhold additional therapy until there were signs of progression. In one patient, a 39-year-old man, bilateral, intermittent swelling of the upper eyelids had been present for one year. Multiple masses were palpable across the superior portions of each orbit, including the lacrimal gland. There was no progression in a follow-up period of 15 months. The swelling stabilized, but the "lumps" were still palpable at the end of the 15-month period.

The other patient, a 54-year-old woman, had noted prominence of the right eye of six weeks' duration. There was no swelling of the eyelids, erythema, diplopia, or palpable masses. The unilateral proptosis measured 6 mm. Visual acuity was 20/20 in each eye. CT scan showed an infiltrative process in the retrobulbar space chiefly involving the tissues adjacent to the lateral rectus muscle. At the time of orbitotomy, it was noted that the tumor was also adherent to the lateral periorbita and lacrimal gland. The proptosis subsequently disappeared without ocular dysfunction or local recurrence of the lesion in the 55-month follow-up.

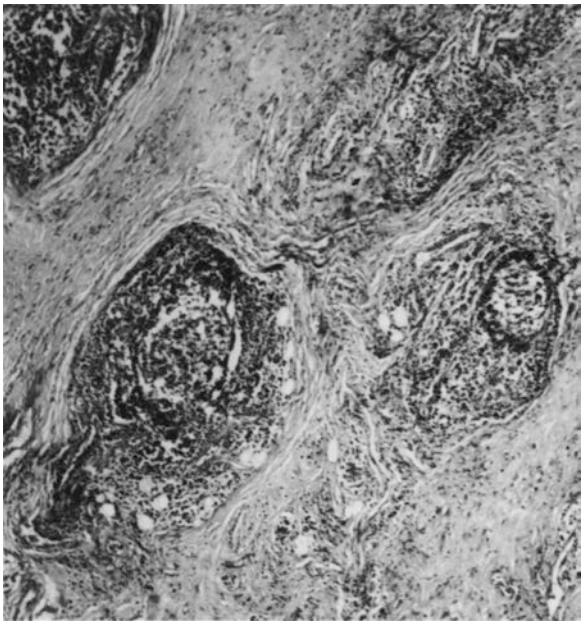


Figure 19.12 Idiopathic orbital inflammation: Oval, cellular aggregates are separated by tracts of collagen (×120).

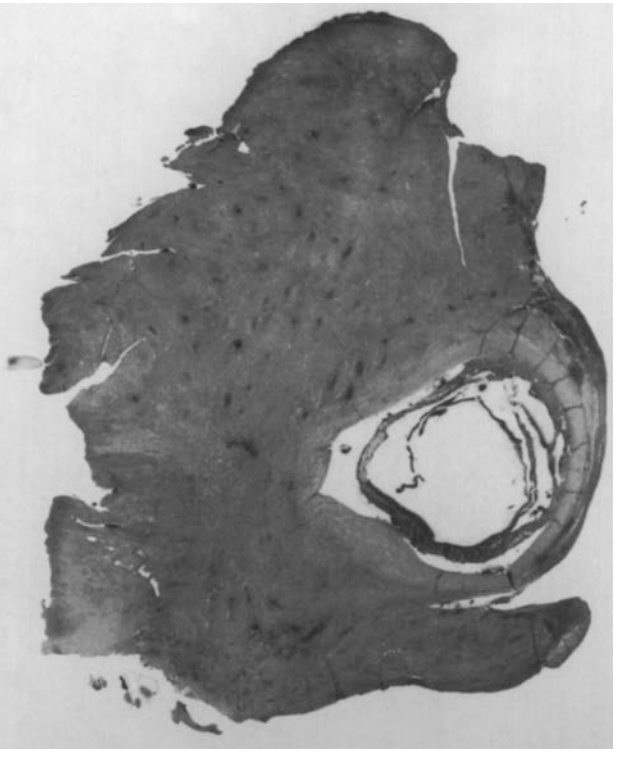


Figure 19.13 Idiopathic orbital inflammation: Exenteration specimen shows entrapment of globe by dense, fibrotic connective tissue. Small dark spots are remnants of lymphoid aggregates (×2 1/2).

In general, the inflammatory process in the 45 patients became inactive over a period of 3 to 12 months.

The course of several patients from our total group of patients (1948–1997), differed in some respect from those listed in Table 19.1. One is a 10-year-old boy with a diffuse inflammatory process of the right orbit associated with 8 mm of proptosis, marked restriction of ocular motility, and 20/400 vision of the right eye. The inflammatory process waxed and waned and was treated with varying courses of steroid drugs over a period of 5 years. At this time, the disease subsided with complete disappearance of the proptosis and recovery of 20/25 vision in the affected eye. Four years later, the inflammatory disorder reappeared in the other orbit, and steroid therapy was again initiated. Soon after, the patient was lost to follow-up. This case illustrates a prolonged course and treatment of the disorder, a surprising resolution without sequelae, and reappearance of the disorder in the other orbit after a period of arrest.

Another patient is a 36-year-old woman with remissions and recurrences of a unilateral orbital inflammatory tumor treated with steroid therapy over a period of 5 years. At this time, the disease stabilized with return of ocular motility, recovery of vision to 20/20, and resolution of proptosis. The patient was followed up for another 29 months without evidence of recurrence of the localized orbital disease. This case also required a longer than average treatment.

A third patient is a 42-year-old man who also had recalcitrant, intermittent, and progressive disease who was treated with several small doses of radiotherapy. Four years after diagnosis, the eye of the affected orbit was enucleated. At the last follow-up, 6 years after diagnosis, a recurrence of the inflammatory disorder in the anophthalmic orbit was again treated with radiotherapy. An anophthalmic orbit is an unusual locus for the disorder.

A fourth patient is a 24-year-old woman whose recalcitrant, unilateral orbital disorder was treated with both radiotherapy and steroids. Even so, the disease remained active and was still being treated with maintenance doses of steroids 9 years after diagnosis. This illustrates the recalcitrant nature of a case regardless of prolonged treatment.

The last patient is a 39-year-old male who was still taking prednisone 6 years after presentation to repress recurrence of the inflammatory process.

With regard to the occurrence of idiopathic orbital inflammation in children, Berger et al. published an extensive review of the literature in 1996. They discuss in some detail the multiple orbital disorders of childhood that must be considered in the differentiation of this inflammatory tumor. One of their conclusions is bilaterality, either at the time of presentation or developing sometime in the course of management, which more common in children when compared to adults; most children show a dramatic, initial improvement with intravenous corticosteroids, but incomplete resolution; recurrences are common steroid dependency was not uncommon and radiotherapy has not been of proven benefit for pediatric patients.

Mombaerts et al. (1996), (Amsterdam, Netherlands) assessed the value of systemic corticosteroids in the

management of 20 adult patients with histopathologically idiopathic proven orbital inflammation. They found a moderate response, a high recurrence, and a low cure rate in these patients. However, in patients with an associated optic neuropathy, corticosteroids were of value. Their study excluded patients with involvement of either lacrimal gland or an extraocular muscle.

Immunosuppressant agents such as methotrexate and low-dose cytokines have also been used for their assumed beneficial effect. However, their role in therapy is not clear. We have recent experience with monoclonal antibodies against tumor necrosis factor (Garrity et al., 2004). At the time of this being written, follow-up was limited but this specific immunotherapy appears to hold promise for the future.

The management of this inflammatory tumor, in reality, is a dilemma. We do not have a time-proven, successful treatment protocol. If the adult patient is seen at the time of initial presentation and, by imaging and palpation, the lesion is found to be in the anterior orbit, I would suggest surgical excision. These lesions are usually located behind the orbital septum in the space between the levator muscle complex and periorbita along the bony roof of the orbit. The mass is well delineated, firm, and has reasonably vascular, features that enable almost total removal. However, if the palpebral lobe of the lacrimal gland is also affected, I would not surgically disturb the gland. After excision, I would wait 2 to 4 weeks to note the clinical effect. Further treatment may not be necessary. If the patient is seen some time after a medical remedy has failed to improve an anterior orbital mass, I would proceed with surgical excision as noted in preceding paragraphs.

Involvement of one or more extraocular muscles and adjoining orbital fat is quite a different matter. After a tiny biopsy has established the diagnosis, I would not recommend any further effort to surgically remove the inflammatory mass. Any further surgery will create such a dysfunction of postoperative ocular motility as to far outweigh any beneficial effect on the resolution of the tumorous mass. Also, an attempt to surgically debulk an infiltrative, inflammatory mass in the rear of the orbit may be an exercise in futility, or could make the position worse.

If, on initial presentation, the patient has edema of the optic disk and a loss of vision, $<20/200$, a neuropathy is probably present. This can be treated with orbital prednisone with a 50–50 chance that vision will improve and pain, if present, will be relieved. However, if the patient is examined late in course of the inflammatory tumor, with edema of the disk, pallor of the disk, and vision is $<20/200$, prednisone still should be given to hasten resolution, but the visual loss probably will be permanent.

In children, if the physician is worried about steroid dependency developing with the use of systemic corticosteroid therapy, this may be delayed or minimized by giving intralesional injection of steroid drugs.

In adults, radiotherapy may be used in cases recalcitrant to other remedies or in cases with recurrence. We have used external beam radiotherapy in the range of total dose 2000 to 2300 cGy with mixed results. I do not believe radiotherapy should be used in children because of the danger of retarding orbital bone development and the ever-present danger of late stage (long term) sarcoma some years later.

Finally, there are patients wherein the inflammatory process seems to run a full course over a period of several years, but the eye is blind, still proptotic, immobile, and painful. Relief of pain necessitates exenteration.

MULTIFOCAL FIBROSCLEROSIS

This disorder is a collection of pathologically similar lesions in varying combinations and various anatomical sites that includes *retroperitoneal fibrosis, sclerosing cholangitis, mediastinal fibrosis, sclerosing thyroiditis, and lacrimal gland and orbital pseudotumor*. Before 1967, all these anatomical sites, either as one or a combination of two, were known to be affected by a disorder of fibroblast proliferation. Comings et al., 1967, invented the term, *multifocal fibrosclerosis*, which denoted the unity of the disorders. All the disorders were characterized by an inflammatory desmoplasia, the cause of which is still unknown. Barrett, 1958, seems to be the first to suggest these disorders were interrelated and probably different manifestations of the same disorder of fibrous tissue proliferation.

The histopathology of these lesions is another unifying factor. All lesions, basically, show some degree of inflammatory influx of, predominantly, lymphocytes (with or without follicles), plasma cells, *eosinophils*, a few neutrophils, occasional monocytes, and the cuffing of small vessels with cellular aggregates, but no true vasculitis. The proportion of inflammatory tissue to the developing fibrosclerosis will vary according to whether the disorder is early or late in its course.

Some of the case reports of multifocal fibrosclerosis with orbital involvement, which have since been published or not included in our third edition, are Levine et al. (1993), Aylward et al. (1995), van der Pol et al. (1999), Schaffler et al. (2000), Reittner et al. (2002), and Oguz et al. (2002). These reports included six cases with bilateral orbital involvement and an additional case with unilateral orbital disease. These seven cases included six males and one female. The age range was 32 to 56 years of age with a mean of 45.5 years and a median of 44 years. I think one of the three cases described by Levine is an example of idiopathic, unilateral, orbital inflammation.

Other clinical features common to these multifocal lesions usually were an elevated sedimentation rate, a rather typical imaging display with magnetic resonance, and failure to respond to any sustained treatment. With magnetic resonance, the orbital lesions were intraconal and

of low intensity with T_1-weighted sequence and an even lower intensity with T_2-weighted sequence. The lesions enhance with gadolinium.

The case of Oguz et al., differed a bit from the other cases in showing secondary extension of the orbital lesions into the maxillary sinus and cavernous sinuses.

At this point, we should address the publication, *Idiopathic Sclerosing Inflammation of the Orbit*, by Rootman et al. (1994). These authors studied 16 patients who presented with a unilateral orbital lesion featuring a chronic inflammatory infiltrate and a desmoplastic tissue stroma, the immunopathologic characteristics of which were similar to retroperitoneal fibrosclerosis. We agree with this association. Rootman et al. thought the sclerosing inflammation is a unique *clinicopathologic entity*. In their Table I describing the pathologic features, 11 cases had an *inflammatory infiltrative* process. However, they ''*disagree*'' with our concept that sclerosing orbital inflammation is a process that is part of a *continuum of idiopathic orbital inflammation that has progressed from acute and subacute to chronic inflammation with fibrosis*, with the primary pathologic process changing from predominantly lymphocytic inflammation to fibroplasia. The cases of Rootman et al. presented with ''*the histopathologic findings of paucicellular chronic inflammatory infiltrates of lymphocytes, plasma cells, histiocytes, occasional neutrophils and eosinophils—within an infiltrative desmoplastic stroma—in variable proportions.*''

In the previous section, we reviewed 45 patients, over a long term, with what is now called *Idiopathic Orbital Inflammation*. Only a few of these cases, at the time of presentation, underwent a spontaneous resolution. The majority presented with an acute or subacute inflammatory process that underwent spontaneous resolution or stabilized with treatment. A few went on to a chronic inflammatory stage and end-stage desmoplasia. Neither our collection of 83 cases of idiopathic orbital *inflammation* nor Rootman et al.'s group of 16 patients with idiopathic *sclerosing* inflammation of the orbit had synchronous involvement of a nonorbital site of multifocal fibrosclerosis.

Summary

We believe physicians interested in this subject should discontinue the assumption that each of the following designations, idiopathic sclerosing inflammation, idiopathic orbital inflammation, orbital pseudotumor, retroperitoneal fibrosis, sclerosing cholangitis, mediastinal fibrosis, Riedel thyroiditis, and sellar fibrosis, is a clinical entity. In our view, all the preceding designations basically have the same immunopathologic characteristics and, simply said, are differing manifestations of the same inflammatory disorder. Should this unifying concept eventually be accepted, new terminology is required. We would suggest the term, *idiopathic fibroblastic proliferation*, for the group as a whole. If only one anatomic site is affected, this term could be modified as follows: *Idiopathic retroperitoneal fibroblastic proliferation or idiopathic orbital fibroblastic proliferation*. If more than one site is involved, the term could be modified as follows: *Idiopathic multifocal fibroblastic proliferation*. Finally, the word, *inflammatory*, could be substituted for idiopathic. If, in the future, terminology is simplified, we may get rid, of the word *pseudotumor* forever.

VASCULITIS

Among the multiple, systemic, clinical entities now included in the spectrum of the vasculitides (Fauci et al., 1978), there are two worthy of note because of orbital involvement. These are: *Wegener granulomatosis and Polyarteritis Nodosa*.

POLYARTERITIS NODOSA

Most recently (Nadeau, 2003), polyarteritis nodosa (PAN) has been subdivided into a *classic form* and a more prevalent form, *microscopic polyangiitis* (MPA). The latter is associated with pulmonary hemorrhages, glomerulonephritis, and a perinuclear pattern of antibodies to neutrophil cytoplasmic antigens (P-ANCA). Classic PAN is related to infection with hepatitis B, C, and HIV. It is the classic form that involves the orbit. This form is ANCA negative. The orbital lesions may remain localized to the orbit, may precede or succeed a systemic vasculitis, or may be concurrent with the MPA form of vasculitis. Koike et al. (1993), report a 58-year-old woman with right proptosis that spontaneously improved. Two months later, a mononeuritis multiplex picture led to a sural nerve biopsy, which established a diagnosis of PAN. If ANCA-negative and P-ANCA–positive forms of vasculitis are simultaneous in the patient, the term *polyangiitis overlap syndrome* is applied. The classic form is also idiopathic in most cases.

Incidence

In our 50-year (1948 through 1997) collection of orbital tumors, there are 22 patients with orbital involvement by polyarteritis nodosa. Strangely, we have not seen a patient with either of the two forms of this vasculitis in the period 1985–1997. Therefore, we will base our incidence data on the 40-year period, 1948 through 1987 (1,376 consecutive patients). Furthermore, we have absolutely no follow-up data on three patients of this 40-year collection. Our objective analysis of incidence is based on the remaining 19 patients.

There are 12 males and 7 females in this reduced collection. The age range of this group is 10 to 79 years with an average of 38.6 years and a median of 27.5 years. The orbital inflammatory process in three patients was associated with disseminated PAN, one patient had the overlap type, and the remainder of the cohort had only the

localized form of polyarteritis. Three of the overall group of 22 patients had bilateral orbital lesions.

Clinical Features

At the time of initial presentation, 18 of 22 patients had proptosis, displacement of the eye, and some degree of ocular motility disturbance. These patients also complained of pain. Four of our patients had no pain or proptosis, only slight tenderness in palpation if the orbital mass was located in the anterior orbit. The latter group also had a very low sedimentation rate. In general, the higher the sedimentation rate, the more aggressive and severe the disease and the more resistant the inflammatory process to treatment. As a rule, the early course of this inflammatory orbital process is very similar to clinical features of the idiopathic orbital tumor discussed in an earlier portion of this chapter except, ocular manifestations are more often associated with vasculitic disease.

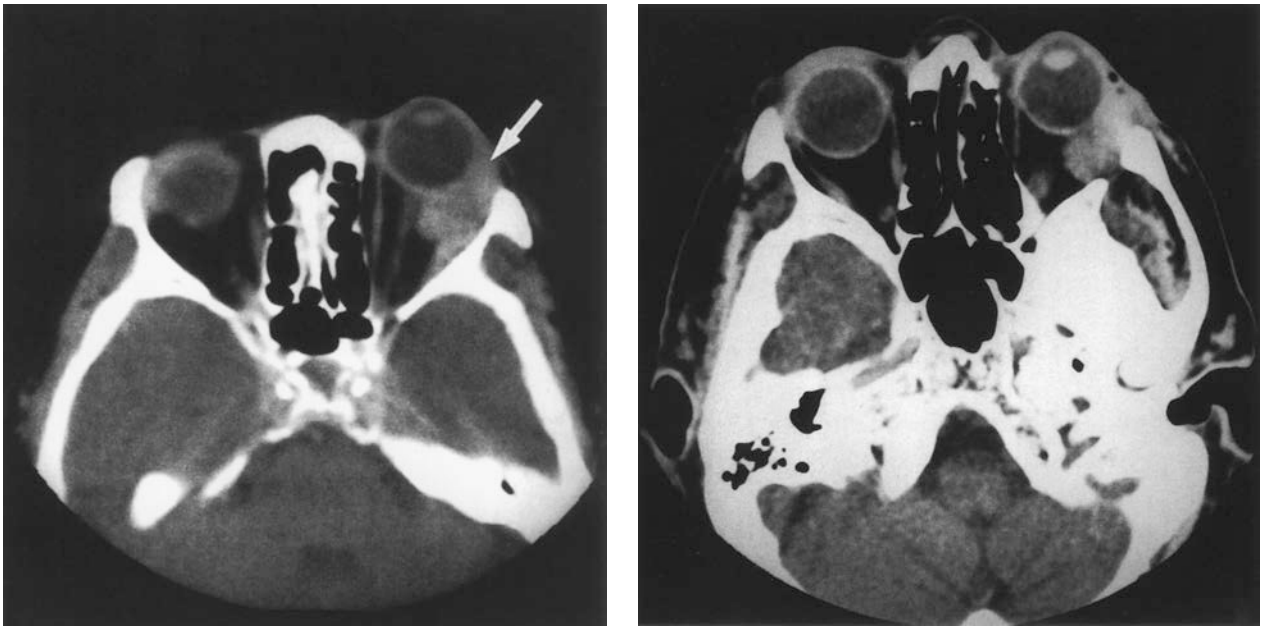
Retinal and optic nerve ischemia, scleritis, corneoscleral ulcers and necrosis, episcleritis, and redness of the eye are more often associated with vasculitis. Systemic symptoms of fever, weight loss, and malaise may herald the disseminated form of PAN. Systemic illness is not a feature of idiopathic orbital inflammation. A routine blood serum ANCA test for proteinase 3 and myeloperoxidase is now available. Patients with classic PAN usually are ANCA negative whereas patients with glomerulonephritis are ANCA positive. Patients with the overlap form of PAN may be either ANCA negative or positive at any given time and, in a long duration of polyangiitis nodosa, may fluctuate from positive to negative ANCA or vice versa.

Imaging Aspects

All of our patients with a vasculitic inflammatory tumor showed an orbital mass. These masses can appear any place in the orbit and can affect any orbital tissue or structure. In this regard, the CT display is very similar to the CT scans of idiopathic orbital inflammation, and I know of no way to differentiate one inflammatory lesion from the other. The lesions show contrast enhancement that increases in density with the severity and duration of the inflammatory process. The reader may choose to review the variety of CT imaging characteristics in the scans illustrated in the preceding section on idiopathic orbital inflammatory tumor. CT imaging of two interesting patients with vasculitis are included in Figures 19.14 and 19.15.

Pathology

The salient features of the histopathology of this vasculitic tumor are illustrated in Figures 19.16–19.19. The inflammatory response is always angiocentric, being limited, initially, to the walls of small- and medium-sized



A B

Figure 19.14 Polyarteritis nodosa: **A:** Axial computed tomography (CT) scan shows large kidney-shaped, well-defined, enhancing mass in the inferolateral left orbit (*arrow*) that appears to involve the sclera and lateral rectus muscle in a 76-year-old woman. The lesion was extensively debulked by a lateral orbitotomy. **B:** Axial CT 5 years later shows less proptosis but definite recurrence of the mass. The posterior border of the mass is irregular when compared to that in **(A)**. Postoperative defect is present in the lateral orbital wall. Clinically, the orbital inflammatory process was still active.

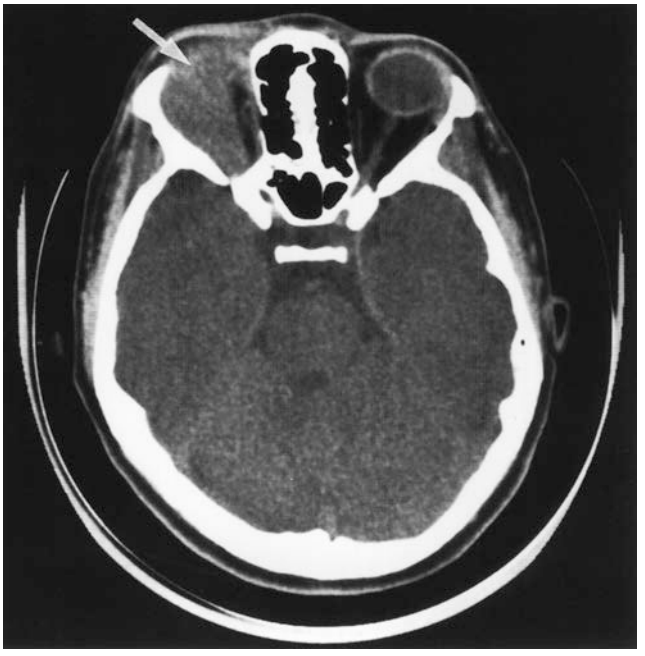


Figure 19.15 Polyarteritis nodosa: Axial computed tomography scan without contrast shows right eye concealed by a large, infiltrative mass (*arrow*) that nearly fills the superior orbit in a 20-year-old woman. Subsequent remissions and recurrence of orbital lesion with only temporary relief from courses of corticosteroids and cyclophosphamide. Orbital mass unchanged over a further 4-year follow-up.

arteries. The inflammatory response principally involves polymorphic leucocytes, lymphocytes, and a smattering of eosinophils. If the inflammatory response progresses, there is narrowing of the lumen of the vessel and extravasation of red blood cells into the interstitium. The latter sets up an inflammatory response in the interstitial tissue associated with an increase of eosinophils and fibrous tissue replacement of orbital fat. If the vasculitis does not come to a spontaneous halt or is resistive to treatment, the affected vessels undergo stellate necrosis, fibrinoid necrosis, and leukocytosis. At this final stage, a subpopulation of granulomatous cells may appear. Finally, all orbital structures and tissues are encompassed by dense fibrous tissue resulting in complete immobility of the eye and severe pain.

Course and Management

The course of our patients is all over the spectrum. Three of our patients experienced spontaneous resolution after no treatment other than biopsy, incomplete removal, or complete excision of the lesion. They have been followed 11, 4, and 2 years, respectively. Three other patients underwent incomplete removal of the vasculitic lesion with additional treatment, two patients with prednisone and the third with a combination of prednisone and radiotherapy. There was no recurrence over a period of 1, 5, and 17 years. Four patients with recurrent tumors were in remission for 1, 3, 7, and 10 years. In addition to incomplete removal of the inflammatory lesion, two were treated with prednisone, and the other two received radiotherapy. Five patients received some combination of cyclophosphamide (Cytoxan), prednisone, and radiotherapy, but the orbital disorder was still active 6, 7, 10, 11, and 14 years later. One of the five also developed the upper respiratory manifestations of Wegener granulosis over a course of 10 years. One patient with both systemic and orbital lesions was treated only with prednisone and was living 6 years after presentation. One patient died nine months after orbital biopsy with disseminated vasculitis. A second patient died two months after diagnosis with extension of the inflammatory process into the cavernous sinus. A third patient was resistant to all modes of therapy and died of WG 10 years after orbital diagnosis.

What conclusions are possible from this heterogeneous data?

1. The course of orbital PAN is unpredictable.
2. The course of the disease may be spontaneous resolution without treatment.
3. Treatment with prednisone is often useful for the control of pain early in the course of orbital PAN.
4. PAN may be fatal among patients who develop disseminated vasculitis during the course of their orbital disease.
5. In the late stages of orbital PAN, enucleation of the eye or exenteration of the orbit may be necessary.
6. Some cases seem resistant to all present modes of therapy.
7. Even though the orbital disease may become quiescent without recurrence after many months or several years, the patient may have sequelae of permanent proptosis, loss of vision, an immobile eye, or blepharoptosis.

WEGENER GRANULOMATOSIS

WG is a disorder of unknown etiology characterized by a necrotizing granulomatous vasculitis that can involve multiple organ systems (Wolff et al., 1974). The disease may exist as a classic triad of respiratory granulomas, generalized vasculitis with or without kidney (glomerulonephritis) involvement. Also, it may occur as a limited form affecting the upper and lower respiratory tract and paranasal sinuses with or without orbital disease. Even a more localized form may involve the orbit with or without ocular manifestations.

Over the 50-year period of my association with the Mayo file of consecutive, pathologically proved orbital tumors, I have been aware of a continuum of WG *variations* that have been noted pertaining to the prior patterns of incidence, clinical features, imaging aspects, histopathology, management, and therapy. In brief, all the preceding features are variable from case to case, and not

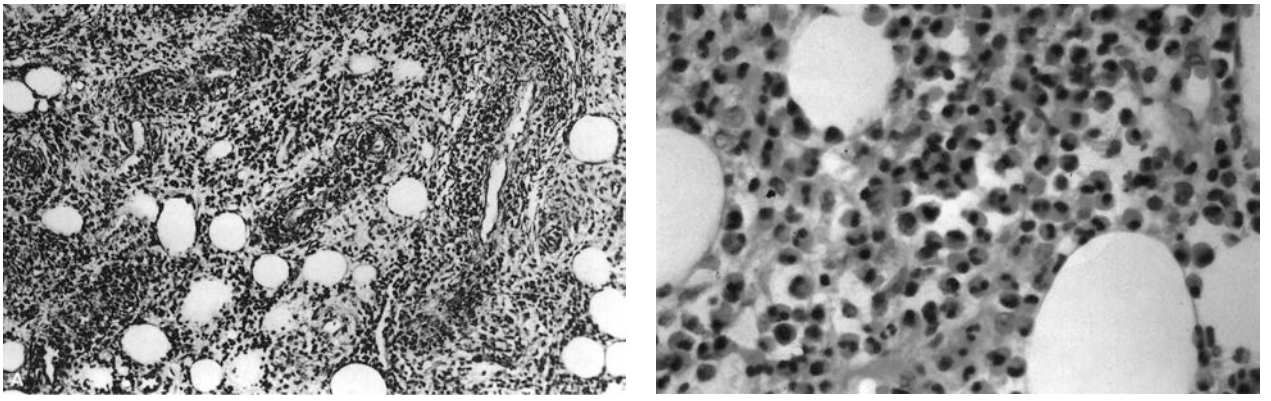


Figure 19.16 **A:** Polyarteritis nodosa: An intense inflammatory reaction associated with multifocal vasculitis and invasion of orbital fat (×120). **B:** A higher power shows a predominance of eosinophils (×400).

all features are necessarily present within a given case, confirmed by biopsy. Before reading the wide range of features attributed to WG in this manuscript, the reader should be aware that all that has been described is not absolute. Many variations exist, as follows:

Variations

1. In regard to incidence, an analysis of the classic form of WG often omits the kidney (glomerulonephritis) arm of the triad.
2. The limited (upper respiratory tract) form and the orbital lesion, if present, is usually considered as one accessory unit if associated with the systemic form of vasculitis.
3. If the limited form of WG is associated with ocular manifestations, the latter is often indexed as an orbital form of the disease, although no orbital lesion is present.
4. If both ocular and orbital WG are present, the two anatomical sites are usually not indexed as separate entities for calculation of incidence data.
5. In the early stages of orbital WG, vasculitis of the arteries may not be present in the biopsy specimen. The ANCA test may also be negative. However, isolated granulomas and stellate areas of necrosis may be present in the interstitial tissue. Both the vasculitis and a positive ANCA pattern evolve as the inflammatory process progresses.
6. A positive ANCA test may become negative or the titer may drop if the WG responds to treatment.
7. The diagnosis of orbital WG must depend on a histopathologic study of an adequate sample of orbital tissue obtained by biopsy.
8. Diagnosis of orbital WG should *not* be made on the basis of ocular symptoms associated with a biopsy specimen from a swollen, florid eyelid.

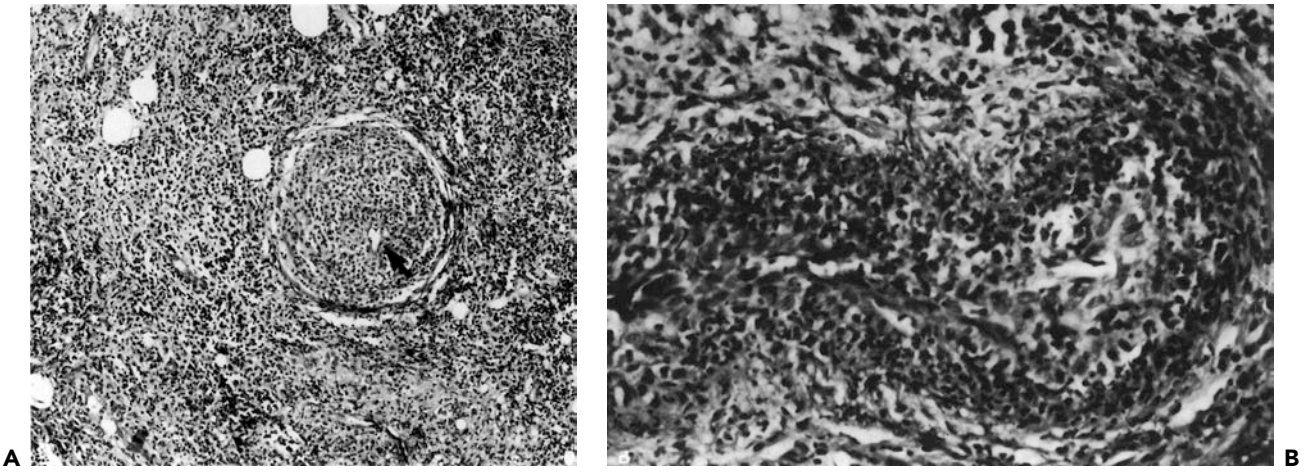


Figure 19.17 Polyarteritis nodosa: **A:** Small artery (*arrow*) shows acute vasculitis in midst of intense inflammation (×160). **B:** Higher power shows massive infiltration of vessel wall by neutrophils and eosinophils (×270).

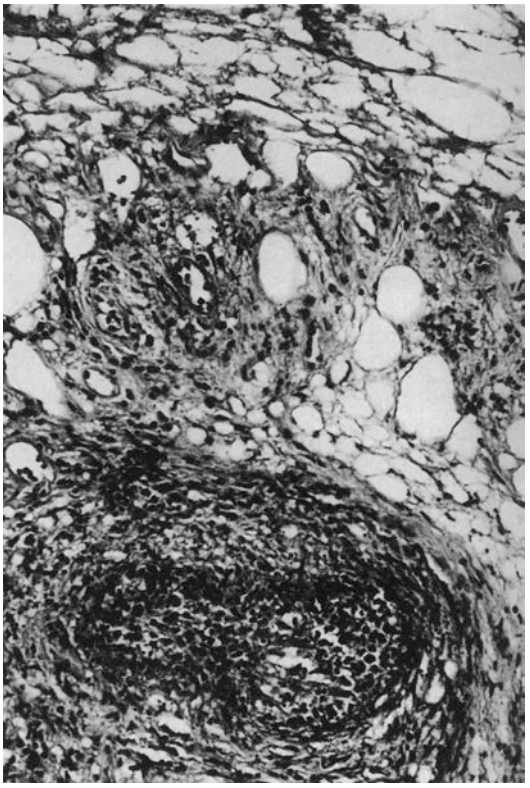


Figure 19.18 Polyarteritis nodosa: Fibrous connective tissue beginning to replace damaged orbital tissue. An area of subacute vasculitis still present below (×160).

Incidence

Fechner et al. (2002) reported a retrospective study of 15 patients with the histologic changes of WG of the orbit presenting over a 23-year period at the Massachusetts General Hospital, Boston, Massachusetts. The median age of these patients was 54 years, with an age range of 6 to 72 years. Eleven were female, and four were male patients. In 12 (80%), the disease was limited to the orbit. In the other three, there was synchronous sinonasal involvement.

In our 50-year survey of orbital tumors (1948–1997), there are 22 cases of biopsy-proved WG, 13 females and 9 males. The age range of the patients is 13 to 77 years with an average of 52 years, and a median of 58 years. Among this group, there are two bilateral cases and one case associated with systemic vasculitis. At this point, our incidence data closely resembles that of Fechner et al. (above). However, the ratio of orbital cases versus synchronous nasosinus involvement differed from the Fechner report. Fifty-nine percent of our cases show sinonasal involvement and 41% orbital lesions. The combined total of sinonasal and orbital cases is 1.5% of total tumors in our 50-year survey.

Other incidence data from the literature are: In more than 90% of patients with WG, the sinonasal tract is most commonly affected (Fauci and Wolff, 1973). WG may affect the eye, orbit, or adnexal structures in up to 50% of cases with the generalized disease (Ahmad et al., 2000). In an analysis of 216 patients with classic WG, orbital disease was found in 14 patients, an incidence of 6.5% (Lie, 1997).

Clinical Features

The *eye* is the fourth most common site of clinical presentation of WG, preceded in decreasing disorder by the upper respiratory tract, lungs, and kidneys (Lie, 1997). The main ocular features are proptosis, a destructive orbital mass with orbital imaging, visual loss secondary to optic neuropathy, scleritis, pain, redness of the eye, and swelling or discoloration of the eyelids. Less common are uveitis, corneoscleral ulceration, and nasolacrimal duct obstruction (Haynes et al., 1977). Initially, the disorder is unilateral, but if WG does not respond to treatment, bilateral involvement is often the rule. These patients with WG localized to either the orbit or the eye or a combination of eye and orbital disease may show involvement of other anatomic sites if WG progresses. However, in general, these patients, as a subgroup, seem to have a less severe form of WG when compared to patients whose orbital disease is preceded by a limited or systemic form of WG.

The latter subgroup of patients presents with involvement of the trachea or lung, have dyspnea, hoarseness, or cough. Those with oral involvement have nonhealing gingival lesions, loose or abscessed teeth, or oronasal fistula. Those with early sinus involvement have face pain and swelling and orbitosinus fistula. Those patients with preceding nasal involvement have rhinorrhea, epistaxis, foul-tasting nasal discharges, mucosal crusting, erosion of the turbinates and nasal septum, and saddle-nose deformity (see Fig. 19.20). Also, there may be severe visceral loss, ophthalmoplegia, erosion of the orbital wall, and epiphora. This subgroup has the worst clinical features of WG.

Tullo et al. (1995) reported four male patients with orbital manifestations of WG who, within a year of onset, developed *bilateral, florid, yellow* eyelid lesions. These eyelid lesions proved to be examples of *xanthelasma*. Abnormalities of lipid metabolism were not identified in these patients. The eyelid lesions gradually resolved as the WG was controlled with immunosuppressive agents.

Imaging Aspects

CT in the earlier stages of orbital involvement usually shows an irregular contoured, infiltrating mass with variable enhancement that may localize to any location in the orbit (see Fig. 19.21). Courcoutsakis et al. (1997) studied magnetic resonance imaging (MRI) of 12 patients with orbital WG. The authors noted that unenhanced, non-fat-suppressed T_1-weighted sequences provided the best contrast between the lesion and normal orbital structures. A variable degree of enhancement is present in lesions of

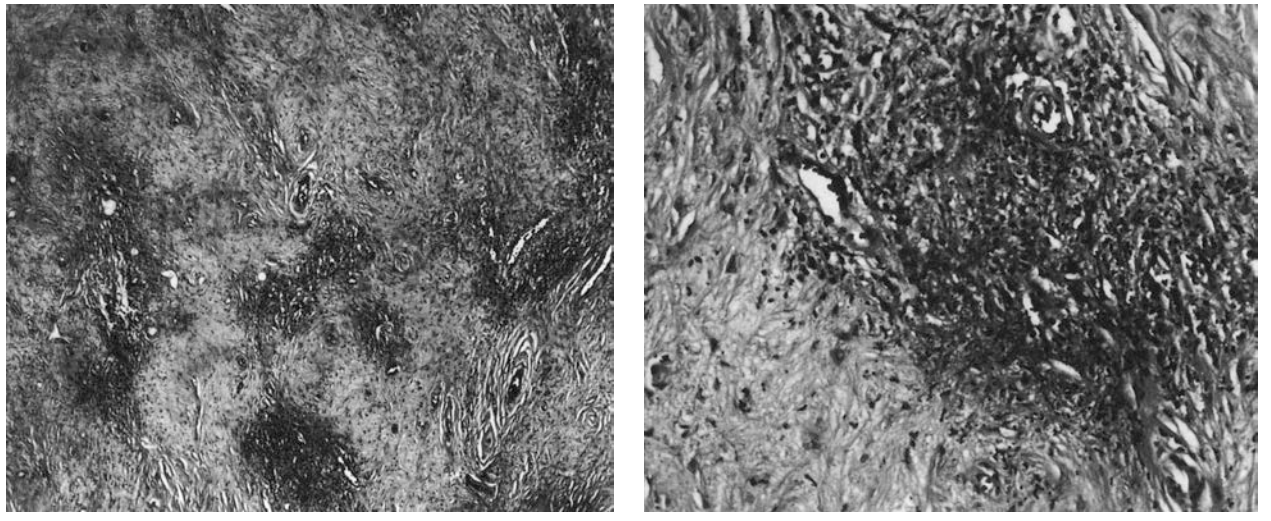


Figure 19.19 Polyarteritis nodosa: **A:** Low power shows scattered foci of necrotizing vasculitis surrounded by dense fibrosis (×40). **B:** Detail of necrotic vessels with nuclear dust and fibrinoid necrosis (×160).

WG. A marked decrease in the T_2 signal is a characteristic feature of these lesions.

In those cases of orbital WG that progress to a final stage of fibrosis, CT will show a more homogeneous mass with minimal enhancement that fills the entire orbital space (see Fig. 19.22). This *wall-to-wall* imaging display is *almost* unique to WG. This feature is also seen in patients with retained foreign bodies of long standing. This overwhelming inflammatory response also occurs among patients who undergo orbital decompression through the sino-orbital route wherein orbital gauze packs impregnated with foreign substances (particularly petroleum jelly [Vaseline]) are placed in the orbital space for various reasons (myospherulosis).

Pathology

WG can involve virtually any, and often, a multitude of organ tissues (Lie, 1997). The histopathologic manifestations of the systemic form of WG include the classic triad of upper airway, lung, and kidney in 87%, 69%, and 48%. Lie also lists 11 other organs or sites that may be affected. These sites are designated as *limited* forms of the disease. The orbit belongs in this latter class.

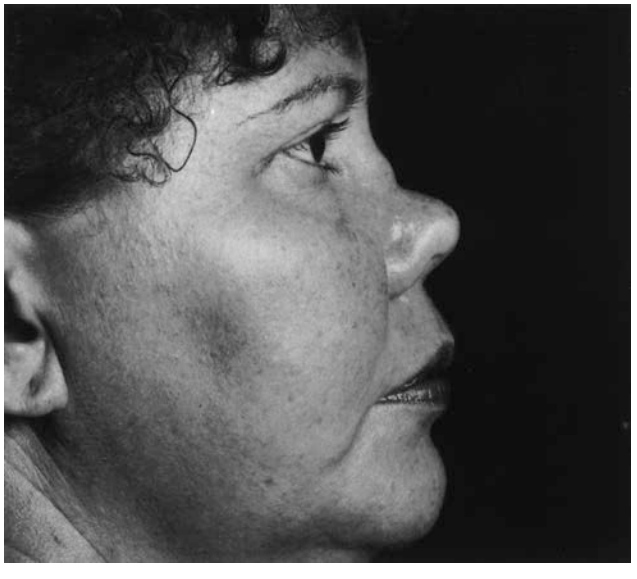


Figure 19.20 Wegener granulomatosis: A 39-year-old woman shows the saddle-nose deformity due to destruction of the intranasal cartilaginous support.

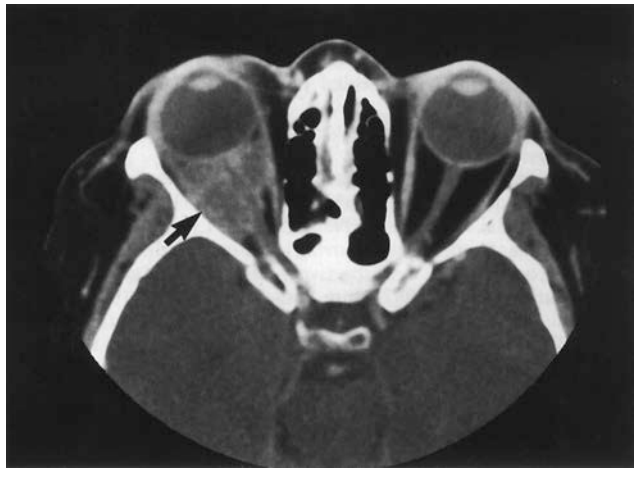


Figure 19.21 Wegener granulomatosis: Axial computed tomography scan shows a large, irregular mass in retrobulbar space (*arrow*) of right orbit with variable enhancement and infiltration of optic nerve sheath in a 46-year-old woman. Compare with Fig. 19.15.

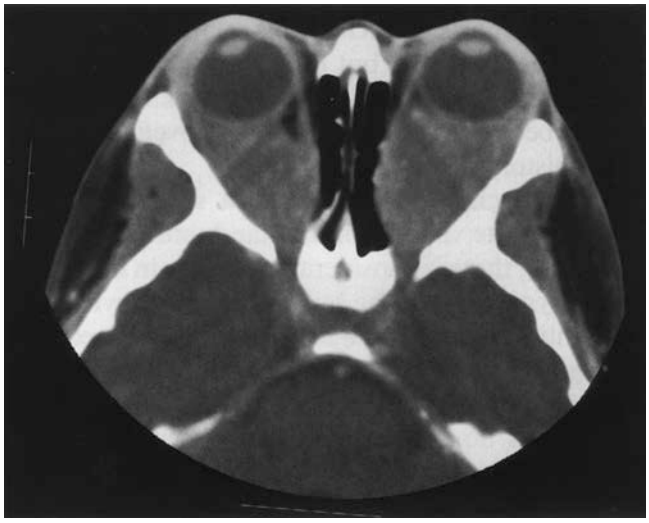


Figure 19.22 Wegener granulomatosis: Axial computed tomography (CT) scan shows bilateral infiltration of the entire retrobulbar orbit and forward extension along the lateral surface of each eye by a slightly enhancing, diffuse mass in a 23-year-old woman. The diffuse, molded, homogeneous appearance of the bilateral mass is not unlike a lymphoma. Also, the proptosis is relatively mild in degree when compared to the extent of the bilateral mass. Seven years earlier, lung and renal biopsies showed active Wegener granulomatosis. The patient was treated with prednisone and cyclophosphamide for $2\frac{1}{2}$ years with remission. One year later, proptosis commenced in the left eye, soon followed by proptosis of the right eye in spite of resumption of systemic therapy. At the time of this CT scan, the serum anticytoplasmic antibody test was slightly positive.

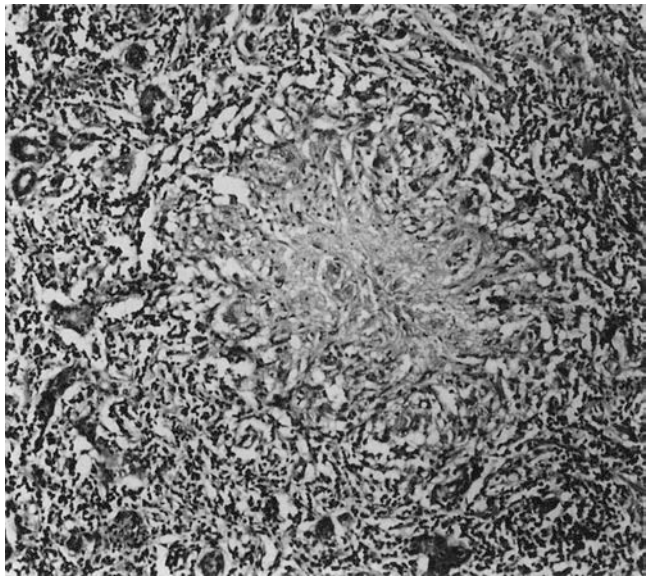


Figure 19.23 Wegener granulomatosis: Dense infiltrate of inflammatory cells with a focal necrotizing granuloma (×64).

The salient histopathologic features of orbital cases include leucocytoclastic vasculitis of arterioles and veins or granulomatous angiitis (see Fig. 19.23) in about equal numbers, some undergoing fibrinoid necrosis, and mixed-cell chronic inflammation of the interstitial tissue or a predominantly granulomatous inflammation with or without giant cells, with multifocal areas of necrosis (see Fig. 19.24). Vasculitis alone is never seen (Kalina et al., 1992). All of the preceding histopathologic components are usually not present at any given time in any patient, but as the inflammatory process evolves, all components will appear at some time or another.

In some cases in which the limited sinonasal form of WG also is present, there may be some difference in the nasal and orbital pathologic findings (Kalina et al.). Nasal biopsies usually show a more severe inflammatory response that includes a greater number of multinucleated giant cells and eosinophils than orbital specimens.

The routine use of the serum ANCA tests as a supplement for the diagnosis of WG occurred in the mid 1990s (Kaufman et al., 1994). They are a specific marker for patients who present with the histopathologic features suggestive of WG (Soukiasian et al., 1992). The tests demonstrate the presence of antibodies toward components of primary granules of neutrophils and monocytes. There are two specific types. In one, radioimmunoassay shows a cytoplasmic pattern of staining (C-ANCA), confirming the presence of auto-antibodies to the proteinase 3 antigen. In the other, perinuclear or nuclear staining (P-ANCA) identifies antibodies to myeloperoxidase. Patients with WG will show positive staining to either of these ANCA tests. At the time of initial presentation of a patient with presumed orbital WG, based on histopathologic features, the ANCA test may be negative, but positivity will appear as the inflammatory process progresses. On the contrary, if a patient's disease improves or becomes stable in response to treatment, a positive ANCA may become negative. The ANCA tests are

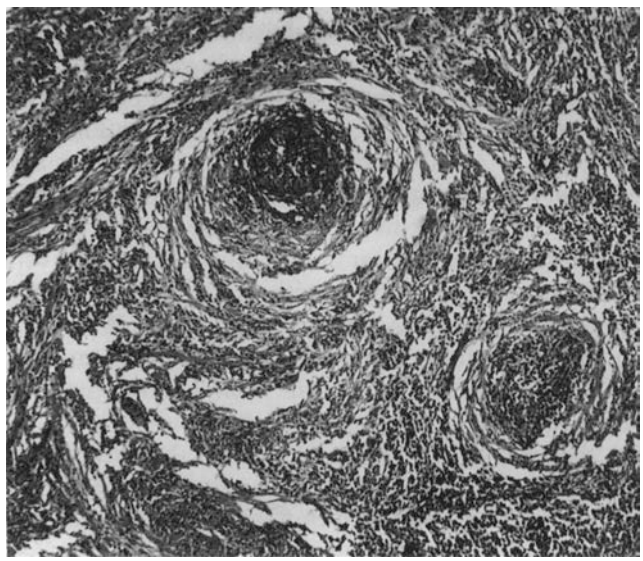


Figure 19.24 Wegener granulomatosis: Vasculitis involving small muscular arteries (×125).

also useful in the differentiated diagnosis of WG and the preceding PAN. In the purely vasculitic type of PAN, the ANCA is negative. However, PAN associated with necrotizing glomerulonephritis will show a positive P-ANCA, probably due to some granulomatous features of the inflammatory response.

Course and Management

There is no other lesion in this volume that, in a high percentage of the affected patients, causes such havoc and destruction of the eye and orbit as WG. The eye and the orbit may be affected either alone or in combination. The longer the duration of the disease, the greater the number and severity of the complications and sequelae.

Our follow-up of the total 22 patients with *orbital* manifestations of WG confirms this assessment. Most (17/22) patients in our 50-year survey have follow-up data longer than 2 years. Our conclusions concerning the course of orbital WG are based on the subpopulation of 17 cases as follows:

1. The range of follow-up is 25 months to 23 years.
2. The median follow-up period approximates 9.5 years.
3. Two patients with synchronous orbital and systemic WG died.
4. Two other patients died, with death being attributed to heart failure in one and cerebral infarct in the other. These patients were under treatment for active WG at the time of death.
5. Two additional patients are deceased, but neither the cause of death nor the status of their disease is known except they were under therapy for active disease up to 2 and 3 years, respectively, before death.
6. In four patients, the disease is stable, and treatment has been discontinued. One was treated for 2 years with no recurrence over an 18-year period. A second patient was treated for 5 years and has been off treatment for 26 months. A third patient was treated for 16 months and has been off treatment for 62 months. The fourth patient is stable after 6 years of therapy.

Patients with active disease, who underwent treatment, usually received a variety of medications, either alone or in combination including corticosteroids, chlorambucil, azathioprine, trimethoprim, sulfamethoxazole, and cyclophosphamide. One patient did not receive any medications but received radiotherapy (3,000 cGy) for want of a more suitable treatment option. In most of our patients, any or all the present therapies are only partially effective.

In 7 of the 17 patients, other manifestations of the limited form of WG were present such as, lung infiltrate, tracheal disease, and sinonasal lesions. In five of these combined cases of disease, bone destruction of the medial or inferior walls of the orbit was present.

Unfortunately, when the inflammatory process reaches the final state of arrest, the damaged orbital tissue does not dissolve or disappear. Instead, there is a residual mass of fibrous tissue. The size of the mass is roughly related to the duration of the orbital WG. Such cases are permanently crippled by various degrees of proptosis, visual loss, cataract, cicatricial contraction of an eyelid, blepharoptosis, nasolacrimal direct obstruction, orbitoantral fistules, and pain. The most common residual is severe impairment of ocular motility. These complications are a tremendous psychological burden. One patient in our series illustrates the acme of despair. This 30-year-old woman was first seen at Mayo with bilateral WG of 14 years' duration affecting the upper respiratory structures, nose, sinuses, orbit, and eye. Eight years later, the disease came to a halt, but in the mean time, enucleation of one eye was performed because of pain.

In the 1950s, in my experience with orbital WG, I assumed that early in the course of the disease, debulking of the inflamed orbital tissue might have a favorable effect by reducing the volume of affected areas requiring treatment. Over the subsequent decades, I realized that surgical debulking, as a treatment option, had no more effect on the course of the disease when compared to either biopsy or simple excision. If, on presentation, the patient has some impairment of visual acuity, probably an indication of compressive optic neuropathy, a subtotal excision of affected tissue should not be attempted. Even though the surgical excision is refined, the patient's vision postoperatively will be worse. Representative biopsy is sufficient. The only reason for debulking or exenterating orbital tissue is the relief of pain in patients with end-stage disease.

In the future, I believe physicians would have a better appreciation of the ravages in the eye or orbit by WG if their hurry to report a patient's favorable response to short-term therapy was postponed until an interval of 5 years had passed. The case reported by LaPointe and Peloquin (2002) illustrates this point. Their patient was a 50-year-old female with orbital WG that had developed over a three-week period. Her initial visit was June 1999. Over the next 4 months, the patient had such a favorable response to intravenous cefuroxime and clindamycin that therapy was stopped. In January 2000, five months later, the orbital disease recurred. She was treated with a combination of sulfamethoxazole/trimethoprim, oral prednisone, and oral cyclophosphamide. Ophthalmologic exam 2 months later revealed a normal visual acuity. She was still in remission at 18 months of follow-up (i.e., a course totally 29 months). This sounds fine. However, recurrent disease is common among patients with orbital WG. If the patient of LaPointe et al. were followed up for another 3 years (5 years total), and such recurrences continued, it is likely the result would be less favorable than initially reported. But, we will never know. Patients suffering the unfavorable sequences of WG are less likely reported when compared to patients with a favorable outcome.

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20 Miscellaneous Orbital Tumors

This chapter is reserved for discussion of tumors that do not quite fit the subject matter or titles of previous chapters, and tumors of such uncertain origin that a classification has not been universally accepted.

ALVEOLAR SOFT PART SARCOMA

The name of this tumor tells us something about its histopathologic pattern (alveolar or pseudoalveolar), its predominant anatomic sites (soft parts), and malignant course (sarcoma). The tumor is unusual because its histogenesis is uncertain and its clinical course is erratic and unpredictable. Also, considering the tumor has been known since 1952 (Christopherson et al., 1952), it is foremost among all the orbital tumors in this text, time-wise, to have the least amount of publications concerning its nature.

Over the past 50 years, several names have been proposed to correctly identify the histogenesis of the tumor. These are: Malignant nonchromaffin paraganglioma, malignant granular cell myoblastoma, malignant angiosarcoma, malignant angioretinoma, and a unique form of rhabdomyosarcoma. Alas, none of these terms have been universally accepted.

Our own experience with alveolar soft part sarcoma (ASPS) is very limited. We have seen a few cases over the past 50 years, which were sent for clinical evaluation of a *probable* ASPS but returned home for ultimate definitive histopathologic diagnosis and management. There are no cases of ASPS listed in our 50-year registry of orbital tumors.

Incidence

Incidence data in the third edition of this text (1994) were largely based on publications before 1990. The two publications of the largest series of cases are Enzinger and Weiss (1978) and Lieberman et al. (1989). The former publication was based on 143 cases from the file of the Armed Forces Institute of Pathology. They listed the cases in the order of decreasing frequency and involvement of soft tissues of the lower extremity (thigh), head and neck, upper extremity, and trunk. In the head and neck, the tongue and orbit are the most frequent locations for ASPS.

Lieberman et al., analyzed 102 patients from the file of the Sloan-Kettering Cancer Center in New York City. Sixty-one of the patients were female, and 41 were male. The median age at diagnosis was 22 years (range 2 to 71 years) for females and 27 years (range 5 to 56 years) for males.

The publication of Font et al. (1982) was 12 cases of strictly orbital involvement, 9 cases from their own files and 3 individual case reports from three other authors. In addition, they acknowledged single case reports of ASPS of four publications prior to their review. The age range of these 16 cases was 10 months to 69 years with a median of approximately 20 years.

A recent update is that of Coupland et al. (1999). Their review of the literature disclosed reports totaling 50 cases of primary orbital ASPS. Orbital cases most often occur in children.

Clinical Features

These patients usually present with a painless, straightforward proptosis due to a soft tissue mass in the retrobulbar space of 4 to 6 weeks' duration. If the mass is more forward in the orbit, between the eyeball and orbital wall, there will be some displacement of the eye with or without diplopia.

Imaging Aspects

On computed tomography (CT), the mass is smooth, well defined with bright enhancement. Magnetic resonance imaging (MRI) shows a high signal intensity relative to

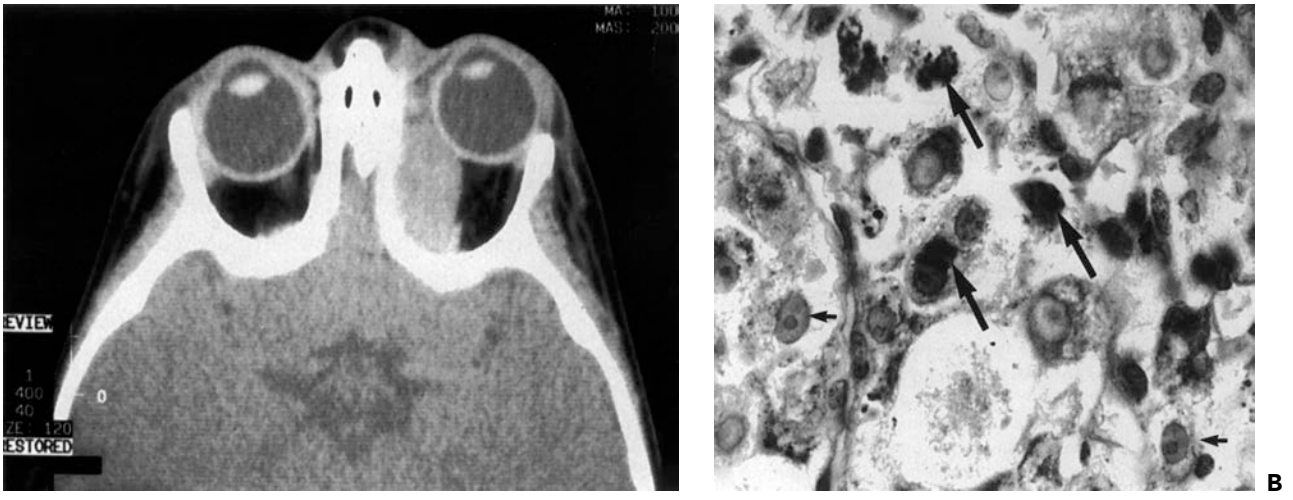

Figure 20.1 Alveolar soft part sarcoma. **A:** Computed tomography scan shows a large, oval, brightly enhancing, circumscribed mass along the medial wall of the left orbital of a 10-month-old boy. **B:** Biopsy specimen shows several tumor cells containing numerous diastase-resistant, periodic acid-Schiff (PAS)-positive granules (*long arrows*) in their cytoplasm. Also note the vesicular nuclei (*short arrow*), with prominent nucleoli (PAS after diastase, ×1,000). (From Jordan DR, MacDonald H, Noel L, et al. Alveolar soft-part sarcoma of the orbit. *Ophthal Surg.* 1995;26(3):269–270, with permission.)

muscle on T_1-weighted scans. Angiography will show flow voids (see Fig. 20.1A).

Pathology

Grossly, these tumors are soft, well circumscribed, with or without a pseudocapsule, well vascularized, and with a pink, tan, or reddish brown color. Microscopically, the polyhedral cells are arranged in an organoid pattern and the groups of cells are delineated by sinusoidal vascular channels (see Fig. 20.1B). The center of a polyhedral group may appear hollow, because of necrosis, and it is responsible for the term, *pseudoalveolar*, rather than alveolar in reference to the gross pattern of the tumor. The cytoplasm is granular, eosinophilic, and periodic acid-Schiff (PAS) reagent positive. The granular material seems to be the precursor of the diastase-resident crystals, which have never been demonstrated in any other neoplasms (Enzinger and Weiss, 1978). The nuclei of the cells are large and vesicular with prominent nucleoli (see Fig. 20.2). Mitosis is sparse.

Immunohistochemistry

"Immunohistochemical staining showed positive immunoreactivity for neuron-specific enolase, vimentin, p53 (30%), p21 (10%) and cyclin D1 (20%), and negative immunoreactivity for CD45, cytokeratins, S-100 protein, glial fibrillary acidic protein, synaptophysin, chromogranin, calcitonin, serotonin, thyroglobulin, desmin, myosin, actin, HMB-45, pRB, p16, and BCL-2. The endothelium of the tumor blood vessels was demonstrated using JC70a and CD34. The growth fraction of the tumor cells was 3%" (Coupland et al., 1999).

Management and Course

Over the 50-year period this neoplasm has been known, wide and complete local excision of the tumor has been accepted as the best means of controlling the disease. Owing to the scarcity of data, the effectiveness of radiotherapy and

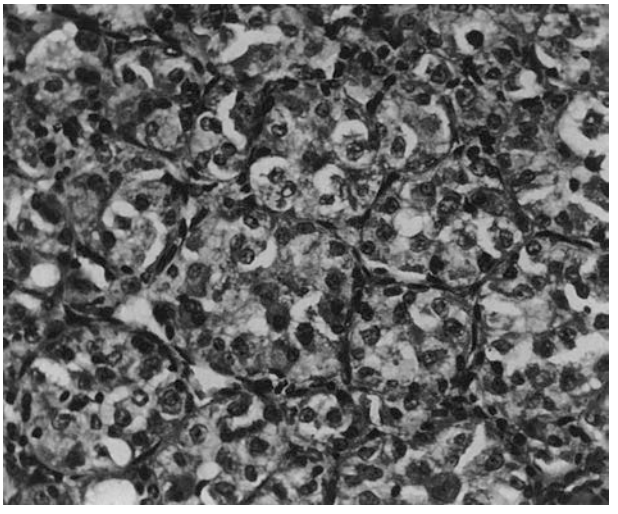

Figure 20.2 Alveolar soft part sarcoma. Specimen from buttock of a 24-year-old woman showing large polygonal cells with abundant cytoplasm arranged in discrete nests, in an organoid pattern. Note some degeneration and sloughing of tumor cells in the center of the nests, simulating an alveolar configuration (×245).

chemotherapy is difficult to evaluate. At present, their roles seem limited to treatment of recurrences. A tumor larger than 50 mm in diameter seems to be associated with higher incidence of local recurrence and metastasis (Lieberman et al., 1989). The tumor may metastasize late in its course, with a median time of 6 years. Thirty-eight percent of recorded metastases appear 10 years after diagnosis. The appearance of metastasis worsens the prognosis, with a median survival of approximately 3 years. There are several exceptions to this survival period reported in the literature. One of these is two survivors of 16 years duration, reported by Font et al., 1982. Metastasis usually occurs in the lung or skeletal bone. Exenteration of the orbit is usually reserved for recurrent tumor.

ECTOPIC LACRIMAL GLAND

The word *ectopic* is applied to the displacement or malposition, especially if congenital, of some tissue or organ from its usual anatomic position. The terms *aberrant* and *heterotopia* are also used in the same context. In ophthalmology, the descriptive designation, aberrant, is usually reserved for isolated choristomatous nodules of lacrimal gland tissue on the surface of the eye. For the deeper deposits of misplaced lacrimal gland in the orbit, ectopic seems to be the preferred term.

In the orbit, we believe it is preferable to restrict these terms to lacrimal gland deposits that are surgically proved to be separate from the normal glandular structure in the lacrimal gland fossa. In the past ophthalmic literature, these terms have sometimes been misused to describe some abnormality in the configuration or function of the lacrimal gland in its normal anatomic site. The latter, in particular, is evident in some case reports, in which lacrimal gland tissue is surgically encountered in the posterolateral retrobulbar space considerably posterior to the normal position of the lacrimal gland. In these cases, a definitive cleavage between the excised tissue and the lacrimal gland is not demonstrated, and the tissue specimens usually show an infiltration of mononuclear cells compatible with nonvasculitic inflammatory tumor in an expanded portion of lacrimal gland.

In the course of an anterolateral orbitotomy, we have occasionally encountered lacrimal gland tissue extending posteriorly toward the orbital apex. These cases always proved to be a posterior extension and enlargement of the lacrimal gland to accommodate a tumefaction associated with a cyst, an inflammatory lesion, or a neoplasm. This situation should not be considered an example of ectopic lacrimal gland.

In a review of the case reports in the literature that fulfill our stricter definition, the ectopic lesion may present in one of three ways. Most often, a small orbital mass is present at birth, or proptosis becomes manifest sometime in the first decade. In either case, the enlargement of the mass is exceedingly slow and, other than proptosis, symptomless. Therefore, removal of the ectopic structure is often delayed. Such was the case with the patients reported by Rush and Leone (1981), a 9-year-old boy; and Baldridge (1970), an 18-year-old male. The ectopic mass removed from a 6-month-old girl (Guy and Quisling, 1989) was believed to be nonprogressive.

In the second type, a relatively sudden proptosis heralds an otherwise dormant heterotopic lesion. The tissue excised from such a case usually shows a diffuse infiltration of inflammatory cells of some degree, suggesting that a reactive response to the ectopic tissue is responsible for the acute proptosis. The cases reported by Jakobiec and Font (1986), a 69-year-old man; Guy and Quisling, a 16-month-old boy; and Green and Zimmerman (1967), a 45-year-old woman may be of this type.

Last is the change that occurs in an ectopic nest that undertakes some secretory function, resulting in an epithelial-lined cyst similar to a ductal structure in the normal gland. Such was the mass near the supraorbital notch of a 16-year-old girl reported by Green and Zimmerman (1967). The cystic structure was drained but not completely excised. Five years later, another orbitotomy was performed to excise a recurrent cyst along the medial orbital wall. Postoperatively, the patient's proptosis persisted. The patient was killed in an automobile accident shortly thereafter. An autopsy was performed that showed a malignant transformation (adenocarcinoma) of the ectopic lacrimal gland remnants.

A recent report of an orbital ectopic gland cyst (Kao et al., 2000) can be added to the preceding list. A 33-year-old man had a palpable mass above the *inferior* medial orbital rim for nearly 2 years. On CT scan, the mass was near the inferior rectus muscle. It appeared to be a thin-walled cyst measuring $15 \times 12 \times 13$ mm containing clear fluid. The cyst was enucleated intact. It consisted of a small nest of normal lacrimal tissue surrounded by a cyst lined with two layers of lacrimal duct epithelial cells. Neither of the reports of lacrimal gland ectopia by McCulley et al. (2002) and Sakurai et al. (1997) meet our strict requirements for inclusion in the preceding lists.

According to Spencer (1996), when the lacrimal anlage is laid down by evagination of the superotemporal embryonic conjunctival epithelium into the anterior orbital soft tissues, small sequestrations apparently are able to migrate farther into the deeper orbital soft tissues. These lacrimal anlagen deeper in the orbit lose their ductular continuity with the conjunctival sac; with the progressive buildup of secretion, the secretory fluids extravasate into the surrounding orbital tissues, inciting an inflammatory and fibroblastic response capable of creating proptosis. These lesions may be found in other quadrants of the orbit as well as in the deep retrobulbar space. Clinical correlation is required to make the diagnosis, because the tail of the lacrimal gland may extend in rare cases almost to the posterior aspect of the globe on the temporal side. Although most of the complications of this ectopic tissue

are inflammatory, vascular lesions, benign mixed tumors, and even poorly differentiated carcinomas have developed in relation to ectopic orbital lacrimal gland tissue.

Management of the ectopic mass is surgical excision, preferably intact removal.

TERATOMA

In the previous three editions of this text, we included teratoma among the developmental cysts, which are thought to be congenital choristomas of the orbit. Currently, it is considered a benign *neoplasm* arising from all three germ layers: Ectoderm, mesoderm, and endoderm. It is principally a tumor affecting the ovary and testis. Early in embryogenesis, germ cells may become misdirected, resulting in multiplication in diverse sites such as the orbit. Teratomas are the most common of the germ cell tumors. The prefix "tera" is derived from the Greek *teras* meaning *monster*. The latter noun is an apt description of the stark, horrendous presentation of many orbital teratomas at birth. Ophthalmologists have long regarded "the monster" tumor as a curiosity and been eager to report its occurrence. In our first edition (1973), we noted 28 case reports of primary orbital tumor, but this did not include cases indexed in the foreign literature, which were not available for review. In our "update" review of the literature since 1989, there are nine additional reports: Weiss et al. (1989); Majak et al. (1991); Spinelli et al. (1993); Assalian et al. (1994); Bilgic et al. (1997); Lee et al. (1997); Sharma et al. (1997); Ameh et al. (1999); and Sreenan et al. (1999). All of these are single cases except the two patients of Weiss et al. (1989). On the basis of the above numbers, a casual reader not knowledgeable on the subject might assume orbital teratomas are not uncommon. However, most of the cases in the world literature are a description of a single case reflecting the author's wish to describe the first, and probably a once-in-a-lifetime, encounter with an orbital teratoma.

Actually, the tumor is rare. Most publications dealing with childhood neoplasms estimate the incidence approximates 1%. In our 50-year (1948 to 1997) survey of 1,795 tumors (Table 3.3), the incidence is 0.0016% (3/1,795). Most reviews of this tumor in the literature include a few reports of malignant teratoma. Since 1989, we found two such references (Steinkuller and Font, 1997; Halperin, 2000). These can be added to the several malignant teratomas cited in previous editions of this text.

Two of the three teratomas in our 50-year survey (Table 3.4) were in newborns. The other was in a 30-year-old man. In the orbit, females are affected more than males in a ratio of about 2:1. For some unexplained reason, the tumor seems to occur more often in the left than in the right orbit. The peak age for presentation is at birth or in the neonatal period. The frequency of the tumor falls off sharply after the age of 2 years. More rare than neonatal teratomas are those occurring in adolescents and adults. There is little factual data about orbital teratomas in age-groups other than infancy. Usually, tumors of adolescents and adults are slow growing and asymptomatic except for proptosis or displacement of the eye. At surgery, such a teratoma resembles a well-circumscribed dermoid cyst, and the histopathologic diagnosis is a surprise to both clinician and pathologist.

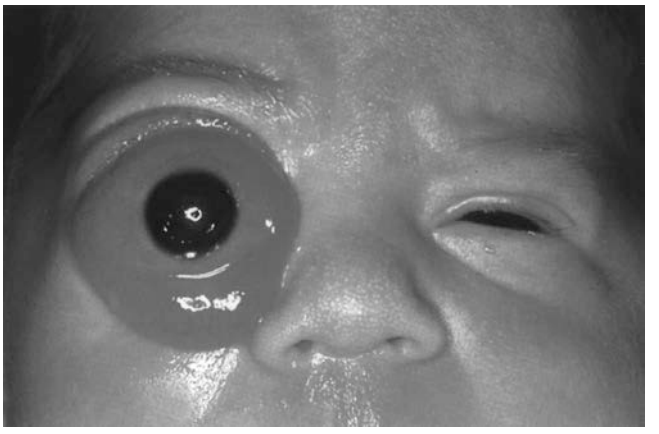

Figure 20.3 Teratoma, right orbit. (From Shields JA, Shields CC. *Orbital tumors*, 3rd ed. New York: Raven Press; 1994:31, with permission.)

Clinical Features

Shocking, startling, spectacular, and horrendous are adjectives used to describe congenital primary orbital teratomas that have grown so large in utero the neonatal eye is pushed far beyond protection of its eyelids and lies helplessly atop a mass resembling a red tomato (see Fig. 20.3). The mass may reach a diameter of 10 cm (Neiger and Sacks, 1989). The case of Assalian et al. (1994) had 20 mm of proptosis. Although these huge tumors remodel bone, they seldom cause osteolysis. Assalian et al., estimated the orbit of their patient was twice normal size. Recurrence is unusual after excision.

Cranio-orbital teratomas are also massive and associated with bone destruction. They are often detected by ultrasonography before birth. Although the cranial lobe of the tumor may be smaller than the orbital lobe, the nidus of tumor is probably on the intracranial surface of the sphenoid bone or orbital fissure. Extirpation or excision by whatever route is difficult and the tumor is prone to recurrence, necessitating multiple surgical procedures before the nidus of the tumor is found and eradicated.

Less dramatic is a bulging but normally developed eye that is still partially covered by eyelids but is obviously displaced by a yellow-white orbital mass (see Fig. 20.4A). Such an eye has a dilated pupil, a defective pupillary light reflex, but still retains vision. Last is the infant who develops a puffiness of a lower eyelid a few weeks after birth, followed

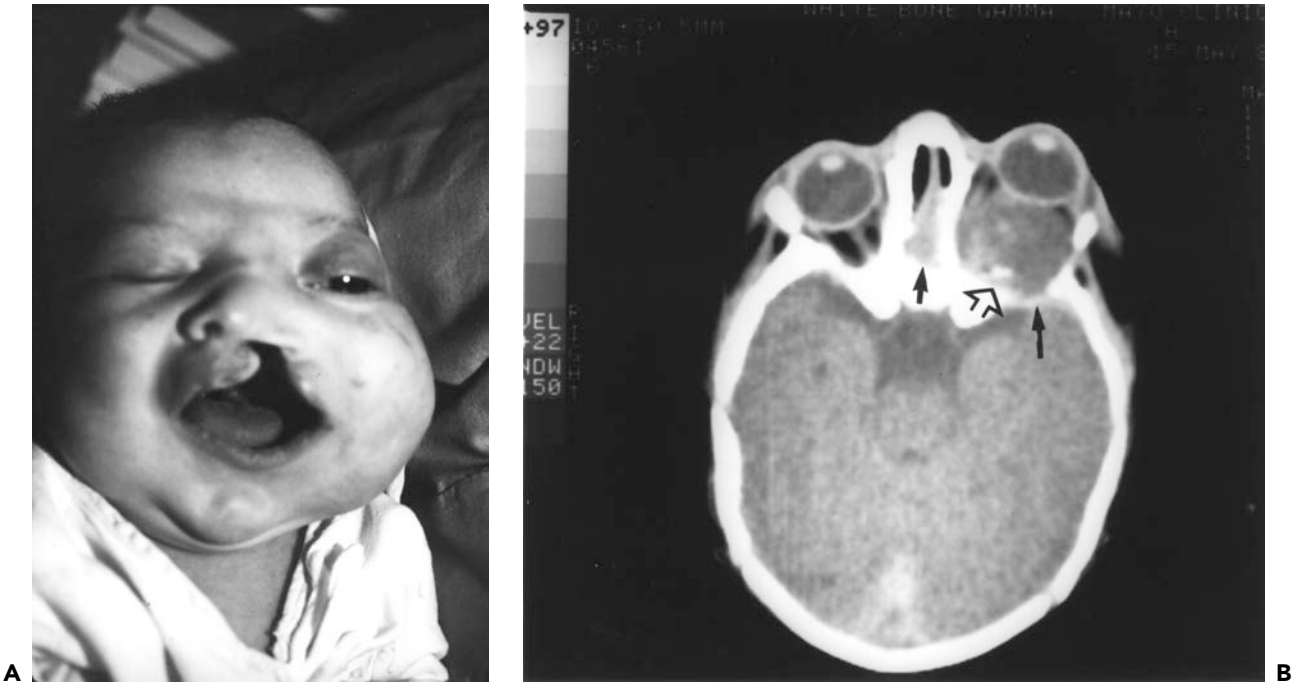

Figure 20.4 **A:** Five-day-old child with teratoma, left orbit and face. **B:** Teratoma: Axial computed Tomogaphy scan of 7-day-old boy with large teratoma (*open arrow*) of left orbit. Note the heterogeneity of contents and calcific densities. Both cartilage and bone were found in the mass after its excision. Note the enlargement of the orbit and erosion of greater wing of sphenoid bone *(long arrow*). Tumor extended into ethmoid sinus (*short arrow*) and pterygopalatine fossa.

by gradual proptosis of the affected eye. A palpable mass develops several months later, which roughly corresponds to the time the infant is brought for consultation.

A CT scan should be performed on all patients presenting with a congenital teratoma. CT scan easily defines the size of the mass, the relationship to the optic nerve, any enlargement of the orbit, and, most important, any bone destruction. The latter would probably indicate involvement of intracranial tissue. CT scan also visualizes the heterogeneous content of the tumor, including calcium deposits (see Fig. 20.4B). Calcific densities differentiate teratoma from other orbital tumors in the neonatal age-group. MRI scans with fat suppression also show a mass with solid and cystic content.

Pathology

Histologically, the primary orbital teratoma shows a variety of tissues derived from the three germ layers in all stages of maturation. Derivatives of ectoderm are keratinizing squamous epithelium and adnexal glandular structures. Mesoderm derivatives are cartilage, fat, fibrous tissue, muscle, and bone. Endoderm is represented by gastrointestinal mucosal and glandular tissue (see Fig. 20.5A, B). Secondary orbital teratomas also have a mixture of immature neurologic tissue, neuroblastic cells, pigmented and nonpigmented neuroepithelium, and calcification (see Fig. 20.5C). The tissue specimen from the case of Assalian et al. (1994) showed positive immunostaining for alpha-fetoprotein, but blood serum levels were normal.

Surgical Management

Currently, the goal of surgery for primary orbital teratoma is removal of tumor, if possible, but retention of the affected eye with its optic nerve. Although the eye has little or no vision, a blind eye is a better cosmetic appendage than no eye at all. Also, a retained eye may preserve orbitofacial development. The larger the tumor, the more difficult is the cleavage of the two masses. Nevertheless, in the past decade or so, surgical techniques have improved. The huge tumor reported by Assalian et al. (1994) (vida supra) was removed with preservation of the eye, by a lateral orbitotomy in spite of firm adherence between posterior wall of the eye and tumor. Vision of the eye was profoundly reduced. No recurrence of tumor occurred over a follow-up of 16 months. Lee et al. (1997) also successfully removed a teratoma preserving the globe and vision.

More heroic are the surgical procedures currently performed for orbitocranial teratomas. Our own approach is an orbitocraniotomy with removal of the bony orbital roof through a coronal incision performed by a team of ophthalmic and neurosurgeons. Jho (1997) recommends an orbital roof craniotomy including supraorbital arch as a single piece bone flap through a 4 to 5 cm long eyebrow incision. Additional removal of bone overlying

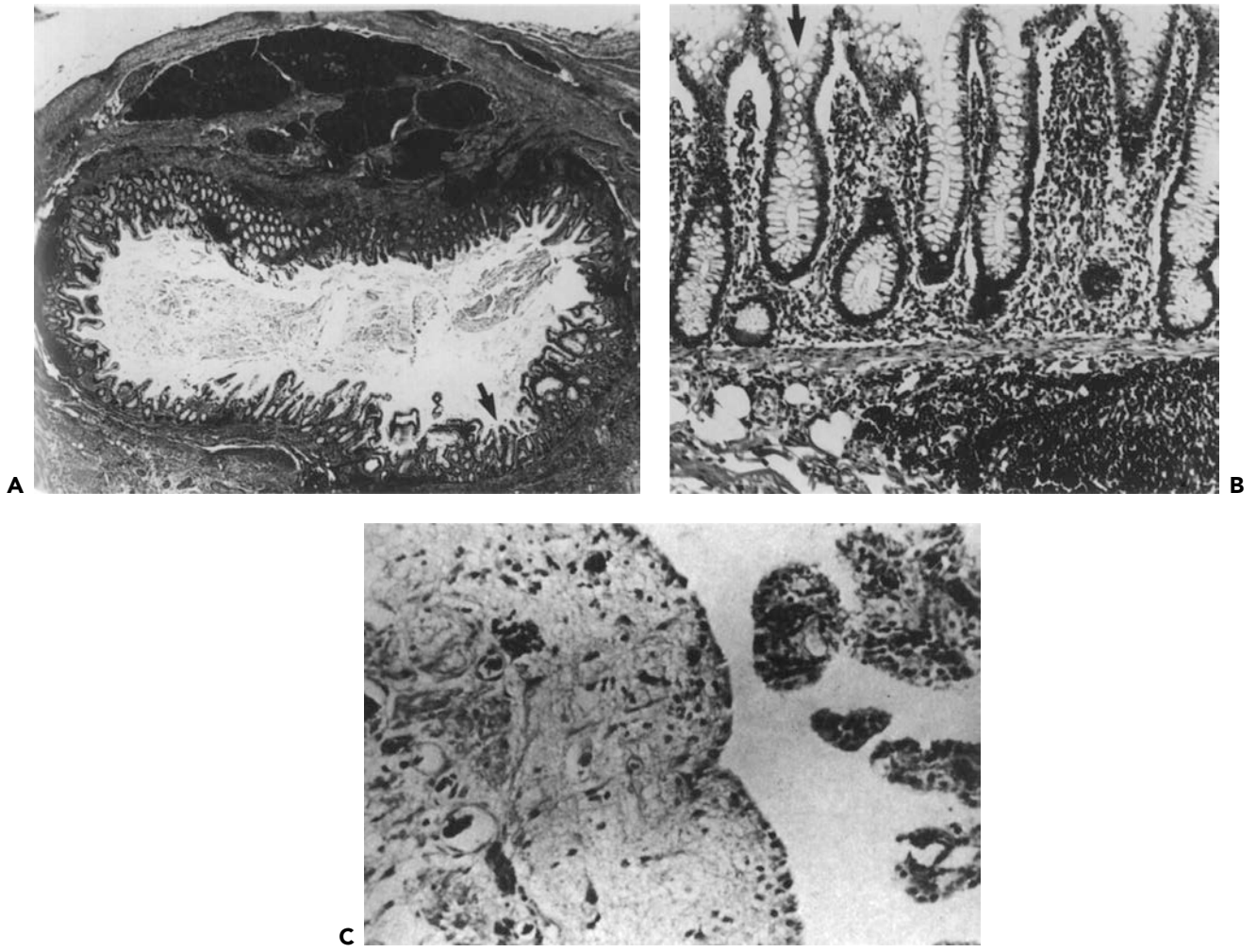

Figure 20.5 Teratoma. **A:** The orbital cyst is lined by enteric epithelium (*arrow*) (×26). **B:** Colonic-like epithelium with goblet cell-rich mucosa (*arrow*), smooth muscle in the underlying lamina propria, and lymphoid patches in the submucosa (×100). (From Ferry AP. Teratoma of the orbit: A report of two cases. *Surv Ophthalmol.* 1965;10:434–442, by permission of the Williams and Wilkins Co.) **C:** Disorganized neuroglial tissue on the left, papillae on the right suggests primitive ependymal differentiation (Hematoxylin and Eosin ×40). (From Spencer WH. *Ophthalmic pathology*, 4th ed. Philadelphia, PA: WB Saunders; 1996:2477, with permission.)

the optic canal will give full exposure of the eyeball and orbitofrontal dura. A dural incision is made at this juncture and orbital contents exposed by tack-up sutures. This permits removal of tumor utilizing orbital space rather than intracranial space. This eliminates the scalp flap of the coronal incision. He used this approach to remove three craniopharyngiomas, seven meningiomas from various sites, and a subfrontal teratoma from a 34-year-old woman.

ENDODERMAL SINUS TUMOR

These neoplasms are also of germ cell lineage (Kivela and Tarkkanen, 1994). They belong in the small group of *yolk-sac tumors*. They are tumors of infancy and early childhood but may also be present at birth. The primary tumors most often occur in the testes or ovaries. However, in extragonadal sites, their origin may not be known. In the head and neck area, the orbit may be an infrequent site for the primary tumor.

Recently, Bresters et al. (2003), found only nine patients with these neoplasms in the orbit and/or maxillary sinus described in the literature up to the time of their publication. They added a 3-year-old girl to this list. The age range of the cases in the literature is 3 months to 4 years (Margo et al., 1983). Unilateral proptosis was present in all cases.

MRI will show a homogeneous tumor. T_1-weighted images show the mass to be uniformly hypodense relative to surrounding tissue. With T_2-weighted images, the mass is relatively hyperintense. A CT scan will show a well-demarcated lesion with no calcification (Appignani et al., 1992). Angiography will demonstrate a vascularized tumor.

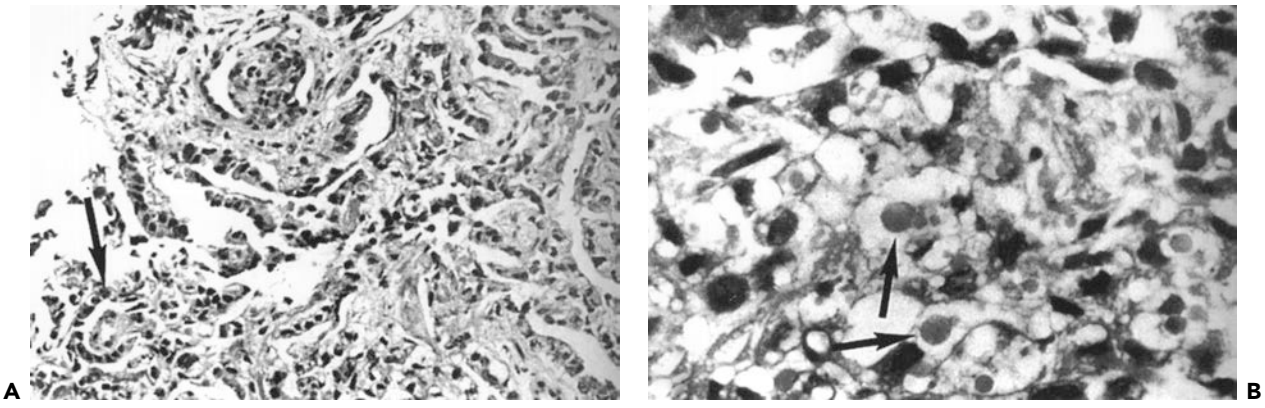

Figure 20.6 Endodermal sinus tumor of the orbit. **A:** Biopsy specimen from a 15-month-old boy shows a pseudopapillary pattern with anaplastic cuboidal cells lining slit-like spaces. Note a glomeris-like structure (*arrow*). **B:** Numerous intra- and extracellular hyaline globules (*arrow*) are present. (From Katz NN, Ruymann FB, Margo CE, et al. Endodermal sinus tumor (yolk-sac carcinoma) of the orbit. *J Pediatr Ophthalmol Strabism*. 1982;19:270–274.)

α-fetoprotein is an immunohistochemical marker for this neoplasm, the cytoplasm of the cells reacting positively.

Another staining feature characteristic of the tumor is numerous PAS-positive diastase-resistant, intra- and extracellular globules. Other histologic features are a pseudopapillary meshwork of slit-like spaces that are lined by anaplastic cuboidal epithelium, conspicuous mitoses, areas of hemorrhage and necrosis, and cystic spaces with invaginating epithelial-lined folds stimulating a glomeris-like structure (see Fig. 20.6).

Endodermal sinus tumors are aggressive malignant neoplasms that metastasize early. Over the time the tumor has been known, a combination of different therapies have been used (chemotherapy and/or radiotherapy and/or surgery). Long-term follow-up has not been available or has not been completely described. Therefore, an optimal therapy regimen has not been described.

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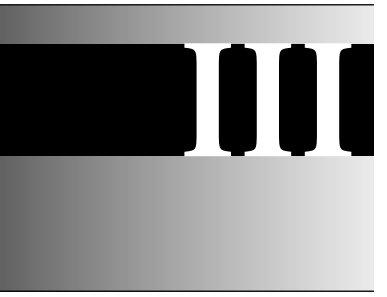
The Surgical Approaches to Orbital Tumors



Orbital Surgery

21

Introduction

In Chapter 1, we first met the patient with an assumed orbital tumor. We listened to the story of progression since the onset of the problem, measured, and recorded the physical and clinical signs and symptoms of orbital presentation, and determined the functional status of the ocular apparatus on the side of the affected orbit. This assessment, although not necessarily providing an accurate orbital diagnosis, is a baseline for future reference and defines the orbital disability that the patient expects to be resolved.

In most patients the problem is protrusion of an eye, alerting the physician to the probable need for surgical removal of an offending tumor, if the mass subsequently proves not to be amenable to nonsurgical methods of therapy. In a lesser number of patients, but one of great importance to the affected individual, the problem is loss of vision. Here, the physician is confronted with the question of whether expectant therapy of any type will make the vision better or worse.

In Chapter 2 of Section I, the "nitty-gritty" of preliminary diagnosis is further refined by a discussion of the principles of computed tomography, magnetic resonance imaging, echography, arteriography, venography, conventional radiography, and fine-needle aspiration biopsy, and their respective roles in the study of orbital tumors. Of these auxiliaries to diagnosis, computed tomography, and magnetic resonance imaging are the most important, and a comparison of their respective roles in diagnosis is again noted in Table 21.1 (see also Chapter 2).

After a long interlude of devoting chapters in Section II of the text to the classification, incidence, clinical features, imaging aspects, pathology, course, and management of the individual tumors, we now address the thrust and contents of Section III. Here, we will review the major surgical approaches to orbital tumors because surgery provides the most accurate access to orbital tissue for diagnosis and is the principal means for the eradication of most tumors.

We are omitting the remarks in the previous editions of this text concerning preoperative preparation of the patient, methods of anesthesia, postoperative care of the patient, the instrumentation necessary for orbital surgery, and the historical aspects of the subject. Nowadays most surgeons who work in this field have usually devoted a year or more to the study of the orbit beyond the usual residency training. Thus, they have an ample grasp of these ancillaries to the surgical management of orbital tumors.

In conclusion, the principal thrust of Section III focuses on the technical aspects of the various surgical approaches, augmented by descriptive modifications and "tricks-of-the-trade" that have proved useful to us.

ORBITOTOMY AND ORBITECTOMY

In the several centuries that barbers, medical practitioners, and surgeons have been removing or incising various lumps or festerings in the orbital space, the orbitotomy—*the operation of incising or opening into the orbit through the orbital margin* (Dorland, 1985)—has been the mainstay approach. The first major departure from this oft-used route was an entry through the thin lateral wall of the orbit, the *Krönlein (1888) approach*. This operation was designed to provide better access to the posterotemporal orbit (the home of most orbital tumors) and bypassed the orbital margin. Subsequently, this operation was modified by many surgeons to include a bone flap encompassing the lateral orbital rim, and thereafter named the *anterolateral* or *lateral orbital approach*.

Other routes of entry into the orbit that evolved next did not include the orbital margin. One of these was the *frontal craniotomy* championed by Dandy (1941) that, by removing the orbital roof, improved access to the superoposterior orbit and the orbital face of the optic canal. An alternate route to the orbital apex as well as to the posteromedial orbit soon followed. This involved removal of the medial wall of the orbit through an *intranasal approach*. A recent modification in the last decade or so has been the elevation of roughly the upper one-fourth of the bony orbit, including the orbital rim, by the *coronal approach*. The most recent modifications of an orbitotomy are the lateral orbitotomy without the use of a bone flap and the transcaruncular medial orbitotomy.

TABLE 21.1
COMPARISON OF COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IN ORBITAL DIAGNOSIS

Strengths	Weaknesses
CT	
Cost-effective	Patient manipulation
Fast	Artifact (fillings, bone)
Orbital fat is inherent contrast	Volume averaging
No magnetic contraindications	Less sensitive to display of different inherent tissue properties
Can involve less artifact in difficult imaging situations	Radiation (2–4 cGy)
Sensitive to calcium	
MR	
More sensitive to display of different inherent tissue properties	Cost
More sensitive to tissue water and paramagnetic materials	Scanning time
Multiplanar	Confining
No bone artifact	May miss calcium
''Dynamic,'' (i.e., flow voids)	Possible blindness with unsuspected intraocular foreign bodies (low risk)
	Caution with aneurysm clips
	Some contraindications exist (e.g., pacemakers and wires)

CT, computed tomography; MR, magnetic resonance.

We have broadened the definition of an orbitotomy to include all of these modifications for the purpose of our discussion. Our exposition of the subject starts with the oldest, straightforward, anterior approach.

ANTERIOR ROUTES

Anterior routes include the superior, inferior, medial, and transconjunctival approaches. All are used less often when compared to their status in the 1973 edition of this text. Nevertheless, these routes remain a favored approach to lesions in the anterior orbit. In this area are the orbital tumors that are palpated through the eyelids or conjunctival fornices.

Tumors frequently managed by these approaches are the dermoid cyst; carcinomas secondarily invading the orbit from a sinonasal source; the frontal mucocele extending into the superonasal orbit; the non-Hodgkin lymphomas clustered around the trochlea or protruding into the conjunctival fornix; the inflammatory tumor extending along the back of the orbital septum; some lymphangiomas, capillary hemangiomas, and rhabdomyosarcomas; and the orbitofrontal organizing hematoma without intracranial extension. Excluded from this list are the palpable lacrimal gland tumors. These lesions are worthy of a wider exposure through a lateral or superolateral orbitotomy because their size is often larger than expected, there is a potential for malignancy, and a tendency for soft tissue seeding if incompletely removed or biopsied. Also, the tumors in this anterior zone may be explored under local anesthesia if the patient is amenable to such management.

In all the anterior approaches except the transconjunctival route, the location and length of the incision is first outlined on the skin with a marking pen. A subcutaneous injection of 1% xylocaine with 1:100,000 epinephrine is then administered along this line primarily for hemostasis but also to augment anesthesia. The same solution may be injected for appropriate nerve blocks if the operation is performed under local anesthesia.

In all the orbital operative procedures, regardless of the approach, we prefer bipolar rather than unipolar cautery for direct hemostasis. We are also strong advocates of meticulous hemostasis throughout the course of the operation rather than deferring this task to later stages of the surgical procedure. Meticulous hemostasis, in addition to facilitating exposure, generally obviates the need for leaving a drain postoperatively.

Superior Approach

Superiorly there are three basic approaches, the lid crease, the sub-brow, and the transmarginal (lid-splitting)

incisions (see labels A, B, and F in Fig. 21.1). With each approach a preliminary marking of the superior orbital notch is made unless the location of the lesion is strictly confined to the superotemporal anterior orbit. This mark is an important reference throughout the subsequent dissection to the orbital exit of the supraorbital artery and nerve. Although the nicking of the artery is a source of annoying bleeding, the nerve is the more important of the two structures. We make every effort to preserve the nerve intact because surgical trauma to this structure usually results in a distressing postoperative anesthesia of the forehead. In the superior approach, we also try to work around the trochlea rather than disengaging this structure from its periosteal base.

The incision is curvilinear and parallel to the arch of the superior orbital rim and slightly below it. The midpoint of the incision lies over the palpable mass and the incision's length can be extended nasally or medially to accommodate the necessary surgical exposure. The skin is incised either with a scalpel or a diathermy knife. We prefer to start with the blade that can be angled slightly to align parallel to the brow hair follicles that helps minimize the scar and preserve follicles. The diathermy or cutting cautery is best for incising the soft tissues underlying the skin.

If the goal of the operation is an evacuation of the cystic contents of a lesion in the peripheral orbital space or the curettement of a lesion extending into this space from the overlying bone (aneurysmal bone cyst, Langerhans cell histiocytosis, plasmacytoma of bone), the dissection is beveled toward the junction of the periorbita, periosteum, and orbital septum along the superior orbital rim. When this junction is incised, the levator complex and orbital contents with the covering periorbita are pushed downward and the peripheral space entered directly. As a rule bleeding is not a problem in this area except for the intrinsic vasculature of the lesion to be removed. At the completion of the operation, a simple approximation of orbital septum to periosteum is performed with interrupted sutures. A tight closure is not necessary. This will permit seepage of serum postoperatively from the peripheral space into the subcutaneous tissues of the upper eyelid.

If the goal of the operation is removal of a lesion in the anterior orbital space the orbit is entered through an incision beneath the arcus marginalis. The preaponeurotic fat is immediately encountered and can be manipulated or retracted with cotton-tipped applicators. In any manipulation of orbital fat, hemostasis must be particularly exquisite. Closure of the orbital septum need not be overly tight. In fact, a loose anatomic approximation is preferred. In this way, a retrobulbar hematoma or fluid collection under pressure may decompress itself before causing irreparable visual loss.

The principal premise of the lid-crease approach is cosmetic because the healed incision is hidden in a skin fold of the upper eyelid (Leone, 1979; Wolfley, 1985; Kronish and Dortzbach, 1988). Other advantages according to these publications are the excellent exposure contingent on the distensibility of the eyelid skin, the minimal dissection through familiar anatomic landmarks that is necessary to reach the offending lesion, and simple wound closure.

The superior palpebral fold usually is the site of the skin incision. If this fold is absent or poorly delineated, another eyelid crease can be selected so long as it is symmetrical with a skin fold in the other upper eyelid. An incision about 15 mm in length is made with a scalpel. Traction sutures can be inserted in the lips of the skin incision to augment exposure. The orbicularis muscle is tented with a forceps and incised down to the suborbicularis fascial plane. The orbitopalpebral mass is reached by blunt dissection along this plane.

Closure of the wound requires no deep sutures. In children the skin incision is closed with a continuous fine-diameter absorbable suture. In adults a nylon suture can be used. If it is necessary to deepen the lid crease at the time of closure, the lower margin of the skin incision can be anchored to the fascial covering of the underlying levator aponeurosis.

We find the lid-crease approach particularly suitable for the removal of small, well-circumscribed dermoid cysts that straddle the attachment of the orbital septum to the superior orbital margin. However, for those cysts and other lesions that are positioned posterior to the orbital septum, we believe the sub-brow approach provides better exposure and roomier working space.

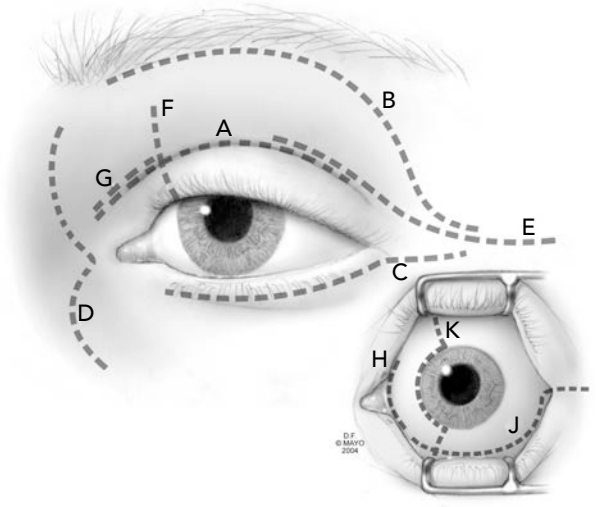


Figure 21.1 Frontal view depicting various possible skin incisions. A, Lid crease giving access to the superior orbit; B, sub-brow approach also giving access to the superior orbit; C, subcilial approach to the inferior orbit; D, external ethmoidectomy incision for medial orbitotomy; E, lateral lid-crease incision extending toward and beyond lateral canthus for lateral orbitotomy; F, transmarginal lid-splitting orbitotomy giving access to the superior nasal orbit; G, medial lid-crease incision giving access to superior nasal orbit; H, transcaruncular incision for medial orbitotomy; J, inferior transconjunctival approach for inferior orbitotomy; K, transconjunctival medial orbitotomy.

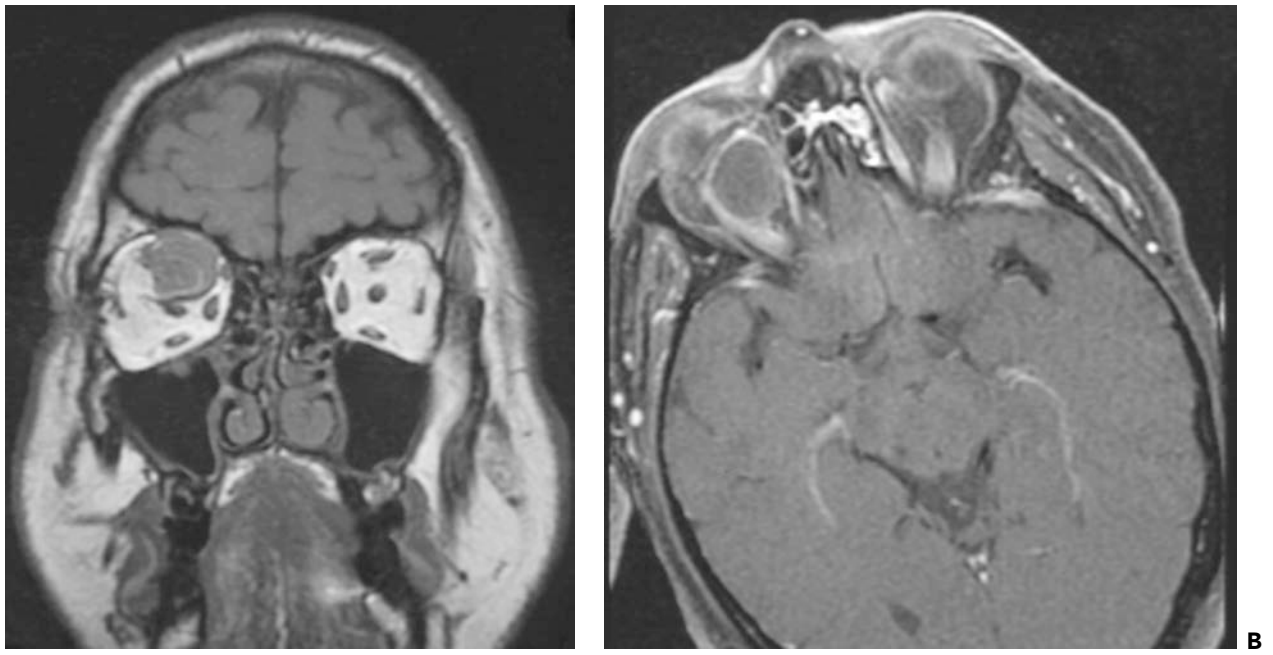


Figure 21.2 Coronal T_1 magnetic resonance image (MRI) **(A)** of an orbital arteriovenous malformation (not included in present series) located primarily in the superior intraconal orbit. Axial MRI **(B)** showing lesion in the superior nasal orbit.

Since the last edition of this book, the transmarginal eyelid incision (lid splitting) (Smith, 1966) has experienced a resurgence of interest (Kersten and Kulwin, 1999). This approach works quite well for lesions situated in the superior nasal quadrant, located primarily in the intraconal location but also for lesions straddling the intraconal/extraconal plane. We found excellent exposure from this incision for the lesion noted in Figure 21.2 (A and B). A straight iris scissor is used to create a perpendicular (to the lid margin) full thickness incision into the superior fornix. The incision is placed at the junction of the medial and central third of the eyelid. For reference, a previously placed superior rectus traction suture is helpful. Traction sutures on each lid margin will facilitate exposure into the orbit as shown (see Fig. 21.3A). Malleable retractors can be used to spread the tissues that expose the superior oblique tendon (Fig. 21.3B). The surgeon should now decide if working above or below the tendon will facilitate the procedure. In this example, the tumor was exposed by working above the tendon (Fig. 21.3C). After hemostasis was secured, the lid was repaired by a standard three-layered lid repair.

Inferior Approach

The inferior orbitotomy is the oldest of the several surgical approaches to orbital tumors. Compared to the superior approach, the inferior route traverses less important anatomic structures, is less vascular, and provides a wider view of the orbital space relative to the length of the incision. Nevertheless, the inferior orbitotomy is less frequently used than other surgical approaches because of a lesser number of primary orbital tumors in the inferior orbit. For the management of secondary tumors that invade the inferior peripheral space from a source in either the nasal cavity or maxillary antrum, the inferior orbitotomy is combined with some sinonasal procedure.

The anatomic objective of the inferior orbitotomy is to gain access to the junction of the periosteum of the maxillary bone with the periorbita covering the floor of the orbit and the fascia separating the tissues of the eyelid from the orbital space. This fascial divider corresponds in function and position to the orbital septum of the upper eyelid, but is much thinner. The skin overlying the inferior orbital rim also is very thin. This feature, combined with the tendency of healing skin to adhere directly to the underlying periosteum, creates a visible scar. This discourages skin incisions directly overlying the orbital rim.

To prevent this complication the incision is offset so that the skin can unite with the underlying layer of subcutaneous fascia or orbicularis muscle rather than the periosteum covering the bony orbital rim. This is done by placing the skin incision somewhere in the lower eyelid superior to the orbital rim. The incision is generally a millimeter or two below the lashes in a subciliary position (label C in Fig. 21.1). One could also use an incision slightly lower in a prominent wrinkle line, but after healing this may produce an obvious asymmetry compared to the other side.

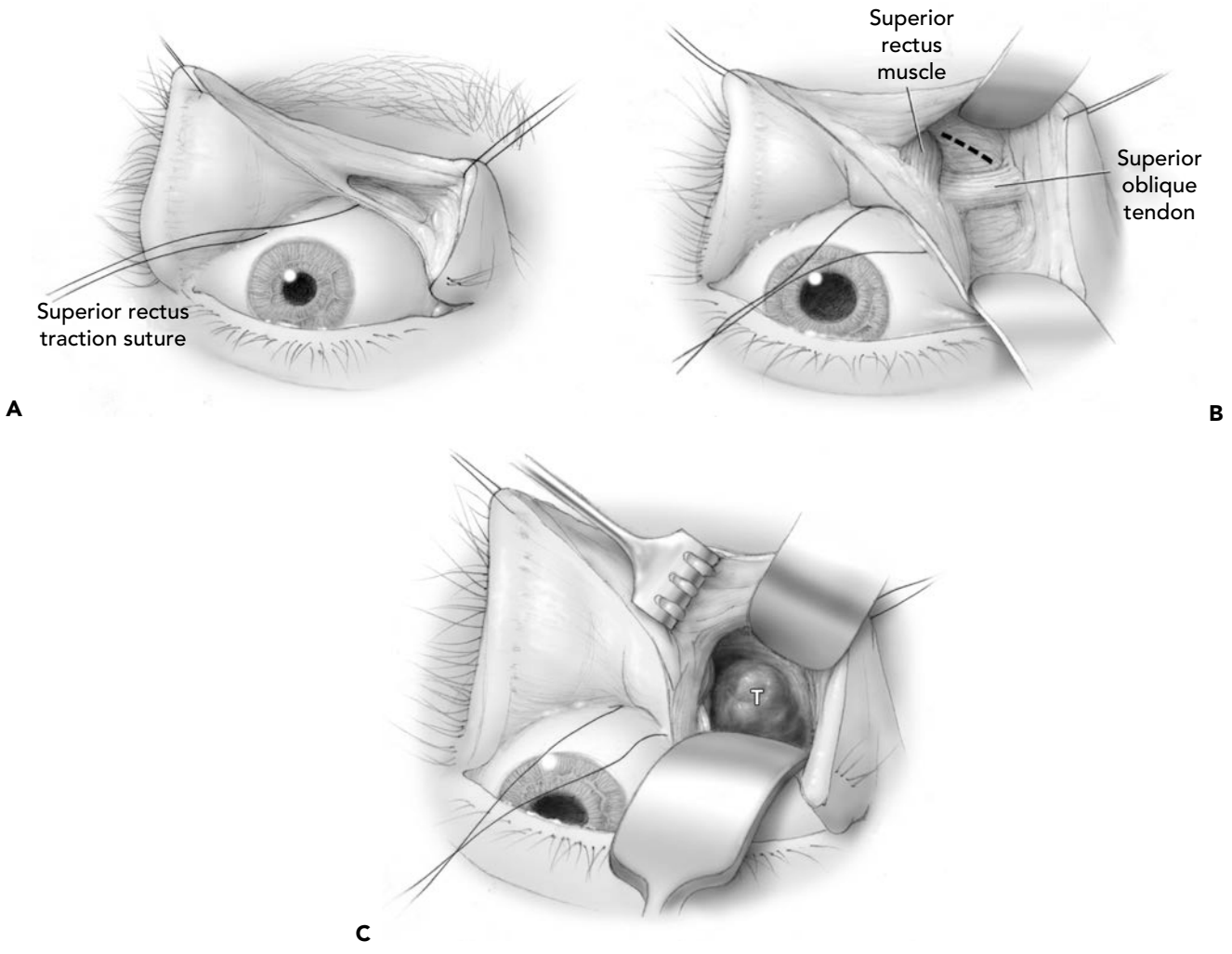


Figure 21.3 **A:** Transmarginal lid-splitting orbitotomy after lid is split and superior fornix is open. Traction sutures through the lid margin facilitate exposure. Preplaced superior rectus traction suture assists identification of the superior rectus muscle. **B:** With retractors in place superior oblique tendon is visualized. Tumor mass depicted in Figure 21.2 is shown by dotted line. **C:** Superior oblique tendon is reflected inferiorly to expose tumor mass.

With either incision some tunneling along fascial planes is necessary to reach the orbital rim. The more inferior the incision the less tunneling required. With the inferior curvilinear incision the inferior rim is easily reached by tunneling between the skin and the surface of the orbicularis oculi muscle. This cleavage plane may also be used with the higher (subcilial) incision, or a plane established between the orbicularis oculi muscle and the thin fascial orbital septum.

Once the inferior orbital space is entered, visibility usually is adequate except for the tendency of the orbital fat to bulge into the entrance space. This fat may be retracted with cotton-tipped applicators or cottonoids. If the prolapsing fat is too exuberant the lobules can be shrunk with a light application of a desiccating current or a bipolar cautery. One must be cognizant of the location of the inferior oblique muscle when dealing with orbital fat during this approach to avoid postoperative diplopia. There are no major sources of hemorrhage in the inferoanterior orbital space but the blood-tinged fluid oozing from orbital fat should not be disregarded. If this source is not staunched it can result in a slowly progressive, postoperative hematoma infiltrating the overlying soft tissues of the eyelid. Closure of the orbital septum and the skin incision does not differ from that described for the superior orbital approach.

Transconjunctival Fornix Approach

If an orbital mass is easily palpated through the conjunctival cul-de-sac, or its bulge into the fornix is obvious, it is tempting to think the lesion can be easily removed by an approach through the conjunctival fornix. Orbital masses with such characteristics are usually seen in

the superotemporal cul-de-sac or the inferior fornix. To facilitate the conjunctival incision and exposure of such tumors, opposing malleable retractors are placed against the eyeball and the palpebral surface of the eyelid. Blunt and sharp dissection along the surface of the mass soon reveals that such tumors extend deeper into the orbit than first assumed. The dissection is prolonged and visibility is reduced by progressive bleeding. Therefore, the removal of the mass often proves incomplete or compromised in some way. Hemostasis in such situations is difficult and closure of the incision often is anatomically incomplete. The clinical result in such a case may be further complicated by a subsequent symblepharon. Obliteration of the orifices of the excretory ducts of the lacrimal gland may also occur if the incision is made in the superotemporal fornix.

For these several reasons, we do not encourage this approach for the routine removal of orbital tumors in the anterior space except for the circumscribed masses that may be near the anterior portion of an extraocular muscle as demonstrated by imaging.

Consequently, the transconjunctival approach is seldom used in our practice except to perform an incisional biopsy on an orbital mass that is pushing into the overlying cul-de-sac. The orbital tumors that frequently show this characteristic are non-Hodgkin lymphomas, sarcoid or sarcoidosis, and lymphangioma.

The exposure through a transconjunctival approach through the inferior fornix can be augmented and facilitated by two methods. If a lesion is located in the inferior-temporal, extraconal quadrant, one can transect the inferior crus of the lateral canthal tendon, the so-called swinging eyelid flap. (McCord and Moses, 1979) to enhance exposure (label J in Fig. 21.1). In fact, this will even facilitate exposure to lesions within the inferior nasal quadrant. Extension of the transconjunctival incision up across the caruncle (transcaruncular approach, see subsequent text) greatly enhances exposure in the inferior nasal quadrant (labels J and H in Fig. 21.1). One must anticipate the inferior oblique muscle. Shorr et al. (2000) either cut across the muscle at its origin and later resutured it or just reflected if off with the periorbita with no postoperative diplopia. After hemostasis is secured, the wound is secured by a simple conjunctival closure in which we use 6-0 plain gut sutures. If the inferior crus of the lateral canthal tendon has been taken down, it can be repaired as would any tarsal strip procedure.

Medial Approach

Lesions in the shaded area of Figure 21.4 are amenable to the several medial approaches that we will discuss. The curved contour of the superonasal orbital rim is the landmark for one of these approaches. The incision is gull-wing shaped over the medial canthal tendon to eliminate webbing. This is the standard external ethmoidectomy incision. Other options include a transmarginal, lid-splitting procedure (label F in Fig. 21.1) as discussed in the preceding text. One could also utilize the medial lid crease as shown in Figure 21.1 (label G). Ophthalmologists usually favor the latter approaches for lesions within the superior anteronasal space (the area between the periorbita and the eyeball), and rhinologists use the former for external ethmoidectomy, frontal sinusotomy, and lesions

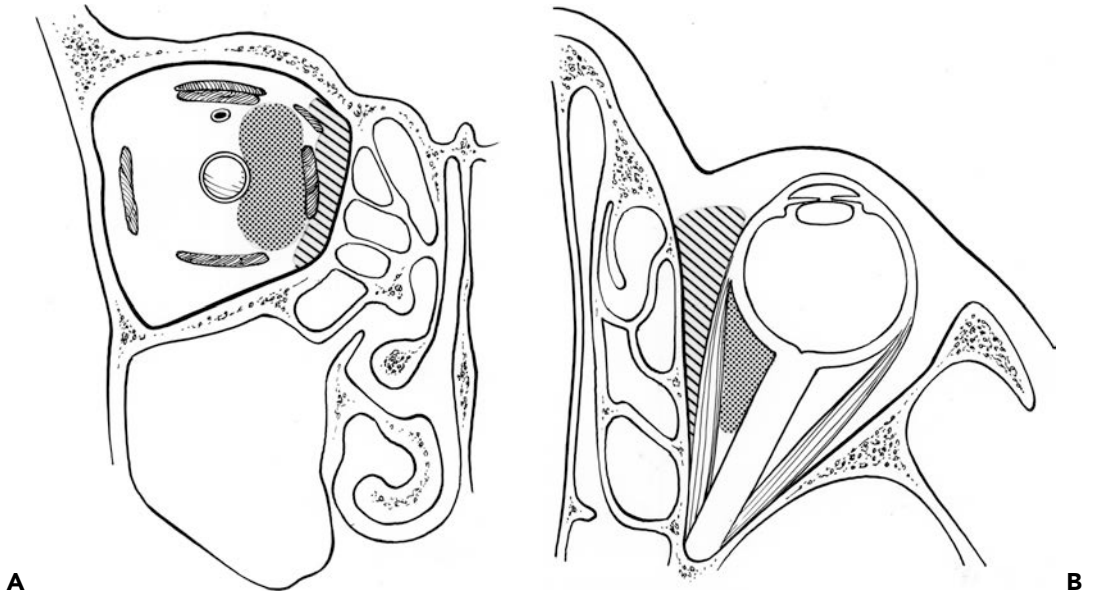


Figure 21.4 Topographic overview of shaded areas amenable to medial orbitotomy, coronal **(A)** and axial **(B)** sections. Dotted area, medial orbitotomy; hatched area, transconjunctival medial orbitotomy.

bulging into the medial peripheral space from a source in the nasal cavity or paranasal sinus.

In any of these approaches, a preliminary mark is made over the supraorbital notch as a reminder of the underlying neurovascular bundle. In addition several cross hatch marks may be made along the length of the external ethmoidectomy incision. These hatch marks serve as a guide for anatomic closure of the soft tissues at the completion of the operation, thus minimizing the puckering of tissues that so easily occurs in this quadrant of the orbit. The external ethmoidectomy incision is 25 to 30 mm in length and is roughly equal to one-fourth the circumference of the orbital rim. Any situation requiring wide exposure or extension below the medial canthal tendon is best served by incision D in Figure 21.1.

In the superonasal quadrant the sources of bleeding are the terminal branches of the frontal and dorsal nasal arteries in the area of the trochlea and the angular vein. The former vessels can be handled with the bipolar cautery but bleeding from the angular vein is better managed by clamping and ligation.

If the goal of the operation is to approach the anteronasal orbital space, the periosteum along the orbital rim need not be elevated. This space is entered as previously described under superior orbitotomy. If the intended approach is the peripheral orbital space, the periosteum is elevated to expose the ascending process of the maxilla and the lacrimal bone proximal to the posterior lacrimal crest. The periorbita likewise is elevated to expose the lamina papyracea and the orbital plate of the frontal bone. The main source of bleeding during this blunt dissection is the anterior ethmoidal artery. Closure of this artery by cautery is not very satisfactory. Instead, hemostasis is better secured by applying a small silver clip or ligation of the vessel.

The foramen of the anterior ethmoidal artery is an important topographic landmark in this dissection. It is located at the level of the cribriform plate and the junction between the ethmoid labyrinth inferiorly and the frontal bone superiorly. If the surgical procedure requires a more posterior extension of the dissection, the foramen of the posterior ethmoidal vessels marks the plane of the most posterior ethmoidal cells. If it is necessary to extend the incision inferiorly along the orbital rim, the periosteal stump of the medial canthal tendon should be preserved for reapproximation with its tendon at the time of closure of the incision.

If the periorbita and periosteum have not been too disrupted during the dissection, they can be loosely approximated at the time of closure. The subcutaneous tissue and skin can be closed in two layers.

In the management of orbital tumors the principal use of the medial orbitotomy is the drainage and evacuation of a mucocele with orbital extension. In our large series of mucoceles of this type in the Mayo Clinic Series (1948 to 1997), 81% were frontal and frontoethmoidal in location (Chapter 4). In Chapter 5 of the previous edition of this book, we also discussed the frequent, sometimes permanent, disabling diplopia in downward gaze that is a postoperative complication of the external surgical approach. This diplopia results from the postoperative malposition of the trochlea and the secondary malfunction of the superior oblique muscle of the affected eye. In turn, the complication is probably secondary to a disengagement of the periosteal base of the trochlea during the course of the elevation of the periosteum from the superonasal orbital rim. This practice was the rule among rhinologists who operated on orbital mucoceles over the 40-year period of the Mayo Clinic Series through the medial orbitotomy. Conversely, ophthalmologists who operated on these lesions were hesitant to disengage the trochlea from its base, and found that mucoceles could be evacuated and the lining of the cyst removed by working around the trochlea. The rhinologists rightly contend that the latter approach is less satisfactory for the surgical exposure necessary to externalize the evacuated cyst into the nasal cavity.

We had mentioned a recent awareness among some rhinologists about this problem of postoperative diplopia and reattachment of the trochlea. We have seen a trend among rhinologists toward an increasing use of the intranasal approach to the mucocele with orbital extension. Issues concerning the trochlea seem to have lessened.

The most recent description of a medial orbitotomy is the transcaruncular approach. Shorr et al. (2000) have been the primary advocates of this versatile approach. We have also been impressed with its utility for anything such as biopsy of the medial rectus muscle belly or for lesions within the medial extraconal or peripheral space. The plica should be identified and avoided. The incision should course just immediately lateral to the caruncle itself (see Fig. 21.5A). After the conjunctiva is incised, either thermal cautery or cutting current can be used to traverse some of the vascular tissues or the caruncular area. Preinjection of a lidocaine preparation with 1:100,000 epinephrine assists in hemostasis. The dissection should continue down to the posterior lacrimal crest. If the goal is to enter the peripheral orbital space, the periosteum/periorbita is incised and reflected off the bone. Familiar landmarks such as the anterior ethmoidal arteries should be sought and dealt with accordingly. Entry into the extraconal space is almost immediate after the initial incision and introduction of retractors (Fig. 21.5B). The medial rectus muscle can be retracted inferiorly (Fig. 21.5C) or superiorly (Fig. 21.5D) to facilitate exposure if required. If the incision is extended inferiorly, the inferior oblique is handled as described in the inferior orbitotomy section. Closure is simple reapproximation of the conjunctiva with 6-0 plain sutures or whatever one would normally use in this situation. We have used a steroid/antibiotic drop postoperatively for a week.

The medial orbitotomy may be used to approach tumors adjacent to the optic nerve in the medial aspect of the orbital apex (see Fig. 21.6). These lesions always proved difficult to manage surgically because of poor visibility, the confined

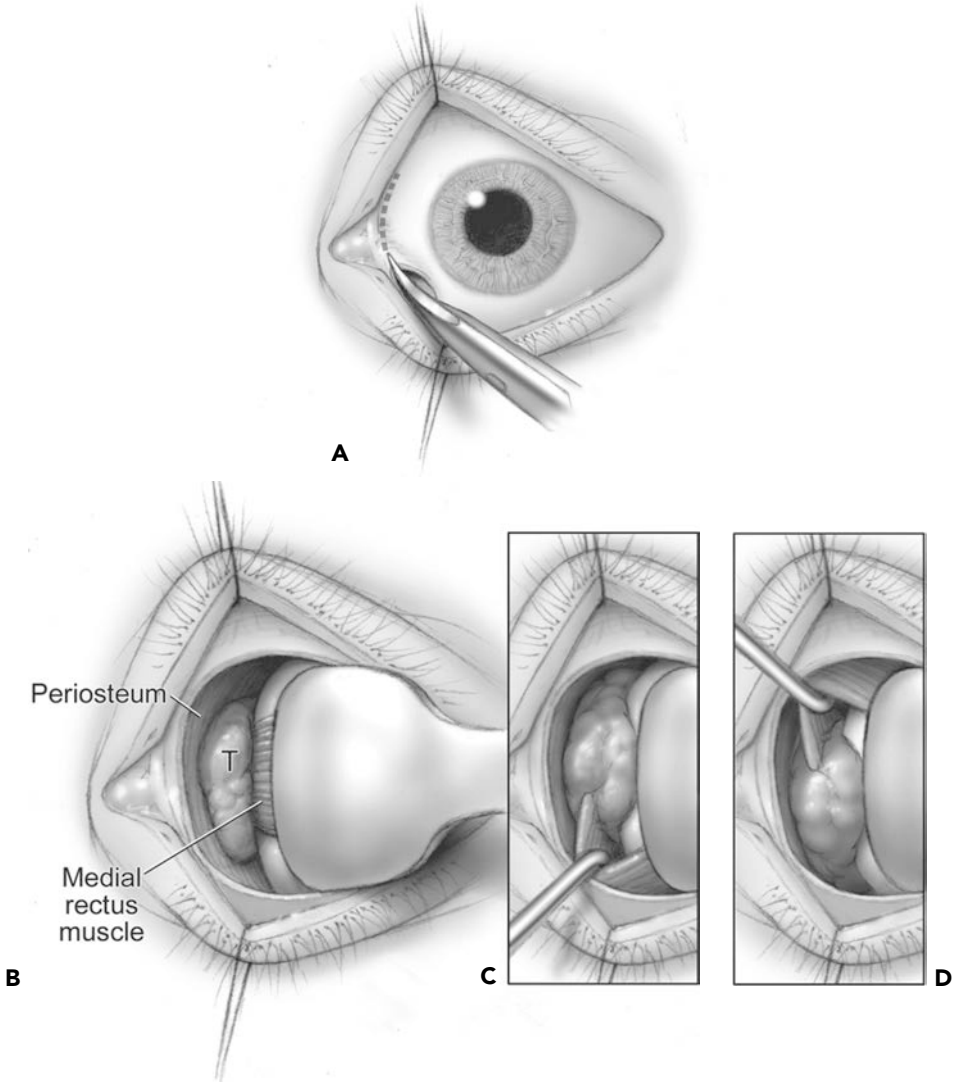


Figure 21.5 **A:** Transcaruncular medial orbitotomy. Incision begins on bulbar conjunctiva and continues just immediately lateral to the caruncle. **B:** Globe is retracted laterally, caruncle can be retracted with 4-prong rake or traction sutures giving exposure to medial extraconal space. **C:** Medial rectus can be retracted inferiorly or **D:** superiorly to facilitate exposure.

working space, and the hazard of central retinal artery or optic nerve injury. Lesions in this location can also be managed either by a transcranial orbitotomy or by an approach utilizing the disinsertion of the medial rectus muscle.

In the latter a peritomy is done at the limbus over the medial 160 degrees and the medial rectus is isolated in a fashion similar to that required for strabismus surgery (label K Fig. 21.1). A 6-0 vicryl suture line is placed at the distal end of the muscle before being severed from its insertion. A silk traction suture is run across the insertion. A malleable retractor medially, an enucleation spoon retractor laterally, and retraction on the previously placed suture through the medial rectus insertion assist retrobulbar exposure. It is helpful to use a fiber-optic headlight or an operating microscope to visualize the depths of the incision. If more posterior exposure is required, medial exposure can be augmented by outfracturing or even temporarily removing the lateral wall. When closing, the medial rectus muscle is resecured to its insertion. To obviate the effects of detachment and reattachment, the medial rectus should be recessed 1 to 2 mm. The ends of the conjunctiva are then reapproximated.

Advantages include ready access to the medial retrobulbar space. Disadvantages include the potential for globe perforation as the medial rectus traction suture is placed and when the muscle itself is reattached. It is possible that excessive amounts of lateral traction on the globe could exceed the ocular perfusion pressure, leading to visual loss. Manipulation of the optic nerve may lead to visual loss, and interfering with the ciliary nerves may give rise to pupillary abnormalities. One must recall that the central retinal artery enters the medial portion of the optic nerve approximately 1 cm behind the globe. This can be injured when dissecting posteriorly. This approach is difficult when the eyes are deep set or sometimes with large myopic globes.

The medial lid crease may also be used to approach lesions in the superior nasal quadrant (see Fig. 21.7)

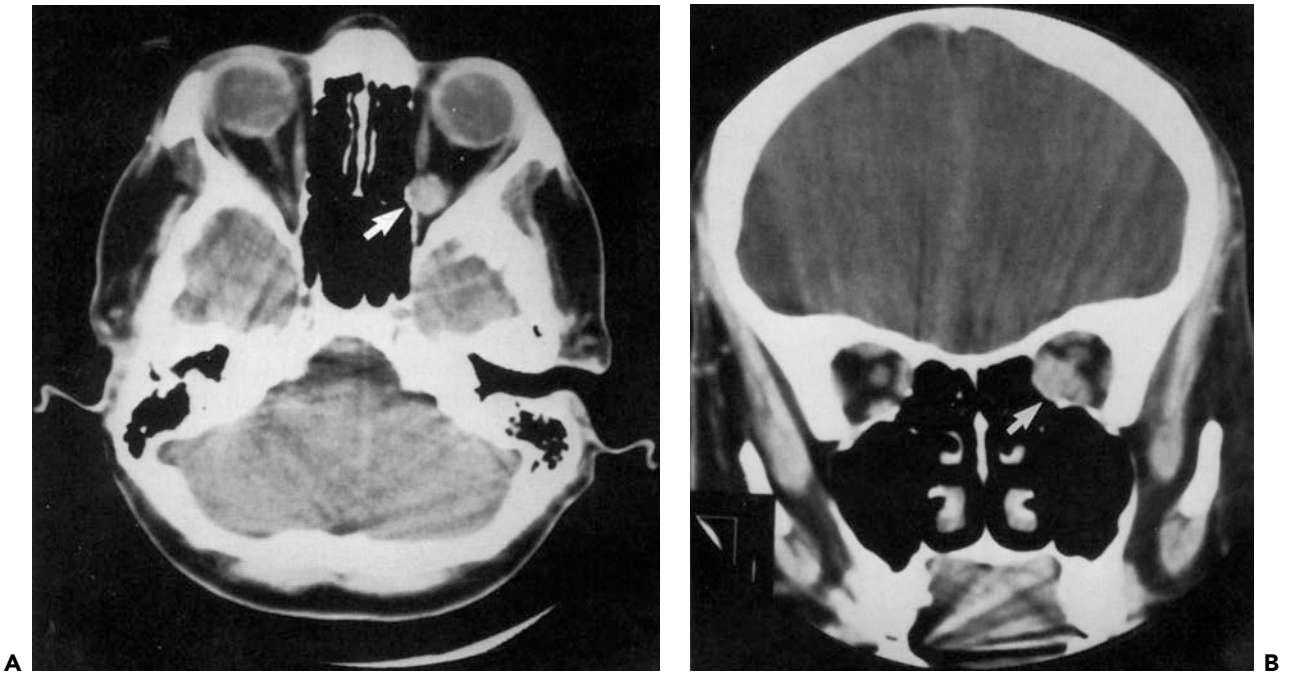


Figure 21.6 Axial **(A)** and coronal **(B)** computed tomography scan of cavernous hemangioma (*arrow*) in left medial, inferior orbital apex (*arrow*). Lesion was excised through medial orbitotomy utilizing an external ethmoidectomy incision. A prior, unsuccessful combined medial (with temporary disinsertion of the medial rectus muscle) and lateral orbitotomy resulted in a partial oculomotor nerve paresis.

(Wolfley, 1985). A traction suture through the lid margin facilitates subsequent dissection. An incision is placed in the lid crease and is taken to the suborbicularis plane to expose the orbital septum (see Fig. 21.8). When this is incised, the levator can be retracted laterally. Upon completion of the operation the incision can be closed in one layer. This approach has also been used for intraconal lesions and even for optic nerve sheath fenestrations (Turbin, R. North American Neuro-Ophthalmology Society poster session, 2-10-2003).

We have not seen any cases of postoperative medial ptosis.

LATERAL ROUTE

In the 50-year period (1948 to 1997) of the Mayo Clinic Series, most orbital tumors have been removed by the lateral orbital route. This approach has served us well. It is used principally for lesions located in the shaded area of

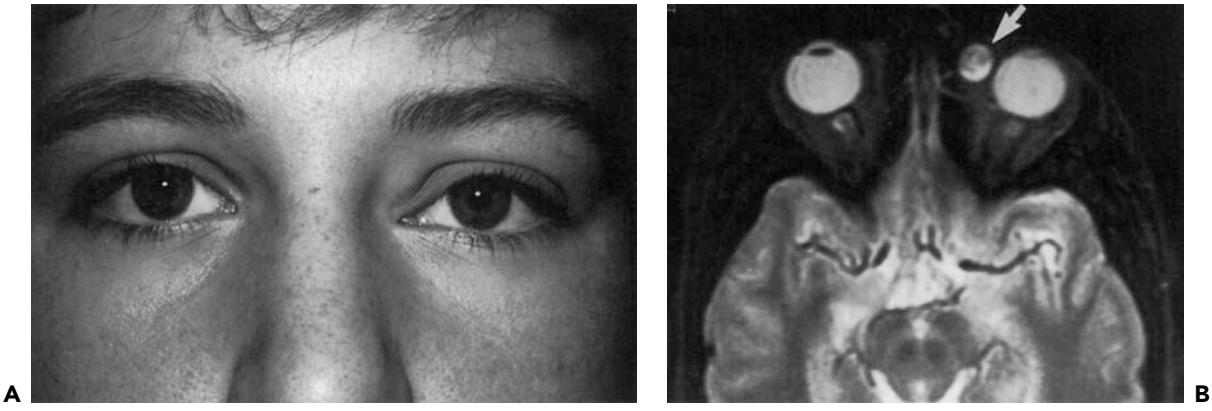


Figure 21.7 Clinical appearance **(A)** and magnetic resonance scan **(B)** of a dermoid cyst (*arrow*) located in the left superior nasal orbit of a 19-year-old girl. The lesion was excised through a medial lid-crease incision.

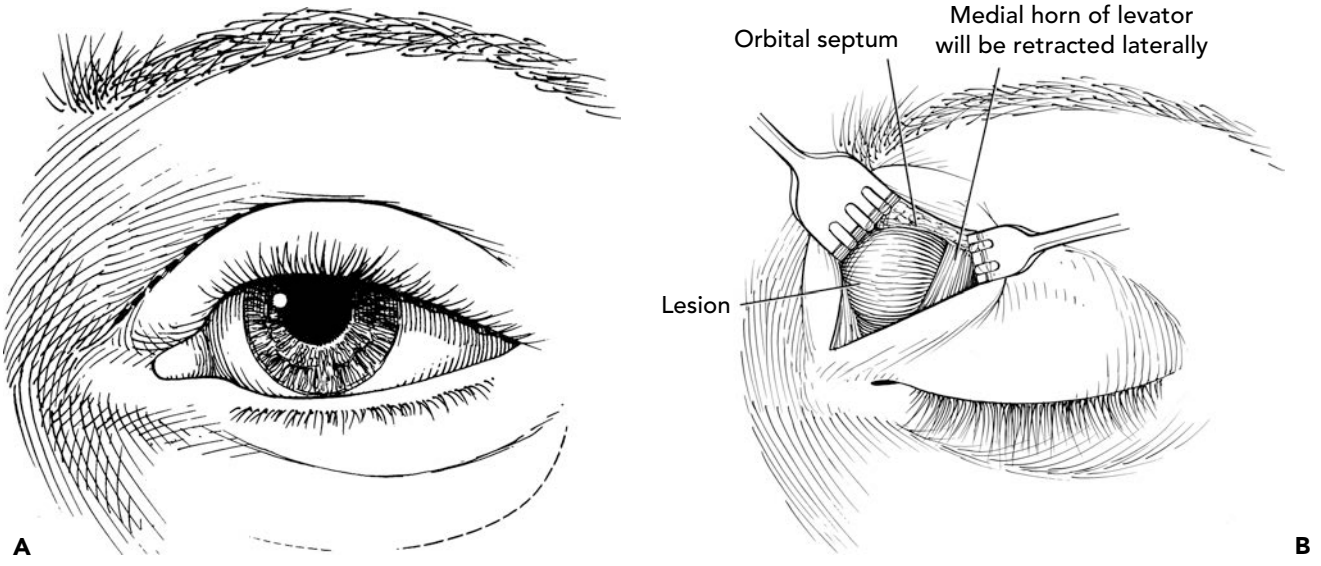


Figure 21.8 Location of incision for medial lid-crease approach **(A)** If lid crease is poorly defined it should be made symmetric with other side. Medial horn of levator is retracted laterally **(B)** to enhance surgical exposure.

Fig. 21.9. Fenestration of the optic nerve sheath and biopsy of the optic nerve also can be performed through this route.

The lateral approach is also recommended for definitive management of most lacrimal gland fossa masses.

Although modifications have been made in the length and position of the skin incision over the 40-year period, the basic approach through the lateral orbital rim and wall remains the same. The incision that we have used most often (see Fig. 21.10) is curvilinear just beneath the superolateral orbital rim curving laterally about 40 mm toward the ear. The horizontal extension can be merged into a skin wrinkle. A shorter version of this incision (Maroon and Kennerdell, 1984) (see Fig. 21.11A) can also be performed, but a lid-crease incision with extension

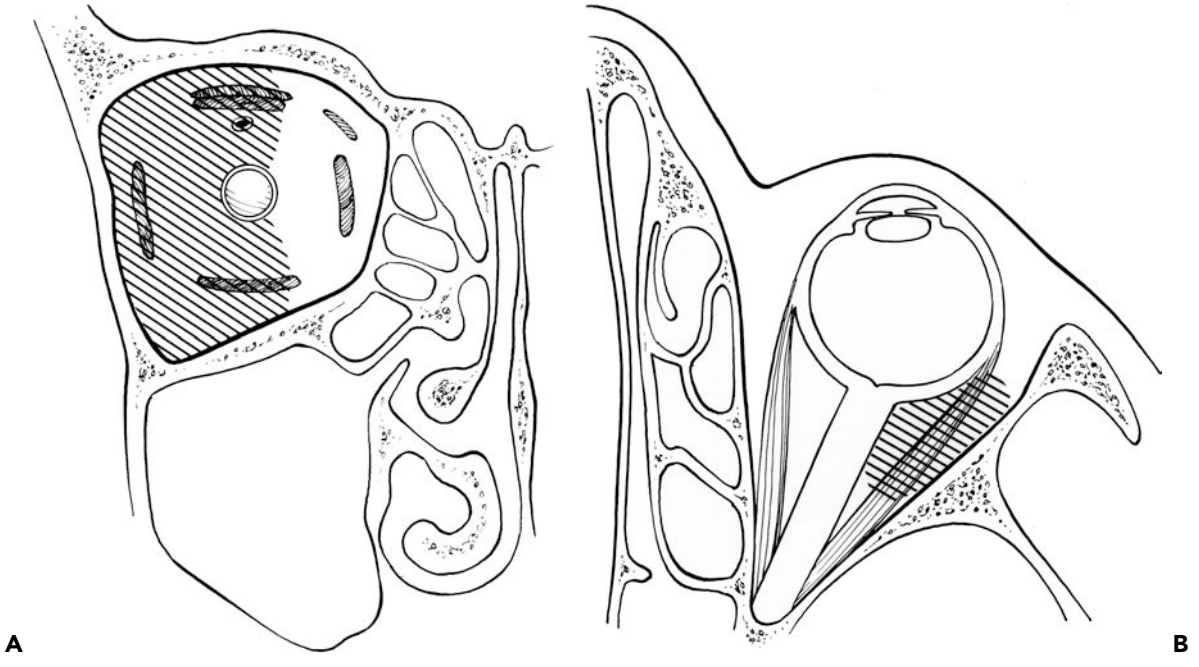


Figure 21.9 Topographic overview of shaded areas amenable to lateral orbitotomy, coronal **(A)** and axial **(B)** sections.

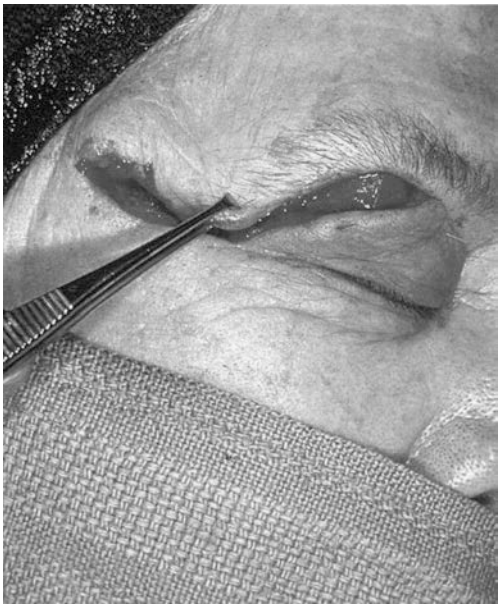


Figure 21.10 Anterolateral orbitotomy: The forceps grasp the upper lip of the incision used for an en bloc removal of an adenocarcinoma of the right lacrimal gland in an 82-year-old man.

toward the lateral canthal tendon is currently our preference (label E in Fig. 21.1). For lesions located in the inferior aspect of Figure 21.9, the incision can be further modified as an extension of the subcilial approach (label C in Fig. 21.1).

Preoperatively, the injection of the xylocaine–epinephrine solution (vida supra) beneath the incision line should also include the temporalis muscle near the lateral orbital rim. In addition, a silk traction suture is passed beneath the lateral rectus tendon to facilitate identification of the muscle after the osteoplastic flap is fashioned.

The incision is carried through the skin and subcutaneous tissue down to the periosteum, covering the temporal orbital rim (anteriorly) and the level of the temporalis fascia (posteriorly). The subcutaneous tissue along these planes is undermined with a minimum of sharp dissection augmented by mobilization of soft tissues by blunt dissection. The latter is accomplished by a gauze wrap around the tip of the index finger, resulting in a nearly bloodless surgical field.

Next an incision is made in the periosteum directly over the lateral orbital rim commencing above the zygomaticfrontal suture and extending to the level of the zygomatic arch, and 2 to 3 mm posterior to the forward edge of the bony rim. The periosteum is peeled away from the underlying bony rim along the entire length of the incision (Fig. 21.11B, C). Opposing edges of the periosteal incision are tagged with fine silk ties for subsequent anatomic closure. This prevents malposition of the lateral canthal tendon. When the periosteum is lifted from the anterior portion of the zygomatic arch and the periorbita reflected from the inner face of the lateral orbital wall, terminal branches of the lacrimal artery will be encountered. These can be coagulated with the bipolar cautery. The temporalis muscle is then released from its attachment to the posterior lip of the orbital rim and the muscle is pealed posteriorly from the surface of the lateral orbital wall to accommodate the depth of the bone cuts.

The osteotomies are angled in the configuration of a keystone (Fig. 21.11D), with the orbital rim forming the base. An osteotomy of this shape allows the bone flap to be repositioned at the close of the operation without fixation sutures in most cases. The orbital contents are protected with ribbon retractors during the placement of the osteotomies.

The upper osteotomy is above the zygomaticofrontal suture and the inferior osteotomy is at the level of the zygomatic arch, and each cut is about 1-cm deep. The lateral orbital rim is next grasped with a double-action forceps and the bone fractured outward and posteriorly (Fig. 21.11E). The fracture line corresponds to the zygomaticosphenoid suture. This suture is positioned on a horizontal axis that would pass just behind the eyeball and is about one-third the distance to the orbital apex.

When the osteotomy is completed the vertical length of the fractured bone should approximate 28 mm in women and 30 mm in men. The bone flap may remain attached to a tongue of the temporalis muscle and moved to the periphery of the surgical field on its soft tissue hinge. The bone may also be peeled from its attachment to the temporalis muscle and temporarily placed in a warm antibiotic solution until the operation is completed. A self-retaining retractor may be inserted at this time or the skin flaps retracted by hand-held instruments.

If additional exposure is required along the posterior edge of the bony orifice, the fractured edge of the sphenoid bone may be nibbled away with a rongeur until marrow is encountered (Fig. 21.11F). Bleeding usually occurs at this point and is controlled with bone wax or heat from a diamond tip drill. All bleeding should be stopped before proceeding into the inner orbital space.

A modification of this procedure is the lack of a bone flap. Many of our lateral orbitotomies have been performed without removal of the bone. The procedure remains the same although it is critical that the lateral canthal tendon be disinserted to facilitate exposure (see Fig. 21.12A, B, C).

The orbital space is entered by a longitudinal incision parallel to the lateral rectus muscle with relaxing incisions anteriorly in the periorbita to increase exposure. The lateral rectus muscle is easily identified by tugging on the previously placed traction suture (Fig. 21.11F). The lateral rectus muscle roughly divides the surgical field into superior and inferior halves. Further entry into the retrobulbar space is aided by retracting the posterior lobe of the lacrimal gland anteriorly and pushing aside the orbital fat with cotton-tipped applicators. The use of Sewell retractors (see Fig. 21.13) facilitates this exposure.

The assumed position of the mass as determined by preoperative imaging is confirmed by digital palpation. Preliminary mobilization of a circumscribed mass is accomplished by blunt manipulation of the mass with the index finger and dissection with cotton-tipped applicators. Delivery of the mass is completed by the application of the cryoprobe.

Infiltrative masses are less easily removed but may be debulked by sharp dissection. This usually results in a great deal of bleeding. Laser vaporization is particularly useful in diffuse lymphangiomas and plexiform neurofibromas. Among the many types of lasers, carbon dioxide, and neodymium: yttrium-aluminum-garnet (ND:YAG) are the principal types with orbital applications. We will confine our discussion to these.

There are four laser-tissue effects to consider: Reflection, transmission, scattering, and absorption. Wavelengths longer than the far ultraviolet must be absorbed by the tissue to produce the laser's therapeutic effect. Scattering will lead to absorption over a larger tissue volume ultimately producing a less intense, less accurately defined thermal effect. Transmission and reflection have no therapeutic effect on tissue.

The wavelength of the laser and hence its physical properties and tissue effects are a function of the lasing media. Carbon dioxide emission is invisible, falling in the infrared portion of the spectrum at 10,600 nm. A system of articulating mirrors transmits the light from the laser to either a hand-held probe or is coupled to an operating microscope. This wavelength is heavily absorbed by water and is not at all influenced by the amount of pigmentation. In fact, the extinction length in water (distance in which 98% of the incident energy is absorbed) for a carbon dioxide laser is only 0.17 mm (Fuller, 1987). Tissue is composed of 70% to 90% water.

The carbon dioxide laser has been used for surgical incisions and volume ablation by vaporization. Both qualities are useful with infiltrating tumors although volume ablation is probably more helpful. One must not forget, as might happen during an ablation procedure, to send enough representative tissue to the pathologist for histopathologic examination. By using a defocused beam and roughly 10 W of power (continuous or pulsed) the beam is "painted" across the surface of the tumor, slowly vaporizing exposed tissue (Kennerdell et al., 1986). The laser plume is drawn off by a separate suction device. The notion that lasers possess unequaled hemostatic abilities is fallacious. Conducted heat from a carbon dioxide laser can coagulate blood vessels up to 0.5 mm in diameter. Larger vessels must be coagulated with bipolar cautery or ligated.

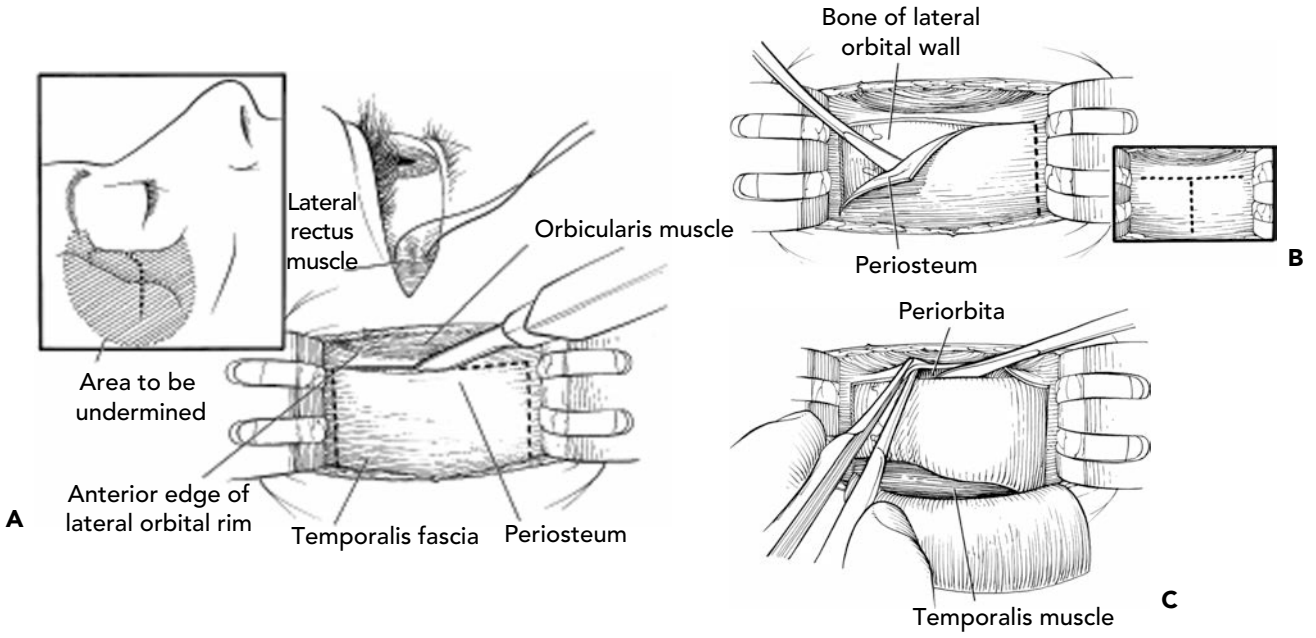


Figure 21.11 Anterolateral orbitotomy: Hockey-stick shaped incision **(A)** is shorter than conventional Wright–Stallard incision. Extensive undermining at the level of the temporalis fascia allows use of smaller incision. Rectangular flap **(B)** or T-shaped flap **(inset)** is created in the periosteum to expose the lateral orbital rim. Periorbita reflected from the lateral orbital wall **(C)** Branches of the zygomatic artery should be coagulated with bipolar cautery and divided prior to creating osteotomies. Keystone-shaped osteotomies **(D)** facilitate later repositioning of bone flap without sutures or wires. Brisk bleeding from the surface of the osteotomies can be controlled with bone wax. Posterior exposure can be enhanced by additional bone removal **(E)** The periorbita can be opened with a rectangular or T-shaped incision similar to the periosteum. Previously placed lateral rectus traction suture allows easy identification of lateral rectus muscle **(F). (*continued*)**

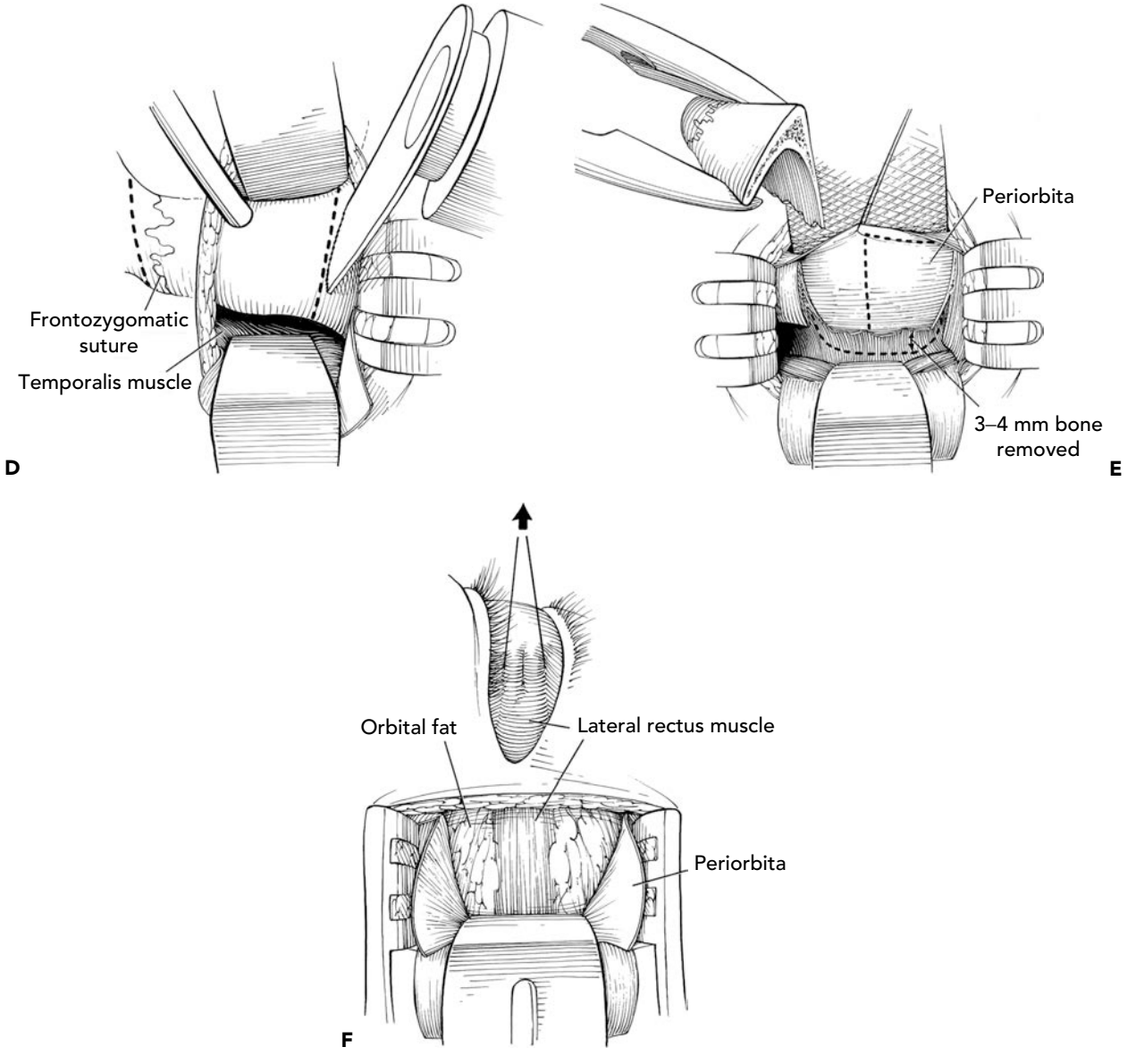


Figure 21.11

Surgery with the laser does offer a hemostatic advantage over conventional techniques, especially when dealing with a lymphangioma.

The ND:YAG laser operates in the near infrared portion of the spectrum at 1,060 rim. It has the advantage of being transmissible through a fiber-optic system. The continuous-wave ND:YAG laser has an extinction length of 60 mm in water, 2.3 mm in the stomach, and 3.5 mm in human brain tissue (Edwards et al., 1983). At wavelengths near the visible range of the spectrum, absorption is less and there is more undesirable scattering by tissue, potentially affecting tissue to a depth of 3 to 5 mm. This allows coagulation of larger blood vessels (up to 3 mm) but the potential for unintended damage to adjacent tissue is higher. Contact ND:YAG lasers that utilize a synthetic sapphire probe obviate many of these problems with scattering (Dickson et al., 1989; Hornblass, 1989).

Infiltrating lesions pose a dilemma to the surgeon, namely, what is the endpoint of the debulking? One must always be cognizant of the underlying and adjacent tissues near the target tissue. The potential for unintended side effects or complications must be considered in light of the intended therapeutic goal. We were fortunate to recognize directional fibers indicative of an extraocular muscle while lasing the lymphangioma depicted in Figures 10.31 and 10.35 before irreparable damage was done. A transient lateral rectus paresis resolved without sequelae.

Upon completion of the intraorbital procedure, the periorbita is loosely approximated. The wedge of bone is replaced and supported by careful approximation of the

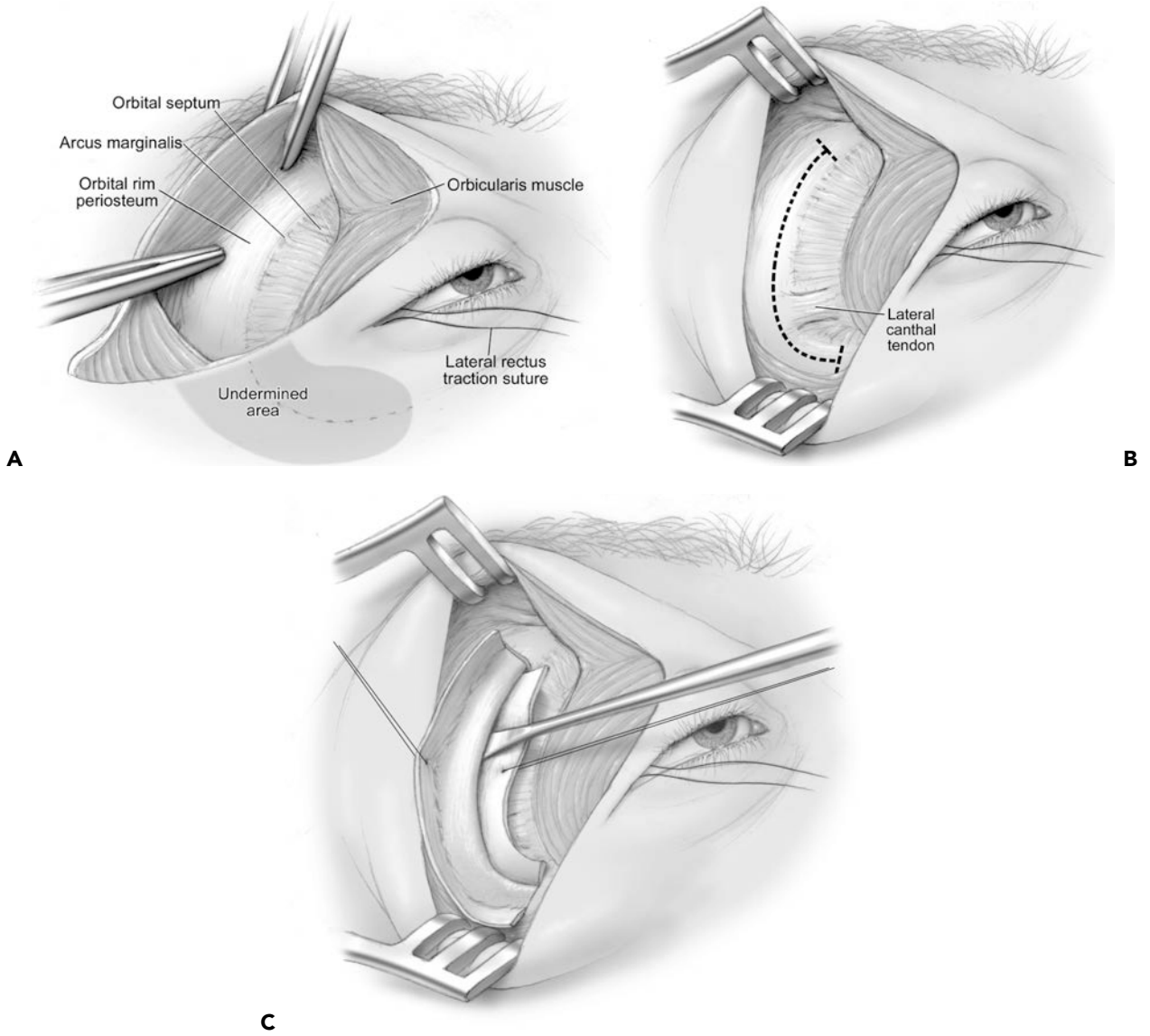


Figure 21.12 No bone flap lateral orbitotomy. **(A)** Initial phase of procedure is the same as the procedure where bone flap is created. Incision is carried down to the lateral orbital rim. Inferior aspect is undermined. **(B)** Periosteum is incised 3 to 4 mm back from the orbital rim to facilitate closure. It is essential that lateral canthal tendon be mobilized. **(C)** Periosteum is marked to avoid lateral canthal tendon malposition when closing. Previously placed lateral rectus traction suture helps to positively identify lateral rectus muscle after periorbita is incised.

periosteum. The subcutaneous tissue and skin are closed in two layers. A mild pressure patch is used overnight.

EXENTERATION

Exenteration of the orbit entails the total removal of the soft tissue of the orbital cavity with or without preservation of portions of the skin of the eyelids. In the context of orbital tumors, the operation is usually interrelated with malignant neoplasms. Here, exenteration is often reserved for recurrent primary and secondary orbital tumors that have resisted prior extirpation or excision and where other management options are no longer effective in arresting the growth of the neoplasm. Also, the operation is used in the early management of a primary orbital malignancy where exenteration may offer the best chance of eradicating the lesion and effecting a cure. In both situations, it is presumed that the malignant neoplasm neither involves bone nor extends beyond the orbit. If such is not the case a partial orbitectomy rather than an exenteration is indicated. Less often exenteration is necessary for the relief of intractable pain associated with vasculitic or nonvasculitic inflammatory tumors that have

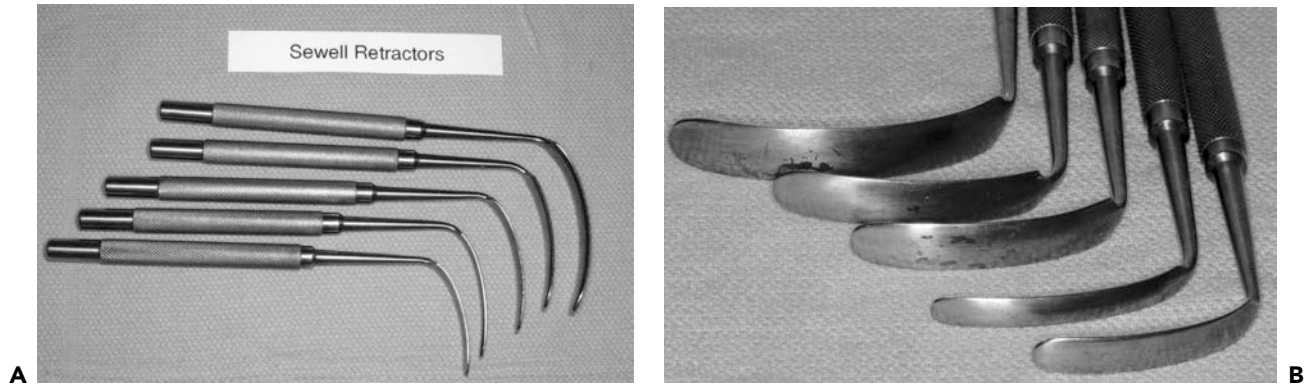


Figure 21.13 Sewell retractors **(A)**. Retractors are available in different sizes and **(B)** blade widths.

resisted all treatment options, and certain instances of metastatic malignancies in the orbit that are not responsive to radiotherapy or chemotherapy.

A less than total exenteration also is a treatment option. A subtotal or partial exenteration may be applicable to indolent malignancies of the eyelids or epibulbar neoplasms that have not extended deeply into the orbit, and for nodules of recurrent benign neoplasms that can be encompassed without sacrifice of all soft tissue components of the orbit. The surgical dissection necessary for such limited exenteration is basically an extended enucleation. The eye and a generous rim of soft tissue surrounding the offending lesion usually are removed *en bloc*. From a patient's standpoint, the cosmetic aftermath of a subtotal or partial exenteration opposed to total exenteration is much preferred.

Nowadays total exenteration is performed less often than in the earlier period of our orbital tumor study. This is particularly evident in children. In all age-groups, the increasing role of chemotherapy and radiotherapy in the primary and adjunctive stages of management has lessened the necessity of exenteration. Even in malignant melanoma, exenteration is being replaced by more conservative surgical options in many cases, an event anticipated in the 1973 edition of this text. Last, another modality, partial orbitectomy, is replacing exenteration for the management of neoplasms involving bone or threatening invasion of the intracranial vault.

These management events coupled with improvements in surgical technique and instrumentation also have spurred interest in the plastic and reconstructive surgery of the orbitofacial area of postexenteration patients. Nevertheless, the basic technique of orbital exenteration is essentially the same as it was 40 years ago (Baylis et al., 1987; Karesh, 1990; Kennedy, 1979; Putterman, 1986; Savage, 1983; Stewart, 1987). It is this facet of exenteration that is the focus of this section.

The line of the incision is first outlined with a suitable marking instrument. For a total exenteration the incision is preferably made just inside the entire orbital rim. This salvages a narrow lip of eyelid skin that can be folded over the relatively avascular bony rim upon completion of the operation. In turn, this skin is a source of granulation tissue that eventually covers the surface of the exenterated orbital cavity. However, if eyelid skin is compromised by an expanding neoplasm, the incision line must curve proximally over the rim to encompass the tumor. If the skin of the eyelids is intact and can be preserved, the incision is marked parallel and several millimeters proximal to the line of cilia of the upper and lower eyelids. Finally, the circumference of the incision line is infiltrated with a solution of 1% lidocaine and 1:100,000 epinephrine.

The initial dissection through skin and subcutaneous tissue is directed toward the junction of the periorbita and periosteum covering the orbital rim. We prefer the Bard-Parker blade (BD Medical Systems, NJ) for the skin incision and the electrosurgical knife for the subcutaneous tract. It seems practical to commence the circumferential incision in the least vascular quadrant (the inferotemporal) and proceed both clockwise and counterclockwise toward the most vascular quadrant (the upper nasal). When the incision nears completion the medial canthal tendon is severed.

We suggest hemostasis of each bleeding point as it occurs during the initial dissection. This eliminates one of the three major sources of bleeding—the incision—and anticipates coping with the other two sources of hemorrhage. The latter are the rupture of intraorbital vessels bridging the peripheral orbital space during stripping of the periorbita and trauma to the major vessels traversing the superior orbital fissure and optic foramen later in the operation. We advocate the bipolar cautery for hemostasis in the deeper areas of the orbital cavity. This will minimize the dispersion of heat into the adjoining intracranial vault that occurs with the high-frequency unipolar cautery.

The intraorbital phase of the operation commences with the entry into the peripheral orbital space after the periosteum along the orbital rim is incised and retracted. Use of a periosteal elevator facilitates separation

of periorbita from the adjacent bone. This maneuver is easiest along the orbital roof and is associated with less bleeding than in other orbital areas. Therefore, separation of the periorbita in this area is usually performed first.

Bleeding becomes more troublesome when the periorbita is separated from the orbital floor. The source of the bleeding is the trauma to the infraorbital artery as it passes along the shallow infraorbital sulcus. At this stage of the procedure, the contents of the lacrimal groove also may be removed. If, during the retraction of periorbita, there is visible roughening of the surface of the orbital bone suggesting invasion by an adjacent neoplasm, this area should be marked for later attention.

As the blunt dissection proceeds posteriorly, the thick pedicle of soft tissue at the orbital apex is palpated. This pedicle contains the major blood vessels and nerves linking the orbital cavity with the intracranial vault through the optic foramen and superior orbital fissure. The soft tissue stalk also contains the extraocular muscles where they funnel into their insertions. Thus the soft tissue stalk is thick, tough, compact, and not easily severed. Each surgeon has a favored routine for the clamping and cutting of this stalk. As a rule, the same combination of curved clamps and curved scissors used for enucleation are employed.

No matter what care is devoted to the severing of the stalk there is almost always some residual bleeding at the orbital apex after the soft tissue contents are delivered. The surgeon should take the time and exercise patience to secure all bleeding points in this area. Oozing from the bared bone may be stopped with bone wax.

Next, attention is given to those areas of rough-surfaced bone that may suggest invasion of neoplasm. Such areas usually will be found in the anterior orbit and along the orbital rim, and represent the extension of a long-standing secondary carcinoma. It is important to remove these suspicious areas to forestall recurrence of the carcinoma. This bone may be removed by grasping with a heavy rongeur or shaving it away with the Stryker saw.

Once hemostasis is secured, attention is given to the management of the exposed bone. Over the 50-year interval of our orbital tumor study, the pros and cons of skin grafting versus nongrafting of the orbital cavity have been discussed in many publications. We have used both the grafting and nongrafting options and, when all factors are considered, we tend to favor the latter. We reserve the skin graft for a persistent orbitosinus fistula that, postoperatively, requires coverage and defects in the orbital wall that are complications of an aseptic necrosis of bone.

The free margin of eyelid skin or flaps of eyelid skin, if such have been fashioned, are inverted so as to cover as much bare bone as possible. The remaining bare bone is covered by N-Terface R sheeting (N-Terface, Winfield Laboratories, Richardson, TX), an interpositional surfacing material that minimizes adhesion between the subsequent packing material and bone. Finally, a vaseline gauze pack is placed in the orbital space so as to fill it to the level of the orbital rim. Dry gauze squares are then placed over the orbital dressing and are held in place with adhesive strips, which exert moderate pressure on the orbital contents.

Postoperatively the patient is given oral antibiotics, the outer gauze pressure dressing is changed daily, and the orbital patch and interpositional sheeting is removed in a few days. The orbital cavity is covered by spontaneous granulation tissue in approximately 4 to 6 weeks.

Several publications (Tse et al., 1984; de Conciliis and Bonavolonta, 1987; Wulc et al., 1989) have discussed the postoperative complication of a cerebrospinal fluid leak. A simple leak without visible bone loss may be covered by a plug of temporalis muscle held in place with a gauze pack, or an application of cyanoacrylate glue. If the fluid leak is persistent or associated with visible loss of bone, the bone defect is enlarged and the dural defect is closed with sutures.

COMBINED APPROACHES

This section is devoted to surgical approaches for lesions in areas that involve several specialties. The management of these lesions benefits from a team approach not only because of the location of the lesion but also because

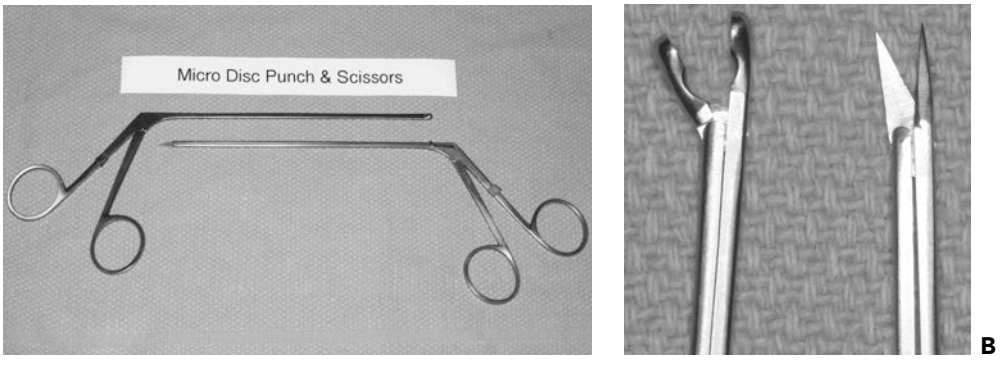


Figure 21.14 Microdisk punch and scissors **(A)** The disk punch is also useful when used as forceps. Tips are seen better with higher magnification **(B)**.

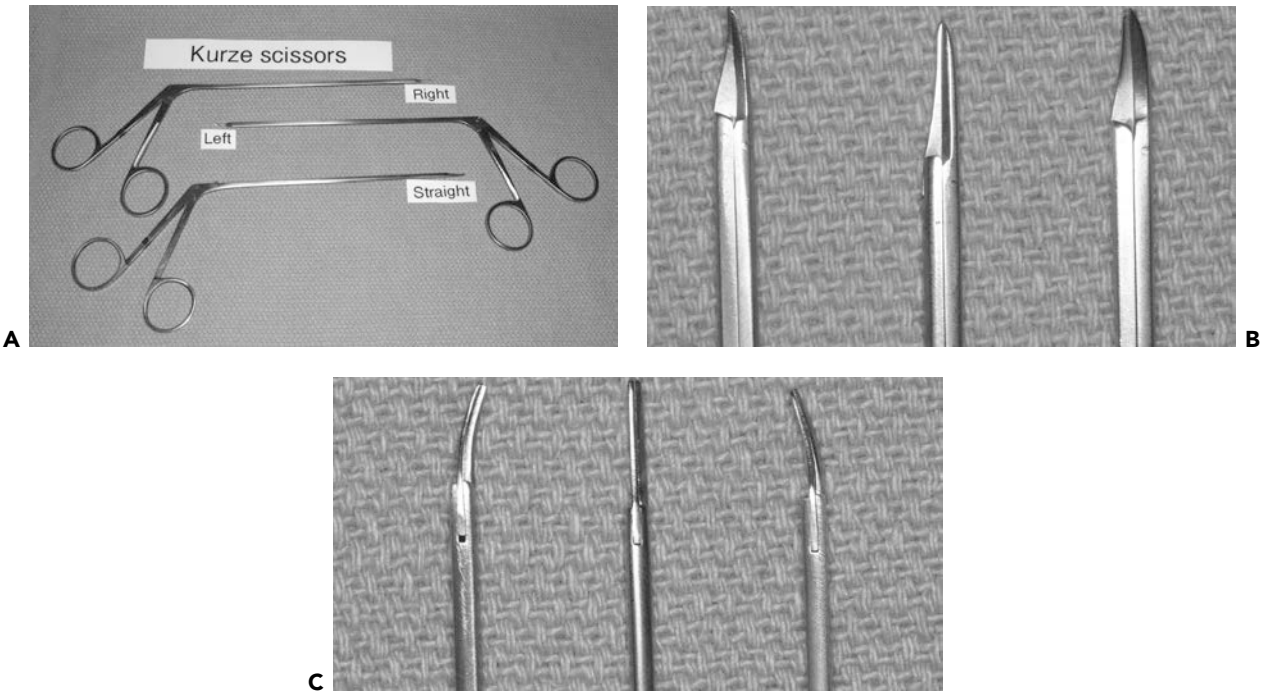


Figure 21.15 Kurze scissors: **(A)** Straight (below), right (above), and left (center). Higher magnification shows side view **(B)** and top view **(C)** of tips.

of fresh ideas concerning surgical techniques and the ability to share each specialty's unique instrumentation (see Figs 21.14–21.19).

Our first example of a combined approach is a lesion in the orbital apex. Dandy (1941), a neurosurgeon, wrote of the advantages of a craniotomy for *all* orbital tumors. This, of course, was in the day when orbital radiography consisted of plain films and a clinical practice that had a neurosurgical referral bias. Today neuroimaging provides location, size, and extent of the lesion, which allows the treating physician to select a more appropriate surgical approach. For lesions located in the shaded area (see Fig. 21.20) an orbitotomy through craniotomy maximizes surgical exposure while minimizing morbidity.

There are two options regarding the craniotomy and they center on whether or not the orbital rim is incorporated in the bone flap. We prefer to incorporate the rim in the bone flap as it increases surgical exposure, and minimal frontal lobe retraction is required (Jane et al., 1982; Maroon and Kennerdell, 1984). In addition the orbital roof, still attached to the bone flap, breaks approximately halfway back. The remaining orbital roof is removed with a rongeur. When the bone flap is replaced there is enough roof present to prevent postoperative globe pulsation. Disadvantages of this approach include forehead dysesthesia related to the supraorbital nerve and the fact that the frontal sinus is invariably violated. When the sinus has been entered the dura must be intact at closure, otherwise a small cerebrospinal fluid leak might occur that would be a potential mechanism for a postoperative meningitis or an eventual cerebral abscess.

A craniotomy that spares the orbital rim is situated more laterally, typically in the pterion. A small chisel is used to fracture the orbital roof and then a rongeur can

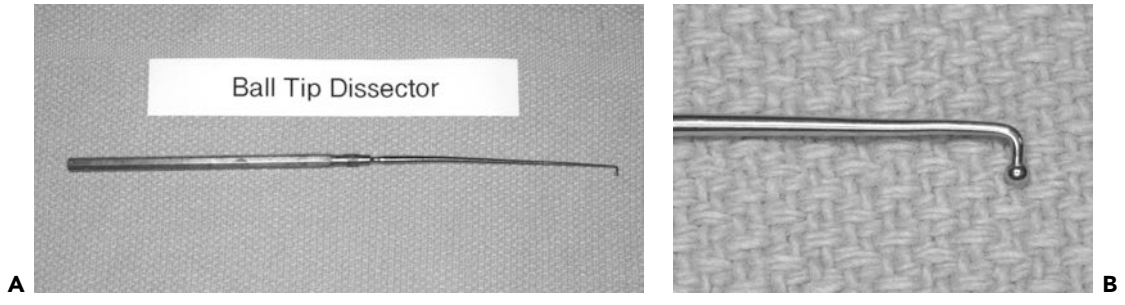


Figure 21.16 Ball tip dissector **(A)** and higher magnification of tip **(B)**.

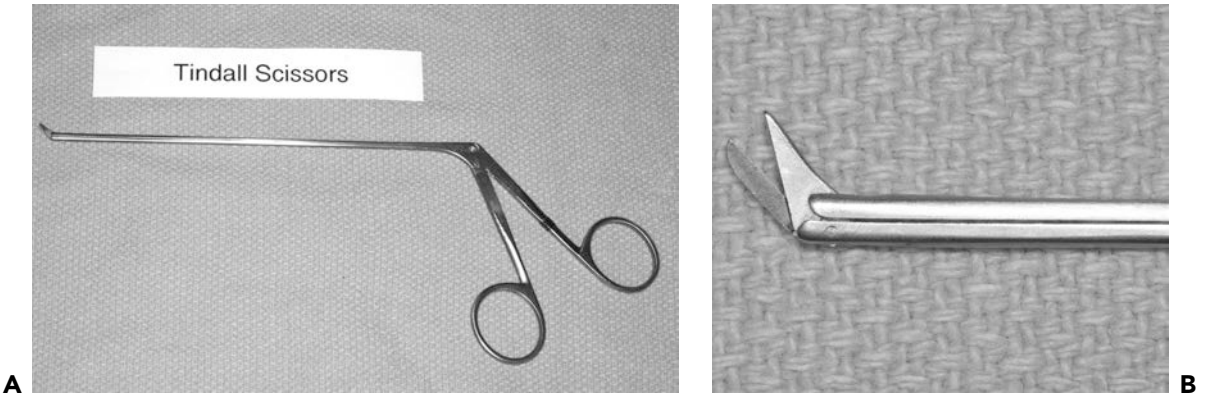


Figure 21.17 Tindall microscissors. Tip is angled 45 degrees **(A)** and seen better in magnified view **(B)**.

be used to complete the bone removal. The advantages of this approach include avoidance of the frontal sinus and the supraorbital nerve. The disadvantages are less intraoperative exposure and more brain retraction. The use of a malleable needle to drain off cerebrospinal fluid enhances exposure and obviates some brain retraction. Postoperative globe pulsation is almost always present but fortunately is rarely symptomatic.

By whatever method the superior periorbita is exposed the landmarks now remain fairly constant. The frontal nerve is often visible through the periorbita. The periorbita can be incised along this landmark and relaxing incisions can be placed anteriorly if desired. Because of the higher concentration of vital structures passing through the superior orbital fissure, dissection in the retrobulbar space should be initiated medial to the frontal nerve and superior rectus/levator muscle complex. Dissection in the apex, on either side of these landmarks, may also injure the trochlear nerve.

Excision of the entire optic nerve can be accomplished by either of the above approaches, which, up to this point, has remained entirely extradural. The intracranial portion of the nerve is addressed initially. A small flap in the dura is created and the nerve is sectioned in front of the chiasm. From an extradural vantage, the optic canal is opened. We place clips on the ophthalmic artery at this point. Postoperative ischemia of the globe, although a concern, has not occurred. The risk of tearing the ophthalmic artery at its junction with the internal carotid artery through intraoperative manipulation is the motivation for ophthalmic artery sacrifice. The optic nerve can be grasped with a small intervertebral disk punch in the orbital apex and pulled through the annulus of Zinn. If this cannot be accomplished the annulus must be opened, which is easier between the superior rectus/levator complex and the medial rectus. The nerve is then followed up to its insertion at the globe and transected. The intracranial communication through the optic canal is filled and sealed with a piece of temporalis muscle before a watertight dural closure is done. The periorbita is reapproximated. A pericranial flap is used to "externalize" the frontal sinus. Postoperative ptosis is usually marked but resolves within 3 to 4 months postoperatively.

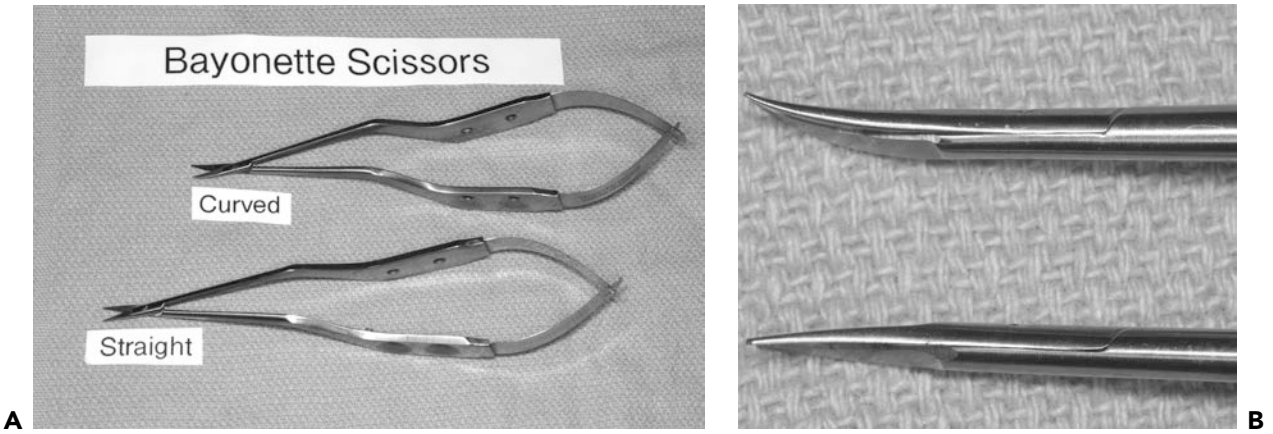


Figure 21.18 Bayonette scissors. **A:** Scissors are available in straight or curved blade styles. **B:** Higher magnification view of tips that can either be blunt (shown) or sharp.

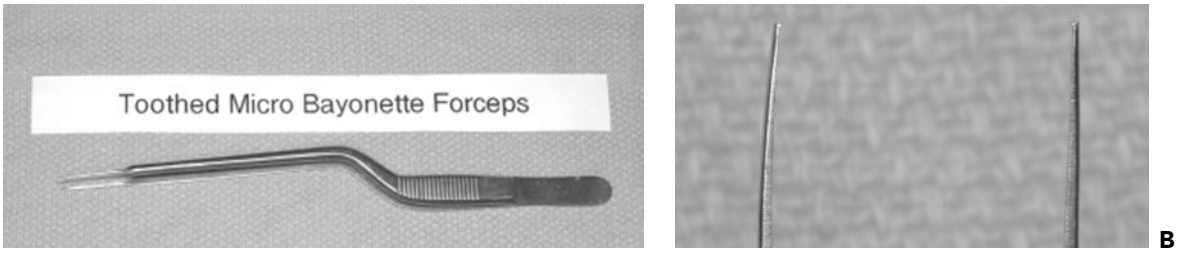


Figure 21.19 Bayonette microforceps **(A)** with 0.5 mm teeth **(B)**.

In the past few years, our surgical approach to malignant lacrimal gland tumors has included a consideration of a craniotomy and excision of the lacrimal gland with a large bony margin (Cheesman et al., 1989). If this does not include an exenteration, reconstruction of the bony rim can be accomplished with either methyl methacrylate (see Fig. 21.21) or bone grafts from split thickness calvarium or rib.

Another combined technique deals with secondary orbital tumors associated with destruction of the cribriform plate (Biller et al., 1989). These tumors tend to be either esthesioneuroblastoma or a malignant tumor arising from the ethmoid sinus, typically squamous cell carcinoma.

The procedure begins with a midline trephine craniotomy under a bicoronal flap to expose the cribriform plate from above. Numerous invaginations of the dura in the cristi galli region produce rents in the dura that must be repaired prior to closure. The tuberculum sella generally represents the posterior extent of the dissection. The rhinologist next proceeds with a lateral rhinotomy. The superior portion of this incision can be curved laterally under the brow to adjust to the orbital component of this case. Bone cuts are made near the junction of the cribriform plate and the orbital roof to isolate the tumor. The ethmoid tumor along with its intracranial and orbital extension can then be taken as a monobloc. Split thickness skin grafts from the thigh are taken to "reconstruct" the cribriform plate and the nose is packed for at least 10 days postoperatively. The trephine plug is wired into position after the frontal sinus has been exenterated. Two areas, besides the obvious tumor, are of special interest to the ophthalmologist; one is the nasolacrimal duct, which is transected during the lateral rhinotomy, and the other is the trochlea. Postoperative dacryocystitis resulting from transection of the nasolacrimal system may be prevented by intubating what remains of the nasolacrimal passages with silastic tubing. Management of the trochlea is more difficult. It is reflected downward with the periosteum and, if it is not involved

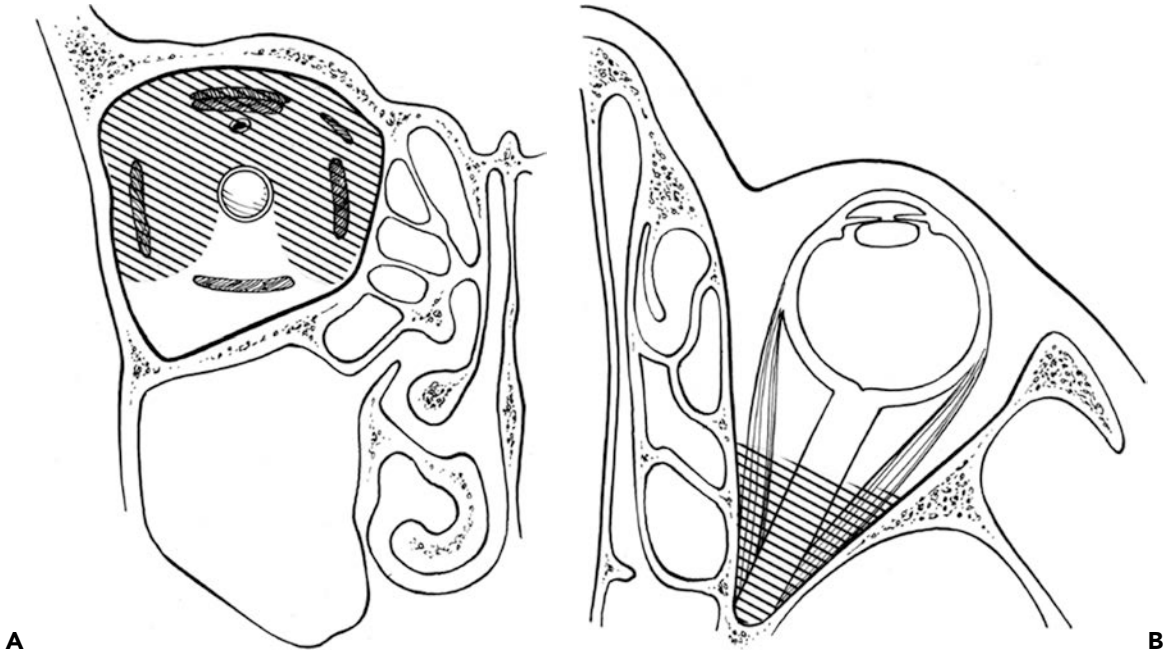


Figure 21.20 Topographic overview of shaded areas amenable to superior orbitotomy by craniotomy, coronal **(A)** and axial **(B)** sections.

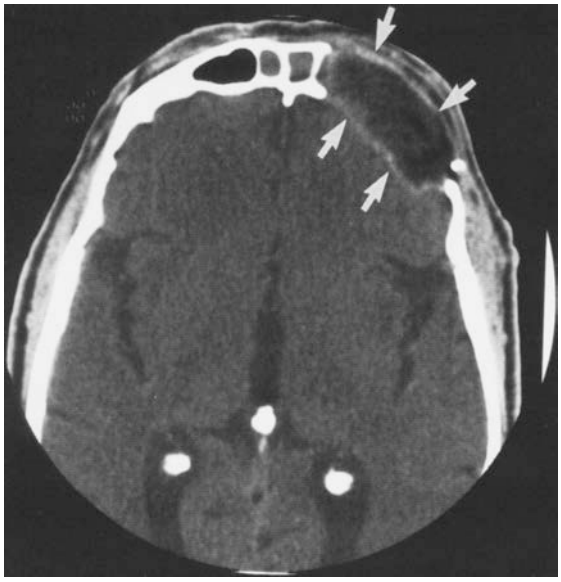


Figure 21.21 Computed tomography appearance of superior orbit following reconstruction of the rim with methylmethacrylate. This appearance can easily be confused with a postoperative infection.

with tumor, can be repositioned at the conclusion of the case. Patients with tumorous involvement of the trochlea and superior oblique muscle must have these structures excised. Diplopia is a common complication of excision of either the trochlea or superior oblique muscle. Temporary disinsertion of the attachment of the inferior oblique muscle to the frontal process of the maxilla during the course of the orbitotomy also contributes to a postoperative muscle imbalance. Those patients with a unilateral, surgically induced trochlear palsy usually compensate with some degree of head tilt. Vertical prism incorporated in the patient's eyeglasses may also assist in minimizing diplopia. We have observed one patient with a surgically induced bilateral trochlear palsy who has a chin-down head posture but only reports difficulty descending steps and stairs. Some of this may be due to the relative inferior oblique weakening, resulting from the temporary disinsertion of the muscle from its attachment to the frontal process of the maxilla.

Exenterations that spare the lids, lashes, and even the conjunctival fornices can also be performed as an extension of the combined bicoronal orbitotomy (vide supra). Thus far, end-stage sphenoid wing meningiomas or any process (typically malignant) that spares the very anterior orbit and lids are the primary indication for this procedure, although it has also been used for two cases of lacrimal gland adenoid cystic carcinoma.

To facilitate the exenteration, we begin with a simple enucleation by the standard anterior approach. For patients

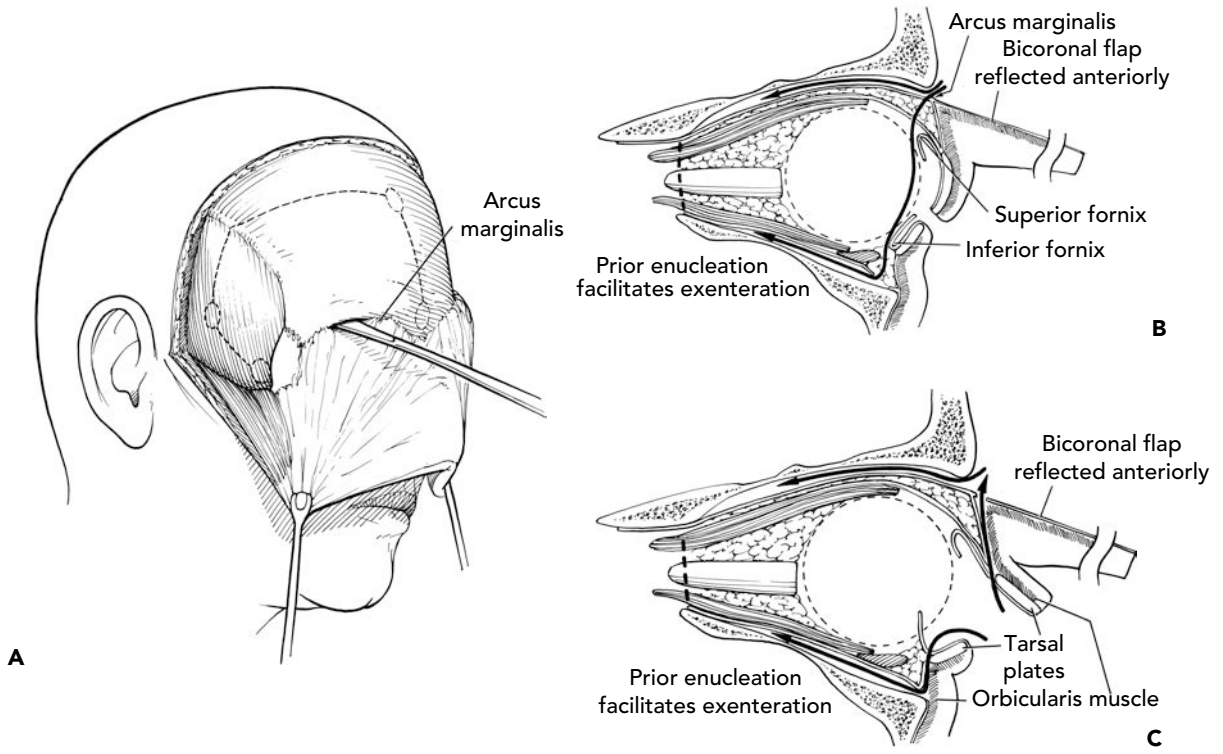


Figure 21.22 With the bicoronal flap reflected forward, the arcus marginalis is identified along the superior orbital rim **(A)** Sagittal view of exenteration, which spares the lids, lashes, and conjunctival fornices. Globe had been removed earlier to facilitate exenteration **(B)** Sagittal view of exenteration, which spares lids and lashes but includes conjunctival fornices **(C)** Exenteration is facilitated by prior enucleation.

willing to donate their cornea for later transplantation this will optimize corneal integrity. As the bicoronal flap is reflected down over the face an incision is made just behind the arcus marginalis (see Fig. 21.22A).

The dissection then continues inferiorly and posteriorly to spare the conjunctival fornices, (Fig. 21.22B). The tissue in the inferior orbit can be transected as a continuation of this route. The medial and lateral canthal structures are spared. After these planes have been developed, the craniotomy continues. Typically the superior orbital rim, roof, and portions of the lateral wall are included in the bone flap. The orbital contents can now easily be transected in the apex and delivered with the tumor in a monobloc. There are two options for filling the exenteration defect, swinging in the temporalis muscle or placing a free flap from the rectus abdominus or other sources (Olsen et al., 1992). The conjunctiva/Tenon layer is then closed as with any routine enucleation. Although the function of the upper eyelid is compromised, a prosthesis will round out the appearance of the adnexal structures. Our initial enthusiasm for temporalis muscle transfers has waned. When this muscle is denervated there is some subsequent atrophy. This results in an eventual "volume deficit" that nullifies the initially pleasing appearance. If the muscle retains its innervation, there is also a noticeable twitch or movement to the lids with chewing. The depression in the temporalis fossa can be filled in with one of many various substances to replace volume.

If the exenteration is to include the conjunctival fornices but one wishes to spare the eyelids and lashes, the globe is still removed first (Fig. 21.22C). The lids are then everted and incised at the base of the tarsal plate. A plane at the suborbicularis level is extended to the orbital rims. This should be done before removal of the superior orbital rim, because loss of this landmark makes the dissection plane difficult to follow. Further dissection behind the canthal tendons can be done underneath the bicoronal flap or more easily through the space created after the globe has been removed. We try to scrape the epithelium off the tarsus to obviate secretions.

Exenterations that include portions of the eyelids have been described in the preceding text. We have used this procedure with sinonasal carcinomas with spread to the overlying skin or with primary lid malignancies with orbital extension. Reconstruction of the orbit is a challenge following these extensive exenterations. The orbital defect may be partially covered by some combination of temporalis muscle flaps and skin grafts, or free flaps. Present-day techniques of soft tissue imaging lessen the risk of masking a tumor recurrence with overlying soft tissue.

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