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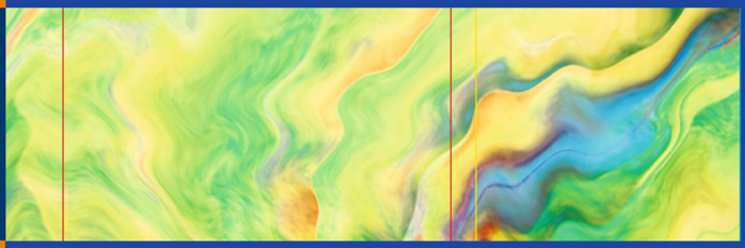

Frozen Section Library: Central Nervous System

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Series Preface

For over 100 years, the frozen section has been utilized as a tool for the rapid diagnosis of specimens while a patient is undergoing surgery, usually under general anesthesia, as a basis for making immediate treatment decisions. Frozen section diagnosis is often a challenge for the pathologist who must render a diagnosis that has crucial import for the patient in a minimal amount of time. In addition to the need for rapid recall of differential diagnoses, there are many pitfalls and artifacts that add to the risk of frozen section diagnosis that are not present with permanent sections of fully processed tissues that can be examined in a more leisurely fashion. Despite the century-long utilization of frozen sections, most standard pathology textbooks, both general and subspecialty, largely ignore the topic of frozen sections. Few textbooks have ever focused exclusively on frozen section diagnosis and those textbooks that have done so are now out-of-date and have limited illustrations.

The Frozen Section Library Series is meant to provide convenient, user-friendly handbooks for each organ system to expedite use in the rushed frozen section situation. These books are small and lightweight, copiously color illustrated with images of actual frozen sections, highlighting pitfalls, artifacts, and differential diagnosis. The advantages of a series of organ-specific handbooks, in addition to the ease-of-use and manageable size, are that (1) a series allows more comprehensive coverage of more diagnoses, both common and rare, than a single volume that tries to highlight a limited number of diagnoses for each organ and (2) a series allows more detailed insight by permitting experienced authorities to emphasize the peculiarities of frozen section for each organ system.

As a handbook for practicing pathologists, these books will be indispensable aids to diagnosis and avoiding dangers in one of the most challenging situations that pathologists encounter. Rapid consideration of differential diagnoses and how to avoid traps caused by frozen section artifacts are emphasized in these handbooks. A series of concise, easy-to-use, well-illustrated handbooks alleviates the often frustrating and time-consuming, sometimes futile, process of searching through bulky textbooks that are unlikely to illustrate or discuss pathologic diagnoses from the perspective of frozen sections in the first place. Tables and charts will provide guidance for differential diagnosis of various histologic patterns. Touch preparations, which are used for some organs such as central nervous system or thyroid more often than others, are appropriately emphasized and illustrated according to the need for each specific organ.

This series is meant to benefit practicing surgical pathologists, both community and academic, and to pathology residents and fellows; and also to provide valuable perspectives to surgeons, surgery residents, and fellows who must rely on frozen section diagnosis by their pathologists. Most of all, we hope that this series contributes to the improved care of patients who rely on the frozen section to help guide their treatment.

Philip T. Cagle, MD

Preface

Intraoperative pathology consultation is a challenging area of Surgical Pathology. It demands a good understanding of the diagnostic considerations, an awareness of the pitfalls associated with intraoperative consultation and an understanding of the clinical implications of diagnoses made in that arena. Diagnosis in the frozen section arena is often a highly demanding situation for the pathologist, who must render an assessment quickly and provide sound guidance and advice. Frozen section of Neuropathology-related cases is used to help guide intraoperative management of the case and to ensure that adequate and appropriate tissue is obtained for purposes of making an accurate final diagnosis. Because of the relative paucity of Neuropathology-related cases relative to other areas of Surgical Pathology, the anxiety and uncertainty levels are often a bit higher. Most standard pathology text books focus primarily on permanent section material and evaluation and largely ignore or only superficially address the topic of frozen section.

This monograph, *Frozen Section Library: Central Nervous System*, is a volume in the *Frozen Section Library* series. The text aims to provide a practical and succinct overview of surgical Neuropathology that is encountered at intraoperative consultation. The attempt is to provide an approach and framework for approaching cases. The thought process associated with evaluation of a Neuropathology frozen section is discussed. The text is divided into 11 chapters with the first 2 providing an introduction and general considerations in approaching a Neuropathology frozen section. Chapter 3 provides a discussion of pathologic findings (flags) which should alert one to the possibility of a nonneoplastic lesion. The remaining eight chapters are organized by site and

provide a discussion of how to differentiate the various pathologies that are likely to arise in a given location, since location is often one of the few pieces of clinical information that is provided at the time of frozen section.

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Karl M. Napekoski, M.D.

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Contents

Chapter 1
Introduction

UTILITY OF FROZEN SECTION IN THE EVALUATION OF NEUROPATHOLOGY CASES

Intraoperative pathologic consultation is an important part of many neurosurgery procedures in which tissue is being obtained for purposes of rendering a diagnosis. The primary goal of the brain biopsy procedure is to ensure that the tissue sampled is adequate to make an accurate final diagnosis. To this end, communication between the neurosurgeon and the pathologist is important. By way of illustration, many lesions in the central nervous system, particularly gliomas, may be heterogeneous in nature, i.e., different areas of the tumor may have a different histologic appearance or grade. Ideally, the neurosurgeon samples the highest grade area of the lesion. If a tumor looks like a grade IV glioma on imaging studies and the frozen section result looks like a low-grade astrocytoma, additional tissue is required. Communication of the imaging findings to the pathologist is important in ultimately arriving at the right diagnosis. A biopsy can then be taken from a different area of the tumor in order to pathologically confirm the radiologic impression of a higher grade tumor.

Given the goal of obtaining tissue that is representative of the lesion, this may necessitate the need to take multiple biopsies. One study, evaluating 188 stereotactic brain biopsy procedures from 185 patients, examined the issue of diagnostic yield of biopsies taken from the stereotactic target or presumed center of the lesion. In about two-thirds of the cases, an accurate diagnosis was obtainable on the first frozen section submitted for evaluation. Additional biopsies, up to as many as four, were required to increase the diagnostic yield in an additional 16% of cases. In 11%

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of the tumor cases, sampling error accounted for inaccurate diagnosis at the time of initial frozen section; these inaccuracies most commonly included undergrading a glioma or the diagnosis of necrosis in the setting of high-grade malignant neoplasm, such as a glioblastoma or metastatic carcinoma. In general, obtaining representative tissue is achievable in most cases, and the diagnostic accuracy is quite high. In addition to sampling issues due to lesion heterogeneity, other factors that may account for a nondiagnostic biopsy taken at a target or center of a lesion include the presence of intraoperative swelling and the level of experience of the neurosurgeon. Edema induced by the surgical procedure itself can shift the location of a lesion slightly, while the procedure is being performed. One must also consider the operator dependent factor, which is contingent upon the neurosurgeon's experience at performing brain biopsies.

In addition to providing information regarding the adequacy of sample for purposes of diagnosis, frozen section consultation can also aid in guiding intraoperative management in a given case. There are occasions when the diagnosis does impact on the surgical approach. A classic example of this is an intramedullary spinal cord tumor with a differential diagnosis of ependymoma versus astrocytoma. In the case of an astrocytoma diagnosis, the surgical procedure may be aborted, since diffuse astrocytomas are not resectable due to their infiltrative nature. If a diagnosis of ependymoma is rendered, an attempt at a gross total resection of the lesion may be made. Ependymomas are generally more circumscribed than their infiltrative astrocytoma counterparts and are thus more amenable to surgical excision. Another scenario in which the intraoperative frozen section diagnosis is important is in cases of documented recurrent or residual high-grade glioma in which the use of chemotherapeutic wafers is being entertained. Insertion of the wafers into the operative bed or residual tumor is generally done if the presence of viable tumor is documented at frozen section.

Care should be taken in the communication of a frozen section diagnosis to patients and their families prior to the final diagnosis on a given case. The frozen section diagnosis is meant to be a preliminary assessment and may not always be entirely accurate for reasons that have been previously discussed.

Frozen section diagnosis also provides the pathologist with some information that may be useful in determining how to triage the remaining tissue or additional tissue that is to be received. When an infectious process is suspected, based on the frozen section diagnosis, a recommendation that tissue be evaluated in the

microbiology laboratory may be made. Diagnostically challenging cases may warrant the utilization of electron microscopy to arrive at a final diagnosis and the triage of a small amount of tissue in glutaraldehyde for ultrastructural evaluation may be justified. In cases of lymphoma where there are adequate amounts of tissue available, excess tissue may be processed for flow cytometric evaluation; this is often not the case, since most suspected lymphomas warrant a small biopsy to confirm a diagnosis, resulting in limited amounts of sampled tissue. Fortunately, most of the molecular technologies that are currently utilized for the evaluation of brain tumors (such as polymerase chain reaction and fluorescence in situ hybridization) can be performed utilizing formalin-fixed, paraffin-embedded tissue. In rare suspected cases of Creutzfeldt–Jakob disease or other prion disease, tissue may be triaged (snap frozen) for a potential Western blot analysis. There is no indication for frozen section evaluation of these specimens. A diagnosis of prion disease cannot be made at frozen section and one then has to deal with the issue of a contaminated cryostat. Frozen section evaluation is not perfect and there is a well-known discrepancy rate between frozen section and final diagnoses due to a variety of factors. One recent large series, evaluating 2,156 brain tumor cases, noted a diagnostic discrepancy between the frozen section and final diagnosis in 2.7% of cases. The most common categories of discrepancy involved errors in the classification of spindle lesions (meningioma vs. schwannoma), differentiating oligodendroglioma from astrocytoma (not a critical error at the time of frozen section), misdiagnosis of lymphoma, differentiating gliosis from glioma, and overgrading. Overgrading tumors is particularly problematic, since it may result in a premature termination of the surgical procedure because the surgeon thinks he/she has obtained diagnostic tissue. A general rule of thumb is that if one is on the fence between two grades of a tumor, defaulting to the lower grade is probably less problematic that risking an overgrade.

Another recent study evaluated the incidence of discrepancies in nonneoplastic central nervous system lesions. Of the 333 cases evaluated, the discrepancy rate between frozen section and permanent section was noted to be 12.9%. The higher rate is probably related to the relative increased discomfort pathologists have with evaluating nonneoplastic lesions as compared with tumors and the relative lack of experience in this arena. The most common types of errors noted were misinterpreting a nonneoplastic lesion for a tumor, misdiagnosis of normal tissue as abnormal, and occasionally misinterpreting one nonneoplastic process for another.

FROZEN SECTION VERSUS SQUASH PREPARATIONS

Frozen section as well as the cytologic preparation (squash preparations) can be variously used to evaluate cases in the intraoperative consultation arena. This text focuses its attention on frozen section, but a brief discussion of the potential utility of a cytologic preparation is warranted. Squash preparations can easily be obtained by taking a small fragment of tissue and placing it between two slides and then with gentle pressure drawing the two slides apart and immediately fixing both slides in 95% alcohol. Touch preparations may also be useful in the evaluation of certain lesions in which tumor cells are easily detachable (lymphoma and metastatic carcinoma are good examples of this). Which methodology is utilized is dependent on the pathologist. There are relative advantages and disadvantages to each approach. The biggest advantage of a frozen section is that it maintains the architecture of the lesion. It is the technique which pathologists generally use to evaluate cases submitted for permanent section. In translation, this means that pathologists are more familiar with looking at neuropathology cases utilizing frozen section on intact tissue fragments. One should not freeze the entire specimen submitted unless the biopsy is too small to reasonably bisect. Saving some tissue for optimal processing results in better histology on permanent sections. Even small stereotactic needle biopsies can usually be bisected in order to save some tissue for permanent section processing.

There are a few artifactual changes that one needs to be aware of in evaluating frozen sections. Ice crystal formation, as part of freezing the tissue, can result in a pseudomicrocystic artifact that at times can result in a severe distortion of the tissue. Sometimes, this is accompanied by a distortion of nuclear shape and contour as well. This makes the evaluation of cellularity and the degree of atypia quite difficult (Fig. 1.1a, b). Another potential challenge which may affect both cytologic as well as frozen section preparations is the extent to which cautery or crush artifact is present in the tissue submitted for evaluation. Cauterization can cause an elongation of cells and their nuclei, as well as nuclear smudging, that can make interpretation difficult at times (Fig. 1.2a, b).

The advantages of cytologic preparation include the following: (1) A cytologic preparation provides better cellular detail. This can be helpful in certain circumstances. A notable example is in the evaluation of macrophages and the avoidance of misinterpreting tissue macrophages as glial cells on frozen section. (2) A cytologic preparation is tissue sparing. Relatively little tissue is required to perform the procedure. (3) A cytologic preparation is often

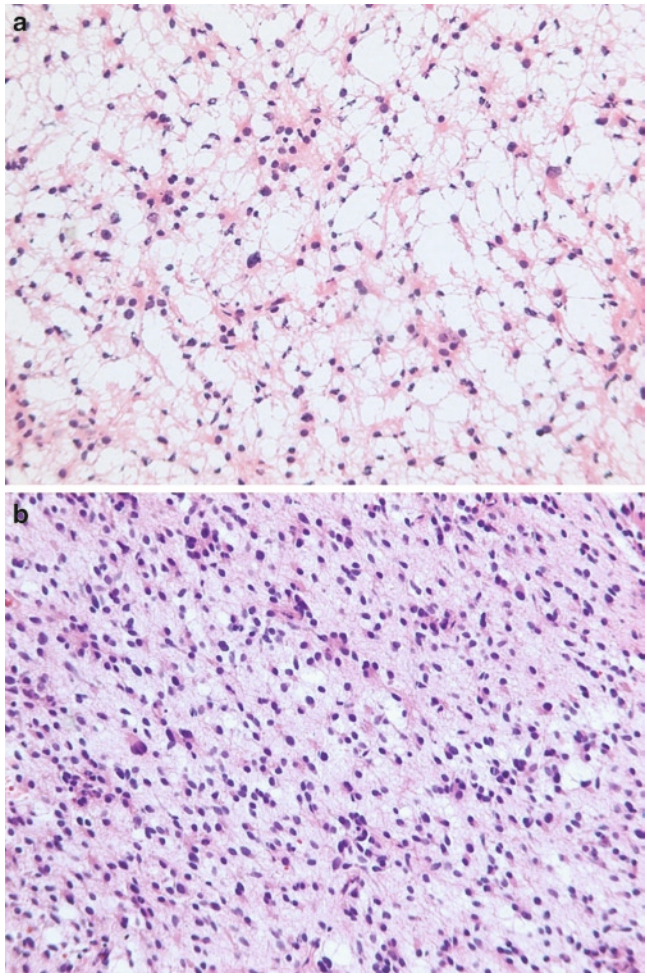

FIG. 1.1 (**a**) Marked microcystic artifact, induced by ice crystal formation while freezing the tissue, can make interpretation of biopsies difficult and assessment of cellularity challenging. (**b**) A formalin-fixed, paraffin-embedded section generated from the same tumor which was evaluated in (**a**) shows no microcystic change in this low-grade astrocytoma.

quicker to perform because it does not require sectioning of tissue prior to staining. What often dictates the extent to which cytological preparations are utilized is the quality of frozen section, as well as the experience of the pathologist and how he or she was

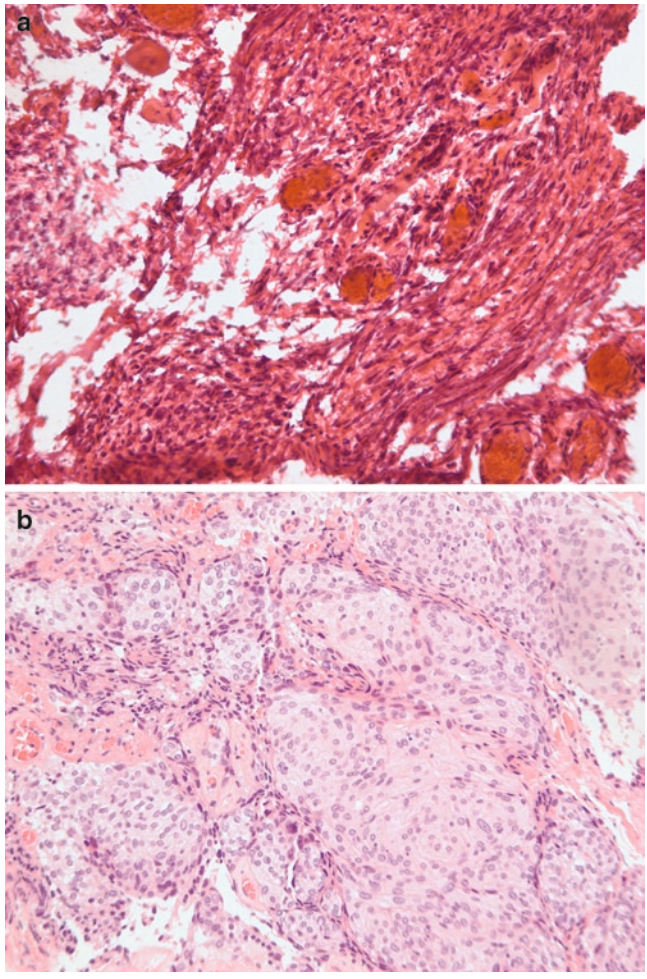

FIG. 1.2 (**a**) Significant crush or cautery artifact can cause cellular elongation and smudging of cells, making interpretation difficult. (**b**) On this permanent section of tumor, evaluated by frozen section in (**a**) the pathology is clearly that of a meningothelial (syncytial) meningioma. This diagnosis is impossible to make on the frozen section in (**a**).

trained to look at neuropathology intraoperative consult material (Fig. 1.3a–c).

With this as a background, let us proceed in Chap. 2 to begin the evaluation of the tissue.

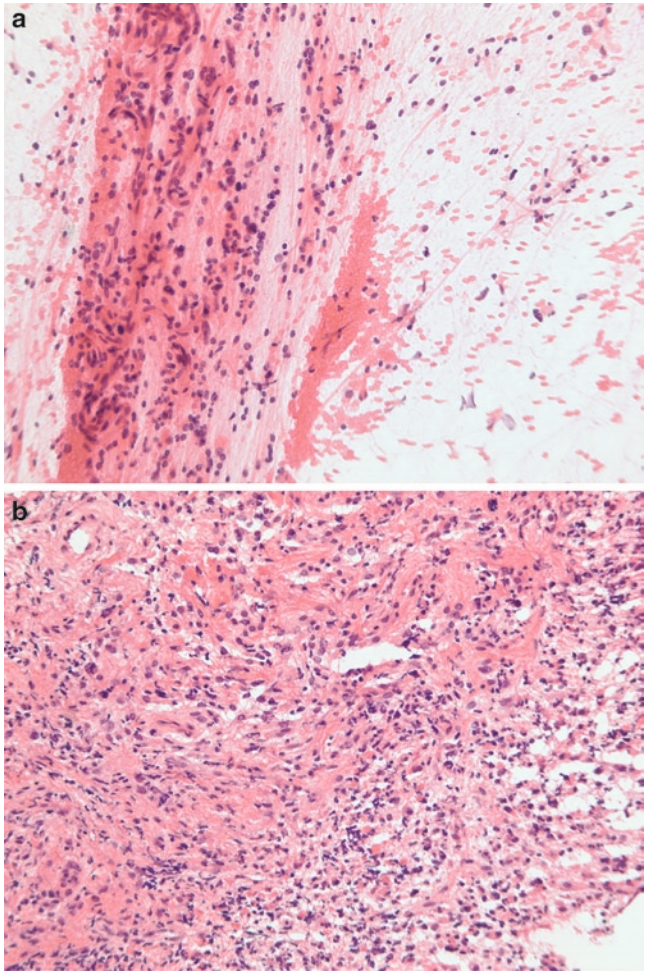

FIG. 1.3 (**a**) Squash preparation showing increased cellularity and clear nuclear atypia in an astrocytoma. (**b**) Frozen section performed on the same tumor as (**a**) shows moderate hypercellularity and atypia. The degree of cellularity is much more readily appreciable in the frozen section slide as compared with the squash preparation. (**c**) Permanent section on the same tumor as (**a**). This moderately hypercellular glioma was diagnosed as an anaplastic astrocytoma (WHO grade III).

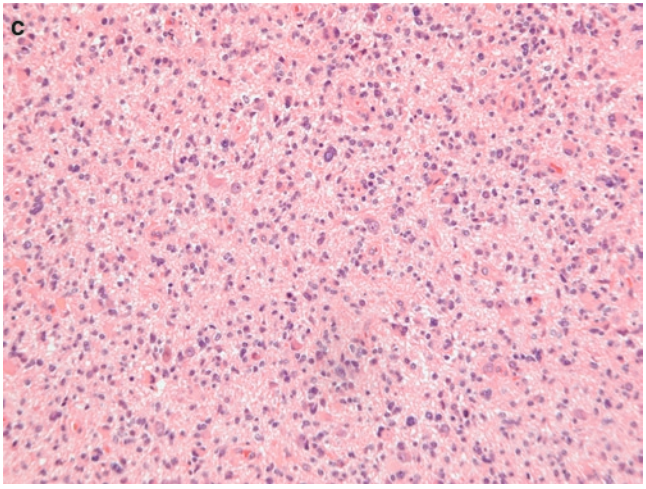

FIG. 1.3 (continued)

Chapter 2
Where to Start

TISSUE HAS BEEN RECEIVED AND A FROZEN SECTION CONSULTATION REQUESTED. THEN WHAT?

Even before one begins to process the tissue, there is some history provided with the specimen. History is important in the evaluation of the biopsy in that it allows the pathologist to commence formulating a differential diagnosis. Critical pieces of history include the age of the patient, location of the lesion, imaging findings, some sense of the clinical course, and prior history. There are a number of lesions that look quite similar to each other and based upon location may result in a different diagnosis or a different pathologic impression. Most of this text (Chaps. 4–11) is organized by location and differential diagnoses that should be considered by site.

A decision needs to be made regarding how one is going to process the specimen received. This is addressed in Chap. 1 under the discussion of frozen section versus squash preparation. Once the slide is ready for review, the first order of business is to make sure that the amount of tissue on the microscopic slide corresponds to the amount of tissue and number of tissue fragments submitted for frozen section processing.

WHERE AM I?

When one starts to examine a microscopic slide of brain tissue, it is useful to try to ascertain or corroborate the location of the tissue, if possible. In high-grade neoplasms which are markedly cellular, there may be no normal tissue evident in a small biopsy and one then has to rely on the information provided by the neurosurgeon

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with regard to the site of the sampled tissue. In larger resections or lower grade lesions, there may be enough recognizable architecture to allow one to make a rudimentary assessment of the area of the brain that is being evaluated. This is useful for two reasons. One, it confirms the surgeon's impression regarding location. Two, this provides another piece of information that may be useful in the generation of a differential diagnosis. Anecdotally, a case is recalled in which the suspected diagnosis clinically was demyelinating disease, possibly progressive multifocal leukoencephalopathy. The surgeon was under the impression that the biopsies which were being sent for frozen section evaluation were from white matter areas (Fig. 2.1). The first several biopsies submitted clearly represented cortical tissue. Progressive multifocal leukoencephalopathy is not diagnosed with a cortical biopsy. Repositioning of the biopsy instrument eventually yielded diagnostic white matter tissue.

Neuroanatomy and neurohistology are difficult, and for most general pathologists, are not encountered frequently enough to engender a sense of confidence. However, there are basic clues which can be useful in ascertaining a location. The presence of neurons tells one that he or she is looking at gray matter areas, perhaps cortex or a nucleus (Fig. 2.2). White matter tissue, in

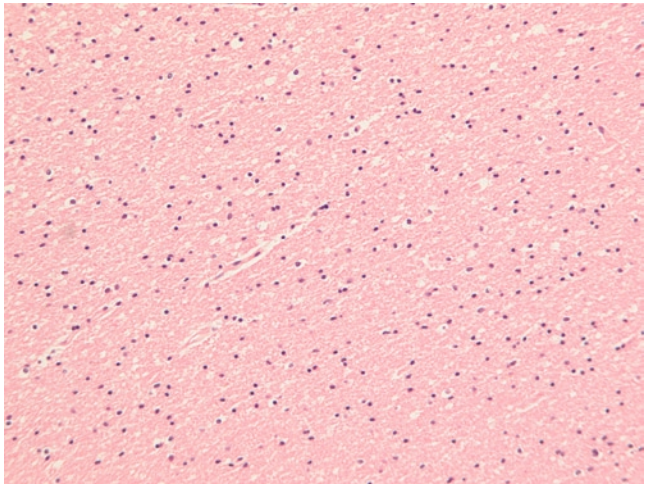

FIG. 2.1 White matter is characterized by cells with rounded nuclei and scant cytoplasm (oligodendrocytes) and a smaller population of cells with larger nuclei (astrocytes). Neurons are generally not observable in the white matter.

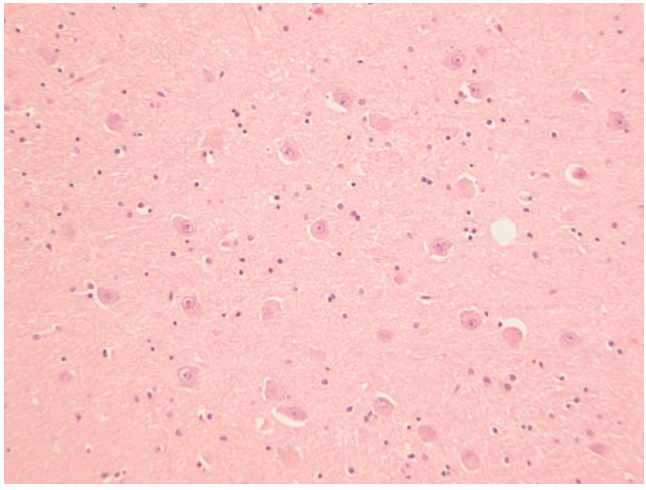

FIG. 2.2 A clue that one is dealing with gray matter tissue is the presence of neurons. Many of the larger size neurons have prominent nucleoli in their round to oval nuclei and show evidence of Nissl substance in their cytoplasm.

contrast, is devoid of neurons. Basal ganglia, particularly the caudate and putamen nuclei, are primarily gray matter tissues that are unique in that they contain small bundles of white matter (the pencil bundles of Wilson) that transverse the gray matter; there are no other areas of the brain that have this architectural configuration (Fig. 2.3). The cerebellum is marked by an architecture which includes a paucicellular molecular layer, a single layer of large Purkinje cell neurons, and a rather densely cellular granular cell layer (Fig. 2.4). In a small biopsy consisting primarily of cells from the cerebellar granular layer, a common pitfall is that the granular cells are misinterpreted as representing lymphocytes and a diagnosis of chronic inflammation or encephalitis is erroneously made. Meninges are a relatively paucicellular tissue. Remember, occasional pigmented, spindled nevus cells may be normally present in the meninges (Fig. 2.5). The unpaired pineal gland and pituitary gland have a unique histologic appearance that may cause some confusion. Particularly problematic is the pineal gland, which can look very much like a glioma to the untrained or unaware individual (Fig. 2.6). The spindled appearance of the pituitary neurohypophysis can also resemble a glial neoplasm, if one is not aware of

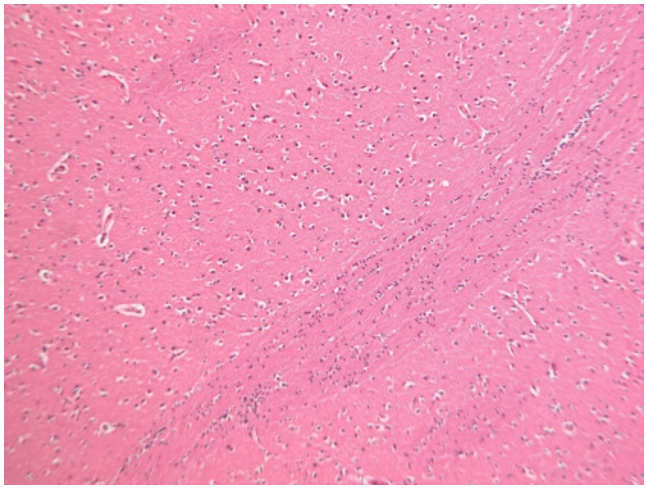

FIG. 2.3 This section from the caudate nucleus shows gray matter with small bundles of fibers with rounded oligodendroglial nuclei. These pencil bundles of Wilson are characteristic of the caudate and putamen nuclei. An ependymal lining on one aspect of the caudate nucleus, if sampled, allows for distinction between the caudate and putamen.

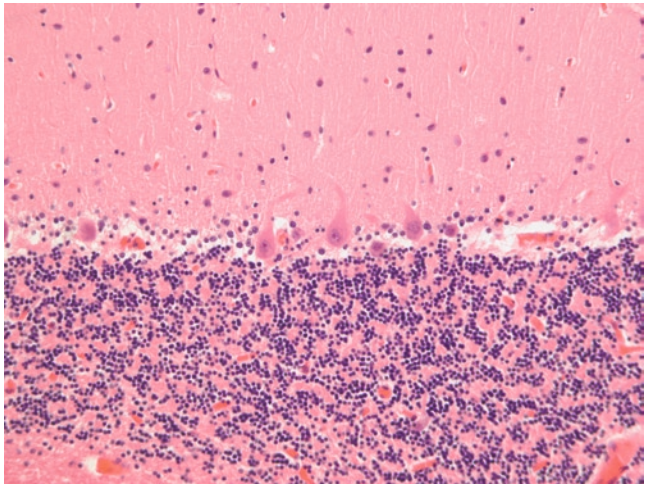

FIG. 2.4 This section of cerebellum shows the three layers of cortex, including the paucicellular molecular layer, Purkinje cell layer, and granular cell layer. A biopsy taken from the granular cell layer only may be misinterpreted as representing chronic inflammation, if one is not aware of the location. Infant brains (*less than 1 year*) may show an additional granular cell layer at the surface.

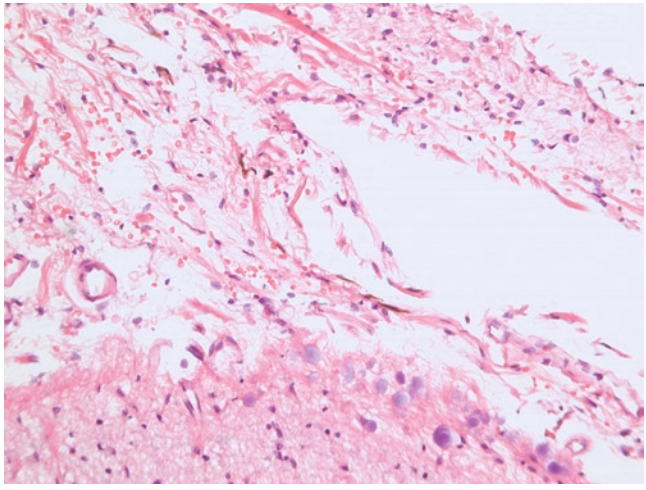

FIG. 2.5 The meninges comprise loose connective tissue with blood vessels, nests of meningothelial or arachnoidal cap cells (*not seen here*) and occasional nevus cells, which are spindled with melanin pigment.

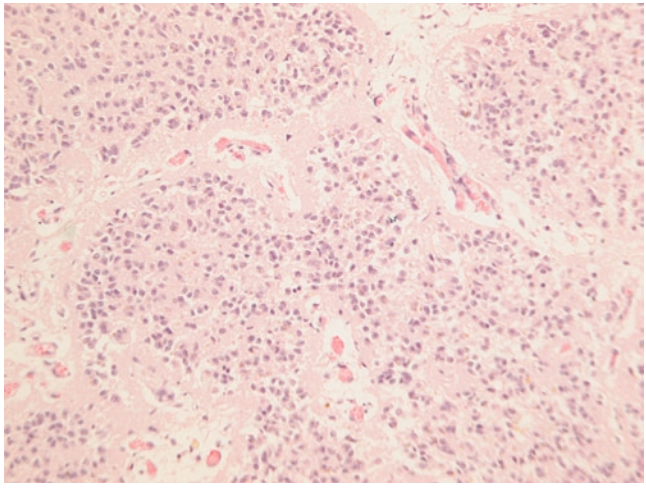

FIG. 2.6 The pineal gland is marked by rounded or slightly elongated cells arranged in lobules, separated by fibrovascular tissue. The background of the gland has a fibrillary appearance. In a small biopsy, it may be difficult to appreciate the lobular architecture and a diagnosis of glioma may be entertained. Microcalcifications are also a frequent finding in the pineal gland in adults.

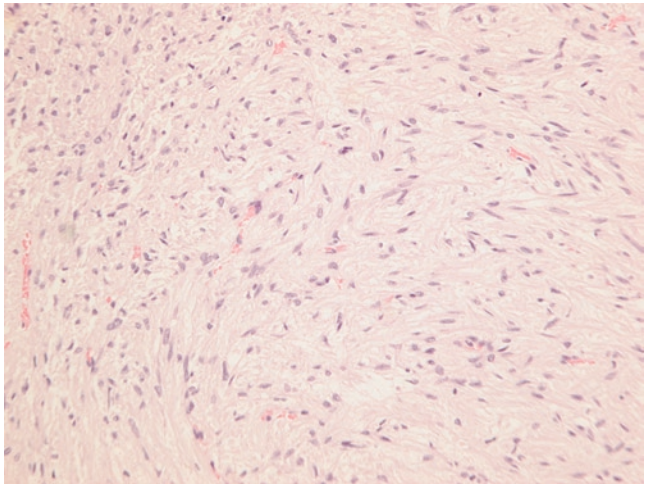

FIG. 2.7 The pituitary neurohypophysis is marked by a loose arrangement of spindled cells, resembling a spindled glioma, if one is not aware of the location. A photomicrograph of the normal adenohypophysis is contained in Chap. 9 (Fig. 9.1).

the location (Fig. 2.7). The subependymal zone may also appear hypercellular, which can be mistaken for low-grade glioma. The optic nerve, which may occasionally be the target of a biopsy or resection, also has a somewhat unique architecture, marked by a glial appearing background separated by a delicate vascular network (Fig. 2.8). Corpora amylacea are round, gray, or light purple staining structures on hematoxylin and eosin staining that are associated with astrocytic processes (Fig. 2.9). They tend to collect in variable numbers in the subpial region or near blood vessels. Their presence is generally not considered pathologic but the misinterpretation of these structures as representing cells may cause an erroneous diagnosis of low-grade glioma. In contrast to real cells, corpora amylacea do not contain a nuclear structure.

Being aware of what normal tissue looks like is important in preventing overinterpretation of a biopsy taken from a more unusual site. Perhaps one of the hardest diagnoses to make at frozen section is a diagnosis of "normal." Presumably, the neurosurgeon is not deliberately targeting normal tissue for the purpose of a biopsy; in some instances, however, normal tissue may be sampled.

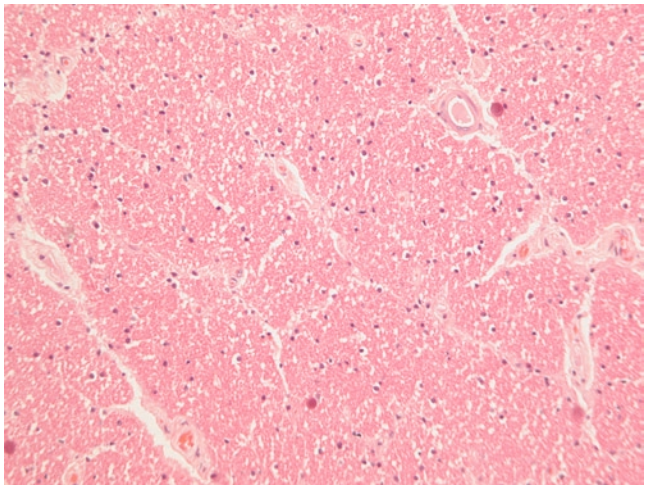

FIG. 2.8 This section of optic nerve shows a lacy fibrillary background. The nerve may have a vaguely nodular architecture to it.

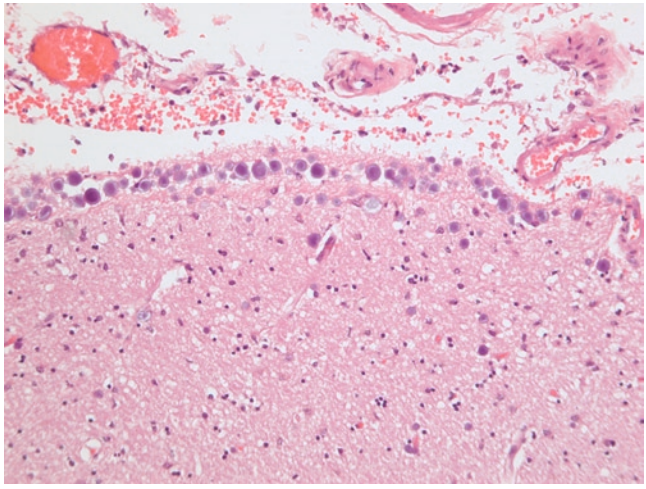

FIG. 2.9 Small, rounded gray–purple corpora amylacea are seen here. They are frequently present in biopsies and represent polyglucosan bodies which accumulate in astrocytic processes, most prominently near the surface of the brain or around blood vessels. On low magnification, they may be misconstrued as representing cells.

GLIOSIS OR SOMETHING MORE?

One of the ways the brain reacts to injury, insult, or something that is not supposed to be there (like a tumor) is gliosis. Gliosis can assume one of several forms. Subacute gliosis is marked by the presence of large reactive astrocytes that are evenly distributed within the tissue sample (Fig. 2.10). Reactive astrocytes are marked by the presence of abundant eosinophilic cytoplasm and a large nucleus which may be round, oval, or slightly indented. The cells have long, tapering, star-like cytoplasmic processes in comparison to the rather blunt and irregular cytoplasmic processes observed in gemistocytic neoplastic astrocytes. On frozen section, these cytologic differences are not readily evident and often require immunohistochemical staining with glial fibrillary acidic protein (GFAP) antibody to discern. Distinction of reactive astrocytes from neoplastic astrocytes may be challenging at times. In general, neoplastic astrocytes are marked by a high nuclear to cytoplasmic ratio, nuclear enlargement, nuclear hyperchromasia,

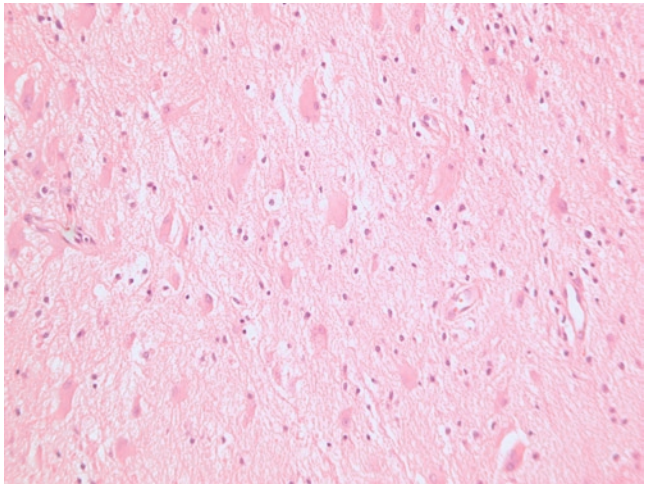

FIG. 2.10 Reactive astrocytes in gliosis are marked by increased eosinophilic cytoplasm and mild nuclear enlargement with displacement of the nucleus to the periphery of the cell. The nuclei may show a round to oval or kidney bean shaped contour. The appearance of reactive astrocytes contrasts with typical malignant astrocytes which are marked by high nuclear cytoplasmic ratio, angular and irregular nuclear contours, and nuclear hyperchromasia.

and nuclear pleomorphism. The malignant cells are generally unevenly distributed in the tissue specimen. Reactive astrocytes, in contrast to tumoral astrocytes, generally do not satellite around preexisting structures. The presence of concomitant microcalcifications and true microcystic degenerative changes are more commonly observed in low-grade gliomas than in gliosis.

Reactive astrocytes, secondary to radiation therapy effect, may demonstrate some evidence of cytologic atypia. This can cause some confusion with tumoral astrocytes. Radiation atypia may be marked by cytomegaly, cytoplasmic vacuolization, and large, bizarre nuclei (Fig. 5.14). Nuclei may appear hyperchromatic and "smudged," with nuclear features similar to cells in a bizarre leiomyoma of the uterus. A history of radiation administration should heighten one's awareness of this possibility. Other changes suggestive of radiation therapy effect, including vascular sclerosis, necrosis with macrophages, and perivascular chronic inflammation, may also be present. In many irradiated high-grade glioma cases, there is still a population of residual malignant astrocytes that demonstrate the usual features of malignancy; one does not have to try and interpret the true nature of these very atypical and bizarre appearing cells.

In the case of trying to distinguish neoplastic gemistocytic astrocytes from reactive astrocytes, the distribution of cellularity can be helpful; the gemistocytic astrocytes are more densely arranged (Fig. 5.7). If one looks carefully in the background of a gemistocytic astrocytoma, evidence of conventionally atypical astrocytoma cells can be seen.

In the areas of more chronic gliosis, the presence of hypertrophic astrocytes may not be as prominent. These areas are frequently marked by a dense fibrillar background, which may be punctuated by Rosenthal fibers (Fig. 2.11). Areas of chronic gliosis may often be seen adjacent to tumors. Care should be taken not to misinterpret chronic gliosis as low-grade glioma. For example, a biopsy taken at the perimeter of a cerebellar cyst with enhancing mural nodule in a young adult conjures up a differential diagnosis of hemangioblastoma versus pilocytic astrocytoma. A biopsy taken at the perimeter of the hemangioblastoma may show a markedly fibrillar background with mild hypercellularity and numerous Rosenthal fibers, which can lead one to consider a pilocytic astrocytoma diagnosis. This chronic gliosis finding is not uncommon around the perimeter of hemangioblastoma. Similar areas of chronic gliosis may be observed around craniopharyngiomas (Fig. 9.9) or lining the walls of pineal cysts (Fig. 10.8).

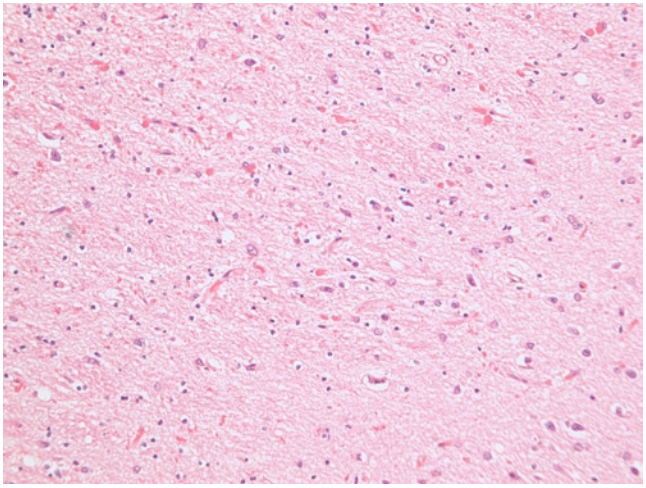

FIG. 2.11 Brightly eosinophilic Rosenthal fibers may be seen in areas of gliosis.

Once an assessment has been made as to location and whether the tissue being examined represents normal or gliosis or something else, the next question to ask is whether or not the lesion may possibly constitute a nonneoplastic process. This is the subject of Chap. 3.

Chapter 3
Nonneoplastic Flags

The majority of neuropathology lesions submitted for frozen section end up representing tumors. We often approach these cases somewhat biased in thinking that we are likely to be dealing with a neoplasm. Consequently, we may be caught off guard by a nonneoplastic process. Additionally, our experience with nonneoplastic lesions in the central nervous system is generally not as extensive as with tumors. Nonneoplastic central nervous system lesions can pose a significant differential diagnostic challenge and are often the source of considerable confusion and anxiety. This chapter focuses on pathologic findings or flags that should raise the possibility of a nonneoplastic process (Table 3.1).

FLAG 1: CHRONIC VASCULAR-BASED INFLAMMATION

Vascular-based chronic inflammation is not an uncommon finding at the time of frozen section. A subset of tumors, as is discussed later, may demonstrate perivascular chronic inflammation marked by benign appearing lymphocytes. Many of these represent low-grade pediatric lesions, including entities such as pilocytic astrocytoma, ganglioglioma, pleomorphic xanthoastrocytoma, germinoma, and the rare lymphoplasmacyte-rich meningioma. However, there are a number of pathologies which may be marked by the presence of vascular-based chronic inflammation that do not represent tumor. The most notable examples of this are infection and vasculitis.

Infectious processes in the central nervous system elicit an inflammatory reaction which may consist of a mixture of both acute and/or chronic inflammatory cells. Viral infections tend

R.A. Prayson and K.M. Napekoski, *Frozen Section Library: Central Nervous System*, Frozen Section Library 6, DOI 10.1007/978-1-4419-7579-9_3,

Table 3.1 Pathologic flags that should raise consideration of a nonneoplastic diagnosis.

Flag 1: Chronic, vascular-based inflammation
Infection
Vasculitis
Lymphoma
Flag 2: Acute inflammation
Meningitis
Abscess
Flag 3: Granulomatous inflammation
Infection – usually necrotizing
Sarcoid – usually nonnecrotizing
Vasculitis
Rarely tumor (germinoma, lymphoma)
Flag 4: Macrophages
Infarct
Demyelination
Radionecrosis
Flag 5: Thickened blood vessel walls
Hypertension/atherosclerosis
Amyloid
CADASIL
Radiation
Flag 6: Too many blood vessels
Vascular malformations – usually arteriovenous malformation, cavernous angioma
Tumors (hemangioblastoma, angiomatous meningoma, pilocytic astrocytoma, hemangiopericytoma)
Sturge Weber
Flag 7: Cysts
Arachnoid
Colloid
Rathke's cleft
Epidermoid
Dermoid
Endodermal
Ependymal
Choroid plexus
Pineal
Cystic neoplasms (such as craniopharyngioma, pilocytic astrocytoma, hemangioblastoma)

to present with a more chronic inflammatory cell infiltrate that may involve the meninges as well as vessels in the parenchyma (Fig. 3.1). In this setting, one should look for evidence of viral inclusions or other findings suggestive of a viral infection, such as microglial nodules (Fig. 3.2).

The presence of inflammatory cells within a vessel wall, often accompanied by vessel wall injury, pathologically defines vasculitis (Figs. 3.3 and 3.4). The etiology of a vasculitic pattern of injury is generally impossible to resolve in many cases at the time of frozen section. Whether the vasculitis represents a true primary angiitis of the central nervous system or is a manifestation of a systemic vasculitic process may be difficult to surmise. Likewise, vasculitis arising as the result of an infectious process or other etiology, such as cocaine use, for example, may also be difficult to discern based on a casual examination of a frozen section slide. Because of this, signing such cases out as "vasculitic pattern of injury present" is generally sufficient for purposes of frozen section consultation. In many cases of expected primary angiitis of the central nervous system, an open biopsy is performed and tissue submitted from the meninges, gray matter, and white matter. Tissue from the meninges is the highest yield location for vasculitis. It is important

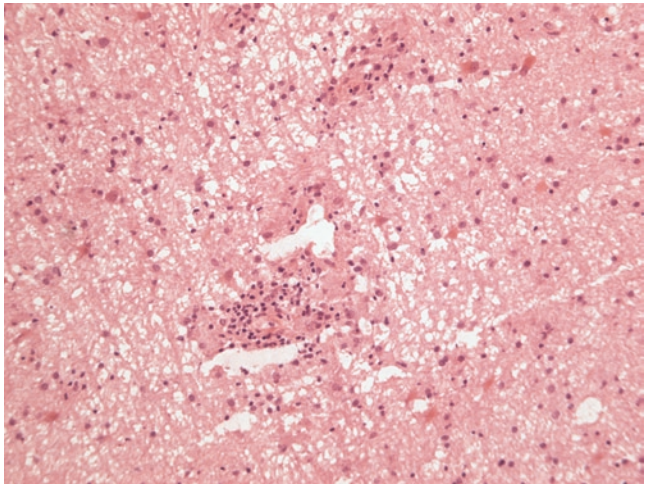

FIG. 3.1 An angiocentric, benign chronic inflammatory infiltrate consisting primarily of lymphocytes with scattered adjacent reactive astrocytes. The final diagnosis on this case was encephalitis.

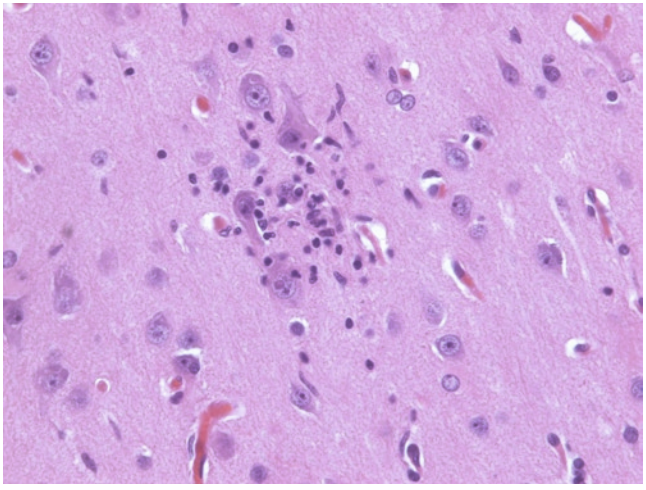

FIG. 3.2 A microglial nodule is a collection of spindled microglial cells and inflammatory cells; it is a clue to a possible infectious etiology.

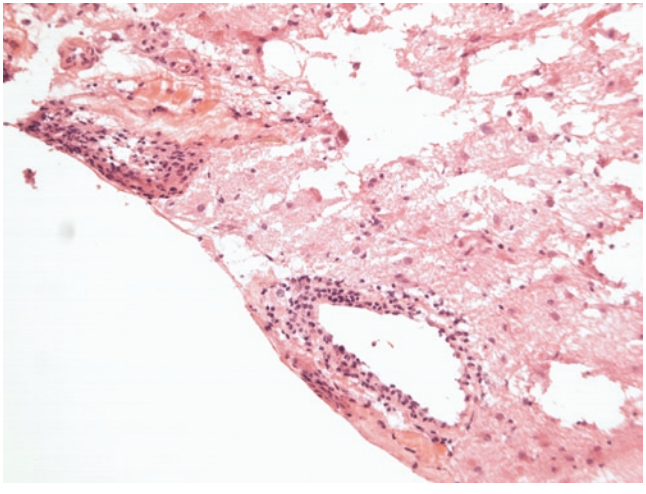

FIG. 3.3 Meningeal vessels with infiltration of vessel walls by chronic inflammatory cells constituting a nonnecrotizing vasculitic pattern of injury.

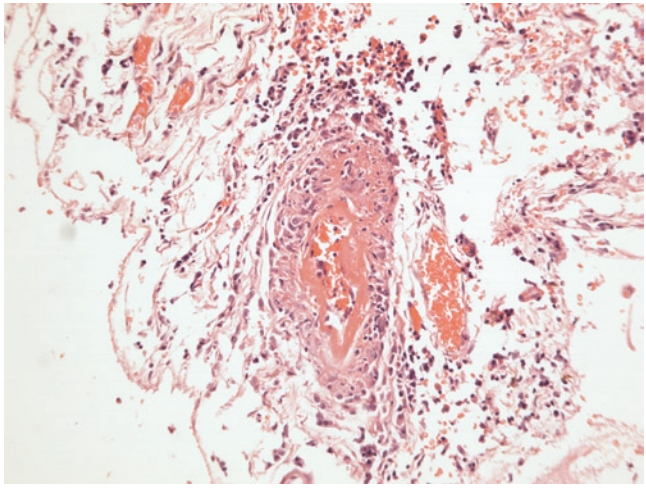

FIG. 3.4 Meningeal vessel with fibrinoid necrosis of the vessel wall consistent with a necrotizing vasculitis (polyarteritis nodosa).

to remember, however, that the absence of vasculitis on such a biopsy does not necessarily exclude the possibility that the patient has vasculitis; vasculitis is a focal process which may demonstrate patchy involvement of blood vessels. The term perivasculitis should be avoided as a diagnosis equivalent with perivascular chronic inflammation; unfortunately, some people only see the "vasculitis" portion of that word and jump to their own conclusions.

Careful examination looking for evidence of cytologic atypia of the lymphoid cells present in such infiltrates is important. The presence of an atypical lymphoid population raises the possibility of a lymphoproliferative process. Most cases of primary central nervous system lymphoma arise as parenchymal masses, frequently in the periventricular region; such lesions may have indistinct borders on imaging studies. Patients who are immunocompromised are prone to develop lymphoma. Patients with a history of an organ transplant may develop a posttransplant lymphoproliferative disorder, which may look histologically indistinguishable from lymphoma at frozen section. In cases in which a history of transplantation is available, a diagnosis of posttransplant lymphoproliferative disorder is preferred, since not all of these processes behave like lymphoma. The vast majority of primary central nervous system lymphomas are diffuse large B cell lymphomas

marked by cells with an irregular nuclear contour. Lymphomas show a predilection for perivascular areas (angiocentric pattern) (Figs. 3.5 and 3.6). Occasionally, lymphomas may grow to be confluent, in which case, the differential diagnosis of lymphoma versus other high-grade malignant small cell neoplasms, including small cell carcinoma, high-grade oligodendroglioma, or small cell glioblastoma may arise (Fig. 3.7). In such cases where there is no angiocentric pattern present to suggest lymphoma, a diagnosis of a small cell neoplasm with a list of the possible differential diagnostic considerations is a reasonable approach. The diagnosis can be resolved on permanent sections with additional studies and sometimes with better histology. Remember, steroid treatment prior to biopsy may cause widespread necrosis of lymphoma (Fig. 3.8). Secondary involvement of the central nervous system by leukemia or lymphoma tends to be meningeal based. Again, a generic diagnosis of atypical cells present consistent with a lymphoproliferative disorder or leukemic disorder (if such a history is available at the time of biopsy) is adequate. More definitive and precise classification of such lesions can be done with permanent sections and additional studies. Remember, the goal is to ensure that there is adequate tumor sampled for diagnosis. Be wary of the rare intravascular or angiotropic lymphoma which is marked by the presence of atypical lymphoid cells confined to vascular lumina (Fig. 3.9).

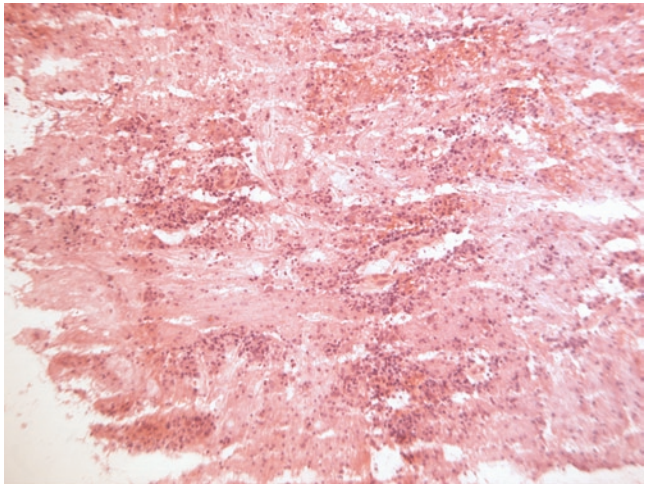

FIG. 3.5 A low magnification appearance of a Non-Hodgkin's lymphoma marked by an angiocentric aggregation of atypical lymphoid cells.

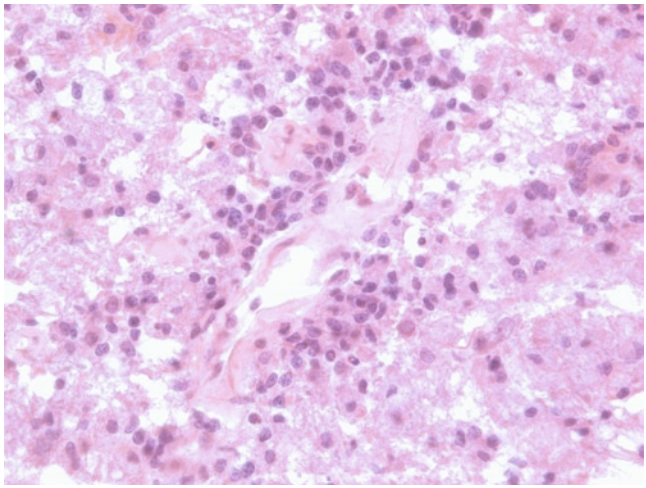

FIG. 3.6 Careful attention should be made when looking for atypia in inflammatory infiltrates. These large atypical lymphoid cells, with an occasional mitotic figure, are suggestive of a diagnosis of a lymphoma.

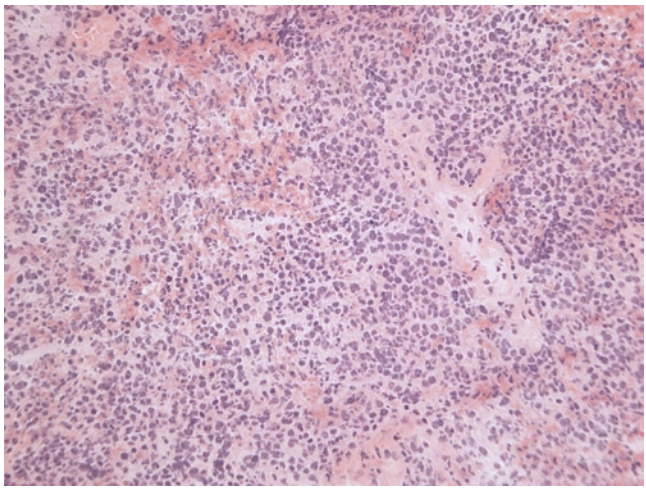

FIG. 3.7 Lymphomas growing in a sheet-like or solid pattern without an angiocentric distribution may be difficult to distinguish from metastatic small cell carcinomas or high-grade small cell gliomas.

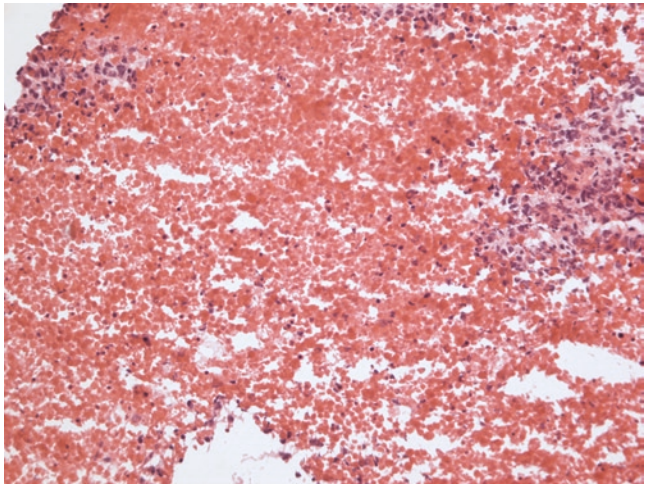

FIG. 3.8 Extensively necrotic neoplasm which was eventually diagnosed as lymphoma. In patients who have been treated with steroids prior to biopsy, one may encounter extensive necrosis at the time of frozen section, making a definitive diagnosis difficult without immunohistochemistry.

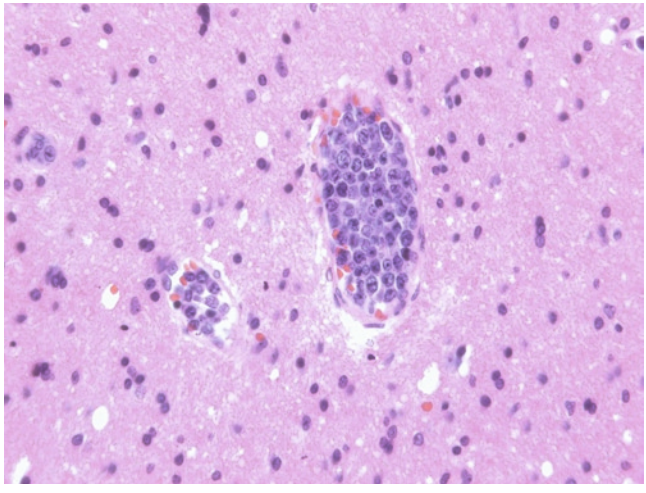

FIG. 3.9 Atypical cells are noted to be confined to vascular lumina. A diagnosis of intravascular lymphoma or angiocentric large cell lymphoma was made in this case.

FLAG 2: ACUTE INFLAMMATION

Acute inflammatory cells are usually not a problem for most pathologists to recognize. They are almost invariably associated with an infectious process. When seen in the meninges, a meningitis diagnosis is appropriate (Fig. 3.10). Recommendation that tissue be sent for microbiological culturing should be made. Likewise, the presence of neutrophils in the parenchyma is likely to be associated with an abscess and recommendations for microbiologic culture should be made. Abscesses can sometimes present a challenge in diagnosis, particularly if the organizing edge of an abscess is sampled. With evolution, abscesses tend to organize in zones (Figs. 3.11 and 3.12). The central portion of the abscess is often marked by necrosis and acute inflammation. One should look for evidence of organisms (fungi or parasites) which may be identifiable at frozen section (Fig. 3.13). Gram stains and stains for fungal organisms are part of the evaluation of these lesions on permanent section. On the perimeter of the central necrotic and acutely inflamed zone is a zone of organization marked by a proliferation of small blood vessels, fibroblasts, and a mixture of acute and chronic inflammatory cells. A biopsy from this hypercellular zone may result in an erroneous diagnosis of glioma (Fig. 3.12). Imaging studies of an organizing abscess may mimic a high-grade tumor. Small vessels that are proliferating in this region may show endothelial mitotic activity, which further heightens one's concern

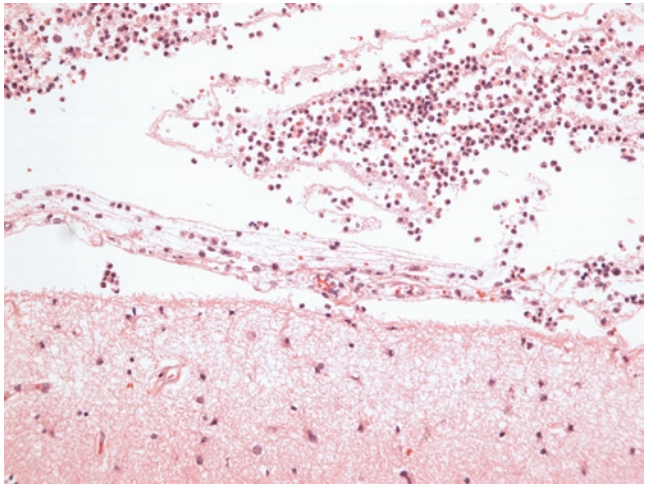

FIG. 3.10 A prominent acute inflammatory infiltrate involving the meninges represents acute meningitis.

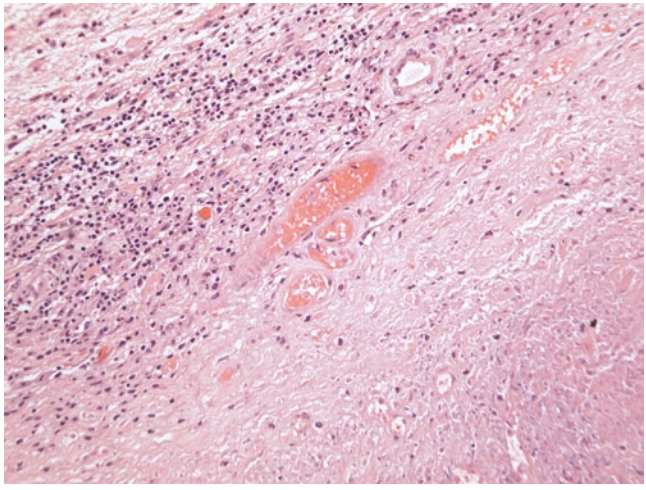

FIG. 3.11 An organizing abscess with a necrotic center in the right lower portion of the field and an area of organization with mixed acute and chronic inflammation, increased blood vessels, and fibroblastic proliferation in the left upper aspect of the microscopic field.

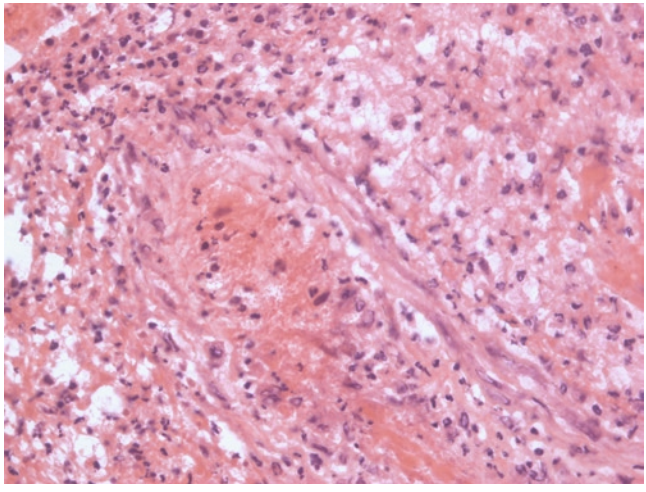

FIG. 3.12 A frozen section of an organizing abscess showing a hypercellular area corresponding to the organizing wall of the abscess. Occasionally, mitotic figures involving fibroblasts or blood vessel endothelium in this region along with the hypercellularity can result in a misdiagnosis of an anaplastic glioma.

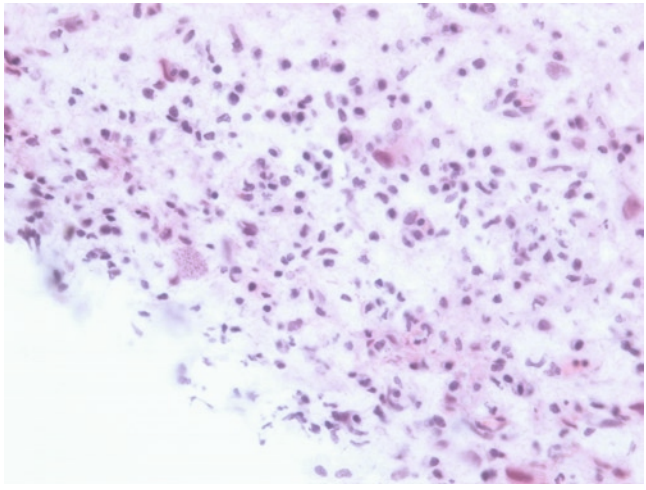

FIG. 3.13 An abscess with evidence of a Toxoplasma cyst.

about a neoplasm. The presence of acute inflammation should be one clue that forces the consideration of an abscess. The perimeter of the abscess is usually marked by a reactive astrocytosis and a diminished number of predominately chronic inflammatory cells.

FLAG 3: GRANULOMATOUS INFLAMMATION

The presence of granulomas at frozen section should raise concern about an infectious process, particularly when necrosis is present. Recommendation for microbiologic culturing should be made. The presence of granulomas should be documented in the frozen section report as well as the presence of any accompanying necrosis. Necrotizing granulomas are more commonly encountered in the setting of infection by Mycobacterial or fungal organisms (Fig. 3.14). Although in most cases, fungal organisms are going to be best seen with special stains that are not available at the time of frozen section, one should nevertheless look for the evidence of hyphae. Sarcoidosis may also result in the presence of granulomatous inflammation that is typically nonnecrotizing (Fig. 3.15). Many of these granulomas are located at the base of the brain. A less common diagnostic consideration includes idiopathic hypertrophic cranial pachymeningitis; these rare cases present as a dural, mass-like lesion that is comprised of chronic meningeal inflammation and nonnecrotizing granulomas. Granulomas also may be encountered in association with a primary vasculitic process and may be seen rarely in association with certain neoplasms, such as germinoma or lymphoma.

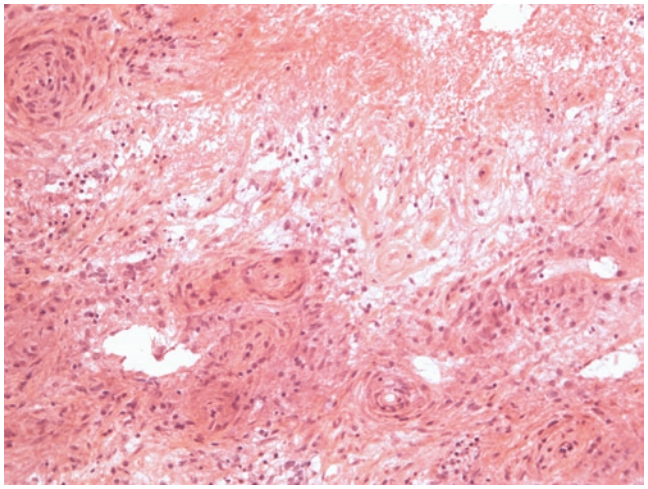

FIG. 3.14 The presence of granulomatous inflammation associated with necrosis should raise the suspicion of a possible infectious etiology. Tuberculosis and fungal infections are most likely. Recommendations that cultures be sent should be made at the time of frozen section.

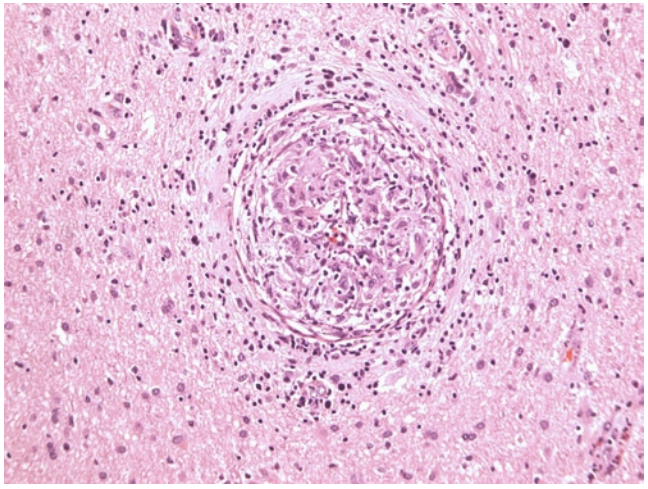

FIG. 3.15 The presence of a nonnecrotizing granuloma should raise the possibility of sarcoidosis. An infectious etiology cannot be excluded.

FLAG 4: MACROPHAGES

There are a variety of pathologic processes that may be associated with the presence of tissue macrophages. Radiation necrosis, which has previously been discussed in Chap. 2, is often marked by macrophages associated with areas of geographic necrosis. Macrophages may also be seen as part of infectious diseases. There are cases of Mycobacterium avium intracellulare involving the central nervous system, characterized by macrophages which are stuffed with organisms. Similarly, Whipple's disease is often marked by numerous macrophages. Amebic organisms can themselves appear similar to macrophages (Fig. 3.16).

The major differential diagnostic considerations, however, often come down to infarct versus demyelinating disease, particularly in a white matter lesion. On frozen section, the recognition of these cells as macrophages can be challenging, as discussed in Chap. 1. This is one instance where sometimes a cytologic preparation provides better detail of the cells in question, more readily allowing the distinction of macrophages from tumoral astrocytes. The typical demyelinating lesion is marked by white matter macrophages, usually associated with scattered, evenly distributed reactive astrocytes (Figs. 3.17–3.19). The astrocytes are seen within the area of demyelination. Many forms of demyelinating disease are also accompanied by a variable number of perivascular, benign lymphocytes (predominantly T-cells).

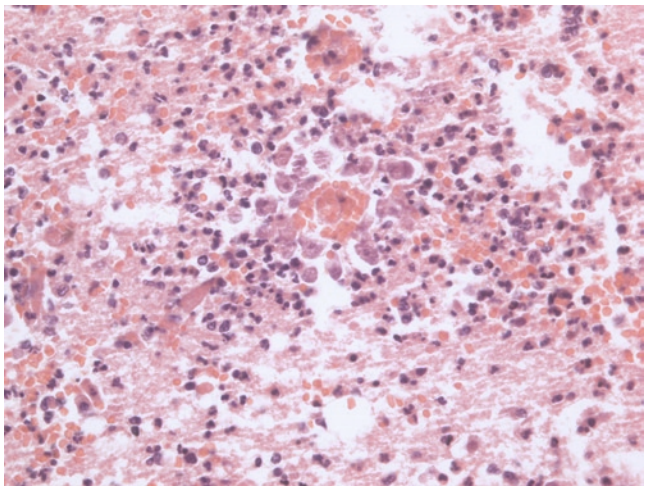

FIG. 3.16 Amebic organisms, seen here, can look like cells and mimic macrophages. Usually, amebic encephalitis arises in the background of acute inflammation and necrosis.

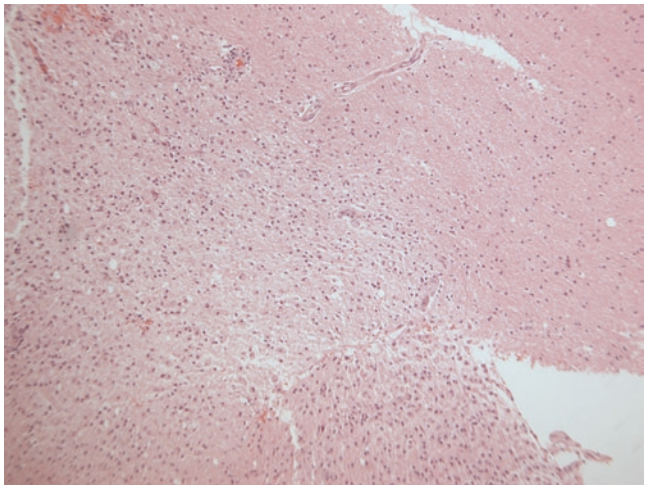

FIG. 3.17 A demyelinating lesion characterized by a sharp interface between the involved and uninvolved white matter. This is typical of multiple sclerosis and the tumor-like demyelinating lesion.

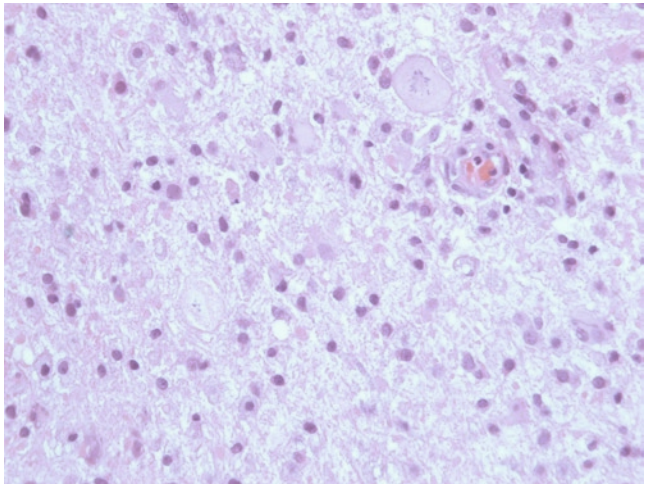

FIG. 3.18 A demyelinating lesion in a patient with multiple sclerosis at high magnification showing Creutzfeldt astrocytes and macrophages. The Creutzfeldt astrocytes are usually associated with demyelinating lesions.

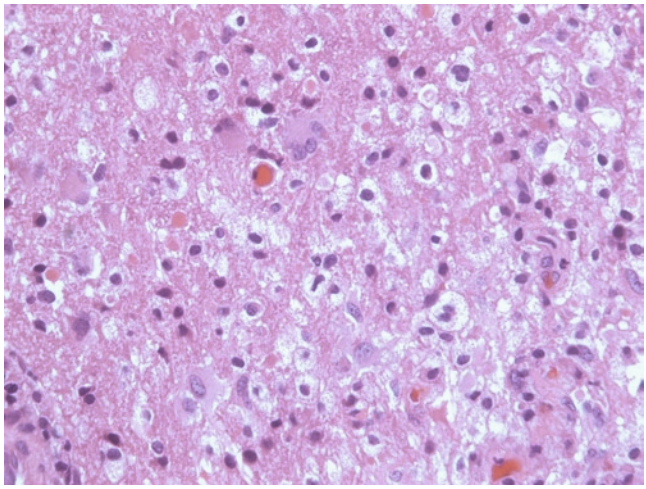

FIG. 3.19 A higher magnification appearance of a multiple sclerosis plaque or geographic area of demyelination with macrophages and astrocytes intermixed in the lesion. This pathology contrasts with an infarct, where the astrocytes are confined to the perimeter of the lesion.

In cases of suspected demyelinating disease, one should look for evidence of intranuclear, basophilic inclusions, suggestive of progressive multifocal leukoencephalopathy (Fig. 3.20). Often, the patients with progressive multifocal leukoencephalopathy have a history of immunosuppression, either due to diseases like AIDS, the presence of a neoplasm, or use of immunomodulatory agents. In contrast to the typical multiple sclerosis lesion, which has a predilection for the periventricular zone, areas of demyelination in progressive multifocal leukoencephalopathy tend to be subcortical. Progressive multifocal leukoencephalopathy also spares the spinal cord and optic nerve, which are often involved in multiple sclerosis. One also needs to be wary of the isolated or single demyelinating lesion or so-called tumor-like demyelinating lesion. These are the cases that usually get the pathologist in trouble, since on imaging, they resemble a neoplasm.

Macrophages may be seen as early as 24 h in the evolution of an infarct and may persist for months afterward. Early changes include reactive endothelium with pallor of staining and rare neutrophils (Fig. 3.21). Infarcts may involve either gray or white matter tissue. The reactive astrocytes that are associated with a subacute infarct are typically located around the perimeter and are not seen in the middle of the infarct, a feature that is useful in distinguishing an infarct from a demyelinating disease at the time of frozen section (Fig. 3.22). The presence of numerous perivascular lymphocytes is also more

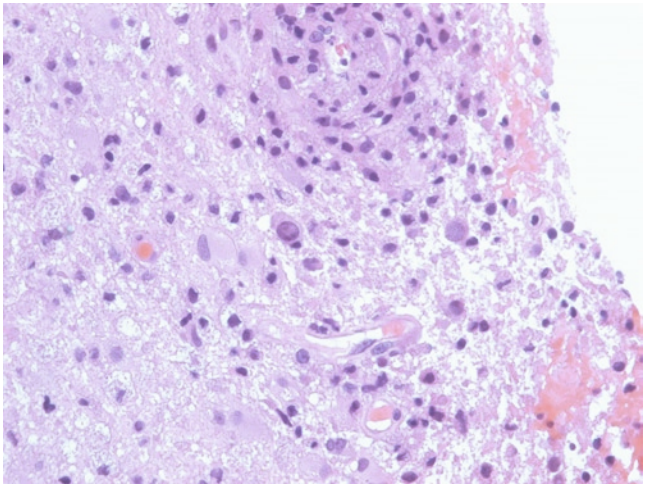

FIG. 3.20 Viral intranuclear inclusions involving oligodendroglial cells in the white matter suggest a diagnosis of progressive multifocal leukoencephalopathy.

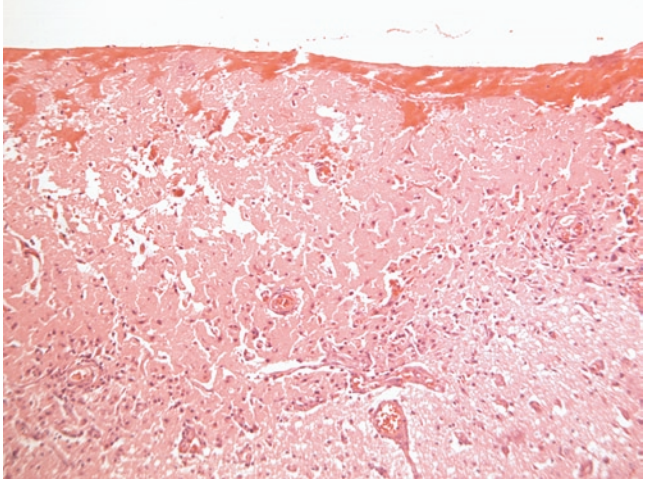

FIG. 3.21 An area of infarct (which is surface based). The infarct tends to stain less intensely than the adjacent viable tissue and may contain a small number of inflammatory cells and reactive appearing vessels. The location of this infarct involving the cortical surface suggests a contusion pattern of injury.

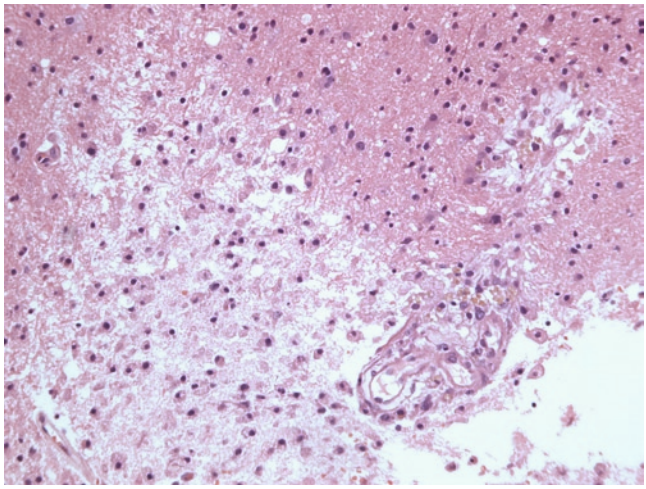

FIG. 3.22 Subacute infarct marked by a prominent number of macrophages with reactive astrocytes at the perimeter of the lesion.

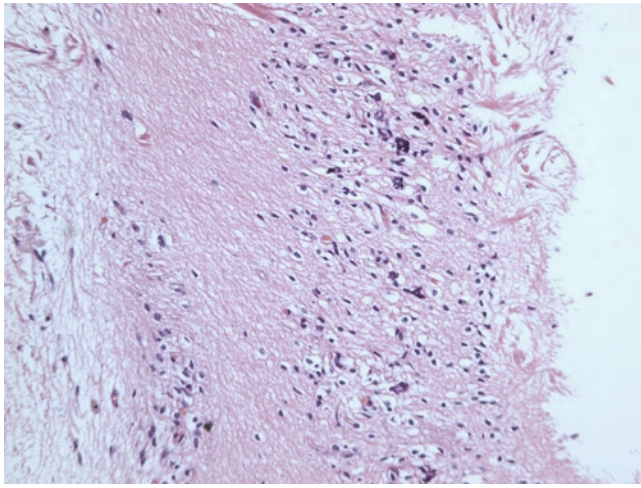

FIG. 3.23 Remote ischemic damage in the cortex marked by significant atrophy of gray matter with the loss of neurons, gliosis, and calcifications.

commonly encountered in the demyelinating lesion than the typical infarct. A remote infarct may be relatively devoid of macrophages and may be marked by prominent atrophy and gliosis (Fig. 3.23).

FLAG 5: THICKENED BLOOD VESSEL WALLS

There are four major entities to be considered in the differential diagnosis of abnormally thickened blood vessel walls. Probably, the most common etiology is hypertension or atherosclerosis. This is generally not a target for biopsy but may be seen in relatively normal tissue of elderly patients who undergo biopsy or resection for some other purpose. As previously mentioned, radiation can result in vascular sclerosis (Fig. 5.14). These cases are usually diagnosed based on a history of prior radiation administration. In elderly patients, particularly those presenting with hemorrhage in a "nonhypertensive" distribution (so-called lobar hemorrhage), a diagnosis of amyloid angiopathy should be considered. The appearance of amyloid angiopathy in the central nervous system is similar to that in other organ systems (Fig. 3.24). This is not a diagnosis that can be definitively made at the time of frozen section. A description of the abnormal vessel wall thickening, however, can be made with a suggestion that amyloid is a possible cause for the thickening. Another rare etiology of abnormal vessel thickening is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). This is an inherited systemic condition; blood vessels from any

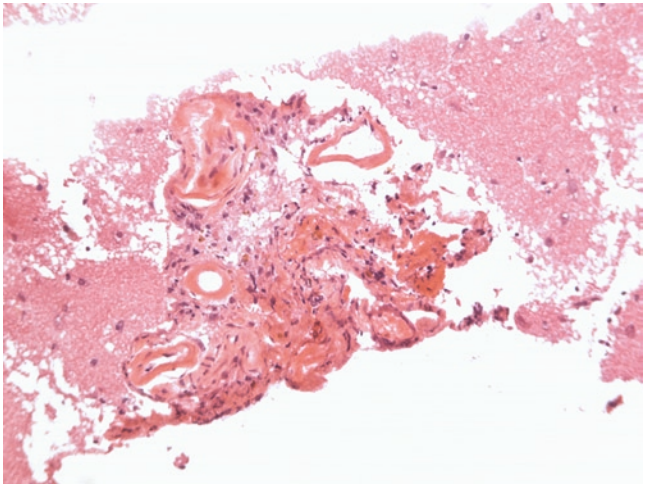

FIG. 3.24 Thickened meningeal blood vessels, which appear slightly hypereosinophilic, are suggestive of possible amyloid accumulation. A Congo red stain or other stain for amyloid should be evaluated on permanent sections in these cases. At frozen section, a diagnosis of vascular wall thickening with a suggestion of possible amyloid accumulation can be made.

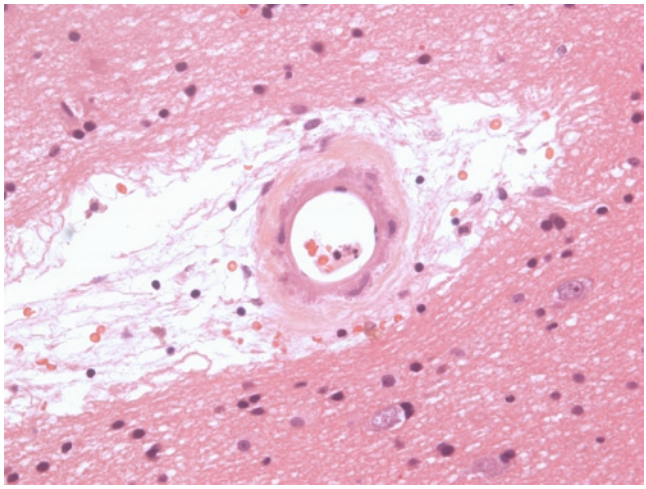

FIG. 3.25 CADASIL is characterized by thickened vessels with basophilic granularity in the vessel wall. This granularity may not always be evident at the time of frozen section and a diagnosis of vascular wall thickening with perivascular atrophy can be made and a suggested differential diagnosis, including CADASIL, amyloid, and atherosclerosis, can be provided.

organ system may demonstrate the pathology. It usually presents with dementia and strokes in middle-age adults. The characteristic histologic feature of CADASIL is the presence of basophilic granularity in the blood vessel wall (Fig. 3.25). Often, there is marked perivascular atrophy around involved blood vessels. In a suspected case, ultrastructural examination of the involved vessel to demonstrate the electron dense granular deposits in the vessel walls may be useful. At the time of frozen section, the basophilic granularity may not be readily discernible and a description of the vessel wall thickening may be as far as one can take the diagnosis.

FLAG 6: TOO MANY BLOOD VESSELS

The presence of increased numbers of blood vessels concentrated in a small area usually raises the differential diagnostic consideration of vascular malformation. Vascular malformations are characterized by the type of blood vessels that comprise the malformation and whether or not intervening brain parenchyma is situated between the vessels. Arteriovenous malformations are marked by the presence of arteries and veins with intervening brain tissue

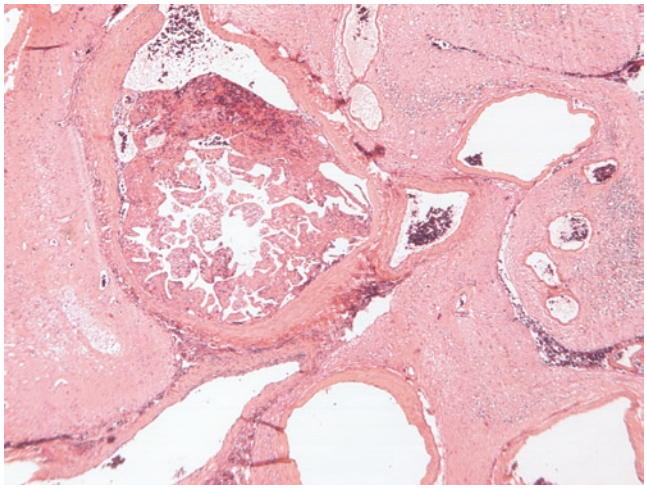

FIG. 3.26 A mixture of arterial and venous blood vessels with intervening cerebellar tissue marks an arteriovenous malformation. Evidence of intravascular embolization is present in this lesion.

(Fig. 3.26). Cavernous angiomas are marked by the presence of veins, some of which may be dilated, that are arranged in a back-to-back configuration with no intervening brain tissue (Fig. 3.27). Venous angioma comprises veins with intervening, relatively normal brain tissue, and the capillary telangiectasia is made up of mostly capillaries with normal intervening brain tissue. Because of the risk of hemorrhage, the arteriovenous malformation is often a target for surgical excision. Sometimes, the adjacent parenchyma shows secondary changes related to hemorrhage and ischemia, which may include hemosiderin deposition, calcification, prominent gliosis and fibrosis, and macrophages (Fig. 3.28). Cavernous angiomas are also a target for surgical excision and they usually present with symptoms associated with a focal lesion or tumor-like mass. Caution needs to be taken in examining cavernous angiomas in that often there are secondary changes in the blood vessels participating in the malformation that result in abnormal thickening or "arterialization" of the venous vessels. Misinterpretation of these abnormally thickened veins as arteries can lead to an erroneous diagnosis. Venous angiomas and capillary telangiectasias are not the target of surgical intervention because of the minimal risk of hemorrhage associated with these entities.

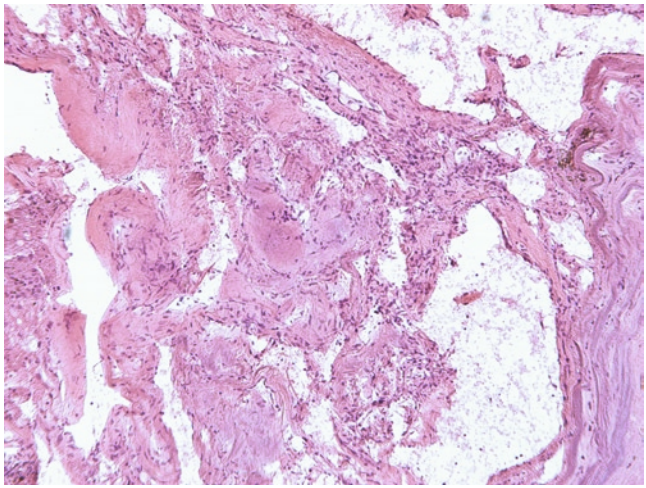

FIG. 3.27 A cavernous angioma marked by a back-to-back proliferation of venous vessels.

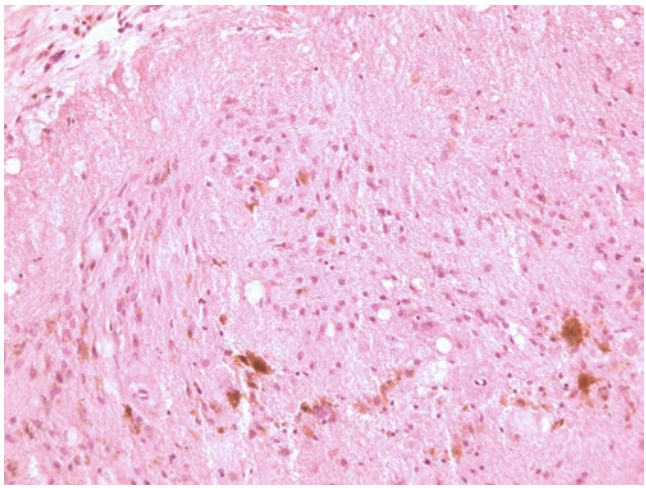

FIG. 3.28 Sometimes, a biopsy taken next to a cavernous angioma or arteriovenous malformation may not contain the vessels necessary to make a diagnosis but shows changes, including gliosis, hemosiderin deposition, microcalcifications, or evidence of ischemic damage.

There are a variety of tumors which also may have a prominent vascular pattern. Most notable in this group are hemangioblastoma, angiomatous meningioma, hemangiopericytoma, and pilocytic astrocytoma. The rare neurocutaneous disorder, Sturge Weber, typically presents in childhood with chronic epilepsy. These patients have a leptomeningeal proliferation of venous vessels, often accompanied by underlying cortical calcifications and gliosis.

FLAG 7: CYSTS

There are a variety of cysts that can arise in the central nervous system. Table 3.2 lists these cysts and describes their typical location and histologic appearance. Occasionally, some of these cysts may be the target of surgical excision, particularly if they are symptomatic. The most commonly encountered cysts

Table 3.2 Cysts of the central nervous system.

Cyst type	Location	Cyst lining
Colloid	Near foramen of Monro	Single layer of columnar cells with goblet and ciliated types
Rathke's cleft	Intrasellar	Single layer of columnar cells, goblet and ciliated types; squamous metaplasia
Endodermal	Most commonly posterior fossa and spinal (intradural, extramedullary)	Columnar or cuboidal; variable cilia, goblet cells, squamous metaplasia; lining can resemble respiratory or gastrointestinal epithelium
Epidermoid	Most commonly cerebellopontine angle	Stratified squamous epithelium with keratohyaline granules
Dermoid	Midline	Stratified squamous epithelial lining with adnexal structures in the wall of the cyst
Arachnoid	Most common in subarachnoid space overlying temporal lobe and cerebellopontine angle	Meningothelial cell or connective tissue lining
Ependymal	Periventricular	Cuboidal to columnar cells which lack cilia
Choroid plexus	Ventricular	Cuboidal cells with a cobblestone profile
Pineal	Pineal gland	Gliotic wall with Rosenthal fibers

in the surgical pathology suite include dermoid and epidermoid cysts, colloid cysts, endodermal cysts, and rarely arachnoid cysts (Figs. 3.29–3.33). One also needs to remember that occasionally, a neoplasm may have a large cystic component to it. Of particular

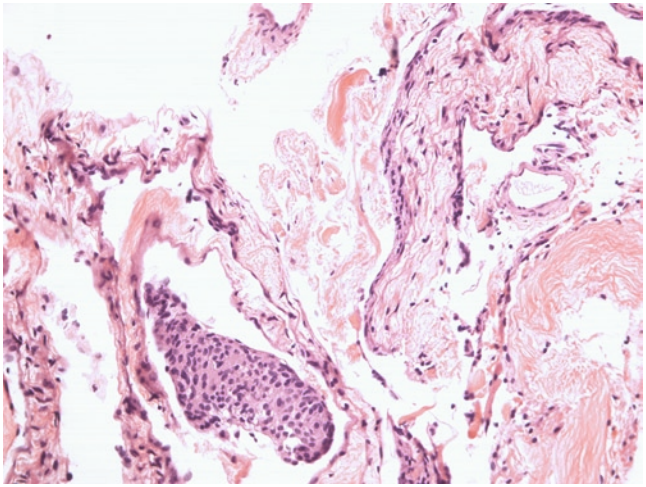

FIG. 3.29 An arachnoid cyst marked by arachnoidal cap cells or meningothelial cells associated with fibrous connective tissue.

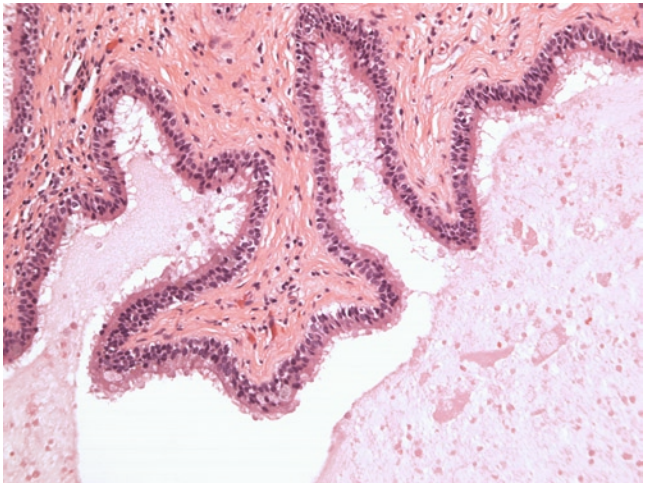

FIG. 3.30 A colloid cyst with a ciliated columnar epithelium and amorphous eosinophilic cystic fluid.

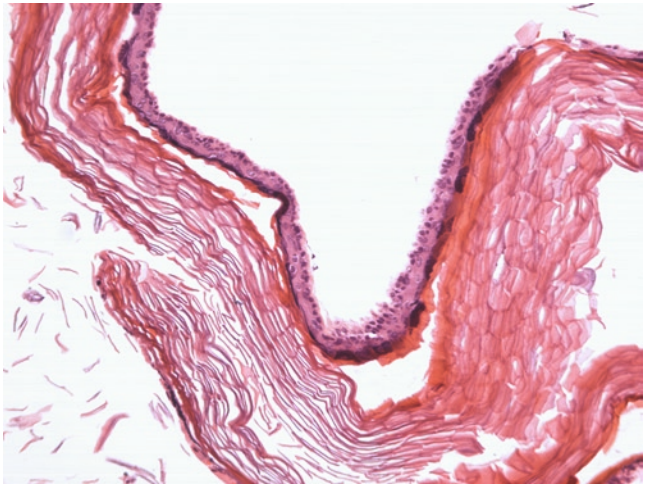

FIG. 3.31 An epidermoid cyst lined by squamous epithelium and showing cells with keratohyaline granules.

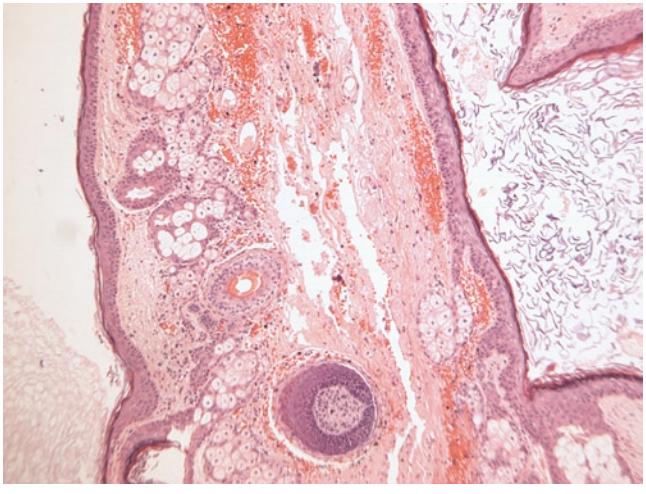

FIG. 3.32 A dermoid cyst is lined by squamous epithelium and has associated subjacent adnexal structures, such as sebaceous glands, hair follicles, and eccrine or apocrine type glands.

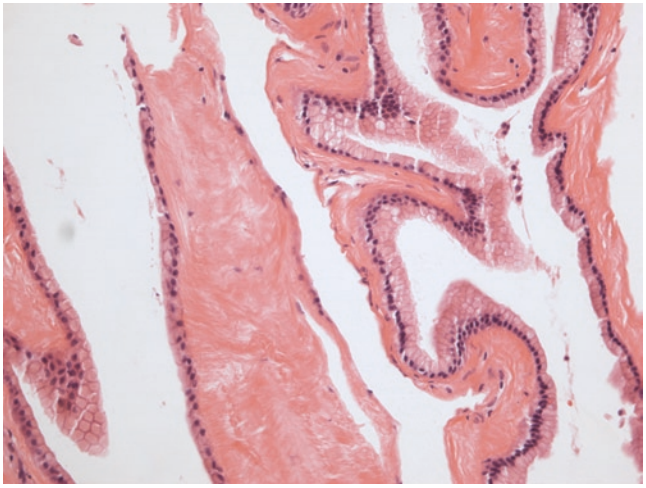

FIG. 3.33 An endodermal cyst with mucinous epithelial lining.

note is the craniopharyngioma, which may have a squamoid lining and resemble an epidermoid cyst (Fig. 9.11). The epidermoid cyst, however, is marked by cells with keratohyaline granules, a feature which is not present in the cystic craniopharyngioma.

Chapter 4
Cerebral Parenchymal Lesions: I. Metastatic Neoplasms

After one has reasonably ruled out the possibility of a nonneoplastic diagnosis (see Chap. 3), one is left with considering a diagnosis of tumor. The first question one needs to ask along these lines is whether or not the neoplasm could represent a metastasis. Metastatic neoplasms are the most commonly encountered tumors in the central nervous system. Because the appearance of these lesions often mimic their appearance elsewhere in the body, most pathologists are relatively more comfortable with evaluating metastases. Metastases are commonly multifocal lesions that are well circumscribed (Fig. 4.1). This is in contrast to many gliomas, which tend to be infiltrative in nature and more typically unifocal. Metastases may be either parenchymal or leptomeningeal in location. This chapter briefly addresses some of the more commonly encountered metastases and potential differential diagnostic considerations (Table 4.1).

Carcinomas are probably the most common type of metastasis that is encountered. The most common sites of origin include lung, breast, kidney, skin (melanoma), and gastrointestinal tract. In many cases, the tumor is so poorly differentiated that discerning the specific tumor type is not always possible, particularly in the frozen section venue. When possible, distinction between small cell carcinoma versus nonsmall cell carcinoma should be made. Small cell carcinoma is generally marked by cells with a high nuclear to cytoplasmic ratio, no prominent nucleolation, and nuclear molding. There is a propensity for the tumor cells to be easily crushed with routine tissue handling (Fig. 4.2a, b).

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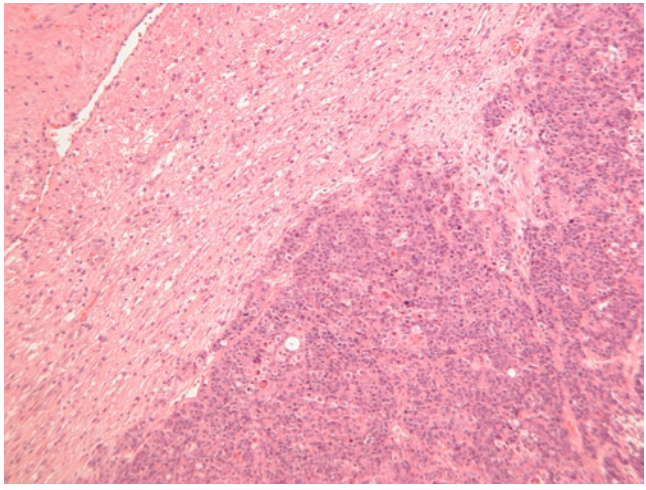

FIG. 4.1 Low magnification appearance of a metastatic nonsmall cell carcinoma from the lung shows the typical sharp interface between the tumor and the adjacent gliotic parenchyma. This is in contrast to the infiltrative nature of most malignant glial neoplasms.

Table 4.1 Metastases.

Carcinoma
Small cell
Adenocarcinoma
Squamous cell carcinoma
Other
Melanoma – great mimicker
Sarcoma
Lymphoma/leukemia
Other
Differential diagnostic cautions and tips:
Metastases are frequently multiple and have a sharp interface with the adjacent parenchyma
Do not overdiagnose the extremely necrotic tumor
Epithelioid glioblastoma can look like carcinoma or melanoma
Small cell glioblastoma, lymphoma, medulloblastoma/neuroblastoma and anaplastic oligodendroglioma can resemble small cell carcinoma
Occasional carcinomas and melanomas can be spindled; other spindle cell tumors to consider are gliosarcoma and anaplastic meningioma

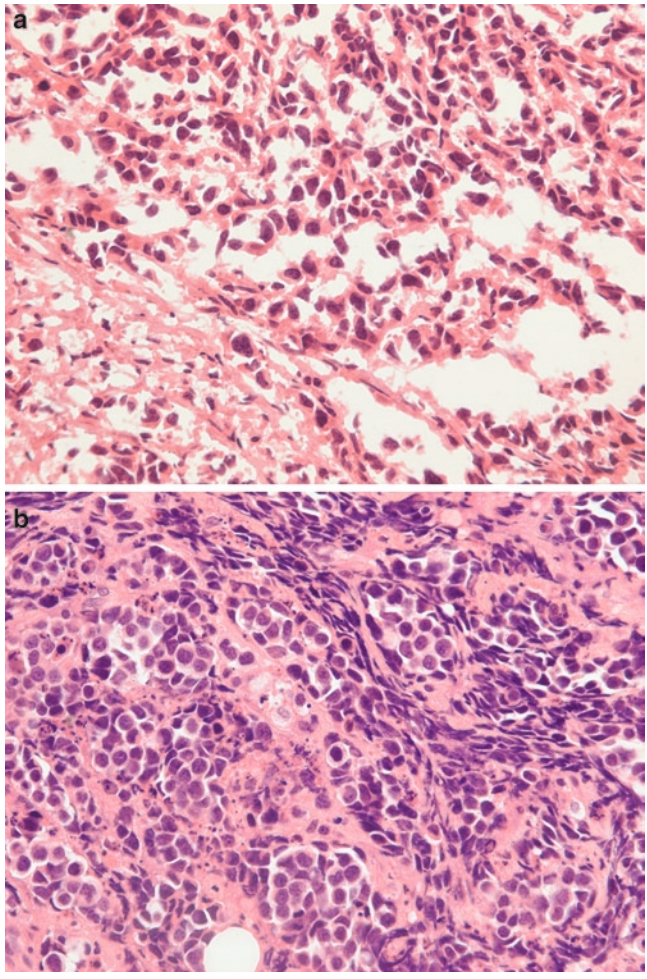

FIG. 4.2 (**a**) A frozen section showing proliferation of cells with high nuclear to cytoplasmic ratio. A moderate degree of pleomorphism is present. A diagnosis of malignant small cell neoplasm was made in this case with the suggestion of a differential diagnosis. (**b**) The permanent section from the tumor in (**a**) shows that the lesion represents a small cell carcinoma. The cells are somewhat more homogeneous in appearance, devoid of nucleoli, and show the evidence of focal crush artifact.

Often, there are large zones of necrosis, readily identifiable mitotic activity, and evidence of apoptosis. In contrast, adenocarcinoma and squamous cell carcinoma are generally marked by cells with prominent nucleolation and more cytoplasm. Evidence of gland formation or mucin production corroborates a diagnosis of adenocarcinoma (Figs. 4.3–4.5). Evidence of keratinized cells or keratin production in the tumor favors a squamous cell cancer (Fig. 4.6). Almost any type of carcinoma may be observable as a metastasis in the brain or spinal cord. A prior history of cancer elsewhere may not be present; a significant subset of brain metastases is the initial presentation of the patient's tumor. In many cases, the metastasis is poorly differentiated and presents few if any clues at frozen section regarding tumor type; a diagnosis of metastatic nonsmall cell carcinoma, malignant spindled cell neoplasm or malignant epithelioid neoplasm (depending on the appearance) may be appropriate (Fig. 4.7).

Care should be taken not to overdiagnose an extensively necrotic tumor. One should not presume a diagnosis of metastasis based on a history of multiple lesions and an entirely necrotic biopsy. From a differential diagnostic standpoint, an epithelioid variant of glioblastoma can mimic metastatic carcinoma or occasionally melanoma. On frozen section, the only clue may lie in finding the evidence of the more characteristic features of adenocarcinoma or squamous cancer or areas of the tumor that look like more

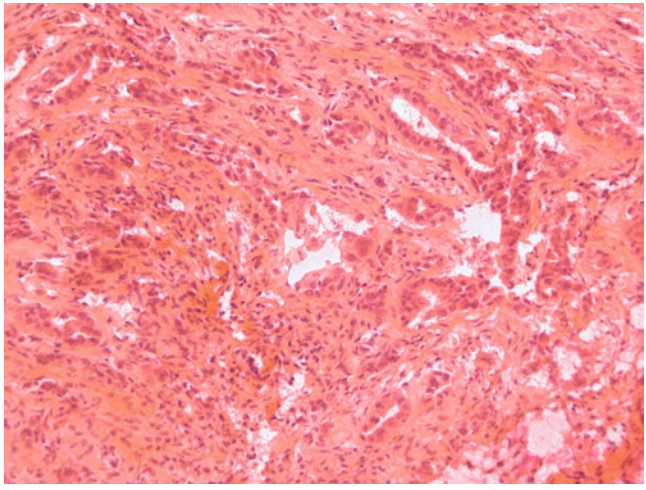

FIG. 4.3 Metastatic breast carcinoma demonstrating gland formation consistent with adenocarcinoma.

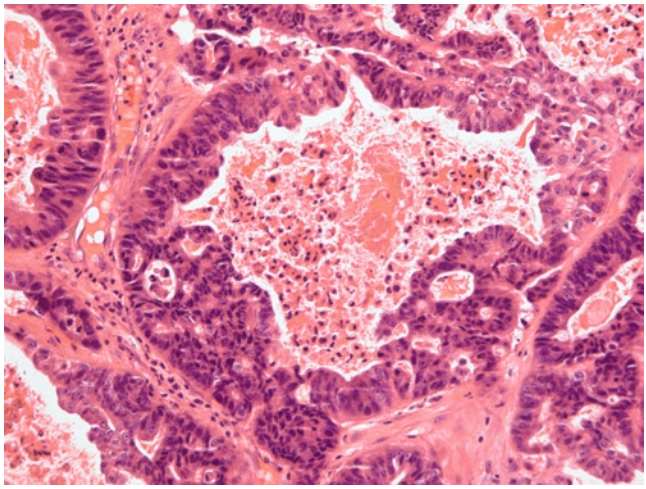

FIG. 4.4 Metastatic colonic adenocarcinoma showing the characteristic garland pattern with central dirty necrosis.

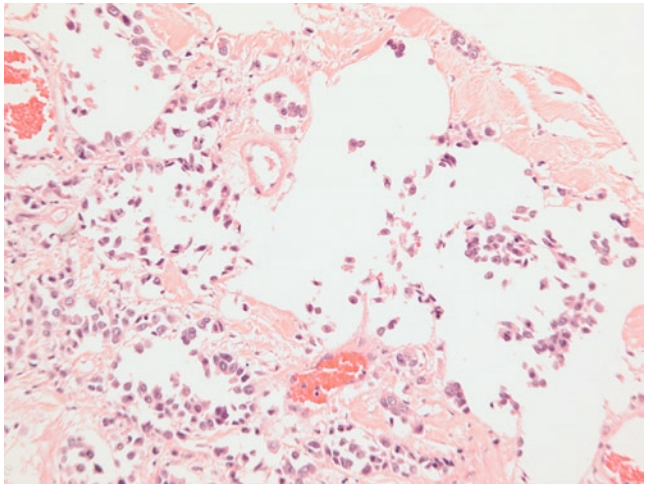

FIG. 4.5 Metastatic adenocarcinoma involving the leptomeninges in a patient with known prostate cancer.

conventional glioblastoma. An even greater challenge is differentiating small cell carcinoma from other small cell tumors which may arise in the brain, including small cell glioblastoma, lymphoma, meduloblastoma/neuroblastoma, or anaplastic oligodendroglioma.

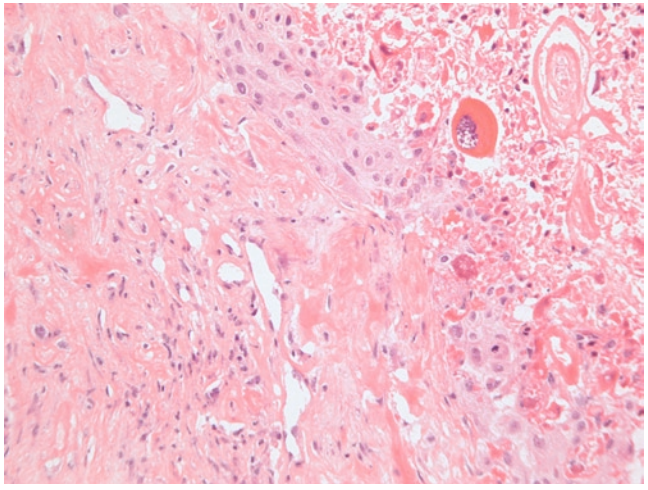

FIG. 4.6 A partially necrotic metastatic nonsmall cell carcinoma with keratinized cells consistent with squamous cell carcinoma.

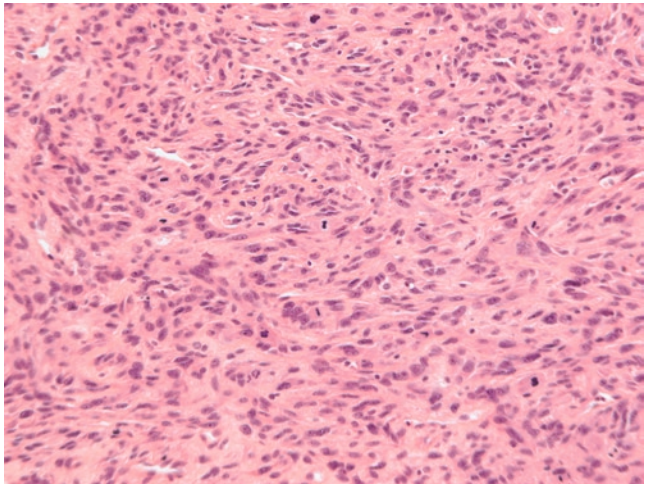

FIG. 4.7 This patient had a known squamous cell carcinoma of the larynx. The spindled cell squamous cell carcinoma represents a metastasis from the laryngeal cancer. A diagnosis of malignant spindled cell neoplasm at the time of frozen section is appropriate with a suggestion that it may represent a metastasis from the patient's known laryngeal carcinoma.

These are all high-grade neoplasms and may be marked by cells with high nuclear to cytoplasmic ratio, readily identifiable mitotic activity, and apoptosis. In some cases, particularly on a limited sample or extensively necrotic sample, immunohistochemistry may be needed to make the final diagnosis. In such cases, a diagnosis of malignant small cell neoplasm with a suggested list of possible diagnostic considerations is appropriate.

Metastatic malignant melanoma is a fairly commonly encountered neoplasm. The challenge with melanoma lies in the fact that it can mimic a whole host of other neoplasms, and it can be particularly difficult to diagnose in the absence of melanin pigment. Large cells with abundant cytoplasm and prominent nucleolation are classic features associated with melanoma; however, occasional tumors may be marked by spindled cells, which open up a broader differential diagnosis which includes sarcoma (Figs. 4.8 and 4.9). Occasionally, the distinction of melanoma from the metastatic nonsmall cell carcinoma or epithelioid glioblastoma may be difficult to make. Again, unless there are specific clues to indicate a particular tumor type, immunohistochemistry may be needed to resolve the differential diagnosis.

Sarcomas can arise either as primary lesions or metastases in the central nervous system (Figs. 4.10 and 4.11). Many primary sarcomas are dural based; whereas, metastases may involve either

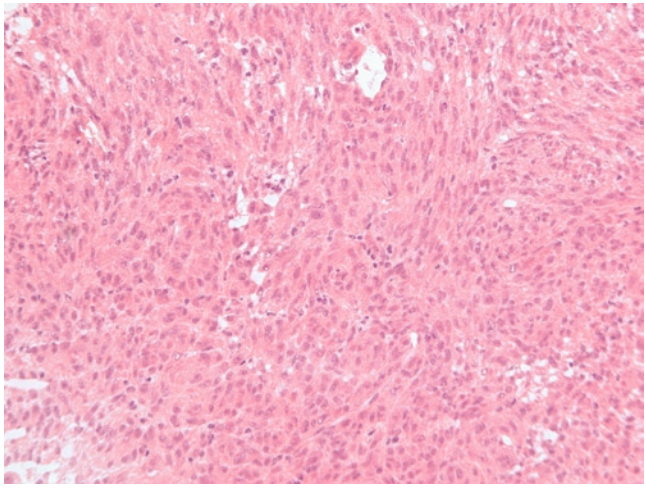

FIG. 4.8 A spindled cell neoplasm, devoid of neuromelanin pigment. Immunostaining eventually proved this to be a malignant melanoma.

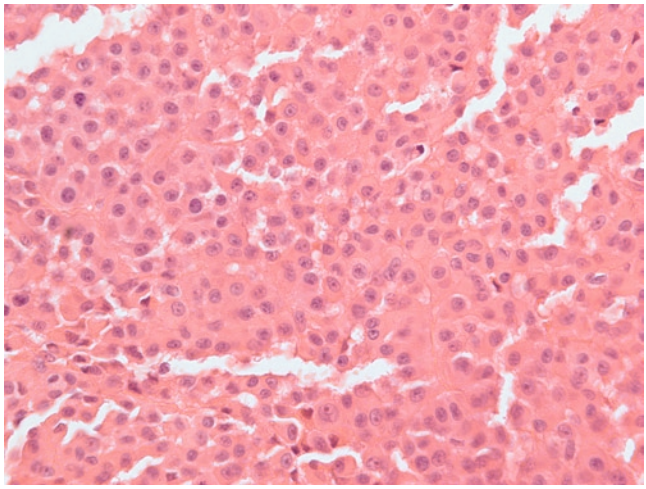

FIG. 4.9 This example represents a more typical appearance for metastatic melanoma-discreet cells with distinct cytoplasmic boundaries, prominent nucleolation, and abundant cytoplasm.

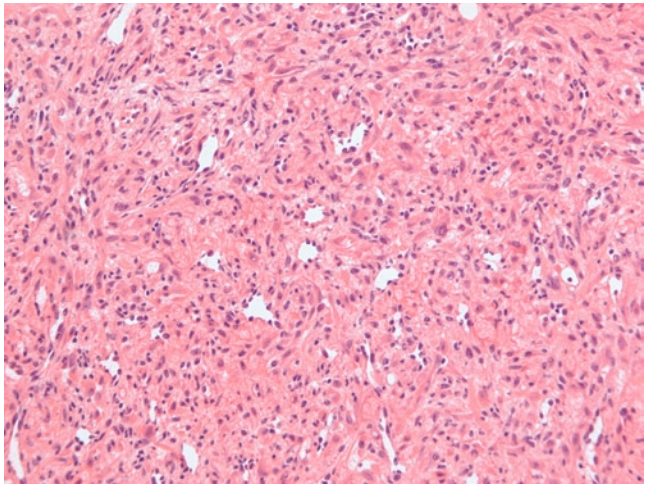

FIG. 4.10 Metastatic angiosarcoma in a patient with a known primary in the head and neck region.

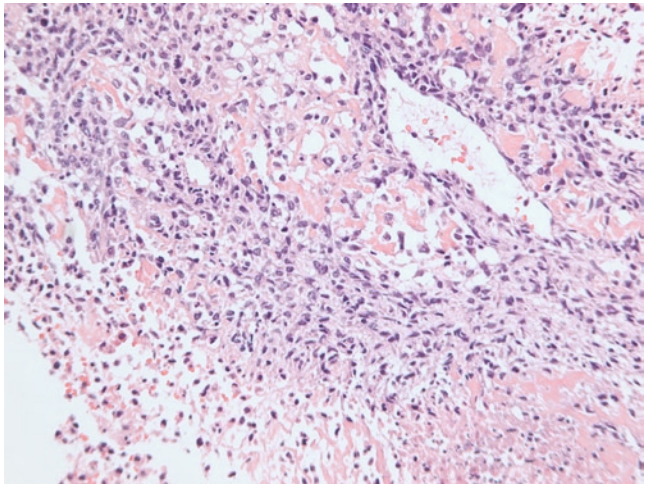

FIG. 4.11 Metastatic osteosarcoma marked by focal osteoid formation. This patient had a skull-based tumor that grew into the frontal lobe.

the dura or parenchyma. Metastatic lesions often resemble the tumor from where they had come, and history is particularly useful in such cases. In a subset of these tumors, the specification of the sarcoma type is not going to be possible at frozen section. In such instances, a more descriptive diagnosis such as "malignant spindle cell neoplasm, rule out sarcoma" may be appropriate. A consideration of other spindled cell neoplasms that include gliosarcoma and anaplastic meningioma should be entertained. Gliosarcoma should have focal areas resembling a more conventional appearing glioblastoma. Anaplastic meningioma may or may not have lower grade areas that resemble a typical low-grade meningioma pattern.

Lymphomas and leukemias can metastasize and involve the central nervous system. As previously discussed in Chap. 3, metastatic lymphoma and leukemia preferentially involve the meninges and dura as compared with primary central nervous system lymphoma, which is more commonly a parenchymal-based lesion.

Less commonly, other neoplasms not discussed here may metastasize to the brain. Inquiry regarding previous history is sometimes useful in these cases.

Chapter 5
Cerebral Parenchymal Lesions: II. Primary Tumors

ASTROCYTOMAS

The most common primary tumor of the central nervous system is astrocytoma, and in particular glioblastoma. The focus of this chapter is to discuss tumors that are most likely to arise in the cerebral hemispheres (in addition to metastatic neoplasms which were addressed in Chap. 4) (Table 5.1). Most of these tumors represent fibrillary or diffuse astrocytomas. These lesions can arise at any age; most present in adults between the third and seventh decades of life. These tumors are notoriously heterogeneous in nature, which means that different areas of the tumor may have a different histologic appearance. Features that are used to grade a diffuse astrocytoma include the degree of cellularity, mitotic activity, vascular proliferative changes, and necrosis. Currently, the World Health Organization (WHO) grading system is the most widely employed. Attempts at providing some information regarding possible tumor grade should be made at the time of frozen section consultation. Any grade that is assigned, of course, is preliminary and hinges on the evaluation of the permanent sections.

In general, low-grade (WHO grade II) astrocytomas are marked by mild hypercellularity and an uneven distribution of atypical cells (Fig. 5.1). The cytologic atypia is marked by nuclear enlargement, nuclear hyperchromasia, and irregularities of nuclear contour (Fig. 5.2). This is in contrast to reactive astrocytes with a low nuclear to cytoplasmic ratio and minimal nuclear atypia (Fig. 5.3). A rare mitotic figure is acceptable. Vascular proliferative changes and necrosis should not be seen.

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Table 5.1 Differential diagnosis of primary cerebral hemispheric tumors.

Astrocytoma (diffuse, fibrillary type)
Astrocytoma variants
Pilocytic and pilomyxoid astrocytoma
Pleomorphic xanthoastrocytoma
Desmoplastic infantile astrocytoma
Subependymal giant cell astrocytoma (intraventricular)
Oligodendroglioma
Mixed glioma (oligoastrocytoma)
Angiocentric glioma
Astroblastoma
Glioneuronal tumors
Ganglioglioma
Dysembryoplastic neuroepithelial tumor
Papillary glioneuronal tumor
Neuroblastoma and atypical teratoid/rhabdoid tumor
Lymphoma

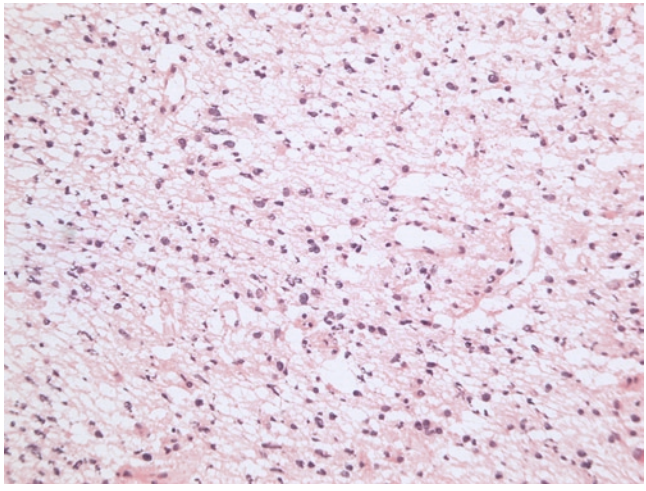

FIG. 5.1 This low-grade astrocytoma (WHO grade II) is marked by mild hypercellularity and mild nuclear pleomorphism.

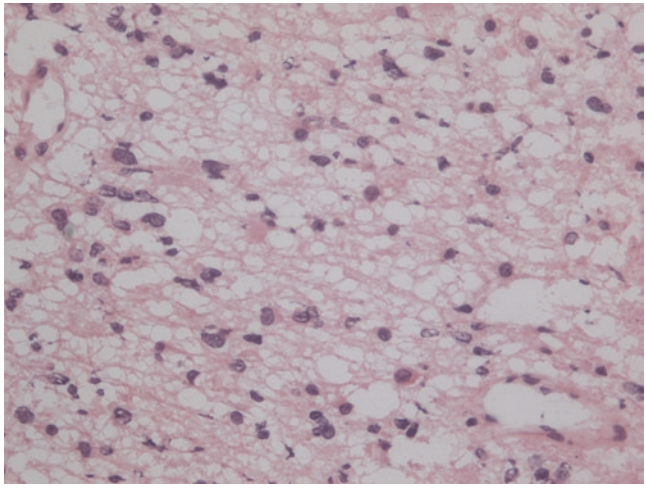

FIG. 5.2 This is a higher magnification view of FIG. 5.1 showing atypical astrocytic cells marked by nuclear enlargement, nuclear hyperchromasia, and angular nuclear contours.

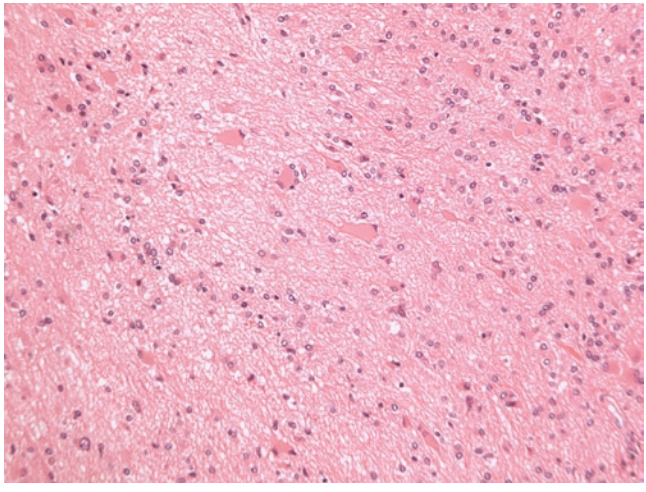

FIG. 5.3 Gliosis marked by scattered reactive astrocytes with abundant eosinophilic cytoplasm and eccentrically placed nucleus.

Focal microcalcifications or microcystic change may be evident. Again, one should be cautious not to overinterpret microcystic freeze artifact as representing true microcystic change. As tumor cells infiltrate the surrounding parenchyma, there is a proclivity toward satelliting around preexisting structures like blood vessels and neurons (secondary structures of Sherer). Both astrocytomas and oligodendrogliomas demonstrate a tendency for subpial aggregation of infiltrating tumor cells. Anaplastic astrocytomas (WHO grade III) are usually marked by increased cellularity and nuclear atypia, as well as more readily identifiable mitotic activity (Fig. 5.4). A glioblastoma (WHO grade IV) is characterized by the presence of either vascular proliferation (proliferation of cells that normally form blood vessel walls) and/or necrosis, which may or may not be rimmed by a pseudopalisade of tumor cells (Figs. 5.5 and 5.6).

Attempts at assigning a grade to the tumor is important in that it provides feedback to the neurosurgeon as to whether or not the tissue sampled is representative when compared with the radiologic impression of a neoplasm. For example, a diagnosis of a WHO grade II astrocytoma should warrant the submission of additional tissue, if a ring-enhancing mass which looks like a glioblastoma is noted on imaging studies. At times, it may be difficult to be absolutely certain about the tumor's grade; this can be particularly

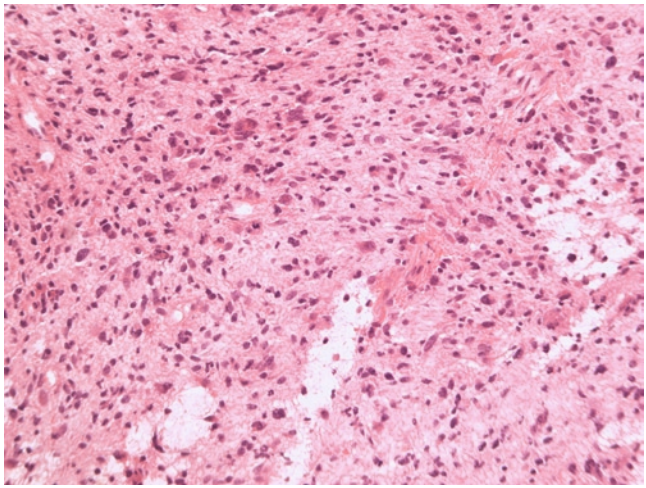

Fig. 5.4 This anaplastic astrocytoma (WHO grade III) is marked by increased cellularity and pleomorphism as compared with a low-grade astrocytoma. Mitotic activity is usually identifiable in most anaplastic astrocytomas.

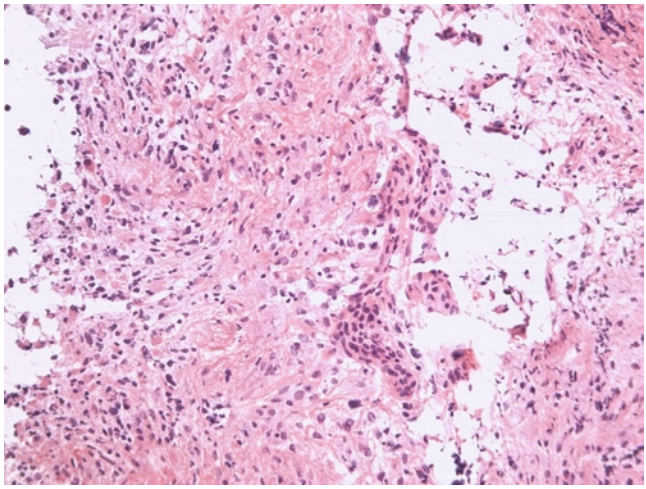

FIG. 5.5 A glioblastoma (WHO grade IV) marked by vascular proliferative changes. Vascular proliferation is characterized by a piling up of cells around vascular lumina; the proliferating cells represent normal blood vessel wall constituents.

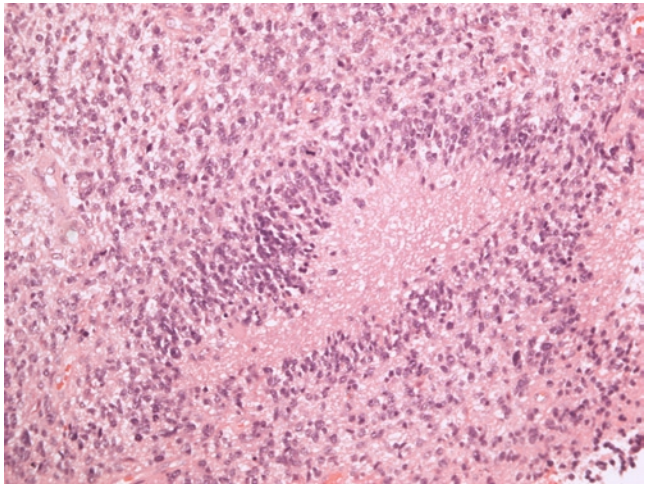

FIG. 5.6 A glioblastoma marked by a pseudopalisade of tumor cells around an area of geographic necrosis. The pseudopalisade does not have to be present to make a diagnosis of glioblastoma.

problematic in differentiating grade II from grade III neoplasms. In such instances, it is better to undergrade the neoplasm rather than potentially overgrading the tumor. Overgrading a lesion may result in a premature abortion of the procedure because the surgeon is under the impression that he or she has obtained diagnostic tissue with a grade compatible with the imaging study.

Occasional tumors may have prominent numbers of gemistocytes. Gemistocytes are hypertrophic astrocytic cells with abundant eosinophilic cytoplasm and an eccentrically placed nucleus (Fig. 5.7). They have short cytoplasmic processes which are generally not well visualized at the time of frozen section. When numerous gemistocytes are present, mention should be made at the time of frozen section. Gemistocytic astrocytomas tend to behave in a more aggressive fashion. Reactive astrocytes should not be misinterpreted as gemistocytes. Reactive astrocytes tend to be more sparsely and evenly distributed in the microscopic field. Typically, gemistocytes in a gemistocytic astrocytoma are much more densely aggregated, sometimes forming large clusters or apparent sheets of cells. If one looks carefully at a gemistocytic astrocytoma, one should be able to locate atypical astrocytes with the usual features of malignancy (high nuclear to cytoplasmic ratio, nuclear hyperchromasia, and irregularities to the nuclear contour).

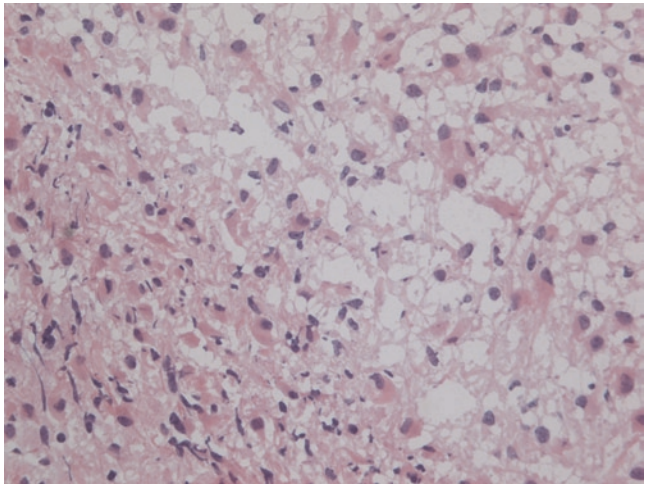

FIG. 5.7 A gemistocytic astrocytoma marked by an increased number of cells with abundant eosinophilic cytoplasm. Intermixed with the cells is a second population of atypical astrocytic cells with high nuclear to cytoplasmic ratios and nuclear irregularities. A prominent gemistocytic component is associated with more aggressive behavior.

The high-grade astrocytoma (glioblastoma) can sometimes present a challenge because of the phenotypic variability that may be seen, hence the designation of "multiforme." Table 5.2 lists some of the more common glioblastoma variants that one may encounter. A gliosarcoma is marked by areas phenotypically resembling the ordinary glioblastoma juxtaposed with areas of sarcomatous differentiation (Figs. 5.8 and 5.9). Genetic studies have shown similar alterations in both components, suggesting that the glioblastoma has the capability of differentiating along both cell lines. The differential diagnosis includes a gliosarcoma and a glioblastoma with a spindled cell component. Ultimately, there is no prognostic or treatment implication to make this distinction,

Table 5.2 Glioblastoma variants.

Gliosarcoma
Giant cell glioblastoma
Epithelioid glioblastoma
Small cell glioblastoma
Granular cell glioblastoma
Glioblastoma with oligodendroglioma component
Glioblastoma with metaplasia

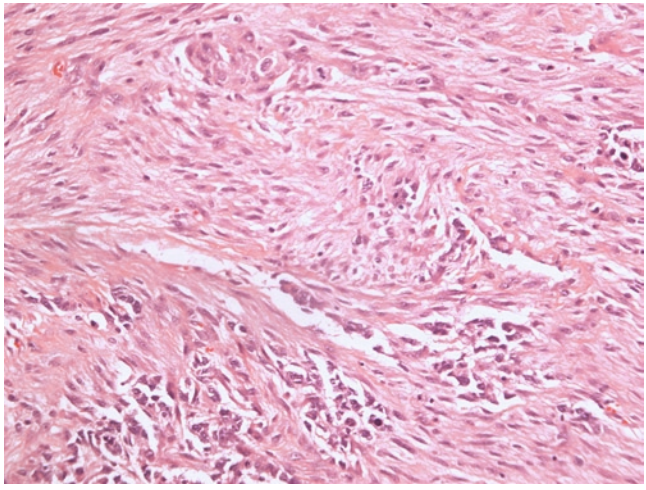

FIG. 5.8 A gliosarcoma marked by areas resembling a glioblastoma juxtaposed with a malignant spindled cell component resembling a sarcoma.

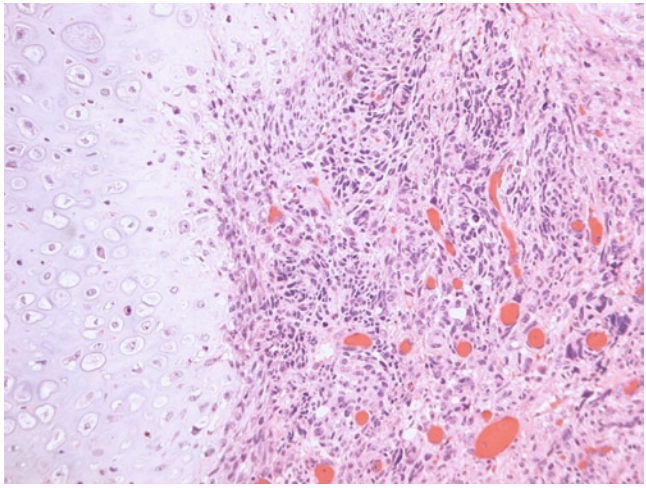

FIG. 5.9 Rare gliosarcomas may demonstrate other atypical mesenchymal components such as cartilage (seen here) or bone.

and certainly this is not a distinction that is required at the time of frozen section. In cases where the sarcomatous component is predominantly sampled at the time of frozen section, the distinction of a gliosarcoma from other spindled cell malignancies, including a sarcoma or an anaplastic meningioma, may be problematic. In such cases, a diagnosis of malignant spindled cell neoplasm with a suggestion of the possible differential diagnostic considerations may be all that one can give.

Occasionally, glioblastoma tumors may be marked by an increased number of giant, multinucleated cells (giant cell glioblastoma) (Fig. 5.10). A differential diagnosis with a pleomorphic xanthoastrocytoma may arise in this setting. In general, the pleomorphic xanthoastrocytoma lacks prominent numbers of mitotic figures and necrosis. The epithelioid glioblastoma, as mentioned in Chap. 4, can mimic a metastatic carcinoma (Fig. 5.11). Unless a more conventional appearing area of the glioblastoma is present on the frozen section slide, the distinction may be impossible. Similarly, a small cell glioblastoma can look like a small cell carcinoma or a high-grade oligodendroglioma at the time of frozen section (Fig. 5.12). A diagnosis of a malignant small cell neoplasm with a suggestion of the differential diagnosis may be suitable, if there are no other definitive clues present on the slide. Rarely, the glioblastoma may demonstrate evidence of granular cell differentiation

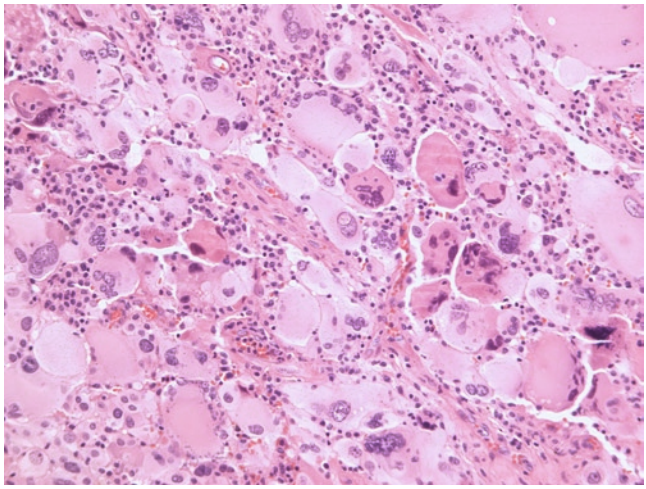

FIG. 5.10 This giant cell glioblastoma is characterized by an increased number of large multinucleated astrocytic cells.

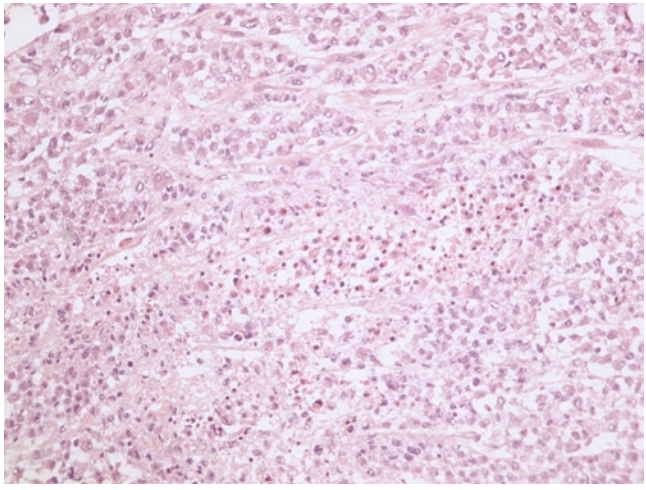

FIG. 5.11 An epithelioid glioblastoma characterized by cells with distinct cytoplasmic boundaries resembling metastatic carcinoma or melanoma. In some of these cases, immunohistochemistry on permanent sections may be required to make a definitive diagnosis. One should look for areas of the tumor that resemble an ordinary glioblastoma or an astrocytoma as a clue to the diagnosis.

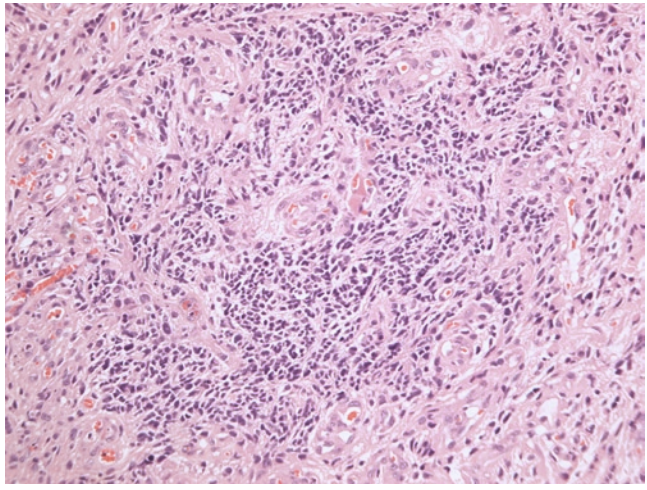

FIG. 5.12 An area of a glioblastoma with cells marked by high nuclear cytoplasmic ratio consistent with a small cell glioblastoma.

(Fig. 5.13). These tumors contain cells with abundant granular, eosinophilic cytoplasm. The only other location where granular cell tumor may be encountered is in the posterior pituitary gland. Glioblastomas that contain an oligodendroglioma component (formally an anaplastic-mixed glioma) may be seen. These tumors are sometimes difficult to recognize in the context of frozen section, given the alterations of nuclear contour that can occur secondary to freezing the tumor. The typical oligodendroglial cell with its round or slightly oval nucleus and scant cytoplasm may appear somewhat differently at the time of frozen section; a severe freeze artifact can significantly distort the nuclear shape of an oligodendroglioma cell and cause it to more closely resemble a malignant astrocyte. Identification of an oligodendroglioma component in a glioblastoma is probably not critical at the time of intraoperative consultation anyway. Rare cases of the glioblastoma may also contain metaplastic elements, such as squamous type epithelium.

Distinction of radiation change from a high-grade astrocytoma can present a challenge. Most high-grade astrocytomas are treated with radiotherapy. Often, the surgeon may inquire whether there is residual tumor present and how much of the sampled tissue is necrotic versus reactive versus viable tumor. Radiation changes include perivascular chronic inflammation, reactive astrocytosis, necrosis with macrophages and microcalcifications, and bizarre cytologic atypia with cytoplasmic vacuolization and smudged nuclei (Fig. 5.14). Residual tumor, in contrast, should

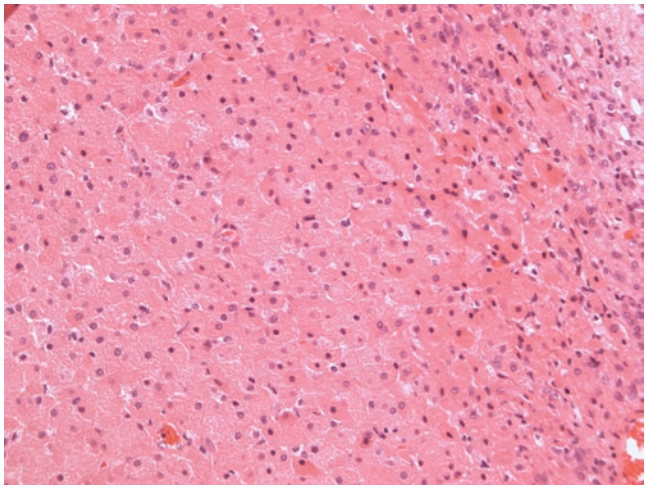

FIG. 5.13 A granular cell glioblastoma contains a population of cells with abundant granular eosinophilic cytoplasm, similar to cells that would be encountered in a granular cell tumor.

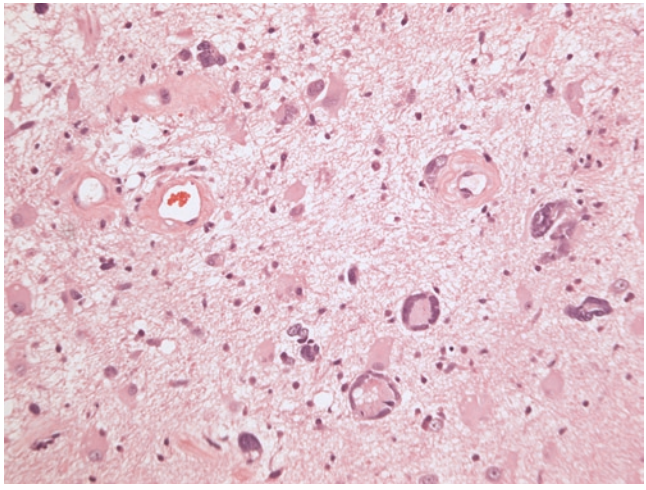

FIG. 5.14 This biopsy represents radiation atypia in a high-grade glioma. Vascular sclerosis, reactive astrocytes, and large atypical multinucleated cells with cytoplasmic vacuoles represent changes related to radiation therapy administration.

demonstrate a population of cells with features of conventional atypia (cells with enlarged nuclei and high nuclear to cytoplasmic ratio, nuclear hyperchromasia, and irregular nuclear contour), vascular proliferative changes, and palisaded necrosis. In cases in which necrosis is not rimmed by a pseudopalisade of tumor cells and shows a paucity of macrophages, it may be difficult to distinguish the necrosis as secondary to the radiation or intrinsic to the tumor.

The term gliomatosis cerebri refers to a widely infiltrative glioma, usually an astrocytoma. On imaging studies, these tumors often involve multiple regions of the brain, often bilaterally, and in a contiguous fashion. At frozen section, one may receive one or two samples of tumor which may resemble anything from a low-grade to high-grade astrocytoma. A diagnosis of gliomatosis requires correlation with the imaging findings and cannot be made based on the examination of the biopsy alone.

There are a number of astrocytoma variant tumors that are important to distinguish from the ordinary diffuse astrocytoma because of the differences in terms of prognosis and treatment. Table 5.3 summarizes a list of clues that suggest that one might be dealing with one of the astrocytoma variant lesions. Tumors that occur in this group that may be located in the cerebral hemispheres include pilocytic (Figs. 5.15–5.17) and pilomyxoid astrocytomas (Fig. 5.18), pleomorphic xanthoastrocytoma (Figs. 5.19 and 5.20), subependymal giant cell astrocytoma (intraventricular) (Fig. 5.21), and desmoplastic infantile astrocytoma (Fig. 5.22). All of these tumors are marked by a generally younger age of presentation, many times in childhood or even infancy. Some of these tumors have characteristic sites of origin. For example, the pilocytic astrocytoma is prone to arise in the cerebellum, the region around the third ventricle, optic nerve, and brain stem.

Table 5.3 Clues to a possible astrocytoma variant diagnosis.

Young age of patient
Location – cerebellum, optic nerve, lateral ventricle
Imaging – cyst with enhancing mural nodule
Leptomeningeal extension
Circumscribed border
Perivascular chronic inflammation
Sclerotic, hyalinized blood vessels (in a tumor that has not been radiated)
Rosenthal fibers and eosinophilic granular bodies
Lipidized astrocytes

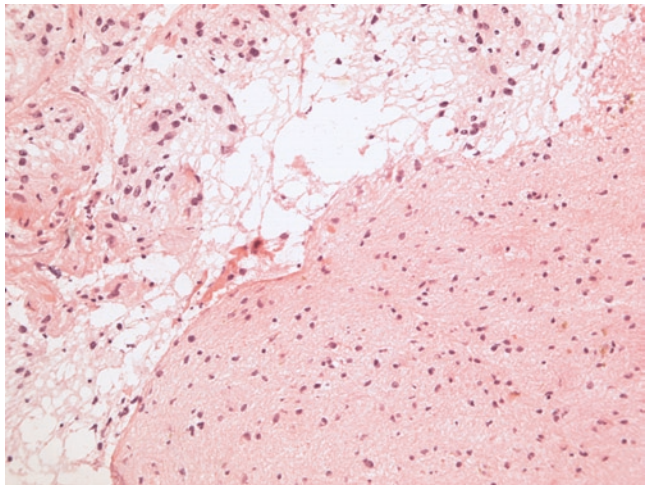

FIG. 5.15 Cerebellar mass in a 4-year-old which represented a pilocytic astrocytoma. This field demonstrates the typical biphasic appearance of the tumor; the lesion is marked by a more densely fibrillary zone alternating with an area that has a looser, microcystic appearance.

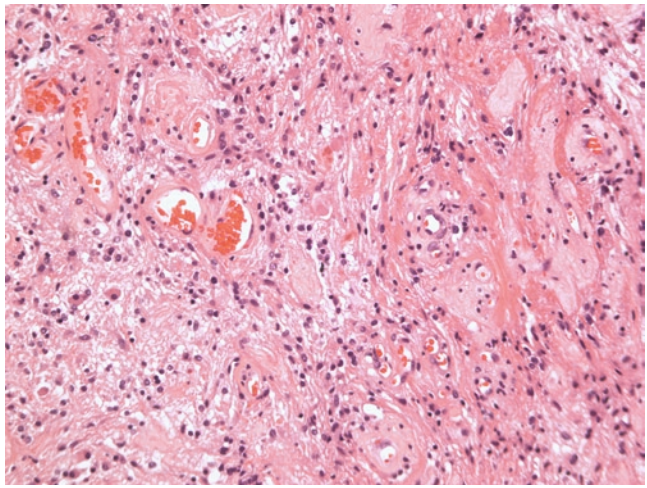

FIG. 5.16 A pilocytic astrocytoma demonstrating focally prominent vascular sclerosis, a fairly common feature of these tumors.

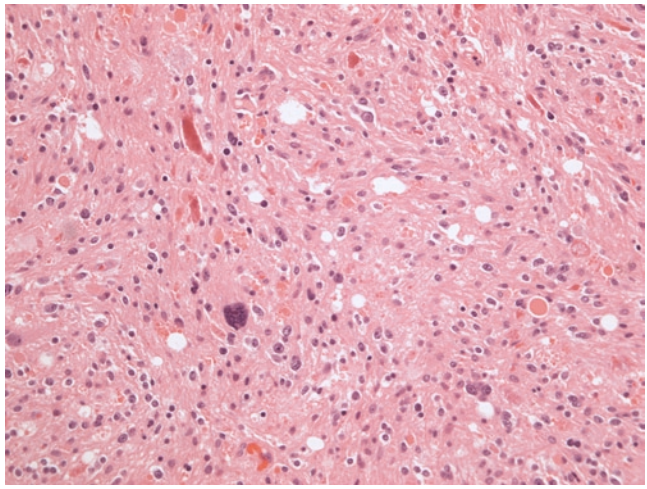

FIG. 5.17 A pilocytic astrocytoma demonstrating Rosenthal fibers, eosinophilic granular bodies, and occasional pleomorphic nuclei. The degree of pleomorphism has no effect on prognosis in these tumors.

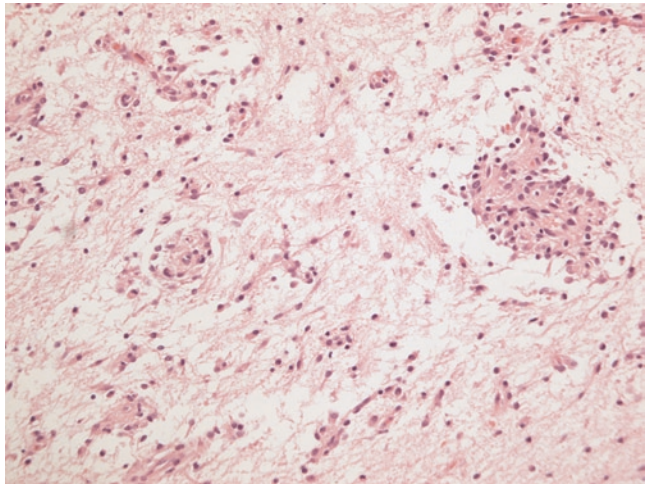

FIG. 5.18 This pilomyxoid astrocytoma demonstrates a general appearance resembling the looser pattern of a pilocytic astrocytoma but is devoid of Rosenthal fibers and eosinophilic granular bodies. A common feature of this tumor is the arrangement of generally rounded cells around blood vessels forming perivascular pseudorosette-like structures.

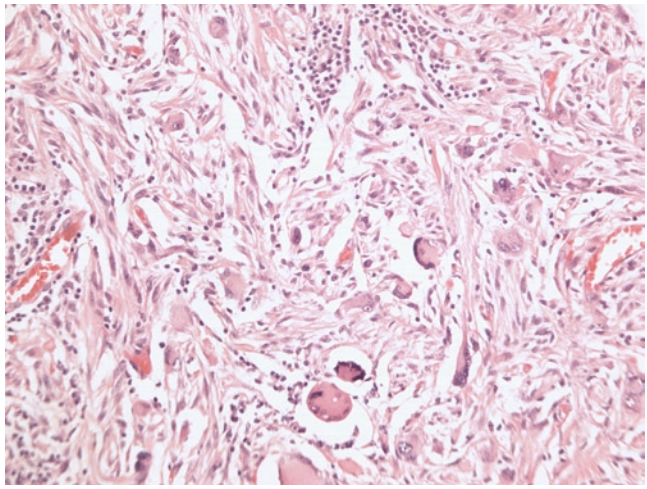

FIG. 5.19 A pleomorphic xanthoastrocytoma characterized by marked cellularity and nuclear pleomorphism. Foci of benign appearing lymphocytes are also commonly observed in this tumor. The xanthomatous astrocytes, although part of the tumor's name, are a variable feature of this neoplasm.

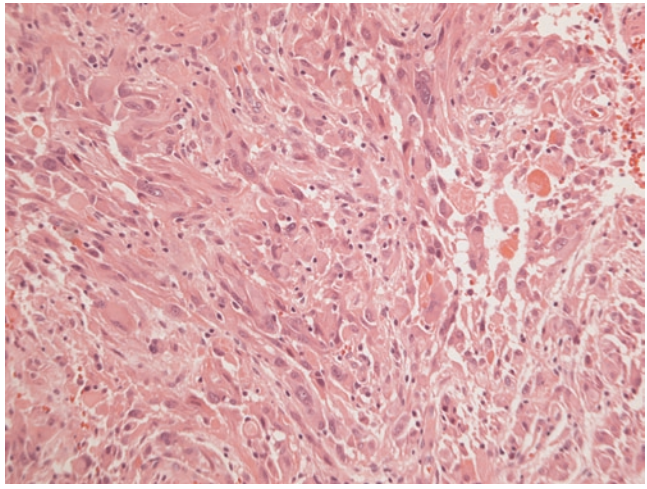

FIG. 5.20 A pleomorphic xanthoastrocytoma marked by prominent numbers of eosinophilic granular bodies.

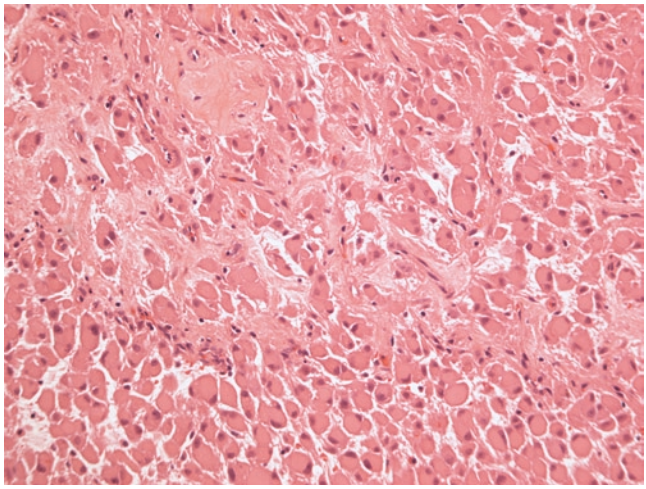

FIG. 5.21 A subependymal giant cell astrocytoma involving the lateral ventricle and characterized by a proliferation of large, plump astrocytic cells.

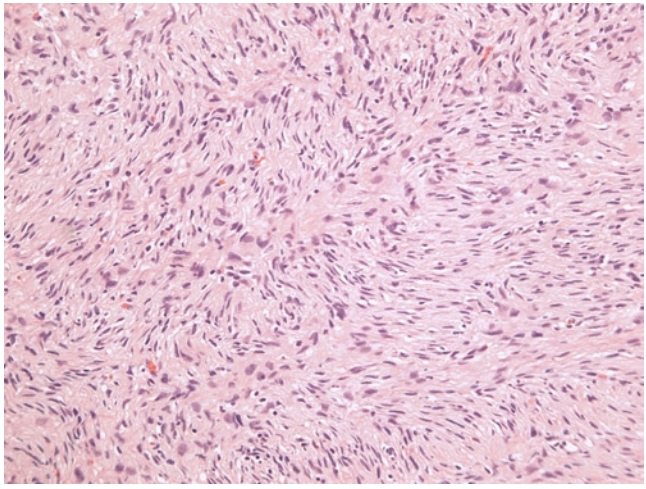

FIG. 5.22 An infant with a cystic tumor characterized by a proliferation of spindled cells. A diagnosis of an infantile desmoplastic astrocytoma was made in this case. Ganglion cells were not identified in the lesion; if they were, a diagnosis of a desmoplastic infantile ganglioglioma would be appropriate.

The pleomorphic xanthoastrocytoma almost exclusively arises in the parietal and temporal lobe regions. The hypothalamic and chiasmic region is the most common site of origin for pilomyxoid astrocytoma. The subependymal giant cell astrocytoma almost always arises in the lateral ventricle.

On imaging, many of these tumors have a circumscribed border and are generally not as infiltrative as the diffuse or fibrillary astrocytomas. A cyst with mural nodule configuration, which may be evident on imaging studies, is characteristic of the pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and desmoplastic infantile astrocytoma. Some of these tumors also demonstrate preferential involvement of the leptomeninges, which is relatively uncommon with diffuse astrocytoma.

Microscopically, the presence of prominent perivascular chronic inflammation is unusual in a diffuse astrocytoma and is fairly common in several of these variant tumors. The presence of Rosenthal fibers and/or eosinophilic granular bodies is more common in a subset of these tumors as well, particularly pilocytic astrocytoma and granular bodies in pleomorphic xanthoastrocytoma. Lipidized astrocytes may be seen in a pleomorphic xanthoastrocytoma. Sclerotic hyalinized blood vessels are a fairly common finding in pilocytic astrocytoma and are otherwise unusual except in the setting of an irradiated diffuse astrocytoma. The presence of any of these aforementioned features should raise the possibility that one is dealing with one of the astrocytoma variant lesions.

OLIGODENDROGLIOMAS

Oligodendrogliomas are less commonly encountered than astrocytomas. On imaging and presentation, they may resemble a diffuse astrocytoma. They are generally graded as low grade (WHO grade II) or high grade (WHO grade III). Many of the same parameters that are used in grading astrocytomas are used to grade oligodendrogliomas (cellularity, mitoses, vascular proliferation, and necrosis). The relative threshold for upgrading a tumor from a grade II to III lesion is different compared to astrocytoma, however. In general, a low-grade oligodendroglioma may contain as many as 3 or 4 mitoses per 10 high power fields, and that is acceptable. Mitotic counts higher than that generally are indicative of a higher grade tumor. Focal areas of increased cellularity may also be tolerable in a low-grade oligodendroglioma.

Distinction of oligodendroglioma from astrocytoma at frozen section may be nearly impossible. In general, oligodendrogliomas tend to have a more monomorphic appearing population of cells with generally round nuclei (Figs. 5.23–5.25). The classic pericellular

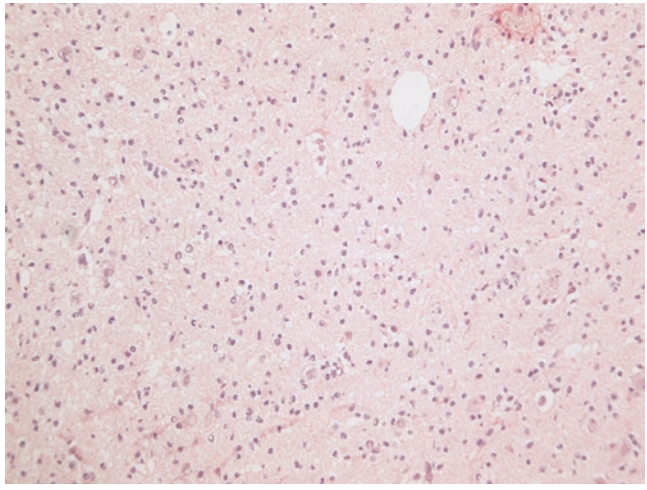

FIG. 5.23 This frozen section shows mildly hypercellular parenchyma marked by a proliferation of generally rounded cells consistent with a low-grade glioma. The final diagnosis on this case was a low-grade oligodendroglioma.

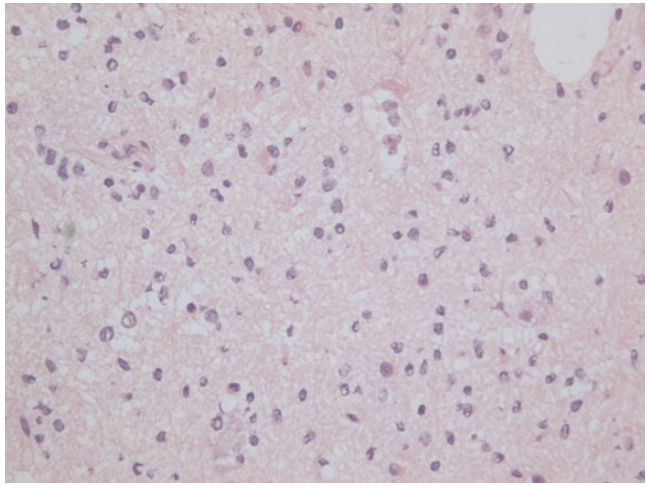

FIG. 5.24 A higher magnification view of a low-grade oligodendroglioma at frozen section underscores the general round nature of the nuclei and monotony of the cells. Remember, the pericellular clearing or "fried egg" change is a feature related to delayed formalin fixation.

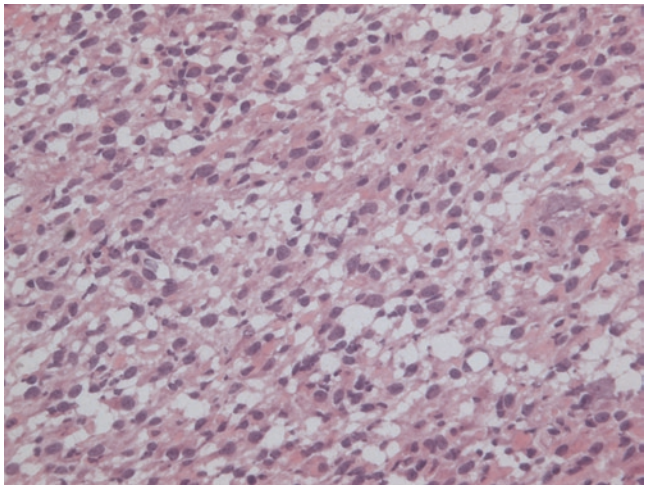

FIG. 5.25 An anaplastic astrocytoma marked by increased cellularity and nuclear pleomorphism. Mitotic figures are often readily identifiable in these tumors.

clearing, which is usually associated with oligodendroglioma, represents an artifact of delayed formalin fixation and is not evident at frozen section. Microcalcifications are a common feature of many oligodendrogliomas (up to 80% of tumors) but are not diagnostic of oligodendrogliomas. Often, they have a prominent capillary vascular pattern due to the paucity of cellular processes in the tumor cells. Satellitosis and subpial aggregation are also common findings in many oligodendrogliomas. In some instances, the use of a cytologic preparation may provide better cellular detail allowing one to better appreciate the monomorphic nature of the generally rounded cells of the oligodendroglioma.

From a practical standpoint, it is not essential to distinguish between an oligodendroglioma and an astrocytoma at the time of frozen section consultation. The approach surgically is not going to be affected by this decision. In many cases, a diagnosis of a low-grade or a high-grade glioma is adequate. Ultimately, the final diagnosis needs to be more accurate; there are implications in terms of prognosis and treatment to distinguish between an oligodendroglioma and an astrocytoma. This is more easily and more reliably done, however, with well-fixed histologic sections. Occasional tumors may show apparent features of both astrocytoma and oligodendroglioma, so-called mixed gliomas or

oligoastrocytomas. Again, the distinction of this lesion from pure astrocytoma or pure oligodendroglioma is not required at the time of frozen section. In truth, a diagnosis of mixed glioma should probably only be made in a tumor that has been well sampled, and after all the material submitted has been examined.

Other tumors that may resemble an oligodendroglioma include the central neurocytoma and dysembryoplastic neuroepithelial tumor. Central neurocytoma classically arises in the lateral ventricle and is marked by generally rounded cells with a salt and pepper chromatin pattern. An arcuate vascular pattern and microcalcifications, similar to what is seen in oligodendrogliomas, may also be present. The best clue one has at the time of frozen section that one may be dealing with a central neurocytoma is the intraventricular location (lateral ventricle) and the nuclear chromatin pattern.

GLIONEURONAL TUMORS

The dysembryoplastic neuroepithelial tumor is considered a glioneuronal neoplasm. It most typically arises in younger patients with a chronic epilepsy history and most commonly in the temporal lobe. Microscopically, the tumor is comprised of cells that resemble oligodendroglial cells intermixed with normal appearing neurons. Clues suggesting a dysembryoplastic neuroepithelial tumor include a predominantly cortical location, multinodularity, paucity of mitotic activity, an absence of subpial aggregation of cells, and an absence of any appreciable cytologic atypia (Figs. 5.26 and 5.27). The adjacent brain tissue often demonstrates architectural disorganization in the dysembryoplastic neuroepithelial tumor. Frequently, this multinodular tumor demonstrates a microcystic background; however, this may be difficult to appreciate at frozen section, given the pseudomicrocystic artifact that can be easily generated. A definitive diagnosis of dysembryoplastic neuroepithelial tumor is difficult to make at frozen section, unless one is dealing with a large resection and a large piece of tissue is sampled. This allows for the possible recognition of a multinodular architecture and predominant cortical location of the nodules. In a smaller biopsy sampling or fragmented specimen, the dysembryoplastic neuroepithelial tumor may be indistinguishable from a low-grade microcystic oligodendroglioma. In a case where the clinical history and imaging studies suggest the possibility of a dysembryoplastic neuroepithelial tumor, a frozen section diagnosis of a low-grade glioma/glioneuronal neoplasm can be made and a suggestion of the possible differential diagnosis offered.

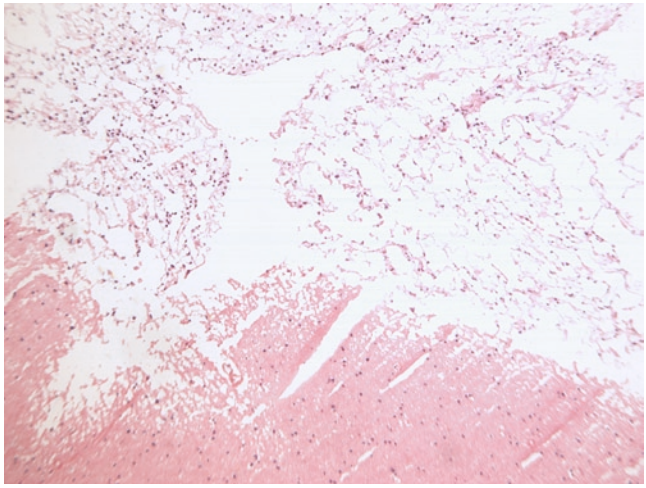

FIG. 5.26 A low magnification view of a dysembryoplastic neuroepithelial tumor showing a sharp interface between one of the tumor nodules on the top and the subjacent parenchyma. These tumors often demonstrate a multinodular architecture, with most nodules being located in the cortex.

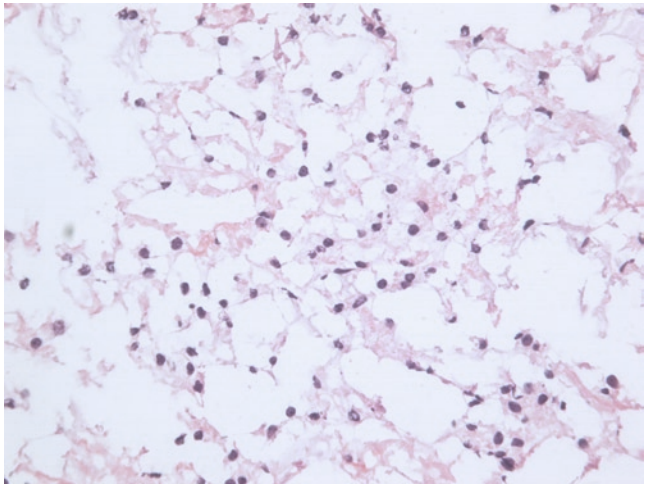

FIG. 5.27 A higher magnification appearance of a dysembryoplastic neuroepithelial tumor showing a proliferation of generally rounded cells, resembling oligodendroglial cells, arranged against a microcystic background. The differential diagnosis includes a low-grade microcystic glioma (oligodendroglioma) and the rare uninodular, cortical based protoplasmic astrocytoma.

Other glioneuronal tumors that can arise in the cerebral hemisphere include the ganglioglioma and the papillary glioneuronal tumor. Gangliogliomas are lesions that comprise a ganglion cell or neuronal cell component mixed with a gliomatous component, usually resembling a low-grade astrocytoma (Figs. 5.28 and 5.29). These tumors often arise in children with chronic epilepsy and preferentially involve the temporal lobe. Often, they are marked by perivascular chronic inflammation, Rosenthal fibers, and eosinophilic granular bodies. Microcalcifications and cystic changes may be evident. They typically lack necrosis and prominent mitotic activity. Extension of the tumor into the meningeal space is not uncommon. Since both components of this tumor may not be evenly admixed throughout the lesion, it is not uncommon to have areas of a ganglioglioma which are relatively devoid of atypical ganglion cells, and therefore resemble an ordinary low-grade glioma. In the proper clinical setting, a diagnosis of a low-grade glioma/glioneuronal neoplasm can be made with a suggestion of the differential diagnosis. In a subset of these cases in which a single frozen section is performed, one can anticipate that an erroneous diagnosis of a low-grade astrocytoma or a low-grade

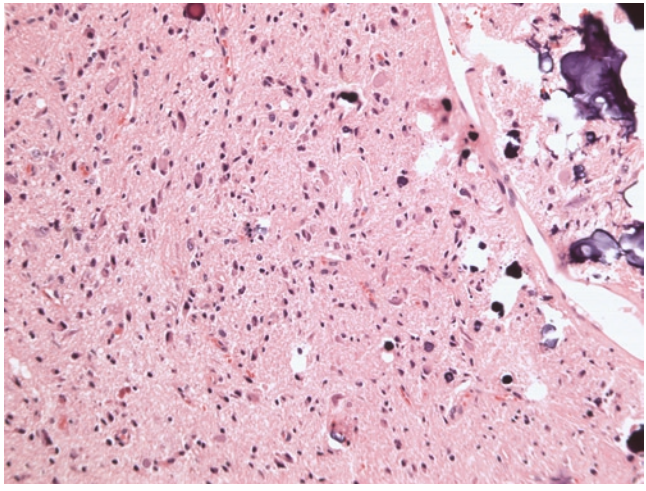

FIG. 5.28 This section of a ganglioglioma highlights an astrocytoma-appearing focus of the tumor with associated dystrophic calcification on the *right*.

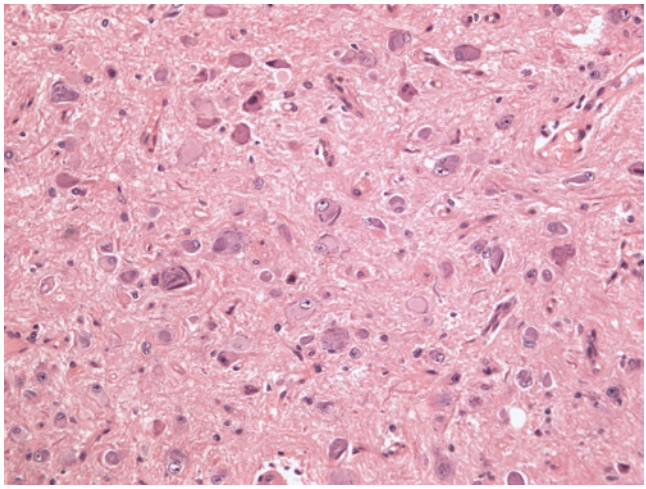

FIG. 5.29 Another area of the same tumor in FIG. 5.28 shows the atypical ganglion cell component of the tumor. Occasional cells in this tumor show evidence of neurofibrillary tangles, a relatively infrequent finding in these tumors.

glioma will be made at frozen section, only to be corrected upon the examination of the remainder of the tumor and the identification of the requisite atypical ganglion cell component. Such an "honest error" due to sampling should not impact the surgical management of the case. Rare cases of ganglion cell tumors (gangliocytomas) have been described, most commonly arising in the cerebellum in the setting of Cowden's disease.

The papillary glioneuronal tumor is a recently described, relatively rare lesion that typically arises in adults in the cerebral hemispheres. This is a difficult tumor to definitively diagnose at the time of frozen section, as it requires immunohistochemistry, in most cases, to delineate both components of this tumor. These tumors are usually diagnosed as a low-grade glioma at frozen section. These neoplasms are marked by a pseudopapillary architectural pattern with hyalinized blood vessels lined by glial cells with intervening, generally rounded neurocytic cells. Vascular proliferation or necrosis is unusual.

OTHER TUMORS

Astroblastoma and angiocentric glioma represent rare parenchymal-based tumors that are marked by characteristic angiomatous pseudorosettes. The finding of pseudorosettes may be localized

in these tumors and therefore may not always be sampled at the time of frozen section. The angiocentric glioma typically arises in children with chronic epilepsy. The astroblastoma may arise in children or young adults and is marked by cells arranged around vessels which have broad nontapering processes radiating toward the central blood vessel.

Central nervous system lymphomas have been previously discussed in Chap. 3 and are fairly common tumors arising in the cerebral hemispheres. Neuroblastomas are small blue cell tumors which resemble medulloblastomas. Medulloblastomas are discussed in Chap. 8. By convention, tumors with this appearance arising in the cerebral hemispheres are designated as a neuroblastoma and not a medulloblastoma. Discussion of their salient histologic features as well as differential diagnostic considerations is addressed in Chap. 8.

Chapter 6
Dural-Based Tumors

Of primary dural-based tumors of the central nervous system, meningiomas are clearly the most commonly encountered and are the primary focus of this chapter. The differential diagnosis of dural-based neoplasms is listed in Table 6.1. Meningiomas arise anywhere in the central nervous system where meningothelial cells can be found, most commonly proximal to the dura. Occasionally, meningiomas arise in unusual places within (such as intraventricular locations) and outside (in ectopic sites such as ear, orbit, skull, and sinuses) the central nervous system.

THE RELATIVELY GOOD

Table 6.2 lists the various types of meningioma and their associated grades. The biggest initial clue to a meningioma diagnosis is the gross appearance and location of the lesion. Grossly, these are circumscribed masses that are generally firm and are frequently situated proximal to the dura. The higher grade meningiomas are the exception to this in that they may demonstrate an infiltrative growth pattern and lack the circumscription typical of grade I meningiomas. The vast majority of tumors are either meningothelial (syncytial) (Fig. 6.1), fibrous (Fig. 6.2), or transitional (mixed) type. Histologic features that typically alert one to the possibility of a meningioma include the arrangement of cells in lobules, a whorled orientation of cells around a central blood vessel, the presence of psammoma bodies, and intranuclear pseudoinclusions (Figs. 6.3 and 6.4). For tumors arising in the typical locations and in which these features are present, the diagnosis of meningioma is usually straightforward. Fortunately, this represents the

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Table 6.1 Differential diagnosis of dural-based tumors.

Meningioma
Solitary fibrous tumor
Sarcoma (primary)
Metastasis

Table 6.2 Meningiomas.

Grade I
Meningothelial (syncytial)
Fibrous (fibroblastic)
Transitional (mixed)
Psammomatous
Secretory
Metaplastic
Lymphoplasmacyte – rich
Angiomatous
Microcystic
Grade II
Clear cell
Chordoid
Atypical
4 or more mitoses/10 high power fields
Brain invasion
3 or more of the following features: sheeting (disordered architecture), small cell change, prominent nucleoli, hypercellularity, necrosis (outside the setting of embolization)
Grade III
Papillary
Rhabdoid
Anaplastic
20 or more mitoses/10 high power fields
Poorly differentiated – resembling carcinoma, melanoma, or sarcoma

majority of cases. However, not all meningiomas demonstrate these features, and these cases may present more of a challenge.

Distinction of fibrous meningioma from other spindled cell lesions that commonly arise in the proximity, including solitary fibrous tumor and schwannoma, can be difficult at frozen section. Especially in the cerebellopontine angle region, the differential diagnosis between a fibrous meningioma and a schwannoma is a frequent question. Both fibrous meningioma and schwannoma contain spindled cells with elongated nuclei and sclerosed vessels. In the absence of other distinguishing

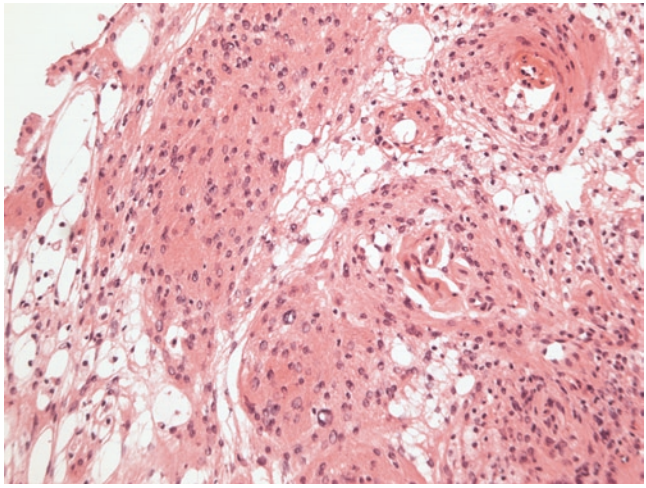

FIG. 6.1 A meningothelial meningioma marked by a whorling pattern in the upper right corner. Nuclear pleomorphism is permissible in a grade I tumor.

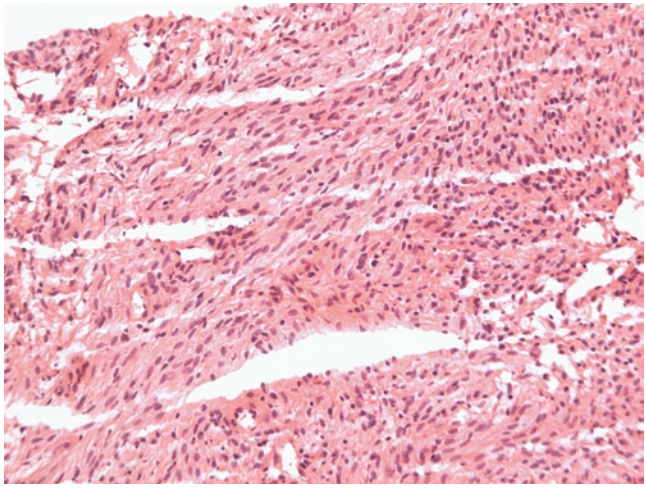

FIG. 6.2 A fibrous meningioma marked by a proliferation of bland appearing spindled cells.

characteristics, including psammoma bodies, intranuclear pseudoinclusions, and whorling (in the case of meningioma) or Verocay bodies and biphasic Antoni A and Antoni B patterns (in the case of schwannoma), the differential diagnosis may be

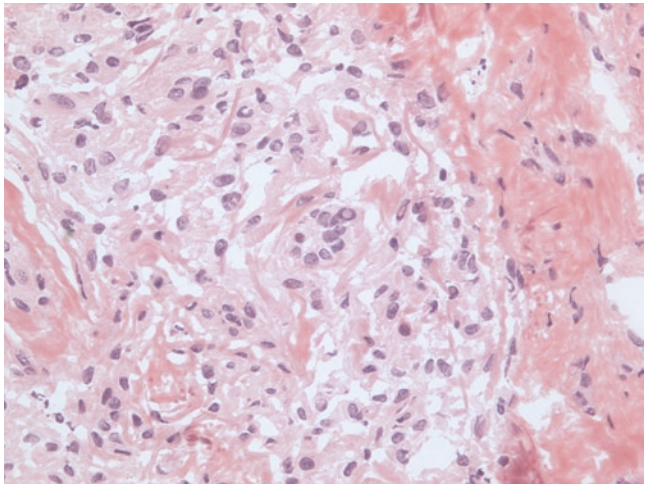

FIG. 6.3 A meningothelial meningioma showing characteristic intranuclear pseudoinclusions which represent invaginations of the cytoplasm into the nucleus.

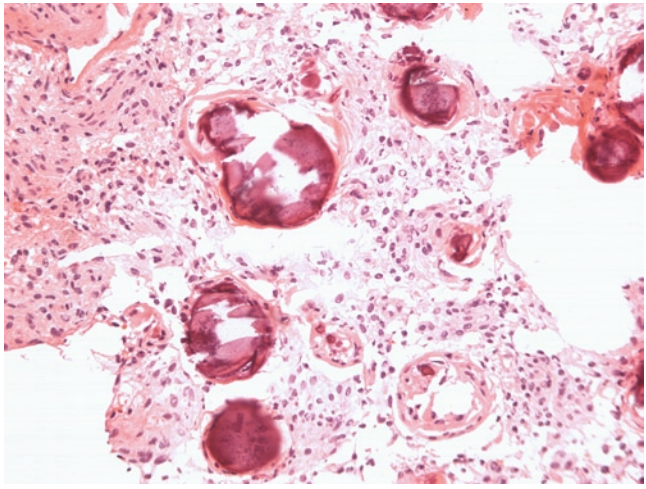

FIG. 6.4 Prominent numbers of psammoma body calcifications mark the psammomatous variant of meningioma.

particularly difficult (Figs. 6.5–6.7). In small samples or samples devoid of characteristic features, one may be able to make only a diagnosis of a low-grade spindled cell neoplasm and suggest the differential diagnosis. Immunohistochemistry on permanent sections readily allows distinction between the two tumors. In most of these cases, the neurosurgeon should know the original location of the lesion, which may also provide a useful clue to the diagnosis. Schwannomas in the cerebellopontine angle region should be seen in association with the cranial nerves versus the dural-based meningiomas.

Other patterns of a WHO grade I meningioma can present diagnostic challenges, in that their appearances can result in a striking alteration in the morphology of the tumor. A prominent microcystic pattern, marked vascular pattern (angiomatous meningioma) (Fig. 6.8) or heavy lymphoplasmacytic infiltrate (Fig. 6.9), may obscure the true nature of the neoplasm. When the location is unclear, the microcystic meningioma may be confused with a parenchymal-based microcystic glioma. The multiple eosinophilic cytoplasmic inclusions of the secretory meningioma are characteristic of that variant (Fig. 6.10). Metaplastic meningiomas, making bone or cartilage, may cause confusion with osseous or cartilaginous tumors. Prominent nuclear pleomorphism, although a striking feature in some tumors, does not affect prognosis but may give the impression that one is dealing with a higher grade

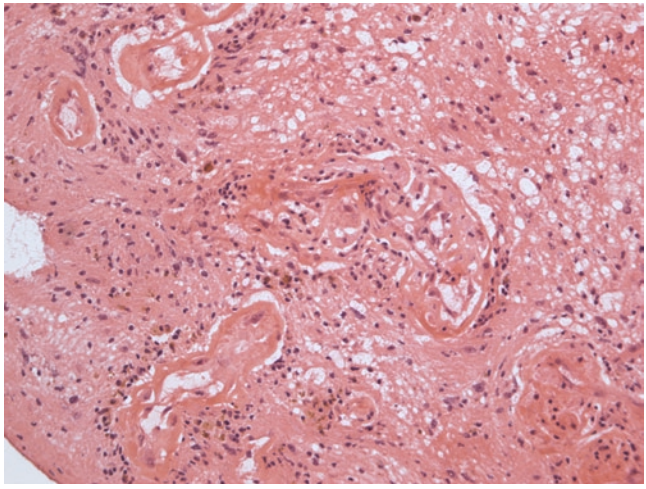

FIG. 6.5 A schwannoma showing characteristic sclerotic blood vessels, a typical feature of many of these tumors.

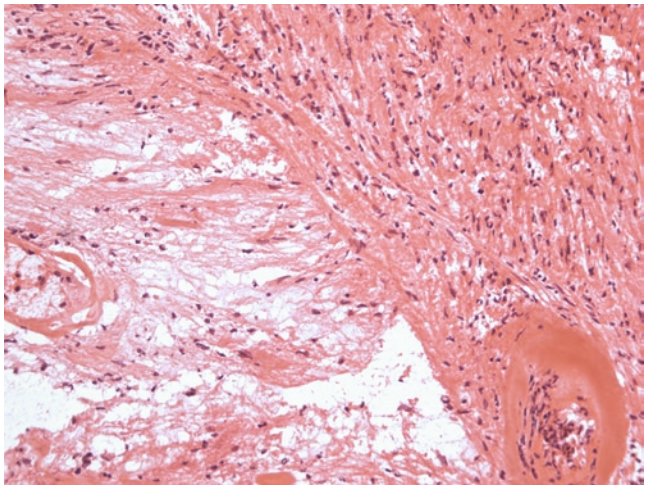

FIG. 6.6 A schwannoma demonstrating characteristic Antoni A and Antoni B patterns. Many times at frozen section, only one or the other pattern may be sampled. The Antoni A pattern may be confused with a fibrous meningioma. The Antoni B pattern may mimic a low-grade glioma.

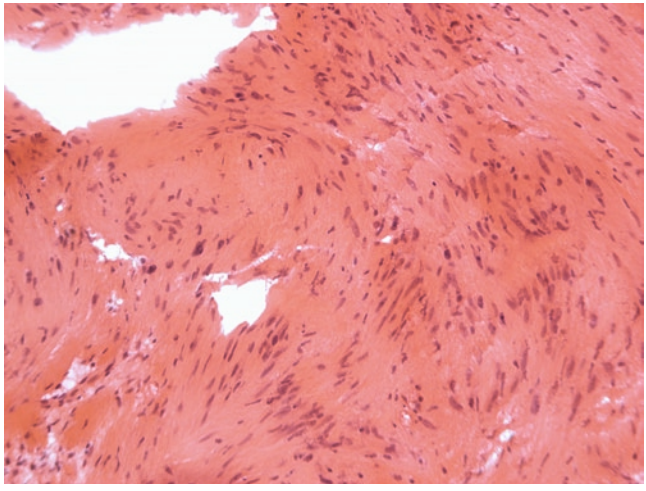

FIG. 6.7 Characteristic verocay bodies in a schwannoma.

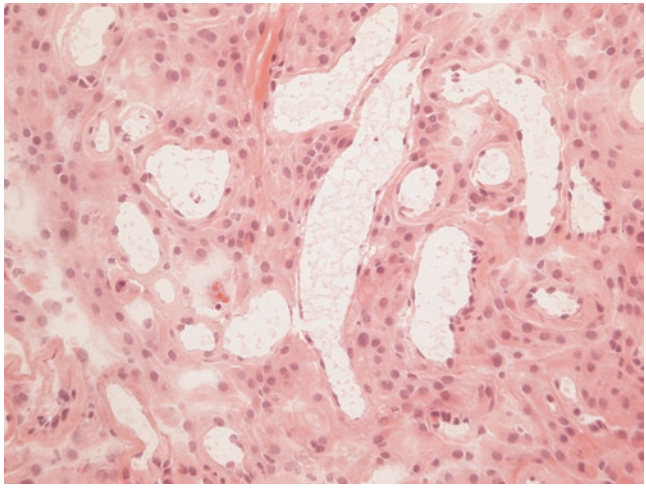

FIG. 6.8 Occasional meningiomas may demonstrate a prominent vascular pattern with a small number of interspersed meningothelial cells. This pattern is characteristic of the angiomatous meningoma.

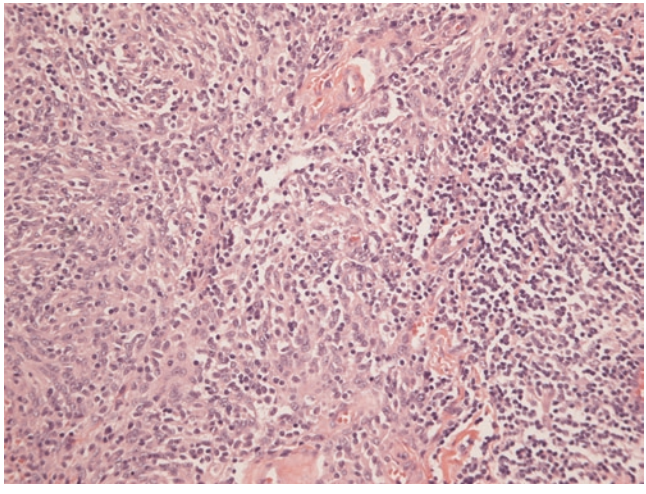

FIG. 6.9 Rare meningiomas may show a prominent lymphoplasmacytic infiltrate, which at times may obscure the meningothelial cells of the tumor. This variant is referred to as a lymphoplasmacyte rich meningioma.

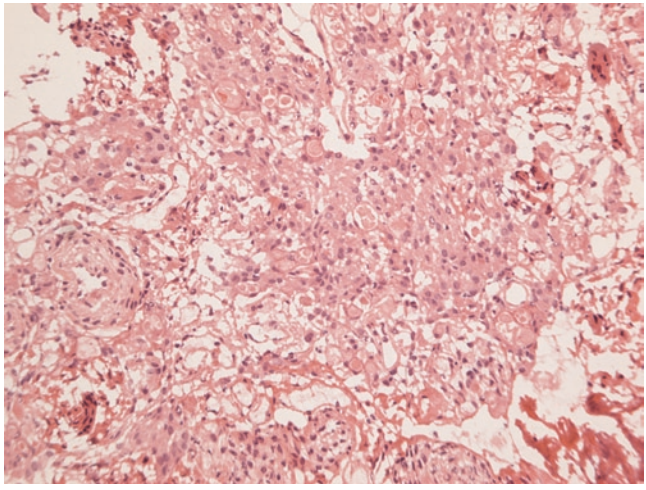

FIG. 6.10 Eosinophilic round structures characterize the secretory meningioma.

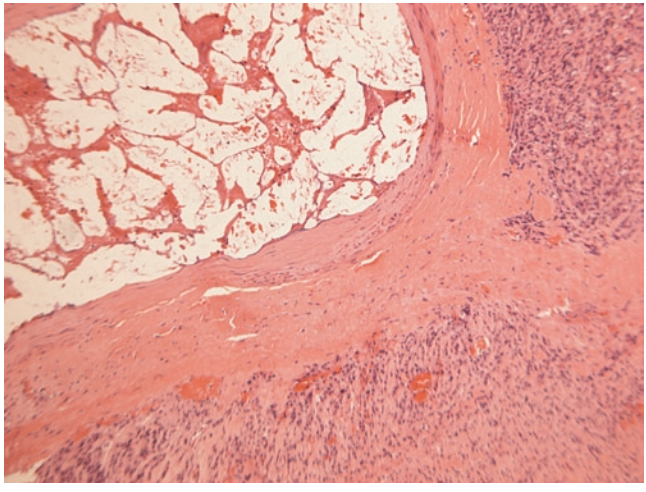

FIG. 6.11 Evidence of embolization in a meningioma. Necrosis that is observed in the setting of an embolized tumor should be disregarded for the purpose of meningioma grading. Evidence of embolization should be noted when observed at frozen section.

neoplasm. Likewise, necrosis secondary to embolization may also create the appearance of a higher grade tumor (Fig. 6.11).

In general, it is not important to distinguish between one type of grade I tumor versus another at the time of intraoperative consultation. A simple diagnosis of meningioma is adequate at this juncture. Having said that, it is important to look for features that may be indicative of more aggressive behavior in meningiomas and to convey that information to the surgeon if identified.

THE NOT SO GOOD

WHO grade II meningiomas are a group of tumors that are more likely to recur in a shorter interval of time. These tumors include two specific histologic types, the clear cell and chordoid meningiomas. The clear cell tumor is comprised cells with abundant cleared out cytoplasm due to increased glycogen accumulation (Fig. 6.12). Often, these cells lack many of the other features typical of a grade I meningioma. A sheet-like or vaguely nested architectural arrangement of cells in some clear cell meningiomas may elicit a differential diagnostic consideration of metastatic clear cell carcinoma, such as renal cell carcinoma. When distinctive

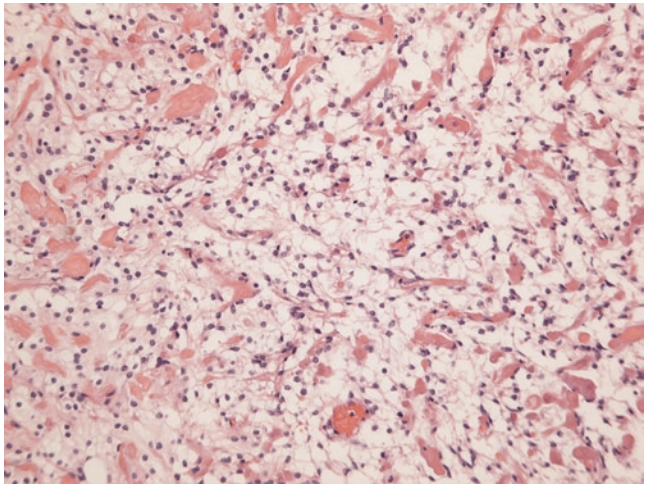

FIG. 6.12 A clear cell meningioma marked by cells with cleared cytoplasm due to increased glycogen accumulation. This variant represents a grade II lesion. There are no precise guidelines as to how much of the tumor needs to demonstrate clear cell change to qualify as a clear cell meningioma; most studies include tumors that have any clear cell pattern to them.

features of meningioma are lacking, a diagnosis of clear cell neoplasm can be made with a suggestion of the differential diagnosis. Immunostains can be used later to distinguish between the clear cell meningioma and metastatic clear cell carcinoma.

The chordoid meningioma is marked by rows or clusters of epithelioid cells arranged against a myxoid background (Fig. 6.13). The general architecture of the lesion is somewhat suggestive of a chordoma. These tumors do not arise in the locations typically associated with chordoma (clivus and sacrococcygeal regions). Chordomas also contain cells with vacuolated cytoplasm (physaliferous cells), a change that is not observed in the typical chordoid meningioma (Fig. 11.4).

Histologic features that one should look for to diagnose an atypical meningioma include the presence of 4 or more mitotic figures per 10 high power fields; brain invasion; or a constellation of three of more of the following features, including increased cellularity, small cell change, prominent nucleolation, loss of lobular architecture, and necrosis not related to embolization (Figs. 6.14–6.16). These are features that should be looked for at the time of frozen section, although they all may not be readily identifiable on the portion of the tumor that is sampled. Invasion of the tumor into the skull or adjacent soft tissue structures is not a criterion for grading the lesion (Fig. 6.17).

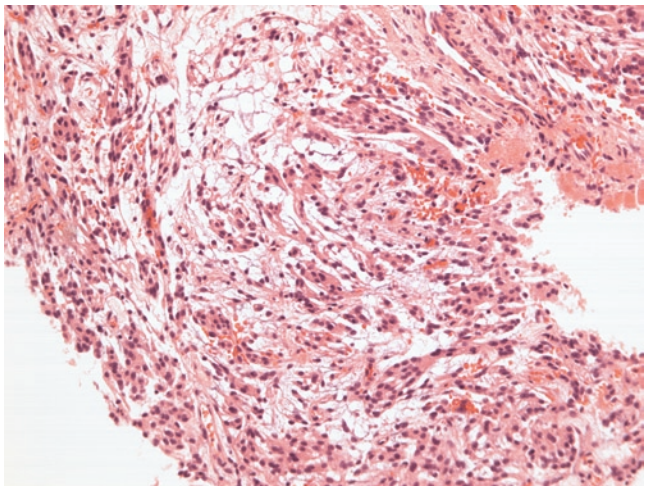

FIG. 6.13 A chordoid meningioma marked by epithelioid cells arranged in nests or trabeculae against a mucoid background. These cells lack the bubble-like change characteristic of chordoma (see Chap. 11).

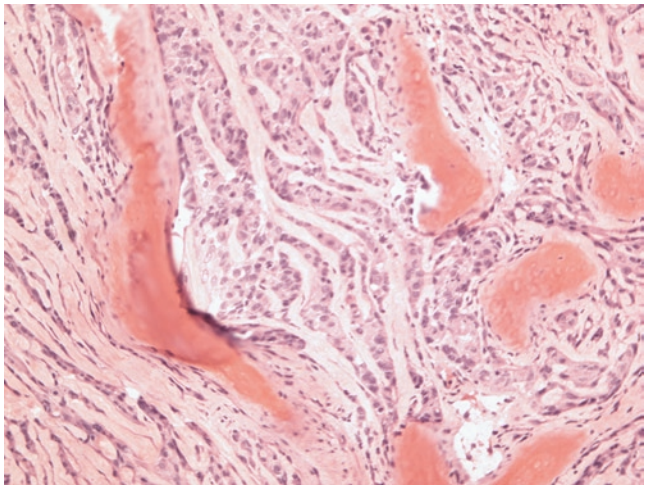

FIG. 6.14 An atypical meningioma marked by architectural disorganization with intervening fibrosis and metaplastic bone formation.

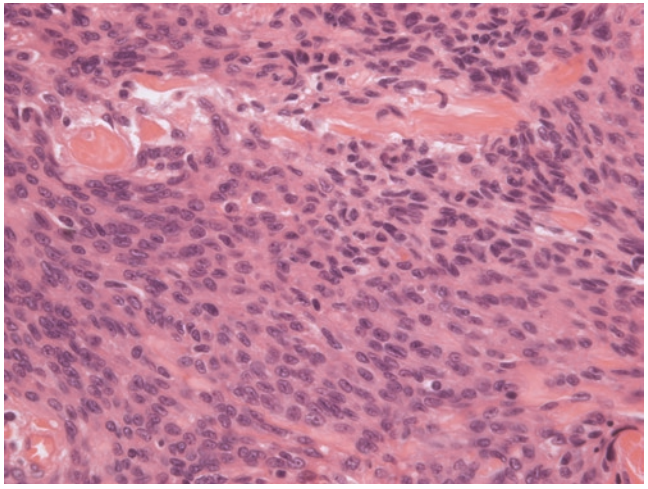

FIG. 6.15 An atypical meningioma marked by hypercellularity and prominent nucleolation.

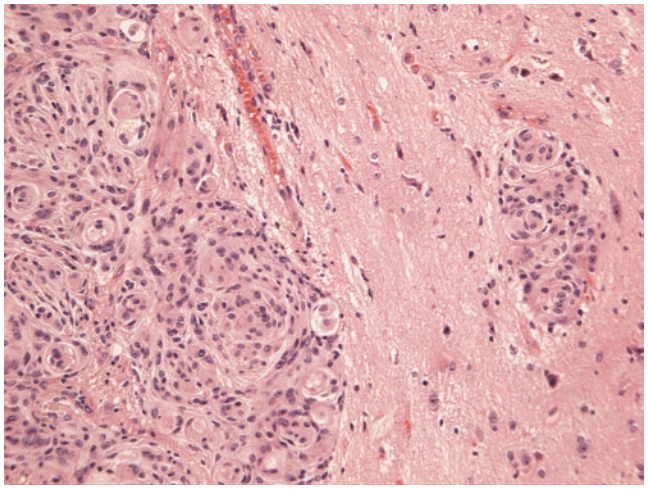

FIG. 6.16 Brain invasion in a meningioma is one of the criteria for a diagnosis of a grade II meningioma. These tumors often are more difficult to excise, since the sharp circumscription that limits the tumor from the subjacent parenchyma is usually not present.

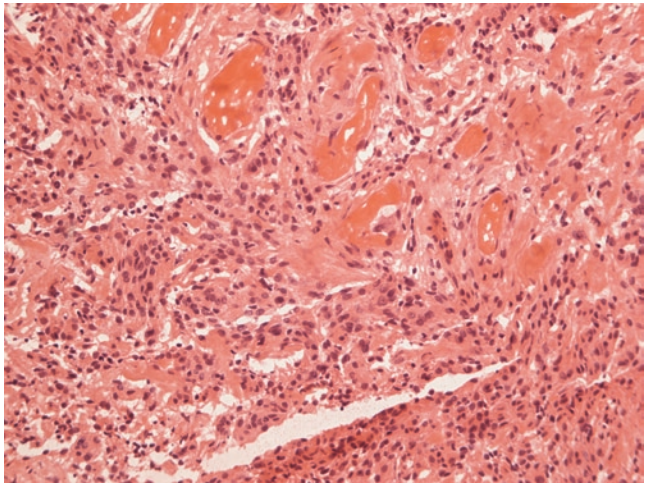

FIG. 6.17 Invasion of other structures, such as skeletal muscle (*as seen in this case*) or overlying skull, does not constitute a higher grade lesion. These tumors are more likely to locally recur in that they are more difficult to totally excise.

THE BAD

There are two histologic phenotypes that are designated as WHO grade III tumors with a particular propensity for recurrence and distant metastasis. The papillary meningioma is marked by collagen vascular cores lined by meningothelial cells (Fig. 6.18). The rhabdoid meningioma is marked by cells with abundant eosinophilic cytoplasm and eccentrically placed nuclei (Fig. 6.19). The cytoplasm contains a circumscribed, mass-like inclusion, similar to what is observed in rhabdoid tumors arising elsewhere in the body. The rare anaplastic meningioma demonstrates evidence of 20 or more mitoses per 10 high power fields or overt anaplasia (Fig. 6.20).

Higher grade meningiomas are often more difficult to appreciate at frozen section because they lack many of the features that are typically recognized as being characteristic of meningioma. The anaplastic meningiomas are particularly problematic in that they are so poorly differentiated that they often resemble a carcinoma, melanoma, or sarcoma. Distinction between these lesions at frozen section may not be possible and a more descriptive diagnosis, suggesting that one is dealing with a high grade neoplasm, and what the possible differential diagnostic considerations are, is acceptable. One should search for clues of

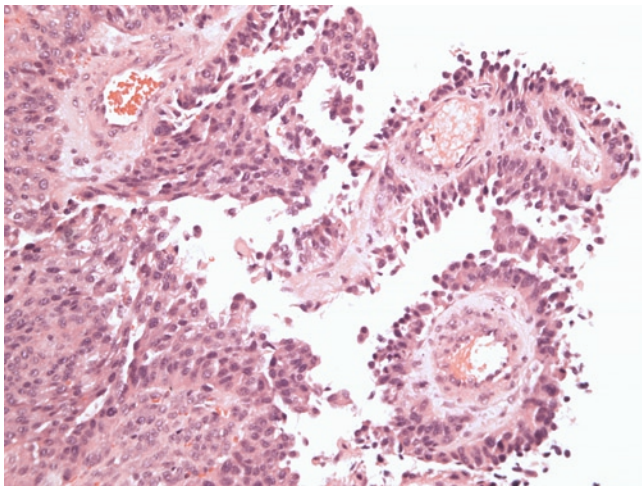

FIG. 6.18 A papillary pattern marked by meningothelial cells arranged on fibrovascular cores is characteristic of the grade III papillary meningioma.

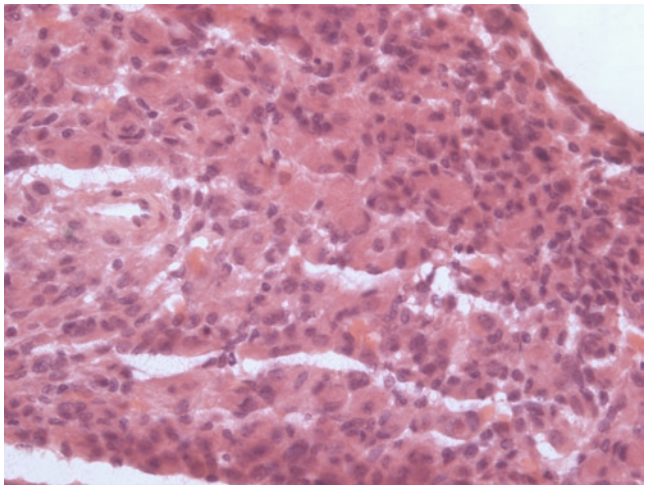

FIG. 6.19 A rhabdoid meningioma marked by abundant cytoplasm with cytoplasmic inclusions, similar to rhabdoid differentiation in other tumors.

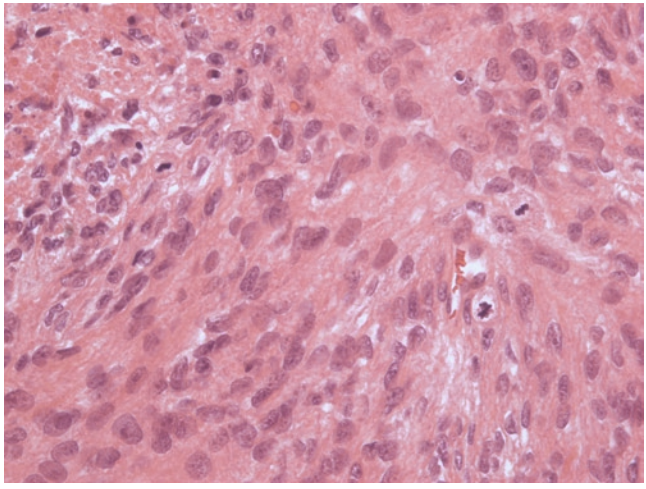

FIG. 6.20 An anaplastic meningioma marked by increased mitotic activity (3 mitotic figures are observed in this single high power field). Tumors with 20 or more mitoses in 10 high power fields qualify as anaplastic meningiomas.

more recognizable meningioma, or conversely, clues that suggest melanoma, metastatic carcinoma, or sarcoma.

Rarely, sarcomas may arise as primary lesions in the central nervous system. The most common of these entities is the solitary fibrous tumor/hemangiopericytoma lesion. The typical solitary fibrous tumor pattern often resembles a fibrous meningioma and is probably quite frequently misdiagnosed as such (likely with minimal adverse implications to the patient in most instances). Solitary fibrous tumor has increased collagen deposition between individual cells in contrast to a meningioma that is generating collagen between the lobules or a meningioma that is infiltrating into the dura with dense fibrous connective tissue separating the infiltrating lobules of meningioma (Fig. 6.21). Hemangiopericytomas tend to have less cytoplasm and lack intranuclear pseudoinclusions. They are often more cellular lesions and frequently demonstrate a characteristic staghorn vascular pattern (Figs. 6.22 and 6.23). The hemangiopericytoma may be architecturally arranged in small lobules or whorls that may create a meningioma-like appearance. In such cases, immunohistochemistry may be useful on permanent sections to help distinguish between these lesions.

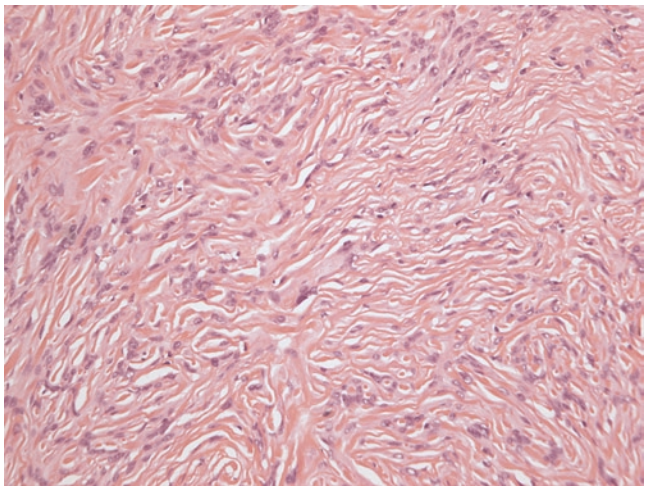

FIG. 6.21 A solitary fibrous tumor of the meninges characterized by a proliferation of bland, spindled cells with intervening collagenous material surrounding individual cells.

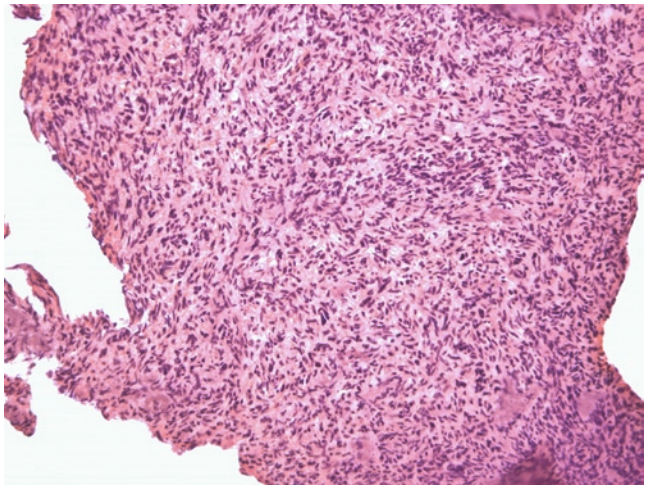

FIG. 6.22 A hemangiopericytoma characterized by prominent hypercellularity and a disordered arrangement of cells. This particular image does not show the characteristic staghorn vascular pattern that might allow for a more confident diagnosis of hemangiopericytoma at the time of frozen section.

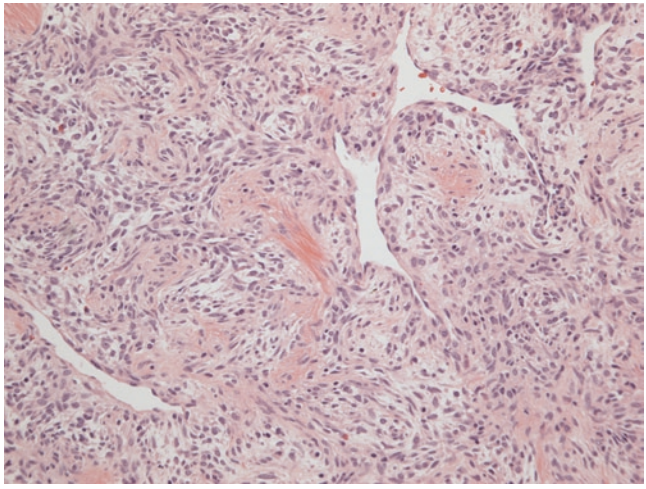

FIG. 6.23 A hemangiopericytoma demonstrating the characteristic staghorn vascular pattern, suggestive of the diagnosis.

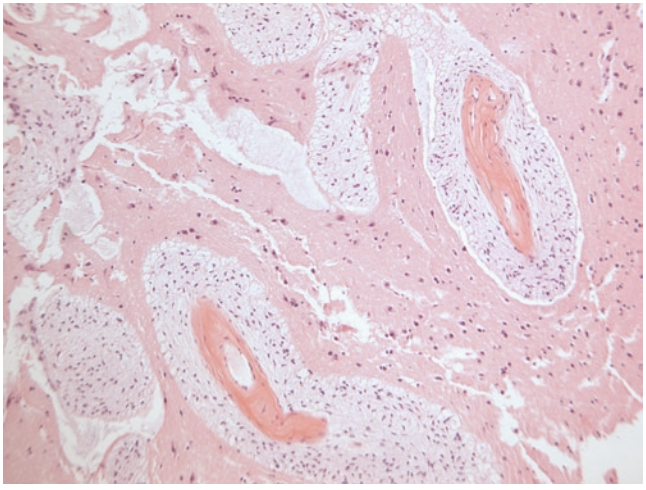

FIG. 6.24 Meningioangiomatosis is characterized by collars of meningothelial cells whorled around central blood vessels. This benign lesion should not be confused with a brain-invasive meningioma.

An entity that deserves a brief mention is meningioangiomatosis. This rare, likely developmental lesion is characterized by a proliferation of meningothelial cells around blood vessels in the parenchyma (Fig. 6.24). Cells are generally spindled and bland in appearance, wrapping around a central vessel. This lesion should not be confused with an invasive meningioma. Some of these meningioangiomatosis lesions are associated with an overlying meningioma. In some cases, the blood vessels become quite thickened and sclerotic and the meningothelial nature of the few cells that may be evident around these vessels may not be obvious on frozen section; such cases resemble a sclerosed vascular malformation.

Chapter 7
Intraventricular Lesions

Table 7.1 summarizes the differential diagnosis of the most commonly encountered intraventricular lesions. The most frequently seen entities in this general grouping include ependymomas, choroid plexus tumors, and central neurocytomas.

EPENDYMAL NEOPLASMS

The majority of ordinary ependymomas arise within the ventricles or in association with the central canal in the spinal cord. These tumors show a propensity to arise in children. Tumors arising in the fourth ventricle are more likely to occur in children as compared with tumors arising in the lateral and third ventricles, which are more common in adults. The clinical presentation, as is the case with many of the intraventricular tumors, is characterized by signs and symptoms secondary to increased intracranial pressure, due to the obstruction of the cerebrospinal fluid flow. Spinal cord tumors are more common in adults and may, on imaging studies, be associated with a syrinx, which is a cavitated, gliotic-lined defect.

The histologic diagnosis of ependymoma is dependent on the identification of rosettes or pseudorosette structures. True ependymal rosettes are marked by the arrangement of ependymal cells around a space or channel (Fig. 7.1). Pseudorosettes are marked by the arrangement of tumor cells with a perivascular fibrillar zone around a central blood vessel. These two characteristic features are best appreciated at low magnification and may be only focally present in a given tumor. On a very small, limited biopsy, particularly from the spinal cord region, there may not be sufficient tissue present to make the diagnosis. The major differential

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Table 7.1 Differential diagnosis of intraventricular lesions.

Ependymoma
Subependymoma
Choroid plexus tumors
Central neurocytoma
Chordoid glioma (third ventricle)
Subependymal giant cell astrocytoma (lateral ventricle)
Meningioma
Rosette forming glioneuronal tumor of the fourth ventricle
Germ cell tumors (third ventricle)
Craniopharyngioma (third ventricle)
Colloid cyst (third ventricle)
Any parenchymal-based tumor can grow in an exophytic pattern into the ventricle (e.g., pilocytic astrocytoma)

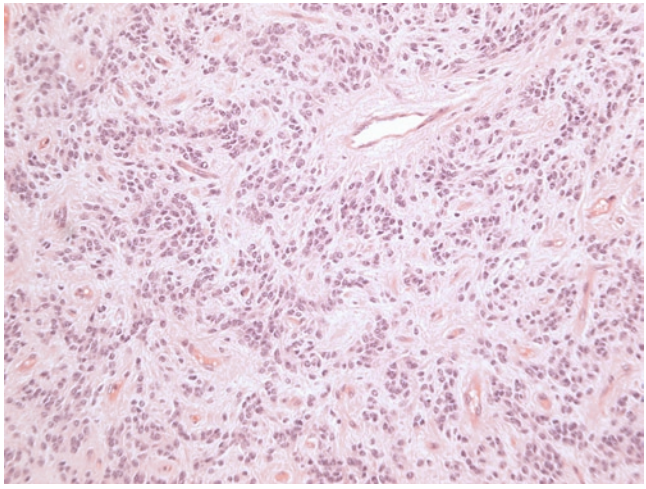

FIG. 7.1 A low-grade ependymoma marked by the presence of perivascular pseudorosettes. One needs to see either pseudorosettes or true ependymal rosettes to make a definitive diagnosis of ependymoma at the time of frozen section.

diagnostic consideration is often astrocytoma (Fig. 7.2). Failure to recognize the rosettes or pseudorosette structures may very easily result in an erroneous diagnosis of astrocytoma. This may occur if one starts looking at the frozen section slide at high magnification, focusing on the cytologic features of the cells rather than the background architecture. In cases where the small spinal cord biopsy

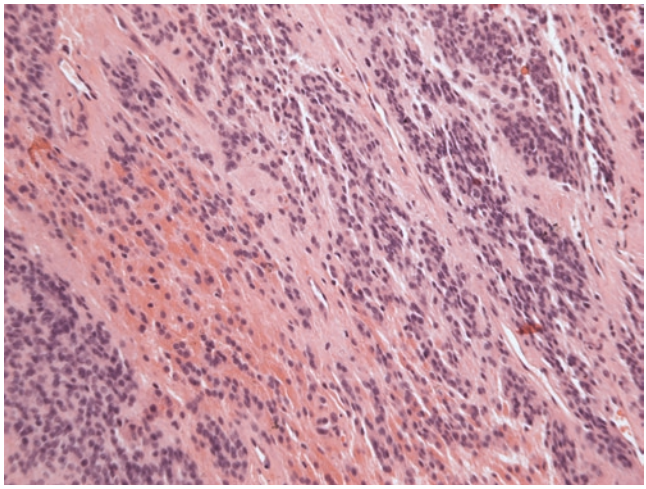

FIG. 7.2 A biopsy of a low-grade ependymoma showing no discernible rosettes. Such a biopsy may conjure a differential diagnosis of infiltrating astrocytoma. In such cases, a frozen section diagnosis of a low-grade glioma is adequate.

clearly shows a hypercellular glial neoplasm but is devoid of obvious rosettes or pseudorosette structures, a diagnosis of glioma should be made with a suggestion of the differential diagnosis. The surgical approach to ependymoma versus astrocytoma in the spinal cord is often different; a diagnosis of ependymoma may result in an attempt at a gross total resection, since these tumors are typically more circumscribed and amenable to surgical resection than the more infiltrative astrocytomas. Because of the limited size of these biopsies, a small amount of tissue may be worth triaging at the time of frozen section for potential electron microscopic evaluation. On these biopsies, distinction between ependymoma and astrocytoma may not be possible on light microscopic and immunohistochemical grounds. Ultrastructurally, ependymomas are marked by cell junctions, cilia, ciliary body attachments, and microvilli (features not present in astrocytoma).

The classic ependymoma pattern is marked by a glial background. Occasional tumors may have a more prominent epithelioid appearance (Fig. 7.3). The tanycytic variant is marked by cellular elongation, assuming a spindled appearance somewhat resembling a pilocytic-type astrocytoma or schwannoma (Fig. 7.4). Rare cases of papillary ependymoma, which may superficially resemble a choroid plexus papilloma, may occur. The core of the papilla

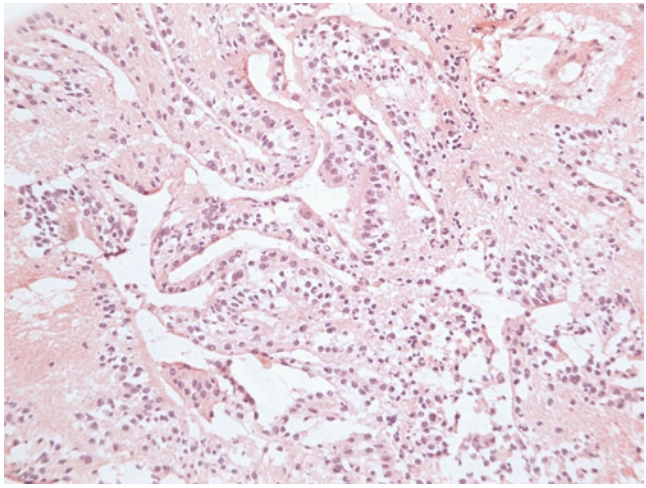

FIG. 7.3 A low-grade ependymoma with columnar cells.

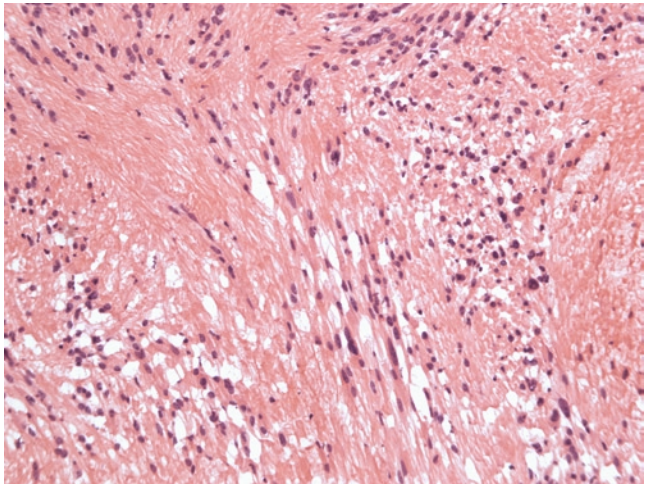

FIG. 7.4 Tanycytic ependymoma characterized by elongated spindled cells.

in the papillary ependymoma is gliovascular in contrast to the collagen vascular core of the choroid plexus papilloma. Rare cases of clear cell ependymoma, which resemble an intraventricular oligodendroglioma, have also been described. The nuclei of the

clear cell ependymomas are more frequently clefted and contain intranuclear pseudoinclusions.

Similar to astrocytomas and oligodendrogliomas, ependymomas are graded using the same histologic parameters of cellularity and atypia, mitotic activity, vascular proliferative changes, and necrosis. Precise criteria for upgrading a tumor to a grade III or anaplastic ependymoma lesion are unclear. In general, tumors with multiple worrisome features, including at least increased mitotic activity, hypercellularity, and vascular proliferation, can be elevated to a higher grade tumor (Fig. 7.5). Nuclear pleomorphism and cytomegaly are not necessarily considered worrisome features and may be present focally in an ordinary low-grade ependymoma (so-called giant cell ependymoma).

There are two variants of ependymoma that are important to distinguish from the ordinary ependymoma lesion because of their favorable prognosis. The subependymoma is a WHO grade I lesion, which arises proximal to the ventricular system in occasional patients where the tumor is large enough to present clinically and require surgical intervention. The tumor may be situated anywhere throughout the ventricular system but most commonly arises in the region of the foramen of Monro. Like ordinary ependymoma, this tumor is best evaluated microscopically

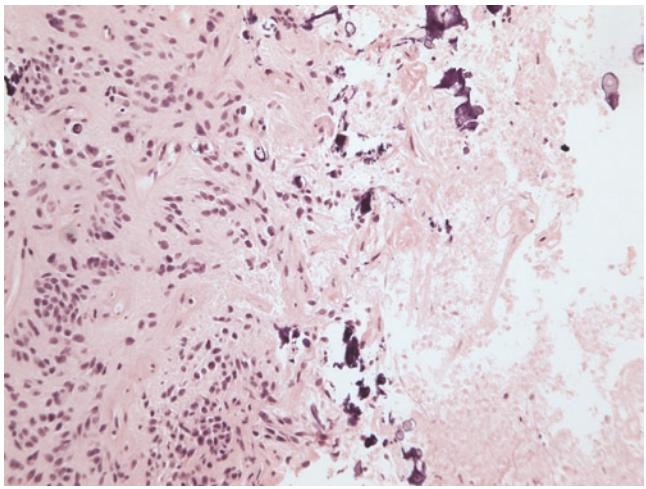

FIG. 7.5 This anaplastic ependymoma shows necrosis and calcification. Vascular proliferative changes and prominent numbers of mitotic figures were noted on permanent sections.

at lower magnification and is marked by a pattern of variable cellularity. Zones of loosely clustered cells and their nuclei alternate with zones which are almost entirely devoid of nuclei (Fig. 7.6). Microcystic change is fairly common, and occasionally, calcifications may be observed. The tumor demonstrates little nuclear pleomorphism and only rare mitotic figures are observable (Fig. 7.7). The presence of rosettes or pseudorosettes is unusual in this tumor arising in its pure form but may be seen in rare cases of hybrid subependymoma/ependymoma neoplasms.

The other ependymoma variant that is important to recognize because of its better prognosis is the myxopapillary ependymoma. These are also WHO grade I tumors that most commonly arise in the filum terminale region, typically presenting in young adults with a history of back pain. These tumors are marked by blood vessels surrounded by a mucinous stroma, which is in turn surrounded by tumor cells (Figs. 7.8 and 7.9). Recognition of the architectural pattern is important in making the diagnosis, in that a true papillary or pseudopapillary architecture is not always evident in these lesions, despite the fact that the name suggests so. Rosettes and pseudorosettes are generally lacking in the myxopapillary ependymoma.

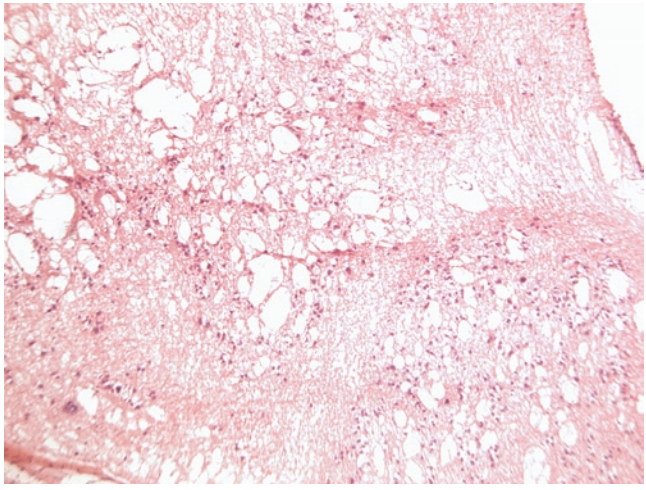

FIG. 7.6 The low magnification appearance of a subependymoma is characteristic. It is marked by islands of cells with intervening paucicellular areas ("islands of blue in a sea of pink").

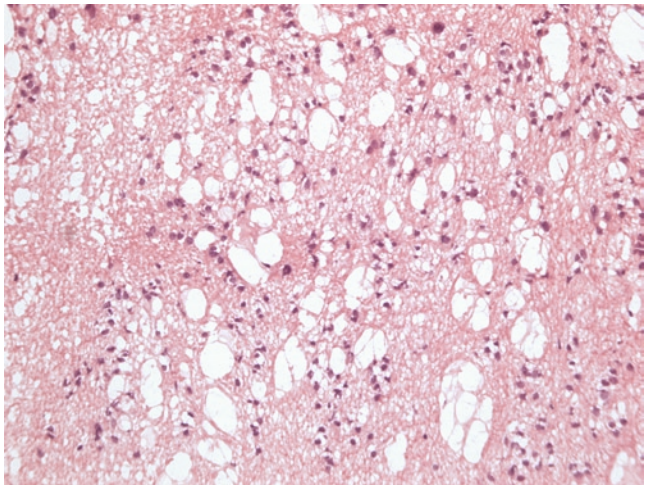

FIG. 7.7 The high magnification appearance of a subependymoma showing bland nuclei and microcystic changes. Mitotic activity is generally not encountered. Pseudorosette structures are also not seen.

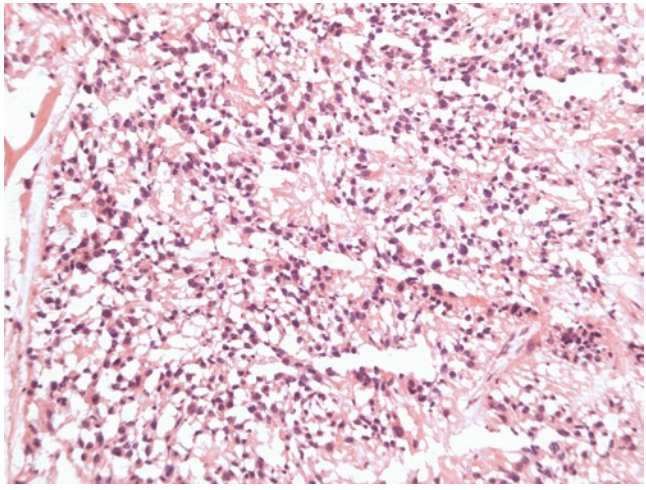

FIG. 7.8 A myxopapillary ependymoma with prominent microcystic appearance and focal architectural changes *in the lower right corner* suggestive of the diagnosis.

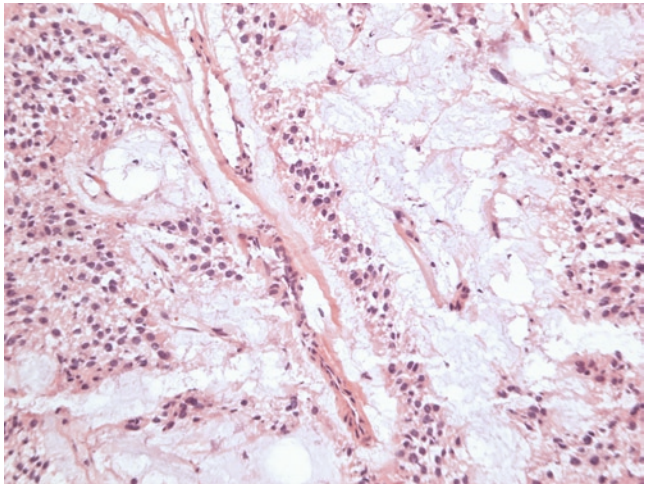

FIG. 7.9 A myxopapillary ependymoma showing microcystic mucinous areas surrounding blood vessels. The mucoid areas are in turn surrounded by tumor cells.

CHOROID PLEXUS TUMORS

The vast majority of choroid plexus neoplasms are choroid plexus papillomas, typically arising within the ventricular system in children. The fourth ventricle is the most common site of origin in adults with the lateral and third ventricles being favored in children. There is an association of choroid plexus papillomas with Li-Fraumeni and Aicardi syndromes. Histologically, the choroid plexus papilloma is marked by a hyperplasia of bland appearing choroid plexus epithelial cells arranged around fibrovascular cores in a papillary architecture (Fig. 7.10). In contrast to the normal hobnail or cobblestone profile of normal choroid plexus epithelium, the profile of the choroid plexus papilloma is often linear or smooth. Occasionally, calcification, oncocytic change, xanthomatous changes, or osseocartilaginous metaplasia may be observed (Fig. 7.11).

An occasional choroid plexus tumor demonstrates more worrisome histologic features suggestive of a higher grade lesion. Findings to be wary of in a choroid plexus tumor include increased mitotic activity (2 or more mitoses per 10 high power fields), nuclear atypia, necrosis, sheets of cells, and brain invasion. These features may be indicative of either an atypical choroid plexus papilloma (WHO grade II lesion with 2 or more mitoses per 10

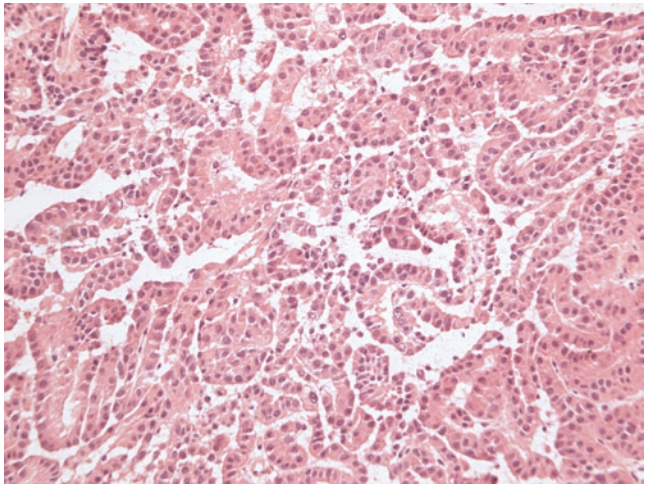

FIG. 7.10 This choroid plexus papilloma is marked by a hyperplasia of bland appearing epithelial cells. The surface contour is smooth and not cobblestoned, like normal choroid plexus epithelium.

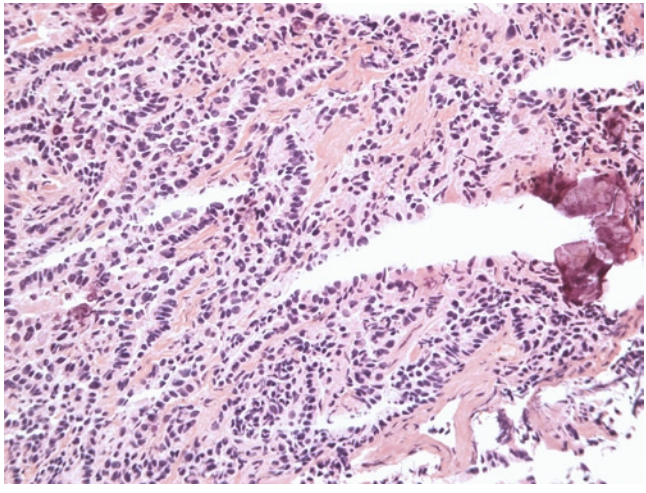

FIG. 7.11 Choroid plexus papilloma with focal microcalcifications and collagen vascular papillary cores.

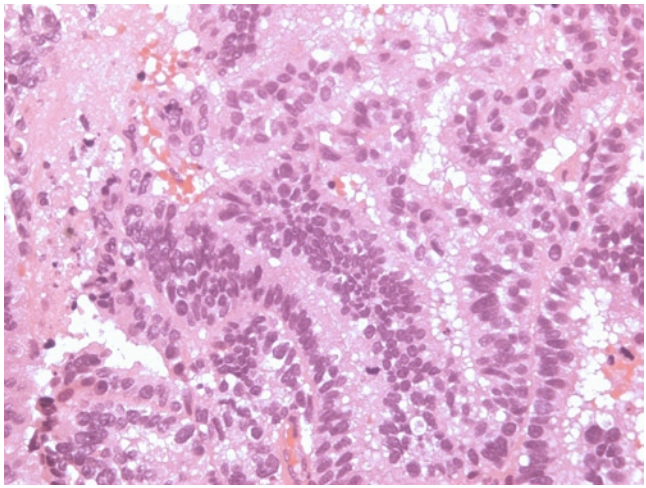

FIG. 7.12 A rare example of choroid plexus carcinoma marked by increased mitoses and necrosis. Cytologic atypia is often prominently seen.

high power fields) or a choroid plexus carcinoma (WHO grade III lesion usually marked by the presence of multiple of these features) (Fig. 7.12).

In adults with choroid plexus carcinomas, a differential diagnosis of metastatic papillary carcinoma should be entertained. The distinction is usually impossible at the time of frozen section and may require immunohistochemistry to sort out. A diagnosis of malignant papillary neoplasm with a suggestion of the differential is adequate at the time of frozen section. Discrimination of choroid plexus carcinoma from other high-grade neoplasms (including the atypical teratoid/rhabdoid tumor, neuroblastoma, or anaplastic ependymoma), which may occasionally arise in this area, needs to be considered. Again, distinction at the time frozen section may not always be possible and a more generic diagnosis of a malignant neoplasm may be as far as one can go.

CENTRAL NEUROCYTOMA

Central neurocytoma is a neural lesion that arises in young and middle-aged adults. The tumor appears well circumscribed and is marked by a proliferation of rounded cells with scant apparent cytoplasm, arranged against a fibrillary background (Fig. 7.13). The monomorphic roundness of the cells is somewhat reminiscent of an oligodendroglioma. The nuclear chromatin pattern has a salt

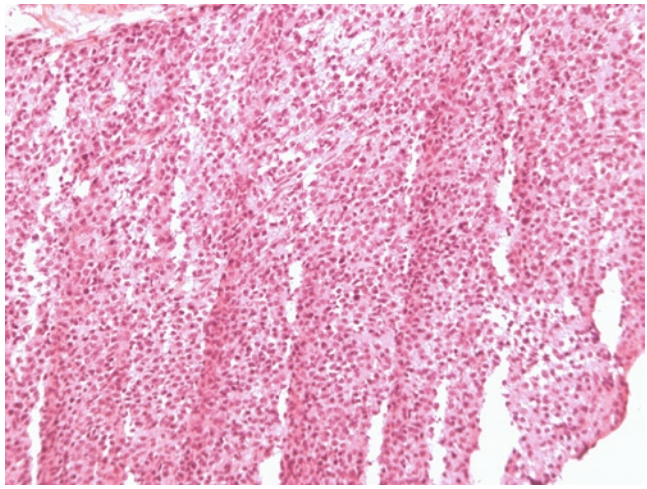

FIG. 7.13 A central neurocytoma at low magnification is marked by a sheet of monomorphic appearing cells. Monomorphic cells with generally round nuclei are also suggestive of an oligodendroglioma.

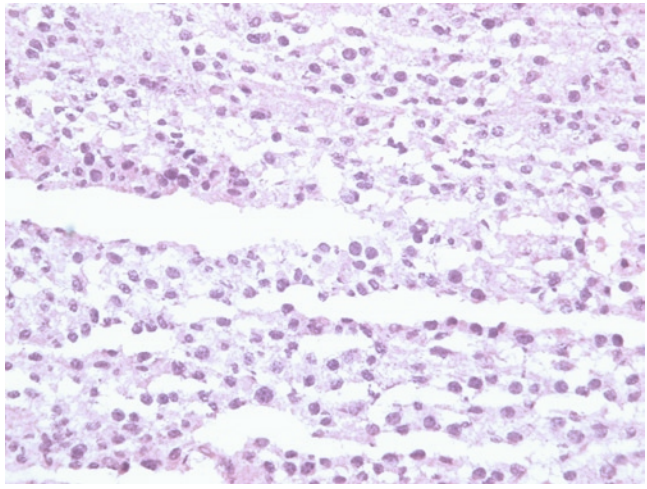

FIG. 7.14 A central neurocytoma at high magnification shows the characteristic neuroendocrine appearing nuclei.

and pepper appearance (Fig. 7.14). Similar to oligodendrogliomas, these tumors may demonstrate a prominent arcuate vascular pattern and microcalcifications. Occasional cells may show prominent nucleolation and resemble ganglion type cells.

The intraventricular location of the tumor should tip one off to the possibility of the diagnosis. Immunohistochemical stains are often required to confirm the diagnosis. Rarely, neurocytomas may be observed in the parenchyma; their histologic appearance is identical to their intraventricular counterpart. Occasionally, lipidized cells may be seen in association with cerebellar tumors (cerebellar liponeurocytoma, see Chap. 8).

OTHER TUMORS

Chordoid glioma is a well circumscribed lesion (WHO grade II) that arises in the third ventricular region. These tumors are associated with adjacent piloid gliosis. The neoplasm itself comprises epithelioid cells arranged in cords or rows against a mucoid background (Fig. 7.15). Tumor cells have prominent eosinophilic cytoplasm and generally round nuclei without prominent nucleolation. Focal infiltrates of lymphocytes and plasma cells and occasional Russell bodies are commonly observed. The tumor does not contain much in the way of mitotic activity. The location and appearance of the tumor is quite characteristic. The chordoid meningioma may resemble the chordoid glioma because of the mucoid type of background and the arrangement of cells in rows or cords. The typical

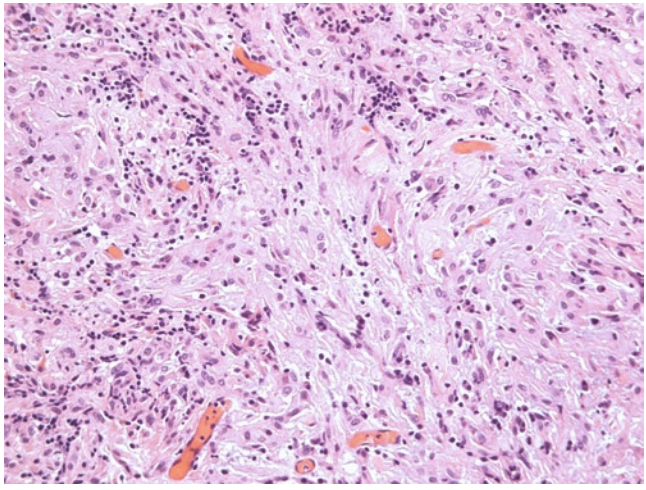

FIG. 7.15 A chordoid glioma marked by epithelioid cells arranged against a myxoid stroma. Focally, benign appearing lymphocytes are also observed. Plasma cells and occasional Russell bodies may be seen.

chordoid meningoma, however, usually demonstrates areas that resemble more ordinary meningioma.

The subependymal giant cell astrocytoma (mentioned in Chap. 5) typically involves the lateral ventricle and is associated with tuberous sclerosis. This neoplasm is marked by large cells with abundant eosinophilic cytoplasm often mixed with a second population of smaller spindled cells.

The rare rosette forming glioneuronal tumor of the fourth ventricle is a recently described entity which may be seen in either children or adults and most commonly involves the fourth ventricle, although case reports of a similar appearing tumor arising elsewhere in the central nervous system have been described. The tumor is marked by rosette-forming structures with fibrillary cores surrounded by neurocytic cells and an arrangement of neurocytic cells around blood vessels. The glial component of the tumor usually resembles a pilocytic astrocytoma with elongated cells, Rosenthal fibers, microcysts, and eosinophilic granular bodies. Because of the location, a diagnosis of pilocytic astrocytoma is likely, if there is a failure to identify the rosette-forming structures (Figs. 7.16 and 7.17). Immunohistochemistry is invariably needed to confirm the diagnosis on permanent sections.

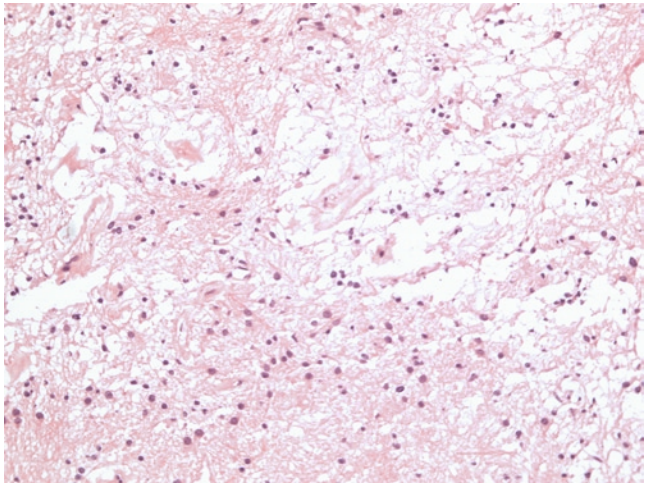

FIG. 7.16 Frozen section of a fourth ventricular tumor which is eventually diagnosed as a rosette forming glioneuronal tumor of the fourth ventricle. At frozen section, this tumor shows a microcystic appearance and resembles a low-grade glioma.

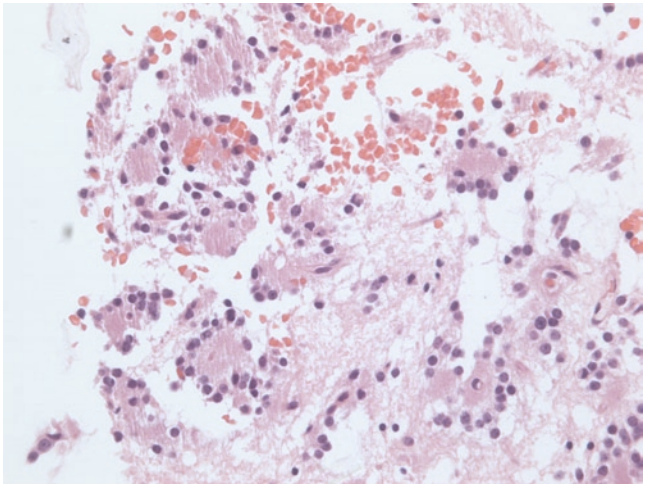

FIG. 7.17 Key to the right microscopic diagnosis of a rosette forming glioneuronal tumor of the fourth ventricle is identification of the rosette structures which are illustrated here.

Other lesions may occasionally involve the ventricular system. Cases of meningoma arising from meningothelial cells located in the ventricles may be seen. Any parenchymal-based tumor (such as pilocytic astrocytoma) arising adjacent to the ventricle can grow into the ventricle in an exophytic pattern. In the third ventricular region, germ cell tumors, (see Chap. 10), craniopharyngioma (see Chap. 9), and colloid cysts (see Chap. 3) may be encountered.

Chapter 8
Cerebellar Lesions

Table 8.1 lists the most common tumors arising in the cerebellar region and Table 8.2 lists lesions most commonly arising in the cerebellopontine angle region. A useful way of thinking about cerebellar lesions is with reference to the age of the patient.

IN KIDS

In the pediatric population, common tumors that one can encounter in this location include ependymomas and choroid plexus tumors (see Chap. 7), pilocytic astrocytoma (see Chap. 5), and medulloblastoma. Medulloblastomas are small cell, embryonal tumors arising in the cerebellum. Similar appearing tumors may be encountered elsewhere in the central nervous system and by convention have a different name based on their location. Similar appearing tumors arising in the cerebral hemispheres are referred to as neuroblastoma and similar lesions arising in the pineal gland are referred to as pineoblastoma. The majority of medulloblastomas arise in pediatric age patients, although rare cases are encountered in adults. There is an association of medulloblastoma with Gorlin's syndrome, Turcot's syndrome, and Li-Fraumeni syndrome.

These tumors are marked by a dense population of cells with generally high nuclear to cytoplasmic ratios (Figs. 8.1–8.3). Nuclei may be round to slightly elongate and cells may extend into the subarachnoid space. Apoptosis, geographic necrosis, and increased mitotic activity are common. Occasional cases may demonstrate perinecrotic pseudopalisading, not to be confused with glioblastoma, particularly the small cell variant of glioblastoma. In a minority of cases, Homer Wright pseudorosettes, marked by

R.A. Prayson and K.M. Napekoski, *Frozen Section Library: Central Nervous System*, Frozen Section Library 6, DOI 10.1007/978-1-4419-7579-9_8,

Table 8.1 Differential diagnosis of cerebellar tumors.

Pilocytic astrocytoma
Ependymoma and choroid plexus tumors arising in the ventricle
Gangliocytoma (in Cowden's disease)
Medulloblastoma
Atypical teratoid/rhabdoid tumor
Hemangioblastoma
Cerebellar liponeurocytoma
Metastasis
Other (rarely diffuse astrocytoma, oligodendroglioma, lymphoma)

Table 8.2 Differential diagnosis of cerebellopontine angle lesions.

Schwannoma
Meningioma
Epidermoid cyst
Ependymoma
Choroid plexus tumor

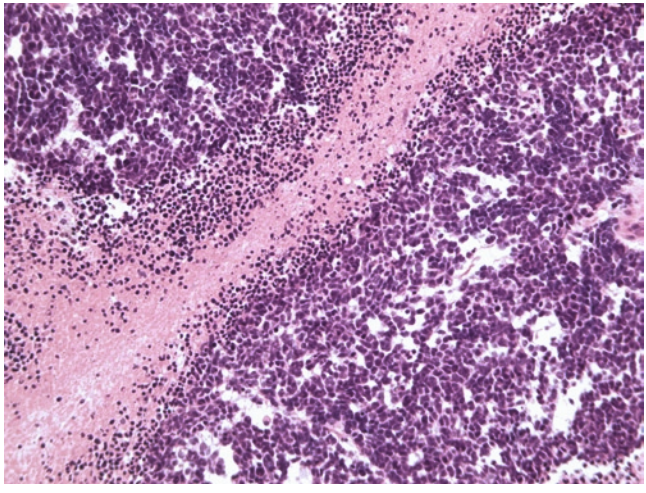

FIG. 8.1 Low magnification appearance of a medulloblastoma showing a sheet-like proliferation of small cells with an area of geographic necrosis.

tumor cells arranged around a fibrillary core, may be observable and are a useful diagnostic clue when present (Fig. 8.4).

There are a variety of subtypes that have been described that may alter the appearance of the tumor. The nodular or

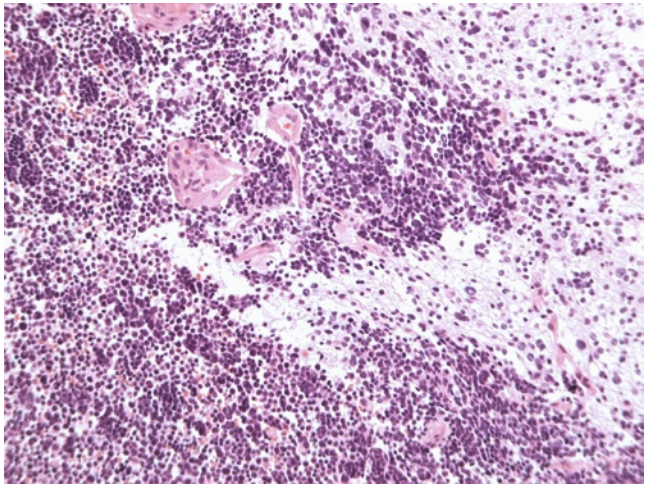

FIG. 8.2 The interface between a medulloblastoma and surrounding tissue showing infiltrating tumor cells and focal vascular proliferative changes.

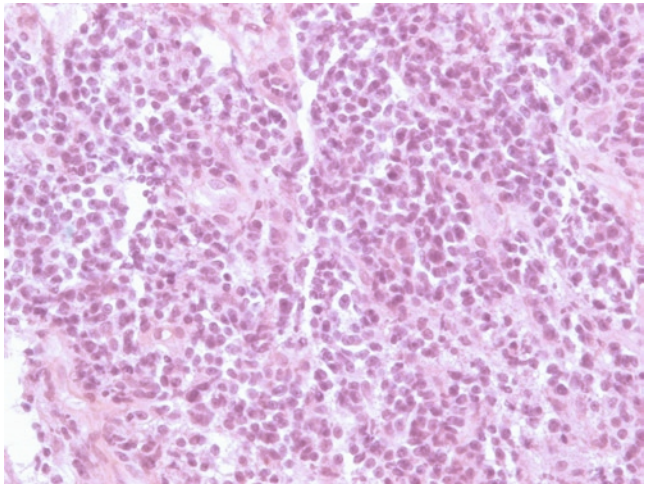

FIG. 8.3 High magnification appearance of a classic medulloblastoma showing cells with a high nuclear to cytoplasmic ratio and lack of nucleoli.

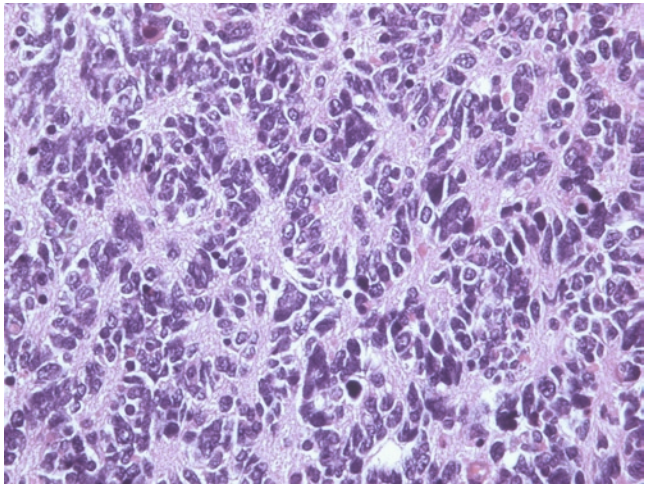

FIG. 8.4 The presence of Homer Wright pseudorosettes is a useful diagnostic clue to a diagnosis of medulloblastoma; however, they are only present in about one third of these tumors.

desmoplastic medulloblastoma is marked by pale islands of less cellular tumor; the cells in these islands are often more cytologically bland and uniform than the adjacent intervening, more classic appearing portion of the tumor. Occasional tumors may show desmoplastic changes with increased collagen, resulting in a single cell filing pattern of infiltrating tumor. Focal evidence of ganglionic or neuronal differentiation may be observed; areas of glial differentiation may also be present. Although the ganglion cells may be recognizable at the time of frozen section, evidence of glial differentiation often requires GFAP immunoreactivity for confirmation on permanent sections. Rare examples of medulloblastoma with excessive nodularity may be encountered in infants and are marked by large, nodular aggregates of less densely arranged cells with increased neuropil. Particularly challenging to diagnose are the large cell and anaplastic medulloblastomas. The anaplastic tumors are marked by increased cellular anaplasia and occasional multinucleation of tumor cells (Fig. 8.5). The nuclei are typically two to three times the size of normal cells encountered in a classic medulloblastoma. Because of the large size and anaplasia of these cells, a differential diagnosis with metastatic carcinoma can present a challenge. Similarly, large cell medulloblastomas show enlarged cells but typically demonstrate more nuclear homogeneity then their anaplastic counterparts.

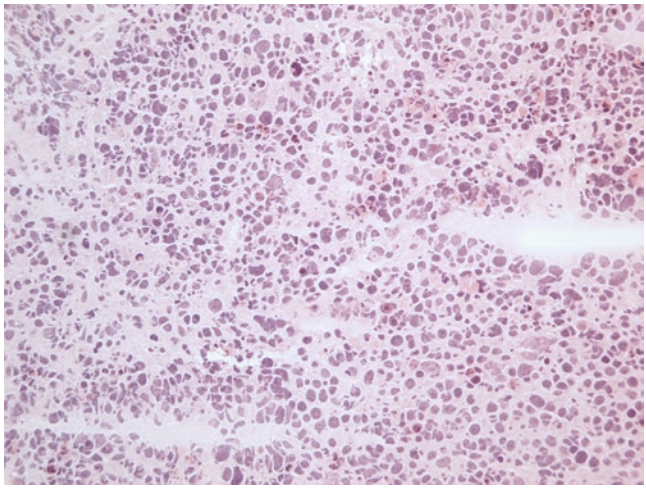

FIG. 8.5 Anaplastic medulloblastoma marked by prominent nuclear pleomorphism. Cells still maintain a high nuclear to cytoplasmic ratio.

The differential diagnosis for medulloblastoma involves a number of lesions. The distinction of medulloblastoma from the normal granular cell layer of the cerebellum needs to be kept in mind. The granular cells generally do not demonstrate evidence of apoptosis, mitotic activity, or anaplasia. This differential diagnosis, however, may be an issue in a patient whose radiologic studies show evidence of a tumor, but the biopsy is slightly off target. Differentiation of medulloblastoma from the rare atypical teratoid/rhabdoid tumor is important. This may be difficult to accomplish at frozen section. Atypical teratoid/rhabdoid tumors may arise either in the cerebellum or in the cerebral hemispheres, typically in very young patients. The tumor may demonstrate areas that are morphologically quite similar to a medulloblastoma. Characteristically, these tumors should contain a population of cells with eccentric nuclei and prominent cytoplasm marked by intracytoplasmic globular inclusions (Fig. 8.6). The diagnosis can be confirmed with molecular testing using FISH (fluorescence in situ hybridization), which demonstrates an alteration on chromosome 22 involving the INI 1 gene. Distinction is ultimately important because of the worse prognosis associated with the atypical teratoid/rhabdoid tumor.

Distinction of medulloblastoma from other small cell neoplasms, such as lymphoma or small cell glioma, may present an issue. The characteristic angiocentric pattern of lymphoma and the presence of large nucleoli in the large cell lymphoma may be

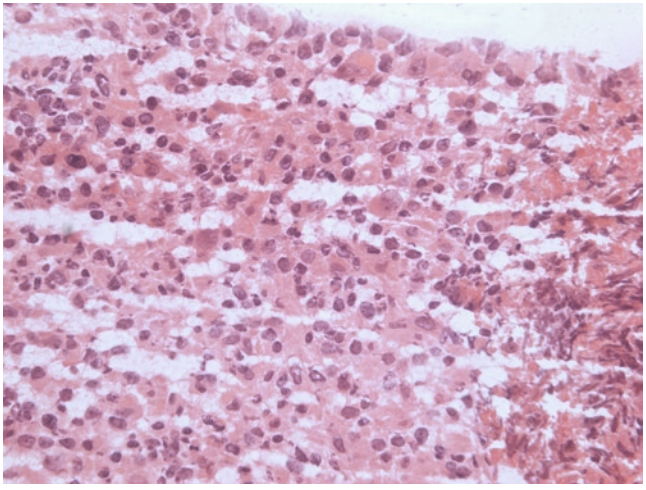

FIG. 8.6 An atypical teratoid/rhabdoid tumor marked by cells with generally more cytoplasm than a classic medulloblastoma and a population of cells with characteristic rounded cytoplasmic inclusions.

helpful in distinguishing lymphoma from medulloblastoma. Small cell gliomas will generally demonstrate areas that are less cellular and lower grade in appearance, if the lesion is adequately sampled. In adults, the differentiation of metastatic small cell carcinoma from medulloblastoma can present a challenge and usually requires immunohistochemistry to sort out. In such cases, a diagnosis of malignant small cell neoplasm with a suggestion of the differential diagnosis is adequate, if there are no clues, such as Homer Wright rosettes to suggest one tumor or the other.

In most instances, differentiating various types of medulloblastoma at the time of frozen section is not necessary, and in many cases may require ancillary stains and additional sections to accurately achieve.

IN YOUNG ADULTS

In dealing with a young adult with a cerebellar mass, the differential diagnosis includes all of the previously mentioned lesions. Additionally, diagnoses of hemangioblastoma and dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease) should be considered. Hemangioblastomas present as a cyst with enhancing nodule lesion (a similar imaging finding to the pilocytic astrocytoma and, because of this, potentially a source of confusion) (Fig. 8.7). Histologically, the hemangioblastoma is marked by an increased number of blood vessels with admixed stromal cells (Fig. 8.8).

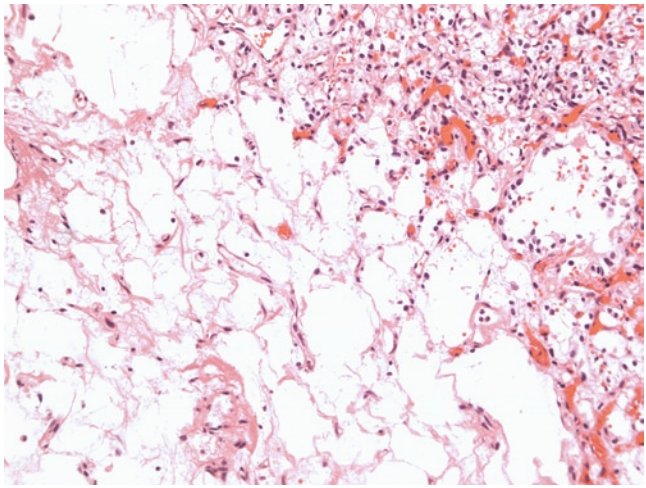

FIG. 8.7 Focally, microcystic changes may be prominently observed in a hemangioblastoma.

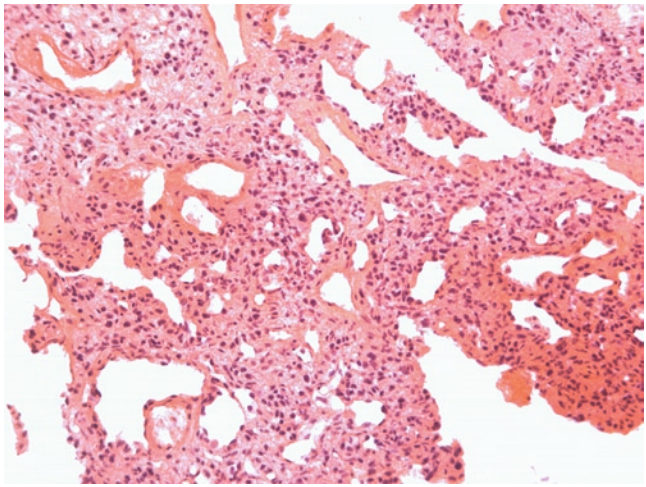

FIG. 8.8 Hemangioblastoma on frozen section demonstrating increased numbers of blood vessels, clearly indicative of a vascular lesion.

The stromal cells are marked by increased clear, vacuolated, or lightly eosinophilic cytoplasm (Fig. 8.9). Scattered nuclear pleomorphism may be evident but is not of clinical consequence. The clear quality to the cytoplasm raises a differential diagnosis of

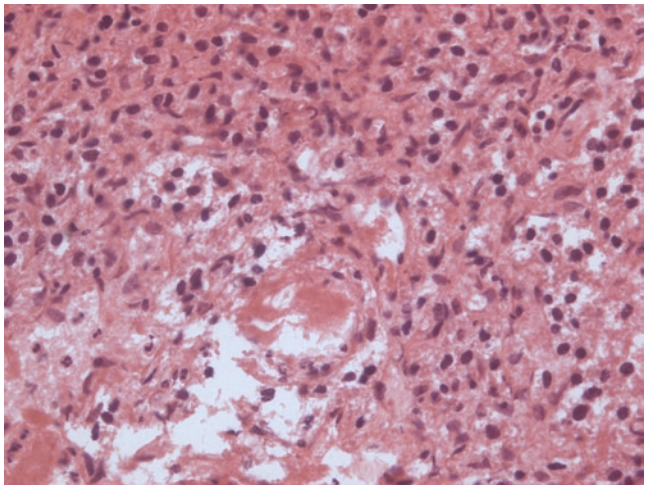

FIG. 8.9 Hemangioblastoma showing stromal cells with a clear or lightly eosinophilic cytoplasm, raising a differential diagnostic consideration with metastatic renal cell carcinoma.

metastatic clear cell carcinoma, such as renal cell carcinoma. This is particularly an issue in patients who have von Hippel Lindau syndrome, where patients are prone to develop both tumors. In the setting of von Hippel Lindau syndrome, it may be difficult to be absolutely certain whether one is dealing with a metastatic renal cell carcinoma or hemangioblastoma at the time of frozen section. In such cases, a diagnosis of clear cell neoplasm with a suggestion of the differential diagnosis is usually adequate. If the clear cell neoplasm demonstrates evidence of necrosis or increased mitotic activity or cells show prominent nucleolation, a metastatic renal cell carcinoma is more likely.

In some cases, the number of stromal cells may be focally sparse and all that is evident is the prominent vasculature. A diagnosis of vascular malformation may be considered in such cases. At times, the blood vessels may be difficult to recognize. They may not contain many red blood cells or the red blood cells may be lysed as part of the frozen section process. Also, one needs to be careful not to confuse an area of piloid gliosis with increased Rosenthal fibers adjacent to a hemangioblastoma (not an uncommon finding) with a pilocytic astrocytoma, particularly given the similarities that the two lesions might have (Fig. 8.10).

The dysplastic cerebellar gangliocytoma is a relatively uncommon lesion that represents a pure ganglion cell tumor (Fig. 8.11).

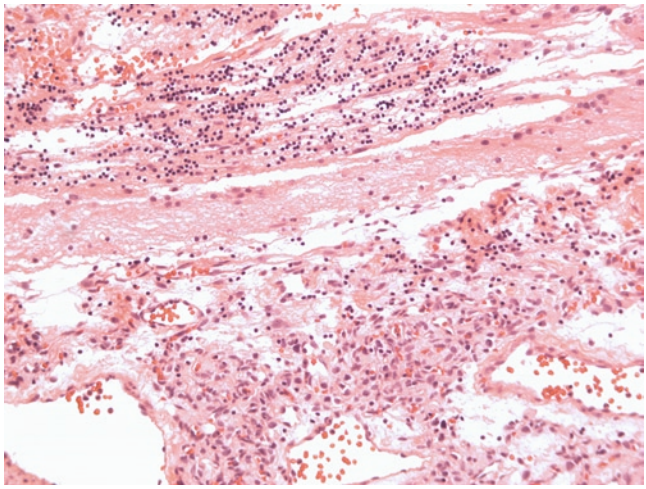

FIG. 8.10 A hemangioblastoma showing a sharp interface between the tumor and adjacent gliotic cerebellum. Occasionally, piloid gliosis with Rosenthal fibers may be observed in the adjacent tissue, which on biopsy, can conjure up a differential diagnosis with pilocytic astrocytoma.

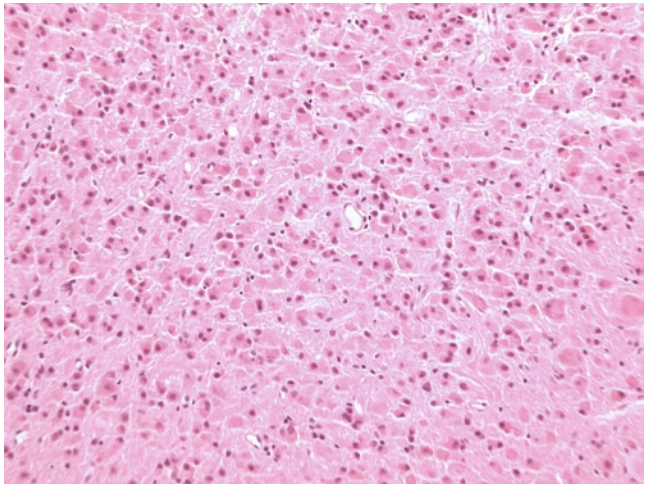

FIG. 8.11 A dysplastic cerebellar gangliocytoma marked by a proliferation of ganglionic cells.

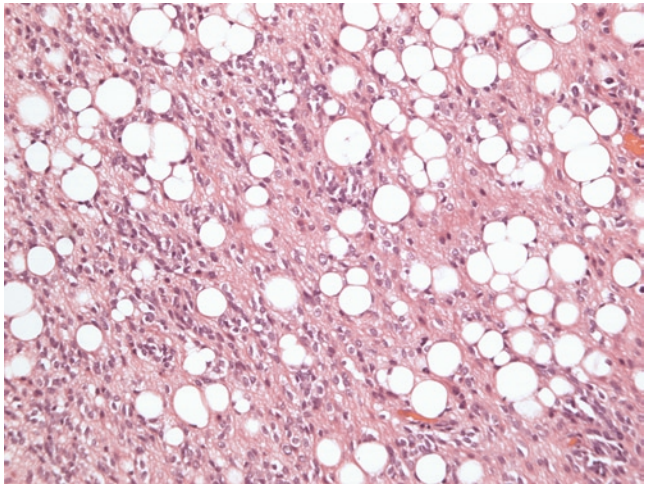

FIG. 8.12 The liponeurocytoma is marked by a proliferation of neurocytic cells intermixed with lipidized cells.

The lesion is associated with Cowden's syndrome and is important to recognize for that reason.

Rare cases of cerebellar liponeurocytoma may also occur in adults. As previously mentioned in the last chapter, these tumors have areas resembling a neurocytoma admixed with fat cells (Fig. 8.12).

IN OLDER ADULTS

In the older adult with a cerebellar mass, the primary consideration and overwhelmingly most commonly encountered lesion is a metastatic neoplasm (see Chap. 4). On occasion, one may encounter ordinary appearing diffuse astrocytomas, oligodendrogliomas, and lymphomas as primary neoplasms in this location.

The cerebellopontine angle region deserves special consideration because of the differential diagnosis. The most commonly encountered lesions in this location have all been described in the previous chapters. Of particular note is the differential diagnosis of a fibrous meningioma versus a schwannoma (see Chap. 6).

Chapter 9
Pituitary Gland and Sellar Lesions

Table 9.1 summarizes the differential diagnostic considerations when one is confronted with a lesion located in the pituitary gland or sellar area.

MOST TUMORS ARE ADENOMAS

In terms of pituitary gland lesions, the most commonly encountered neoplasm in the surgical pathology suite is the pituitary adenoma. These tumors arise in the adenohypophyseal or anterior portion of the gland. Clinically, they present either as a mass, frequently compressing adjacent structures, such as the optic nerve, or causing signs and symptoms related to the production of pituitary hormones. If the adenoma is secreting a hormone, the most common secretory products are prolactin, growth hormone, and adrenocorticotropic hormone (ACTH). About 20% of adenomas may not be secreting any active hormone. About 10–15% of adenomas may be secreting more than one hormonal product.

Histologically, adenomas are marked by a proliferation of monomorphic appearing cells. The normal anterior pituitary gland is marked by nests of epithelioid cells separated by a delicate fibrovascular network (Fig. 9.1). The epithelioid cells may have cytoplasm which is either eosinophilic, basophilic, or clear/lightly eosinophilic (chromophobic). In a normal gland, there is an admixture of these various cell types in each nest. However, there is some regional variability with regard to the types of cells that are seen, i.e., nests in some areas of the gland may have a predominance of eosinophilic cells; whereas, other nests may demonstrate a predominance of basophilic cells. There is not a

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Table 9.1 Differential diagnosis of pituitary/sellar lesions.

Pituitary adenoma
Granular cell tumor
Pituicytoma
Craniopharyngioma
Germ cell tumors
Rathke's cleft cyst
Adjacent lesion growing into the region (meningioma, glioma)
Lymphocytic hypophysitis

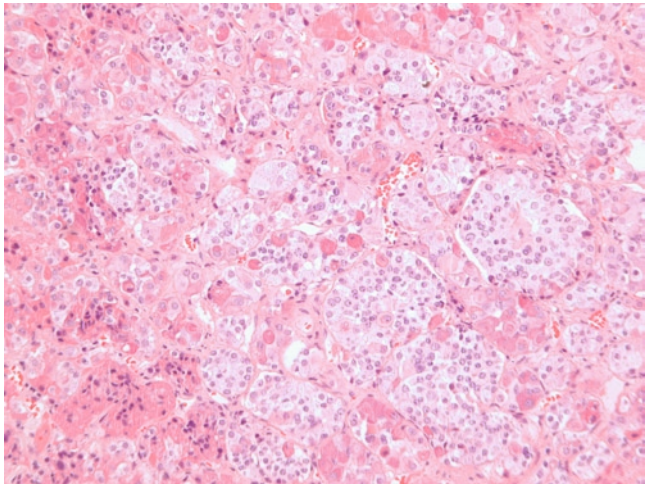

FIG. 9.1 A section from a normal adenohypophysis showing nests of cells separated by a delicate fibrovascular network. Each nest comprises a mixture of cell types with regard to cytoplasmic staining (acidophilic, basophilic, and chromophobic).

reliable correlation between the cells seen histologically and the hormonal production of the adenoma.

The adenoma is marked by a monomorphic proliferation of cells, typically arranged in a sheet-like configuration (Fig. 9.2). Nuclear pleomorphism may be focally prominent in an adenoma and does not have any significance. Tumors may show a focal trabecular pattern or discohesiveness of cells resulting in pseudorosette-like structures, and they may demonstrate areas of necrosis (apoplexy) (Fig. 9.3). Microcalcifications may also be present.

Entities to consider in a differential diagnosis of pituitary adenoma include the rare invasive adenoma and pituitary carcinoma. An invasive adenoma is defined by the extent of tumor infiltration into

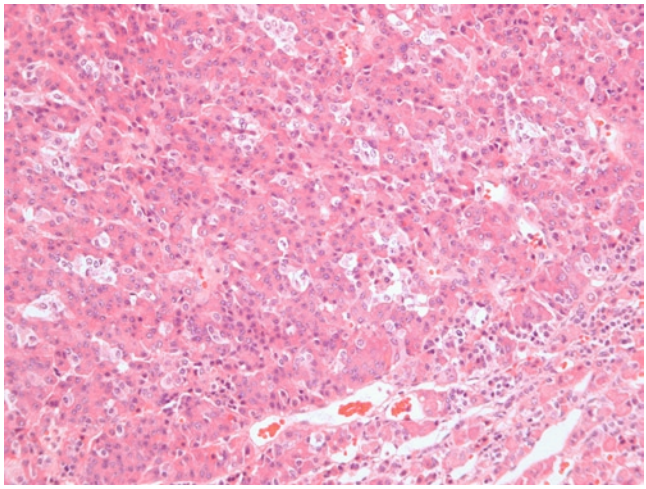

FIG. 9.2 An acidophilic adenoma with adjacent normal pituitary gland (*lower right corner*). The adenoma is marked by a sheet-like proliferation of monomorphic appearing cells.

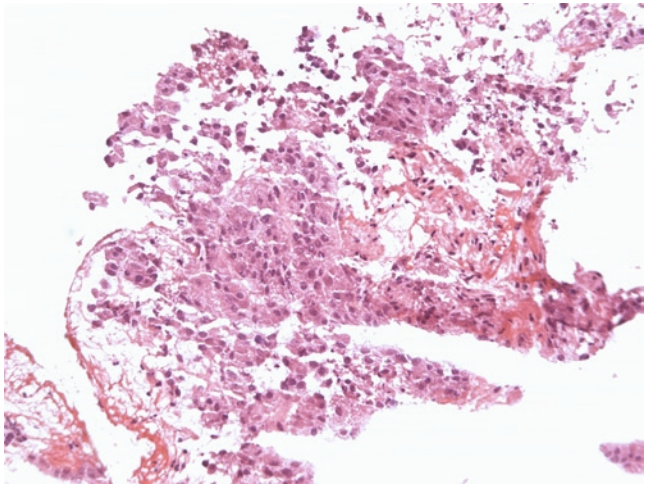

FIG. 9.3 A pituitary adenoma marked by a proliferation of cells with evidence of discohesion.

adjacent structures; this diagnosis is best made in conjunction with the imaging and intraoperative impression of the tumor and its distribution and does not need to be made at the time of frozen section.

A diagnosis of pituitary carcinoma requires the demonstration of noncontiguous spread. There is no reliable way, based on the histologic appearance of an adenoma, to predict which tumors behave more aggressively. One needs to be aware that occasional adenomas may arise in unusual or ectopic locations in the head and neck region; in these unusual locations, a diagnosis at frozen section may be difficult, and there may be a need to evaluate the neoplasm with immunohistochemistry to eventually arrive at the proper diagnosis. In such cases, a diagnosis of an epithelioid neoplasm may be all that one is comfortable making at the time of frozen section.

BUT NOT ALL OF THEM

The granular cell tumor is the most common tumor arising in the neurohypophysis or posterior pituitary gland. This lesion can also enter into the differential diagnosis of a pituitary adenoma. The granular cell tumor, like the pituitary adenoma, is characterized by a sheet-like proliferation of monomorphic appearing cells with abundant eosinophilic cytoplasm. Careful attention to the quality of the cytoplasm shows more granularity than is usually seen in the typical adenoma (Fig. 9.4). The granular cells often have more cytoplasm than the cells of most adenomas.

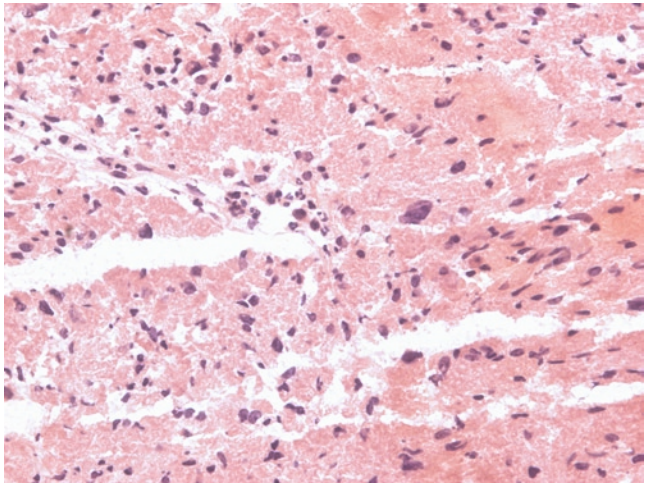

FIG. 9.4 A granular cell tumor arising in the neurohypophysis. The cells in a granular cell tumor contain more cytoplasm than a typical adenoma and are marked by a granular quality due to an accumulation of lysosomes. Nuclear pleomorphism in a granular cell tumor has no clinical significance.

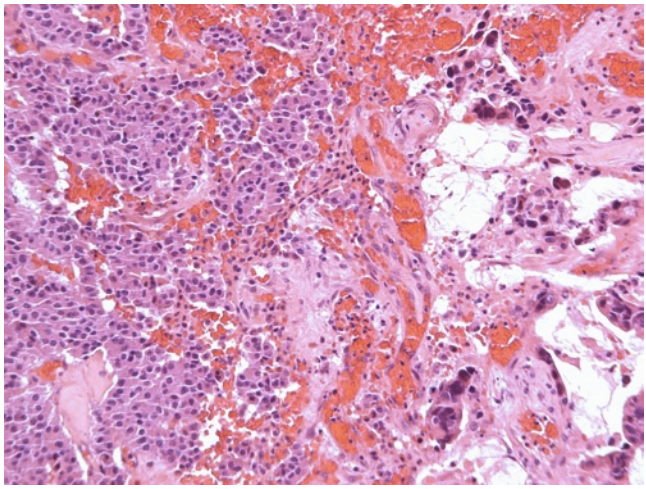

FIG. 9.5 A metastatic colonic adenocarcinoma (*right*) involving a pituitary adenoma (*left*).

The other entity to consider in the differential diagnosis of a pituitary adenoma is metastatic carcinoma. In general, metastases tend to be more pleomorphic, may demonstrate evidence of glandular differentiation or mucin production, and often are marked by prominent nucleoli (Fig. 9.5). Differentiation of a neuroendocrine carcinoma or a bland metastatic adenocarcinoma from sites, such as breast, may be more difficult to distinguish definitively at frozen section and may require additional stains on permanent section to differentiate.

A pituicytoma is a well-differentiated (WHO grade I) lesion arising in the posterior pituitary gland. The tumor is generally well circumscribed and is marked by a mixture of rounded to spindled cells with prominent eosinophilic cytoplasm and small nucleoli (Fig. 9.6). Necrosis and mitotic activity are rather uncommon. These tumors are similar in appearance to a glioma, particularly a pilocytic astrocytoma, but lack Rosenthal fibers, eosinophilic granular bodies, and microcystic changes. In less cellular areas of the tumor, distinction of the tumor from normal neurohypophysis may be an issue at the time of frozen section.

Occasionally, nonneoplastic lesions in the pituitary gland are the target of a biopsy. The Rathke's cleft cyst has been previously discussed in Chap. 3. Rarely, lymphocytic hypophysitis may present as a mass-like lesion, usually in a postpartum

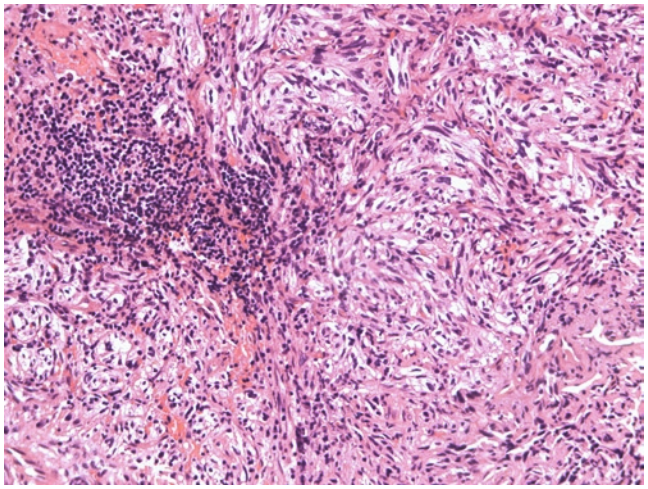

FIG. 9.6 A pituicytoma marked by a proliferation of spindled cells resembling a glioma. Lymphocytes are often present in these tumors.

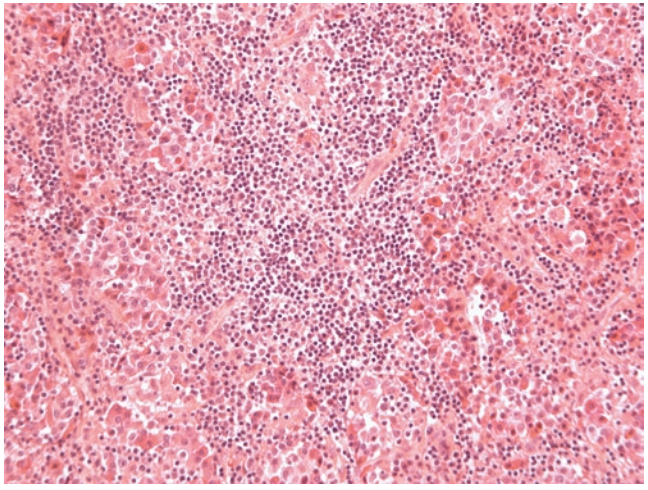

FIG. 9.7 Marked chronic inflammation consisting of lymphocytes and plasma cells involving the adenohypophysis in a case of lymphocytic hypophysitis.

woman. Histologically, these lesions are marked by a prominent lymphoplasmacytic infiltrate with destruction of the epithelioid cells in the anterior pituitary gland and eventual development of fibrosis (Fig. 9.7). This results clinically in pituitary insufficiency.

Distinction of this entity from a potential infectious disease or lymphomatous involvement of the gland should be entertained before a diagnosis is made. One may encounter an abscess or evidence of granulomatous inflammation secondary to infection or sarcoidosis in the pituitary.

CRANIOPHARYNGIOMA

Craniopharyngiomas are low grade (WHO grade I) tumors that most commonly arise in the sellar or suprasellar region. Rare cases have been described in other locations, including the pineal gland, cerebellopontine angle region, posterior fossa, and sphenoid. Grossly, the lesion often has a cystic component and the cyst fluid has been likened to motor oil. Microscopically, the most common pattern (adamantinomatous) is marked by islands of epithelial cells with a distinctive peripheral basaloid layer and a more central, loosely textured stellate reticulum (Fig. 9.8). Intervening tissue is marked by fibrosis and calcification. Leakage of the fluid may elicit a xanthogranulomatous reaction complete with inflammatory cells, giant cells, and pigmented material. Prominent gliosis and Rosenthal fiber formation may be observed in the surrounding brain tissue (Fig. 9.9). Variable amounts of wet keratin may be present in association with the tumor.

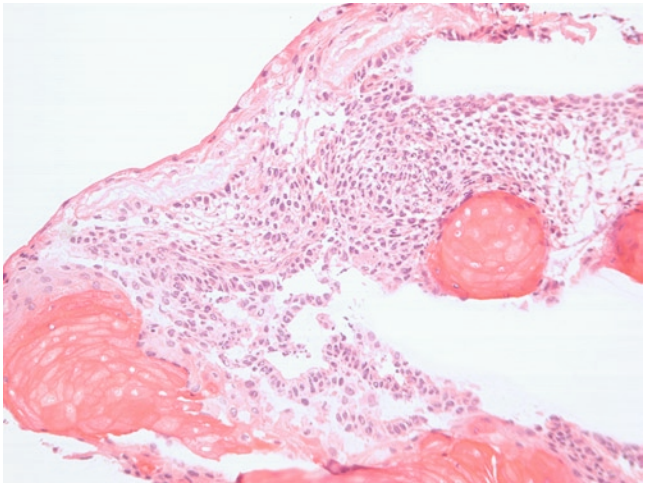

FIG. 9.8 Adamantinomatous craniopharyngioma marked by epithelioid islands of cells (peripheral basaloid cells and central stellate reticulum with wet keratin material).

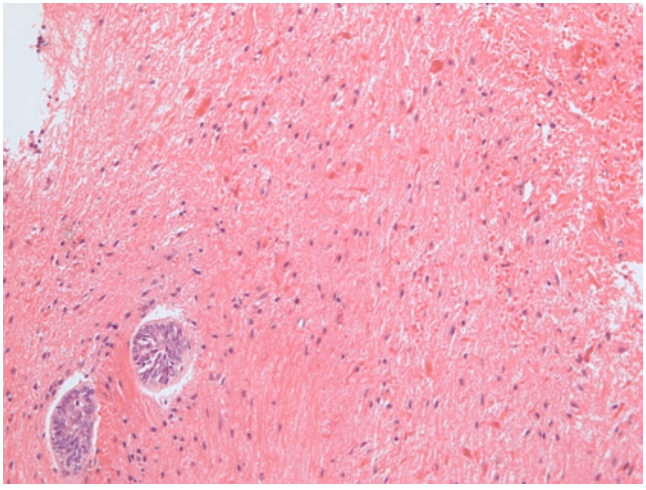

FIG. 9.9 Rosenthal fibers adjacent to a craniopharyngioma.

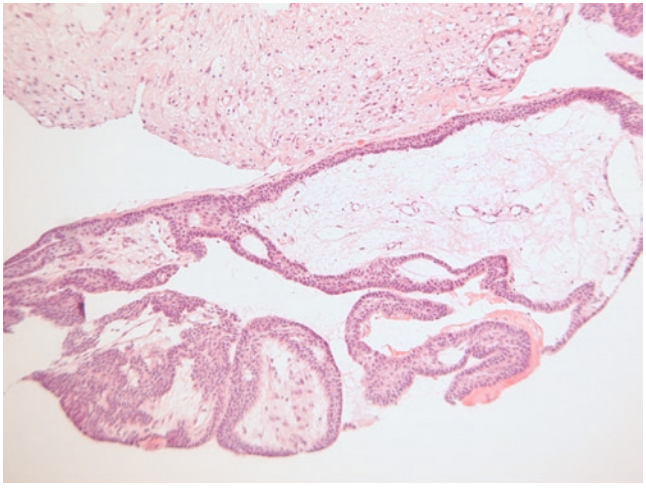

FIG. 9.10 A papillary craniopharyngioma marked by squamoid cells arranged on fibrovascular cores.

Craniopharyngiomas may demonstrate a papillary architectural pattern. These lesions are marked by solid sheets of squamoid epithelial cells with prominent fibrovascular stromal cores (Fig. 9.10). These tumor cells are frequently discohesive and may

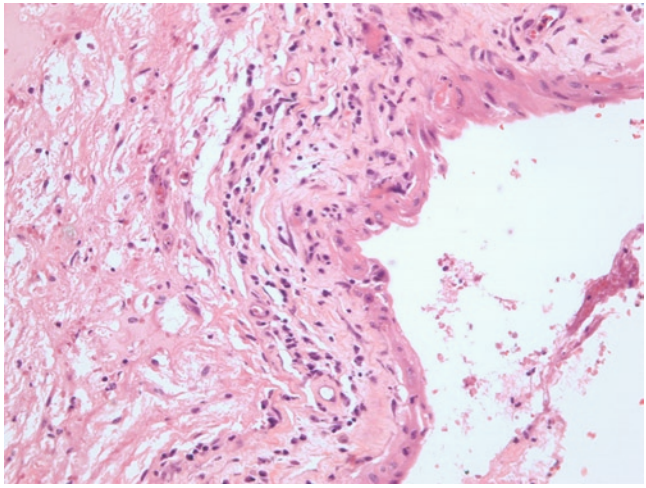

FIG. 9.11 A cystic craniopharyngioma lined by squamoid-type epithelium. The lining cells lack keratohyaline granules, which would be seen in an epidermoid cyst.

create a prominent pseudopapillary architectural pattern. Focally, goblet and/or ciliated cells might be observed.

In classic cases, the diagnosis of craniopharyngioma is fairly straightforward, since the morphologic appearance is distinctive. In some cases, the frozen section may only be comprised of the wet keratin material. In these instances, a diagnosis of craniopharyngioma can be strongly suggested. An epidermoid cyst can resemble a cystic craniopharyngioma (Fig. 9.11). The epidermoid cyst, in contrast to a cystic craniopharyngioma, contains cells with keratohyaline granules and generally lacks the wet keratin and calcifications. Adnexal structures suggestive of a dermoid cyst are absent. Occasionally, differentiation of a papillary craniopharyngioma pattern from a Rathke's cleft cyst with extensive squamous metaplasia may present a challenge. Usually, more solid areas of the tumor provide a clue to the craniopharyngioma diagnosis.

In addition to the above lesions, which are fairly unique to this location, one needs to remember that tumors growing in from surrounding areas may involve the pituitary and sellar region. Occasionally, meningiomas, gliomas, and lymphomas may be encountered in this location.

Chapter 10
Pineal Gland Lesions

Lesions arising in the pineal gland present a particular challenge in the context of intraoperative consultation. The organ is difficult to access, and so biopsies are often small in size. Lesions arising in this area are not frequent, and therefore, the experience level of most pathologists is relatively lacking. Table 10.1 summarizes the differential diagnosis of the most commonly encountered lesions in this location.

GERMINOMAS AND GERM CELL TUMORS

The most frequently encountered neoplasm in the pineal gland is the germinoma (over half of pineal gland tumors are germinomas). For the pathologist faced with a frozen section case of a pineal gland mass, this is somewhat fortuitous, in that most practicing pathologists are familiar with the appearance of a germinoma. The tumor is histologically identical to a testicular seminoma or dysgerminoma of the ovary. Germinoma is marked by a proliferation of large germ cells with abundant eosinophilic cytoplasm, large nuclei, and prominent nucleoli (Figs. 10.1 and 10.2). Remember, occasional syncytiotrophoblastic giant cells and nonnecrotizing granulomas may be observed. Mixed with the large germ cells is a population of small, benign appearing lymphocytes. Mitotic figures may be readily identifiable. A careful search for other germ cell components is warranted, in that some of these tumors demonstrate multiple components (mixed germ cell tumors). Teratoma (both mature and immature), yolk sac tumor, embryonal carcinoma, and choriocarcinoma components may be present, either in pure form or as part of a mixed germ cell

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Table 10.1 Differential diagnosis of pineal lesions.

Germ cell tumors (germinoma – most common; teratomas, yolk sac tumor, embryonal carcinoma, choriocarcinoma, mixed type)
Pineoblastoma
Pineocytoma
Pineal parenchymal tumor of intermediate differentiation
Papillary tumor of the pineal region
Pineal cyst

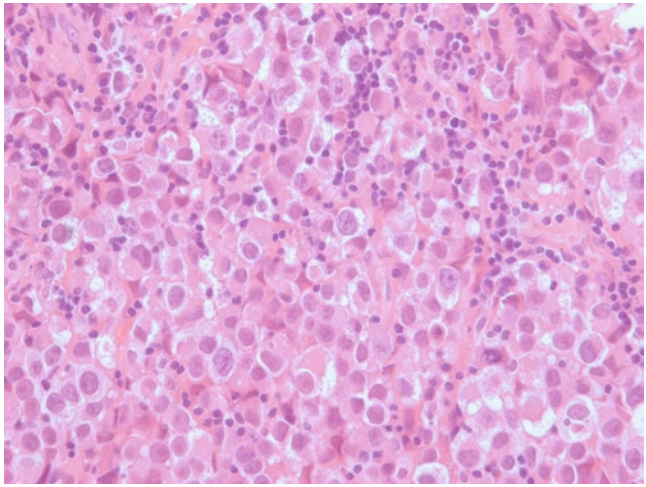

FIG. 10.1 Germinoma is the most common tumor of the pineal gland. The germinoma is marked by a proliferation of large germ cells with prominent nucleoli and abundant lightly eosinophilic or cleared cytoplasm, often intermixed with benign appearing lymphocytes.

tumor. The histologic features of the various germ cell tumors are identical to their counterpart's appearance in the ovary and testis (Figs. 10.3–10.5).

EVERYTHING ELSE

Pineal parenchymal tumors run the gamut from the poorly differentiated, small blue cell tumor, pineoblastoma, to the better differentiated pineocytoma. These tumors collectively are not as common as the germ cell neoplasms. Pineoblastoma histologically resembles a medulloblastoma of the cerebellum. These rare tumors are more commonly encountered in children, and demonstrate many of the same histologic features of medulloblastoma,

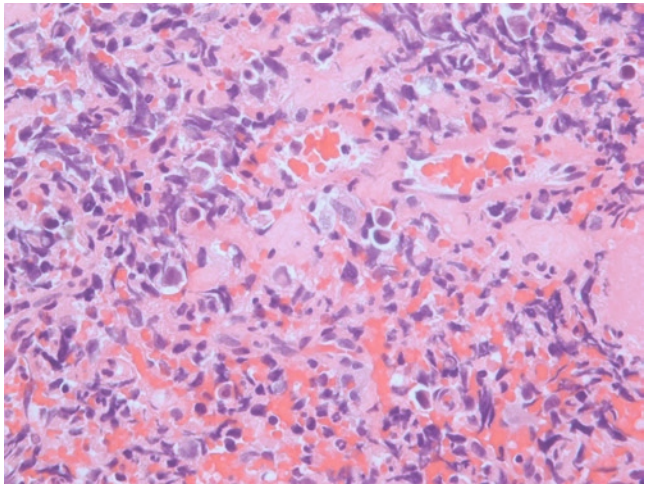

FIG. 10.2 Biopsies from the pineal gland are often small and may be distorted by crush artifact, as in this case. Despite that, occasional large cells and a population of smaller lymphoid cells are noted, suggestive of a germinoma.

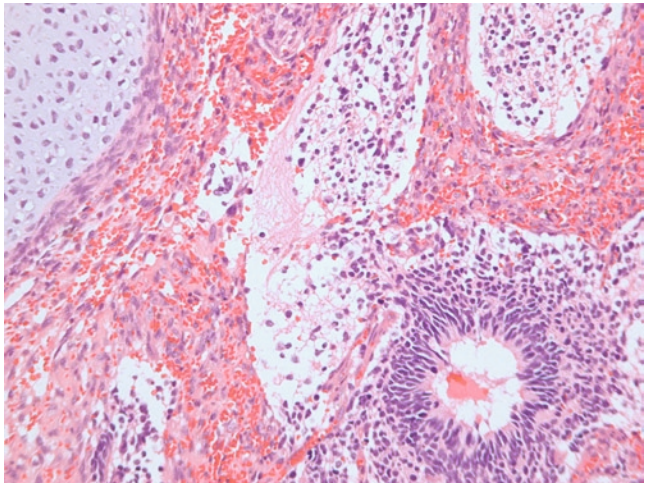

FIG. 10.3 This immature teratoma shows an area of chondroid differentiation on the left and a more primitive neuroblastic rosette on the right lower aspect. This tumor also contained a small component of germinoma and represented a mixed germ cell tumor.

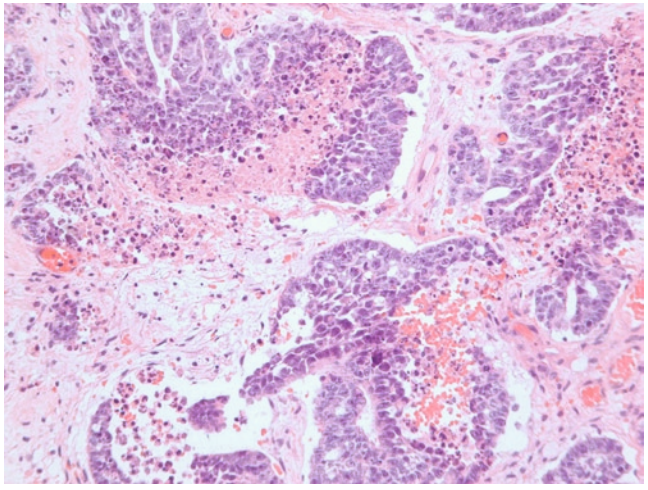

FIG. 10.4 An embryonal carcinoma arising in the pineal gland region characterized by large, atypical prominently nucleolated cells with geographic necrosis.

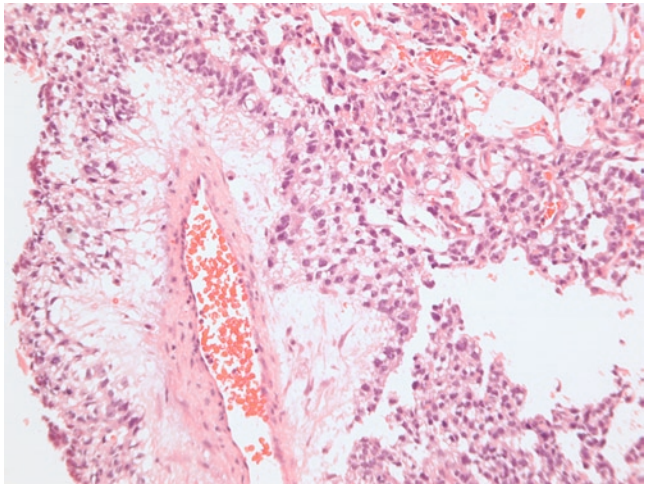

FIG. 10.5 This mixed germ cell tumor contained an area of yolk sac tumor, seen here. A lacy network of delicate epithelium marks the vitelline pattern of the yolk sac tumor. More cuboidal epithelial cells and hyaline droplets are common features of these tumors.

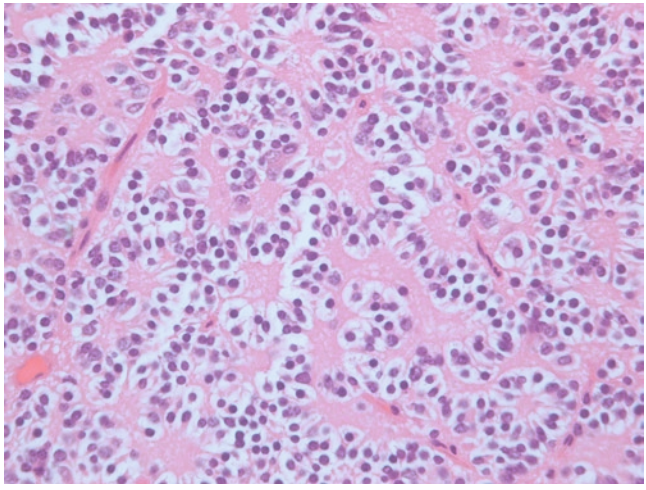

FIG. 10.6 A pineocytoma marked by the presence of pineocytomatous pseudorosettes in which tumor cells are arranged around a fibrillary core.

including a dense cellularity, high nuclear to cytoplasmic ratio, prominent mitotic activity, areas of necrosis, and vascular proliferative changes. Large cell or anaplastic features may be present in some tumors. Homer Wright neuroblastic pseudorosettes or Flexner –Wintersteiner true rosettes may be observed in a subset of these tumors.

The pineocytoma is a low-grade (WHO grade I) neoplasm marked by the presence of pineocytomatous rosettes in which the tumor cells are arranged against a fibrillary core (Fig. 10.6). Small biopsies at frozen section may demonstrate only the solid or nonrosette-forming areas of the tumor, which may make distinction from normal pineal gland tissue difficult, if not impossible (Fig. 10.7). Pineal tumors can demonstrate nuclear pleomorphism and increased cellularity. Rarely, mature appearing ganglion cells may be observed in the tumor and cause potential confusion with a gangliogliomа. In contrast to the normal pineal gland, the pineocytoma does not have a lobular architecture.

The pineal parenchymal tumor of intermediate differentiation is a lesion that is characterized by increased cell density, as compared with ordinary pineocytomas, increased cytologic anaplasia, and increased mitoses. The tumor cells have a higher nuclear to cytoplasmic ratio than the cells seen in a pineocytoma. In some

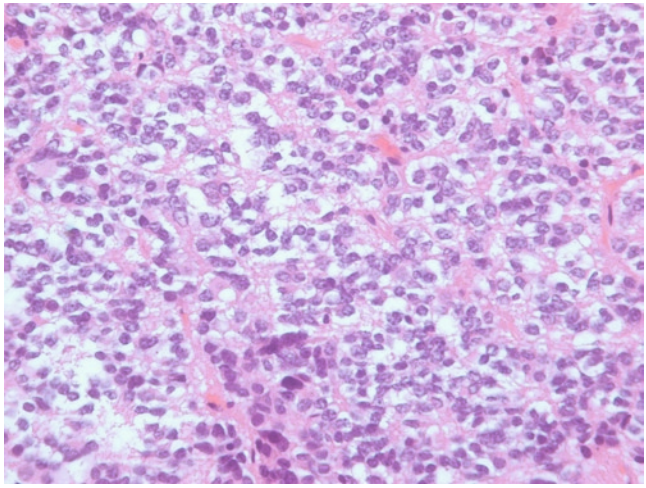

FIG. 10.7 A solid area of a pineocytoma devoid of pineocytomatous rosettes. This lesion is more difficult to classify at frozen section and may be a challenge to differentiate from normal pineal gland tissue.

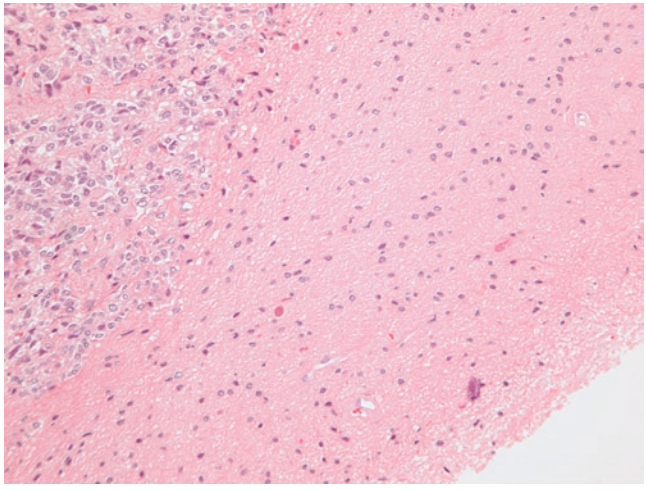

FIG. 10.8 The lining of a benign pineal cyst marked by prominent gliosis and Rosenthal fibers.

cases, a frozen section diagnosis suggesting a pineal parenchymal tumor and deferring definitive classification, pending review of permanent sections, is appropriate.

Rare examples of a papillary tumor of the pineal region have been described. These usually present in adults as an enhancing, well-demarcated neoplasm. Microscopically, the tumor is marked by a pseudopapillary architectural pattern with epithelioid appearing cells characterized by discrete cell boarders. Cytoplasmic vacuolization is fairly common. Mitotic counts are variable and vascular sclerosis may be present. Necrosis and vascular proliferative changes are not common.

Cysts arising in the pineal gland are common and may occasionally be the accidental target of a biopsy (see Chap. 3). These cysts are characterized by a gliotic wall often punctuated by Rosenthal fibers (Fig. 10.8). They should not be confused with low-grade gliomas, such as pilocytic astrocytoma or pineocytoma. Occasionally, tumors arising in the neighboring region may expand to involve the pineal gland area.

Chapter 11
Spinal Cord Lesions

There are a whole host of lesions that may involve the spinal cord and be the target of a biopsy. These lesions are summarized in Table 11.1 according to their location within the spinal cord parenchyma itself (intramedullary), between the spinal cord and dura (intradural, extramedullary), and arising outside the dura (extradural). Most of these lesions have been addressed elsewhere in this book in previous chapters.

INTRAMEDULLARY

As previously discussed in Chap. 7, biopsies from the intramedullary compartment tend to be quite small. The most common tumors arising in the intramedullary location include ependymomas and astrocytomas. Diffuse and pilocytic type astrocytomas may be encountered. Additionally, ependymoma variants, including myxopapillary ependymoma and subependymoma may be seen. One may also encounter hemangioblastomas and occasional metastases to the cord parenchyma.

In the filum terminale region, paragangliomas may arise. These tumors appear the same here as they do when they arise elsewhere in the body. Typically, they are well-circumscribed masses marked by a proliferation of cells which are arranged in a nested or acinar architecture (zellballen) and limited by spindled sustentacular cells (Fig. 11.1). Ganglionic cells, nuclear pleomorphism, or alternative architectural patterns, such as ribboning or trabeculae, may be seen in a subset of paragangliomas. Occasionally, pleomorphic nuclei may also be observed but have no known significance (Fig. 11.2). The biggest challenge at frozen section is the fact that the typical nested architectural pattern may not be obvious and

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Table 11.1 Differential diagnosis of spinal cord lesions.

Intramedullary
Ependymoma
Myxopapillary ependymoma
Subependymoma
Astrocytoma – diffuse and pilocytic types
Hemangioblastoma
Paraganglioma (filum terminale region)
Metastasis
Nonneoplastic lesions (demyelinating disease, granulomatous disease, vascular malformations)
Intradural, extramedullary
Schwannoma
Meningioma
Sarcoma
Solitary fibrous tumor
Melanocytic neoplasms (e.g., melanocytoma)
Metastasis
Nonneoplastic lesions (endodermal cysts, granulomatous disease, vascular malformations)
Extradural
Metastasis
Lymphoma
Myeloma
Tumors encroaching from adjacent structures
Nonneoplastic lesions (infarction, calcific pseudoneoplasm of the neuroaxis, vascular malformations)

the tumor resembles ependymoma or neuroendocrine carcinoma, due to the salt and pepper speckled chromatin pattern that is typical of these tumors.

Nonneoplastic lesions that involve the spinal cord can be challenging. These have been previously described in Chap. 3 and include most commonly demyelinating disease (multiple sclerosis), granulomatous disease, and vascular malformations.

INTRADURAL, EXTRAMEDULLARY

In the intradural, extramedullary compartment, schwannomas, meningiomas, solitary fibrous tumors, sarcomas, melanocytic neoplasms, and metastases are common. Among the nonneoplastic lesions, endodermal cysts (see Chap. 3), granulomatous disease, and vascular malformations may also be encountered.

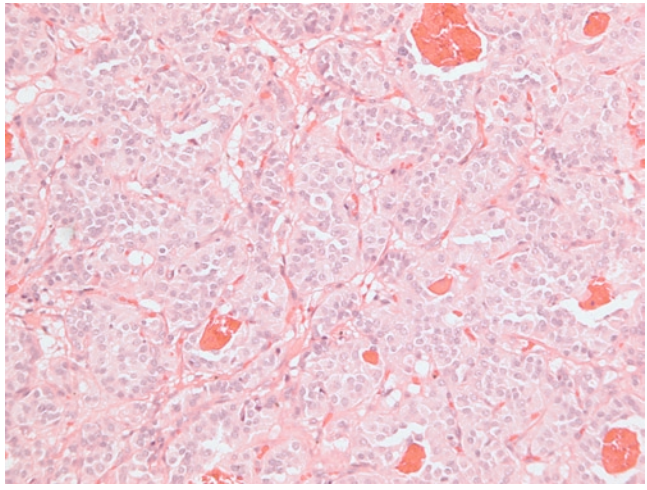

FIG. 11.1 A paraganglioma showing the characteristic nested architectural pattern (zellballen), which may be difficult to appreciate on a frozen section.

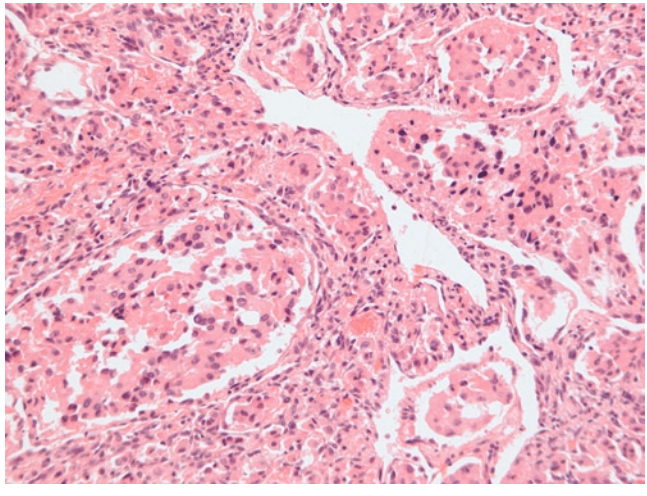

FIG. 11.2 Pleomorphic nuclei may be focally prominent in a paraganglioma.

EXTRADURAL

In the extradural compartment, the differential diagnosis is quite broad and includes a variety of neoplasms that can arise in neighboring organs or tissues. Most commonly, metastases and lymphoma occur in this area. One may also see meningiomas located on the outer aspect of the dura. Tumors extending from bone in the spine or sacrococcygeal area may also occur. Of particular note is the chordoma. Chordomas arise from notochordal tissue and are found either in the sacrum or clivus. Typically, they occur in adults as lobulated, mucoid masses which destroy the bone that they involve. Microscopically, the tumor has a roughly lobular architectural pattern. The lobules comprise epithelioid cells arranged in rows or cords within a mucoid matrix (Fig. 11.3). Many of these cells have a multivacuolated cytoplasm (so-called physaliferous cells) (Fig. 11.4). Mitoses are rare. Occasionally, chondroid areas may be observed and occasional tumors may demonstrate evidence of dedifferentiation, containing areas resembling sarcoma.

Chordomas with a cartilaginous component may raise a differential diagnostic consideration with a low-grade chondrosarcoma. The distinction may be difficult at the time of frozen section, unless the more recognizable physaliferous cells are

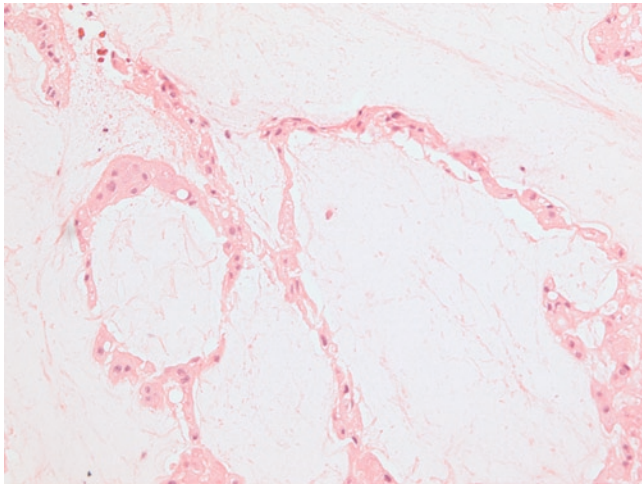

FIG. 11.3 The chordoma is marked by a myxoid stroma and epithelioid-type cells, resembling a myxopapillary ependymoma or a mucinous adenocarcinoma.

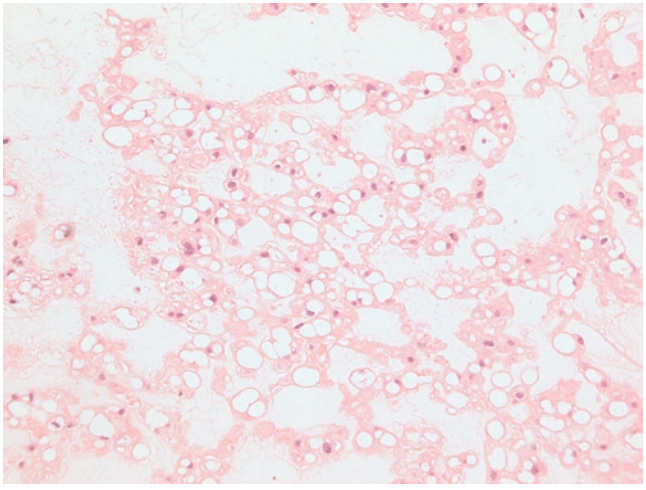

FIG. 11.4 The presence of bubble-like cytoplasm in some of the chordoma cells (physaliferous cells) is suggestive of the chordoma diagnosis.

readily observable. Metastatic mucinous adenocarcinomas may also resemble a chordoma and may require immunohistochemistry or special stains to distinguish.

Nonneoplastic lesions commonly seen in the extradural compartment include a variety of infectious processes, vascular malformations, and the calcific pseudoneoplasm of the neuroaxis. The calcifying or calcific pseudoneoplasm of the neuroaxis is a nonneoplastic calcified mass that may occur in patients with meningioangiomatosis and neurofibromatosis type II. These lesions often present as multinodular masses of granular and fibrillar material with a radial fibrillary component in the outer rind of the calcified mass and a covering of epithelioid cells and occasional giant cells. Areas of metaplastic bone and adipose tissue may be observed in the lesion.

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