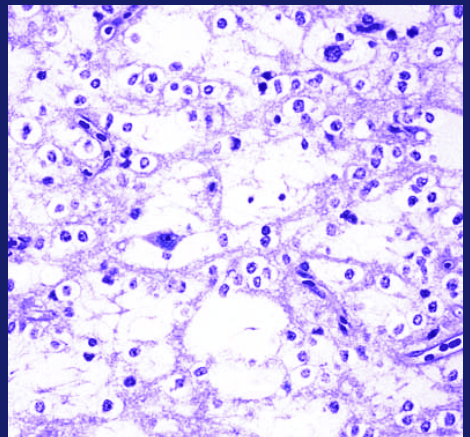
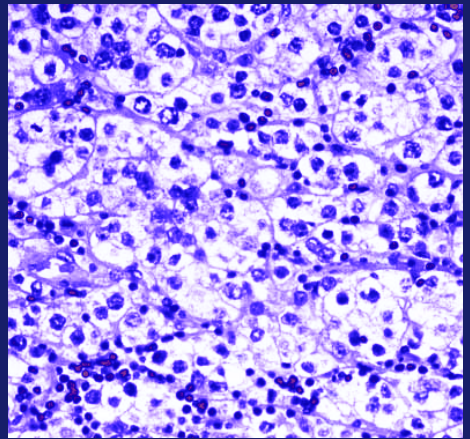
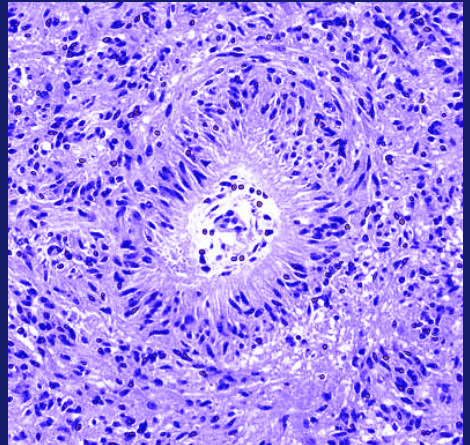
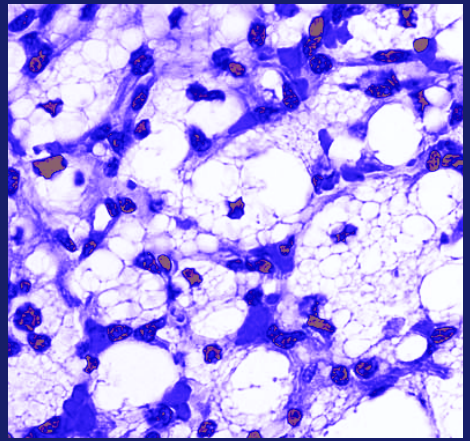

Practical Differential Diagnosis in Surgical Neuropathology

By

Richard A. Prayson, MD

Mark L. Cohen, MD



PRACTICAL DIFFERENTIAL DIAGNOSIS
IN SURGICAL NEUROPATHOLOGY

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Dedication
To Beth, Brigid, and Nick (Richard A. Prayson)
To Yvonne, Gary, Alan, Jason, Jamie, and Justin (Mark L. Cohen)

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PREFACE

Not another textbook for neuropathology! Yes, we hear you and feel your pain. In fact, that was our initial response when we were approached to write the book you are now holding. In surveying the expanse of currently available neuropathology textbooks, we felt there was a place for a book that could combine our career experiences of trying to discern what is known (and knowable) with the perennially proposed question, “What do we *need* to know?” Together we tried to produce a book that would be practical, understandable, and to the point (minimizing reading time during intraoperative consultation). We have concentrated our efforts on elucidating important neuropathologic entities that fall outside of general surgical pathologic practice. Conversely, we have given short shrift to disease entities falling well within the purview of the general surgical pathologist, but which also tend to involve the nervous system. Despite using this mental targeting to bring coherence and a sense of purpose to our writing, we believe this book will also prove helpful to pathology, radiology, and neurosurgery residents and staff as well as to others interested in a practical histopathologic approach to neurosurgical diseases.

We have found that much of the anxiety related to surgical pathology revolves around several major themes:

1. It is generally believed that though one can do without much of one’s liver or colon, every neuron counts. Therefore, we are sometimes asked to make very big diagnoses on very small amounts of tissue.
2. This request usually comes as an intraoperative consultation, where time is of the essence, and

technical aspects of the preparations may be less than ideal.

3. Everything looks pink.

Our publishers helped us with this last problem by insisting on black and white photographs. We initially protested, noting that many recent textbook reviews seemed to be primarily guided by whether illustrations were in color (good) or black and white (bad). However, upon further reflection we accepted this mandate as a blessing in disguise, allowing the reader to focus on differences in morphology, rather than tincture, as a guide to correct diagnosis. In fact, one of us (M.C.) has always been a fan of black and white photography, both in histologic atlases as well as in the immortal photographs of artists ranging from Ansel Adams to Diane Arbus. Within this framework, we have attempted to produce a user-friendly guide to the exciting world of neuropathologic diagnosis. Although Chapter 1 covers intraoperative neurosurgical diagnosis in general, we never strayed far from the frozen section room, either in body or in spirit, as we attempted to elucidate the neuropathologic entities comprising the remainder of the book. Though we realize that it is neither possible nor desirable to remove all anxiety from surgical neuropathologic diagnosis (after all, it *is* brain surgery), we hope that *Practical Differential Diagnosis in Surgical Neuropathology* will help focus the reader’s energy toward optimizing our common goal: the care of the patient.

Special thanks to Denise Egleton and Marilyn Taylor for their help in the preparation of this manuscript. Thanks also to Dr. Kymberly Gyure for supplying figures.

Richard A. Prayson, MD
Mark L. Cohen, MD

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1 Intraoperative Consultation

LET'S START WITH THE PROVERBIAL good news/bad news dilemma: The bad news is that modern neuroimaging and neurosurgical techniques have resulted in an increasing number of intraoperative consultations on ever smaller samples of tissue. The good news is that with modern neuroimaging and neurosurgical techniques, the surgeon is usually fairly certain about the histologic diagnosis and operative treatment of the lesion before the tissue parts ways with the patient.

While some surgeons still argue that the pathologist should not be privy to such clinical and radiographic information for fear that it might bias the histopathologic assessment, this is a dangerous argument that does not truly serve the patient's best interest (1). Another critical piece of information (which may also need to be forcibly extracted from the surgeon) is the reason for the intraoperative consultation. Almost always, the surgeon is interested in the answer to one of two questions: 1) "Do you have enough representative tissue to (eventually) provide us with a definitive diagnosis?" This may include triaging tissue to electron microscopy, frozen archive, cytogenetics, and/or microbiology (although we encourage the surgeons to send cultures directly to microbiology from the operating room), or 2) "Is this lesion what we think it is, or should we alter our surgical procedure?"

While decisions concerning tissue triaging may apply either to "open" surgical resections or "closed" stereotactic/endoscopic biopsy procedures, the question being asked usually can be surmised from the neurosurgical procedure—adequacy for "closed" procedures and guidance for "open" procedures.

When plenty of tissue is available, initial processing and microscopic examination may be performed "in a vacuum" to preserve histopathologic objectivity. However, a final intraoperative consultation should never be rendered without clinical and radiographic correlation. With limited amounts of tissue available for examination,

clinical and radiographic information is critical to guide your approach to triaging and processing the specimen. Specifically, you have to decide whether to examine the tissue cytologically (using smear, crush, or touch preparations) or histologically (using frozen sections). Arguments for or against using either of these techniques parallel those in general surgical pathology (2), and their use with specific entities will be covered in the chapters that follow. We must admit, however, that a large part of the decision about which technique to use depends upon personal experience and preference. One of us (R.P.) uses frozen sections nearly exclusively, while the other (M.C.) relies almost entirely on smear preparations.

Both techniques begin (as does all of microscopic pathology) with gross examination of the specimen. As absurd as it may seem, this is as important, if not more so, in the assessment of small stereotactic/endoscopic biopsy specimens. It doesn't matter how good a microscopist you are, if you don't select the correct area to process, you can't make the correct diagnosis. Two guidelines should be followed in the selection of tissue for intraoperative processing:

1. Include portions of the softest, darkest regions of the specimen.
2. *NEVER* process all of the abnormal appearing tissue.

One of us (M.C.) likes to smear anything that will lay down flat between two slides, for the following reasons:

1. It's fast.
2. With the exception of using too much tissue per slide, it is nearly impossible to technically screw up.
3. Immediate fixation in 95% alcohol followed by routine H&E staining yields beautiful nuclear and cytoplasmic detail.

4. Multiple areas of the specimen can be sampled while still leaving plenty of pristine tissue for permanent sections.
5. If the case turns out to be infectious, cryostat decontamination will not be necessary.

There are, however, some drawbacks associated with the smear technique:

1. Architectural details are lost. Specifically (among small, smearable tumors) the microvascular proliferation and necrosis, which allows us to diagnose glioblastoma multiforme, may be very difficult to appreciate (3).
2. Evaluation time is longer because there is usually more to look at, compared with a frozen section.
3. Some lesions just don't smear well.

This leads us to a consideration of the advantages of frozen sections:

1. Just about anything (short of bone) can be frozen and sectioned, although highly mucoid lesions (e.g., dysembryoplastic neuroepithelial tumor) may require considerable skill to freeze and section adequately.
2. Many pathologists are more familiar with frozen section techniques and interpretation.
3. Preservation of architectural details may improve diagnostic accuracy in certain situations (e.g., microvascular proliferation/necrosis in gliomas, perivascular pseudorosettes in ependymal tumors).

The main drawback in the use of frozen sections for intraoperative consultation is the marked susceptibility of parenchymal CNS tissue to freezing artifact. Perhaps as a result of its relatively high water and lipid content, very rapid freezing of CNS tissue is critical to prevent marked artifactual disruption of the tissue specimen. Liquid nitrogen-cooled isopentane (2-methylbutane) provides the ideal combination of low temperature and high specific heat required to produce optimal frozen section histology.

Interpretation of either cytologic or histologic preparations always begins with deciding whether the material obtained is normal or abnormal. If the latter is the case (it almost always is), we need first to consider whether we could be dealing with a non-neoplastic lesion (we almost never are, but avoiding the overdiagnosis of malignancy during intraoperative consultation is paramount). In either case (neoplastic or non-neoplastic), an assessment of specimen adequacy needs also to be communicated to the surgeon. One should never be timid about requesting additional tissue, either for intraoperative consultation or for permanent section processing, when neces-

sary. While the surgeon may grumble at the time, it's a heck of a lot easier than having to go back later (4). It is during this final step in the intraoperative consultation where knowledge of the patient's history, presentation, and imaging is critical to optimally serving both the surgeon and the patient. Although it is ultimately up to the surgeon to decide on a course of action based upon our histopathological assessment, as well as their knowledge of the clinical and neuroradiologic aspects of the case, we believe that a more active role for the pathologist usually leads to better outcomes for all concerned.

Useful clinical information includes:

1. The age of the patient
2. The region of the nervous system which is involved
3. Whether the lesion is within the neural parenchyma ("intra-axial") or adjacent to it ("extra-axial")
4. Whether the patient has other significant medical problems or a previous history of CNS disease and/or treatment.

Two clinical features, which suggest the possibility of a low-grade neoplasm or a nonneoplastic process, are a long (≥ 5 years) history of symptoms and a recent history of trauma (5).

Ideally, we would also like to know the full neuroradiologic interpretation of the lesion or lesions we are being called to consult on. Short of that, a general awareness of fundamental neuroradiologic principles and their relevance to intraoperative consultation will go far toward providing an optimal intraoperative assessment. We have tried to integrate these principles into each chapter, as they apply to specific neuropathologic entities. For additional details, two recent articles from the pathology literature are highly recommended (6,7).

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2 Gliosis

ONE OF THE MOST CHALLENGING differential diagnostic problems encountered in the setting of surgical neuropathology is distinguishing between gliosis or reactive astrocytosis and a low-grade glial neoplasm. Gliosis is the brain's way of reacting to injury, insult, or "something" that should not be there (e.g., a tumor). Therefore, it is common to observe at least some degree of reactive astrocytosis adjacent to and associated with a tumor. This problem is further magnified by the paucity of material that is typically available for evaluation, particularly in this age of stereotactic biopsies. Compound this with all the artifacts and limitations one can encounter in the setting of intraoperative consultation, and the distinction between gliosis and an infiltrating, low-grade glioma often tops the list as one of the more difficult challenges of diagnostic neuropathology.

Before one even looks at the biopsy, basic clinical and radiographic information should be available or sought out. Information with regard to the age of the patient, precise location of the lesion or lesions seen radiographically, a prior history of central nervous system disease or disease that may potentially involve the central nervous system, and some sense of the time course of the disease process in question, are all important and potentially useful pieces of information. A previous history of radiation therapy or trauma involving the brain should alert one to expect to see some gliosis. All too frequently, the pathologist is asked to interpret a biopsy, given nothing more than an age on a requisition form (which may or may not be always accurate!), a "useful" site designation, and clinical information such as "brain," "lesion," or "tumor." This form of communication is woefully inadequate.

The radiographic appearance of the lesion is of critical importance. The presence of a mass or tumor radiographically most certainly does not represent simply a reactive astrocytosis. Unfortunately, there are a variety of nonneoplastic

conditions, such as infarct, demyelinating disease, or infection (abscess), that may radiographically mimic a tumor and most certainly will demonstrate areas of astrocytosis. However, most of these other conditions are characterized by features that generally allow for their recognition. The presence of prominent numbers of macrophages, which are commonly encountered in an infarct or demyelinating condition, are distinctly uncommon in most fibrillary astrocytomas (1,2).

Reactive astrocytosis, similar to gliomas, may involve both gray and white matter. Areas of astrocytosis associated with tumors tends to be most noticeable at the infiltrating edge of the lesion and may be accompanied by edema, particularly in a higher grade neoplasm. Gliosis often results in parenchyma that is firm in consistency, a feature that does not prove very useful in the routine evaluation of small biopsy specimens. Likewise, many of the gross and radiographic features of a tumor such as microcystic degeneration or calcification are not going to be grossly appreciable in a small biopsy core.

Microscopically, similar to low-grade tumors, astrocytosis may result in a slight increase in cellularity (Figs. 2-1 and 2-2). The increased cellularity associated with reactive astrocytosis is generally evenly distributed from microscopic field to field, in contrast to tumors, where the increased cellularity is generally unevenly distributed. Again, in a small biopsy or smear/crush preparation, this distinction may be subtle or not evident. Care must be taken in the setting of the biopsy which appears hypercellular, but which lacks any appreciable atypia or cells with prominent eosinophilic cytoplasm; this picture may be seen in a thickly cut biopsy of normal parenchyma. Both astrocytosis and infiltrating glioma result in some degree of cytologic "atypia" or cellular alteration. However, there are some differences between the cytologic alterations in these processes. Reactive astrocytes frequently have a slightly enlarged nucleus, which is generally eccentrically

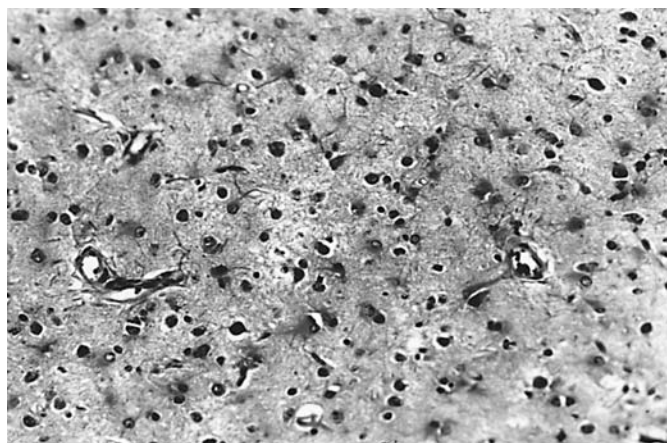


Fig. 2-1. Increased, evenly distributed cellularity in reactive astrocytosis.

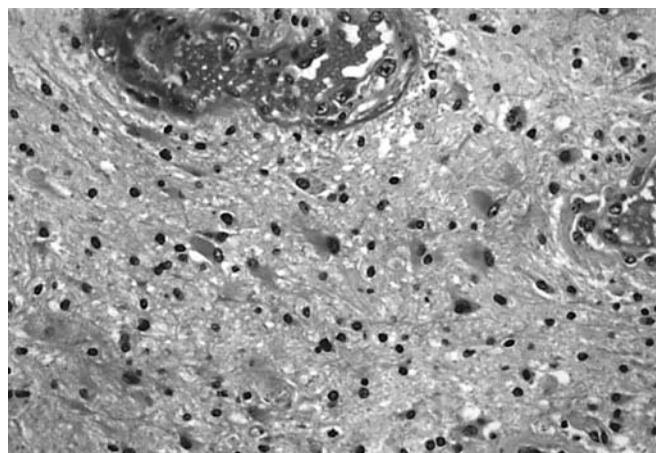


Fig. 2-3. Reactive astrocytes with abundant eosinophilic cytoplasm.

placed and often associated with prominent eosinophilic cytoplasm and stellate cytoplasmic processes (3) (Fig. 2-3). Nuclear contours in reactive astrocytes are generally rounded or slightly oval and cells are generally monomorphic in their appearance. Binucleate cells are not uncommon. The atypia encountered in a low-grade astrocytoma is characteristically different (4). Cells generally have a high nuclear to cytoplasmic ratio (i.e., they contain little or no discernible cytoplasm). The nuclei are enlarged in the order of two to three times the size of normal astrocytic nuclei. Nuclei have markedly irregular contours with indentations and irregularities. Nuclear chromatin often is more clumped and unevenly distributed. Nuclei are generally more hyperchromatic or darker staining. Oligodendroglial cells are characterized by round nuclei with scant cytoplasm.

Distinction of gemistocytic astrocytes in a gemistocytic astrocytoma from reactive astrocytes, particularly at the infiltrative edge of a tumor, may be more difficult. Gemi-

stocytic astrocytoma cells tend to have shorter and thinner cytoplasmic processes, in contrast to the longer, tapering processes of reactive astrocytes. These subtle differences may not be readily apparent on routine hematoxylin–eosin staining and may require a cytologic preparation or immunostains such as glial fibrillary acidic protein stain (GFAP) to visualize (5) (Fig. 2-4).

There are other features which are more variably present in tumors, but can serve as soft clues in this differential diagnosis between gliosis and glioma. Identification of a mitotic figure in an astrocytic cell is evidence in support of a neoplastic process. Caution should be taken not to confuse a mitotic figure in a vessel wall or in coexistent granulation tissue as indicative of tumor. An atypical mitotic figure is most certainly indicative of a neoplasm. The formation of granulation tissue is relatively uncommon in the central nervous system, as compared with other organ systems, where this is a common pattern of injury repair. Granulation tissue observed in the brain or

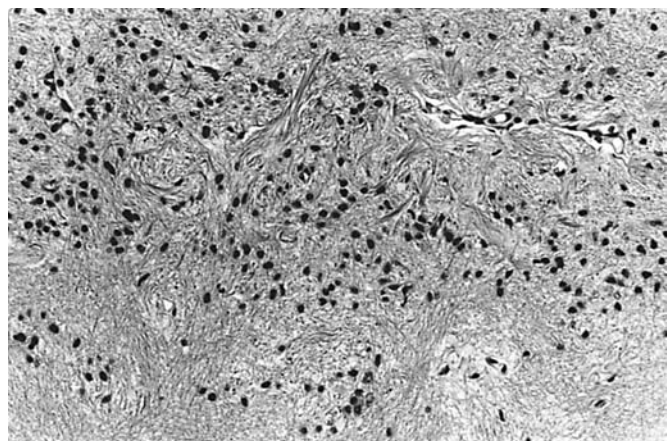


Fig. 2-2. Reactive astrocytosis and gliosis in a region adjacent to infarct.

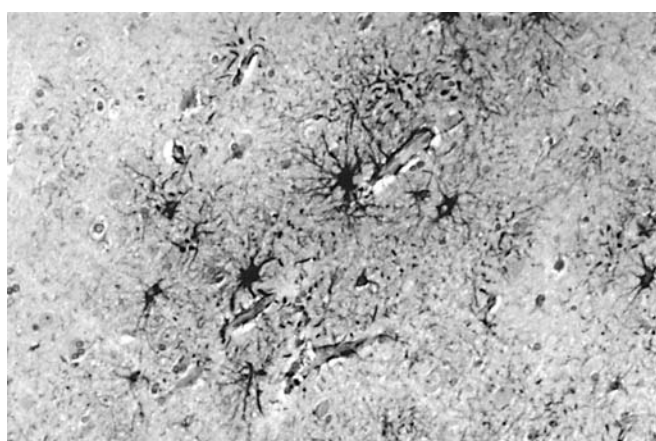


Fig. 2-4. Glial fibrillary acidic protein stain highlighting long, tapering processes in reactive astrocytes.

Table 2-1.
Gliosis Versus Glioma

<i>Gliosis</i>		<i>Glioma</i>
Age	Any	Peak 3 rd to 5 th decade, but can occur at any age
Location	Gray or white matter	White > gray matter
Gross	Firm	Firm; obliterate gray-white junction, may be cystic
Hypervascularity	Evenly distributed	Unevenly distributed
Atypia	Binucleate cells, more eosinophilic cytoplasm with long tapered processes	High nuclear/cytoplasmic ratio, hyperchromatic, nuclear irregularity and pleomorphism
Mitoses	Usually absent	May be present
Calcification	—	±
Microcystic change	—	±
Satellitosis	—	±
Distribution	Generally focal	Diffuse infiltration

spinal cord develops from fibroblasts and mesenchymal cells normally encountered around vessels and in the leptomeninges.

The presence of true microcystic degeneration is strongly indicative of a neoplastic process, rather than simply reactive astrocytosis. Care should be taken not to interpret the pseudomicrocystic change one can generate as an artefact at frozen section intraoperative consultation as true microcystic degeneration. One should also not misinterpret cystic degeneration in an area of remote infarct or demyelinating disease as being suggestive of a tumor. Both of these processes will show prominent numbers of reactive astrocytes.

Microcalcifications may be seen in up to 15% of fibrillary astrocytomas and in the vast majority of oligodendrogliomas (6). Calcifications are generally not part of the gliosis process, although calcification may develop in association with other processes in which gliosis is a prominent feature, including remote ischemic injury or organized hematoma.

Satellitosis is a particularly common occurrence at the gray-white interface, where oligodendroglial cells normally arrange themselves around neurons. Occasionally, satellitosis of tumor cells around preexisting structures such as neurons or vessels may be seen at the infiltrating edge of astrocytomas (secondary structures of Scherer) (7) or of oligodendrogliomas. Reactive astrocytes do not typically arrange themselves around other structures. The presence of eosinophilic Rosenthal fibers or granular bodies, although more typically thought of as being associated with low grade neoplasms such as pilocytic astrocytoma or ganglioglioma, may on occasion be observed in areas

of long-standing reactive astrocytosis and in a variety of non-neoplastic conditions. Care should be taken not to confuse piloid gliosis with a pilocytic astrocytoma (8).

Table 2-1 summarizes features that may be useful in differentiating gliosis from a low-grade glioma. Often times, the single most useful parameter histologically is the quality of cytologic atypia. Specific issues surrounding reactive changes as they pertain to radiation therapy will be discussed in Chapter 6.

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3 Fibrillary Astrocytoma

FIBRILLARY ASTROCYTOMAS ARE THE most common primary tumors of the central nervous system. Historically, there have been numerous attempts at stratifying and grading astrocytomas, which have proven variably successful. The early grading schema of Bailey and Cushing was predicated on the presumed embryogenetic derivation of cells comprising the given tumor (1). The grading schema resulted in a three-tiered system in which tumors were designated as low-grade astrocytoma, astroblastoma, and the high grade spongioblastoma multiforme. In 1949, Kernohan and Sayre proposed a four-tiered numerical grading schema based on the tumor's degree of dedifferentiation (2). Tumors were designated as grades 1 through 4. In general, there was fairly good correlation between tumor grade and the length of post-operative survival. At about the same time, the original Ringertz classification schema was proposed (3). In the Ringertz system, tumors were classified into three grades which were designated as astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme. Again, prognostic significance was associated with each grade designation.

Currently there are three major grading schemas that are being utilized. One is a modification of the Ringertz system described by Burger et al. in 1985 (4). Tumors are stratified into three tiers. Low-grade astrocytomas are designated as mildly hypercellular, astrocytic neoplasms with nuclear pleomorphism but no vascular proliferation or necrosis. The designation of anaplastic astrocytoma or astrocytoma with atypical anaplastic features refer to tumors which show moderate hypercellularity and pleomorphism. Vascular proliferation is permitted in this grouping, but no necrosis. The glioblastoma multiforme designation is used for a moderately to markedly hypercellular, pleomorphic neoplasm in which necrosis with or without pseudopalisading is required and vascular proliferation is optional.

The World Health Organization (WHO) schema was most recently revised in 1993 (5). This system is four-tiered and uses Roman numeral designations for each level. Unlike most other astrocytoma grading systems, the WHO system encompasses a broader group of lesions and includes a variety of astrocytoma variant tumors. Fibrillary astrocytomas are generally assigned to grades II–IV, which roughly correlates with the Ringertz system as follows: *grade II*, well-differentiated fibrillary astrocytoma, *grade III*, anaplastic or malignant astrocytoma, and *grade IV*, glioblastoma multiforme. One important distinction between these two systems is the lack of an absolute requirement for necrosis in the diagnosis of glioblastoma multiforme in the WHO system. Tumors with prominent vascular proliferation and significant nuclear pleomorphism may be designated as glioblastoma multiforme. A WHO grade I tumor refers to some of the low-grade astrocytoma variant lesions, such as the pilocytic astrocytoma and the subependymal giant cell astrocytoma. In addition, to the well-differentiated fibrillary astrocytoma, WHO grade II lesions also include the pleomorphic xanthoastrocytoma, the so-called protoplasmic astrocytoma, and the gemistocytic astrocytoma.

In 1988, the St. Anne-Mayo grading schema was proposed (6). The St. Anne-Mayo grading schema is a four-tiered system based on the presence of four specific histologic features, including nuclear atypia, mitoses, endothelial proliferation, and necrosis. Depending on the number of these histologic features which can be identified, tumors are designated as grades 1 through 4, using ordinal numeral designations. Tumors with none of the previously mentioned histologic features are designated as grade 1 lesions. Tumors with one of the above-mentioned features, usually nuclear atypia, are designated as grade 2 neoplasms. Tumors with two of the above-mentioned features, usually nuclear atypia and mitoses, are designated as grade 3 lesions, and tumors with three or four

of the previously mentioned features are designated as grade 4 neoplasms. Similar to the WHO system, the St. Anne-Mayo schema does not require necrosis to be present in order to designate the tumor as high grade. One problem with the system centers on the grade 1 designation. The number of lesions that fulfill the criteria for grade 1 astrocytoma (i.e., devoid of atypia) is very small and in reality practically nonexistent; therefore, in its working form, the St. Anne-Mayo system ends up being essentially a three tiered system.

There is considerable debate as to the relative merits and drawbacks of each system. The differences and ramifications of each system are important to understand. Because of the nature of these systems, there is a certain lack of reproducibility associated with the systems, particularly the Ringertz and WHO system (7,8). Although the St. Anne-Mayo schema is an attempt at a somewhat more objective approach to grading astrocytomas, problems are also associated with the somewhat rigid criteria of the system (9). For example, is one mitotic figure in a otherwise low grade appearing fibrillary astrocytoma sufficient enough to warrant advancing the tumor a grade? Beside the interobserver variability associated with different interpretations of generally descriptive criteria, one also needs to take into consideration issues of tumor sampling and heterogeneity (10,11). Particularly, in this age of stereotactic biopsies, one is often looking at a very small sampling of a total tumor. It is well known that different areas of an astrocytoma may have different histologic features and unless one is sampling the highest grade areas of a tumor, one will certainly underestimate the true grade of the lesion (12). This problem underscores the importance of intraoperative consultation and communication between the neurosurgeon and the pathologist with regard to what is clinically and radiographically observed and what is being seen at the time of intraoperative consultation. One biopsy taken at the stereotactic target is frequently insufficient for definitive and accurate diagnosis and classification of an astrocytic neoplasm (13,14).

Irrespective of which grading schema one decides to employ, it is important that there is consistency in one's use of a particular system within a given institution. It should be obvious from the pathology report which grading schema is being used, and care should be taken not to mix Roman numeral and ordinal numeral designations between the WHO and the St. Anne-Mayo systems. Unfortunately, it is impossible to avoid potential confusion when the patient desires a second opinion or when a patient is being entered into a treatment protocol that may be utilizing a different grading approach and for which the biases of the study pathologist will come into play. The three main grading schemas and their equivalent designations are summarized in Table 3-1.

Table 3-1
Astrocytoma Grading Approaches

I.	Modified Ringertz (1950, modified 1985) Low-grade astrocytoma Anaplastic astrocytoma Glioblastoma multiforme
II.	World Health Organization (revised 1993) Grade I: Pilocytic astrocytoma, subependymal giant cell astrocytoma Grade II: Well-differentiated astrocytoma (fibrillary, protoplasmic, and gemistocytic), pleomorphic xanthoastrocytoma Grade III: Anaplastic astrocytoma Grade IV: Glioblastoma multiforme
III.	St. Anne-Mayo (1988) Grade 1: 0/4 features present Grade 2: 1/4 feature present Grade 3: 2/4 features present Grade 4: 3-4/4 features present Features: Nuclear atypia, mitoses, endothelial proliferation, necrosis
IV.	General equivalent designations: WHO Grade I = No equivalent Ringertz or St. Anne Mayo designation WHO Grade II = Low-grade astrocytoma (modified Ringertz), grades 1 and 2 and subset of grade 3 (St. Anne-Mayo) WHO Grade III = Anaplastic astrocytoma (modified Ringertz), grade 3 (St. Anne-Mayo) WHO Grade IV = Glioblastoma multiforme and subset of anaplastic astrocytoma with vascular proliferation (modified Ringertz), grade 4 (St. Anne-Mayo)

Although it is beyond the scope of this text to examine all of the myriad proposed grading schemas, needless to say, other approaches are constantly being explored in the literature. Systems utilizing morphometric approaches, neural networks, and cell proliferation markers have been variously suggested. More recently, molecular genetic events associated with the various grades of fibrillary astrocytoma and progression from lower to higher grade lesions are being elucidated (15). This may provide the future framework upon which the grading of astrocytomas is predicated.

Fibrillary astrocytomas typically present with a peak incidence between the third and fifth decades of life. Cases presenting in childhood and presenting later in life have also been described. Fibrillary astrocytomas presumably arise from fibrillary-type astrocytes which are situated primarily within the white matter. In general, the distribution of fibrillary astrocytomas within the central nervous system roughly correlates with the amount of white matter in various regions of the brain. The frontal lobe has more white matter than other cortical lobes; therefore, the frontal lobe is a more common site of origin for fibrillary astrocytomas. Fibrillary astrocytic tumors may also arise

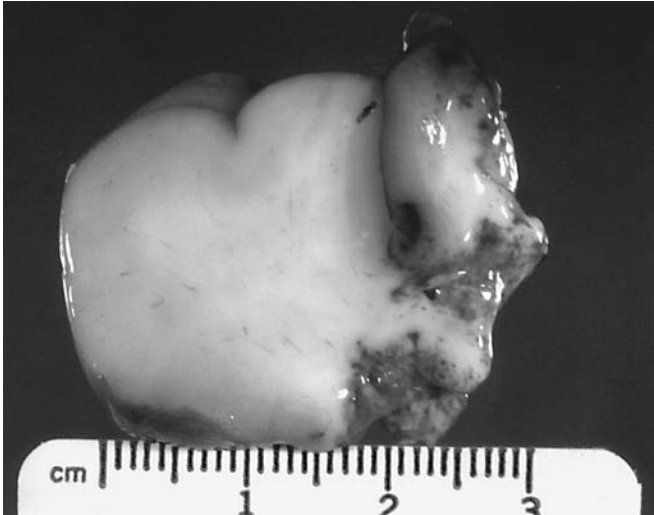


Fig. 3-1. Gross appearance of a low-grade fibrillary astrocytoma marked by obliteration of the gray-white junction.

in the cerebellum; however, particularly in children, pilocytic astrocytomas are more commonly encountered in this location. So-called brainstem and optic nerve gliomas may also be of the fibrillary astrocytoma type. Rather than using the nondescript terms optic nerve and brainstem glioma, one should attempt to classify the tumor by astrocytoma type, and if the tumor is of the fibrillary type, assign the tumor a grade. Along with ependymomas, astrocytomas comprise the bulk of intramedullary spinal cord gliomas. The clinical presentation of fibrillary astrocytomas is quite variable and dependent upon the location, size of the tumor, and rate of growth of the neoplasm. Most patients present with signs and symptoms related to seizures, sensory motor deficits, and increased intracranial pressure.

The radiographic appearance of fibrillary astrocytomas is also quite variable and dependent a good part upon the grade of the lesion. In general, low-grade astrocytomas are low signal intensity lesions, which appear somewhat ill-defined on MRI studies (1). Higher grade tumors frequently show areas of enhancement, corresponding to vascular proliferation. Calcifications are observed in a minority of astrocytomas. The classic ring-enhancing configuration of glioblastoma multiforme results from a central zone of necrosis rimmed by viable tumor with prominent vascular proliferation. Astrocytomas, irrespective of tumor grade, are widely infiltrative lesions and often extend microscopically far beyond what their gross or radiographic appearance would suggest. If one has adequate tissue available for gross examination, one may note an obliteration or obscuring of the gray-white junction due to tumor infiltrating the cortex (Fig. 3-1).

The histologic features that most of the grading schemas are primarily based upon (i.e., nuclear atypia, mitoses,

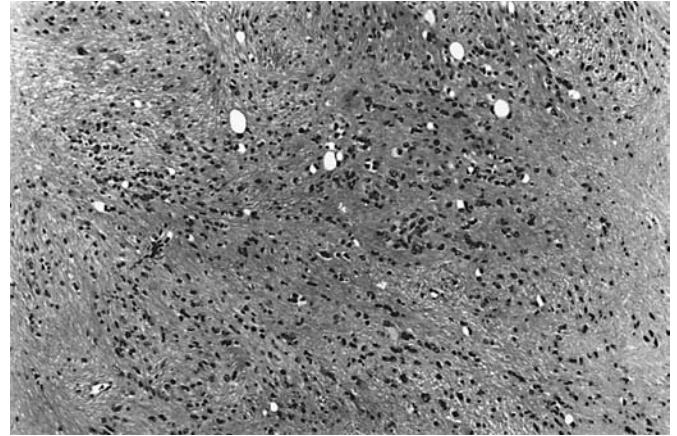


Fig. 3-2. Hypercellularity of uneven distribution in a low-grade fibrillary astrocytoma.

vascular proliferation, necrosis) turn out to be the most salient histologic features of fibrillary astrocytomas (16–22). In general, the more of these features that are identifiable in a given neoplasm, the higher the grade. Most low-grade astrocytomas are characterized by hypercellular tissue (Fig. 3-2). Cells characteristically show mild nuclear atypia characterized by nuclear pleomorphism, hyperchromasia, and enlargement (Figs. 3-3 and 3-4). In low-grade astrocytoma, these atypical astrocytic cells are unevenly distributed in a microscopic field, in contrast to gliosis, where the reactive astrocytes are evenly distributed across the microscopic field. Rarely in a low-grade astrocytoma, one may encounter a mitotic figure. In an otherwise low-grade-appearing lesion, a rare mitotic figure is not thought by most to be sufficient to warrant an increase in tumor grade (unless one is using the St. Anne-Mayo approach to grading). Areas of microcystic degeneration may be present, and if so, may be a useful clue indicating that one may be dealing with a tumor rather

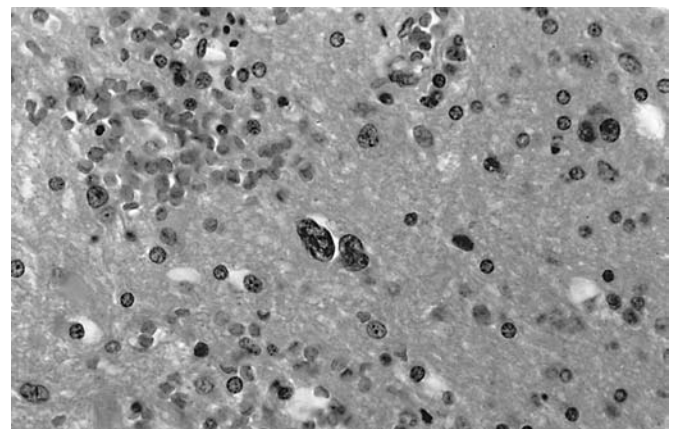


Fig. 3-3. Nuclear atypia in a low-grade fibrillary astrocytoma characterized by nuclear enlargement, coarse chromatin pattern and irregularity to the nuclear contour.

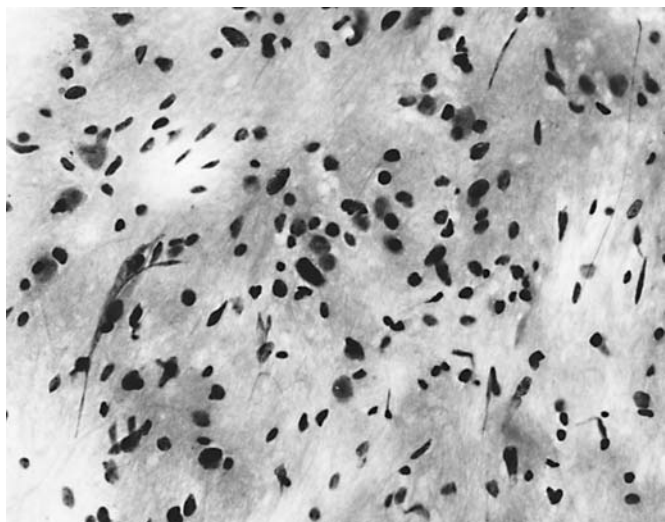


Fig. 3-4. Cytologic preparation of a low-grade fibrillary astrocytoma showing cells with clear evidence of cytologic atypia.

than a reactive process. With infiltration, tumor cells may arrange themselves around preexisting structures including vessels or neurons. The term “secondary structure of Scherer” has been used for this feature, which is more commonly seen at the infiltrating edge of higher grades of fibrillary astrocytoma (Fig. 3-5). In most fibrillary astrocytomas, perivascular lymphocytes, which are more prominently noted in the gemistocytic astrocytoma variant, are not prominently seen. Vascular proliferation and necrosis are not features of low grade astrocytoma.

Anaplastic astrocytomas are generally more cellular and demonstrate more nuclear atypia than low grade astrocytomas (Fig. 3-6). Clearly, these criteria are somewhat subjective; what may be “more” for one pathologist may not be sufficient enough to a second pathologist to warrant an upgrading of the tumor. Usually in anaplastic astrocy-

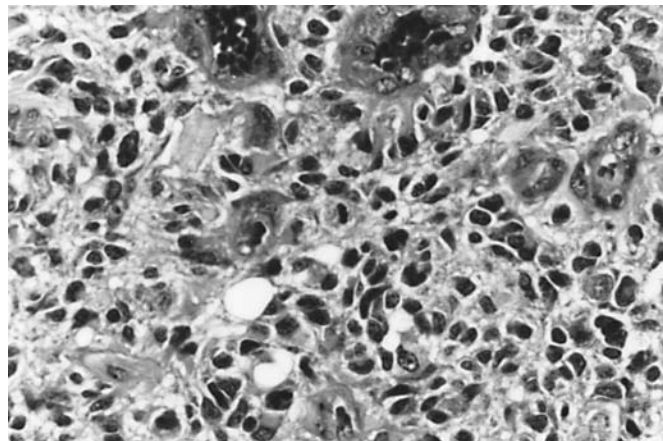


Fig. 3-6. Anaplastic astrocytoma with increased cellularity and prominent nuclear atypia as compared with a low-grade tumor.

toma, mitotic figures are more readily identifiable (Fig. 3-7). One may also begin to see evidence of vascular proliferation, a feature more commonly associated with glioblastoma multiforme. When referring to vascular proliferation in fibrillary astrocytomas, one is describing a proliferation of cell components or piling up of cells around blood vessels (Figs. 3-8 and 3-9). Unfortunately, the term endothelial cell proliferation has been frequently used for this lesion. This is a misnomer in the sense that the cells that proliferate and pile up around vascular lumina include not only endothelial cells but many of the other normal constituents of vessel walls including smooth muscle cells, pericytes, and fibroblasts (23). Occasionally, the vascular proliferation may be exuberant enough to assume a so-called glomeruloid configuration. In addition to the piling up of cells around vessel lumina, one also frequently sees increased numbers of small caliber vessels in higher grades of astrocytoma.

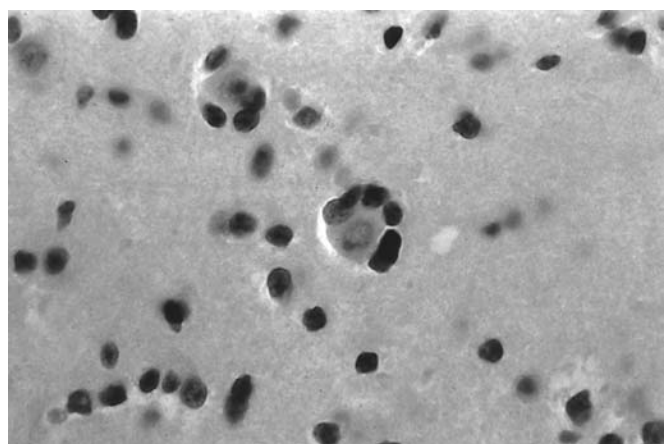


Fig. 3-5. Secondary structures of Scherer in an infiltrating astrocytoma.

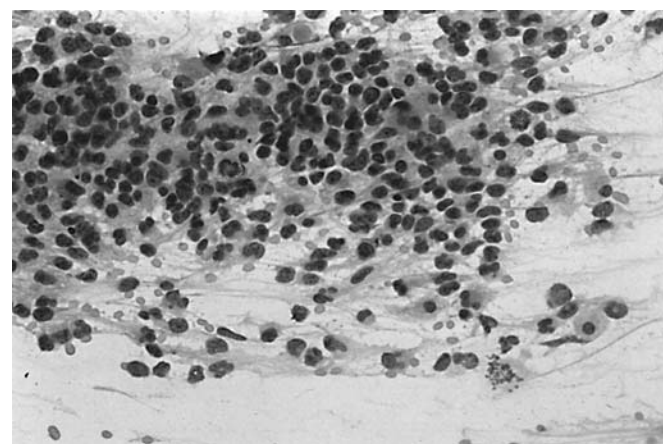


Fig. 3-7. Cytologic preparation showing identifiable mitotic figures in an anaplastic astrocytoma.

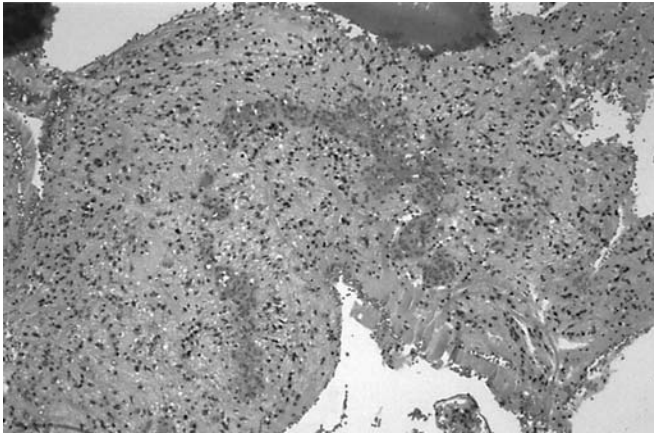


Fig. 3-8. Stereotactic biopsy showing areas of vascular proliferation in an anaplastic astrocytoma.

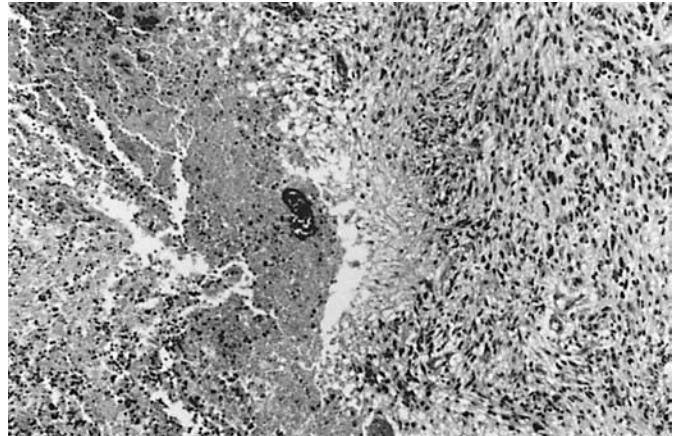


Fig. 3-10. Geographic necrosis in a glioblastoma multiforme.

The histologic hallmark of glioblastoma multiforme is necrosis (Figs. 3-10 and 3-11). However, if one utilizes the WHO or St. Anne-Mayo grading schemas, prominent vascular proliferation, even in the absence of necrosis, may be sufficient to warrant the diagnosis of high grade astrocytoma. Necrotic foci may or may not be rimmed by a pseudopalisade of tumor cells (Fig. 3-12). Discussion regarding histologic variants of glioblastoma multiforme is covered in Chapter 5.

In general, immunohistochemistry is not helpful in the grading or routine evaluation of fibrillary astrocytomas, but it may be useful, on occasion, in differentiating the astrocytoma from nonglioma differential diagnostic considerations such as demyelinating disease, metastasis, or lymphoma. Fibrillary astrocytomas characteristically stain positively for glial fibrillary acidic protein (GFAP) and S-100 protein. In general, with higher grades of astrocytoma, one may observe tumor cells which do not stain for GFAP as they become more poorly differentiated.

Caution should be taken when using keratin markers in evaluation of fibrillary-type astrocytomas, particularly in distinguishing these lesions from metastatic carcinomas (24). Some keratin markers such as cytokeratins AE1/3 will frequently demonstrate a diffuse positive staining pattern, even in glioblastoma multiforme. Use of cytokeratin CAM5.2 seems to avoid this problem (25).

The exact role of cell proliferation markers in the evaluation of fibrillary type astrocytomas is still debatable. A number of studies have shown a trend toward increased labeling indices with increased tumor grade (19,26–28). There are, nevertheless, limitations to the use of cell proliferation markers in the evaluation of astrocytomas. There are enough differences in terms of staining technique and interpretation for a given stain that comparison of indices needs to be done within the known parameters of a given laboratory. In other words, a labeling index of 5% in one laboratory may not necessarily translate into a labeling index of 5% in another laboratory. Again, issues of tumor

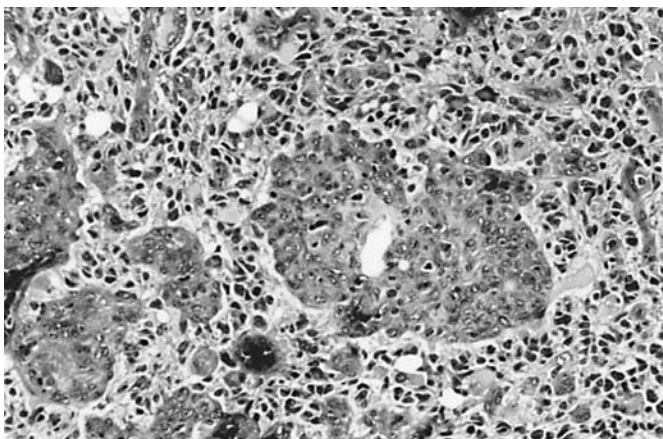


Fig. 3-9. Exuberant vascular proliferation in a glioblastoma multiforme.



Fig. 3-11. Cytologic preparation marked by malignant astrocytic cells with necrosis.

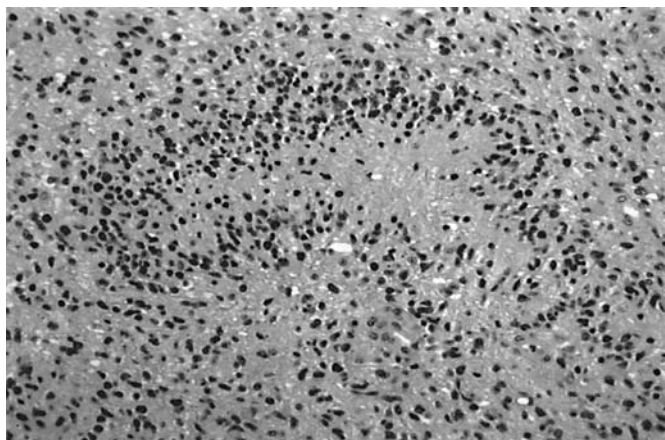


Fig. 3-12. Perinecrotic pseudopalisade of tumor cells in a glioblastoma multiforme.

heterogeneity and sampling are important to consider. A slide chosen for purposes of cell proliferation immunohistochemistry may or may not represent the most proliferative area of a given tumor. Likewise, tissue surgically sampled may not represent the most proliferative area of a given neoplasm. In addition, there appears to be overlap in terms of ranges of labeling indices at the interface between tumor grades. All of these issues should cause one to be cautious in the interpretation of labeling indices. Despite all these limitations, cell proliferation markers may be useful in selected circumstances. A very high labeling index in a tumor that looks low or intermediate grade, may be evidence in support of a higher grade lesion. Low labeling indices tend to be less helpful, in that one is not able to entirely exclude the possibility of tumor sampling or tumor heterogeneity being the cause of the lower labeling index.

Electron microscopic evaluation of fibrillary astrocytomas adds very little but cost to the routine grading and evaluation of fibrillary astrocytomas. There may be circumstances in which a differential diagnosis between astrocytoma and another lesion such as ependymoma may arise, and where immunohistochemistry may be useful. In such cases, electron microscopy may be helpful. In the case of differentiating ependymoma from astrocytoma, the identification of microvilli, cilia or blepharoplasts (all features of ependymoma) are useful.

Multifocal gliomas are a well-described phenomenon (29). Incidence rates are, however, difficult to establish, but have been described in range of 2–5%. Because of the widely infiltrative nature of fibrillary astrocytomas, this incidence probably represents an overestimate of the true occurrence of this phenomenon. Radiographically apparent, multifocal lesions, may in many circumstances be connected by infiltrating tumor microscopically.

All three grading schemas, which have been previously

enumerated, demonstrate significant prognostic differences between grades. From a therapeutic standpoint, distinction of low-grade astrocytoma from anaplastic astrocytoma and glioblastoma multiforme is a significant cutoff point. In general, malignant astrocytomas, which include the later two lesions, are treated with radiation therapy. Unfortunately, most fibrillary astrocytomas are not particularly sensitive to chemotherapeutic agents, although rare cases of response to chemotherapy have been encountered. Whether or not radiation therapy is utilized in the treatment or management of a low-grade astrocytoma is dependent upon a number of factors. In recent years, there are a variety of exciting new approaches to treating brain tumors in the areas of gene therapy and immunotherapy which are currently being explored and may prove useful. Unfortunately, a significant number of low-grade astrocytomas will progress to higher grade lesions over time. Data with regard to the exact frequency or interval of time to this occurrence is difficult to assess. Dissemination of tumor tends to occur most frequently with glioblastoma multiforme and rare cases of metastasis to a site distant from the central nervous system have also been described (30,31).

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4 Low-Grade Astrocytoma Variants

THIS CHAPTER DEALS WITH a miscellaneous group of astrocytoma variant lesions. Some of the more distinctive variants are separately dealt with in other chapters, including the pilocytic astrocytoma (Chapter 7), pleomorphic xanthoastrocytoma (Chapter 8), and subependymal giant cell astrocytoma (Chapter 9). This chapter will focus on four particular astrocytoma variants including the gemistocytic astrocytoma, protoplasmic astrocytoma, infantile desmoplastic astrocytoma, and the gliofibroma.

According to the WHO classification schema, gemistocytic astrocytoma is considered a variant of astrocytoma, which is predominantly comprised of gemistocytic astrocytes (1). The definition is vague enough to encompass a range of lesions due to considerable observer interpretation, resulting in incidence rates ranging anywhere from 9% to 24% of astrocytomas (2). Although designated as a WHO grade II astrocytoma, a number of studies have suggested that this particular lesion represents a more aggressive behaving tumor, with an increased propensity for anaplastic transformation (2,3). Interestingly, it has been shown that the gemistocytic astrocytes, themselves, demonstrate very little, if any, proliferative potential (3,4). In its clinical presentation and radiographically, there is no obvious difference between this particular variant and ordinary type fibrillary astrocytomas. Histologically, however, the gemistocytic astrocytoma consists of large numbers of plump astrocytes with abundant eosinophilic cytoplasm and one or more eccentric nuclei (Fig. 4-1). Nuclei are generally round to slightly oval in configuration and may have a small nucleolus. The cytoplasm forms a rim of short processes. Reactive astrocytes may look quite similar but tend to have longer, more tapered processes. Often in the background of the tumor, one sees more elongated appearing fibrillary type astrocytes. Frequently, the tumor contains perivascular lymphocytes. Historically, gemistocytic astrocytomas were often assigned a higher grade because of their more aggressive behavior.

Krouwer et al. (2) suggested that tumors with a 20% gemistocytic component generally had a poor prognostic outcome and warrant an anaplastic astrocytoma diagnosis with the appropriate treatment. Whether one advocates advancing the tumor a grade or not, recognition of the lesion in some form and acknowledgment of its potentially more aggressive behavior is warranted. Distinction of the gemistocytic astrocytoma from a low grade fibrillary type astrocytoma, even though both lesions are designated as WHO grade II tumors, is important from a prognostic standpoint. It is not unusual to see occasional gemistocytic cells in an otherwise ordinary low-grade fibrillary astrocytoma. The 20% cutoff suggested by Krouwer et al, although arbitrary, provides a general guideline to the approach of these lesions (2).

Also grouped together with low-grade fibrillary astrocytomas by the WHO classification schema is the rare protoplasmic astrocytoma. These tumors presumably arise from process-poor protoplasmic-type astrocytes, which

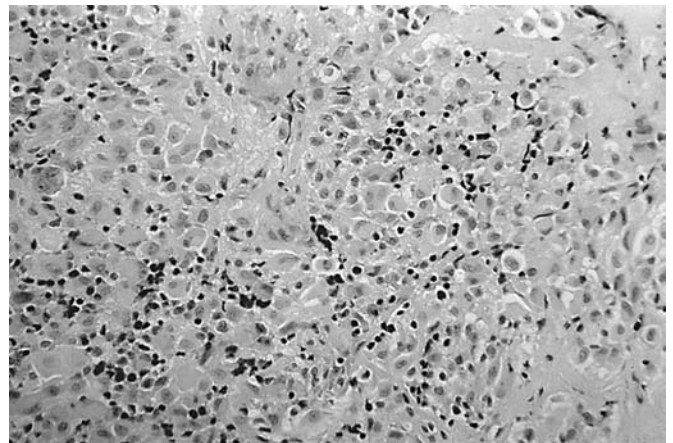


Fig. 4-1. Gemistocytic astrocytoma characterized by a proliferation of astrocytic cells with abundant eosinophilic cytoplasm and eccentric nucleus.

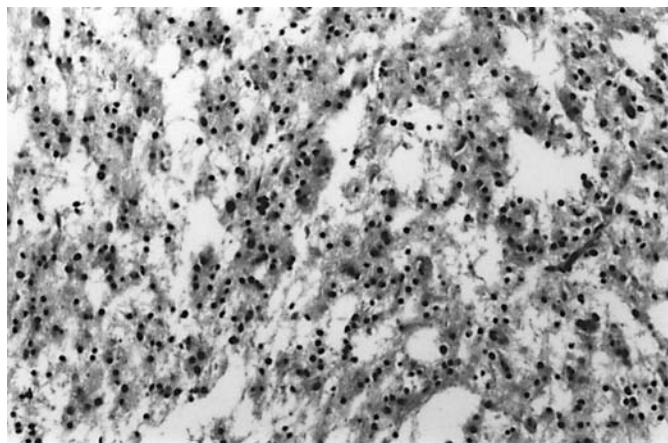


Fig. 4-2. Protoplasmic astrocytoma marked by cells with generally rounded nuclei and scant cytoplasm arranged against a microcystic background.

are found more predominantly in gray matter. The amount of literature specifically examining the protoplasmic astrocytoma is sparse and consists mainly of anecdotal reports of these lesions. One report of 16 such tumors describes an astrocytic tumor with cells characterized by generally round to oval nuclear contours, a paucity of cytoplasm, and a lack of prominent nucleoli (5). These cells are often arranged against a microcystic background, with cytoplasmic processes extending into the microcystic spaces (Fig. 4-2). The tumor often appears to be predominantly cortical based. Mitotic figures were generally absent and only mild nuclear pleomorphism is observed in a minority of cases. Vascular proliferation and necrosis are not prominently noted. Perivascular lymphocytes were only observed in a few of the tumors studied. Glial fibrillary acidic protein (GFAP) positive immunostaining is often variable. Interesting, most of the protoplasmic astrocytomas in this series arose in younger age patients. Most patients were male, and most tumors arose in the temporal or frontal lobes (5). Many of the patients presented with a chronic history of epilepsy and did well clinically after tumor resection. It was suggested that perhaps the more superficial location of the lesion made it more amenable to surgical resection (5). One study of the cell proliferation marker MIB-1 and protoplasmic astrocytomas showed a low degree of cell proliferation (mean MIB-1 labeling index of 0.7 in 18 tumors) (6).

From a differential diagnostic standpoint it would appear that the pure protoplasmic astrocytoma, because of its potentially better prognosis, needs to be distinguished from ordinary low-grade fibrillary type astrocytoma. In general, fibrillary astrocytomas will have slightly more elongated nuclei and only variable microcystic change. It also appears that GFAP positive immunostaining may be more diffuse in a fibrillary astrocytoma, as compared

with the focal staining pattern observed in the protoplasmic tumor.

Distinguishing the protoplasmic astrocytoma from microcystic areas of a pilocytic astrocytoma may also be difficult. The preferential locations of the two tumors are quite different. Most pilocytic astrocytomas do contain some compact areas with Rosenthal fibers, which may be helpful in making the distinction. The eosinophilic granular bodies, which are commonly, although not invariably, encountered in the microcystic areas of a pilocytic astrocytoma, are distinctly uncommon in the protoplasmic astrocytoma. The perivascular chronic inflammation, vascular proliferation, and nuclear pleomorphism, which may be focally prominent in pilocytic astrocytomas, are all distinctly uncommon in the protoplasmic astrocytoma.

More challenging and difficult differential diagnostic considerations involve distinguishing the protoplasmic astrocytoma from a low grade oligodendroglioma and dysembryoplastic neuroepithelial tumor. Oligodendrogliomas tend to be white matter-based lesions and are less frequently cystic. The arcuate vascular pattern which characterizes oligodendrogliomas is generally not a prominent feature of the protoplasmic astrocytoma. Oligodendrogliomas are more frequently calcified and tend to be more infiltrative. Prominent satellitosis and subpial aggregation of infiltrating oligodendroglial cells are also distinguishing characteristics. Because of the lack of a reliable marker for oligodendroglial differentiation, immunohistochemical staining is of little value in terms of differential diagnosis in this case (oligodendrogliomas may demonstrate focal positive immunostaining with GFAP similar to the protoplasmic astrocytoma). Particularly with a small biopsy specimen, distinction of the lesions may be quite difficult, if not impossible. The similarities between the dysembryoplastic neuroepithelial tumor and the protoplasmic astrocytoma are even more striking. This has caused some people to suggest that the protoplasmic astrocytoma may represent a variant of the dysembryoplastic neuroepithelial tumor (7). Both lesions generally occur in younger individuals and are associated frequently with a history of chronic epilepsy. In addition, both appear to be predominantly cortical based and do well clinically after surgical resection. Histologic features of the dysembryoplastic neuroepithelial tumor which may allow the distinction from protoplasmic astrocytoma includes its characteristic multinodular/multifocal architecture, participation of both glial and neuronal cells in the formation of tumor, and an association with cortical dysplasia; none of these features are seen in the protoplasmic astrocytoma.

Another fairly uncommonly encountered low-grade astrocytic lesion is the infantile desmoplastic astrocytoma or neoplastic cerebral astrocytoma of infancy. These

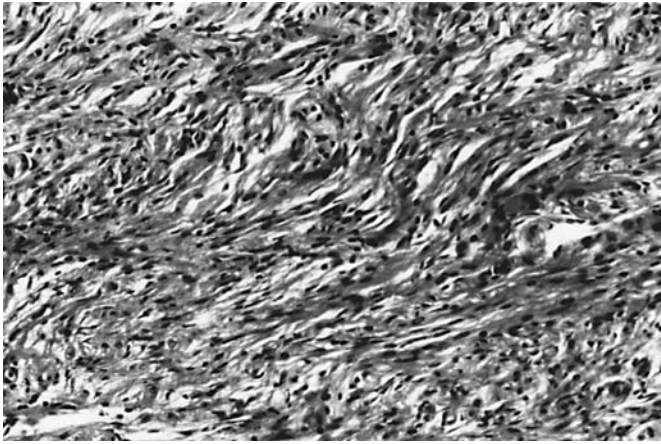


Fig. 4-3. Spindled astrocytic cells with increased collagen deposits (reticulin rich material) in a desmoplastic astrocytoma of infancy.

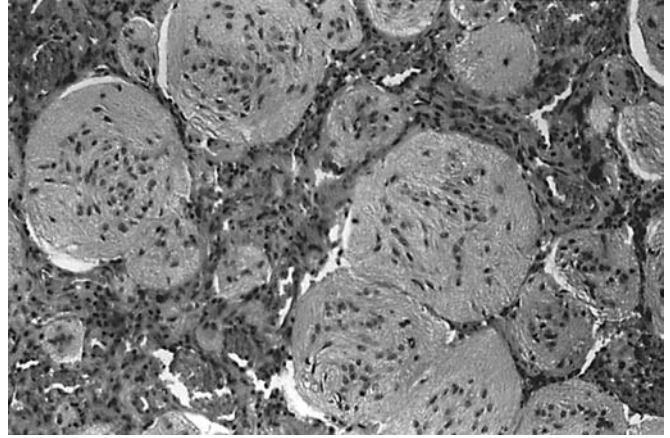


Fig. 4-5. Nasal "glioma" consisting of neuroglial tissue admixed with collagen.

tumors most commonly occur in the first year or two of life and are often large cystic, hemispheric neoplasms involving cortex and leptomeninges (8–10). Histologically, the tumor is characterized by marked desmoplasia with intermixed spindled astrocytic cells (Fig. 4-3). The cellularity may be quite variable and focal areas of marked cellularity may be seen with readily identifiable mitotic figures. Pleomorphism is often minimal and there is generally no significant degree of vascular proliferation. The spindled cells stain diffusely positive with GFAP. Most patients do well clinically with a good surgical resection. Care should be taken not to confuse this lesion with a high-grade astrocytoma, sarcoma, or gliosarcoma. If ganglion cells are identified, the term desmoplastic infantile ganglioglioma is the preferred designation. The significance of distinguishing the ganglioglioma variant from this astrocytoma is still debatable.

The so-called gliofibroma is an extremely rare lesion characterized by a prominent collagenous and fibroblastic

component associated with what generally appears to resemble a low-grade astrocytoma. Most cases of gliofibroma have been fairly well-circumscribed parenchymal masses consisting of an admixture of fibrous connective tissue and glial tissue (11–13) (Fig. 4-4). In contrast to the infantile desmoplastic astrocytoma, gliofibromas have been described in both children as well as adults, and examples of malignant behavior have been noted. The rarity of gliofibroma makes predicting prognosis difficult. However, many of the more aggressively behaving examples had worrisome histologic features. Whether more aggressively behaving tumors with worrisome histology should be designated as gliofibroma or as a malignant astrocytoma with a prominent mesenchymal component is a matter of debate. Unlike gliosarcoma, the mesenchymal component of the gliofibroma is not felt to be histologically malignant (i.e., sarcomatous).

Although not an astrocytic tumor per se, the nasal "glioma" is worth particular mention (14,15). This lesion represents the presence of heterotopic cerebral tissue in the nasopharyngeal region. These lesions do not represent gliomas in that they are not neoplasms. Distinction from an encephalocele is important; encephaloceles demonstrate a clear connection of the neuroglial tissue to the brain itself. Nasal glioma often presents clinically as a nasal mass and is curable by simple excision. Histologically, the lesion is comprised of an admixture of neuroglial tissue and variable amounts of chronic inflammation and collagen.

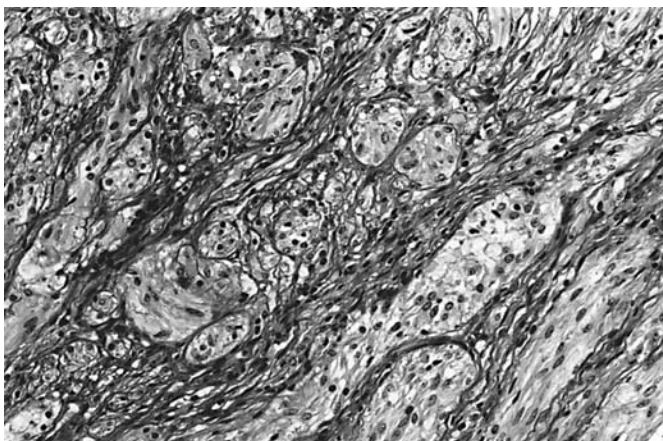


Fig. 4-4. Nests of astrocytomatous tissue separated by intervening collagen bundles in a gliofibroma.

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5 High-Grade Astrocytoma Variants

MOST FORMS OF GLIOBLASTOMA multiforme, despite their high grade nature, show some areas of obvious glial differentiation. Often the glial nature of the tumor is more evident at the peripheral, infiltrative edge of the tumor. This glial appearance allows for the recognition of glioblastoma multiforme as an astrocytic lesion. There are, however, a number of histologic phenotypes one might encounter in the spectrum of glioblastoma multiforme. Occasionally, the glioblastoma multiforme may be comprised mostly of small round cells with scant cytoplasm, morphologically similar to a small cell carcinoma (Fig. 5-1). Frequently, this pattern is intermixed with more recognizable astrocytic cells and is, therefore, not usually difficult to recognize. However, on a small biopsy, a differential diagnosis with metastatic small cell carcinoma may be entertained. In such cases, a combination of immunostains including glial fibrillary acidic protein (GFAP), cytokeratins, or neuroendocrine markers may resolve the issue. In most cases, at least focal GFAP positive staining will be observed in the small cell areas of glioblastoma multiforme. Keratin and neuroendocrine markers may variably stain small cell carcinomas. Certain keratin markers will also stain malignant astrocytomas. Low molecular weight keratin markers such as CAM5.2 seem to be less likely to stain astrocytomas. Often this differential depends on whether or not the patient has a known primary tumor, usually in the lung.

Rarely, glioblastoma multiforme may be composed primarily of giant cells (giant cell glioblastoma multiforme). This lesion consists primarily of large, multinucleated astrocytic cells (Fig. 5-2). This particular variant has been more commonly described in children, more frequently in females, and has been associated with a slightly better prognosis (1). The major differential diagnostic consideration with this lesion is with the lower grade pleomorphic xanthoastrocytoma. The giant cell glioblastoma generally demonstrates all the worrisome histo-

logic features that mark other glioblastoma multiforme lesions including necrosis, increased mitotic activity, and prominent vascular proliferation, features which are uncommon in the pleomorphic xanthoastrocytoma.

Glioblastoma multiforme occasionally assumes an epithelioid appearance or may rarely show differentiated epithelial elements (2,3). In 1991, Rosenbaum reported four cases of a so-called lipid-rich, epithelioid glioblastoma multiforme in which cells showed extensive cytoplasmic lipidization and cohesive architectural disposition in epithelioid nests and sheets (2). Histologically, the tumor can resemble metastatic clear cell carcinoma of renal or adrenocortical origin. Some of these tumors demonstrated areas of more conventional-appearing fibrillary-type astrocytoma. Tumor cells by immunohistochemistry stained positively for GFAP and were generally negative for cytokeratin markers, supporting the astrocytic lineage of these tumors. Again, care should be taken in the use of keratin markers in the evaluation of a epithelial-appearing lesion. Certain keratin markers, particularly cytokeratins AE1/3, will stain astrocytomas.

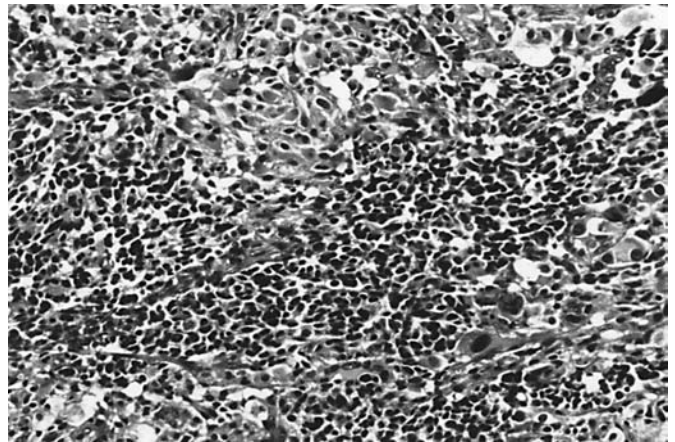


Fig. 5-1. Small cell component in a glioblastoma multiforme.

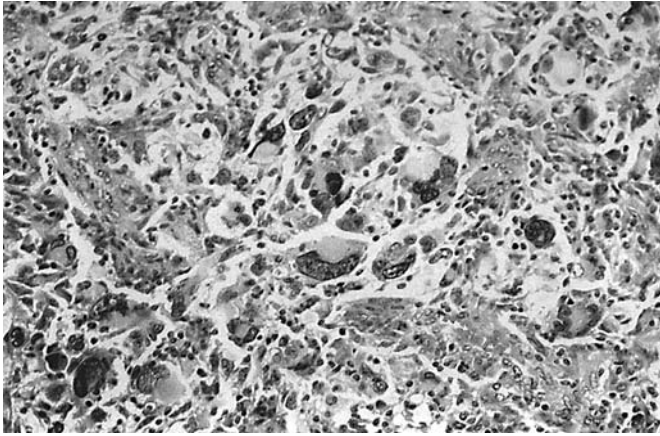


Fig. 5-2. Increased numbers of multinucleated giant cells in an giant cell glioblastoma multiforme.

Rare examples of granular cell-type differentiation in astrocytic tumors have also been described (4–6). These tumors generally show areas of transition from usually high-grade fibrillary astrocytoma to areas which resemble granular cell tumor. Cells show abundant cytoplasm, have a generally rounded contour with coarse granular eosinophilic cytoplasm and eccentrically placed nuclei (Fig. 5-3). Many of these cells stain positively for GFAP and show ultrastructural features reminiscent of granular cell tumors i.e. membrane-bound autophagic vacuoles and secondary lysosomes. Most cases in which granular cell areas have been observed in an astrocytoma have been higher grade tumors. It is felt that the granular cell change represents a degenerative phenomenon. From a differential diagnostic standpoint, care should be taken not to confuse the granular cells in a granular cell-rich area with macrophages in an infarct or demyelinating disorder. From an immunohistochemical standpoint, macrophage markers may be helpful in avoiding this confusion. In

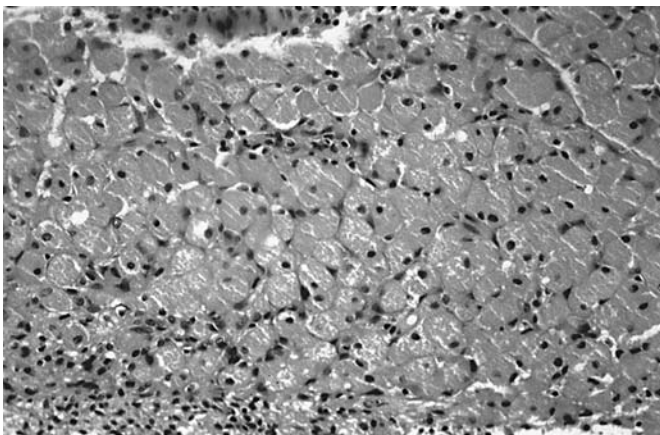


Fig. 5-3. Cells with abundant granular eosinophilic cytoplasm in an astrocytoma with granular cell differentiation.

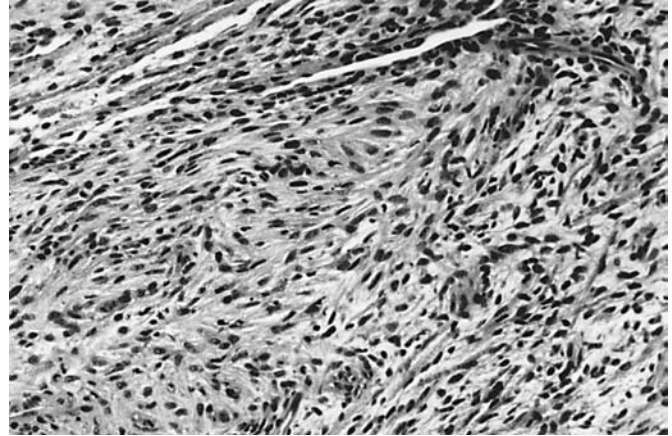


Fig. 5-4. Spindled cell appearance of glioblastoma multiforme.

addition, most granular cell astrocytomas show transition to areas having a more traditional fibrillary astrocytoma appearance.

Glioblastoma multiforme may also assume a number of other appearances histologically. Occasionally tumors may have a predominantly spindled cell appearance in which case distinguishing the lesion from a gliosarcoma or sarcoma may be of consideration (Fig. 5-4). Spindled glioblastoma multiforme should be reticulin poor but still demonstrate GFAP positive staining, in contrast to sarcomas or the sarcomatous components of a gliosarcoma which are GFAP negative and reticulin rich. Occasionally, cells in glioblastoma multiforme may become discohesive and cell boundaries may become more distinctive, in which case differential diagnosis with malignant melanoma may be entertained (Fig. 5-5). Again, immunohistochemistry should easily resolve the issue in these cases (melanomas are S-100 protein positive and HMB45 positive; keratin negative and GFAP negative). Rarely, a so-called spongioblastomatous pattern characterized by cords

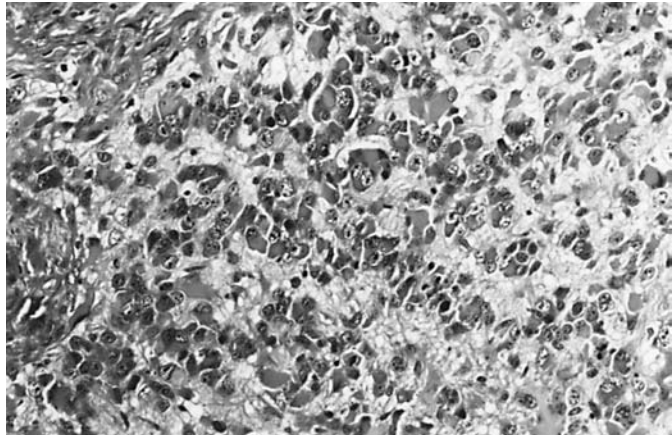


Fig. 5-5. Discohesive large cells in a glioblastoma multiforme resembling melanoma.

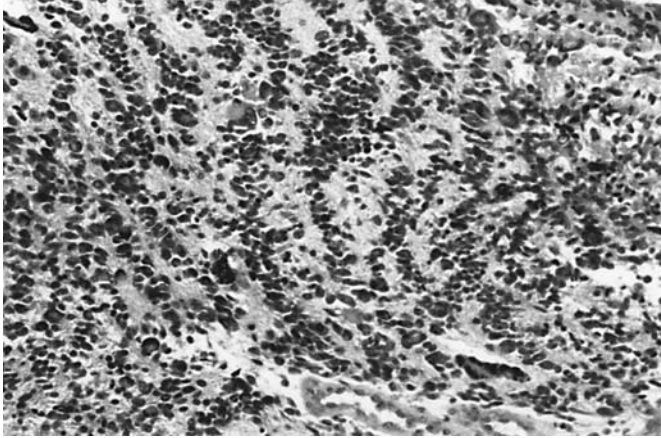


Fig. 5-6. Palisaded or spongioblastomatous appearance of a glioblastoma multiforme.

of tumor cell nuclei arranged in a palisaded fashion may be seen (Fig. 5-6).

A lesion that is somewhat akin to the glioblastoma multiforme, but has generated considerable interest in the literature, is the gliosarcoma (7–10). Gliosarcoma is a high-grade neoplasm consisting of a malignant glial component, typically resembling glioblastoma multiforme, and a malignant mesenchymal component, typically resembling some form of sarcoma. Approximately 2% of glioblastoma multiforme have a gliosarcomatous pattern (9,10). Histologically, these tumors consist of a glioblastoma multiforme component intermixed with a sarcomatous component (Fig. 5-7). The sarcomatous component may be of any type, but most frequently resembles fibrosarcoma or malignant fibrous histiocytoma (7). In general, the two patterns of this lesion are geographically arranged. In suspected cases, additional stains may be helpful in delineating the biphasic nature of the neoplasm. A GFAP stain should highlight and be restricted to the glioblastoma

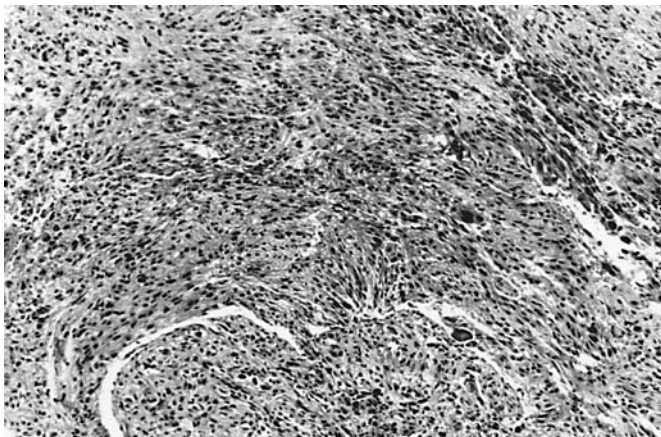


Fig. 5-7. Gliosarcoma characterized by an admixture of a high grade astrocytoma component and spindled sarcoma component.

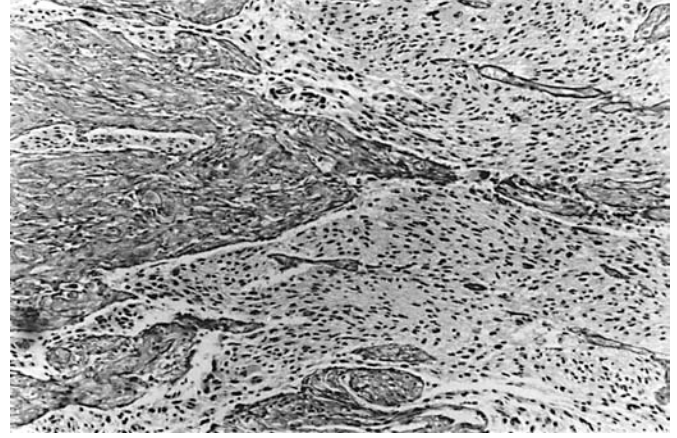


Fig. 5-8. Reticulin stain in a gliosarcoma showing increased reticulin staining in the sarcomatous area and reticulin confined to vessel walls in the astrocytoma component.

multiforme component of the tumor. The sarcomatous component is characteristically reticulin-rich. A reticulin stain should show increased reticulin staining around individual cells in the sarcomatous areas and shows a general absence of staining, except around vessels, in the malignant glioma regions (Fig. 5-8). Confusion with a spindled cell glioblastoma multiforme or a pure sarcoma can be avoided with this combination of stains. From a prognostic standpoint, there is little difference with regard to survival between glioblastoma multiforme and gliosarcoma (11). Reportedly, gliosarcoma has a slightly greater propensity for metastasis than glioblastoma multiforme. Either component of the tumor may be involved in the metastasis (7).

The exact nature of the gliosarcoma and the origin of the sarcomatous component is still a matter of debate. Historically, it has been thought the sarcomatous component of the gliosarcoma arose from a malignant transformation of the proliferative vasculature and vascular adventitia within a preexisting glioblastoma multiforme (7). More recent data looking at p53 mutations and interface cytogenetics have demonstrated similar cytogenetic DNA mutation abnormalities in both the gliomatous and sarcomatous component of gliosarcoma, suggesting a common origin of both components from glial cell lines in perhaps a subset of gliosarcomas (12,13). Examples of radiation induced gliosarcomas have also been described in the literature (14,15). Rare examples of so-called sarcoglioma have been described in which one starts with a preexisting sarcoma that presumably induces malignant gliomatous transformation in adjacent tissue (16). Whether this lesion represents a distinct entity or represents a gliosarcoma is not known.

The entity of gliomatosis cerebri represents a rare, diffusely infiltrative glioma, characterized by a widespread infiltration of glial neoplasm (17–20). Most com-

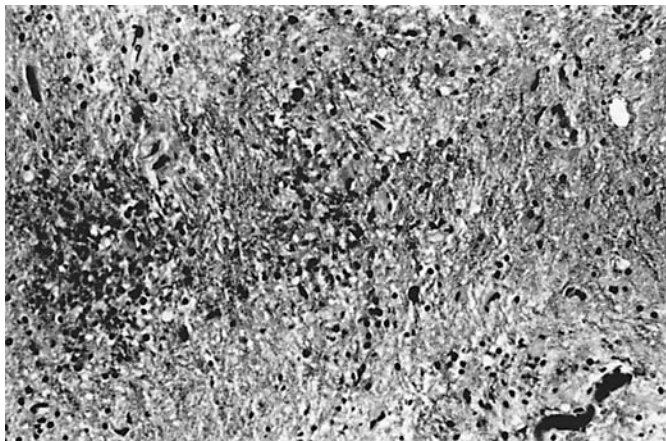


Fig. 5-9. Gliomatosis cerebri characterized by a mild degree of hypercellularity and scattered atypical astrocytic cells.

monly, the tumor histologically resembles a fibrillary-type astrocytic neoplasm. The lesion may be seen at any age and is characterized radiographically by widespread tumor. Histologically, a variety of findings may be seen. In most cases, the bulk of the tumor has a low-grade appearance with a mild degree of hypercellularity (Fig. 5-9). Cells in these regions often assume an elongated or spindle configuration. Foci of tumor, however, may be markedly cellular with marked nuclear atypia and abundant secondary structures of Scherer. In general, vascular proliferation and necrosis are not prominently noted. Mitotic figures may be infrequently identified. Rare cases of gliomatosis cerebri which have a predominantly oligodendroglial phenotype have also been described (18).

Diagnosis of the entity gliomatosis cerebri is a clinicopathologic one, unless one is dealing with autopsy material. Biopsies showing evidence of an infiltrating glial neoplasm combined with radiographic images suggesting a widespread process are suggestive of the diagnosis. At what point a lesion becomes widespread enough to warrant a designation of gliomatous cerebri is certainly a matter of debate. A rare entity referred to as microgliomatosis, which presumably represents a macrophage lesion, may histologically resemble gliomatosis cerebri (21). The cells in microgliomatosis tend to be more elongated and narrowed in appearance. Immunohistochemical markers for macrophage differentiation should allow for the distinction between these two rare lesions.

Due to the problems in precisely defining the entity gliomatosis cerebri, it is difficult to establish a sense of the lesion's behavioral characteristics. Tumors with areas of a high-grade appearance tend to behave in a more aggressive fashion. In general, the widespread distribution of the lesion forebodes a poor outcome.

Metastatic neoplasms are often the major differential diagnostic consideration in the evaluation of a poorly

Table 5-1
Glioblastoma Multiforme Versus Metastatic Carcinoma

	<i>Glioblastoma Multiforme</i>	<i>Metastatic Carcinoma</i>
Age	Any	Older
Multifocal	Less common	More common
Tumor border	Infiltrative	More discrete
Leptomeningeal involvement	±	±
Fibrillary background	+	—
Desmoplastic stroma	—	+
Discrete cell borders	±	—
Vascular proliferation	+	—
Perinecrotic pseudopalisading	±	—
GFAP	+	—
Cytokeratins	±	+

differentiated, high-grade neoplasm in the brain and spinal cord. Table 5-1 summarizes differential features between metastatic carcinoma and glioblastoma multiforme. Metastases are the most common tumors encountered in the central nervous system. They typically arise in older patients, in contrast to glioblastoma multiforme which more frequently arise in younger age patients. The majority of metastases are multifocal and they tend to be preferentially distributed in arterial watershed zones (22,23). Spinal cord parenchymal metastases are rare and are generally seen at the terminal stage of the disease process. Involvement of the leptomeninges by tumor (meningeal carcinomatosis) is a well recognized phenomenon, clinically marked by headaches, altered mental status and cranial nerve deficits. The most common tumors to metastasize to the brain include lung carcinoma, breast carcinoma, melanoma and renal cell carcinoma (24,25).

Grossly, metastatic lesions tend to be discrete and characterized by a sharp interface between tumor and the adjacent edematous and gliotic parenchyma (Figs. 5-10

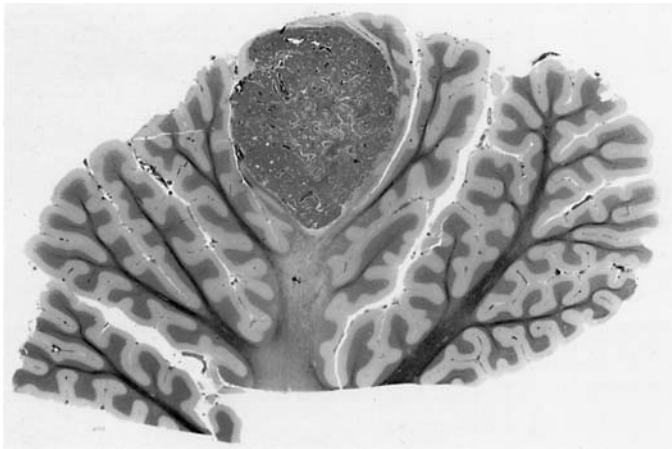


Fig. 5-10. Cerebellum with a well demarcated focus of metastatic carcinoma.

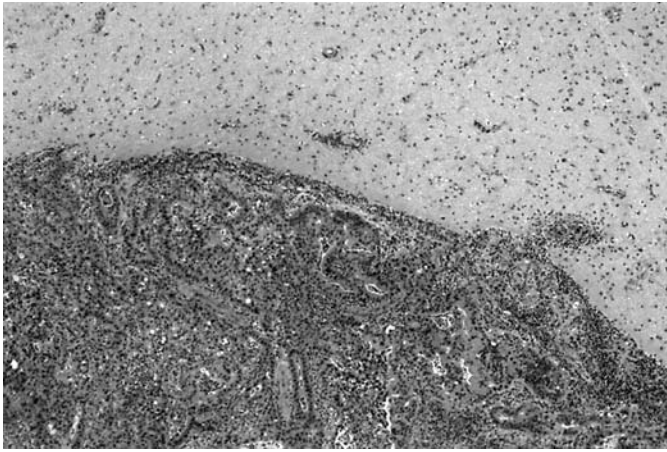


Fig. 5-11. Typical sharp interface between the metastatic tumor and the adjacent reactive parenchyma.

and 5-11). The tumor's gross appearance may be altered by a variety of features including necrosis, hemorrhage, calcification or melanin pigment.

Histologically, most metastases resemble the original tumor and have features that help to readily distinguish it from a glioma (Figs. 5-12 and 12-13). The fibrillary background, vascular proliferation, perinecrotic pseudopalisading by tumor cells and lack of discrete cell borders are features of glioma, not metastatic tumor. Desmoplastic stroma is more common in metastatic tumors, particularly carcinoma, than glioma. If one resorts to immunohistochemistry to distinguish a metastatic lesion from glioma, care needs to be taken in not confusing cross reactivity patterns of staining with certain markers (such as keratin marker), as previously discussed. Use of antibody panels including keratin subsets in trying to predict site of origin for a metastatic adenocarcinoma has been only variably successful, except for these rare tumors that have specific

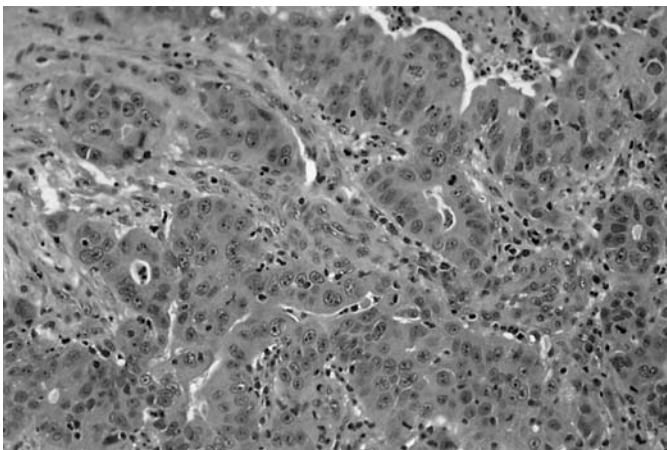


Fig. 5-12. Epithelial appearance of cells forming glands in a metastatic adenocarcinoma of lung origin.

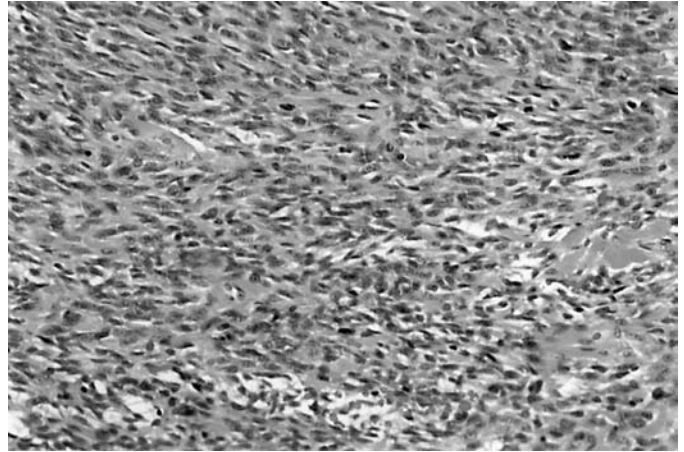


Fig. 5-13. Malignant spindle cell neoplasm representing a metastasis from a malignant peripheral nerve sheath tumor.

immunomarkers associated with them (e.g., thyroglobulin for thyroid carcinoma and prostatic specific antigen (PSA) for prostatic carcinoma (26).

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6 Radiation Change

UTILIZATION OF RADIATION THERAPY in the treatment of high-grade tumors of the central nervous system is common. The techniques used for delivering radiation and dosages administered are frequently determined by the tumor type one is dealing with, the age of the patient, and the extent and grade of the lesion. The main goal of utilizing radiotherapy is to maximize tumor cell death, while minimizing the effects of radiation on uninvolved surrounding tissue (1,2). Three major pathophysiologic mechanisms underlie the rationale for utilizing radiotherapy: 1) radiation causes an inhibition of mitotic activity; 2) radiation causes chromosomal damage; and 3) radiation causes cell death. Tumors with a high rate of cell proliferation tend to make better targets for radiotherapy than low grade, slowly proliferative neoplasms. Although, ideally, one would like to concentrate the effects of radiotherapy exclusively on the neoplasm, brain parenchyma immediately adjacent to the tumor is unavoidably involved as well. Many of the adverse effects associated with radiation therapy may be due to the effects seen in the nontumorous areas.

Adverse effects of radiation therapy are dependent upon a variety of parameters including total dosage administered, how the dose is administered (fractionation), age of patient, beam energy and composition, and utilization of concomitant chemotherapeutic agents, some of which may enhance the effects of radiation therapy. In general, cell death correlates with dosage administered. Smaller tumors tend to respond better; more hypoxic regions in the center of larger neoplasms may require higher dosages of radiation to achieve the same amount of cell death than better oxygenated tissue at the edge of the tumor (3). Time intervals between administrations of radiation are also important. Most current protocols make use of fractionation or dividing the total dose administered into smaller amounts. Fractionation takes advantage of the normal brain's capability of repairing DNA damage

faster than tumor cells can (4). It is well known that there are differences in vulnerability to radiation therapy in normal tissue by region as well as age. For example, tissue in the brainstem area is more susceptible to the effects of radiation therapy as compared to cortical tissue (5). Adverse effects of radiation therapy also appear to be more severe at the extremes of age (i.e., geriatric and pediatric age patients).

The histologic effects of radiation therapy can be divided into several time frames, ranging from acute to subacute and remote (5,6). Acute effects of radiotherapy often occur immediately during or after treatment and roughly correlate with the dose administered. Clinical symptoms include headaches, vomiting and nausea, and focal neurologic signs and symptoms (6). Most of these symptoms are attributable to an increase in edema.

In the subacute phase, reactive astrocytosis and gliosis develop in radiated areas (7) (Fig. 6-1). Diffuse microglial cell proliferation and mild perivascular chronic inflammation consisting primarily of lymphocytes and macrophages is also noted (Fig. 6-2). Focal transient demyelination

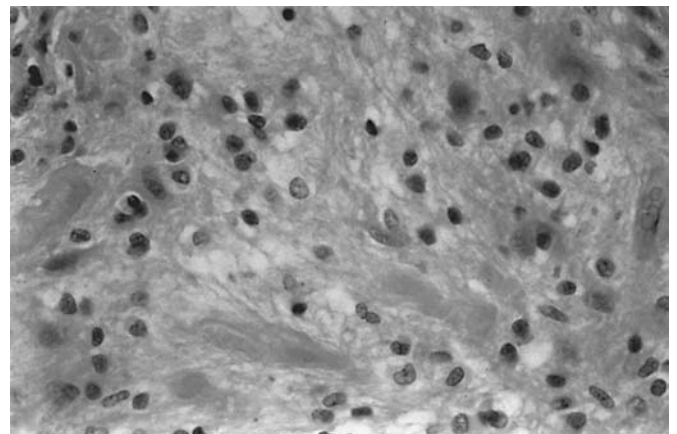


Fig. 6-1. Marked astrogliosis in the setting of radiation.

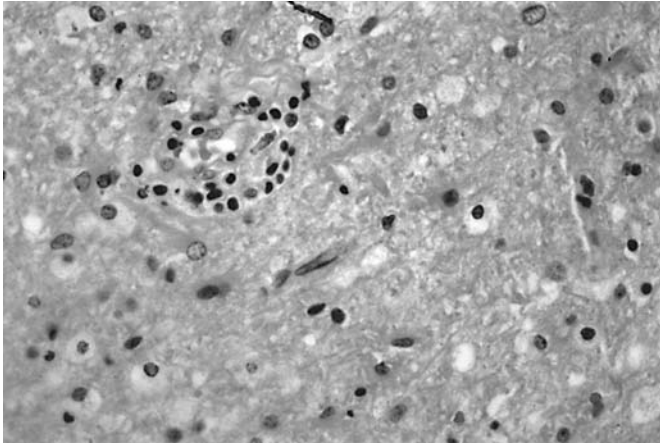


Fig. 6-2. Perivascular lymphocytes and reactive astrocytes secondary to radiation.

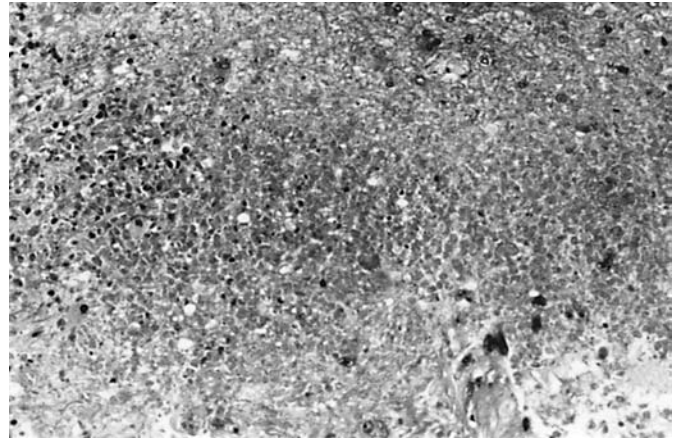


Fig. 6-4. An area of coagulative necrosis secondary to radiation.

ation may occur and is thought to be related to direct injury to oligodendroglial cells (6) (Fig. 6-3). Clinical symptoms of somnolence, anorexia and headaches are often associated with this period, which extends from about 2 to 12 weeks after administration of therapy (8).

Delayed effects of radiation therapy may occur anywhere from months to years after treatment. The most prominent features of this phase include vascular changes and coagulative necrosis (2,5,6,9). The coagulative necrosis is frequently observed to involve white matter and is often associated with edema (Figs. 6-4 and 6-5). The extent of radionecrosis is generally limited to the treatment field. Radiographically, these areas may enhance with contrast, and with surrounding edema, may mimic tumor (10,11). The thought is that the radiation necrosis is probably related to the extensive blood vessel changes which become evident during this period of time. Vessels frequently undergo a hyalinization or sclerosis of their wall accompanied by perivascular fibrosis (Fig. 6-6). Vessel

endothelial cells frequently are reactive in appearance. Radiation associated vasculitis or occlusion by atherosclerotic plaque or thrombus may be seen. Mineralization within vessel walls and dystrophic calcification in adjacent parenchyma and in areas of necrosis is also a fairly common occurrence (Fig. 6-7). Areas of petechial hemorrhage may be observed. Granulation tissue formation, increased collagen deposition and prominent reactive astrocytosis surrounding areas of necrosis are not uncommon (Fig. 6-8). In addition, radiation induced cytologic atypia involving reactive astrocytes including multinucleation and cytoplasmic vacuolization may be seen (Fig. 6-9).

A potential long term risk of radiation therapy is the development of a secondary neoplasm (5,6). Secondary neoplasms frequently develop several years after administration of radiation therapy. The development of these tumors has occurred in the setting of a wide range of dosages and treatment conditions. The most common tumors described arising in this scenario include various



Fig. 6-3. Luxol fast blue myelin stain highlighting a pale staining area of postradiation demyelination.

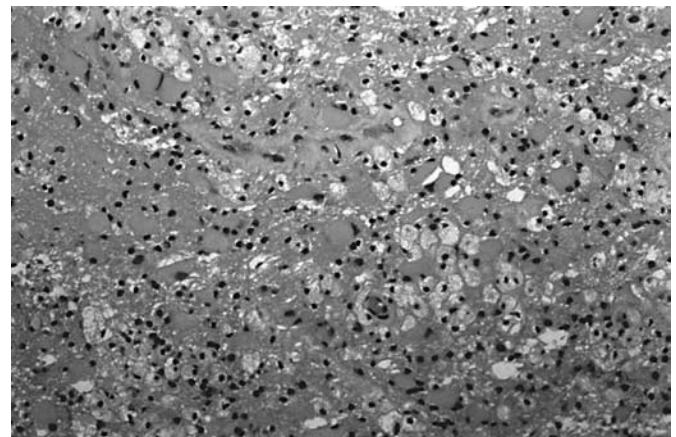


Fig. 6-5. Infiltrating macrophages and reactive astrocytes adjacent to a focus of radiation-induced necrosis.

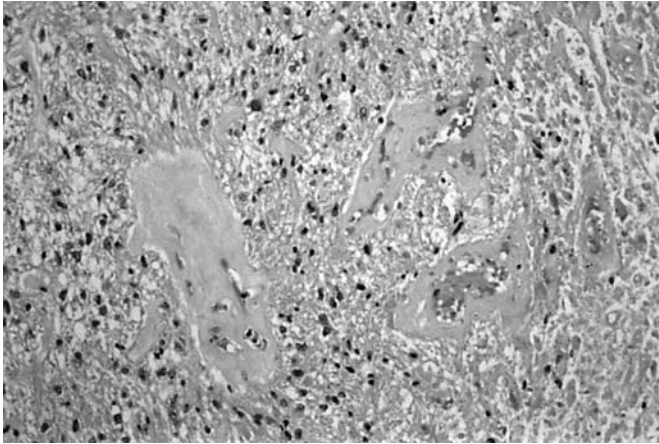


Fig. 6-6. Prominent vascular sclerosis adjacent to an infarct secondary to radiation.

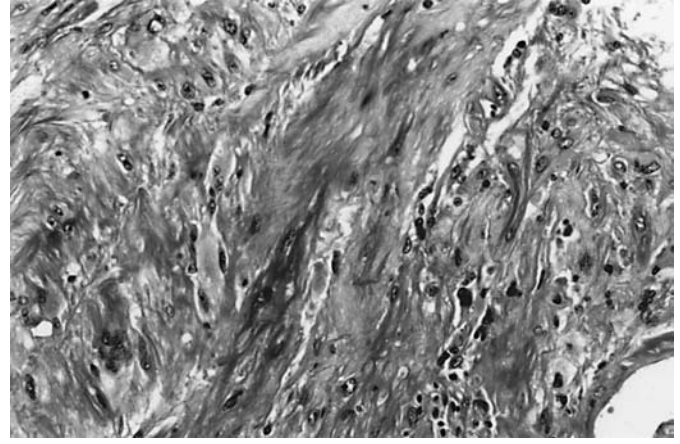


Fig. 6-8. A focus of marked parenchymal fibrosis in remotely radiated brain parenchyma.

types of meningioma, sarcoma, and glioma (5,6,12–16). In addition, rare reports of structural abnormalities of the cortex have been attributed to radiation therapy as well (17).

Among the more common tumors of the central nervous system for which radiation therapy is utilized includes high grade gliomas, where it currently is the standard approach to the treatment of many anaplastic and malignant gliomas. A fairly common scenario involves the patient with a previous biopsy diagnosis of a malignant glioma. A course of radiation therapy is administered. The patient is followed by serial imaging studies and develops radiographic changes. The question arises whether these changes are secondary to radiation or are the result of the neoplasm which has continued to expand despite radiation therapy. At this point, a biopsy is often performed and the pathologist is faced with the task of assessing whether or not there is tumor present and to what degree the changes are due to radiation therapy.

Table 6-1 summarizes histopathologic features which may be useful in differentiating radiation changes from recurrent glioma. Both lesions are clearly associated with a reactive astrocytosis/gliosis. The increased cellularity associated with tumor is often unevenly distributed throughout the neoplasm; gliosis associated with radiation therapy tends to be distributed evenly throughout the entire radiated field. Edema is also a common finding associated with both lesions and is similar in distribution. Cytologically, many of the cells have the appearance of reactive astrocytes. Radiation associated atypia with markedly enlarged and bizarre-appearing cells, frequent multinucleation, highly irregular nuclear contours, and frequently vacuolated cytoplasm is common. These cells are frequently more atypical and bizarre than cells routinely encountered even in high grade gliomas. Looking for cells which have a “conventional” malignant appearance is perhaps more useful in distinguishing the two processes. Cells with a high nuclear to cytoplasmic ratio, single enlarged nucleus

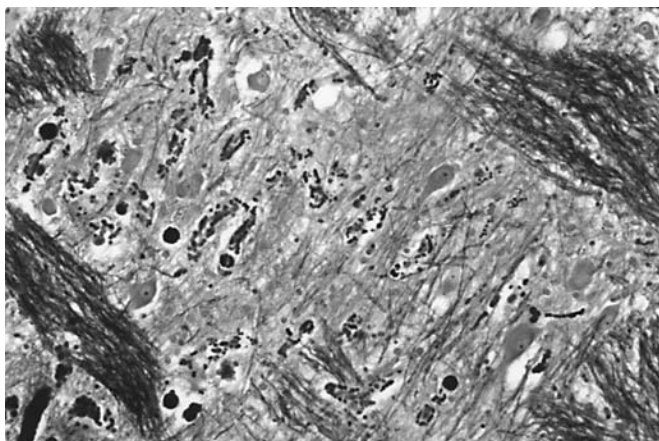


Fig. 6-7. Luxol fast blue myelin stained section of pons showing prominent perivascular mineralization due to remote radiation therapy.

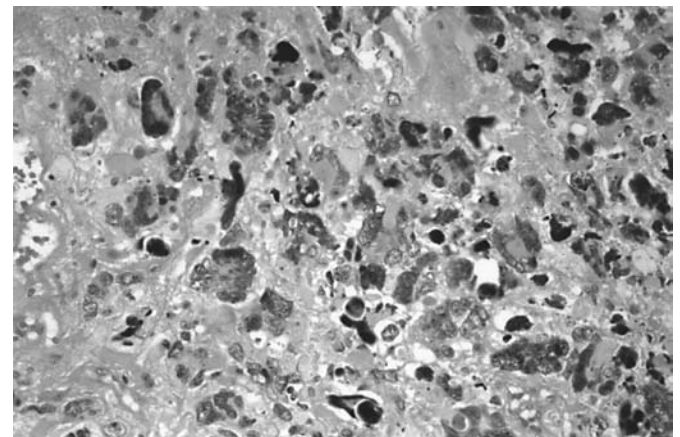


Fig. 6-9. Radiation-induced atypia in an anaplastic astrocytoma.

Table 6-1
Radiation Changes Versus Recurrent High-Grade Glioma

	<i>Radiation</i>	<i>High-Grade Glioma</i>
Edema	+	+
Cell distribution	Even	Uneven
Vessels	Hyalinization	Vascular endothelial proliferation
Atypia	+(reactive astrocytes and bizarre cells)	+
High nuclear/cytoplasmic ratio	—	+
Perinecrotic palisading	—	+
Necrosis without palisading	±	±
Calcification in necrosis	±	— (rarely +)
Macrophages	+	— (rarely +)

with irregular nuclear contour, and nuclear hyperchromasia are clearly indicative of tumor, irrespective of whether the lesion has been radiated or not. Hyalinized vessel changes are quite common in the setting of radiation therapy and are only rarely observed in high grade gliomas. In general, vessels associated with higher grade gliomas show evidence of vascular endothelial proliferation. Necrosis may be observed in either process. If necrosis is rimmed by a pseudopalisade of tumor cells, this necrosis is most certainly tumor related. However, it is common for necrotic foci of tumor such as glioblastoma multiforme to be devoid of a pseudopalisade of the tumor cells, in which the case distinction of intrinsic tumor necrosis from radiation necrosis may be impossible to make with absolute certainty. More commonly, radiation associated necrosis is accompanied by a variable macrophage infiltrate and may demonstrate microcalcifications. Prominent macrophages or calcification within areas of necrosis, although not common in high grade gliomas, can rarely be seen.

Ultimately, making a decision as to whether or not changes seen on histologic sections are entirely due to radiation therapy or whether there are radiation effects superimposed upon a recurrent or residual malignant glioma may be difficult. Caution should be taken in grading recurrent tumors. Certainly, the tumor initially designated as a glioblastoma multiforme or grade IV astrocytoma, remains high grade. Problems arise when trying to assess whether or not an anaplastic astrocytoma or grade III astrocytic lesion has upgraded. The presence of necrosis rimmed by a pseudopalisade of tumor cells would be definitive evidence in support of tumor progression. Likewise, prominent vascular endothelial proliferation, if one is utilizing the WHO or St. Anne-Mayo grading schemas would also be indicative of a high-grade lesion. However, necrosis in the absence of a pseudopalisade may be impossible to assign to the radiation therapy or to the intrinsic behavior of the tumor itself and, therefore, should not necessarily prompt a change in tumor grade.

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7 Pilocytic Astrocytoma

THERE IS A VARIETY OF subtypes of astrocytoma that are important to distinguish from the fibrillary-type astrocytic neoplasms because of differences with regard to clinical presentation, prognosis, and ultimately therapy. Probably the most common of these variant tumors is the pilocytic astrocytoma. With the exception of the World Health Organization (WHO) grading schema, pilocytic astrocytomas are generally not graded (1). According to the revised WHO schema for grading astrocytic neoplasms, pilocytic astrocytomas are designated as grade I neoplasms (1).

Pilocytic astrocytomas have been described as arising throughout the neural axis; however, they are most frequently encountered in the cerebellum (juvenile cerebellar astrocytoma), adjacent to the third ventricle, optic chiasm and optic nerves, brainstem, and thalamus. This is in contrast to the typical fibrillary astrocytoma, whose distribution roughly correlates with the amount of white matter in various regions of the brain (frontal lobe being the single most common site of origin for fibrillary astrocytomas). Occasionally, pilocytic tumors may also arise in other sites. The peak incidence for pilocytic astrocytomas is the first two decades of life. There is no definite gender preference among patients. Similar to other CNS neoplasms, clinical signs and symptoms are often dependent on the size and location of the tumor. Rare cases of multifocal pilocytic astrocytomas have been described, and predominantly occur in the setting of neurofibromatosis type I (von Recklinghausen's disease) (2).

The typical radiographic appearance of a pilocytic astrocytoma is different than the usual fibrillary astrocytic tumor (3–6). The classic gross and radiographic appearance is that of a cystic or multicystic neoplasm with a mural nodule or nodules. Radiographically, nodules often show areas of enhancement, corresponding to the vascular proliferation that is quite common in these tumors. Although the tumor frequently has a fairly discrete appear-

ance grossly, microscopically the lesion typically has an infiltrative margin. Focal leptomeningeal involvement by pilocytic astrocytoma has been described, but does not appear to alter prognosis in any negative fashion (7). Occasionally, particularly in the brainstem location, pilocytic astrocytomas may assume a predominantly exophytic growth pattern (2). These tumors tend to do better than their fibrillary astrocytoma counterpart in this location. Although historically, the term brainstem glioma and optic nerve glioma have been used for tumors arising in the brainstem and optic nerve regions, use of such terminology should be abandoned. Such terms provide little information with regard to tumor type or grade, both of which are important from a prognostic standpoint.

The typical histologic appearance of the pilocytic astrocytoma is a biphasic neoplasm consisting of areas in which the cells are loosely arranged against a microcystic background, alternating with more compact areas in which spindled or piloid cells are arranged against a densely fibrillary background (Figs. 7-1, 7-2, and 7-3). In any

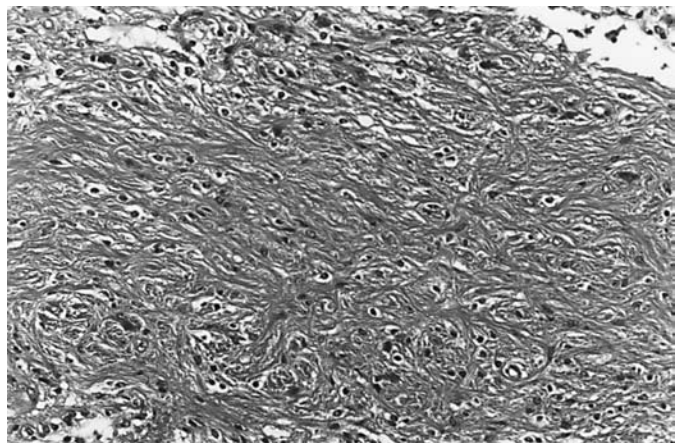


Fig. 7-1. Compact area of pilocytic astrocytoma with densely fibrillary background.

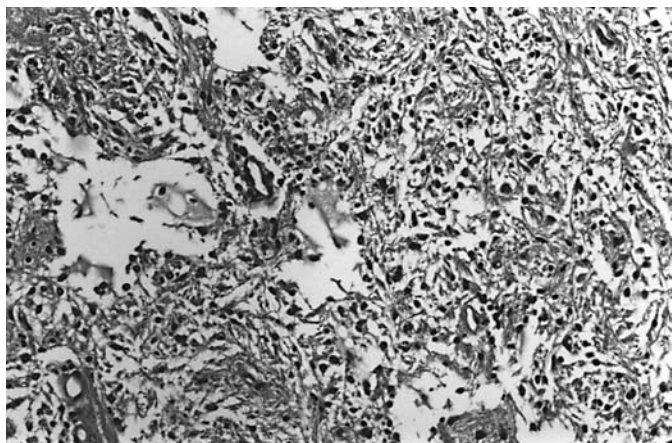


Fig. 7-2. Microcystic area of pilocytic astrocytoma.

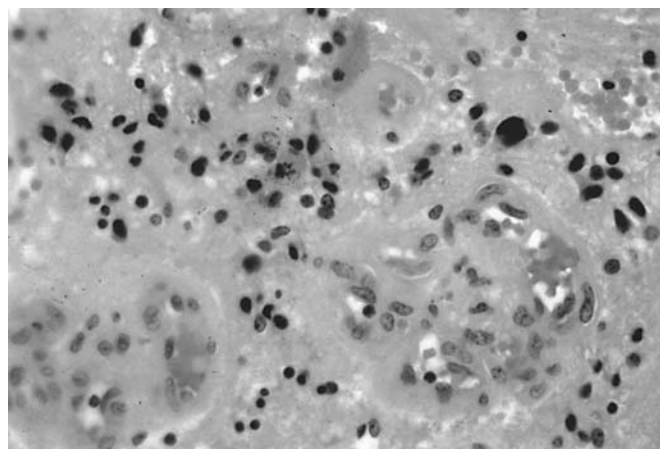


Fig. 7-4. Prominent nuclear pleomorphism and rare mitotic figure in a pilocytic astrocytoma.

given tumor, the percentage of each component can be quite variable. Tumors comprised of exclusively one pattern or the other have been described, including the so-called adult variant which tends to be monophasic, consisting of predominantly elongated cells (2). Many of the histologic features typically used in grading and evaluating fibrillary astrocytomas do not seem to hold the same significance when dealing with pilocytic tumors. Focally prominent nuclear pleomorphism may be observed in a pilocytic astrocytoma, but is thought to represent a degenerative change. Occasional multinucleated giant cells may also be identified. Rare mitotic figures may be observed in a pilocytic astrocytoma; however, they are generally not seen in great numbers (Fig. 7-4). The low degree of cell proliferation in pilocytic tumors has been further substantiated by studies which have examined cell proliferation markers in these tumors (8–11). Such studies have

shown very low labeling indices, even when compared with those seen in a low grade fibrillary type astrocytoma. Vascular proliferation, similar to that seen in malignant astrocytomas, is common in a pilocytic tumor, but it does not hold the same negative prognostic significance as it does in fibrillary astrocytomas. Hyalinized vascular sclerosis may also be focally prominent in pilocytic astrocytomas (Fig. 7-5). Perivascular chronic inflammatory cells consisting primarily of lymphocytes are quite common. Tumor cell necrosis is generally not a feature of pilocytic astrocytoma. If such necrosis is seen, one should reevaluate one's initial interpretation. Occasionally, pilocytic astrocytomas may demonstrate infarct-associated necrosis. Similarly, tumors that have been recently operated on or have been radiated may also contain areas of necrosis.

Two histologic features which are quite distinctive of pilocytic astrocytomas, particularly when contrasted with the fibrillary-type astrocytoma, are the presence of eosinophilic granular bodies and Rosenthal fibers. Both of these

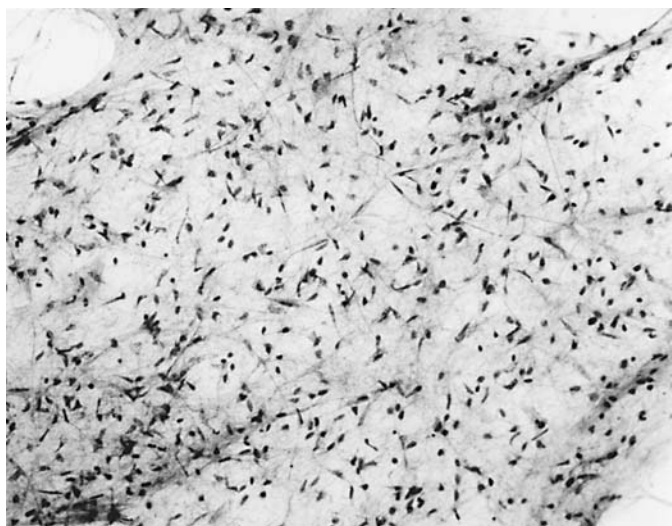


Fig. 7-3. Cytologic preparation showing an increased number of cells with elongated (piloid) nuclei.

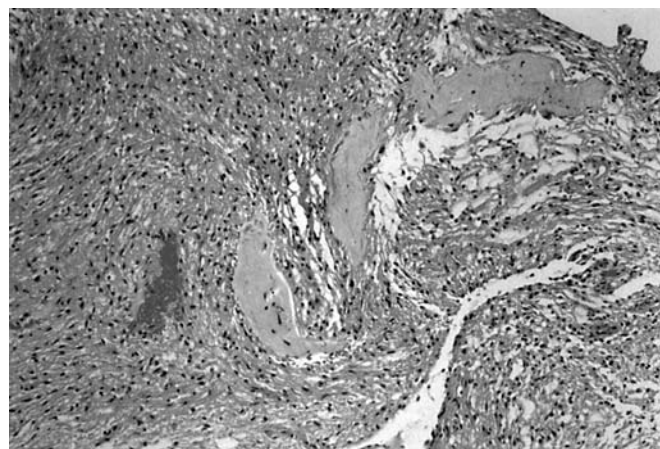


Fig. 7-5. Hyalinized vascular sclerosis in a pilocytic astrocytoma.

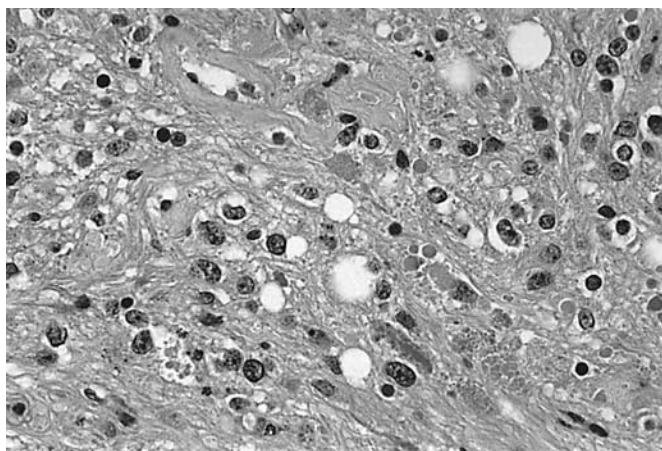


Fig. 7-6. Several granular bodies and eosinophilic droplets in a pilocytic astrocytoma.

features are not exclusively seen in pilocytic astrocytomas in that they can be encountered in association with other low grade neoplasms, gliosis, and certain nonneoplastic conditions. However, both of these features are distinctly uncommon in ordinary fibrillary type astrocytomas. These features are also not an invariable finding in all pilocytic tumors. One study found evidence of Rosenthal fibers in 83% of pilocytic tumors examined and granular bodies in 75% of the tumors (12).

Granular bodies are eosinophilic, rounded structures comprised of granular material (13) (Fig. 7-6). Occasionally, they can assume a brightly eosinophilic droplet-like configuration and may stain positively with PAS. Ultrastructurally, granular bodies consist of intermediate filaments, lipid droplets, myelin figures, and granular debris (13). Rosenthal fibers are brightly eosinophilic, elongated, and sometimes twisted appearing structures (Fig. 7-7). They are most prominently observed in the compact areas of a pilocytic astrocytoma. Care should be

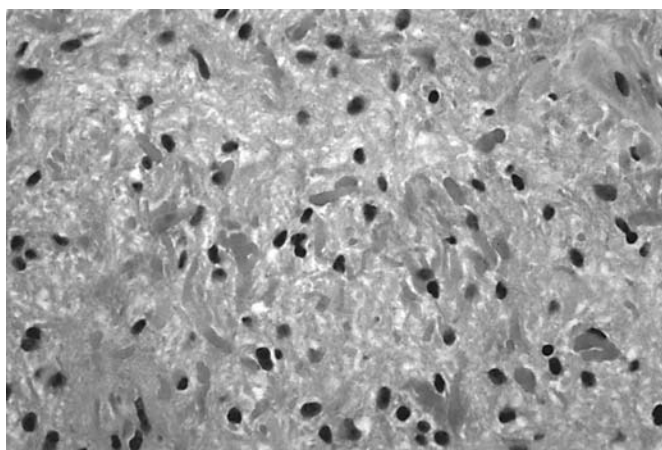


Fig. 7-7. Prominent numbers of Rosenthal fibers in the compact area of a pilocytic astrocytoma.

taken, during intraoperative frozen section consultation, not to mistake small congested capillaries with intraluminal lysed red cells for Rosenthal fibers. Ultrastructurally, Rosenthal fibers consist of electron dense granular material and condensed glial filaments and may stain around the periphery for glial fibrillary acidic protein (GFAP) (14).

Distinction of the pilocytic astrocytoma from fibrillary astrocytomas, as mentioned before, is important from a prognostic and subsequently therapeutic standpoint. Most pilocytic astrocytomas are slow growing lesions, which if completely excised, do very well. In one series, 41 pilocytic astrocytomas were compared with 90 fibrillary astrocytic neoplasms; five and ten year survival rates for pilocytic astrocytomas were 85% and 79%, respectively, as compared with the fibrillary astrocytoma group where five and ten year survival rates were 46% and 17%, respectively (15). Unlike fibrillary astrocytomas, which have a propensity to progress from low to high grade lesions over time, pilocytic astrocytomas generally do not progress or undergo malignant degeneration. Whether or not pilocytic tumors can degenerate into higher grade lesions is still a matter of debate. Many such reported cases involve patients who received prior radiation therapy, raising the question as to whether or not the higher grade lesion represents a radiation-induced neoplasm. Those who advocate the existence of malignant pilocytic astrocytomas describe tumors with markedly increased mitotic activity and cellularity, prominent vascular proliferation, and foci of necrosis with pseudopalisading (5,9). Frequently the cellularity is marked to such a degree that the typical biphasic pattern of pilocytic astrocytoma is obscured. In general, radiation therapy is not routinely employed in the therapeutic management of a pilocytic tumor, and it does not appear to be associated with improved survival (16,17).

Ancillary studies, including cell proliferation markers and DNA indices, have generally not provided useful prognostic or diagnostic information. A particularly high cell proliferation labeling index may sway one away from a diagnosis of pilocytic astrocytoma. A number of the molecular genetic abnormalities that have been described in association with fibrillary type astrocytomas, such as p53 mutations, have not been noted in pilocytic tumors (10,17).

Although fibrillary astrocytomas are often the major differential diagnostic consideration when confronted with the pilocytic tumor (see Table 7-1), the histologic appearance of a pilocytic astrocytoma can be varied enough, on occasion, to warrant consideration of other neoplasms. Focal areas of pilocytic astrocytoma can resemble low grade oligodendroglioma, consisting of cells with generally rounded nuclei and perinuclear halos (Fig.

Table 7-1
Pilocytic Versus Low-Grade Fibrillary Astrocytoma

	<i>Pilocytic</i>	<i>Fibrillary</i>
Age	Children, young adults	Young and middle age adults
Location	Cerebellum, 3 rd ventricle region, optic nerve, thalamus	Frontal lobe>parietal>temporal>occipital
Imaging studies	Cystic with enhancing mural nodule(s)	Ill-defined low density (enhancement with higher grade tumors)
Gross	Well circumscribed, cystic	Ill-defined, obliterate gray-white junction
Leptomeningeal involvement	±	+(higher grade)/ –
Biphasic histology	+	–
Pleomorphism	Mild to marked	Mild (low grade) to marked (high grade)
Mitoses	±	– (low grade) to + (high grade)
Vascular proliferation	+	+(high grade)
Necrosis	–	+(glioblastoma multiforme)
Granular bodies	+	–
Rosenthal fibers	+	–
Hyalinized vessels	±	–
Infiltrating pattern	+	+
GFAP	Variable +	+
Vimentin	Variable +	+
Treatment	Excision	Excision ± radiation
Prognosis	Better	Variable/generally worse
Malignant degeneration	Rare (<1%)	More common
Cell proliferation markers	Lower	Higher
p53 (chromo 17p loss)	–	+(25–45%)

7-8). In general, this finding is focal in a pilocytic tumor, and other areas of the lesion have a more characteristic appearance. Similar to fibrillary astrocytomas, distinguishing a pilocytic tumor from an exuberant gliosis may be difficult with a small biopsy, particularly if the compact area of the pilocytic tumor is all one has to look at.

Differentiating between a pilocytic astrocytoma and a ganglioglioma may, at times, also be difficult. It is not unusual for the glial component of a ganglioglioma to resemble a pilocytic tumor. Pilocytic tumors may entrap adjacent neuronal cells and give the impression of a glial-neuronal neoplasm. In addition, a number of features commonly observed in pilocytic astrocytoma, including the presence of perivascular chronic inflammation and eosinophilic granular bodies, are also quite commonly encountered in gangliogliomas. The major key to the differential diagnosis lies in recognizing an atypical neuronal cell component in the ganglioglioma, as opposed to entrapped, cytologically normal neurons in a pilocytic tumor. Care should be taken in utilizing immunohistochemistry to demonstrate neuronal differentiation or to identify neuronal or ganglion cells. The presence of such cells, as evidenced by positive staining, does not necessarily equate with the diagnosis of a ganglion cell tumor. One needs to demonstrate atypia or an abnormal distribution/collection of such cells to diagnose ganglioglioma. In addition to the histologic similarity, gangliogliomas share many features both clinically and radiographically with pilocytic astrocytomas as well. Sites typically common for pilocytic tumors are fairly uncommon for ganglioglioma.

Similar to gangliogliomas, the pleomorphic xanthoastrocytoma also shares several features in common with pilocytic astrocytoma, including generally young age of presentation and the cyst/multicystic lesion with enhancing neural nodule(s) configuration. In contrast to the typical locations of pilocytic astrocytoma, the pleomorphic xanthoastrocytoma tends to be a superficial, leptomeningeal-based lesion. The degree of nuclear pleomorphism encountered in a pleomorphic xanthoastrocytoma often far exceeds that seen in the typical pilocytic astrocytoma. Xanthomatous or lipidized appearing astrocytes are also not a feature of pilocytic astrocytomas. In addition, the presence of abundant reticulin material deposited between

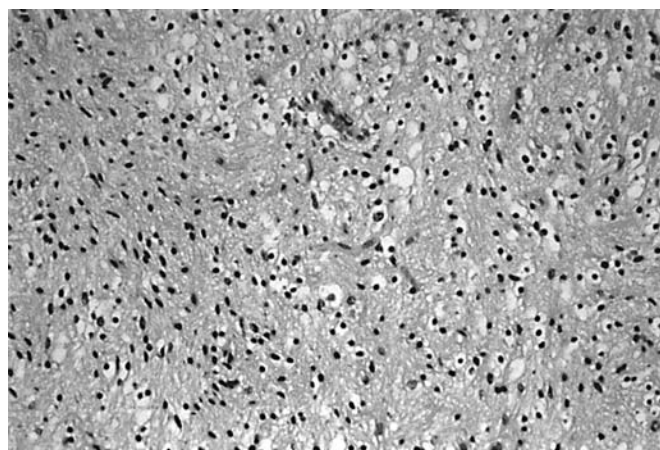


Fig. 7-8. Perinuclear halos around cells in a pilocytic astrocytoma resembling oligodendroglioma.

tumor cells is quite characteristic of pleomorphic xanthoastrocytoma, but is distinctly absent in pilocytic tumors, which like fibrillary astrocytomas, are generally reticulin-poor lesions.

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8 Pleomorphic Xanthoastrocytoma

IN 1973, DR. JOHN KEPES REPORTED three cases of superficial temporal lobe tumors occurring in 11- and 12-year-old children (1). These tumors involved both the leptomeninges and superficial cerebral cortex, were composed of spindle shaped and multinucleated giant cells containing abundant lipid droplets, and were rich in reticulin fibers that surrounded individual tumor cells. Based on their location and these histopathologic features, they were considered to represent fibrous xanthomas of the meninges invading the brain. It was noted, however, that in less lipidized areas of the tumors, the tumor cells resembled astrocytes. With the development of antibodies to glial fibrillary acidic protein in the late 1970s, Drs. Kepes and Rubinstein went back to these cases (as well as nine others), and reclassified them as astrocytic tumors, suggesting the name “pleomorphic xanthoastrocytoma” (PXA) (2). In this landmark article, Drs. Kepes, Rubinstein, and Eng described 12 supratentorial astrocytomas occurring in patients ranging from 7 to 25 (average 12) years of age. The tumors were superficial, usually involved the leptomeninges, and most often were grossly cystic. The cardinal histopathologic features described in the earlier study (pleomorphism, cytoplasmic lipidization, and dense pericellular reticulum) were reemphasized, and several other important microscopic features were defined, including eosinophilic granular bodies, variable numbers of lymphocytes and plasma cells, a paucity of mitotic figures, and the absence of necrosis (Figs. 8-1 through 8-5). The authors suggested that the tumors may have arisen from subpial astrocytes, as these cells were known to be normally invested by basal laminae that appear to be a product of the astrocytes themselves, and not that of the pial elements. Most importantly, they stressed the relatively favorable biologic behavior of these tumors, as most of their patients were alive at the time of follow-up, which for several was 16 to 25 years after diagnosis.

Since the publication of this article in 1979, approximately 200 PXAs have been reported (3). While the age range has broadened to include patients from age 2 to 82, the majority of patients present in the second decade, usually after several years of seizures. Ninety percent of these tumors are superficial and supratentorial, with temporal and parietal lobes predominating (4). Unusual reported locations include the thalamus, cerebellum, spinal cord, and retina (5–8). Half demonstrate a cystic component on neuroimaging, and the majority show marked enhancement. At operation, two-thirds demonstrate leptomeningeal involvement, with 10–15% involving the dura as well. Due to the abundant reticulin seen microscopically, PXAs are virtually always described by the surgeon as firm or rubbery. Over the years, a variety of histopathologic variants of PXA have been described including tumors with epithelioid (but GFAP-positive) areas, richly vascularized (“angiomatous”) forms (9), and tumors with gangliogliomatous differentiation. In addition, a PXA was

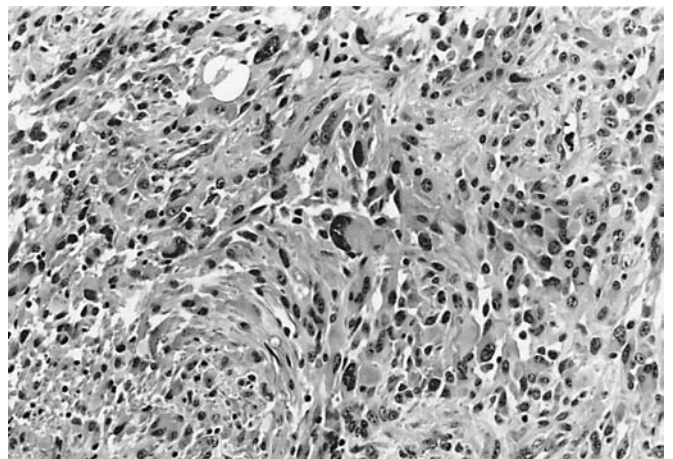


Fig. 8-1. Cellular pleomorphism in a pleomorphic xanthoastrocytoma.

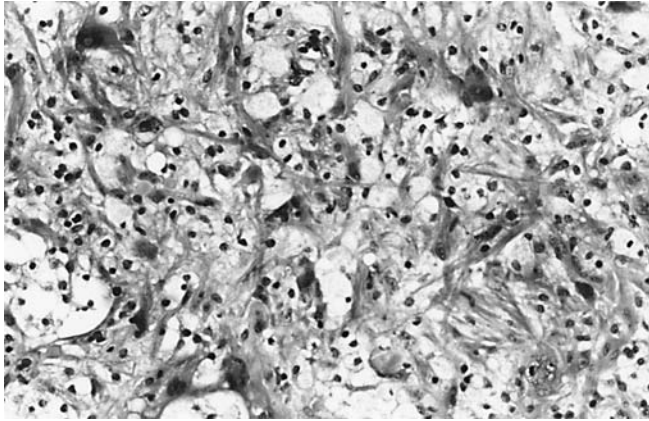


Fig. 8-2. A focus of marked cytoplasmic lipidization within a pleomorphic xanthoastrocytoma.

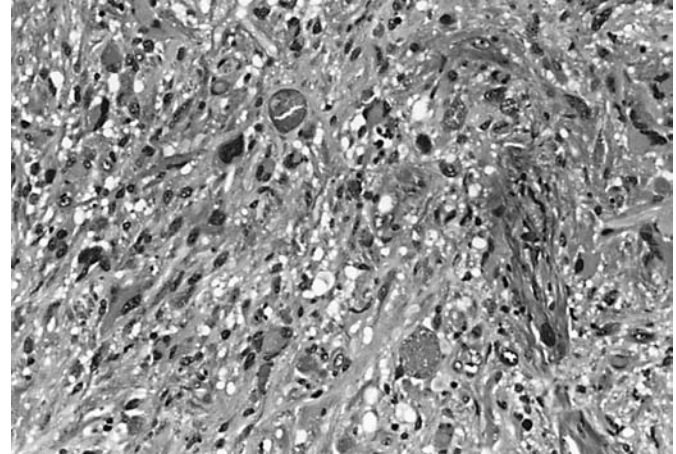


Fig. 8-4. Protein granular bodies in a pleomorphic xanthoastrocytoma.

recently described in a patient with neurofibromatosis (10).

Actuarial survival rates at 5, 10, and 15 years after operation are 91%, 82%, and 77%, with a median survival time of 18 years. Recent articles have emphasized the relevance of traditional histopathologic predictors such as mitoses and necrosis (Fig. 8-6) (11–13). Unfortunately, quantitation of mitotic activity has been all but absent in the literature, with a wide range of subjective terms (scarce, sporadic, uncommon, few, occasional, remarkable, etc.) as a substitute. A recent, careful study of 71 PXAs with literature review found that, in multivariate analysis, only the mitotic index (≥ 5 mitoses/10 high-powered fields) was an independent predictor of survival (3) and recommended that such tumors be designated “pleomorphic xanthoastrocytoma with anaplastic features.” Although in this study necrosis was only significant in univariate analysis, an earlier study demonstrated that the presence of necrosis either at initial surgery (seen in

approximately 10% of patients) or at the time of tumor recurrence (seen in another 10%) predicted a markedly foreshortened postoperative survival—usually on the order of about 2 years (12). In this study, the presence or absence of necrosis was also felt to be useful in guiding surgical therapy: in non-necrotic PXAs, complete resection was associated with a significant increase in survival, while complete resection did not appear to provide much benefit for patients with PXAs containing necrosis (12). At present, adjuvant radiation and/or chemotherapy is generally felt to be unnecessary for patients with completely resected, non-necrotic PXAs; the role for adjuvant therapy in other settings remains to be defined.

While heavily lipidized malignant gliomas (glioblastomas) have been described, it is generally felt that these are distinct from PXAs containing necrosis on the basis of the abundance of pericellular reticulin and absence of microvascular proliferation in the latter. The relationship

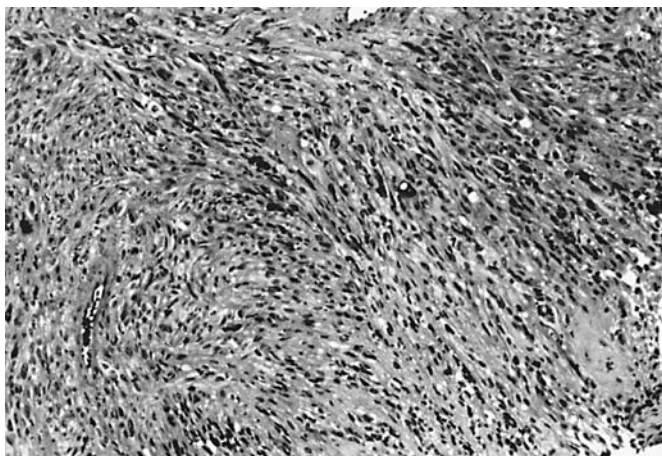


Fig. 8-3. Prominent spindle cell differentiation in a pleomorphic xanthoastrocytoma.

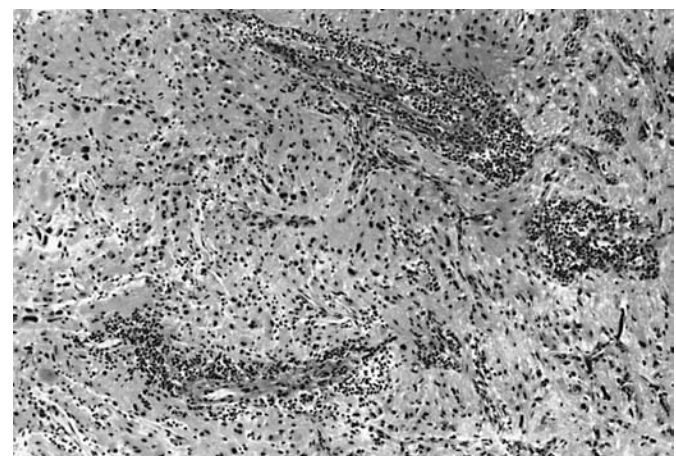


Fig. 8-5. Perivascular lymphocytic infiltrates in a pleomorphic xanthoastrocytoma.

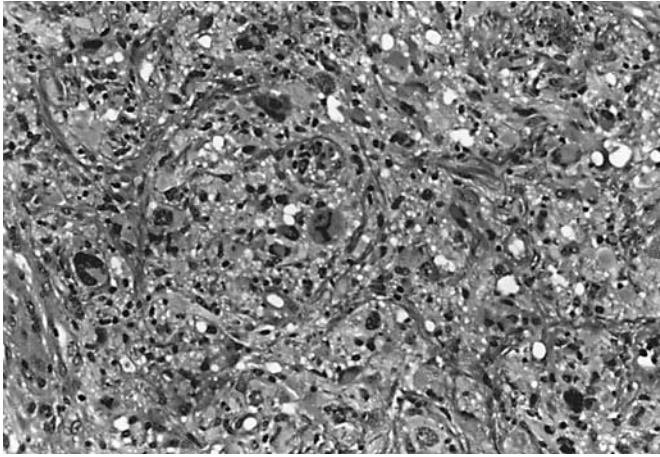


Fig. 8-6. An atypical mitotic figure in a pleomorphic xanthoastrocytoma with anaplastic features.

between necrotic PXAs and giant-cell glioblastoma multiforme is more problematic, as features of the latter include relative circumscription, abundant reticulin, and long survival in some cases. Hopefully, future clinicopathologic and/or molecular studies will clarify what, if any, relationship exists between these two entities.

As PXAs may pursue an aggressive course either immediately or many years after initial resection, they need to be distinguished from other tumors known to behave in a more reliably benign manner. Indeed, one of the radiographic “signatures” of benign central nervous system tumors is the macrocyst/(enhancing) mural nodule combination. Distinction from juvenile pilocytic astrocytomas may be difficult as the two tumors may share several microscopic features, including prominent fibrillarity and abundant eosinophilic granular bodies. Prominent nuclear pleomorphism and abundant pericellular reticulin are distinctly unusual in pilocytic astrocytomas, and thus are useful differential diagnostic features. Despite the name, xanthomatous change may be minimal in PXAs, and therefore tends not to be particularly helpful in differential

diagnosis. A more problematic distinction is between PXAs and mixed neuroglial tumors such as gangliogliomas and, to a lesser extent, dysembryoplastic neuroepithelial tumors. Atypical ganglionic cells within a PXA were first described in 1983 (14), 5 years after the initial codification of PXA as a discreet entity. Since then, neuronal differentiation in PXA has been recognized with increasing frequency, either occurring synchronously within the astrocytic tumor or appearing *de novo* in subsequent tumor recurrences. Double immunostaining has demonstrated rare tumor cells containing both GFAP and either synaptophysin or neurofilament protein immunoreactivity (15). It has even been suggested that this aberrant intermediate filament expression may be causative in producing the large pleomorphic cell morphologies often observed in PXAs and related “maldevelopmental” tumors, such as the subependymal giant cell “astrocytomas” of tuberous sclerosis. Frequent localization of both PXAs and gangliogliomas in the temporal lobe, their similar clinical and radiographic features, and the existence of tumors with combined or intermediate features all suggest that these two neoplasms may have a common derivation. Another rare pattern of gangliogliomatous differentiation in pleomorphic astrocytomas has recently been described in the form of a “collision” tumor with minimal intermingling of the two divergent elements (16). While the number of cases showing this pattern is too small to allow analysis of the biologic behavior of this variant, the current recommendation is to consider these to be of low malignant potential similar to “pure” pleomorphic xanthoastrocytomas. A recent small, but careful, study which included extensive sectioning of PXAs as well as peritumoral brain tissue demonstrated multiple associated neuronal abnormalities ranging from gangliogliomatous differentiation to cortical dysplasias resembling dysembryoplastic neuroepithelial tumors (17). This raises the possibility that certain PXAs may represent gangliogliomas in which the astrocytic component overshadows the frequently subtle neuronal elements within the neoplasm. Thus, it may be

Table 8-1
Differential Diagnosis of Pleomorphic Xanthoastrocytoma

	PXA	Pilocytic Astrocytoma	Ganglioglioma	Giant Cell Glioblastoma
Pleomorphism	+	+/-s	+	+
Xanthomatous change	+	-	+/-	+
Pericellular reticulin	+	-	+/-	+/-
Perivascular lymphocytes	+	+/-	+	+
Rosenthal fibers	+/-	+	+/-	-
Eosinophilic granular bodies	+	+	+	-
Mitotic figures	Rare	Rare	Rare	Frequent
Necrosis	Rare	Rare	Rare	Prominent
Neuronal component	Rare	-	+	-

that there exists a spectrum of “desmoplastic” brain tumors occurring in young patients which result from the deposition of abundant basal laminae by the tumor cells. The proteoglycan constituents of these basal laminae may in turn inhibit the growth and spread of the neoplastic glial cells (18). While further studies are needed to clarify these relationships, avoiding the overdiagnosis of PXAs as malignant glial or mesenchymal tumors and their underdiagnosis as pilocytic astrocytomas is important for optimal follow-up and treatment of these unusual patients (Table 8-1).

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9 Subependymal Giant Cell Astrocytoma

SUBEPENDYMAL GIANT CELL ASTROCYTOMA is a relatively infrequently encountered tumor of astrocytic derivation that most commonly arises in the region of the foramen of Monro and may extend into either the lateral ventricle or third ventricle. Because of location, the most common clinical presentations are related to signs and symptoms of increased intracranial pressure. There is a well-established association of this lesion with tuberous sclerosis, and it has been hypothesized that these tumors might evolve from enlargement of subependymal hamartomatous nodules which are quite frequently found in tuberous sclerosis (1–3). The radiographic appearance of the lesion is often that of an intraventricular based tumor with variable amounts of calcification and variable degrees of enhancement (1,4). Concomittant hydrocephalus is frequently noted. In the setting of tuberous sclerosis, smaller periventricular nodules, corresponding to small subependymal hamartomatous lesions, are frequently seen.

Histologically, subependymal giant cell astrocytoma consists of large, somewhat rounded cells with abundant eosinophilic cytoplasm, frequently intermixed with smaller, more spindled cells (Figs. 9-1 and 9-2). Cells may be arranged in clusters, sheets, or in a perivascular distribution. Cells generally contain eccentrically placed, round to slightly oval nuclei with evenly distributed, finely granular chromatin and a small nucleolus. Occasional nuclear pseudoinclusions or cytoplasmic invaginations can be seen (Fig. 9-3). In general, there is a sharp demarcation between the subependymal giant cell astrocytoma and adjacent brain parenchyma. Rarely, cells with neuronal-type features, including vesicular nuclei and prominent nucleoli, can be seen (5). Mitotic figures are rare or absent. Microcalcifications are a commonly seen feature, as are scattered mast cells. Exuberant vascular proliferation, such as one encounters in high-grade fibrillary type astrocytomas, is distinctly uncommon, as is tumor cell necrosis. Occasionally, areas of autoinfarction may be observed, as well as

mild vascular proliferation; these findings have not been associated with a poor prognosis (6–8).

Immunohistochemical and ultrastructural studies interestingly show evidence of divergent glial-neuronal differentiation (5,9,10). Tumor cells may stain focally for glial fibrillary acidic protein (GFAP), S-100 protein, as well as for markers of neuronal differentiation, including neurofilament proteins or class III beta-tubulin (11). Evidence of both glial and neuronal type differentiation in these tumors along with clinical presentation and an association with tuberous sclerosis support the probable hamartomatous nature of this lesion. MIB-1 labeling indices, in one recent series of these tumors, generally indicated low rates of cell proliferation (mean labeling index of 1.1 in six tumors studied) (7).

Although the subependymal giant cell astrocytoma is intrinsically considered a low grade lesion (WHO grade I tumor), rare cases of radiographic progression have been documented (2,4). Rarely, recurrence and death have been associated with the lesion (6). The approach to treatment is

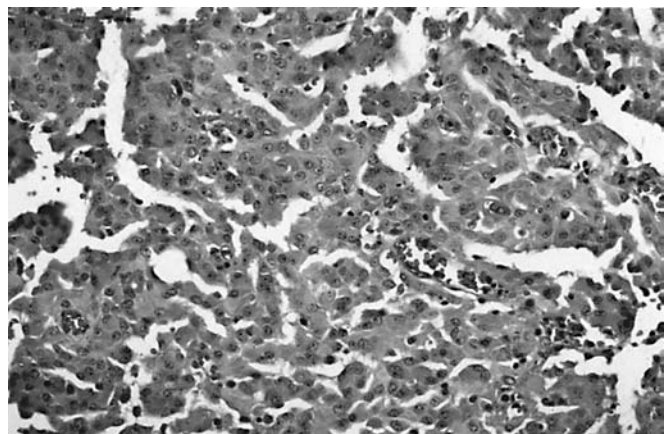


Fig. 9-1. Large, generally rounded cells with abundant eosinophilic cytoplasm in a subependymal giant cell astrocytoma.

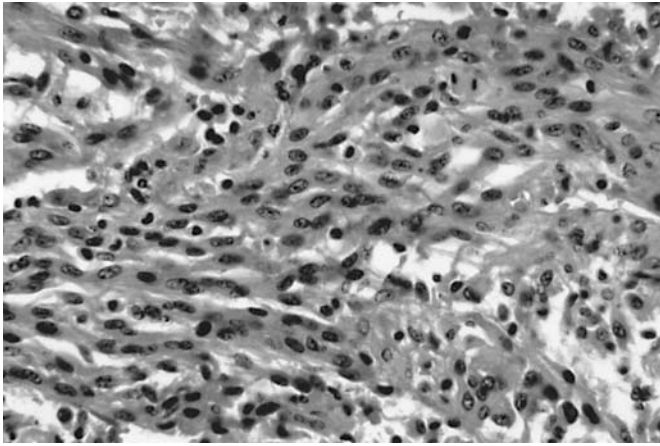


Fig. 9-2. Spindled tumor cells in a subependymal giant-cell astrocytoma.

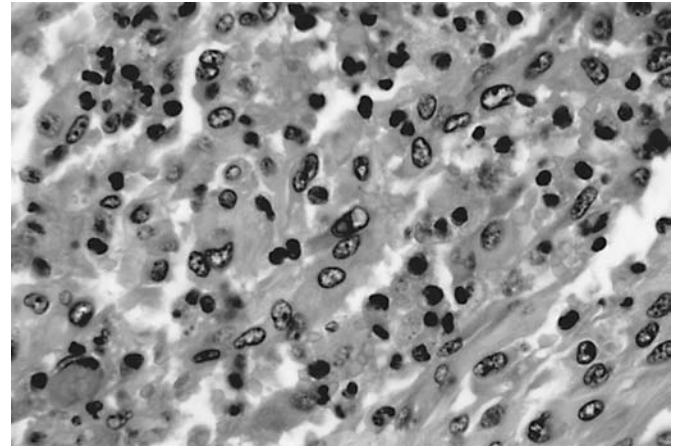


Fig. 9-3. A rare nuclear pseudoinclusion in a subependymal giant-cell astrocytoma.

typically surgical, and generally does not include adjuvant chemotherapy and/or radiation therapy.

Because of the association with tuberous sclerosis and the generally good prognosis of the subependymal giant cell astrocytoma, distinction of this lesion from other forms of astrocytoma is important. The lesion that perhaps most closely resembles the subependymal giant cell astrocytoma histologically is the gemistocytic astrocytoma. Similarities and differences between these two lesions are outlined in Table 9-1. In contrast to the subependymal giant cell astrocytoma, the gemistocytic astrocytoma more commonly presents in adulthood as a white matter, parenchymal-based lesion with infiltrative borders. There is no

known association of the gemistocytic astrocytoma with tuberous sclerosis. Histologically, the gemistocytic astrocytoma also consists of somewhat rounded, eosinophilic cells, although they are generally smaller in size and typically have small, circumferentially arranged, radiating cytoplasmic processes, as compared with the more polar arrangement of cytoplasmic processes in the subependymal giant cell astrocytoma. Nuclear pseudoinclusions and mast cells are uncommon in gemistocytic astrocytomas, whereas lymphocytes are more frequently encountered. Gemistocytic astrocytomas generally do not show evidence of neuronal differentiation. Distinguishing between the two lesions is critically important from a prognostic

Table 9-1
Subependymal Giant Cell Astrocytoma (SEGA) Versus Gemistocytic Astrocytoma (GA)

	SEGA	GA
Age	Generally pediatric age	Adult, 3 rd to 5 th decade peak
Tuberous sclerosis	±	—
Location	Region around foramen of Monro	Generally not intraventricular, same distribution as fibrillary astrocytoma
Gross	Circumscribed, predominantly intraventricular	Infiltrative, generally parenchymal (white matter) based
Calcification	±	± (rare)
Large round eosinophilic cells	+	+ (cells generally smaller in size)
Spindle cell component	±	±
Cytoplasmic processes	Polar	Circumferentially radiating
Nuclear pseudoinclusions	+	—
Mast cells	+	—
Lymphocytes	—	+
Mitoses	Variable generally rare	Rare
Vascular proliferation	—	—
Necrosis	— (rarely autoinfarct)	—
Malignant transformation	— (rare?)	Frequent
Treatment	Surgical excision	Surgical excision ± radiation
GFAP	+ (focal)	+ (more diffuse)
S-100	+	+
Neurofilament markers	+	—

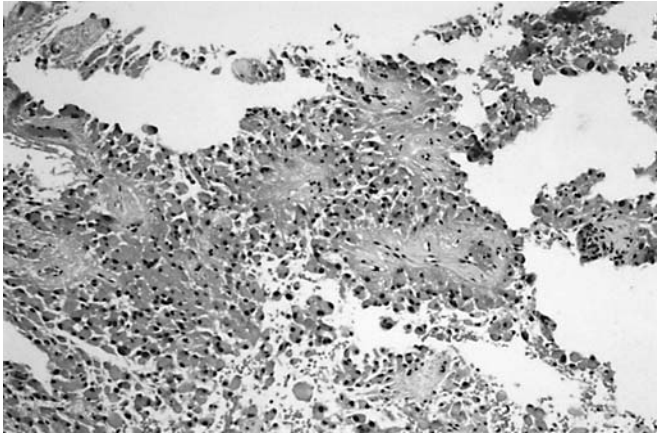


Fig. 9-4. Pseudopapillary, perivascular arrangement of cells in a subependymal giant-cell astrocytoma.

standpoint in that a significant number of gemistocytic astrocytomas will undergo malignant transformation or progression to higher grade lesions.

Other lesions which, on occasion, may focally mimic the subependymal giant cell astrocytoma include choroid plexus tumors and pleomorphic xanthoastrocytoma. The perivascular arrangement of cells in a subependymal giant cell astrocytoma may on occasion give the tumor a vaguely papillary appearance (Fig. 9-4). Similar to subependymal giant cell astrocytomas, choroid plexus tumors are primarily ventricular in location and often arise in younger patients. Calcifications are also quite commonly seen in these lesions. In contrast, choroid plexus tumors generally do not contain the large rounded, eosinophilic cells typical of the subependymal giant cell tumor. By immunohistochemistry, the lesions can be distinguished by the cytokeratin immunoreactivity of most choroid plexus tumors and the general lack of immunostaining with markers of neuronal differentiation of choroid plexus lesions.

The pleomorphic xanthoastrocytoma, in contrast to the subependymal giant cell astrocytoma, tends to be a more parenchymal-based lesion, frequently superficial or dural based. There is no known association of pleomorphic xanthoastrocytoma with tuberous sclerosis. The pleomorphic xanthoastrocytoma may be relatively circumscribed in appearance. Pleomorphic xanthoastrocytoma frequently demonstrates more exuberant cytologic atypia and pleomorphism, along with lipidization of astrocytic cells, both of which are uncommon in the subependymal giant cell astrocytoma. Another distinguishing characteristic is the reticulin-rich nature of the pleomorphic xanthoastrocytoma.

Distinction of the subependymal giant cell astrocytoma from the hamartomatous lesions of tuberous sclerosis is probably more of academic interest than true clinical sig-

nificance. Histologically, the hamartomas seen in tuberous sclerosis may be quite similar to the subependymal giant cell tumor. The distinction between hamartoma and tumor in this scenario is somewhat arbitrary and is principally based on differences in size between the two lesions. Similarly appearing large eosinophilic cells have also been noted in the cortical tubers, which likewise, have been shown to demonstrate divergent glial-neuronal differentiation (5). It is unlikely, however, that a cortical tuber will be confused with the subependymal giant cell tumor. The cortical tuber grossly appears as an enlarged gyrus and is often firm in consistency. Microscopically, the tuber consists of dysplastic cortex associated with prominent gliosis (5).

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10 Oligodendroglioma

IMMUNOHISTOCHEMICAL AND MOLECULAR biologic techniques have done much to advance our understanding of many CNS and non-CNS tumors. Unfortunately, there is no reliable immunohistochemical stain for neoplastic oligodendroglial cells, and recent advances in the molecular biology of these tumors have not yet been parlayed into the diagnostic armamentarium of practicing pathologists. Therefore, the oligodendroglioma currently remains a tumor whose diagnosis is based entirely on the “good old H&E.” In addition, we have been provided with a variety of look-alikes serving to constantly challenge, and more than occasionally, humble us. While some of these rather uncommon “oligo-mimics” will be covered below, our usual challenge is separating oligodendroglial tumors from those of astrocytic lineage (1). This is particularly important for three reasons:

1. Oligodendroglial tumors, particularly the high-grade ones, respond well to a variety chemotherapeutic regimens, while astrocytic tumors generally do not (2).
2. Exclusive of this chemoresponsiveness, oligodendrogliomas are biologically less aggressive than astrocytomas of similar grade.
3. Due to their relatively high cellularity, the failure to recognize low-grade oligodendroglial tumors generally leads to diagnoses of high-grade astrocytomas, resulting in unnecessary therapeutic interventions which may cause significant morbidity.

While there are several histopathologic features that aid in the distinction between these two tumor lineages, this relative hypercellularity usually provides the first clue—that is, you are confronted with a tumor where the cellularity seems excessively high relative to the degree of nuclear pleomorphism. It is this almost painful nuclear monomorphism which typifies low-grade oligodendrogliomas. Like their normal counterparts, the tumor cell nuclei

appear nearly perfectly round and uniformly hyperchromatic. The “excessive” cellularity is related to the paucity of processes elaborated by these cells (as their name indicates). This paucity of processes also probably accounts for the second helpful diagnostic feature of these tumors: a (usually) conspicuous delicate branching arcuate capillary vascular pattern seen between the nests of tumor cells (Fig. 10-1). Five other histopathologic features which support the diagnosis of oligodendroglioma are:

1. the ease with which the cells appear to spread into the cerebral cortex, resulting in prominent perineuronal satellitosis, accompanied by perivascular and subpial aggregates of tumor cells (Fig. 10-2).
2. calcifications, especially when present in a band-like pattern within the cerebral cortex (Fig. 10-3).
3. germinal-like nodules of hypercellularity (Fig. 10-4).
4. admixed “minigemistocytes”—small cells with round “oligodendroglial” nuclei and cytoplasmic

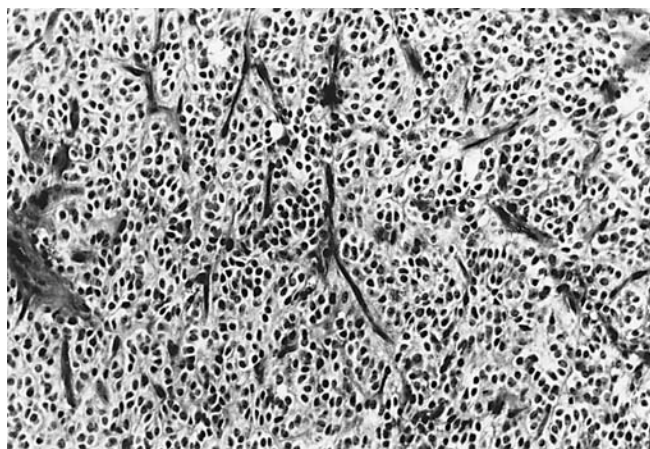


Fig. 10-1. Sheets of monomorphous cells with round, regular nuclei punctuated by arcuate branching capillaries in an oligodendroglioma.

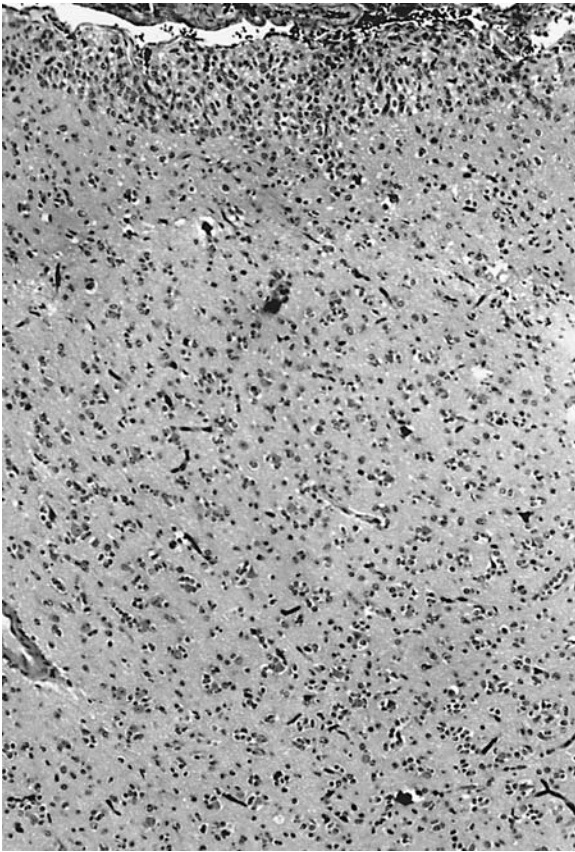


Fig. 10-2. Oligodendrogliomas permeating the cerebral cortex with subpial aggregation.

glial filaments forming an inclusion-like cytoplasm (Figs. 10-5 and 10-6). These cells appear spherical and lack the fibrillary ramifying processes of typical gemistocytic astrocytes (3).

5. perinuclear halos (Fig. 10-7). As perinuclear halos result from artifactual cytoplasmic retraction secondary to delayed fixation, they are seen much less often in current clinical practice and are notably absent in frozen section material and small stereotactic biopsy specimens. In addition, similar features may be seen from time to time in tumors which otherwise demonstrate typical astrocytic differentiation.

While the distinction between one low-grade glioma and another is not critical during intraoperative consultations, it is important to make a mistaken diagnosis of *high-grade* astrocytoma in a patient with a low-grade oligodendroglioma. Cytologic (squash) preparations are very useful in this regard as they highlight the round regular appearance of the oligodendroglial nuclei (Fig. 10-8).

While we have established that strictly defined minigemistocytes are an integral diagnostic feature of many oligodendrogliomas, we must consider the issue of true

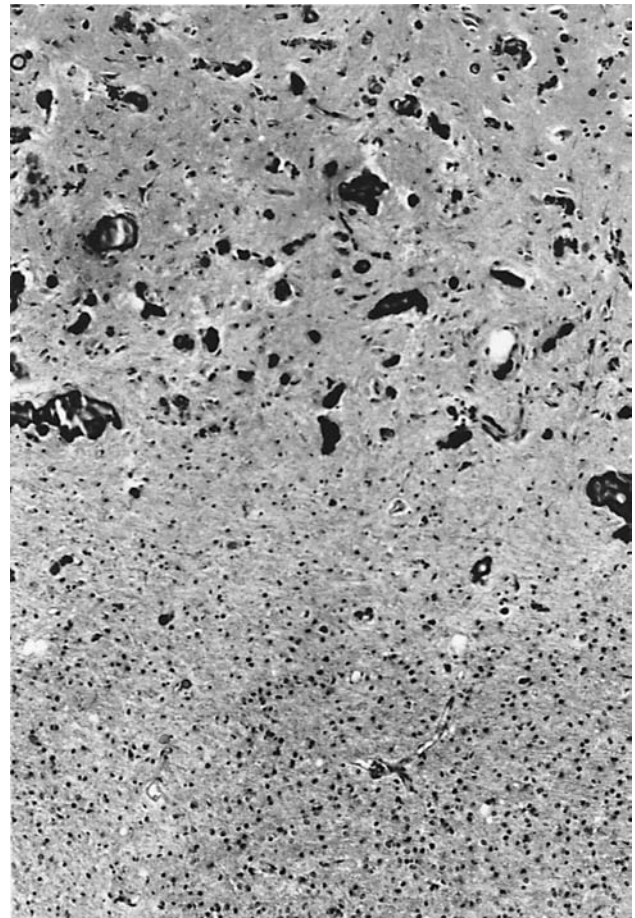


Fig. 10-3. Band-like microcalcifications within the cerebral cortex in an oligodendroglioma.

astrocytic differentiation in oligodendroglial tumors. Animal studies have established that both oligodendroglial cells and a subtype of astrocytes (type 2A) arise from a common progenitor cell (called, surprisingly enough, the O-2A cell). Recent in vitro studies with oligodendroglial



Fig. 10-4. Germinal-like nodules of hypercellularity within an oligodendroglioma.

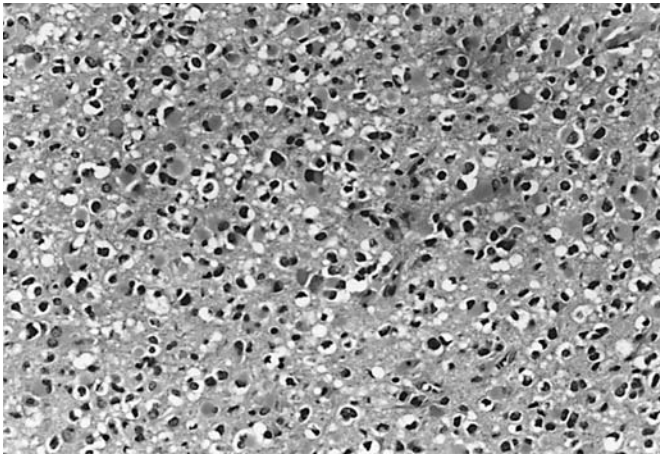


Fig. 10-5. Admixture of cells with oligodendroglial nuclei and inclusionlike fibrillary cytoplasm (minigemistocytes) in an oligodendroglioma.

tumor cells have demonstrated similar differentiating capacities within these tumors (4). If the same capabilities are retained *in vivo*, we should *expect* some degree of astrocytic differentiation within oligodendroglial tumors. Thus, it has been recommended that the appellation “mixed oligoastrocytoma” be restricted to those rare tumors with geographically separate areas of astrocytic and oligodendroglial differentiation (5). Recent molecular biologic studies have indicated that even these “mixed” tumors may represent part of the oligodendroglial spectrum, as genetic abnormalities commonly seen in oligodendrogliomas (allelic losses of chromosomes 1p and 19q) can be demonstrated both in the oligodendroglial *and* astrocytic appearing areas of these “mixed gliomas” (6).

The problems began to multiply as we encounter higher grade tumors. The first and most obvious difficulty arises in trying to determine prognostic and therapeutically

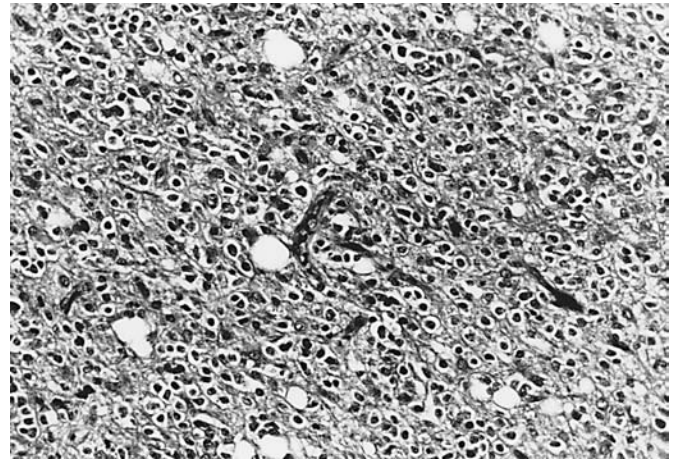


Fig. 10-7. Perinuclear halos imparting a fried-egg appearance to the oligodendroglial tumor cells.

meaningful divisions within this spectrum of tumors (7). While a number of 3 and 4 tiered grading systems have been proposed over the years, retrospective analyses of much of these data indicate that oligodendrogliomas are either anaplastic or they are not (8). Thus, the current WHO classification is two-tiered, with the anaplastic oligodendroglioma defined by a brisk mitotic rate, which is often accompanied by microvascular proliferation and/or necrosis (Fig. 10-9). Note that, with the exception of the brisk mitotic rate, the histopathologic features defining anaplastic oligodendroglioma (WHO grade III) are identical to those that would classify an astrocytic tumor as glioblastoma multiforme (WHO grade IV). This once again underscores the importance of recognizing the oligodendroglial nature of the tumor cells before applying grading criteria. While quantitation of the mitotic frequency has not been incorporated into this grading system, recent studies utilizing MIB-1 antibodies to the cell cycle

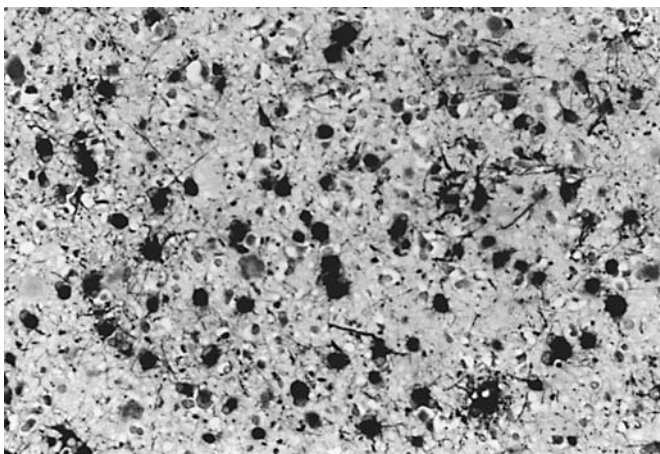


Fig. 10-6. GFAP immunohistochemistry highlights minigemistocytes within an oligodendroglioma.

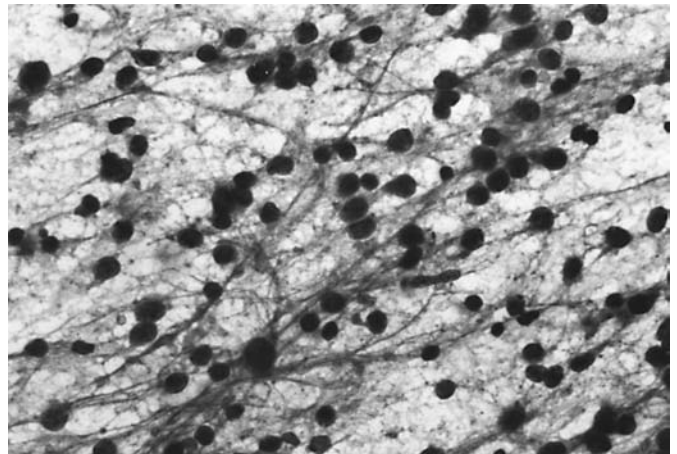


Fig. 10-8. Intraoperative squash preparation of an oligodendroglioma demonstrating round, regular, monomorphic tumor cell nuclei.

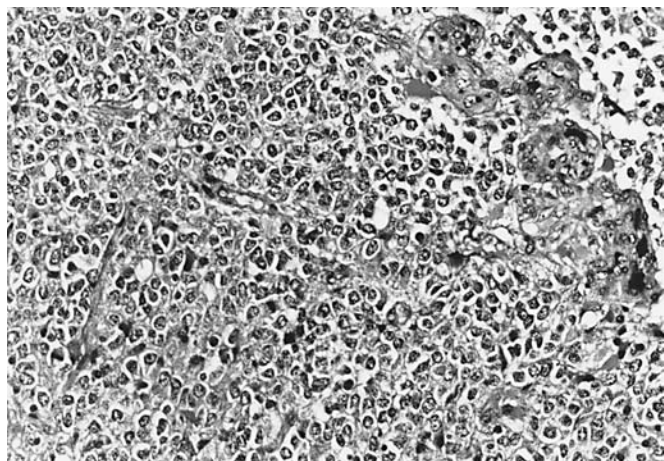


Fig. 10-9. Microvascular proliferation in an anaplastic oligodendroglioma.

marker, Ki-67, indicate that histopathologically low grade oligodendrogliomas with labeling indices greater than 2% tend to behave in a more aggressive fashion (9). However, it has been cautioned that this figure may not extrapolate precisely to other labs due to differences in staining methodology.

Nosologic difficulties are compounded as astrocytic differentiation tends to increase in parallel with the grade of the oligodendroglioma. We are thus not infrequently faced with glioblastomas that have a peculiarly oligodendroglial look to them. These are a real problem, and molecular genetic studies are underway to try to better define these entities. Recent data indicate that the absence of deletions on chromosomes 1 and 19 or the presence of ring-enhancement on neuroimaging studies predicts a poor response to chemotherapy (10). At present, these tumors are best designated as glioblastomas with a note describing the histopathologic features, as some oncologists will still consider using PCV chemotherapy in such patients.

In addition to the often rather difficult differential diag-

nosis between oligodendroglial and astroglial tumors, three other entities (two of presumed neuronal derivation) need to be distinguished from (low-grade) oligodendrogliomas (Table 10-1) (11).

The *dysembryoplastic neuroepithelial tumor* is a mixed glio-neuronal tumor which is most often encountered in the temporal lobes of young patients with complex partial seizures. "Oligodendroglial-like cells" comprise a large part of this entity, and small biopsy specimens may be difficult or impossible to distinguish from pure oligodendroglioma. This distinction is important, however, in that DNTs are benign, probably hamartomatous, entities without the risk of tumor progression, morbidity, and mortality expected from oligodendrogliomas. Radiographic aids to the differential diagnosis include multinodularity and a predominantly intracortical location for DNTs. Histopathologically, cellular heterogeneity (in a large enough specimen) favors DNT. The perineuronal satellitosis so characteristic of oligodendrogliomas may be absent or focal within DNT's, a feature which may be helpful in small biopsy specimens.

This oligodendroglial-like component of DNTs may be seen in pure form (and, thankfully, with somewhat more obvious neuronal differentiation) in *central neurocytomas*. These tumors were first recognized when synapses were seen during ultrastructural examination of intraventricular "oligodendrogliomas." The subsequent development of sensitive markers of neuronal differentiation (especially synaptophysin) confirmed the neuronal nature of these tumors, which most often arise in the septum pellucidum of young adults. Similar to DNTs, these are best treated by surgery alone, and are much less biologically aggressive than oligodendrogliomas. While careful examination of H&E stained sections will often reveal the presence of "neuropil" within these tumors, it is the awareness of this entity, coupled with the judicious use of synaptophysin immunostaining which enable us to distinguish these tumors from oligodendrogliomas. It is important to keep in mind that extraventricular neurocyto-

Table 10-1
Differential Diagnosis of Oligodendroglioma

	<i>Oligodendroglioma</i>	<i>Dysembryoplastic Neuroepithelial Tumor</i>	<i>Central Neurocytoma</i>	<i>Clear Cell Ependymomas</i>
Infiltration	+	Focal	—	—
Perineuronal satellitosis	+	—	—	—
Minigemistocytes	+	—	—	—
Floating neurons	+	—	—	—
Cellular heterogeneity	+/-	+	—	+/-
Neuropil	—	—	+	—
Perivascular pseudorosettes	—	—	—	+/-
GFAP	Minigemistocytes	Astrocytic areas	Weak/focal coexpression	Punctate cytoplasmic
Synaptophysin	—	+/-	+	—

mas are being recognized with increased frequency (12). Therefore, a low threshold for requesting synaptophysin immunostaining is recommended in the evaluation of low grade oligodendroglial neoplasms.

While clear cell differentiation may occasionally be encountered in otherwise typical ependymomas, we may rarely be challenged by ependymomas composed virtually entirely of clear cells. The difficulty in diagnosing this unusual tumor is perhaps best exemplified in the first comprehensive study of clear cell ependymomas, where three of the eight cases reported were first recognized during an ultrastructural study of oligodendrogliomas (13). While most of these cases also demonstrated punctate cytoplasmic GFAP reactivity, diagnostic hallmarks were reported to be present only on ultrastructural examination. Thus, it may be prudent to reserve a small piece of tissue in electron microscopy fixative when you suspect the diagnosis of oligodendroglioma. If the diagnosis remains unclear after examination of permanent H&E and immunohistochemically stained sections, the gluteraldehyde fixed tissue can be examined or sent off in consultation. As a result of their rarity, the behavior and therapy of clear cell ependymomas has not been established.

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11

Mixed Gliomas

THE SUBJECT OF MIXED GLIAL neoplasms has continued to be a source of considerable debate. Most people recognize that a glial neoplasm may show phenotypic features of more than one glioma type, most commonly a mixture of astrocytoma and oligodendroglioma (oligoastrocytoma). The major question arises, however, as to exactly what point one crosses the threshold in designating the lesion as mixed as opposed to calling it a pure glioma. Unfortunately, the literature has not been terribly helpful in this arena; many of the articles that have dealt with the subject have not specifically defined what is meant by a mixed glioma and those that do, do so somewhat arbitrarily, resulting in a lack of uniformity or agreement. Precise guidelines as to what percentage of a second glial component one needs to see in order to designate a tumor as “mixed” remains unclear. In the single largest series of mixed gliomas published to date, written over twenty years ago, mixed gliomas were simply defined as tumors of the brain and spinal cord comprised of two or more neoplastic counterparts of the normal glial cellular constituents of the central nervous system, without further specification with regard to how much of a second component one needed to see in order to designate the lesion as “mixed glioma” (1). In the recent World Health Organization Histological Typing of Tumours of the Central Nervous System, the definition remained vague and essentially the same (2). The most recent Armed Forces Institute of Pathology Fascicle states that some have used the designation of mixed glioma when the minority cell type exceeds some arbitrary proportion of the total tumor, “perhaps 20%” (3). Others have recommended 25% of a minor component as a possible point of division (4,5). Even with establishment of a minimum percentage for the minor component, it may be difficult in practice to apply such a rule. There are relatively few tumors which have distinct and pure oligodendroglioma areas juxtaposed with distinct and pure astrocytoma regions (Figs.

11-1 and 11-2). However, it is in such cases that the terminology of mixed glioma is probably best applied. More commonly, one encounters tumors in which there is a diffuse admixture of astrocytoma and oligodendroglioma type cells. These lesions are more problematic in terms of classification, and generally one attempts to classify the tumor based on the predominant pattern or cell type present. Because of the lack of uniform criteria in the designation of mixed glioma, interpretation of the literature with regard to outcome in these patients is also problematic. On the one hand, it may be argued that mixed gliomas of the oligoastrocytoma type will have a intermediate prognosis as compared with pure low-grade oligodendrogliomas and pure low grade fibrillary astrocytomas. Others have suggested that the presence of a significant fibrillary astrocytoma component, being the more aggressive of the two tumor patterns, ultimately dictates the tumor’s behavior, and the potential risk for progression is roughly in proportion to the amount of astrocytoma in

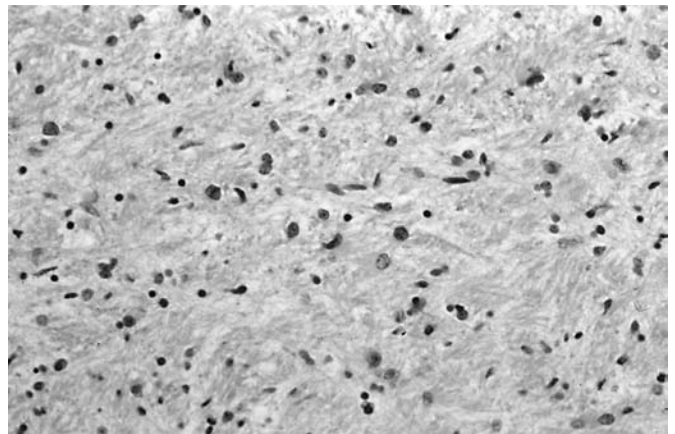


Fig. 11-1. An oligoastrocytoma with a focal area resembling a low-grade fibrillary astrocytoma.

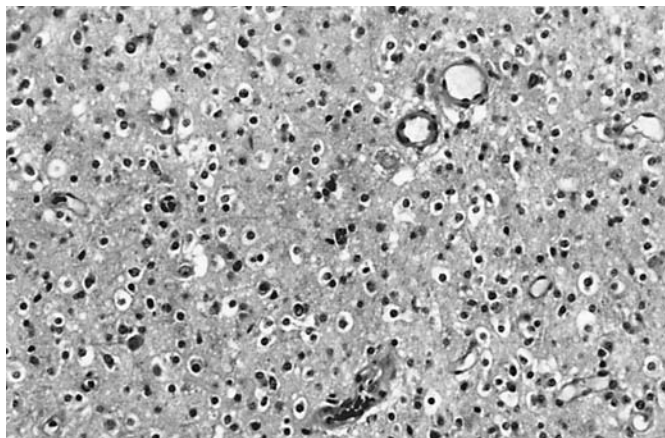


Fig. 11-2. The same tumor as in Fig. 11-1. Other areas of the tumor resembled a low-grade oligodendroglioma.

a given neoplasm. Unfortunately, these issues are far from being resolved.

Molecular biologic studies have indicated that some mixed oligoastrocytomas demonstrate genetic abnormalities commonly observed in oligodendrogliomas, including allelic losses of chromosomes 1p and 19q (6). Interestingly, these chromosomal abnormalities are demonstrated in both oligodendroglial and astrocytic appearing areas of these so-called mixed gliomas, suggesting that these tumors may represent part of the oligodendroglioma spectrum (6). p53 studies have indicated no significant difference between mixed glial neoplasms and pure fibrillary astrocytomas with regard to p53 alterations (7). A progenitor cell has also been identified which gives rise to type II astrocytes and oligodendrocytes (8). It has been hypothesized that this progenitor cell type might potentially give rise to a neoplasm with the capability of differentiating along both astrocytic and oligodendroglial cell lines. Cell culture studies have shown that glial progenitor cells can also develop into either astrocytic or oligodendroglial cells depending on their environment (9,10). Ultrastructural studies of oligodendrogliomas which appear to be morphologically pure show a variety of ultrastructural features ranging from cells which are clearly oligodendroglial to those that are clearly astrocytic (11).

From a practical standpoint, the diagnosis of mixed glioma should not be made at the time of intraoperative consultation. One could also argue that the diagnosis should not be made on small stereotactic biopsy specimens, and should be utilized only when there is adequate sampling of the tumor. The term is best probably best reserved for lesions which have discrete areas with different glial cell phenotypes. Beside oligoastrocytoma, which is the most commonly encountered mixed glioma type, one may on occasion observe mixtures of oligodendroglioma and ependymoma (oligoependymoma), which should

not be confused with clear cell ependymoma, and ependymoma and astrocytoma (ependymoastrocytoma). Use of a 20% or 25% minor component as a rough guideline seems appropriate until further studies have more definitively addressed this issue.

Occasionally, one may encounter tumors which have more aggressive histology (i.e. increased mitoses, vascular endothelial proliferation, or necrosis) and which appear to have mixed phenotypes. The use of the term *malignant mixed glioma* or more specific term of *malignant mixed oligoastrocytoma* can be used for those cases. Because of suggestion in the literature that oligodendroglial tumors may be more chemotherapy responsive, attempts should be made in malignant gliomas to differentiate between a high grade oligodendroglioma and high grade fibrillary astrocytoma. In the case of a mixed tumor, the presence of a significant oligodendroglial component may be enough to influence the therapeutic approach and so acknowledgment of this is important; this information should be stated in the pathology report. In general, the term glioblastoma multiforme should be reserved for tumors which appear to be of fibrillary astrocytic derivation. Others have suggested that the term can also be used for high-grade mixed gliomas or high grade gliomas of oligodendroglial or ependymal origin. Again, because of potential differences with regard to therapeutic intervention and protocols for different glioma types, an attempt should be made, if possible, to differentiate different glioma types in high-grade tumors and acknowledge their presence by use of more specific designations such as malignant (anaplastic) oligodendroglioma or malignant (anaplastic) ependymoma.

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12 Ependymoma

EPENDYMOMAS ARE THE LEAST commonly encountered tumor of the three major glioma tumor groups which include astrocytomas and oligodendrogliomas. They comprise approximately 3–5% of all tumors in the central nervous system (1). Ependymomas are more commonly encountered in children, where they rank third behind low grade astrocytomas and medulloblastomas in terms of incidence (1). These tumors are derived from ependymal cells, and their location is most commonly proximal to the normal locations of ependymal cells throughout the central nervous system axis. Rarely, examples of ependymoma arising in ectopic locations including sacral region, mediastinum, ovary, broad ligament, and lung have been described (2).

Clinical symptoms at presentation most typically are related to increased intracranial pressure or mass effect related to obstruction of cerebrospinal fluid flow. Spinal cord ependymomas frequently present with sensory motor deficits. An association with neurofibromatosis type II is well established. Radiographically, ependymomas appear most commonly as intraventricular or paraventricular tumors. Areas of cystic degeneration or calcification are common. On MRI studies, areas of focal enhancement may be seen. Spinal ependymomas are frequently associated with syringomyelia in the adjacent spinal cord. Intraoperatively, ependymomas tend to be fairly discrete appearing lesions with a fleshy, gray-tan appearance.

Table 12-1 represents a histologic classification for ependymal neoplasms. Most tumors fall into one of the first three categories: glial, epithelial, or mixed glial-epithelial types. Less commonly encountered are examples of papillary, clear cell, tanycytic, and melanotic ependymoma. Similar to astrocytic and oligodendroglial neoplasms, ependymoma may progress to or degenerate into a higher grade tumor, generally referred to as anaplastic or malignant ependymoma. In contrast to astrocytomas where there are widely utilized grading schemas available,

the grading of ependymomas is more problematic and even less well established. Two particular variants of ependymoma, the subependymoma and myxopapillary ependymoma, because of distinct clinicopathologic features and better prognosis, warrant separate designation and will be discussed separately in this text (Chapters 13 and 14, respectively).

Histologically, the classic pattern of ependymoma is that of a fairly well circumscribed lesion. The tumor at low magnification shows a variable cellularity pattern. Tumor cell nuclei are generally uniform in appearance with slight elongation and irregularity to the nuclear contour. Cells are moderately hyperchromatic and frequently contain small nucleoli. In the classic ependymoma, cells frequently arrange themselves around a vessel to form the perivascular pseudorosette, which is characteristic of this tumor (Fig. 12-1). Frequently, the zone immediately adjacent to the vessel is hypocellular and consists primarily of ependymal cytoplasmic processes. Perivascular rosettes should be distinguished from perivascular collagen deposition which is a frequent finding in many neoplasms. Occasionally, in tumors which have a more predominant epithelial pattern, true ependymal rosettes may be observed. True ependymal rosettes are defined as the

Table 12-1
Ependymoma Histologic Classification

Classic (glial)
Epithelial
Mixed (usually glial and epithelial)
Papillary
Clear cell
Tanycytic
Melanotic
Anaplastic (or malignant)
Subependymoma (see Chapter 13)
Myxopapillary (see Chapter 14)

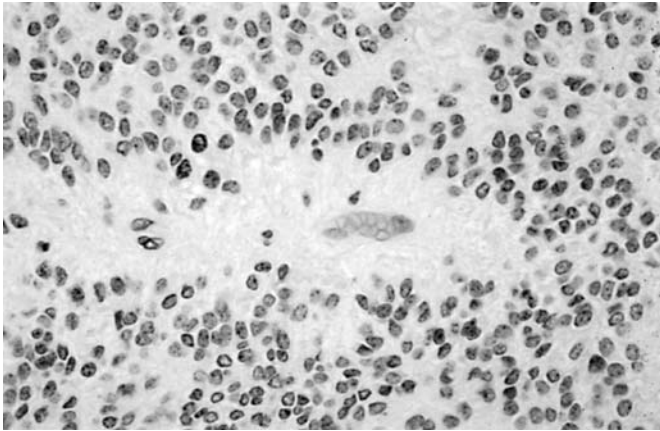


Fig. 12-1. Perivascular pseudorosette in an ependymoma. Tumor cell nuclei are generally uniform in appearance with slight irregularities to the nuclear contour.

formation of a central cavity or lumen by neoplastic ependymal cells (Fig. 12-2). These are thought to represent a recapitulation of the ependymal cell's normal function of lining spaces or cavities. In the usual low grade ependymoma, prominent mitotic activity, necrosis, and vascular proliferation are not commonly observed. Focal areas of hypercellularity in an otherwise ordinary appearing ependymoma may be observed and do not appear to adversely affect outcome. Frequently, in these hypercellular zones, there may be an increased number of identifiable mitotic figures and cell proliferation labeling indices may be quite high.

Less commonly, a variety of other ependymoma patterns may be observed. Usually, these patterns are intermixed with more readily identifiable glial or epithelial ependymal patterns. Ependymomas may assume a papillary configuration. Papillary ependymomas are characterized by the arrangement of ependymal cells around a

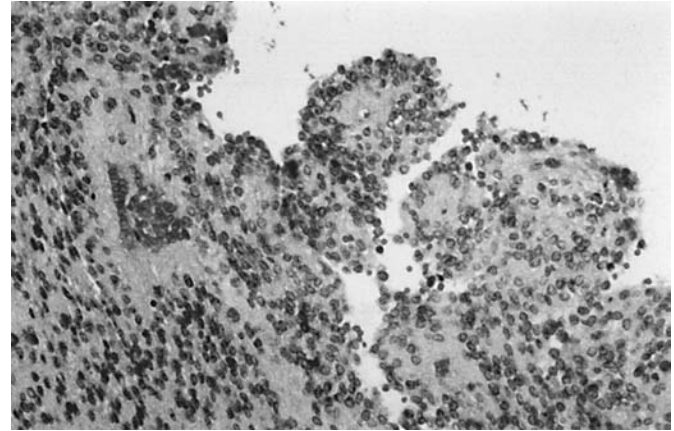


Fig. 12-3. Focal papillary architecture in an ependymoma.

gliovascular core (Fig. 12-3). The papillae are generally not well formed in contrast to the more overtly papillary characteristics of the choroid plexus papilloma. Choroid plexus tumors are in the differential diagnosis of a predominantly papillary appearing ependymoma. In contrast to ependymomas, papillary structures in choroid plexus papillomas have fibrovascular cores and generally do not demonstrate the degree of glial fibrillary acidic protein (GFAP) positive staining which characterizes ependymal neoplasms.

Occasionally, ependymomas may demonstrate focal areas of perinuclear clearing, somewhat reminiscent of oligodendrogliomas (Fig. 12-4). Nuclei in these areas tend to be more uniform and round in appearance and cells are often separated by a delicate arcuate vascular pattern, again reminiscent of an oligodendroglial neoplasm. In contrast to the oligodendroglioma, however, the clear cell ependymoma tends to be less infiltrative and frequently shows focal areas that resemble more common ependymoma patterns with perivascular pseudorosettes or true

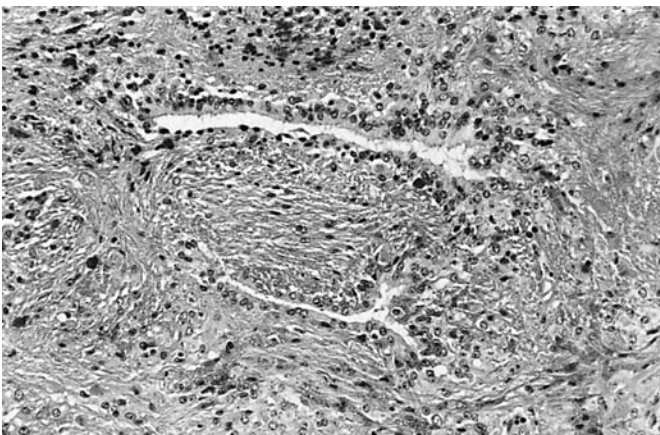


Fig. 12-2. Epithelial appearing ependymal cells lining channels in an ependymoma.

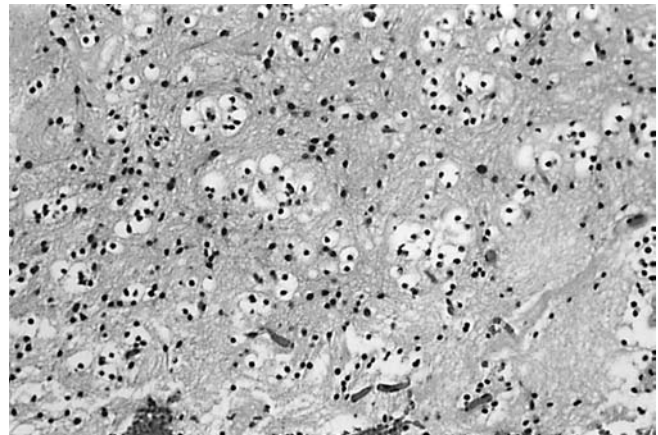


Fig. 12-4. Prominent perinuclear clearing resembling an oligodendroglioma in a clear cell ependymoma.

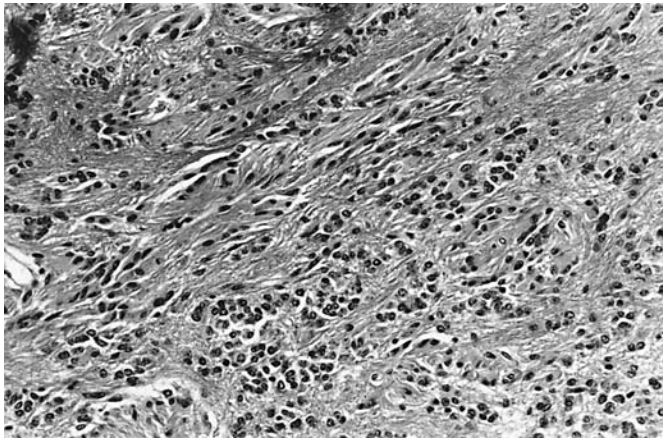


Fig. 12-5. More elongated cells characterize the tanyctic ependymoma.

ependymal rosettes. Ultrastructural examination of the tumor also allows for a distinction between these two entities. Some of the cleared cells may also demonstrate positive staining for GFAP (3,4).

The tanyctic variant of ependymoma represents another differential diagnostic problem. This lesion is characterized by more elongated cells with abundant processes which histologically are more reminiscent of astrocytic cells (5) (Fig. 12-5). Careful examination of this lesion frequently shows areas of perivascular pseudorosette formation that betray the lesion's true nature.

Rare examples of pigmented or melanotic ependymomas have also been described (6). These tumors generally have the appearance of ordinary types of ependymoma, but in addition, demonstrate cells which contain melanin and ultrastructurally demonstrate electron dense granules in the cytoplasm of tumor cells. The pigmented material in these tumors generally shows the staining characteristics of melanin, but ultrastructural evidence of premelanosomes has not been forthcoming and the exact nature of the pigment is still debated. Occasionally, one may also encounter areas of mesenchymal metaplasia in the form of bone and cartilage (7) or lipomatous differentiation (8). Tumors arising in the fourth ventricular region may also show focal areas with a subependymoma pattern. In tumors where there is a significant ordinary ependymoma pattern recognized, the lesion is probably best classified as an ordinary ependymoma, rather than the more benign subependymoma lesion.

From an immunohistochemical standpoint, ependymomas, like astrocytomas, generally demonstrate diffuse positive immunostaining for GFAP. Variable staining with epithelial membrane antigen and a variety of cytokeratins has also been described; however, the diffuse positive cytokeratin staining which is prominent in choroid plexus tumors is generally absent in ependymomas



Fig. 12-6. Ultrastructural appearance of cilia and ciliary body attachments (blepharoplasts) in an ependymoma.

(9–11). Ultrastructural examination of ependymal neoplasms may, on occasion, be warranted; this may arise when one is dealing with a very small biopsy specimen (such as from the spinal cord) that clearly represents a glial neoplasm, but because of the paucity of material, the rosette and pseudorosette architecture that is defining of ependymoma is not recognizable. In such cases, distinguishing ependymoma from an astrocytoma may become an issue. Unfortunately, immunohistochemistry is of little assistance in this differential diagnosis. Ultrastructural features suggestive of ependymal differentiation include the presence of microvilli, which are often contained within small lumina, cilia, and ciliary body attachments referred to as blepharoplasts (12) (Fig. 12-6).

Approaches to grading ependymomas are still varied, and there is lack of uniform agreement as to what exactly is needed to render a diagnosis of anaplastic or malignant ependymoma. In general, tumors with some combination of increased mitotic activity, prominent vascular proliferation, extensive tumor cell necrosis, widespread hypercellularity, and cytologic atypia are more likely to act in an aggressive fashion (Figs. 12-7 and 12-8). However, the threshold with regard to the number of these features which need to be present or the degree to which they need to be seen in order to designate a tumor as anaplastic or malignant have yet to be determined. There are a number of factors which make this evaluation more complicated. Many studies which have attempted to correlate histology with outcome lack long term follow-up, particularly when dealing with tumors which have aggressive histologic features. There also appears to be a number of other factors which perhaps are even more important than histology with regard to outcome (1,13–22) Age of the

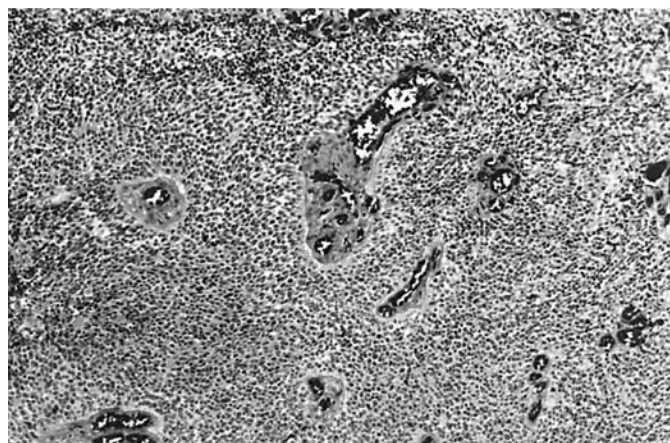


Fig. 12-7. Markedly cellular anaplastic ependymoma with vascular proliferation.

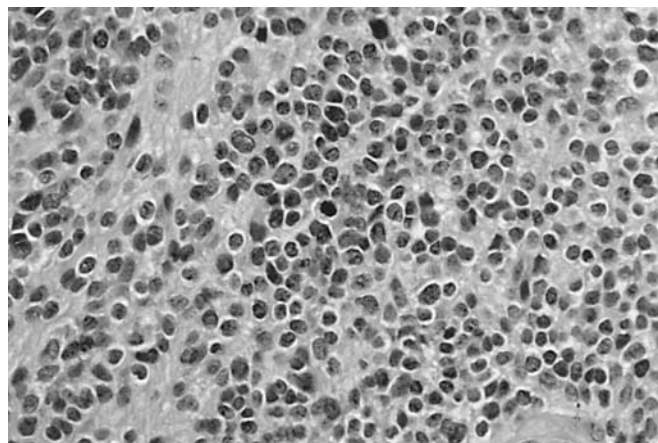


Fig. 12-8. Prominent cytologic atypia and mitotic figure in an anaplastic ependymoma.

patient may be important, with younger age patients usually doing worse than older patients (1). Location of the tumor may also play a role since tumors situated in the spinal cord tend to have a better outcome than intracranial ependymomas. However, the single most important prognostic variable in most studies has been the extent of surgical resection (1). Most of the literature has indicated that patients receiving postoperative radiation therapy tend to have longer survivals. The utilization of chemotherapy has not shown any significant improvement with regard to overall outcome in patients with ependymoma. Cell proliferation studies have shown a general trend toward increased labeling indices in poor outcome tumors and tumors with high grade histology; however, the correlation is far from reliable (23,24).

In general, tumors with classic ependymoma features are not difficult to diagnose. Many of the differential diagnostic problems arise in either small biopsies or when the classic perivascular pseudorosettes or true ependymal rosettes are not obvious by light microscopy. Features one can use to distinguish an ependymoma from astrocytomas are outlined in Table 12-2. Again with a small biopsy, ultrastructural examination of the neoplasm may be required to definitively define the lesion as ependymal. On occasion, anaplastic or malignant ependymomas may be difficult to recognize as such. Recognition of these high grade tumors as ependymal in derivation often rests on the identification of characteristic histologic features in lower grade areas of the tumor. Admittedly in some very high grade tumors, the distinction between a malignant

Table 12.2
Ependymoma Versus Fibrillary Astrocytoma

	<i>Ependymoma</i>	<i>Astrocytoma</i>
Peak age	Children > adults	3 rd to 5 th decades
Site of origin	Ventricular/periventricular/central canal region	White matter
Infiltrative	± (more circumscribed)	+
Fibrillary background	+	+
Perivascular pseudorosettes	+	—
True rosettes	+	—
Calcification	±	±
Mitoses	±	±
Necrosis	±	±
Vascular proliferation	±	±
GFAP	+	+
Keratin	±	— (some cross-immunoreactivity may be seen with certain keratin markers)
Epithelial membrane antigen	±	—
Microvilli/cilia (electron microscopy)	+	—
Blepharoplasts (electron microscopy)	+	—

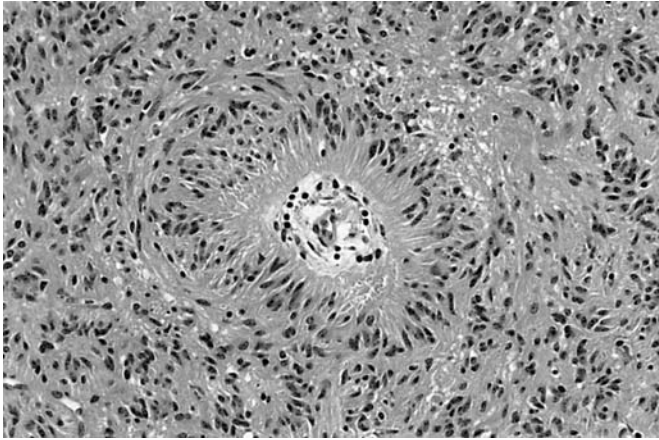


Fig. 12-9. Astroblastomatous perivascular pseudorosette in an astroblastoma.

astrocytoma (glioblastoma multiforme) and a malignant ependymoma may be difficult. Occasionally one may entertain a diagnosis of a primitive neuroectodermal tumor or embryonal tumor such as medulloblastoma in the differential of higher grade ependymal lesions. It is a well known fact that embryonal tumors can demonstrate focal areas of ependymal differentiation which may make the problem even more complicated. Most embryonal tumors, however, will demonstrate some focal positive staining with synaptophysin or other marker of neuronal differentiation. Rare cases of so-called ependymoblastoma are probably more akin to primitive neuroectodermal or embryonal tumors rather than ependymoma.

Another glial tumor which may mimic the pseudorosette pattern of ependymoma is the astroblastoma. Most have been described predominantly in children or young adults (25,26). Unfortunately, the term has been variously misused in the literature to refer to a variety of other tumors including fibrillary astrocytomas which demonstrate an astroblastic pattern and ependymal tumors. Most astroblastomas are fairly well circumscribed, supratentorial masses which histologically show prominent cellularity and a characteristic arrangement of cells around vessels forming perivascular astroblastic pseudorosettes (Fig. 12-9). Tumor cells stain GFAP positive and EMA positivity has also been reported. Ultrastructurally, these tumor demonstrate features of both astrocytic and ependymal differentiation. Features more suggestive of astroblastoma rather than ependymoma include sharp demarcation between tumor and adjacent parenchyma, vascular hyalinization and a less fibrillary perivascular zone. Bonnin and Rubinstein suggested that the clinical behavior of astroblastomas was unpredictable and their prognosis was probably intermediate between low-grade astrocytoma and glioblastoma multiforme (25).

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13 Subependymoma

SUBEPENDYMOMA IS CONSIDERED by many to be a variant or subtype of ependymoma, which is important to distinguish from an ordinary ependymoma because it has a generally better prognosis. Subependymomas are slow growing lesions, which most commonly present incidentally at the time of autopsy. The tumor is more frequent in men and tends to be seen predominantly in adults, although rare cases of pediatric presentation have been described (1–3). Occasionally, cases may present antemortem with signs and symptoms related to cerebrospinal fluid obstruction (1,4). Subependymomas arising in the spinal cord region generally cause symptoms related to a slow growing intramedullary lesion (3).

Most tumors arise in association with the ventricular system and are most commonly encountered in the region of the septum pellucidum and arising from the floor and lateral recess of the fourth ventricle. Radiographically, tumors appear fairly discrete and may demonstrate areas of calcification, hemorrhage or cyst formation.

Histologically, subependymomas have a distinctive appearance. On low magnification, the tumor has a variably cellular appearance with small clusters of nuclei and intervening hypocellular areas with a highly fibrillary background (Fig. 13-1). Microcystic changes are frequently observed (Fig. 13-2). An occasional mitotic figures may be encountered, reflected in the general low rate of cell proliferation as evidenced by MIB-1 cell proliferation marker studies (3–5). Cell nuclei have a generally oval to slightly elongated appearance and uniform chromatin pattern (Fig. 13-3). Mild degrees of nuclear pleomorphism may be also evident. Vascular endothelial proliferation is not a feature of subependymoma. Necrosis is also uncommonly seen, and if present, is usually the result of infarct. The interface between the neoplasm and adjacent parenchyma is often sharp. Adjacent parenchymal tissue may show prominent reactive astrocytosis and Rosenthal fiber formation.

From an immunohistochemical standpoint, subependymomas stain diffusely with S-100 protein and glial fibrillary acidic protein (GFAP). Ultrastructurally, the tumor shows features of both astrocytic as well as ependymal differentiation (6,7). This has prompted considerable debate with regard to the exact nature of this neoplasm and presumed cell of origin.

Subependymomas clinically are considered low grade lesions (WHO grade I). In larger tumors requiring surgical intervention, lesions located in the lateral ventricle tend to be fairly easily excised; those that arise from the floor of the fourth ventricle are often more difficult to remove (2,8). In general, adjuvant therapy is not recommended for subependymomas except perhaps in symptomatic, incompletely excised tumors. Subependymomas are not thought to undergo malignant transformation or progression, although rare instances of supposed sarcomatous change in the tumor's vasculature or rhabdomyosarcomatous differentiation have been reported (9,10).

From a histologic standpoint, the major differential

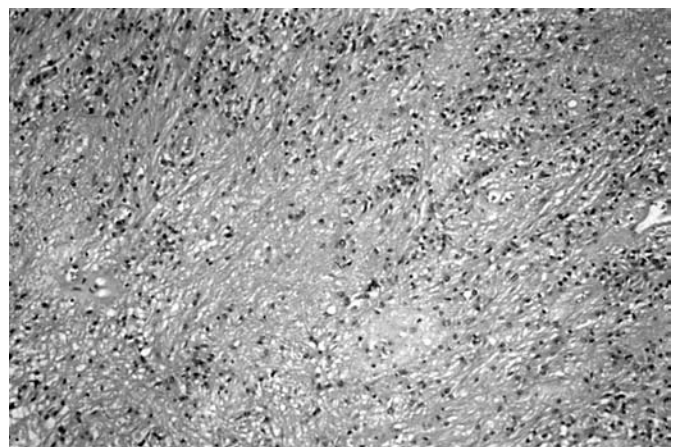


Fig. 13-1. Cell nuclei in a subependymoma vaguely arranged in clusters against a highly fibrillary background.

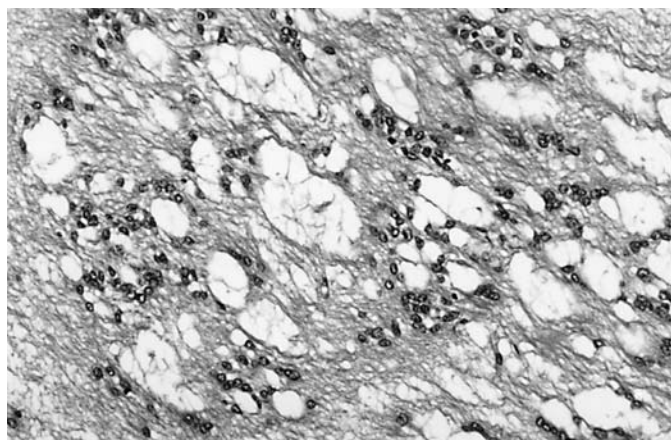


Fig. 13-2. Microcystic changes are common in subependymoma.

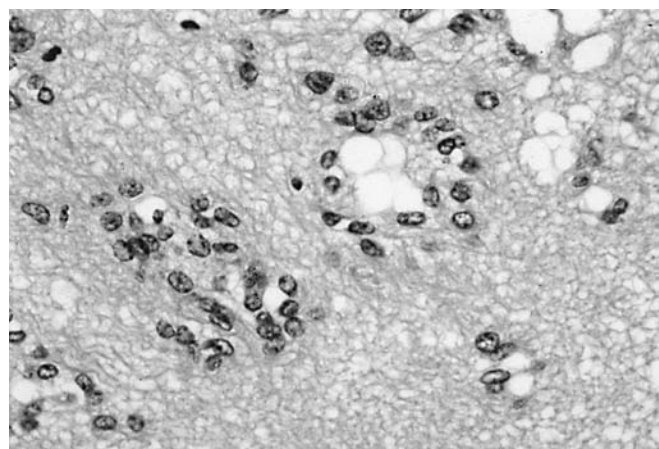


Fig. 13-3. Oval to slightly elongated nuclei with a uniform chromatin pattern in subependymoma.

diagnostic consideration is distinguishing subependymoma from an ordinary ependymoma. Similarities and differences between these tumors are outlined in Table 13-1. Ependymomas, in contrast to subependymomas, are more commonly encountered in children and do not have an obvious gender predilection. Ependymomas are characterized by perivascular pseudorosettes and true ependymal rosettes, which are not prominently observed in subependymoma. Ependymomas tend to be more cellular than the subependymoma. Immunohistochemistry is generally not useful in differentiating the two lesions. Ultrastructurally, subependymoma shows features of both astrocytic and ependymal differentiation. The importance in making the distinction from an ordinary ependymoma rests on the differences with regard to prognosis. Ependymomas have a greater potential for poor outcome. Occasionally, cases which contain a mixture of subependy-

ma and ependymoma patterns have been encountered. In general, it is better to treat these lesions as ependymoma, unless the subependymoma pattern is clearly the predominant pattern of the neoplasm.

Other differential diagnostic considerations by location would include the subependymal giant cell astrocytoma and rare cases of a predominantly intraventricular fibrillary-type astrocytoma. Subependymomas lack the plump, eosinophilic astrocytic cells, cellularity, and association with tuberous sclerosis that mark the subependymal giant cell astrocytoma. The fibrillary type astrocytoma may be of differential diagnostic consideration, particularly in small biopsies from the spinal cord region. Differences in the low magnification architectural pattern between the two lesions may be helpful, in that one does not typically see clustered groups of nuclei with intervening hypocellu-

Table 13-1
Subependymoma Versus Ependymoma

	<i>Subependymoma</i>	<i>Ependymoma</i>
Peak age	Adults	Children (may occur in adults)
Gender	Males > females	Males = females
Location	Proximal to ventricular system/ central canal	Proximal to ventricular system/central canal
True ependymal rosettes	—	+
Perivascular pseudorosettes	—	+
Cellularity	Less	More
Mitoses	±	±
Calcification	±	±
Vascular proliferation	—	— (+ in anaplastic tumor)
Necrosis	± (infarct type)	± (infarct type or in high-grade tumor)
Nuclear pleomorphism	±	±
GFAP	+	+
S-100	+	+
Electron microscopic features	Overlap astrocytic/ ependymal features	Ependymal (zipper-like junctions, microvilli, cilia, blepharoplasts)
Prognosis	Generally excellent	More variable, often dependent on extent of resection

lar parenchyma in an infiltrating fibrillary type astrocytoma. With limited material, distinguishing an ependymoma or subependymoma from astrocytoma may be difficult and one may need to resort to ultrastructural examination of the tumor if there is not sufficient material to assess the overall architecture and recognize characteristic ependymal and subependymal light microscopic features.

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14 Myxopapillary Ependymoma

MYXOPAPILLARY EPENDYMOMA is an infrequently encountered ependymoma variant that is important to distinguish from the ordinary type of ependymoma because of its generally better prognosis. Classically, myxopapillary ependymoma arises in the distal portion of the spinal cord and filum terminale region. Rarely, however, cases of myxopapillary ependymoma have been described arising in other regions of the spinal cord, intracranially, and in the subcutaneous soft tissues of the sacrococcygeal region (1–6). As documented in the single largest group of these tumors reported in 1985 by Sonneland et al, there appears to be a slight male predominance and mean age at presentation of 36.4 years (range 6–82 yrs) (1). The most common presenting symptoms are related to low back pain with or without sciatica which was reported in the 96% of the patients in Sonneland's study (1). Interestingly, cerebrospinal fluid protein levels were markedly elevated in most patients in whom this was evaluated.

The gross appearance of myxopapillary ependymoma is that of a generally soft, fairly discrete appearing mass. A substantial subset of tumors appears to be completely encapsulated by a delicate fibrous capsule (1). Tumors generally have a mucoid and focally hemorrhagic appearance. Cyst formation and calcifications are not prominently noted.

Histologically, the classic appearance of the myxopapillary ependymoma is marked by a focally pseudopapillary architecture (Fig. 14-1). In the center of the pseudopapillae are vessels which are surrounded by pools of mucin material which readily stain positively for a variety of mucin stains including mucicarmine and alcian blue (Fig. 14-2). Many of the pseudopapillae are lined by ependymal cells, which have a low columnar or at times more elongated configuration. The more elongated cells tend to have more centrally directed cytoplasmic processes and peripherally situated nuclei. Focal areas in which solid

clusters of tumor cells, not associated with an apparent pseudopapillary architecture, are fairly common (Fig. 14-3). The cells contain a variable amount of eosinophilic fibrillary appearing cytoplasm with generally oval, slightly irregular nuclei and finely delicate nuclear chromatin pattern (Fig. 14-4). Small nucleoli are frequently noted. Occasionally, cytoplasmic vacuolization may be quite common and signet ring type cells may be encountered (1). Focally prominent nuclear pleomorphism may be seen and does not appear to influence prognosis (Fig. 14-5). Mitotic figures are not commonly seen (1,7). Marked vascular sclerosis may be present (Fig. 14-6). Vascular proliferation, such as one sees with high-grade fibrillary-type astrocytomas, is generally not a feature of myxopapillary ependymoma. Necrosis is also not a common finding. Focal areas of hemorrhage, intravascular thrombi, and hemosiderin deposition may also be encountered in these tumors.

Similar to ordinary ependymomas, myxopapillary ependymomas frequently stain positively with immuno-

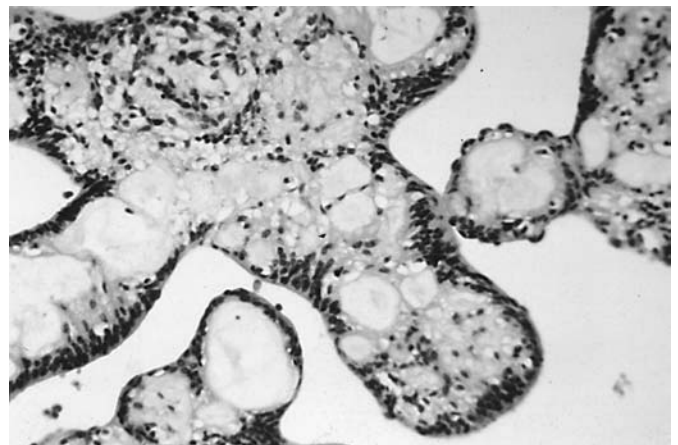


Fig. 14-1. Focal papillary architecture in a myxopapillary ependymoma.

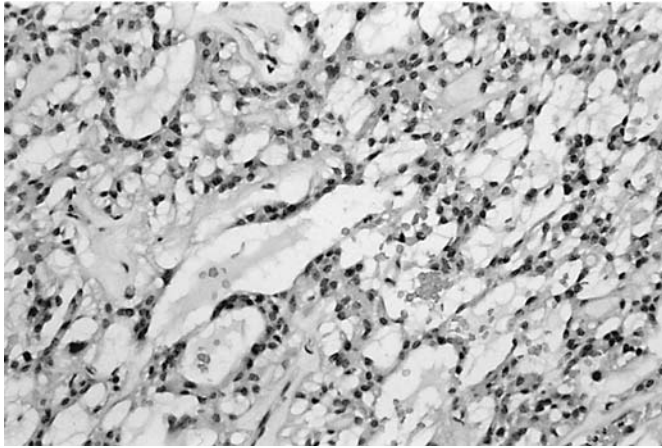


Fig. 14-2. Abundant mucin pools in a myxopapillary ependymoma.

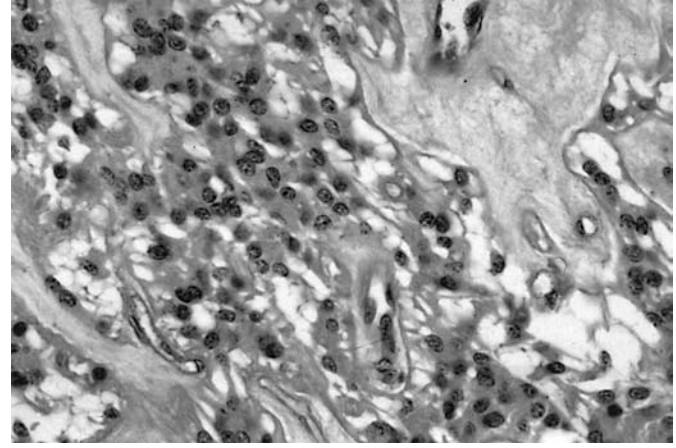


Fig. 14-4. Cells in myxopapillary ependymoma are marked by a variable amount of eosinophilic cytoplasm, slight irregular nuclear contours with occasional small nucleoli.

stains for glial fibrillary acidic protein (GFAP) and variably with S-100 protein. Tumors generally do not stain for markers of neuronal differentiation. Examination of cell proliferation markers in myxopapillary ependymal tumors is somewhat limited in the literature, but indicates a low level of cell proliferation when compared with ordinary types of ependymoma (7,8); this is in keeping with the general slow growth and benign clinical behavior that marks most myxopapillary ependymomas.

The best predictor of outcome in patients with myxopapillary ependymoma is the extent of surgical resection. Sonneland et al reported a mean survival of 19 years in patients who underwent gross total resection as compared with 14 years for patients who underwent subtotal resection (1). The few patients with poor outcome were generally those whose clinical course was marked by multiple recurrences. Histologic appearance and cell proliferation marker labeling indices do not appear to be predictive of more aggressive behavior (1,7). Rare cases of aggressive

behavior have been reported in myxopapillary ependymomas involving dissemination within and rarely outside the central nervous system (9–12).

Distinction of myxopapillary ependymoma from an ordinary ependymoma is important from a clinical and therapeutic standpoint. Although ependymomas may rarely arise in the sacrococcygeal and filum terminale region in young adults, they are more commonly encountered in children and in other locations. The true ependymal rosettes and perivascular pseudorosettes that mark ependymoma histologically are generally absent or not well formed in the myxopapillary ependymoma. The mucoid stroma, which is a distinctive feature of myxopapillary ependymoma, is not observed in ependymomas. The distinction of these two lesions is predicated primarily on the histologic appearance, in that their immunohistochemical profiles are overlapping. Table 14-1 compares

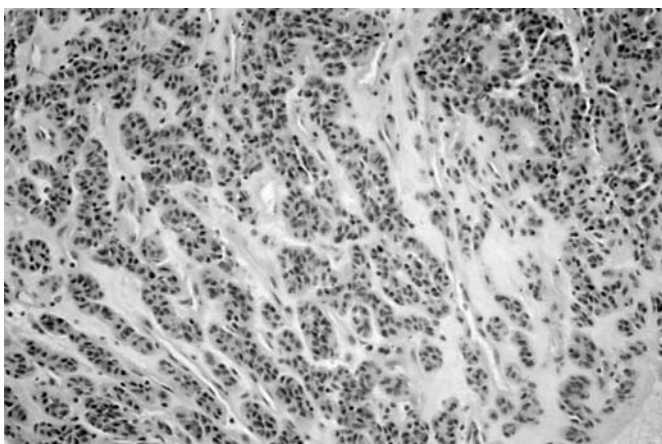


Fig. 14-3. Myxopapillary ependymoma with small nests and cords of cells.

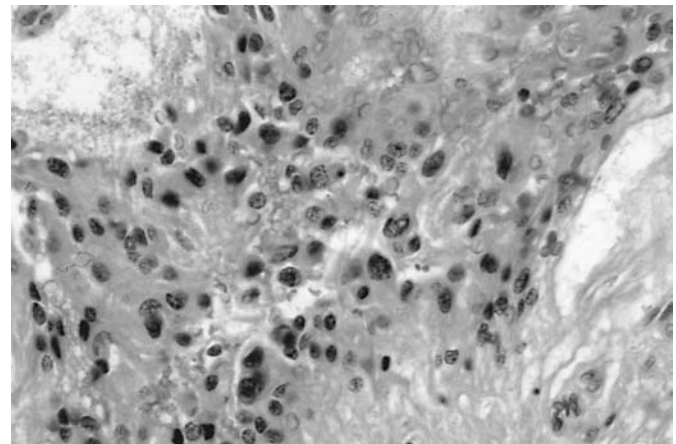


Fig. 14-5. Focally prominent nuclear pleomorphism in a myxopapillary ependymoma.

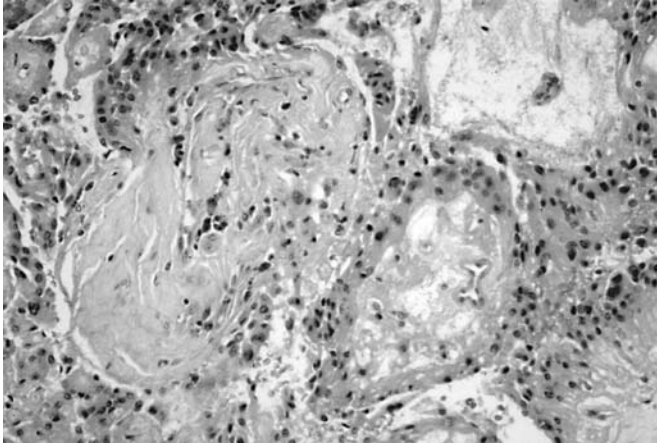


Fig. 14-6. Perivascular sclerosis is a commonly encountered finding in myxopapillary ependymoma.

the clinicopathologic features of myxopapillary ependymoma and ependymoma.

Other lesions which are in the differential diagnosis of myxopapillary ependymoma, more by location than histologic appearance, include schwannoma, paraganglioma, and chordoma. The classic biphasic pattern of schwannoma (Antoni A and B patterns), and the occasional presence of Verocay bodies, are distinctive features of schwannoma that are generally not encountered in the myxopapillary ependymoma. Schwannomas also lack the mucin positive stroma that characterizes myxopapillary ependymoma. Schwannomas stain negatively for GFAP, and similar to myxopapillary ependymoma, they stain positively for S-100 protein. Cases of paraganglioma arising in cauda equina region have been described and can rarely mimic myxopapillary ependymoma, due to the general perivascular orientation of cells. However, paragangliomas tend to have a more nested architectural pattern

(so-called zellballen) and frequently show areas of ganglionic differentiation, features not commonly observed in myxopapillary ependymoma. From an immunohistochemical standpoint, the two lesions are distinctive in that paragangliomas stain negatively for GFAP and positively for markers of neuroendocrine differentiation, including neuron specific enolase, neurofilament proteins, somatostatin, and serotonin. The characteristic myxoid or mucoid background of chordoma may also superficially resemble a myxopapillary ependymoma. Chordomas, however, are typically bone-based lesions which stain negatively for GFAP and positively for cytokeratin markers.

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Table 14-1
Myxopapillary Ependymoma Versus Ependymoma

	<i>Myxopapillary Ependymoma</i>	<i>Ependymoma</i>
Peak age	Young adults	Children
Location	Primarily filum terminale, sacrococcygeal region	Any ventricle or spinal cord
Papillary architecture	±	– (rare +)
True ependymal rosettes	–	+
Perivascular pseudorosettes	–	+
Mucoid stroma (mucin +)	+	–
Nuclear pleomorphism	±	±
Vascular hyalinization	±	Rare +
Mitoses	± (rare)	±
Vascular proliferation	–	– (± high grade)
Necrosis	–	– (± high grade)
S-100	+	+
GFAP	+	+
Cell proliferation indices	Low	Higher
Prognosis	Better	Worse

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15 Central Neurocytoma

CENTRAL NEUROCYTOMA REFERS TO a generally low grade, predominantly intraventricular tumor which demonstrates evidence of a neuronal differentiation (1). The tumor is rather uncommonly encountered and comprises less than 1% of central nervous system neoplasms. There is no obvious gender predilection. Most neurocytomas are diagnosed between the ages of 20 and 40 years, although rare cases have been described in children and older patients. Most are situated in the lateral or third ventricle, with the anterior half of the lateral ventricle being the most common site of origin. Rare cases of so-called extraventricular neurocytoma have been described, and with the routine usage of immunohistochemical stains for identifying neuronal differentiation in oligodendroglial-like neoplasms, they are being increasingly recognized (2-4). Presenting signs and symptoms are often related to increased intracranial pressure or disturbances in vision. Radiographically, the tumor appears rounded or polylobated, is generally well-circumscribed, and may demonstrate areas of cystic degeneration or calcification.

Histologically, the central neurocytoma is characterized by a proliferation of fairly monomorphic appearing cells with scant cytoplasm (Fig. 15-1). Cell nuclei generally have a rounded configuration, finely granular chromatin pattern and lack a prominent nucleolus (Fig. 15-2). Cells are arranged against a fibrillary background, which may also contain a significant number of small caliber vessels, somewhat reminiscent of oligodendroglioma (Fig. 15-3). Occasionally a perinuclear halo artefact, similar to what one encounters with oligodendrogliomas that have been fixed in formalin, may also be seen in neurocytoma (Fig. 15-4). Areas of microcystic degeneration or calcification may be present. Rarely, ganglionic appearing cells may be identified (1,5). Prominent mitotic activity, vascular proliferation, and necrosis are unusual features in neurocytoma. Rare central neurocytomas with increased mitotic activity, vascular proliferation, and/or

necrosis have been described in the literature and have been associated with invasive growth and recurrence (6-8). These tumors tend to have a higher MIB-1 labeling indices compared to ordinary type central neurocytomas (8).

Immunohistochemical evaluation of central neurocytomas demonstrates neuronal differentiation as evidenced by expression of neuron specific enolase and synaptophysin (Fig. 15-5). These tumors have also been reported to stain positively for Leu7. They generally stain negatively for glial fibrillary acidic protein (GFAP); although rare positively staining tumors have been reported (9,10). Ultrastructural examination of central neurocytomas demonstrates evidence of neuronal differentiation in the form of dense core neurosecretory granules and specialized synaptic junctions (1,10) (Fig. 15-6).

The clinical course of most central neurocytomas is that of benign, low grade lesions which can potentially be cured with a gross total resection. If not completely excised, residual tumor can regrow over time. The role

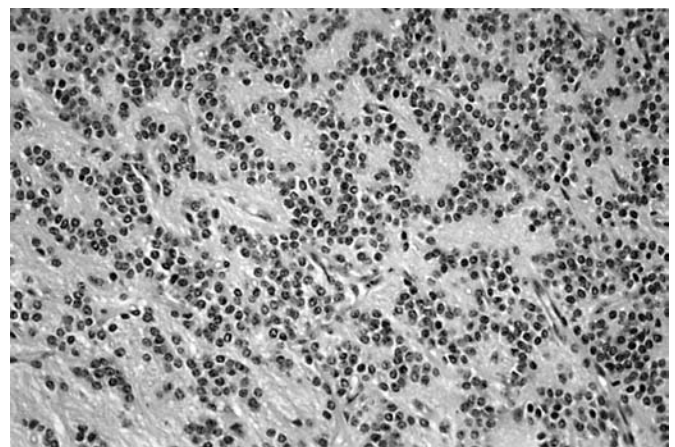


Fig. 15-1. Central neurocytoma marked by a monomorphic proliferation of cells with scant cytoplasm.

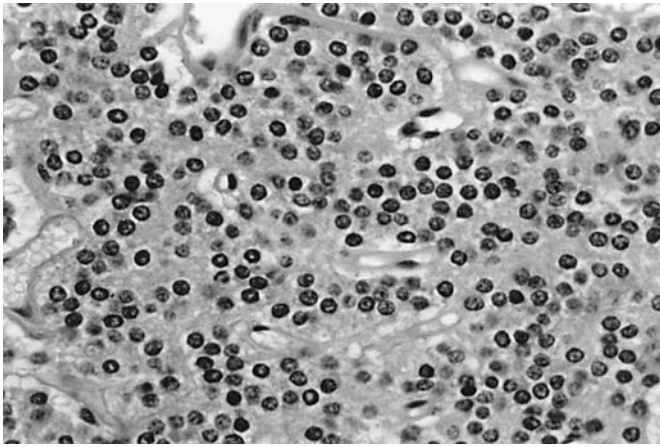


Fig. 15-2. Cells in central neurocytoma have generally rounded nuclei with a finely granular chromatin pattern and lack of prominent nucleoli.

of adjuvant radiation therapy remains debatable, but has often been administered to subtotally resected tumors (1). Again, a smaller subset of these tumors do appear to behave in a more aggressive fashion, and often these are marked by more worrisome histologic features or higher labeling indices with cell proliferation markers (8,11). Five year survival rates have been reported to range from 80% to over 90% (12,13).

The major differential diagnosis from a histologic standpoint centers on not confusing central neurocytoma and low grade oligodendroglioma. Table 15-1 summarizes the clinical and pathologic features of these two tumors. Although rare cases of intraventricular oligodendroglioma have been described, the intraventricular location of an oligodendroglial-like neoplasm should prompt consideration of central neurocytoma. Unlike oligodendrogliomas, central neurocytomas tend to be more circumscribed and less infiltrative. Cytologically, the tumors may look very

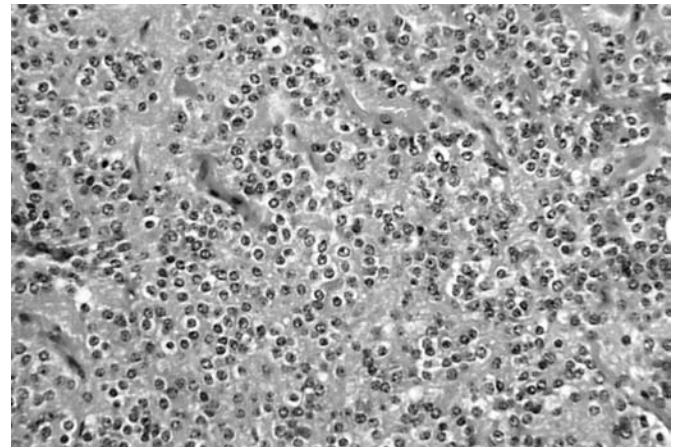


Fig. 15-4. Central neurocytoma with perinuclear halo artefact similar to what one encounters in an oligodendroglioma.

similar, although there are subtle differences with regard to chromatin pattern between the lesions. Histologic differences are frequently subtle enough that immunohistochemical confirmation of neuronal differentiation with synaptophysin staining is generally warranted. Ultrastructural examination may also be used to confirm the presence of neural differentiation in the cells which comprise neurocytoma.

Because of their predominantly intraventricular location, ependymomas are included in the differential diagnosis of central neurocytoma. In particular, the so-called clear cell variant of ependymoma, with its oligodendroglial-like phenotype, may mimic the central neurocytoma. More commonly, central neurocytomas tend to be midline-based, ventricular lesions as opposed to the more unilateral-based ependymomas. The hypocellular, fibrillary background of the central neurocytoma may give one the false sense of perivascular pseudorosetting at low magnification and can cause confusion with ependymoma

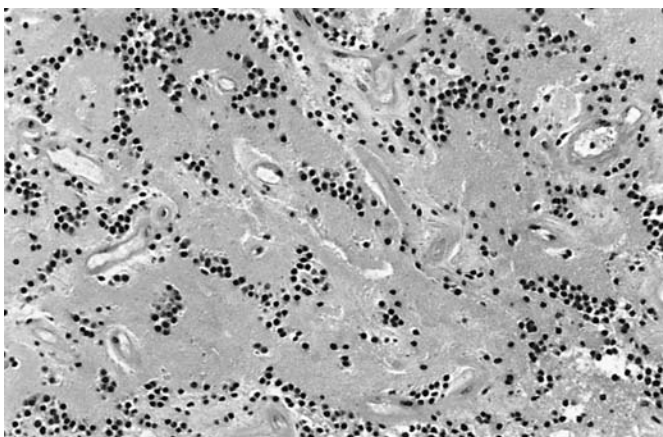


Fig. 15-3. Prominent fibrillary background and capillary vascular pattern in a central neurocytoma.

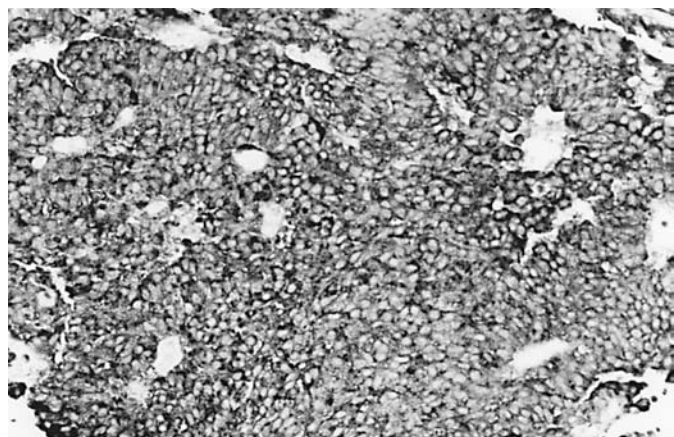


Fig. 15-5. Diffuse positive cytoplasmic staining with synaptophysin in a central neurocytoma.

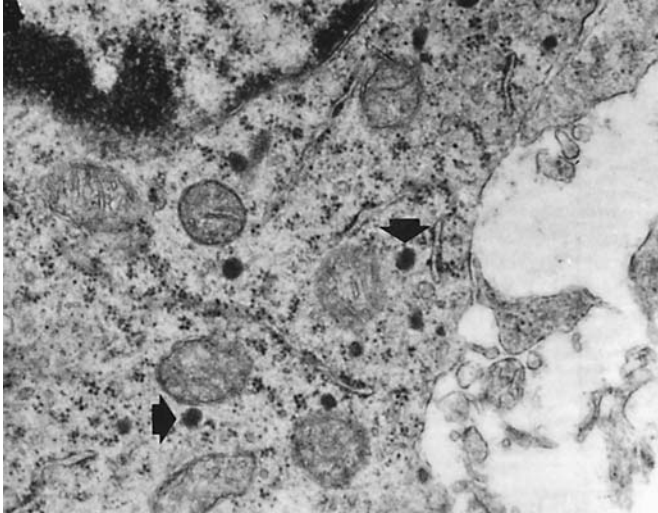


Fig. 15-6. Ultrastructural appearance of central neurocytoma with neurosecretory granules (arrows).

as well. Again, immunohistochemistry readily resolves the issue in that ependymomas stain diffusely with GFAP and negatively for synaptophysin.

From a historical standpoint, there has been confusion in the past with regard to use of the term “cerebral neuroblastoma” as being synonymous with central neurocytoma. These two terms should not be used synonymously. Central neuroblastomas are generally pediatric neoplasms that are parenchymal based and often look like high grade tumors with marked cytologic atypia, increased cellularity, and prominent mitotic activity. Necrosis and infiltrating growth pattern are characteristic features of the neuroblastoma. Although the immunohistochemical profile and ultrastructural features may overlap between central neu-

roblastoma and central neurocytoma, their light microscopic features are distinctively different.

Recently recognized are rare tumors that are extraventricular in location and have neurocytomatous features (14). Some of these tumors have mixed features and contain areas of prominent hyalinized vascular sclerosis, ganglionic differentiation, or areas of astrocytic differentiation. The exact relationship of the neoplasms to the central neurocytoma remains to be elucidated.

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Table 15-1
Central Neurocytoma Versus Oligodendroglioma

	<i>Central Neurocytoma</i>	<i>Low-Grade Oligodendroglioma</i>
Peak age	Adults	Adults
Location	Most intraventricular, rarely parenchymal-based	Parenchymal-based,
Infiltration	Uncommon	Common
Calcification	±	+ (majority)
Cystic	±	±
Atypia	–	–
Neuronal differentiation	+	–
Mitoses	Rare +	±
Arcuate vasculature	±	+
Necrosis	–	–
Cell proliferation	Generally lower	Generally low
Synaptophysin	+	–
GFAP	Most –	Usually +
Neurosecretory granules (on electron microscopy)	+	–
Prognosis	Better	Generally worse

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16 Dysembryoplastic Neuroepithelial Tumor

IN 1988, DAUMAS-DUPORT ET AL. reported a series of 39 morphologically unique neuroepithelial tumors associated with medically intractable partial complex seizures and coined the term “dysembryoplastic neuroepithelial tumor” (DNT) for these lesions (1). This lesion has subsequently been included in the most recent World Health Organization Histologic Typing of Tumours of the Central Nervous System as a “benign supratentorial mixed glial-neuronal neoplasm characterized by its intracortical location, multinodular architecture, and heterogeneous cellular composition” (2). Since its recognition as a distinct entity, identification of this lesion has increased. The tumor most frequently presents in pediatric-aged patients. In the series of 39 tumors reported by Dumas-Duport et al., the mean age of symptom onset was 9 years (1). The most common presentation included chronic seizures ranging from 2 to 18 years (mean 9 years) in duration. Similar to ganglioglioma, another chronic epilepsy related tumor, the most common site of origin for DNT is the temporal lobe. Cases have been described in all three of the remaining cortical lobes and rarely in other locations in the central nervous system (1,3–5). Rare cases of DNT arising in the setting of neurofibromatosis type I have also been reported (6).

Imaging studies show that most cases of DNT appear to be cortical based. Focal areas of white matter extension may be present. Characteristically, the tumor has a multinodular and cystic appearance. Gross examination of the surface of the brain may show gyral expansion in areas involved by the tumor with multiple foci of “blisterlike nodules” (4). Rarely, leptomeningeal involvement by tumor has been described, but similar to ganglioglioma, there is no adverse effect on prognosis associated with this finding. Microcalcification is variably encountered.

Histologically, the tumor is characterized by multinodularity (Fig. 16-1). Most of the nodules appear to be predominantly cortical based; although focal extension

into the underlying white matter may be seen (Fig. 16-2). The predominant cell type is the oligodendrocyte. Cells are typically arranged against a focally microcystic background (Fig. 16-3). Cysts may be filled with a faintly eosinophilic acid mucopolysaccharide material. Other nodules may have a more solid configuration (Fig. 16-4). Intermixed with the oligodendrocytes are smaller numbers of neurons and astrocytes (Fig. 16-5). There is no cytologic atypia to any of the cellular components of the DNT. Mitoses may be rarely observed. Vascular endothelial hyperplasia and necrosis are not features of DNT. Occasionally, eosinophilic granular bodies or Rosenthal fibers may be seen adjacent to or in association with the neoplasm. In areas, a proliferation of small capillaries, similar to what one encounters in oligodendrogliomas may be present. Similar to gangliogliomas, cortical dysplasia (cortical architectural abnormalities) has also been frequently described adjacent to DNTs (1,7-11) (Fig. 16-6). Patterns of dysplasia seen in association with DNTs

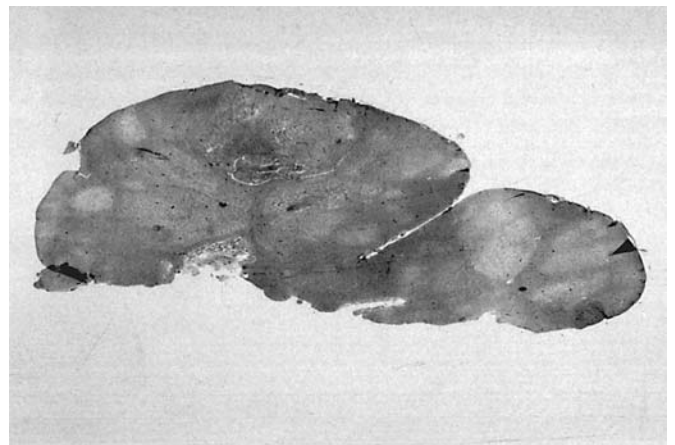


Fig. 16-1. Low magnification appearance of a dysembryoplastic neuroepithelial tumor marked by multiple, predominantly cortical-based nodules.

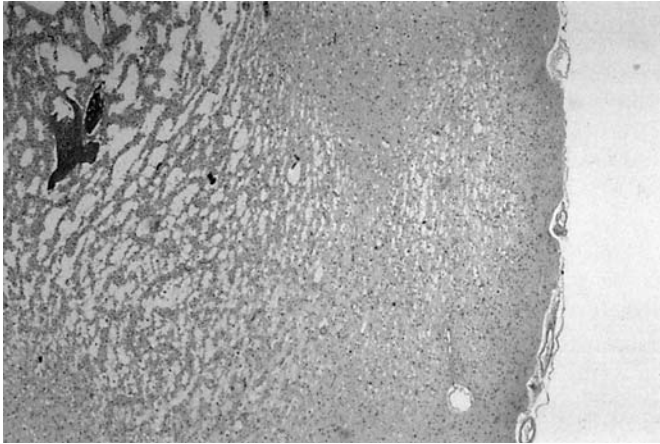


Fig. 16-2. Two cortical based nodules situated in cortical layers 2 and 3 and 3-6 in a dysembryoplastic neuroepithelial tumor.

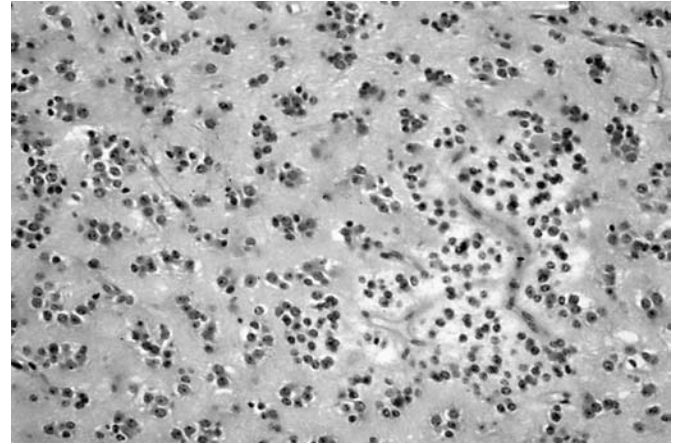


Fig. 16-4. A solid focus of dysembryoplastic neuroepithelial tumor consisting of oligodendroglial cells arranged around neuronal cells.

include disturbances in the laminar cortical architecture, abnormal arrangements of neurons within the cortex, and increased numbers of neurons within the molecular layer of the cortex (7).

Similar to gangliogliomas, immunohistochemistry and ultrastructural studies add little in terms of diagnosis. Immunohistochemical stains may be used to confirm the presence of a neuronal component to the tumor. Oligodendrogliallike cells have been shown to stain positively for CD57 (Leu7) and ultrastructurally appear to resemble oligodendrocytes (7,12). A small number of oligodendroglial-like cells show evidence of astrocytic or neuronal differentiation, a finding that has been confirmed by both ultrastructural and immunohistochemical studies (12,13). Studies which have examined cell proliferation markers in DNTs have shown a very low level of immunostaining with Ki-67, MIB-1, and PCNA (7,14–16).

Total excision of the tumor has yielded excellent results and is regarded by many to be curative. Residual foci of

tumor in a subtotal resection may be cause for additional surgery, due to residual or recurrent seizures. To date, there have been no credible cases of malignant transformation or metastatic disease associated with the DNT. There is no role currently for adjuvant therapy in the management of these tumors.

Similar to the ganglioglioma, there has been considerable debate regarding the exact nature of the DNT. The origin of the tumor still remains somewhat obscure. The tumor's association with cortical dysplasia is suggestive of a developmental origin. Daumas-Duport et al hypothesized that the DNT may have its origin in the secondary germinal layers of the developing central nervous system (11). The low cell proliferation indices which have been reported in a majority of cases and the clinical course suggest a very slow growing or perhaps even a static lesion. From a purely morphologic viewpoint, DNT appears to fulfill criteria for hamartoma, defined as a malformative

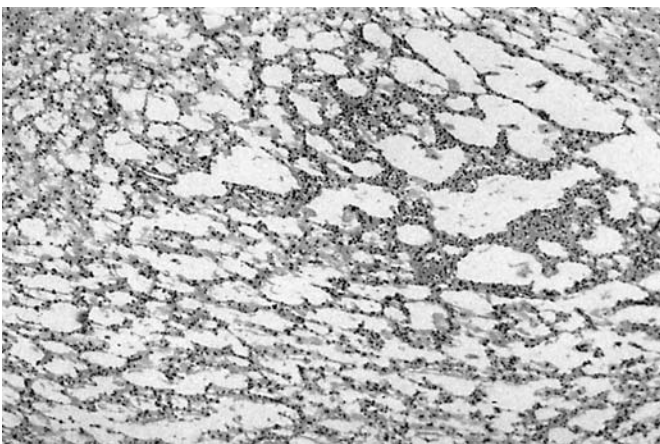


Fig. 16-3. Cells in the dysembryoplastic neuroepithelial tumor are often arranged, at least focally, against a microcystic background.

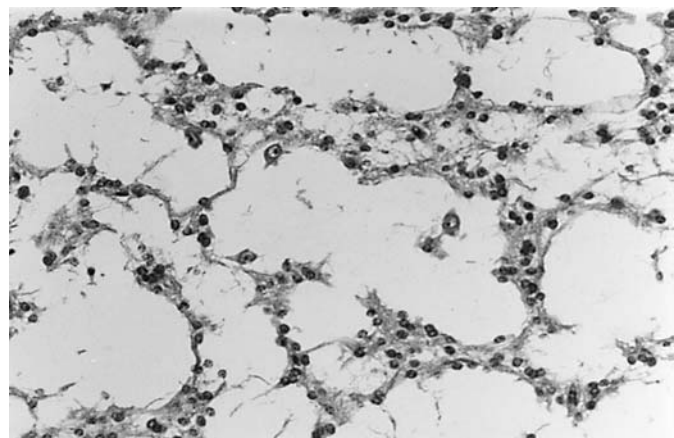


Fig. 16-5. Oligodendroglial cells arranged against a microcystic background with interspersed neuronal cells which are devoid of cytologic atypia.

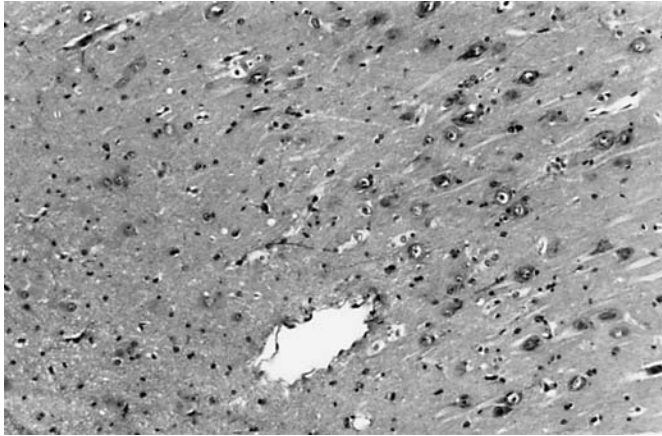


Fig. 16-6. Area of cortical architectural disorganization (cortical dysplasia) adjacent to a dysembryoplastic neuroepithelial tumor.

abnormality of tissue development characterized by a haphazard arrangement of mature cells indigenous to a particular site. Debate still continues as to whether or not the DNT represents a true neoplasm or hamartoma.

From a histologic standpoint, there are a number of lesions that come into the differential diagnosis of DNT. One of the most difficult, as well as important, differential diagnostic considerations is distinguishing DNT from oligodendroglioma. Features of these two lesions are summarized in Table 16-1. Unlike DNT, oligodendroglioma generally does not have a multinodular architecture and it arises primarily within the white matter. Oligodendrogliomas frequently infiltrate overlying gray matter, and one must be careful not to misinterpret entrapped cortical neurons in an infiltrating oligodendroglioma as an intrinsic part of the neoplasm. The arcuate vascular pattern and microcalcifications which are so common in oligodendroglioma may also both be seen in DNT and are not generally helpful in terms of differential diagnosis.

Although oligodendrogliomas are more common in the frontal and parietal lobes, cases arising in the temporal lobe have certainly been described and in an individual case, location is also not a helpful parameter. Oligodendrogliomas have a generally more infiltrative growth pattern. The piling up of infiltrating tumor cells in the subpial region of an infiltrating oligodendroglioma is generally not seen in the DNT. Areas of cortical dysplasia have not been described adjacent to oligodendroglioma. One might also expect a slightly higher cell proliferation marker labeling index in oligodendroglioma as compared with DNT. Despite these differences, there are certainly instances, particularly in a small biopsy, in which distinction between the two lesions may be impossible.

Another lesion which may be potentially confused with a DNT is the protoplasmic astrocytoma. Currently, protoplasmic astrocytomas are classified as a variant of low grade astrocytoma (WHO grade II) along with fibrillary and gemistocytic types in the WHO classification. However, very little has been written regarding this tumor and it is still somewhat controversial whether or not it warrants a separate designation (17). It has been suggested that protoplasmic astrocytoma represents a uninodular variant of the DNT (14). There are a number of similarities between the two lesions with regard to clinical presentation, i.e. younger patients with history of seizures and predilection for temporal and frontal lobes. However, protoplasmic astrocytomas are generally not multifocal and in 16 cases which were reported in one series, there was no evidence of cortical dysplasia adjacent to any of the tumors (16). One also does not get a sense there are multiple cell types (oligodendrocytes, neurons, and astrocytes) participating in the formation of the protoplasmic astrocytoma, as is the case with DNT.

Finally, distinction of gangliogliomas from DNTs should be briefly addressed. There are numerous similari-

Table 16-1
Dysembryoplastic Neuroepithelial Tumor Versus Low Grade Oligodendroglioma

	<i>DNT</i>	<i>Low-Grade Oligodendroglioma</i>
Peak age	Children	Adults
Location	Temporal lobe most common, cortical based	Frontal lobe most common, white matter based
Architecture	Multinodular	Uninodular
Infiltration	Minimal	Common
Cortical dysplasia	+	—
Calcification	±	+ (majority of cases)
Cystic	+ (most cases)	±
Atypia	—	±
Neuronal component	+	—
Mitoses	Rare	±
Arcuate vasculature	+	+
Necrosis	—	—
Cell proliferation	Low	Generally higher
Prognosis	Excellent	More aggressive

ties between the two tumors. Both of these neoplasms occur predominantly in younger patients with a history of chronic epilepsy and most frequently involve the temporal lobe. Both lesions are characterized by biphasic histology involving both neuronal and glial cell types. The apparent association of both lesions with cortical dysplasia, their generally low levels of cell proliferation, and good prognosis are additional similarities. Despite these numerous similarities, there are differences that allow distinction in most cases. The multinodularity that is characteristic of DNT is unusual in ganglioglioma. The glial component in most gangliogliomas resembles a low grade fibrillary astrocytoma; most DNTs resemble an oligodendroglial tumor. Cytologic atypia or abnormalities which are required for the diagnosis of ganglioglioma are absent in DNT. Despite these phenotypic differences, the degree of similarity and apparent developmental nature of these tumors has caused some to suggest that these two lesions may be more alike than dissimilar. Rare examples of composite or mixed tumors comprised of DNT and ganglioglioma add further support for a possible shared etiology (18,19).

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17 Ganglioglioma and Ganglion Cell Tumors

THERE HAS MUCH LITERATURE in recent years examining the pathology of chronic, medically intractable epilepsy. In many of these cases, the etiology or morphologic basis for seizures continues to be elusive. However, in some instances, the patient's seizures can be attributed to a number of identifiable morphologic abnormalities including hippocampal sclerosis (mesial temporal sclerosis), cortical dysplasia and a variety of low grade tumors. In the last several years, a number of institutions have reviewed their experience with tumors arising in the setting of chronic epilepsy. In a number of these series, ganglioglioma is one of the most commonly encountered tumors, along with low-grade astrocytoma (1–4). Distinction of gangliogliomas from other low-grade glial tumors, in particular fibrillary astrocytomas, is important from a prognostic viewpoint.

Gangliogliomas have been recognized as a distinct entity since the mid-1920s (5–12). In the most recent World Health Organization Histologic Typing of Tumours of the Central Nervous System, ganglioglioma is defined as “a benign tumour composed of neoplastic astrocytes (rarely oligodendrocytes) and ganglion cells” (13). Most gangliogliomas are diagnosed in pediatric patients who typically present with a long history of medically intractable epilepsy. In one review of 60 intracranial gangliogliomas, 90% of the patients (mean age 20 years) presented with seizures ranging in duration from 1 to 38 years (mean: 14 years) (14). The most common location for ganglioglioma is the temporal lobe; however, they have been documented to arise in a variety of locations throughout the central nervous system including brain-stem and spinal cord (15). Although not typically thought of as arising in the setting of phacomatoses, rare cases of gangliogliomas have been described in patients with neurofibromatosis type I (16).

Radiographically, gangliogliomas are somewhat similar to pilocytic astrocytomas in that they typically appear

as cystic lesions with enhancing mural nodules. Extension of the tumor into the subarachnoid space is a relatively common occurrence and does not appear to adversely alter prognosis (14) (Fig. 17-1). Although the classic appearance of the tumor is that of a cystic neoplasm, this is not an invariable finding, and often these tumors appear as solid neoplasms on imaging studies and gross examination. Calcification is present in about half of cases and may be quite extensive in some (Fig. 17-2). Most of these tumors arise in the white matter and appear to be relatively well-circumscribed.

The histologic diagnosis of ganglioglioma is dependent upon recognition of both an atypical neuronal or ganglion cell component and an atypical glial component (Fig. 17-3). The distribution of these two components within the tumor may be quite variable. Sometimes, extensive sampling of the tumor may be required to identify the second component. The neuronal component consists of an abnormal arrangement of ganglion cells with atypical cytologic features which may include binucleation, ballooned cyto-

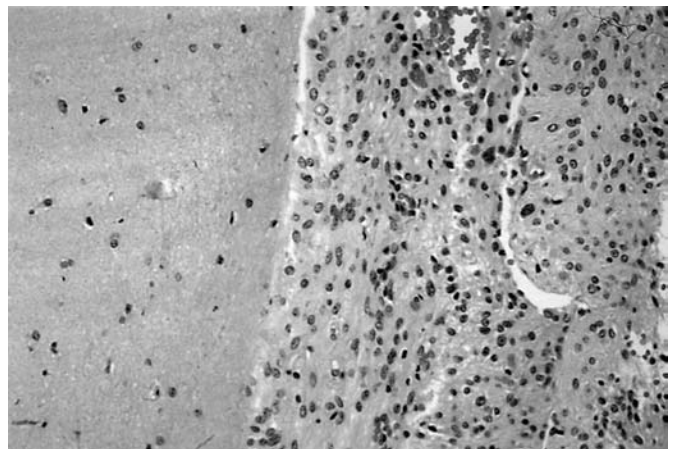


Fig. 17-1. Leptomeningeal extension of ganglioglioma does not appear to adversely effect prognosis.

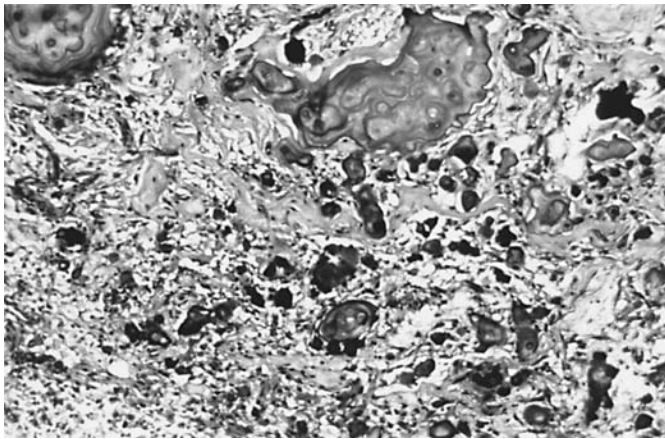


Fig. 17-2. Extensive mineralization in a ganglioglioma.

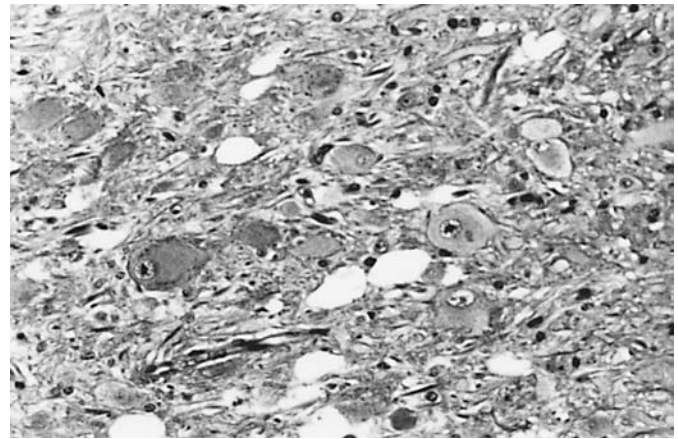


Fig. 17-4. Atypical, ballooned neuronal cells in a ganglioglioma.

plasm and irregular nuclear contours (Fig. 17-4). Binucleate neurons were observed in as many as 60% of gangliogliomas in one large series (14). The glial component of the tumor most frequently resembles a low grade astrocytoma (Fig. 17-5). Occasionally, areas resembling low grade oligodendroglioma may be present (Fig. 17-6). Increased mitoses, prominent vascular endothelial proliferation, and necrosis are not typical features of ganglioglioma. These histologic features have been rarely described in the so-called anaplastic or malignant ganglioglioma variant, which tends to behave in a more aggressive fashion. Similar to pilocytic astrocytomas, eosinophilic granular bodies are often readily identifiable in gangliogliomas (Fig. 17-7). Perivascular chronic inflammatory cells, consisting primarily of lymphocytes, are also present in a majority of cases. Occasional tumors may be rather paucicellular and contain a prominent collagenous stroma.

Immunohistochemistry and ultrastructural evaluation add little in the way of diagnostic assistance. In rare cases when the ganglion cell component of the tumor may not

be readily apparent by routine light microscopy, stains for neuronal differentiation such as synaptophysin, class III beta-tubulin, and neurofilament protein may be useful in identifying ganglion cells (15,17). Care must be taken not to misinterpret normal, entrapped neurons in a fibrillary astrocytoma as atypical ganglion cells, a problem one may encounter if relying entirely on immunohistochemistry. The ultrastructural features of both the ganglion cell and astrocytic cell components are as anticipated and add little to the routine work-up of these cases.

Recently, a number of studies have identified cortical dysplasia or cortical architectural abnormalities in the parenchyma adjacent to gangliogliomas. Wolf et al., in 1994, described what he referred to as “glioneuronal hamartias” in 13% of 61 gangliogliomas studied (18). Similarly, another series found evidence of cortical dysplasia in 50% of 38 tumors in which there was adequate tissue adjacent to the neoplasm for evaluation (14). The presence of this finding raises interesting questions with regard to the relationship of these two lesions. Debate

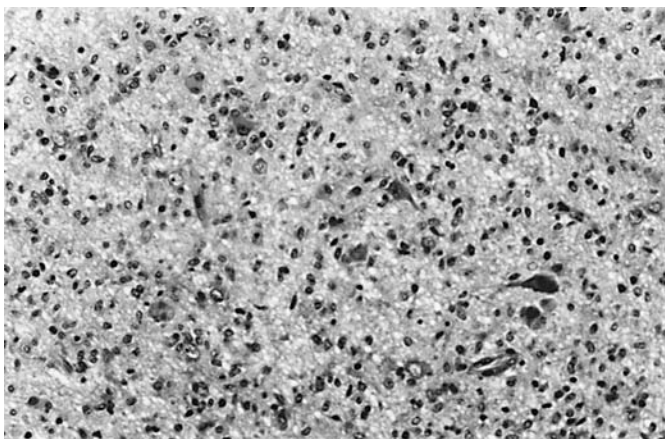


Fig. 17-3. Mixture of atypical neuronal/ganglion cells and an atypical glial cell proliferation in ganglioglioma.

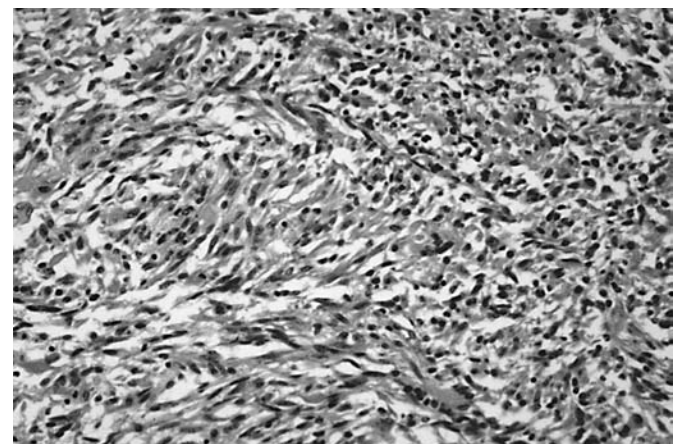


Fig. 17-5. A predominant astrocytoma pattern in a ganglioglioma.

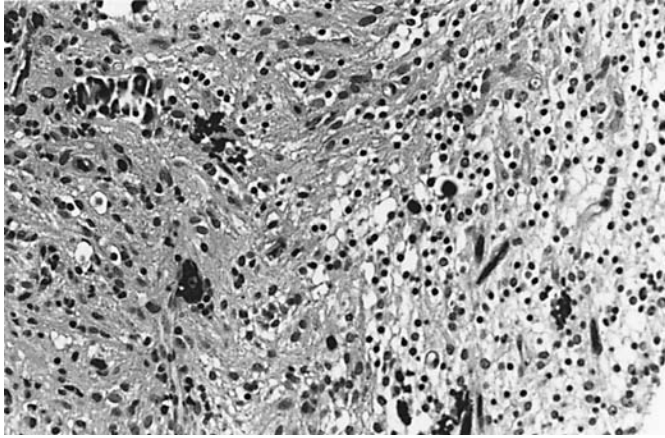


Fig. 17-6. Focal oligodendroglioma appearance and microcalcifications in a ganglioglioma.

continues as to 1) whether the dysplasia serves as a marker for developmental abnormalities, of which ganglioglioma might be one form; 2) whether ganglioglioma represents a tumoral form of cortical dysplasia; or 3) whether ganglioglioma represents the neoplastic transformation of a dysplastic focus.

Several recent cell proliferation studies on gangliogliomas have shown a very low level of cell proliferation. Wolf et al. found that the vast majority of gangliogliomas (45 of 61 tumors) had a Ki-67 labeling index of less than 1% of tumor cells (18). In the 54 out of 60 gangliogliomas immunostained with MIB-1 antibody in another series, a mean labeling index of 1.1 ± 1.0 was observed (14). The lack of identifiable mitotic activity in the majority of gangliogliomas, their long clinical course, and cell proliferation studies all support the notion that gangliogliomas are very slow growing or perhaps, in some cases, static lesions.

In general, gangliogliomas respond well to surgical intervention. The vast majority of the patients will be

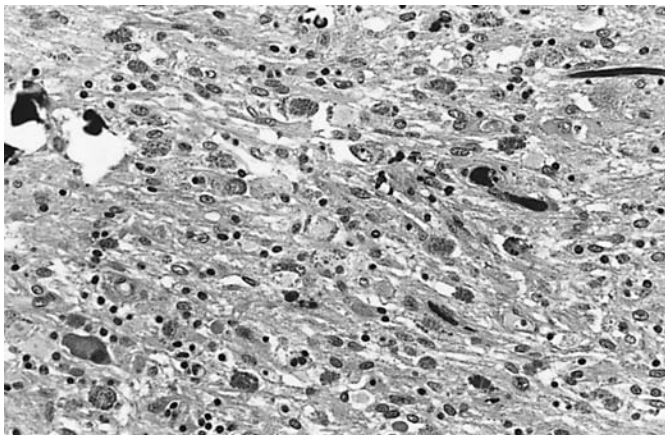


Fig. 17-7. Ganglioglioma with numerous eosinophilic granular bodies.

either seizure free or have a significant reduction (greater than 90%) in seizure frequency postoperatively (19). Rarely, aggressive behavior has been described in gangliogliomas (20–22). Only one of 60 tumors in one large series was histologically anaplastic (14). This particular tumor had a MIB-1 labeling index of 10.2 and ultimately caused death of the patient. There is still some controversy over whether appropriate surgical management includes a complete excision of the tumor alone or resection of tumor plus epileptogenic zones for additional seizure control. It is now thought that the parenchyma surrounding the tumor is responsible for the origin of seizures in a number of these cases. There is no role, except perhaps in rare anaplastic cases, for adjuvant therapy.

Distinction of gangliogliomas from other low-grade gliomas, particularly fibrillary astrocytomas and oligodendrogliomas, is important from a prognostic standpoint. The major distinction lies in recognition of both the atypical neuronal and glial components of the ganglioglioma. On a small biopsy, however, the possibility of identifying only one component of the tumor, namely, the glial component, increases the likelihood of misinterpreting the lesion as a fibrillary astrocytoma. The presence of eosinophilic granular bodies and focally prominent perivascular chronic inflammation may be useful clues. Coexisting cortical dysplasia is generally not a feature of fibrillary astrocytomas or oligodendrogliomas and its presence in association with “tumor” should evoke a differential diagnosis which includes ganglioglioma, dysembryoplastic neuroepithelial tumor, and hamartoma.

Distinction of gangliogliomas from glial-neuronal hamartomas and from cortical dysplasia itself may be problematic. Differences between these lesions may be more a matter of definition. Very little has been written regarding glial-neuronal hamartomas arising in the setting of chronic epilepsy. By definition, hamartomas generally lack the cytologic atypia that helps define gangliogliomas (23) (Fig. 17-8). However, the biphasic nature of glial-neuronal hamartomas, their association with cortical dysplasia, a low or absent level of cell proliferation, and early age of presentation may make them difficult to distinguish from gangliogliomas. Likewise, some forms of cortical dysplasia may be histologically identical to ganglioglioma. Again, distinction of these two lesions may be more definitional. Generally, the designation of ganglioglioma is used in reference to a tumor or mass. Microscopic foci which may resemble ganglioglioma are frequently referred to as dysplasia (24).

One of the rarely encountered variants of ganglioglioma is the desmoplastic infantile ganglioglioma. Most of these tumors present in the first few years of life as supratentorial, partially cystic lesions with a contrast enhancing focus or foci (25–27). Histologically, the tumor

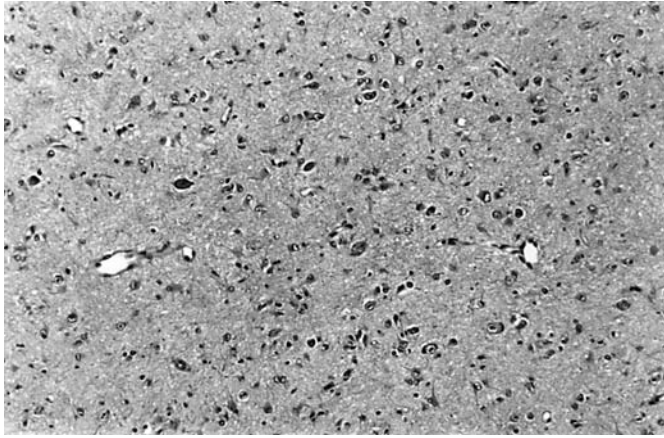


Fig. 17-8. Glial-neuronal hamartoma with slight increased cellularity and minimal cytologic atypia.

is characterized by a prominent collagenous stroma with variable cellularity. The tumor is often superficially based and appears to expand into the subarachnoid space and extend along the Virchow Robbin spaces into the cortex. Most of the cells have a spindled appearance and are arranged in a storiform pattern. Interspersed between this glial component is a variable number of small to medium sized neuronal or ganglion cells. The ganglion cells demonstrate some degree of nuclear atypia and irregular clustering which allow for their distinction from entrapped cortical neuronal cells. Mitotic activity may be quite variable and may be focally high in this neoplasm. The glial component of the tumor may be highlighted with a glial fibrillary acidic protein (GFAP) stain and the neuronal component will frequently stain with synaptophysin or neuron specific enolase. Occasional S-100 positive, GFAP negative cells have been described in this lesion and have prompted some to suggest a Schwann cell component to this neoplasm.

Distinction of the desmoplastic infantile ganglioglioma from more conventional type ganglion cell tumors is based on recognition of the dysplastic infantile ganglioglioma's typical clinical and radiographic presentation as well as desmoplastic and spindle cell morphology. A number of features more typically seen in ordinary gangliogliomas such as focal chronic inflammation and eosinophilic granular bodies are distinctly uncommon in the desmoplastic infantile ganglioglioma. Again, failure to recognize a ganglion cell component, may result in an erroneous diagnosis of a fibrillary astrocytoma. Fibrillary astrocytomas are distinctly uncommon in infancy and in general to do not display prominent desmoplastic or collagenous, reticulin-rich stroma. Failure to recognize the ganglion cell component of the dysplastic infantile ganglioglioma may also result in a diagnosis of infantile desmoplastic astrocy-

toma. The exact nature and relationship of these two lesions is still a matter of considerable debate. An occasional desmoplastic infantile ganglioglioma may demonstrate focal areas of marked hypercellularity and prominent mitotic activity, prompting consideration of sarcoma or gliosarcoma. Sarcoma or gliosarcoma, would both be distinctly uncommon in this age group. Immunohistochemistry as well as lack of prominent vascular proliferation and necrosis would hopefully avoid this confusion. In the few cases of desmoplastic infantile ganglioglioma that have been reported, most patients have done well clinically.

Tumors consisting exclusively of a ganglion cell component (gangliocytoma) are also uncommon. Those arising in the hypothalamic region have been frequently associated with endocrine dysfunction (28). One particular variant of gangliocytoma that is worth special mention is the dysplastic cerebellar gangliocytoma or Lhermitte-Duclos disease. The desmoplastic cerebellar gangliocytoma is considered a non-neoplastic hamartomatous lesion, characterized as a well demarcated, cerebellar mass, causing enlargement of the folia and increased signal intensity on T2-weighted magnetic resonance images (29,30). Association of the dysplastic cerebellar gangliocytoma lesion with developmental anomalies such as polydactyly and megaencephaly as well as Cowden's disease have been reported (29–31). Cowden's disease is a syndrome marked by multiple hamartomata including skin tricholemmomas, hamartomas of the breast, thyroid, oral mucosa, intestinal epithelium, and breast carcinoma (31). The Lhermitte-Duclos lesion histologically consists of a proliferation of larger-sized ganglion cells which are typically situated predominantly in the granular cell layer region, although focal extension into the overlying molecular layer can be seen (Fig. 17-9). A glial cell component

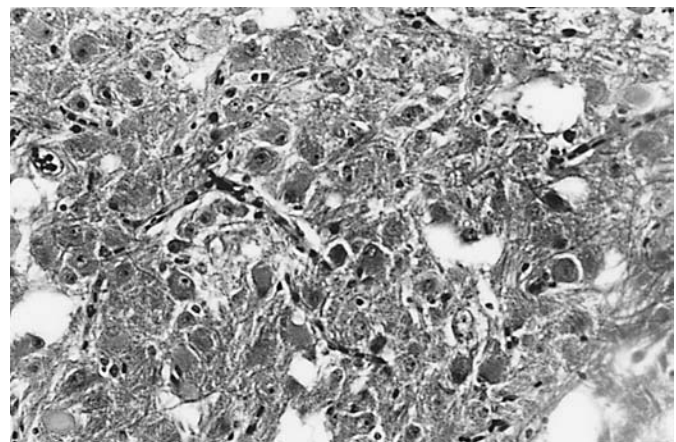


Fig. 17-9. Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease) characterized by a proliferation of ganglionic cells in the cerebellum.

to the lesion does not exist. Differentiation of this lesion from ordinary type gangliogliomas, which can also rarely arise in the cerebellum, is important because of the potential Cowden's disease association. Dysplastic cerebellar gangliocytomas are considered cured with excision.

In recent years, descriptions of phenotypically distinctive glial-neuronal tumors that do not precisely fit into current classifications have been published. Komori et al described nine cases of a papillary glioneuronal tumor histologically characterized by an astrocytic component and neuronal elements, often lying between "pseudopapillae" containing a central vessel core (32). In 1999, Teo et al described four cases of glioneuronal tumor marked by distinctive synaptophysin positive neuropil-like islands which were sometimes rimmed in a rosetted fashion by cells demonstrating immunohistochemical evidence of neuronal differentiation; the glial component of the tumor generally resembled a WHO grade II or III astrocytoma (33).

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18

Choroid Plexus Tumors

WHILE CHOROID PLEXUS TUMORS represent less than 1% of CNS tumors overall, they are responsible for a much greater proportion of CNS tumors in the early years of life. Of 170 newborn brain tumors (reported from twelve institutions), 12% were choroid plexus papillomas (CPPs) (1). CPPs preferentially involve the lateral ventricles in children, while the fourth ventricle is most often involved in adults. CPPs have occasionally arisen within the third ventricle (2). Presentation as a cerebellopontine angle tumor is also unusual. In the latter location, CPPs may either arise from the choroid plexus emanating from the foramen of Lushka, extend out from other locations within the fourth ventricle, or represent leptomeningeal dissemination (3). Bilaterality is distinctly unusual, may result in congenital hydrocephalus, has been reported in infants with duplication of chromosome 9p, and is also referred to as hyperplasia or villous hypertrophy of the choroid plexus (4). CPPs usually present with headaches, most often secondary to increased intracranial pressure as a result of excessive CSF production by the overgrown choroid plexus epithelium. Retention of this functional capacity is accompanied by retention of most of the morphologic characteristics of normal choroid plexus epithelium. While the usual cytologic and architectural features of low-grade papillary tumors (overgrowth, crowding, nuclear hyperchromasia and pleomorphism) may or may not be apparent, a fairly reliable feature of CPPs is *loss* of the normal hobnail appearance of nonneoplastic choroid plexus epithelium (Figs. 18-1 and 18-2). CPPs may, on occasion, demonstrate epithelial variations including tubule formation (5), oncocytic change, and pigmentation (6). Stromal lamellar calcification may frequently be seen within CPPs and may be so heavy as to interfere with tissue sectioning (7).

Once the presence of a papillary neoplastic process is

recognized, we must distinguish the CPP from both the (rare) papillary ependymoma and the (uncommon) choroid plexus carcinoma. CPPs contain a fibrovascular stroma, with the epithelial cells resting on a basement membrane, while papillary ependymomas manufacture a glial stroma (8). In atypical or difficult cases immunostaining with antibodies to low molecular weight cytokeratin and glial fibrillary acidic protein may be useful, as CPPs react with the former and not with the latter, while the reverse is true for papillary ependymomas (8,9). Focal ependymal differentiation may be seen in about a quarter of CPPs, and does not adversely affect the benign behavior of the tumor (7).

Carcinomas of the choroid plexus (CPCs), also tumors of early childhood, are significantly less common than CPPs (10). CPCs are aggressive tumors, with an overall 5-year survival rate of 26%, although with aggressive (total) surgical resection a 5 year survival rate of 86%

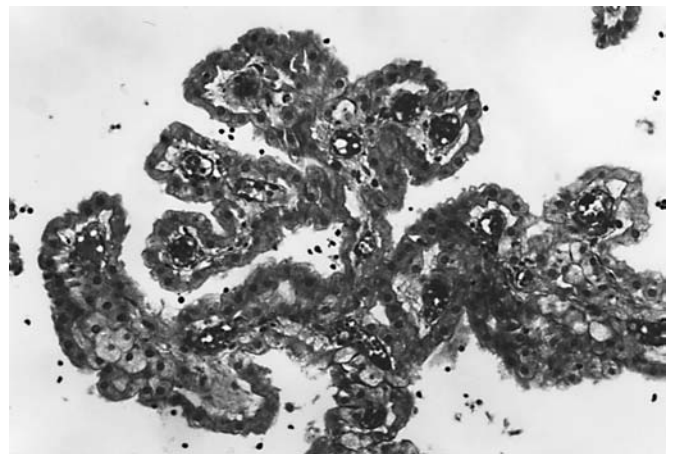


Fig. 18-1. Hobnail appearance of normal choroid plexus epithelium.

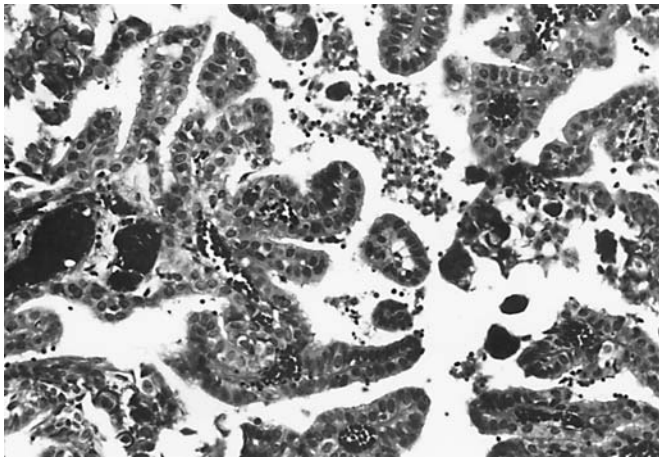


Fig. 18-2. Increased cellular crowding and nuclear hyperchromasia in a choroid plexus papilloma.

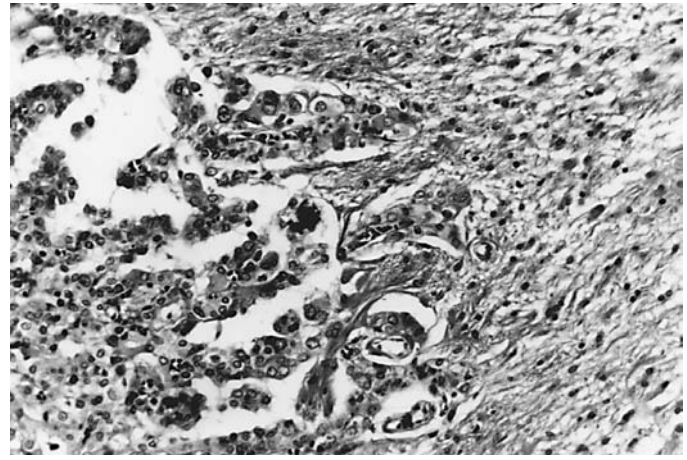


Fig. 18-4. Periventricular brain invasion by a choroid plexus carcinoma.

has been reported in one recent study (11). Histopathologically, CPCs are defined by brisk mitotic activity, nuclear atypia, loss of papillary architecture, and coagulative tumor necrosis (Fig. 18-3) (12). Significant parenchymal invasion is also a feature of CPCs, (Fig. 18-4) although focal microscopic invasion in otherwise typical CPPs should not be cause for alarm (7).

While “atypical CPPs” have been discussed by several authors, varying definitions (accompanied by various outcomes) have led to considerable confusion within the literature. For practical purposes, architectural and cytologic features analogous to low-grade dysplasia in other glandular tissues should not lead to the overdiagnosis of malignancy in choroid plexus tumors, as these neoplasms pursue a benign course typical of CPPs (7). On the other hand, one also may rarely encounter histopathologically typical CPPs associated with either leptomeningeal “drop

metastases,” or, even more exceptionally, extensive leptomeningeal dissemination (13).

The differential diagnosis of CPCs in children includes three other rare CNS tumors: medulloepithelioma, embryonal carcinoma, and atypical teratoid/rhabdoid tumor (Table 18-1). Medulloepitheliomas recapitulate primitive neural tubes and are thus tubular rather than papillary. The tubules are lined by PAS positive basement membrane material both basally and apically. While most CPCs react with antibodies to cytokeratins, medulloepitheliomas are uniformly negative. Embryonal carcinomas may closely mimic CPCs. A diligent search for other malignant germ cell elements including immunohistochemical staining with antibodies to placental alkaline phosphatase, alpha-fetoprotein, and CD30 will usually resolve this differential diagnostic problem. Many atypical teratoid/rhabdoid tumors manifest epithelial differentiation, which may also be confused with CPC. The presence of classic rhabdoid cells and primitive neuroectodermal elements in the former should allow proper diagnosis.

CPCs are vanishingly rare in adults, where the sole differential diagnostic consideration is metastatic carcinoma. Although several studies concerning immunocytochemical differentiation of these two diagnostic possibilities have been reported, none has provided a clear separation of CPCs from metastatic adenocarcinoma. We subscribe to the following statement made by Drs. Russell and Rubinstein in their classic textbook on CNS tumors (page 102): “Individual case reports describing choroid plexus carcinomas originating in adults have continued to appear in the literature in recent years: most of them seem to be examples of premature publication” (13). We sign these cases out as moderately (to poorly) differentiated papillary carcinomas and recommend a diligent search for a systemic primary.

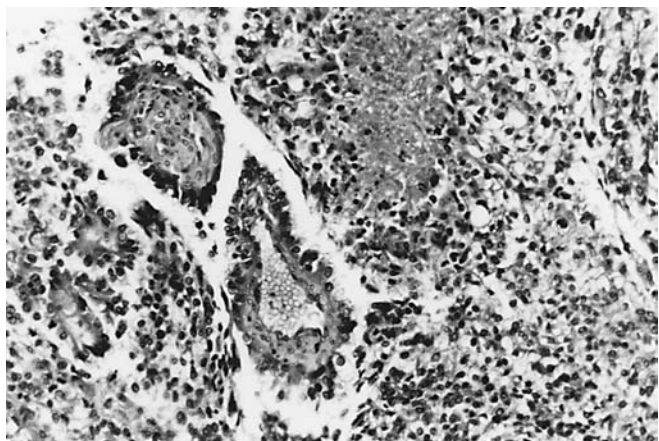


Fig. 18-3. Choroid plexus carcinoma demonstrating architectural loss, cytologic atypia, mitotic figures, and necrosis.

Table 18-1
Differential Diagnosis of Choroid Plexus Carcinoma

	<i>Choroid Plexus Carcinoma</i>	<i>Medulloepithelioma</i>	<i>Embryonal Carcinoma</i>	<i>Atypical Teratoid Rhabdoid Tumor</i>
Apical basement membrane	—	+	—	—
PNET component	—	—	+/-	+/-
Cytokeratin	+	—	+/-	+
EMA	+/-	—	+/-	+
S100 protein	+	+/-	+/-	+
Synaptophysin	—	+	+/-	+/-
PLAP/AFP/CD30	—	—	+/-	—

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19 Meningioma

IN 1922, HARVEY CUSHING ADOPTED the term “meningioma” to include a variety of meningeal based neoplasms which had been previously described under a variety of names including meningothelioma, endothelioma, arachnotherioma, meningocytoma, leptomeningioma, dural exotherioma, arachnoidal fibroblastoma, and fungus of the dura mater (1,2). The morphologic heterogeneity of this group of neoplasms has been recognized for a long time. Despite the wide variety of phenotypic appearances of meningioma, it is thought that this group of neoplasms is similar in that they are derived from arachnoidal cap cells which are most frequently situated within the leptomeninges and that they share certain immunohistochemical and ultrastructural features which allow their identification. However, they continue to provide a challenge from a differential diagnostic standpoint because of the wide variation in appearance. They also continue to challenge the efforts of most to reliably predict, based on histopathology, which tumors are more likely to behave in an aggressive manner.

The etiology of meningioma still remains unknown in most cases. Clearly, a subset of tumors appear to arise as a result of prior radiation therapy (3,4). In cytogenetic studies, an association with neurofibromatosis type II has pointed to an abnormality of chromosome 22 as an underlying etiology in a number of these neoplasms (5,6). Alterations in other chromosomes have been described in a subset of these tumors (7,8).

Meningiomas comprise anywhere from 10-20% of all adult intracranial tumors (6). The vast majority of meningiomas arise in adults; however, pediatric-aged patients may also be affected. Intracranial meningiomas clearly show a female predominance. Some studies have suggested that growth of meningiomas may be accelerated during the luteal phase of the menstrual cycle and during pregnancy (9,10). An association between meningiomas and other hormonally dependent tumors, in particular

breast carcinoma and certain gynecologic malignancies, has also been documented (11,12). These findings have prompted some to examine the potential role of estrogen and progesterone and their receptors, as well as androgen receptors in meningiomas (13–15). Despite the presence of estrogen and progesterone receptors in a subset of meningiomas, attempts at hormonal manipulation of the tumor, utilizing a variety of agents, have proven to be generally unsatisfactory and are not utilized in the routine management of these neoplasms (15).

Meningiomas have been described in a variety of locations and generally are seen arising in association with the dura and leptomeninges. The most common sites of origin include the parasagittal region, cavernous sinus region, tuberculum sellae, lamina cribrosa, foramen magnum, and torcular zones. Less commonly, they can occur in other locations including the optic nerve sheath, spinal cord region, intraventricular region and a variety of ectopic sites throughout the body. Clinical presentation is often dependent on the location, size, and rate of growth of the neoplasm. Focal neurologic deficits, signs and symptoms associated with increased intracranial pressure and seizures are the most common presentations.

The gross appearance of most meningiomas is that of a well-circumscribed, dural based mass which typically compresses rather than infiltrates the underlying brain parenchyma (Fig. 19-1). The gross appearance is dependent upon the histologic subtype of meningioma. A variety of gross features including cystic degeneration, prominent calcification, metaplastic bone or cartilage formation, and pigmentation may all be present. Rarely meningiomas grow in an *en plaque* fashion. Hyperostosis of the skull overlying the tumor is sometimes encountered. Radiographically, the appearance of the tumor mirrors the gross appearance of the lesion. Meningiomas are generally contrast enhancing, fairly discrete lesions. Often there is extension of the contrast enhancement along the inner

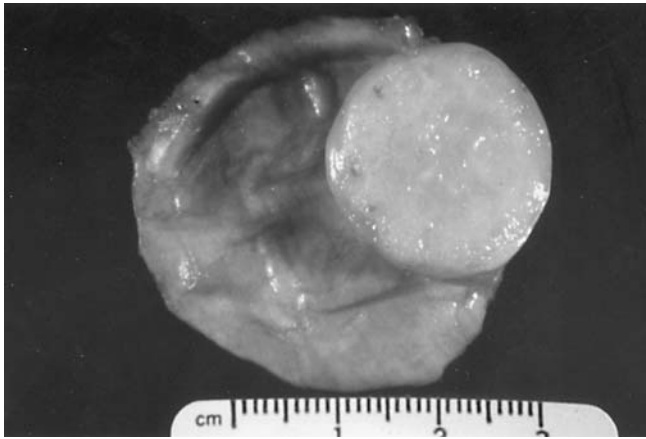


Fig. 19-1. Well circumscribed meningioma attached to the dura.

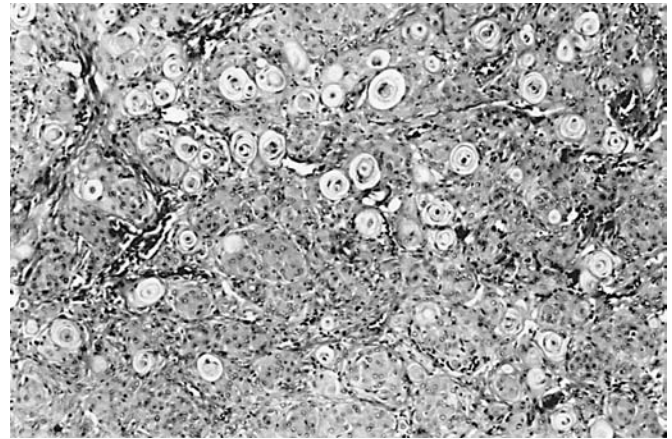


Fig. 19-2. Syncytial meningioma composed of lobules of of plump meningothelial cells.

surface of the dura at the lateral borders of the meningioma which has been referred to as a “dural tail”. Edema of the underlying parenchyma may be quite prominent, particularly in more aggressive behaving neoplasms (16,17). In the rare tumors that invade the underlying parenchyma (malignant meningiomas), the circumscription that is characteristic of most ordinary types of meningioma may be absent. Areas of necrosis and peritumoral edema are often more prominent in these cases as well.

Table 19-1 summarizes the histologic subtypes of meningioma that are currently recognized by the World Health Organization Histological Classification of Tumours of the Central Nervous System (18). Most meningiomas fall into one of the first four categories which include meningothelial or syncytial, fibrous or fibroblastic, transitional or mixed, and psammomatous types. Briefly, meningothelial meningiomas are comprised of lobules of plump meningioma cells with ill-defined cell borders (Figs. 19-

2 and 19-3). Cells are often arranged in a whorled configuration. Intracellular pseudoinclusions, which represent cytoplasmic invaginations into the nucleus, are most commonly seen in association with this type. Fibrous meningioma is characterized by a fascicular architecture and is composed of elongated cells with increased collagen and reticulin deposition (Fig. 19-4). The so-called transitional meningioma represents a combination of both the meningothelial and fibrous patterns. Exact criteria as to how much of a minor component needs to be present in order to use this designation do not exist. Psammomatous meningiomas often have a background meningotheliomatous meningioma pattern with an abundance of psammoma bodies (Fig. 19-5). In general, distinction of one of the aforementioned types of meningioma from another is not of clinical significance.

Other less commonly encountered subtypes of meningioma which similarly act in a low-grade fashion include

Table 19-1
Meningioma Classification-Variants

Meningothelial (syncytial)
Fibrous (fibroblastic)
Transitional (mixed)
Psammomatous
Angiomatous (angioblastic)
Microcystic (humid)
Secretory (pseudopsammomatous)
Chordoid
Lymphoplasmacyte-rich
Metaplastic
*Rhabdoid
*Papillary
*Clear cell
*Atypical meningioma
*Malignant/anaplastic meningioma

*Histologic variants associated with more aggressive behavior.

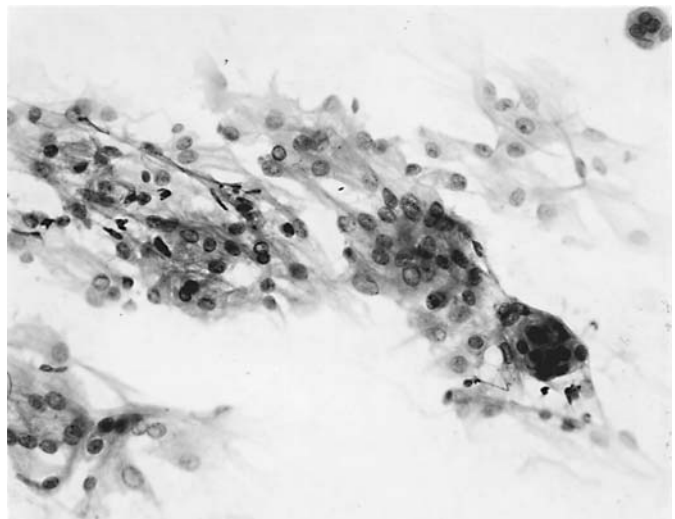


Fig. 19-3. Cytologic preparation of syncytial meningioma.

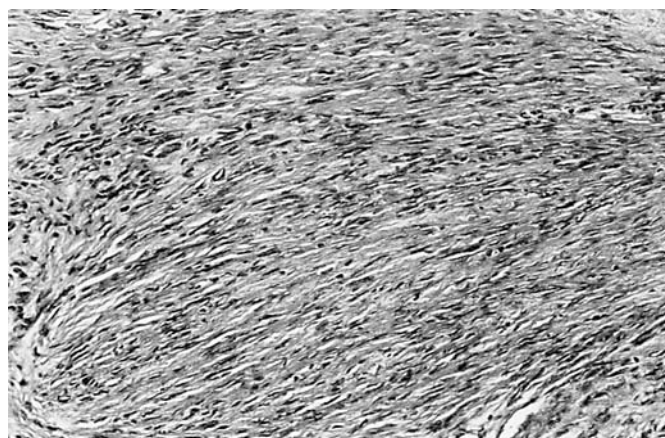


Fig. 19-4. Spindled arrangement of cells in a fibrous meningioma.

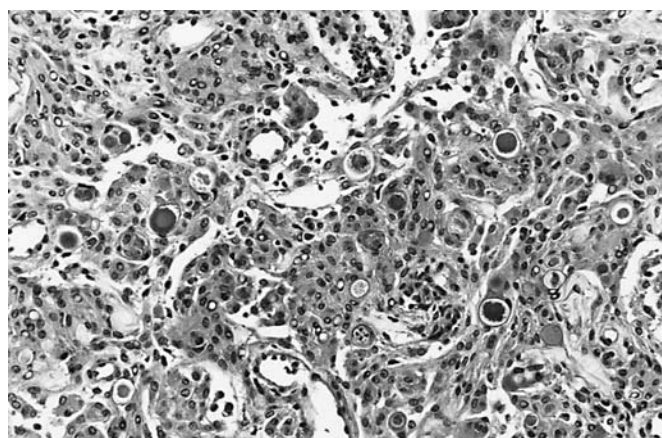


Fig. 19-6. Scattered large hyaline-like cytoplasmic inclusions in a secretory meningioma.

the so-called microcystic meningioma, secretory meningioma, lymphoplasmocyte rich meningioma, metaplastic variants of meningioma and chordoid meningioma. As its name suggests, the microcystic (humid) meningioma is characterized by cystic spaces with scattered meningeothelial cells often demonstrating elongated cell processes (19–22). Differential diagnostic considerations particular to this meningioma variant include pilocytic astrocytoma and rarely hemangioblastoma (in cases when one also has lipidized meningeothelial cells). The secretory (pseudopsammomatous) meningioma is characterized by eosinophilic, hyalinelike cytoplasmic inclusions which ultrastructurally represent microvillous-lined spaces filled with membranous debris (23–25) (Fig. 19-6). The lymphoplasmocyte-rich or lymphofollicular variant is marked by a prominent lymphoplasmocytic infiltrate, frequently accompanied by lymphoid follicles (26,27). Metaplastic variants contain a variety of mesenchymal elements which have included bone, cartilage, fat and myxoid tissue (2,28,29). The rare chordoid variant is histologically char-

acterized by cords and small clusters of epithelioid cells arranged against a mucinous background (30) (Fig. 19-7). Although previously melanotic meningioma was recognized as a distinct entity, the current thinking is that many of these tumors represent examples of so-called melanocytoma.

Angiomatous or angioblastic meningiomas deserve special mention from a historical viewpoint. In many of the earlier classification schemas for meningioma, hemangiopericytomas and hemangioblastomas were grouped together with a subset of meningiomas rich in blood vessels under the designation of angiomatous or angioblastic meningioma. In more recent years, both hemangioblastomas and hemangiopericytomas have been separated out as distinct entities because of differences in terms of cell of origin, prognosis, and associations. Whether the remaining small number of so-called angiomatous meningiomas are more aggressive behaving tumors or not is still debatable. De le Monte's study on meningioma recurrence

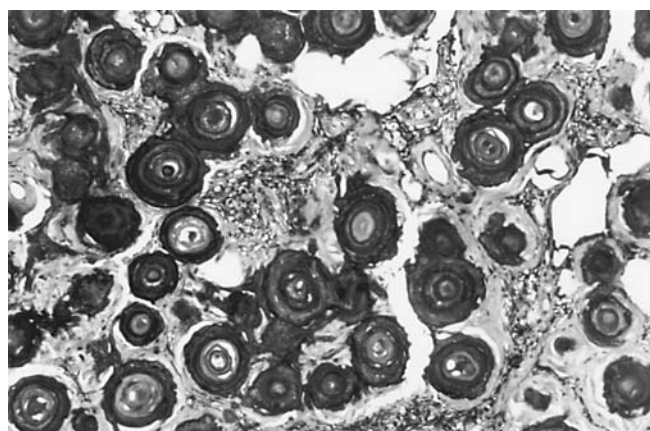


Fig. 19-5. Numerous psammoma bodies with interspersed nests of meningeothelial cells in a psammomatous meningioma.

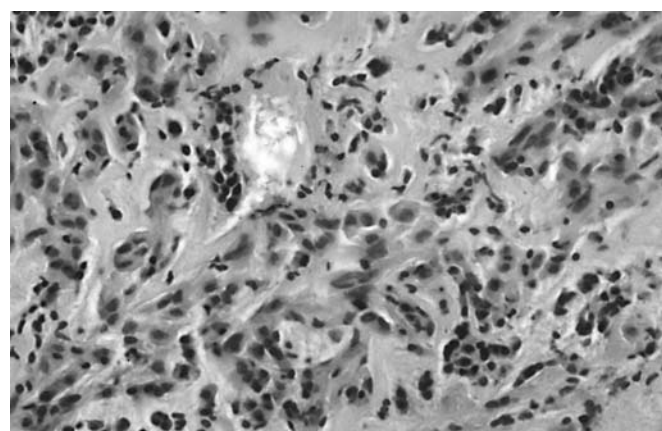


Fig. 19-7. Chordoid meningioma with cords and clusters of cells arranged against a mucinous background.

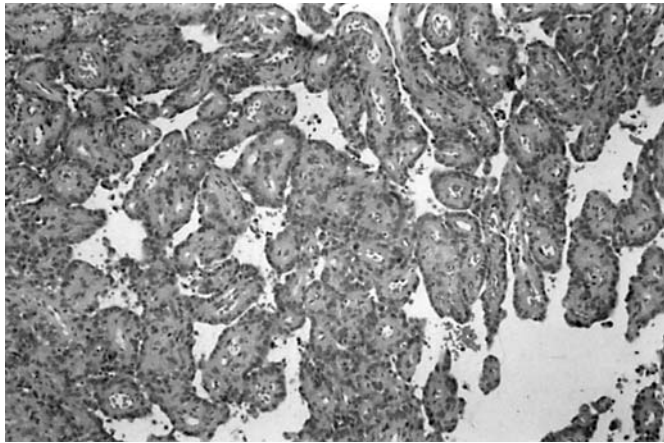


Fig. 19-8. Meningeothelial cells arranged around fibrovascular cores in a papillary meningioma.

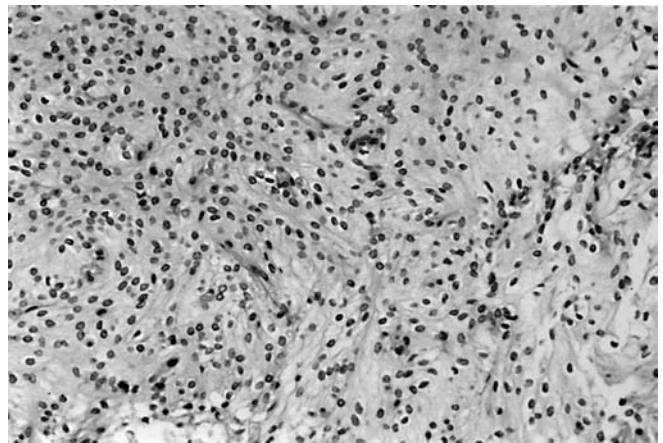


Fig. 19-9. Vague lobules of meningeothelial cells with cleared cytoplasm in a clear cell meningioma.

following subtotal resection noted that hypervascularity and hemosiderin deposition are two histologic features which were more likely to be present in meningiomas that recurred as opposed to those tumors which did not recur (31).

Three particular histologic variants of meningioma which are thought by many to be associated with more aggressive behavior and include the papillary meningioma, the clear cell meningioma, and rhabdoid meningioma. In 1975, Ludwin et al reported 17 cases of so-called papillary meningioma (32). These tumors were characterized by distinctive pseudorosette arrangement of meningeothelial cells around blood vessels (Fig. 19-8). Eight of the 17 cases arose in childhood and 10 of the patients (59%) had local recurrence of the tumor anywhere from 4 to 16 months after surgery. Distant metastasis occurred in 5 of the 17 patients. Others have reported similarly aggressive behavior for this subset of meningioma (33). Fortunately, most of these cases demonstrate a clearly recognizable meningioma component in association with the papillary areas, which allow for their recognition.

More recently, the clear cell meningioma has been reported to be a potentially more aggressive variant. In 1995, Zorludemir et al reported 14 examples of so-called clear cell meningioma consisting of sheet-like or lobulated proliferations of polygonal cells with clear cytoplasm (34) (Fig. 19-9). Nuclei are generally uniform and round with delicate chromatin and inconspicuous nucleoli. Tumor cells contain abundant cytoplasmic glycogen as evidenced by strong PAS positivity. Mitotic figures were only rarely identified; foci of necrosis were seen in three of the tumors. Eight patients developed tumor recurrence. Local discontinuous spread was noted in two of those eight cases. Three patients died of disease.

Most recently, Kepes et al. (35) reported four cases of

meningioma which contained areas in which the cells assumed a rhabdoid morphology. These cells are round to oval with prominent eosinophilic cytoplasm and eccentric nuclei (Fig. 19-10). Three of the four patients developed a tumor recurrence within 20 months of the initial surgery; the fourth patient died in the immediate postoperative period. Others have confirmed the aggressive nature of this subgroup of meningiomas (36).

In recent years, considerable literature has been afforded meningiomas, attempting to predict tumor behavior based on the presence of certain histopathologic features. A number of studies have shown that tumors which are characterized by prominent nuclear pleomorphism, necrosis, increased mitotic activity, disorganized architectural pattern, macronucleoli, small cell formation, brain invasion and distant metastasis are more frequently aggressive behaving neoplasms (16,37-46). Unfortunately, not all aggressive behaving meningiomas display worrisome histologic features. In 1986, de la Monte et al. (31) outlined a useful approach to these atypical menin-

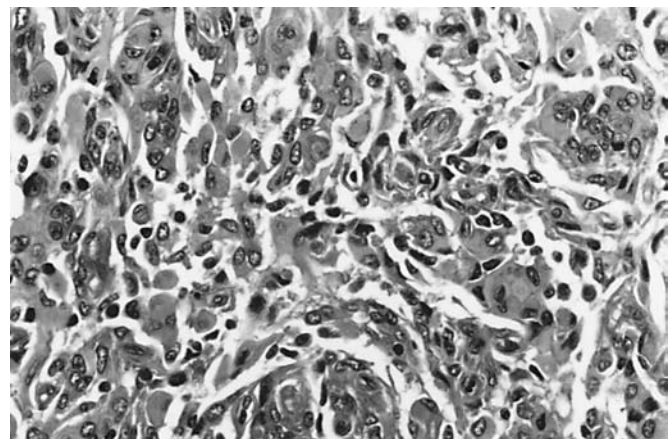


Fig. 19-10. Meningioma with cells demonstrating rhabdoid features.

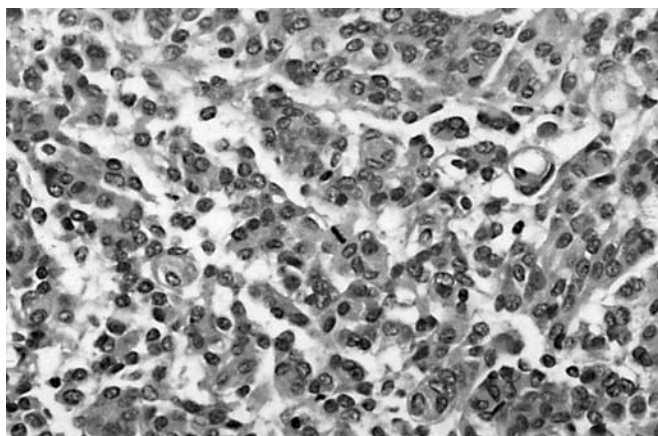


Fig. 19-11. Loss of architectural pattern and mitosis figure in a meningioma with aggressive features or atypical meningioma.

giomas. In this study, a number of histopathologic features were examined, specifically looking for those which correlated with tumor recurrence. The histologic features which were found to be statistically significant in terms of association with tumor recurrence included hyper-vascularity, hemosiderin deposition, loss of architectural pattern or sheeting, prominent nucleoli, mitotic figures, single cell and small group necrosis, nuclear pleomorphism, and overall atypical or malignant tumor grade (Figs. 19-11 and 19-12). Many of these same histologic features were also observed in the nonrecurrent tumor group. In general, meningiomas with two or more of the above-mentioned histologic features can be designated as atypical meningiomas or meningiomas with aggressive features. Others have established slightly different thresholds. Maier et al. (43) defined atypical meningiomas as tumors exhibiting hypercellularity and 5 or more mitotic figures per 10 high-power fields. Perry et al. (47,48) lowered the mitotic threshold to four or more per ten high power fields; in the absence of sufficient mitotic activity,

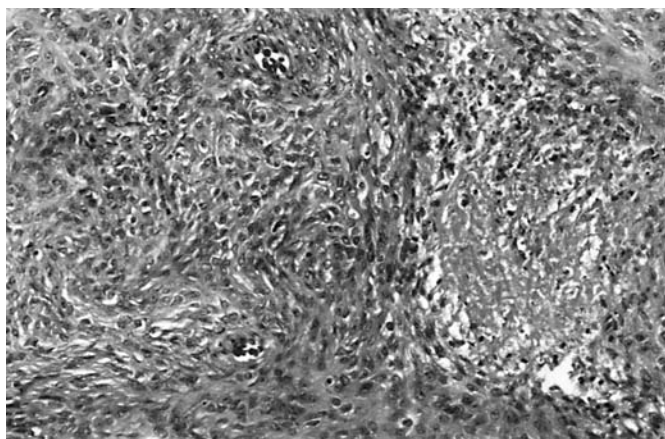


Fig. 19-12. Necrosis in an aggressive/atypical meningioma.

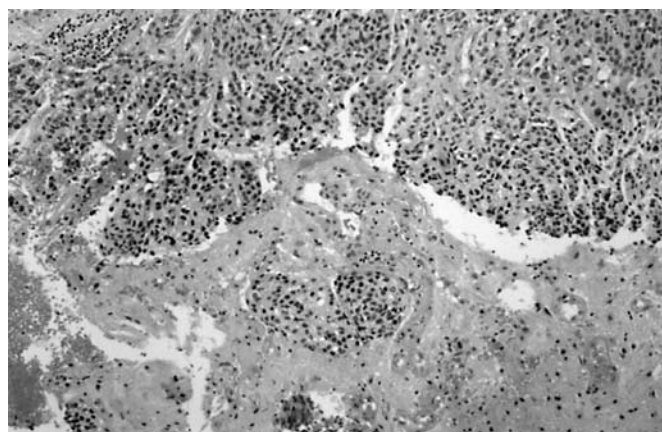


Fig. 19-13. Parenchymal invasion in a malignant meningioma.

brain invasion or the presence of three of four histologic parameters including sheeting architecture, hypercellularity, small cell formation, and prominent nucleoli were sufficient for the designation. As always, clinical history is important in the evaluation of any lesion, particularly with regard to the presence of necrosis. A tumor that has been recently operated on, embolized, or irradiated may demonstrate necrosis that should not necessarily be interpreted as intrinsic to the neoplasm (49).

So-called malignant or anaplastic meningiomas are relatively uncommon lesions and represent the high grade end of the meningioma spectrum. There is still some debate as to what exactly constitutes a malignant meningioma. Most agree that brain invasion or metastasis are features of malignancy (Fig. 19-13). The precise histologic definition of what constitutes brain invasion however is still debated, e.g., whether or not extension of tumor into Virchow-Robin spaces constitutes invasion. Most malignant meningiomas in one series (50) demonstrated most of the histologic features which had been previously associated with aggressive behavior: nuclear pleomorphism in 20 of 23 tumors, disorganized architecture in 22 of 22 tumors, necrosis in 20 of 23 tumors, prominent nucleoli in 17 of 23 tumors, and mitotic figures in 22 of 23 tumors ranging from 1 to 18 mitotic figures per 10 high-power fields (mean 6.1). Six of the patients developed metastasis which were most commonly to bone, lung, and skin. Of the 20 patients in whom follow-up information was available in that series, six died of tumor (mean follow-up: 27 months), nine were alive with residual tumor (mean: 35 months) and five were alive with no evidence of tumor (median: 12 months). Recently, Perry et al. (48) have stated that brain invasion alone is not enough to define malignant meningioma. They defined anaplastic meningioma as a tumor marked by either excessive mitotic activity (≥ 20 mitosis figures/10 high-power fields) or at least focal loss of meningothelial differentiation, resulting in a sarcoma,

carcinoma or melanoma-like appearance (48). Use of the term meningosarcoma in reference to malignant meningioma should be abandoned, because of the incorrect inference that these tumors are somehow sarcomatous in nature.

Because of the problem associated with trying to predict tumor behavior based on histopathology, a number of individuals have attempted to utilize a variety of cell proliferation markers in order to predict tumor behavior. A number of studies employing a variety of modalities have generally indicated a tendency for higher grade tumors to demonstrate higher levels of cell proliferation (51–59). Most of these studies demonstrate an overlap in terms of the degree of cell proliferation between benign, aggressive, and malignant tumors. Differences in methodology between laboratories, differences in interpretation of staining, and variability within a given tumor related to tumor heterogeneity are all factors which make interpretation of a labeling index or value in a particular case potentially misleading. As a prospective independent predictor of aggressive behavior, these studies generally fall short. However, in conjunction with other histologic features, such data may serve as additional evidence for potentially aggressive or malignant behavior.

In general, electron microscopic examination of meningiomas adds little to the routine evaluation. In selected cases, it may be useful in distinguishing meningiomas from other dural based lesions of fibroblastic or smooth muscle origin. Characteristic ultrastructural features include the presence of interdigitating processes, cytoplasmic intermediate filaments, and well-formed cell junctions.

Most cases of meningioma do not require immunohistochemical staining for confirmation of diagnosis. Similar to electron microscopy, immunohistochemical staining may be useful in rare cases in distinguishing certain tumor types from meningioma. Meningiomas characteristically demonstrate diffuse positive immunoreactivity for vimentin. Most meningiomas show focal positive staining with epithelial membrane antigen (EMA). A minority of meningiomas stain positively for S-100 protein in a focal pattern and may demonstrate focal positive staining with a variety of cytokeratin markers.

The differential diagnosis of meningioma is widespread, given the marked variability with regard to histology one can encounter in this group of neoplasms. Distinction of meningioma from hemangiopericytoma and meningeal sarcomas will be discussed in chapter 20. Many of the remaining differential diagnostic considerations can be fairly easily resolved utilizing immunohistochemistry. Distinction of meningioma from glioma is generally not difficult from a light microscopic standpoint. Most astrocytomas will stain positively for glial fibrillary acidic protein (GFAP), as compared to meningiomas which are

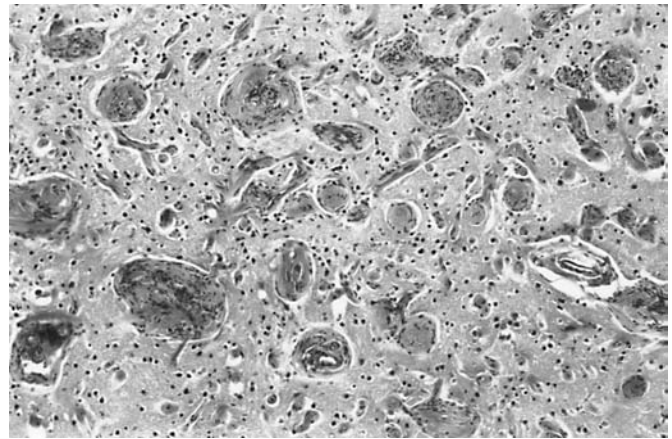


Fig. 19-14. Proliferation of meningeothelial cells around parenchymal vessels in meningioangiomatosis.

GFAP negative. Occasionally, an infiltrating squamous cell carcinoma may involve the leptomeningeal region and may ostensibly mimic a meningioma. In general, the histologic appearance of the carcinoma, in particular, the anaplastic appearance, as compared with the ordinary meningioma, and often diffuse positive cytokeratin immunostaining should allow for easy distinction. Meningiomas may occasionally stain very focally for cytokeratin markers. Distinction of the fibroblastic variant of meningioma from schwannoma may be a diagnostic issue, particularly in small biopsies from the cerebellopontine angle and spinal cord regions. Lesions that may be obviously schwannoma or meningioma, based on radiographic or intraoperative appearances, may be more challenging, particularly at the time of intraoperative consultation. In general, schwannomas are characterized by a mixture of loose, Antoni B and more compact, Antoni A patterns, a feature that is generally not observed in meningiomas. Verocay bodies, although not always noted in schwannomas, are a particularly useful histologic feature, when present, in distinguishing the two lesions. In general, the nuclei in the fibrous meningioma tend to be more elongated with rounder ends, as opposed to the longer, club shaped nuclei of schwannoma. From an immunohistochemical standpoint, schwannomas stain diffusely and strongly for S-100 protein; whereas in meningiomas, S-100 immunoreactivity, if present, is focal and somewhat limited. The membranous pattern of staining with epithelial membrane antigen which marks meningiomas is generally absent in schwannomas.

A somewhat unusual lesion that can closely mimic a meningioma is an entity referred to as meningioangiomatosis. Meningioangiomatosis is a rare condition characterized histologically by a proliferation of blood vessels and perivascular cuffs of meningeothelial cells (60–61) (Fig. 19-14). The adjacent brain parenchyma often shows

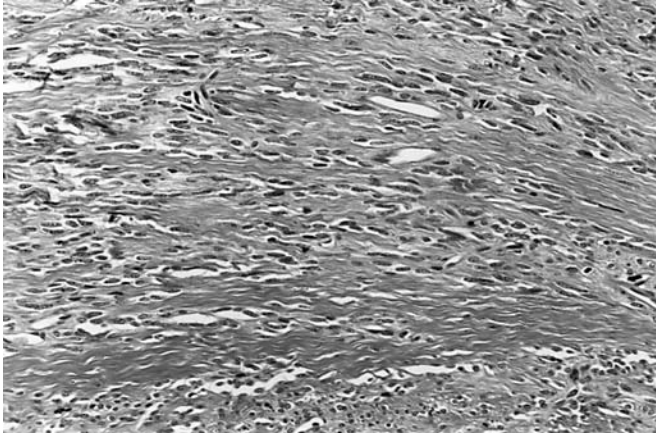


Fig. 19-15. Generally spindled cells set against a collagen background in a solitary fibrous tumor of the meninges.

some degree of gliosis and the lesion is often accompanied by psammoma bodies or calcifications. The association of meningioangiomatosis with von Recklinghausen's disease has been well documented. Distinction of meningioangiomatosis from an ordinary type meningioma is predicated on recognition of the predominantly parenchymal based blood vessel and meningotheelial cell proliferation and the lack of discrete mass.

Rare cases of other spindled cell proliferations which may mimic meningiomas have been described. Many of these lesions have probably been designated as meningioma in the past and have been only recently recognized as distinct entities. Although the numbers of these cases reported in the literature are somewhat limited, most of these lesions have behaved in a generally benign fashion. These tumors can arise from a whole variety of mesenchymal cell types including fibroblasts, myofibroblasts, and smooth muscle cells. This list of lesions includes entities which have been referred to as fibromas and fibro-osseous lesions (62,63), solitary fibrous tumor (64,65) (Fig. 19-15), leiomyoma (66,67), and myofibroblastoma (68). Table 19-2 summarizes the differential immunohistochemical features of these lesions.

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Table 19-2
Differential Diagnosis by Immunohistochemistry of Spindled, Meningeal-Based Tumors

	<i>Meningioma</i>	<i>Schwannoma</i>	<i>Myofibroblastoma</i>	<i>Solitary Fibrous Tumor</i>	<i>Leiomyoma</i>
Vimentin	+	+	+	+	+
EMA(membranous)	+	-	-	-	-
S-100 protein	±	+	-	-	-
CD34	±(weak)	-	-	+(strong)	-
GFAP	-	-	-	-	-
Cytokeratins	±	-	-	-	-
Desmin	-	-	±	-	+
Smooth muscle actin	-	-	±	-	+

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20 Meningeal Sarcoma

HISTORICALLY, THE HEMANGIOPERICYTOMA has been grouped together with a subset of meningiomas and hemangioblastoma under the designation of angioblastic meningioma. It is the general consensus now that the hemangiopericytoma is a distinct lesion from meningioma and generally more aggressive in behavior. Most frequently, the tumor is seen proximal to the leptomeninges, but may on rare occasion arise in the brain parenchyma and commonly in the spinal cord region. The tumor is most frequently encountered in adults; however, rare cases have presented in the second and third decades of life. In contrast to meningiomas, there is no definite gender predilection for hemangiopericytomas; the single largest series to date, showed only a slight male predominance (*1*). The hemangiopericytoma most frequently presents as a fairly discrete, nonencapsulated mass. The tumor generally does not elicit the same degree of osteoblastic reaction and hyperostosis that is frequently encountered in meningiomas. The gross and radiographic appearance of the lesion may be altered by areas of hemorrhage, cystic degeneration, or necrosis.

Histologically, hemangiopericytomas are often cellular lesions accompanied by a rich vascular background. Vessels are classically described as having a staghorn configuration (Fig. 20-1). Cells with variable degrees of nuclear pleomorphism are haphazardly arranged (Fig. 20-2). Nucleoli are generally inconspicuous and cytoplasm scant. Cell borders are often not clearly defined. Psammomatous calcifications or tight whorls, which may be encountered in meningiomas, are not seen in hemangiopericytomas. Mitotic activity may be quite variable and range from few to greater than ten mitotic figures per 10 high-power fields (*1*). Foci of necrosis and hemorrhage are observed in a significant percentage of hemangiopericytomas. Similar to meningiomas, hemangiopericytomas are reticulin rich lesions.

Although hemangiopericytomas are thought to be peri-

cytic in origin, ultrastructural examination of these tumors demonstrates a range of tumor cell differentiation including pericytic, myoid, and fibroblastic (*2–4*). There are, however, ultrastructural features which allow distinction of this tumor from meningiomas, including the lack of well-formed desmosomes or interdigitating cell membranes. There have been a number of studies that have examined the immunohistochemical profile of hemangiopericytomas (*3,5–10*). Similar to meningioma, hemangiopericytoma will stain positively for vimentin. Meningiomas generally stain negatively for epithelial membrane antigen (EMA), S-100 protein, and glial fibrillary acidic protein (GFAP). Positive staining with CD34 and factor XIIIa has been reported. MIB-1 labeling indices in one study ranged between 0.2% and 9.9% and appeared to be unrelated to tumor grade (*11*).

Based on a series of 94 cases, Mena et al stratified central nervous system hemangiopericytomas into differentiated and anaplastic categories (*1*). Anaplastic hemangiopericytomas were characterized by necrosis and/or

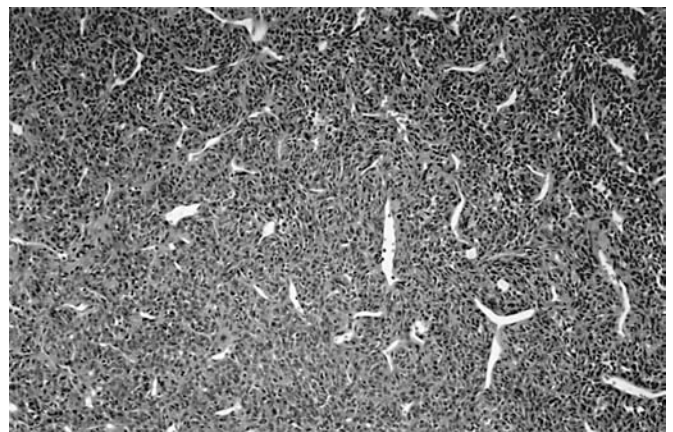


Fig. 20-1. Hemanigopericytoma with prominent staghorn vascular pattern.

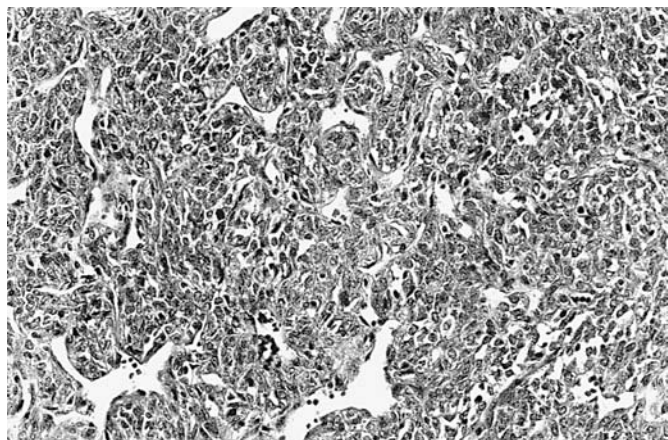


Fig. 20-2. Moderate nuclear pleomorphism and disorganized arrangement of cells in a hemangiopericytoma.

greater than 5 mitotic figures per 10 high-power fields and at least two additional histologic features including hemorrhage, moderate to high nuclear atypia and moderate to high cellularity. Median survival in the differentiated tumor group was 144 months versus 62 months for the anaplastic group. In contrast to meningiomas, a significant percentage of hemangiopericytomas, 60.6% in Mena's series, experienced one or more tumor recurrences and metastasis developed in 23.4% (1). The most common sites of metastasis included bone, liver, lung, central nervous system, and abdominal cavity in descending order of frequency. It has been suggested that postoperative radiation therapy may increase the time to recurrence and extend survival (12).

The major differential diagnostic consideration of hemangiopericytoma is meningioma, particularly atypical meningioma. Table 20-1 outlines a number of clinicopathologic features that may be useful in distinguishing the

two lesions, many of which have already been discussed. The other major differential diagnostic consideration is distinguishing hemangiopericytoma from other sarcomas with hemangiopericytomatous pattern. The key to distinguishing hemangiopericytomas from these other forms of sarcoma often rests in recognizing defining features which allows one to more definitively characterize the lesion as another form of sarcoma e.g. finding areas of cartilage differentiation in a chondrosarcoma.

Involvement of the central nervous system by primary sarcoma is relatively uncommon. Well-known is the association of cranial sarcomas with prior radiation therapy (13). Criteria for diagnosis and classification should be the same as for sarcomas arising elsewhere in the body. Although many of these sarcomas appear to be skull-based, occasional examples of primarily parenchymal lesions have also been described. Care should be taken not to misdiagnose a sarcoma as primary in the central nervous system, when it is metastatic. The sarcoma types that have been described are quite myriad and have included examples of chondrosarcoma (14,15), mesenchymal chondrosarcoma (16,17) (Fig. 20-3), rhabdomyosarcoma (18,19), fibrosarcoma (20,21), malignant fibrous histiocytoma (22,23) (Fig. 20-4), leiomyosarcoma (24,25) (Fig. 20-5), osteosarcoma (26,27) and angiosarcoma (28,29) (Fig. 20-6). Use of the term meningiosarcoma in reference to meningeal based sarcomas should be abandoned in favor of specific sarcoma classification. Unfortunately, the term meningiosarcoma has also been used in reference to malignant meningiomas. Occasionally, sarcomas may not demonstrate specific histologic features which allow their classification, in which case designation of the lesion as a sarcoma without differentiation or not otherwise specified may be appropriate.

Occasionally, one may also encounter benign

Table 20-1
Hemangiopericytoma Versus Meningioma

	<i>Hemangiopericytoma</i>	<i>Meningioma</i>
Age	Adult >> children	Adult >> children
Gender	Females = males	Females > males
Hyperostosis	—	±
Calcification/psammoma bodies	—	±
Cell of origin	Pericyte	Arachnoidal cap cell
Staghorn vascular pattern	+	—
Nuclear atypia	±	±
Mitoses	Generally +	+
Intranuclear pseudoinclusions	—	+
Necrosis	±	±
Reticulin rich	+	+
Vimentin	+	+
EMA	—	+
CD34	+	± (weak)
Prognosis	Generally more aggressive	Generally less aggressive

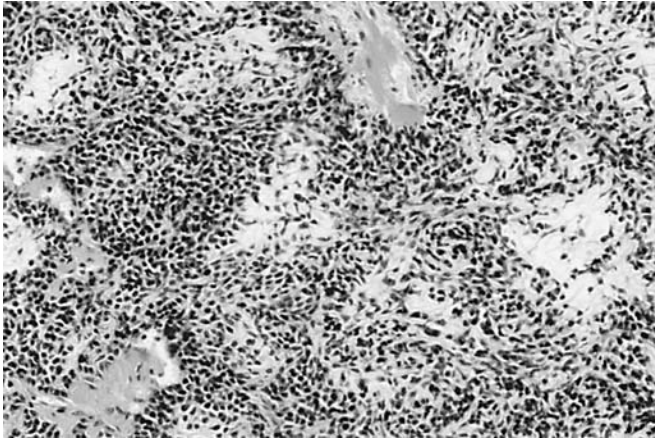


Fig. 20-3. Mesenchymal chondrosarcoma composed of undifferentiated cells and foci of cartilaginous differentiation.

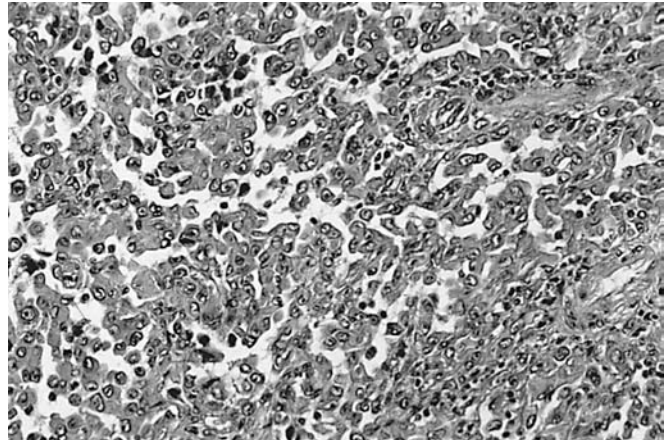


Fig. 20-6. Vascular channels lined by tumor cells in an angiosarcoma.

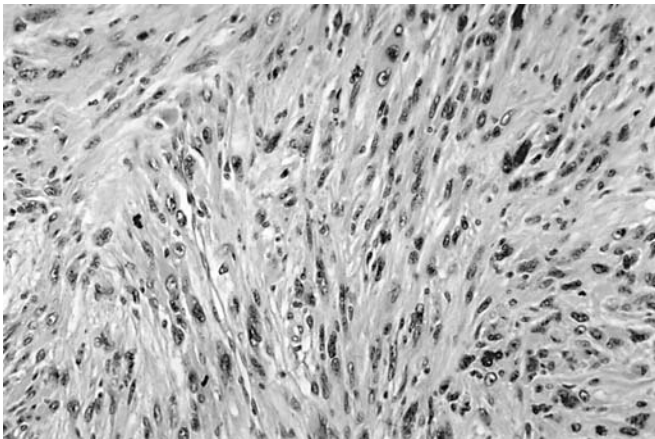


Fig. 20-4. Storiform, pleomorphic malignant fibrous histiocytoma of the meninges.

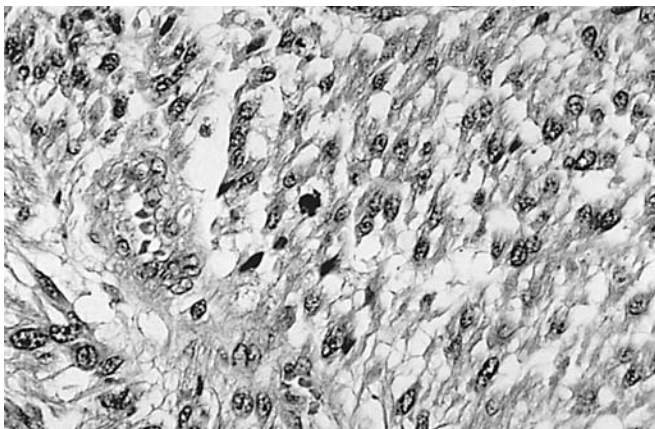


Fig. 20-5. Leiomyosarcoma characterized by smooth muscle actin and desmin positive spindled cells.

mesenchymal lesions in the central nervous system. Mention of fibromas, myofibroblastomas and solitary fibrous tumors was made in the previous chapter in the discussion of differential diagnosis with meningiomas. Occasionally, low grade vascular lesions (30) and hemangiomas have been described. Lipomas, chondromas, and osteochondromas have also been reported to rarely involve the central nervous system (31–32).

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21 Hemangioblastoma

THE (CAPILLARY) HEMANGIOBLASTOMA has the dubious distinction of comprising the sole entity listed under “Tumors of Uncertain Histogenesis” in the 1993 W.H.O. classification of central nervous system tumors (1). In addition, it does not possess an obvious counterpart outside the nervous system, and therefore might prove particularly perplexing when first encountered. Although an uncommon tumor, it represents a major differential diagnostic consideration in young to middle-aged adults with either intracerebellar or intraspinal masses. While hemangioblastomas are among the histopathologic hallmarks of von Hippel-Lindau disease (VHL, discussed below), most are encountered as sporadic tumors, which often then prompt evaluation for VHL.

Hemangioblastomas generally occur in patients 30–50 years of age. There is a tendency for earlier presentation in tumors associated with VHL. Hemangioblastomas are most frequently encountered within the cerebellum, where they typically present as a cystic mass with a contrast-enhancing mural nodule (similar to cerebellar juvenile pilocytic astrocytomas). Less common locations include the cerebrum, brainstem, and spinal cord, with the latter predominating (2). Spinal cord hemangioblastomas are classically associated with a syrinx extending rostrally from the tumor (a characteristic shared with ependymal, but usually not astrocytic, tumors of the spinal cord). In addition, prominent leptomeningeal feeding vessels may simulate a vascular malformation. While hemangioblastomas have been considered by some to be vanishingly rare in the supratentorial compartment, this is largely a result of their previous classification as a subtype of angioblastic meningioma. Such tumors are now considered to be meningeal hemangioblastomas, and may be encountered anywhere along the neuraxis, including the optic nerve (3).

Intraoperatively, these tumors appear as discrete, highly vascular nodules. Although not always apparent,

the tumors usually abut the leptomeninges. On section, which surgeons generally try to avoid, hemangioblastomas are spongy and tend to exude blood. Depending on their content of lipid-laden stromal cells, they may appear somewhat to strikingly yellow. Microscopically, hemangioblastomas are composed of varying proportions of primitive, thin-walled blood vessels and lipid-laden stromal cells. It is the resistance of these latter cells to ultrastructural and immunohistochemical characterization that is responsible for this tumor’s condemnation to nosologic purgatory. They seem to be strongly to weakly negative with antibodies to endothelial, glial, and neuroectodermal antibodies and show no defining features by electron microscopy. Interestingly, studies of vasculogenesis in the chick embryo (during the early 1930s) demonstrated a stage characterized by lipid-laden cells appearing remarkably similar to those seen in hemangioblastomas. However, deforestation continues as the attempt to classify these elusive cells presses on.

Two histopathologic variants are recognized based on the relative proportion of stromal cells and capillaries (1). In the reticular variant (Fig. 21-1), stromal cells are uniformly distributed within an intricate network of capillaries, while in the cellular variant (Fig. 21-2), the stromal cells are clustered and delimited by the capillaries. Like many meningioma subtypes, these variants have no prognostic or syndromic importance. However, awareness of this histopathologic variation is important in preventing misdiagnoses. Specifically, the cellular variant may be confused with renal cell carcinoma (another cardinal feature of von Hippel-Lindau disease) (Table 21-1). Useful differentiating histopathologic characteristics of hemangioblastomas are the similarity in nuclear morphology between the capillary endothelial cells and stromal cells, and a more xanthomatous than clear cytoplasm (the latter being more characteristic of glycogen-rich metastatic renal cell carcinomas). Histochemical staining for reti-

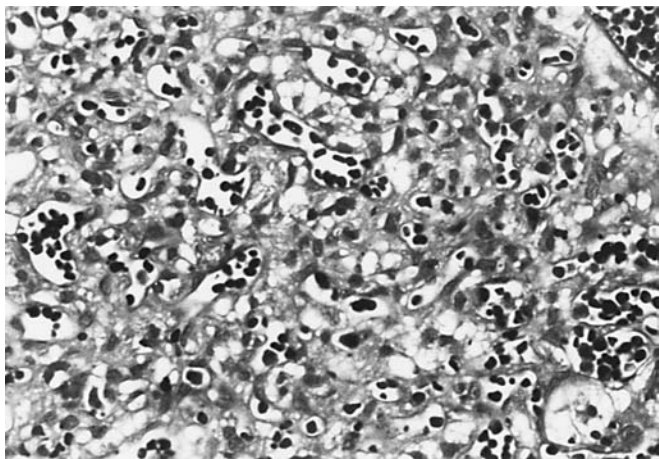


Fig. 21-1. Lipid laden stromal cells distributed within an intricate network of capillaries in the reticular variant of hemangioblastoma.

culin will highlight the abundant thin-walled blood vessels in hemangioblastomas (Fig. 21-3), while showing a weaker nested pattern in renal cell carcinoma (4). Immunohistochemical staining with antibodies to cytokeratins and epithelial membrane antigen will be reactive with renal cell carcinomas and non-reactive with hemangioblastomas (5).

During intraoperative consultation, the other main differential diagnostic consideration is astrocytoma. Confusion may arise as a result of sampling error (surrounding gliotic tissue or syrinx wall) or as a result of compression of the delicate capillary component during the preparation of frozen sections. Cytologic (touch) preparations may be a valuable diagnostic aid, allowing appreciation of the lipid-laden stromal cells (6). This differential diagnostic dilemma is virtually never a problem on permanent sections, as these two tumors appear so distinct as to be sometimes painfully embarrassing.

Two other interesting histopathologic features occa-

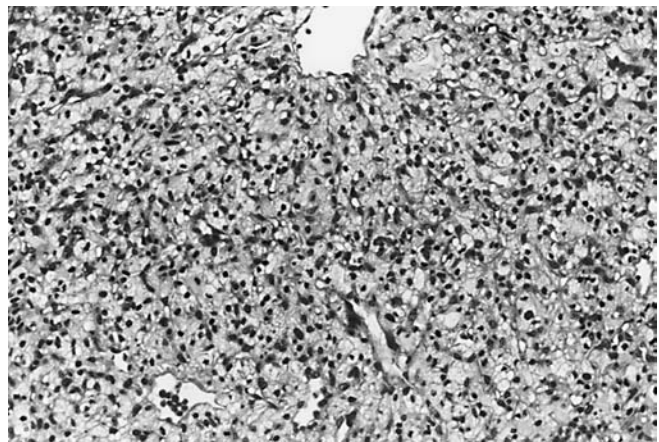


Fig. 21-2. Nests of xanthomatous stromal cells dominate the cellular variant of hemangioblastoma.

Table 21-1
Hemangioblastoma Versus Renal Cell Carcinoma

	<i>Hemangioblastoma</i>	<i>Renal Cell Carcinoma</i>
Intracellular lipid	+	–
Intracellular glycogen	–	+
Reticulin	Individual cells	Cell nests
Cytokeratin	–	+
EMA	–	+
Von Hippel-Lindau	+/–	+/–

sionally encountered in hemangioblastomas are significant numbers of mast cells (7) and extramedullary erythropoiesis (8). The latter presumably results from erythropoietin production by the tumor, which may also cause polycythemia, seen in approximately 10% of patients at presentation.

Approximately 25% of patients diagnosed with CNS hemangioblastoma will have von Hippel-Lindau disease (9). An earlier age of onset and/or multifocally favors VHL, which may be defined syndromically by a minimum of CNS hemangioblastoma or retinal angioma with at least one other typical VHL lesion or an affected first-degree relative. Interestingly, the mean age of onset varies for the various syndromic manifestations (10). While VHL associated hemangioblastomas tend to be seen in patients in their 30's, retinal angiomas usually develop several years earlier. Therefore, careful fundoscopic examination of hemangioblastoma patients (and their first-degree relatives) may cinch the diagnosis. Renal cell carcinomas, which are often bilateral, tend to occur somewhat later in the syndrome, although still at a much younger age than sporadic renal cell carcinomas. Renal cysts, adrenal pheochromocytomas, and pancreatic and

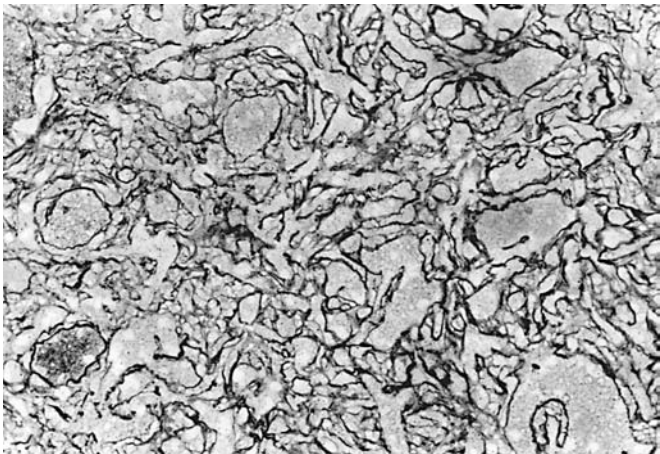


Fig. 21-3. Histochemical staining for reticulin demonstrates envelopment of individual stromal cells by reticulin and highlights thin walled vascular spaces.

epididymal cysts also occur in many patients with VHL, although the prevalence of these manifestations varies quite widely from family to family.

The VHL gene is a tumor suppressor gene found on the short arm of chromosome 3. The gene product is a protein which has been observed to inhibit the binding of transcriptional elongation factors. When the gene is mutated, transcriptional regulation is impaired. Germ line mutations have been identified in 85 of 114 VHL families (75%). It also appears that the types of mutations responsible for VHL with pheochromocytoma differ from those responsible for VHL without pheochromocytoma.

Amongst patients with VHL, cerebellar hemangioblastoma is the most common presenting manifestation. The overall prevalence of tumors in patients with VHL varies from pedigree to pedigree, but approximates:

Tumor	Prevalence
Cerebellar hemangioblastoma	60%
Retinal angioma	40%
Renal cell carcinoma	25%
Spinal hemangioblastoma	15%
Pheochromocytoma	15%

In past decades, patients with VHL tended to die at around 40 years of age, most commonly as a result of cerebellar hemangioblastomas. Although this outcome has been dramatically ameliorated by modern microsurgical techniques, the development of multiple CNS tumors is still a major problem, as is the development of metastatic renal

cell carcinoma, which is currently the proximate cause of death in up to 50% of VHL patients.

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22 Central Nervous System Primitive Neuroectodermal Tumors

IN 1910, JAMES HOMER WRIGHT (of Homer Wright rosette fame) first separated the medulloblastoma from other CNS tumors. His concept was further refined by Percival Bailey, who defined a group of 29 tumors arising in the cerebellar vermis, primarily in children. Following the lead of the nineteenth century German pathology school, where tumors were named based on the concept of a cell of origin, Bailey named these tumors medulloblastomas. The cell of origin model then continued to be used in CNS tumor nomenclature, leading to the definition of a variety of “embryonal” tumors of the nervous system. This nomenclatural system is predicated on the assertion by the late Dr. Lucien Rubenstein that the central nervous system contains several unique types of neuroepithelial precursor cells in different locations which may undergo transformation giving rise to a variety of morphologically similar, but biologically distinct, CNS tumors (1). In 1973, Hart and Earle described a group of small round blue cell tumors of the central nervous system in children and introduced the diagnostic appellation “primitive neuroectodermal tumor” (PNET) (2). Dr. Lucy Rorke subsequently suggested that the term be broadened to include all primary CNS tumors composed of primitive neuroepithelial cells regardless of their location within the CNS. The codification of these previously disparate entities into a unique class of tumors is eloquently supported in her recent review (3)

While this conceptual/nomenclatural debate still rages (4), current therapy and prognosis appears to be determined primarily by phenotypic rather than histogenetic parameters. However, this may in part be due to the rarity of non-medulloblastoma embryonal tumors of the central nervous system, precluding adequate biologic distinctions.

Medulloblastomas (PNET-MBs) comprise 15% to 25% of brain tumors in children and account for one-third

of pediatric posterior fossa neoplasms. Three-quarters of medulloblastomas occur before age 15, 50% occur during the first decade, and the peak incidence is around age 5. Along with supratentorial primitive neuroectodermal tumors, PNET-MBs represent one of the most common CNS tumors encountered in the first years of life.

The typical medulloblastoma presents an appearance all too familiar to the pediatric surgical pathologist—a monotonous sea of cells with small, relatively round, hyperchromatic nuclei and virtually unidentifiable cytoplasm (the “small, round, blue cell tumor of childhood”) (Fig. 22-1). Similar to other small round blue cell tumors, mitoses, apoptotic cells and geographic tumor necrosis are typical. The classic Homer Wright rosette, consisting of a ring of nuclei surrounding a fibrillary core composed of eosinophilic cell processes (neurites) is a fairly unusual finding in medulloblastomas, and represents primitive neuronal (neuroblastic) differentiation (Fig. 22-2). Neu-

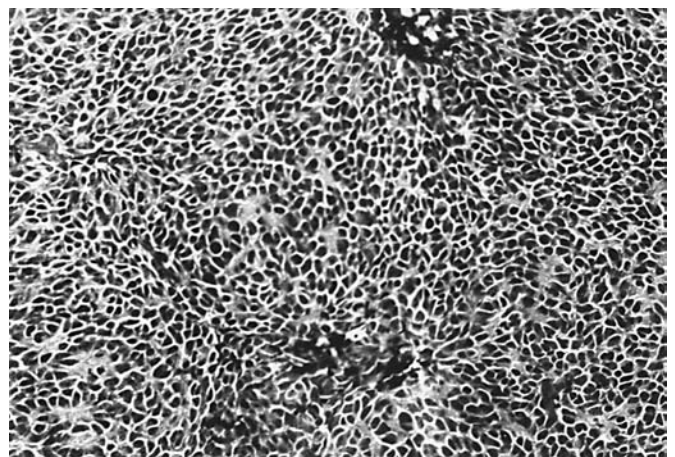


Fig. 22-1. A typical undifferentiated medulloblastoma composed of a monotonous sea of primitive tumor cells.

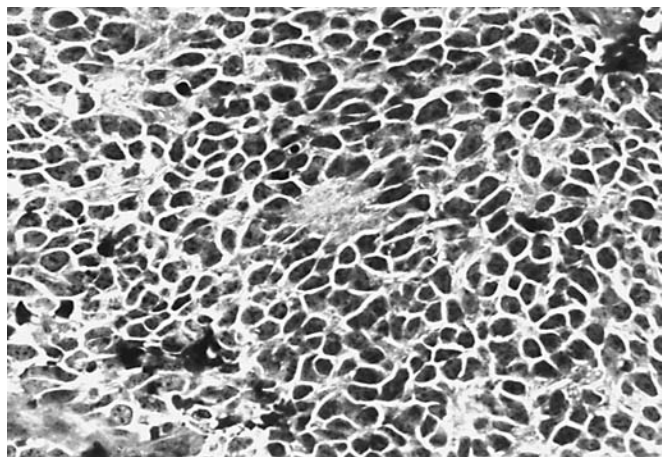


Fig. 22-2. Homer Wright rosette in a medulloblastoma.

ronal differentiation in medulloblastomas may also manifest as nodules of pale, synaptophysin-positive islands floating within an otherwise undifferentiated sea of tumor cells (Fig. 22-3). Tumors expressing this histopathologic pattern have occasionally been referred to as “cerebellar neuroblastomas,” though we prefer to sign such cerebellar tumors out as PNET-MB with neuroblastic differentiation. It is a small step from this appearance to that of the desmoplastic medulloblastoma, where cords of primitive tumor cells between the pale synaptophysin-positive islands are embedded in a dense reticulin meshwork (Fig. 22-4).

While the biologic behavior of tumors with neuroblastic differentiation does not appear to differ significantly from typical medulloblastomas, desmoplastic medulloblastomas represent the predominant type of medulloblastomas in children with the nevoid basal cell carcinoma syndrome, and show a loss of heterozygosity (LOH) on chromosome 9q corresponding to deletion of the PTCH gene locus. This LOH of chromosome 9q has

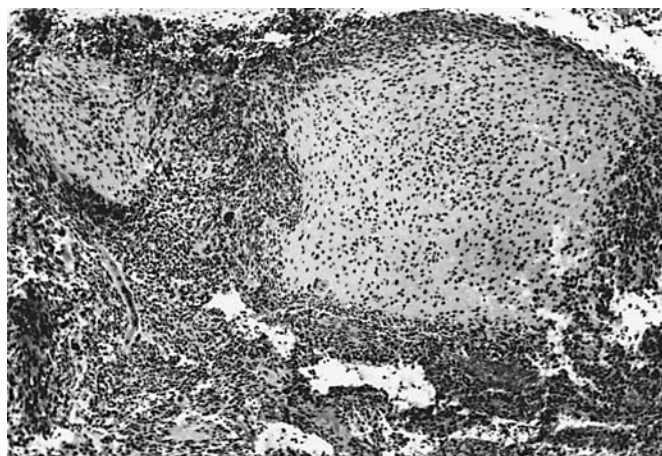


Fig. 22-3. Pale neuroblastic islands in a medulloblastoma.

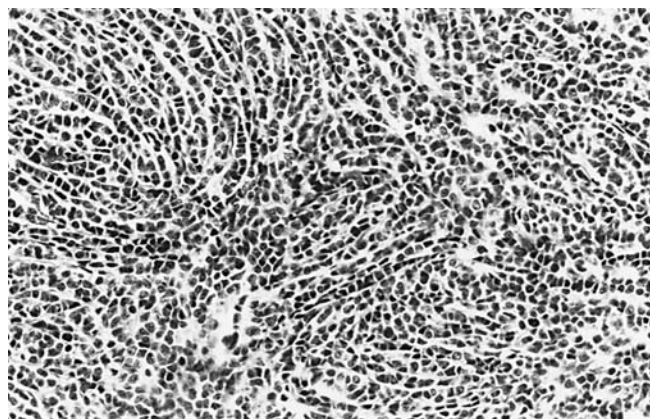


Fig. 22-4. Cords of tumor cells in a desmoplastic medulloblastoma.

also been demonstrated in desmoplastic medulloblastomas not associated with the nevoid basal cell carcinoma syndrome, and contrasts with chromosome 17p abnormalities seen in 30–40% of nondesmoplastic medulloblastomas (5,6). With very rare exceptions, the t(11;22) translocation typical of peripheral PNETs is not present within central nervous system PNETs (7).

Unlike peripheral neuroblastomas, where *n-myc* amplification and *trk-B* expression carry important prognostic significance, efforts to identify biologic factors of prognostic significance for CNS PNETs, including oncogene amplification, DNA ploidy, and mitotic index have been unsuccessful or inconsistent. Similarly, the prognostic relevance of astrocytic differentiation within PNET-MBs has been controversial. This has been true in part due to difficulties in distinguishing trapped, dysmorphic astrocytes from astrocytic differentiation within neoplastic cells. While there will always be cases in which distinguishing reactive from neoplastic astrocytes will prove either extremely difficult or impossible, glial fibrillary acidic protein immunostaining generally discloses two patterns of immunopositivity (Figs. 22-5 and 22-6): 1) scattered perivascular forms with extensive branching processes—this pattern is seen most frequently and represents astroglial reaction to the medulloblastoma, and 2) clumps or compact sheets of small poorly differentiated cells with scant GFAP immunopositivity. This uncommon pattern is felt to represent true glial differentiation within the tumor. Primitive neuroectodermal tumors containing such clumps or sheets of GFAP positive cells are associated with a three-fold increased risk of relapse compared with tumors demonstrating either no GFAP immunoreactivity or scattered GFAP immunopositive cells (8).

Distinctly less common, but no less confusing, is “oligodendroglial” and “ependymal” differentiation. The former is manifest as foci of cells with round dark nuclei and perinuclear halos. While the absence of a reliable

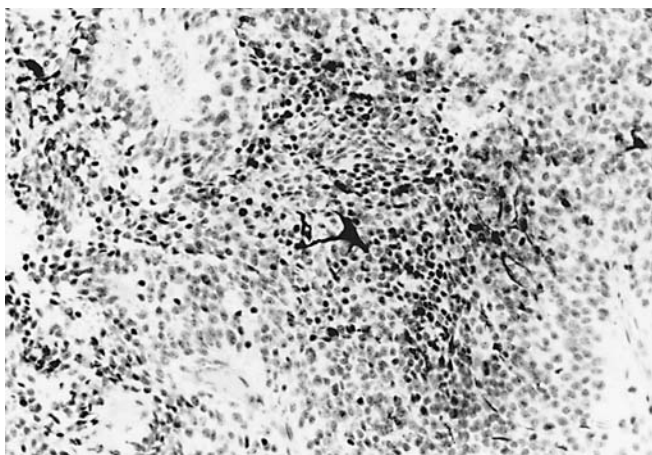


Fig. 22-5. Scattered, reactive GFAP-positive cells in a medulloblastoma.

marker for neoplastic oligodendroglia precludes definitive assessment, such cells are generally felt to represent neuroblastic rather than true oligodendroglial differentiation. Perivascular pseudorosettes identical to those seen in ependymal tumors may also rarely be encountered in PNETs. When the perivascular processes react with antibodies to GFAP, we consider such structures to represent true ependymal differentiation, and sign such tumors out as ependymoblastoma or PNET with ependymal differentiation. A word of caution is in order, however, in that we have also seen cases in which the perivascular processes reacted with synaptophysin, and not with GFAP, in which case we make a note of it, but do not further subclassify the tumor.

Two exceedingly rare PNET-MB variants recognized by the WHO are the medulloblastoma (or PNET with muscle elements) and the melanotic medulloblastoma (PNET with melanin pigment). Fewer than 40 medullo-

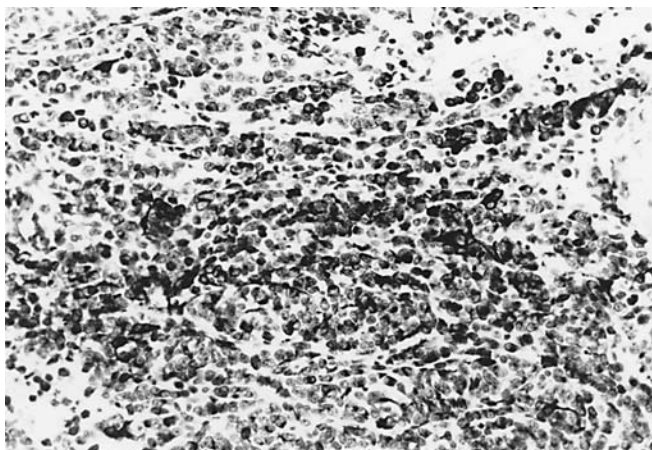


Fig. 22-6. Clusters of GFAP-positive tumor cells in a medulloblastoma with glial differentiation.

myoblastomas have been reported (9,10). In nearly all cases cross-striations have been evident on light microscopic examination. Melanotic medulloblastomas are similarly defined based on light microscopic examination. Both of these subtypes have been reported to exhibit aggressive behavior compared with typical medulloblastomas.

The treatment of CNS-PNETs centers around local and craniospinal radiation therapy, often combined with various chemotherapy regimens. The latter is particularly important in very young patients, where chemotherapy is often used in an attempt to keep the neoplasm at bay while the nervous system develops to a stage where radiation therapy will be somewhat less devastating. While the addition of chemotherapy, particularly in high-risk patients (incomplete resections, CSF seeding at diagnosis) appears to have markedly improved short-term survival of children with PNET-MBs, long-term follow-up data is just beginning to become available, and will likely determine the optimal treatment of patients with medulloblastomas/CNS-PNETs (11). Long-term follow-up of PNET-MB patients treated with craniospinal irradiation therapy during the computed tomography era (approximately 1980 to present) reveals a median survival of 58 months, with 25% survival at 10 years. Patients with non-localized disease (positive CSF cytology) do significantly worse, with a 30% 5-year survival (12). While there are exceptions, the risk of tumor recurrence for PNET-MBs in children aged 8 and younger closely adheres to Collins' Law, which defines the period of risk for tumor recurrence as equal to the patient's age at diagnosis in months plus nine months (originally derived from observations of children with congenital Wilms tumors) (13). Failure usually occurs at the primary tumor site, but supratentorial metastases, diffuse leptomeningeal seeding, and systemic metastases may each be seen in approximately 20% of patients. While systemic metastases have often been blamed on seeding through ventricular shunts, this complication also occurs in the absence of CSF shunting. In fact, a recent review of the literature indicates that of 160 cases of systemic PNET-MB metastases, only 11(7%) could have occurred through or been facilitated by ventriculosystemic shunts (14). The most common locations for extraneural PNET-MB metastases are bone/bone marrow, lymph nodes, lungs, and liver.

Dr. Rorke has recently defined a clinicopathologic entity closely related to CNS-PNETs, which she has named the atypical teratoid/rhabdoid tumor (ATT/RhT) (15). These tumors generally present in the first two years of life, and their confusion with PNETs may account in large part for the worse prognosis generally ascribed to PNETs in children under the age of two. The diagnostic confusion arises not in the 10–15% of tumors consisting

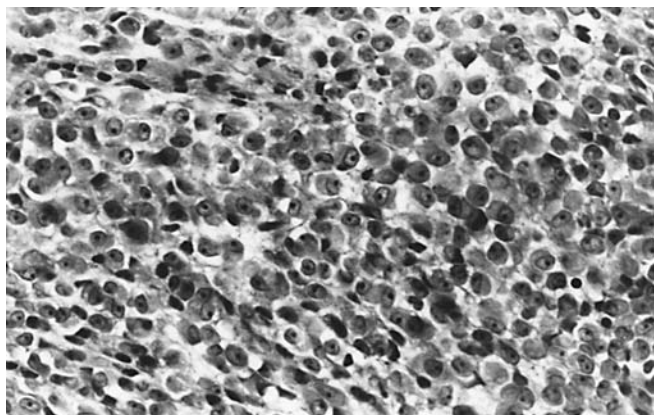


Fig. 22-7. Rhabdoid cells in an atypical teratoid/rhabdoid tumor.

entirely of rhabdoid cells, similar to those seen in extra-neural malignant rhabdoid tumors (Fig. 22-7), but in the two-thirds of cases where rhabdoid cells are admixed with classic primitive neuroectodermal tumor cells, or where the teratoid (teratoma-like) components consist of mesenchymal or epithelial (usually adenomatous) differentiation (Table 22-1 and Fig. 22-8). Mesenchymal differentiation, seen in about a third of ATT/RhTs, consists of loosely arrayed spindle-shaped cells separated by pale “ground substance,” (Fig. 22-9) and should not be confused with the reticulin-rich spindle cell elements of the desmoplastic medulloblastoma (Figs. 22-9 and 22-4).

As a supplement to careful light microscopic examination of PNETs obtained from very young children, the following patterns of immunohistochemical staining are characteristic of atypical teratoid/rhabdoid tumors:

1. Epithelial membrane antigen is always positive and is primarily expressed in the rhabdoid cells, and less consistently in the epithelioid cells.
2. Strong vimentin immunopositivity is seen within the cytoplasm of the rhabdoid cells.
3. Smooth muscle actin is seen in nearly all cases;

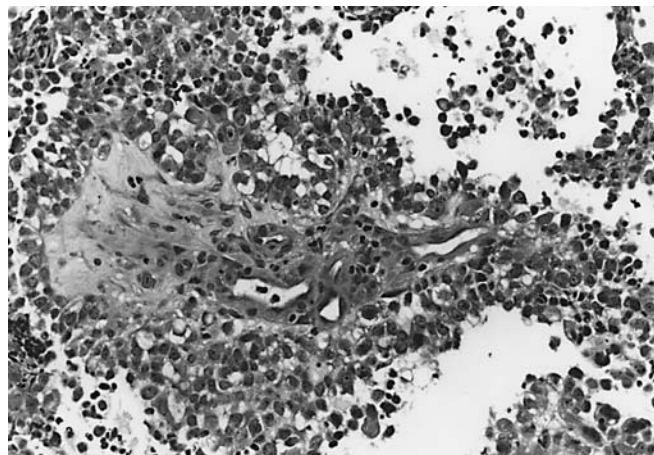


Fig. 22-8. Epithelial differentiation in an atypical teratoid/rhabdoid tumor.

while this immunopositivity is also usually localized to the rhabdoid cells (and the blood vessels), the mesenchymal component is occasionally stained.

4. GFAP and neurofilament immunostains may be positive in both the PNET fields and the rhabdoid cells.
5. Cytokeratins are confined to the epithelial elements and the rhabdoid cells.
6. Desmin expression is absent or weak, and is typically confined to the mesenchymal and PNET elements.

Further evidence for separating this aggressive neoplasm from other PNETs of childhood is cytogenetic: most ATT/RhTs examined so far have shown abnormalities of chromosome 22, which contrasts with the chromosome 17 abnormalities usually associated with CNS-PNETs (15,16). Recent studies have demonstrated

Table 22-1
PNET Versus Atypical Teratoid/Rhabdoid Tumor

	<i>PNET</i>	<i>AT/RT</i>
Age	Peak = 5 75% < 20	Peak = 1.5 75% < 3
Small, blue cells	+	±
Large cells/prominent nucleoli	Rare	+
Spindle cells	Desmoplasia	Sarcomatoid
Epithelial differentiation	—	±
Synaptophysin	±	±
Vimentin	+	Inclusions
EMA	—	+
Smooth muscle actin	—	+
Chromosomal Abnormalities	17,9	22

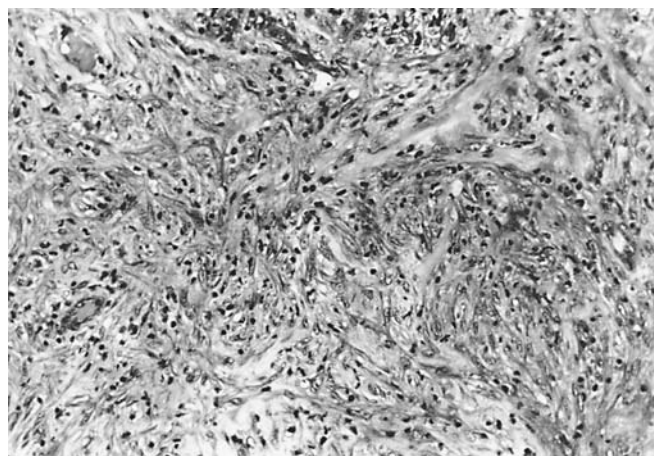


Fig. 22-9. Mesenchymal differentiation in an atypical teratoid/rhabdoid tumor.

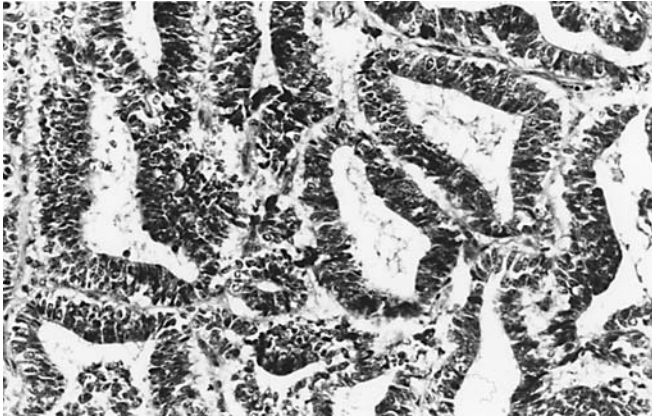


Fig. 22-10. Primitive neural tube formations in a medulloepithelioma.

abnormalities of the INI1 gene on chromosome 22 in both CNS and non-CNS ATT/RhTs (17,18).

ATT/RhTs usually present in very early childhood, with three quarters diagnosed in patients less than 3 years old. While most are infratentorial, supratentorial tumors are not uncommon, and predominate in older children. Radiologic findings are not distinctive. Approximately a third of patients with ATT/RhTs demonstrate leptomeningeal seeding at diagnosis. Unfortunately, the majority of patients with ATT/RhT rapidly progress both at the primary site and via leptomeningeal dissemination, with a median survival of less than a year. In contrast to children with CNS-PNETs, among whom there is at least a transient response to chemotherapy, patients with ATT/RhT often don't respond even to aggressive chemo- and/or radiation therapy.

In 1992, Giangaspero et al. reported four highly aggressive infantile cerebellar tumors composed of cells with relatively abundant cytoplasm and large vesicular nuclei with prominent nucleoli, which they termed "large cell medulloblastoma" (19). Review of the Pediatric Oncology Group's experience with PNET-MBs supports the existence of this aggressive subtype (independent of ATT/RhT) which comprised approximately 4% of their PNET-MBs (20).

A final rare, but aggressive and poorly responsive primitive CNS tumor of early childhood is the medulloepithelioma. The name derives from its epithelioid appearance as it pathologically recapitulates the primitive neural tube. Children with this tumor generally present with non-enhancing periventricular hemispheric masses during the first five years of life. The characteristic neural tube like structures are composed of a pseudostratified arrangement of primitive neural cells with an external and sometimes internal PAS positive limiting membrane (Fig. 22-10). Divergent differentiation along neuronal, glial and mesenchymal lines may also be seen. As with the ATT/

RhTs and large cell medulloblastomas, early tumor progression with leptomeningeal dissemination and poor response to therapy sets these tumors apart from conventional CNS-PNETs (21).

While this chapter has concentrated on PNET-MB as a cerebellar tumor, PNETs may be encountered, albeit much less frequently, in many other locations within the neuraxis, including the spinal cord (22). However, due to their relative rarity in these other locations, considerably less is known regarding their biologic behavior. A recent, small institutional study found a decreased overall survival and recurrence free survival in supratentorial PNETs compared with PNET-MBs (23), and comparative genomic hybridization studies indicate differing genetic aberrations between these two histologically similar groups of tumors (24). In general, supratentorial PNETs are treated similarly to PNET-MBs.

PNET-MBs are rare in adults, comprising only about 1% of primary central nervous system tumors in patients over 18 years old (25). While 80% of these occur between the ages of 21 and 40 years, cases have been reported in the over 50 crowd, with the eldest so far being a 73-year old woman. 5 and 10-year survival rates are similar to those observed in pediatric populations. Absence of fourth ventricular floor involvement and a high radiation dose to the spinal cord are correlated with a good prognosis. One recent study found that adults with desmoplastic medulloblastomas demonstrated significantly better 5 and 10 year survival rates (75%) than did similar patients with classical medulloblastomas (60% and 40%), but no central histopathologic review was performed (26).

The main problem in adult PNET-MB is distinguishing it from metastatic small cell carcinoma. In practice this is difficult, if not impossible, to accomplish due to tremendous overlap in their ultrastructural and immunocytochemical features. We find the following guidelines useful in signing out these cases:

1. If the tumor is not in the cerebellum, consider metastatic small cell carcinoma.
2. If there are multiple lesions, consider metastatic small cell carcinoma.
3. If there is no neoplastic glial differentiation, consider metastatic small cell carcinoma.
4. If there is a lung lesion, consider metastatic small cell carcinoma.
5. Consider metastatic small cell carcinoma.

On the other side of the biologic coin is a recently described intracerebellar tumor of adults referred to variously as lipidized medulloblastoma, lipomatous medulloblastoma, or medulloctoma (27). As the latter designation implies, this is a primary neuroectodermal tumor with a favorable prognosis. Approximately a dozen cases have

been reported, with a mean age of 50 years. These tumors are characterized by

1. a neuroectodermal component with low proliferative activity resembling the cerebral neurocytoma,
2. areas of lipomatous differentiation, and
3. an apparently favorable prognosis without the need for adjuvant therapy.

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23 Pineal Region Tumors

PINEAL REGION TUMORS comprise approximately 5% of pediatric central nervous system tumors, and may be seen (albeit less commonly) in adults as well. Although the majority of pineal region tumors are germinomas, a wide variety of tumor types may be found in this region. As the morbidity and mortality rates for surgical treatment of pineal region tumors prior to 1940 approached 90%, standard therapy consisted of shunting followed by empiric radiation therapy. With the advent of modern surgical techniques, particularly the minimally invasive stereotactic and endoscopic approaches to the pineal region, modern treatment protocols are now based on histopathologic diagnosis.

The pineal (Latin “pine cone”) was described by Herophilus, an Alexandrian anatomist, over 2300 years ago. He believed the pineal was a valve that controlled the flow of memories from the rear brain ventricles, where they were stored, forward to the consciousness-serving portions of the brain. Descartes considered the pineal body to be the seat of the soul, as it was the only unpaired structure within the brain. The first description of a pineal tumor is credited to Virchow (surprised?) in 1865.

The pineal gland occupies a central position within the brain, attached to the posterior roof of the third ventricle between the posterior and habenular commissures. Pineal cells are specialized neurosecretory cells with elongated cytoplasmic processes which end chiefly in the perivascular space around capillaries. They synthesize melatonin which is packaged in granular (dense-cored) vesicles, which can be appreciated ultrastructurally. For reasons which are not entirely clear, foci of mineralization develop during infancy, increase with age, and are generally radiographically demonstrable by the second decade of life.

Pineal region tumors may become symptomatic by one of three mechanisms (1):

1. Increased intracranial pressure due to hydrocephalus resulting from aqueductal compression obstructing third ventricular outflow. Hydrocephalus occurs in 80% of pineal region tumors, with nausea, vomiting, and obtundation ensuing as the hydrocephalus progresses.
2. Direct brainstem and cerebellar compression. Local compression of the superior colliculus can lead to impairment of extraocular movements, especially upgaze and convergence (Parinaud syndrome). Compression further caudally (of the inferior colliculus) can lead to impairment of downgaze as well. Cerebellar compression, if it occurs, results in ataxia and dysmetria.
3. Endocrine dysfunction is unusual with pineal region tumors.

Precocious puberty may result from

1. pineal destruction with disinhibition of gonadal secretion,
2. hypothalamic destruction, with similar effects, and
3. ectopic gonadotropin production by the tumor, which is most often seen in choriocarcinomas and mixed germ cell tumors of the pineal and virtually only affects boys.

Because of the large number of histologically distinct tumors and the variability of associated magnetic resonance signal characteristics, neuroimaging is rarely specific. However, several generalizations can be made (1):

1. Malignant germ cell tumors and pineoblastomas tend to be large (>4 cm) and irregular in shape.
2. Fat signal is characteristic of mature teratoma and dermoid cysts.
3. Hemorrhage is most common in choriocarcinoma.
4. Tumors originating from the collicular plate are likely to be gliomas or pineocytomas.

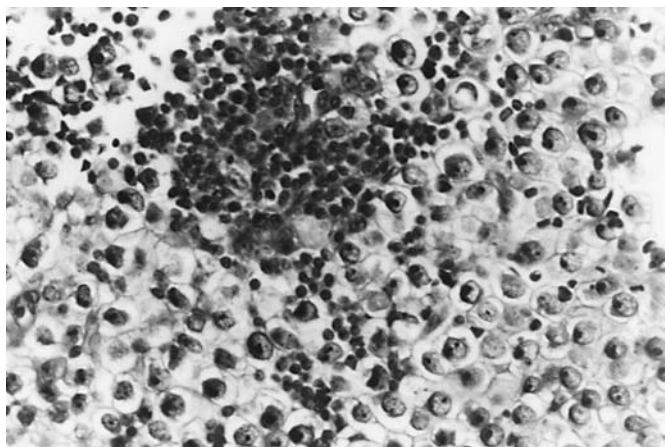


Fig. 23-1. A combination of epithelioid cells with prominent central nucleoli and small, reactive appearing lymphocytes in a pineal region germinoma.

5. Males with Parinaud's syndrome and diabetes insipidus with subependymal metastases or involvement of the hypothalamus most often harbor germinomas.
6. Radiographically demonstrable pineal calcifications under the age of 6 are abnormal.

Pathologically, pineal region masses can be subdivided into three major categories: 1) germ cell tumors, 2) pineal parenchymal tumors, and 3) other.

Germ cell tumors are by far the most common pineal regions tumors in the pediatric population, with germinomas comprising the majority of these (2). Pineal region germ cell tumors are seen nearly exclusively in boys, with the peak age of onset corresponding roughly with the onset of puberty. While the distinctive histopathologic appearance of germinomas is usually readily recognizable (Fig. 23-1) (3), two considerations must be kept in mind when interpreting small stereotactic or endoscopic biopsies obtained from this region:

1. Stereotactic biopsies showing lymphocytic or granulomatous inflammation most likely represent the stromal component of a pineal region germinoma (4). If such findings are discovered during intraoperative consultation, the surgeon should be encouraged (pushed) to obtain additional samples from other parts of the lesion. If more tissue is not forthcoming, or if the material is received as permanent sections after the operation, extensive sectioning, along with immunohistochemical staining with antibodies to placental alkaline phosphatase, may disclose rare islands of tumor cells within the inflammation.
2. Stereotactic biopsies showing obvious germinoma may be derived from a mixed germ cell tumor.

Once again, the ideal time for consultation is during the operation, where radiographic correlation should be sought, and additional material requested in the case of irregular, heterogeneous, or hemorrhagic lesions.

Correlation with the tumor markers alpha-fetoprotein and beta-hCG is also an important part of the evaluation of pineal region germ cell tumors, with a couple of important caveats: 1) These tumor markers are insensitive to the presence of most nongerminomatous components of mixed germ cell tumors and 2) beta-hCG is elevated in approximately 10% of germinomas, although the levels are usually only mildly increased compared with those seen in patients with choriocarcinomas (5). Similarly, the finding of occasional beta-hCG positive syncytiotrophoblast-like giant cells in these germinomas should not lead to the overdiagnosis of choriocarcinoma.

Teratomas comprise the next most common group of pineal region tumors. The recognition of mature and immature teratomas usually is not problematic when large amounts of tissue are available for examination (Fig. 23-2). The diagnostic pitfalls discussed for germinomas also apply to the intraoperative interpretation of small specimens showing teratomatous elements, with one additional differential diagnostic consideration: epidermoid/dermoid cysts. These cysts may appear identical to ectodermal components of a mature teratoma. Once again, radiographic correlation is paramount. A helpful histologic feature, however, is presence (or absence) of a well-developed keratohyaline granular layer. While this layer may be well-developed either in epidermoid/dermoid cysts or in areas of mature teratoma, its absence should raise the suspicion that one is dealing with the latter possibility.

In most institutions, pineal germinomas are treated with

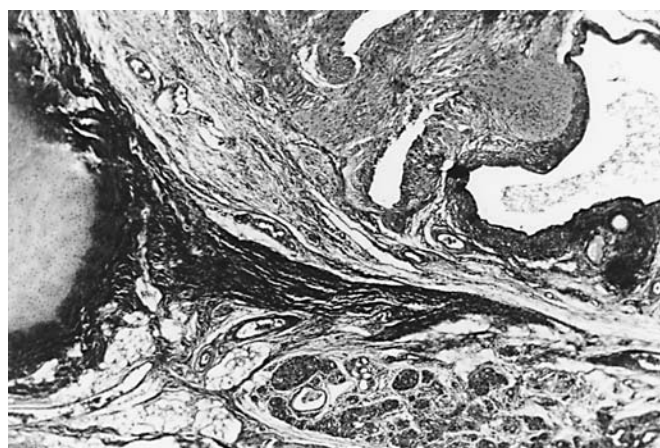


Fig. 23-2. Tissues derived from multiple germ cell layers in a pineal region teratoma.

radiation therapy, as they tend to be distinctively radiosensitive. (As indicated in the introduction, radioresponsiveness was, at one time, the diagnostic method of choice.) Failure of the tumor to respond to radiation therapy, or recurrence within the irradiated field, should prompt re-examination of the specimen for non-germinomatous elements, although a small proportion (approximately 15%) of pure germinomas will recur within the radiation field (6). Leptomeningeal seeding, while unusual at diagnosis, also ensues in about 15% of patients, and some authors recommend prophylactic craniospinal irradiation for these tumors. Generally speaking, however, the long term outlook for patients with pineal region germinomas is excellent, with 10- and 20-year survival rates of 90% and 80%, respectively (7). Survival of patients with nongerminomatous germ cell tumors is dependent on histology and the extent of surgical resection. Adjuvant chemotherapy in addition to radiation therapy, appears to be of benefit in nongerminomatous germ cell tumors other than teratomas.

Recent studies (8,9) examining nongerminomatous germ cell tumors (NGGCTs) of the brain have reported the following:

	3-year Survival	Probability of Leptomeningeal Dissemination
Mature teratomas	86%	0
Immature teratomas	67%	0
Mixed germ cell tumors	44%	4%
Pure NGGCTs	13%	33%

The neurohypophysis represents the second major site of origin for intracranial germ cell tumors, and the most common site of origin for primary intracranial germ cell tumors in females (7). These usually present with diabetes insipidus, visual disturbances, and/or amenorrhea (in females). An additional differential diagnostic consideration in this region is Langerhans cell histiocytosis (LCH), which may also present as an isolated hypothalamic/neurohypophyseal mass (8). The differential diagnosis may be particularly problematic in that there are significant histopathologic similarities: both are characterized by large cells with abundant cytoplasm embedded in an inflammatory stroma (Table 23-1). While the inflammatory stroma of LCH more often demonstrates a predominance of eosinophils, there may be considerable overlap in the cellular composition of the inflammatory infiltrates within these lesions. Intraoperatively, the distinction between these two disorders rests on nuclear morphology; germinomas usually demonstrate prominent central

Table 23-1
Germinoma Versus Langerhans Cell Histiocytosis (LCH)

	<i>Germinoma</i>	<i>LCH</i>
Age	Child/young adult	Child/young adult
Location	Pineal/pituitary region	Pituitary stalk
Inflammatory stroma	+	+
Large discohesive cells	+	+
Prominent nucleoli	+	—
Nuclear grooves	—	+
Placental alkaline phosphatase	+	+
S-100 protein	±	+
CD1a	—	+

nucleoli while the nuclei of langerhans cells generally show longitudinal grooves and rather indistinct nucleoli. These distinguishing characteristics are much more easily appreciated in cytologic (touch/smear) preparations than in frozen sections. In addition, cytologic preparations allow initial assessment of these often miniscule biopsy specimens with maximal preservation of tissue for permanent sectioning, at which time the entities can readily be differentiated through the use of immunohistochemical stains for CD1a (LCH) and placental alkaline phosphatase (germinoma).

Pineal parenchymal tumors (PPTs) comprise approximately 10% of pineal region tumors. While they have traditionally been separated into malignant, embryonal pineoblastomas and more mature, indolent pineocytomas, mixed pineocytomas/pineoblastomas as well as the recently described pineal parenchymal tumors with intermediate differentiation may also be encountered (11–13). Pineoblastomas represent the pineal equivalent of the cerebellar medulloblastoma (PNET-MB), both epidemiologically and histopathologically (Fig. 23-3). They show a marked propensity to present during childhood, but have

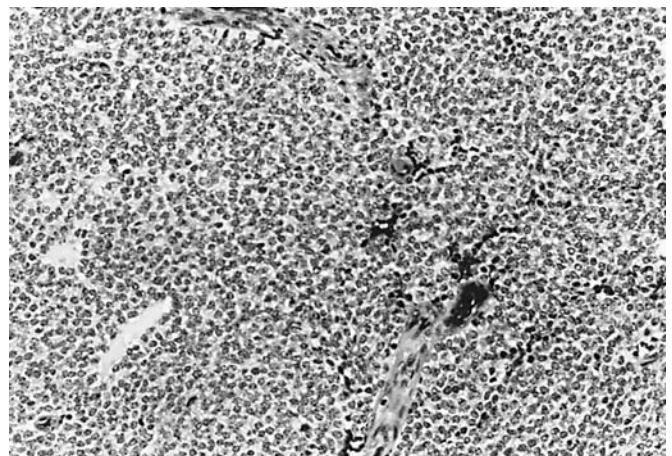


Fig. 23-3. A monotonous sea of small, round blue cells characterizes the pineoblastoma.

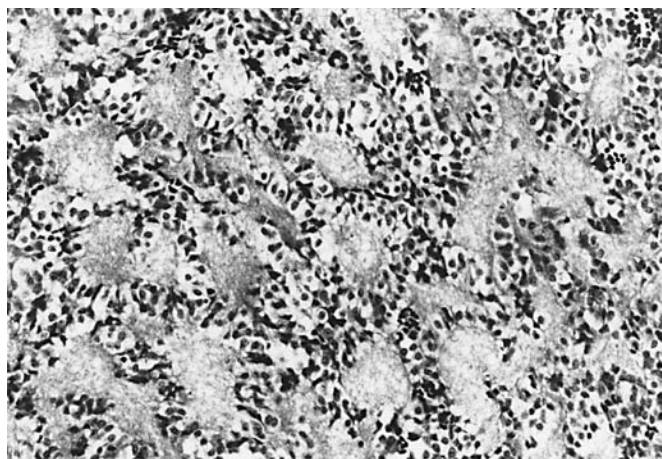


Fig. 23-4. Pineocytomatous rosettes in a pineocytoma.

been reported in adults even into their 60s. Microscopically, pineoblastomas closely resemble PNET-MBs, which are described in detail in Chapter 22. Rarely, retinoblastomatous differentiation may be encountered. While such differentiation does not appear to carry prognostic significance, it does highlight the relationship between the pineal gland (the “third eye”) and the retina. Unfortunately, this close relationship may also be recapitulated in children with “trilateral” retinoblastomas (bilateral retinoblastomas with pineoblastoma).

At the benign end of the histopathologic spectrum is the pineocytoma. While these benign tumors may present during the second decade of life, they are most commonly seen in adults, and are extremely rare in children under the age of 10. Pineocytomas resemble central neurocytomas, with sheets of round monomorphic cells punctuated by roughly spherical areas of neuropil delimited by a necklace of monomorphic tumor cells, giving the appearance of loose, oversized Homer Wright rosettes (Fig. 23-4). These pineocytomatous rosettes are the histopathologic hallmark of the pineocytoma (14), and bring with them the promise of a relatively benign course, without the propensity for invasion and leptomeningeal seeding common to the other PPTs. While considerable pleomorphism, as well as astrocytic and gangliogliomatous differentiation may be encountered in pineocytomas (15), mitotic figures and necrosis are usually absent or inconspicuous. Mixed pineocytoma-pineoblastomas demonstrate a biphasic pattern of typical pineoblastoma and less cellular areas comprised of monomorphic cells resembling pineocytoma. Well developed pineocytomatous rosettes are generally not seen in these tumors, which take on the behavior of the malignant pineoblastomatous component.

Pineal parenchymal tumors with intermediate differentiation show neither the malignant small round blue cell appearance of pineoblastomas, nor the monotonous,

mitotically inactive appearance of pineocytomas. Even the rosettes in these tumors appear intermediate in differentiation, falling between the large, relaxed appearing pineocytomatous rosette and the dense crowded hyperchromatic Homer Wright rosette. Unfortunately, the behavior of these tumors is usually driven by the latter tendency, with the capacity for leptomeningeal dissemination.

Symptomatic glial cysts of the pineal region are rare and are usually encountered in adults (15). Asymptomatic glial cysts are being diagnosed with increased frequency as MRI has become more common. When the imaging findings are straightforward, these cysts are followed with serial MRI scans. In cases in which the imaging characteristics are atypical, they may be biopsied. When the cyst wall is obtained with the biopsy specimen, it consists of densely fibrillary but hypocellular glial tissue which often contains abundant Rosenthal fibers and/or eosinophilic protein granular bodies. The pineal parenchyma adjacent to the cyst may show architectural disorganization, presumably due to chronic compression, and should not be overinterpreted as a pineal parenchymal or glial neoplasm (Fig. 23-5).

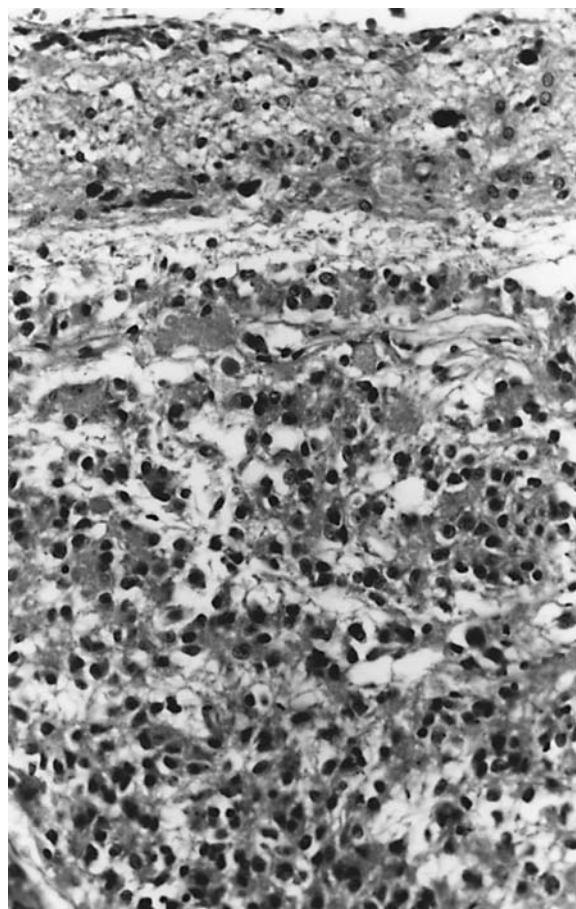


Fig. 23-5. Pineal cyst demonstrating a glial lining containing Rosenthal fibers with compression of adjacent pineal parenchyma.

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24 Pituitary Gland Lesions

PROBABLY THE MOST COMMONLY encountered lesion of the pituitary gland which one is likely to see in the surgical neuropathology arena is the pituitary adenoma. In general, adenomas present in one of two ways. If they attain sufficient size, they can produce symptoms related to mass effect. They also may present via endocrine symptomatology related to secretion of one or more hormonal substances. The peak incidence of adenomas is between the third and sixth decades of life and there appears to be a female predominance in cases reported in the literature. Pituitary adenomas, however, can occur at any age. There is an association of pituitary adenomas with multiple endocrine neoplasia type I (MEN I) (1); adenomas that arise in this setting tend to be relatively small in size (microadenomas - < 1 cm in diameter) and are associated with growth hormone and prolactin secretion. Incidence rates of pituitary adenomas in autopsied patients have been estimated to run as high as 25%.

Historically, adenomas have been categorized according to the cytoplasmic quality of the cells comprising the tumor (i.e., acidophilic, basophilic, and chromophobic). With the widespread use of immunohistochemistry, the current preferred method for categorizing pituitary adenomas is according to the hormonal products generated. The most common secreting adenoma type is the prolactinoma followed by ACTH cell adenoma, FSH/LH cell adenoma, growth hormone adenoma, and TSH adenoma (2,3). A significant percentage (approximately 20%) of adenomas will be nonsecretory and are designated as null cell adenomas. A significant percentage of adenomas will also secrete more than one hormone. The relative importance of characterizing adenomas by immunohistochemistry can be debated from a practical standpoint. Patients with a known hormone secreting adenoma can be followed postoperatively with endocrine testing. Not all adenomas that necessarily secrete hormonal proteins will secrete an active product that is clinically significant. The exact role

of immunohistochemistry ultrastructural examination, or molecular biologic analysis of adenomas continues to be a subject of debate.

Histologically, adenomas are characterized by a wide variety of appearances. Certain patterns and cell morphologies tend to be associated with specific hormonal cell types. The generic adenoma is characterized by a loss of the normal pituitary gland architecture. In the normal adenohypophysis, cells are arranged in small nests or groups separated by a delicate fibrovascular stroma (Fig. 24-1). Frequently, within a given nest or group, different cell types may be observed. It is well-known that certain areas of the gland show a preferential predominance of certain hormonal cell types. In adenoma, one generally encounters a diffuse proliferation or sheet of fairly monomorphic appearing cells which have a generally epithelial appearance (Figs. 24-2 and 24-3). Nuclear pleomorphism may be quite prominent and binucleation is not unusual (Fig. 24-4). A variety of other patterns of adenoma may be observed histologically including an acinar configuration,

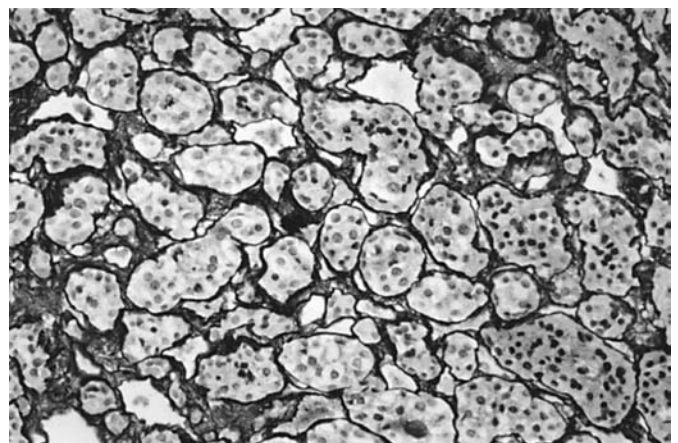


Fig. 24-1. Normal nested architectural pattern of the pituitary adenohypophysis highlighted with a reticulin stain.

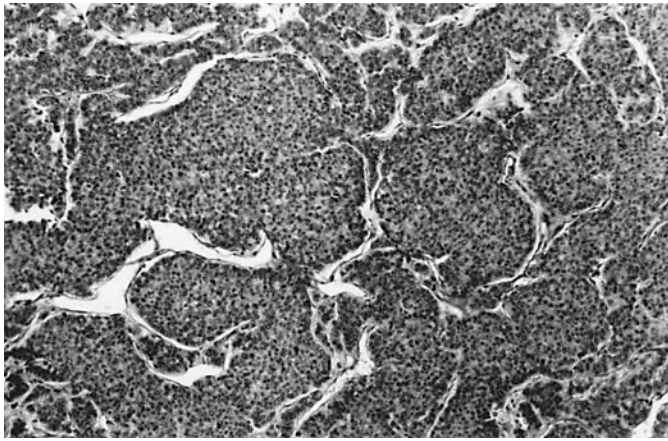


Fig. 24-2. Vaguely nodular proliferation of a monomorphic population of cells in an adenoma.

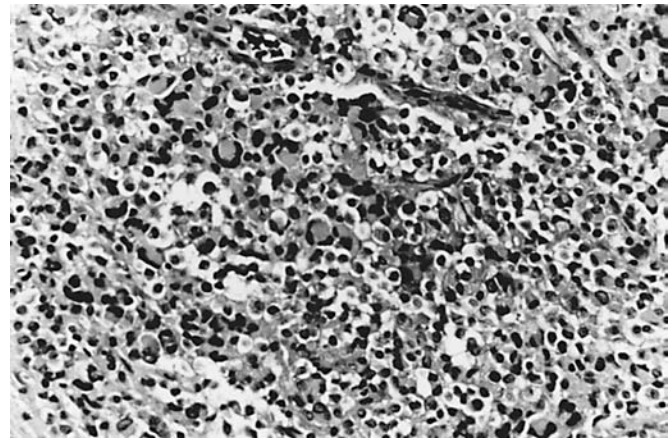


Fig. 24-4. Multinucleation and nuclear pleomorphism in an adenoma.

anastomosing ribbons of cells, nested architecture with dense fibrovascular stroma and papillary or pseudopapillary architecture (Fig. 24-5). Occasionally, areas of hemorrhage or necrosis (pituitary apoplexy) can be seen in an adenoma (4,5). These patients often present acutely with visual disturbances related to pressure on the optic chiasm, due to sudden enlargement of the adenoma. Occasionally, amyloid deposition may be observed within an adenoma, particularly in association with prolactinomas (6,7). Psammomatous calcifications may be seen in up to 20% of prolactinomas (8). Growth hormone adenomas frequently contain cells with eosinophilic paranuclear masses of cytokeratin filaments called fibrous bodies (9). There are a number of other sources which discuss in more detail specifics with regard to various hormonal types clinically, histologically, immunocytochemically,

and ultrastructurally that is beyond the scope of this text (2,3,10–12).

Distinction of adenoma from ordinary adenohypophysis is often a major differential diagnostic consideration during intraoperative consultation. Distinguishing features are summarized in Table 24-1. Adenomas generally show a monomorphic proliferation of cells with loss of the normal acinar or lobular pattern that characterizes adenohypophysis. Distinction of hyperplasia from normal adenohypophysis may be more difficult. Hyperplasia refers to an increased number of a particular cell type (13). Hyperplasia may assume either a nodular or diffuse configuration. Diagnosis of hyperplasia is very difficult on small biopsy specimens. Diffuse hyperplasia may be almost impossible to discern by routine light microscopic examination of the biopsy specimen and may require actual cell counts and correlation of these with normal counts in a particular region of the adenohypophysis. Different regions of the normal adenohypophysis show a predominance of one cell type versus another. Nodular

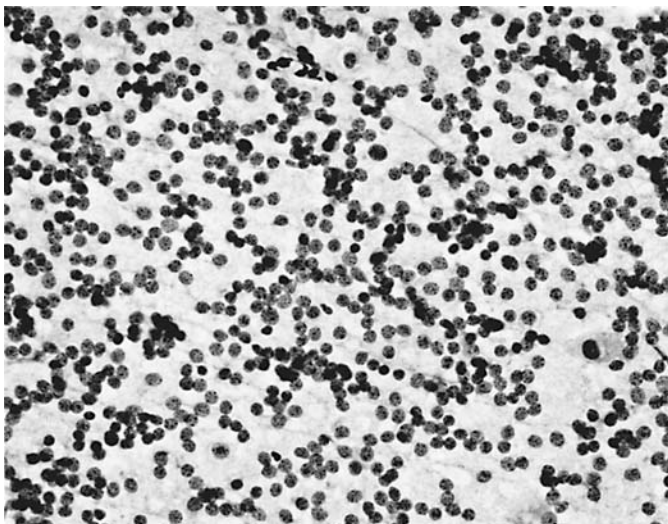


Fig. 24-3. Cytologic preparation showing a monomorphic population of epithelioid cells consistent with an adenoma.

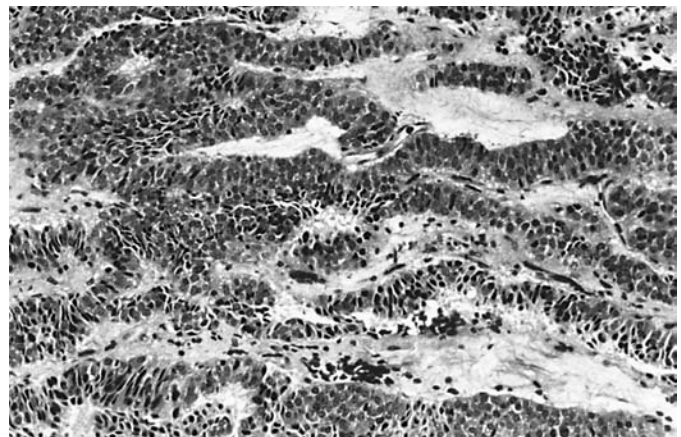


Fig. 24-5. Trabecular arrangement of cells in a pituitary adenoma.

Table 24-1
Normal Adenohypophysis, Hyperplasia, and Adenoma

	Adenohypophysis	Hyperplasia	Adenoma
Mixture of cell types	+	±	± (rarely)
Acinar/lobular pattern	+	± (expanded)	–
Homogeneous Reticulin	–	+	+
	Lobular	Limited focal disruption	Disrupted

hyperplasia may be more readily diagnosable on biopsy material. Histologically, nodular hyperplasia is characterized by enlargement of pituitary cords and lobules, often by a monomorphic population of cells. The normal lobular pattern of adenohypophysis, highlighted on reticulin staining, may show focal disruption of the reticulin network by expansion of the lobules, with the outside portion of the lobule still being limited by reticulin. Hyperplasias are probably the cause of increased pituitary hormones in a subset of a patients who do not have an obvious lesion radiographically or intraoperatively.

The term invasive adenoma has been used to refer to tumors with extensive dural, osseous, and sinus invasion. The incidence of invasion is quite variable, depending on the modality of assessment (i.e., radiographic, intraoperative, or pathologic). Most people consider the intraoperative findings as the most important assessment. Histologically, tumors that are invasive tend to encase nerve, invade the walls of vessels, and invade dural sinuses. The term “pituitary carcinoma” is used for the rare tumor which demonstrates discontinuous spread within the central nervous system (14) (Fig. 24-6). The most common sites of distant metastasis include lymph nodes, lungs, liver, and bone. Histologically, these tumors frequently demonstrate increased cell proliferation in the form of increased mitotic

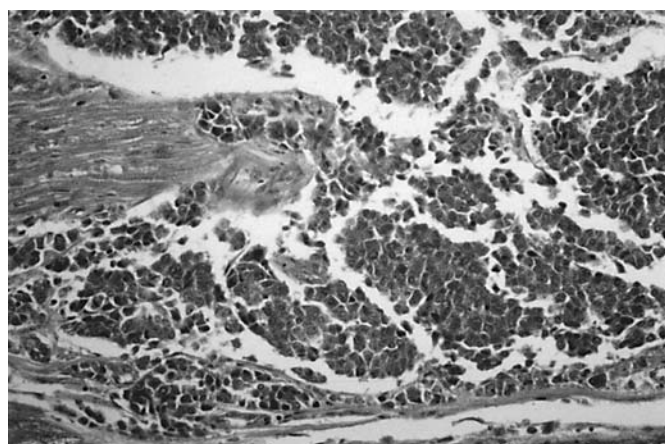


Fig. 24-6. Involvement of sacral cord posterior nerve roots by pituitary carcinoma.

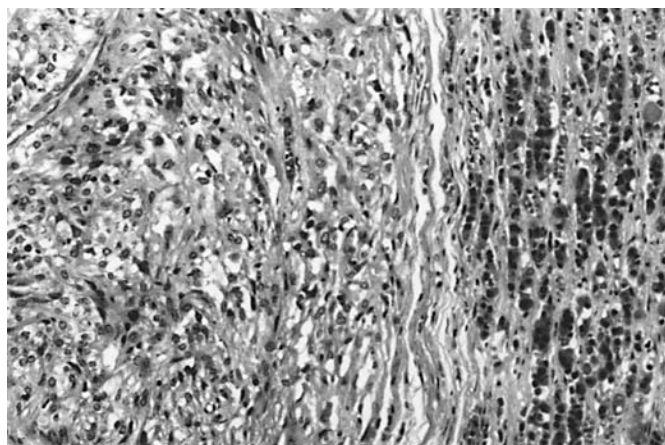


Fig. 24-7. Metastatic lung carcinoma involving the pituitary adenohypophysis.

activity and increased cell proliferation labeling indices (15). Nuclear atypia and foci of necrosis are also fairly common. There is some indication that p53 expression, when definitely present in a pituitary tumor, may be a useful marker of biologically aggressive behavior (16). Unfortunately, as is the case with many endocrine tumors, predicting a tumor's behavior based on histology alone is not reliable.

When one is confronted with a pituitary gland biopsy of a tumor, one usually thinks of pituitary adenoma first. However, there are variety of other lesions that may also, on occasion, involve the pituitary gland that are worth considering in the differential diagnosis. Pituitary involvement by metastatic neoplasms is not rare (17–19) (Fig. 24-7). The posterior lobe of the pituitary gland is the most common location for metastasis; this may be related to its direct arterial supply. Tumors which have been found to frequently metastasize to the pituitary gland include lung carcinoma, breast carcinoma, renal cell carcinoma, and pancreatic carcinoma. The histologic features that mark the tumor as malignant are often present histologically within the metastasis, and so in most cases, distinction of the metastasis from the primary tumor is not problematic. Unfortunately, immunohistochemistry may not be helpful in rare cases of metastatic carcinoma that are morphologically similar to pituitary adenoma. Carcinomas generally do not stain positively for pituitary hormones; although not all adenomas will stain positively either. Both adenomas and carcinomas will stain positively for cytokeratin markers. Carcinomas generally stain positively for epithelial membrane antigen, whereas most adenomas do not. Adenomas also invariably stain positively for neuroendocrine markers such as synaptophysin and neuron specific enolase (20).

Hematopoietic lesions including lymphomas, leukemias and plasmacytomas may occasionally involve the

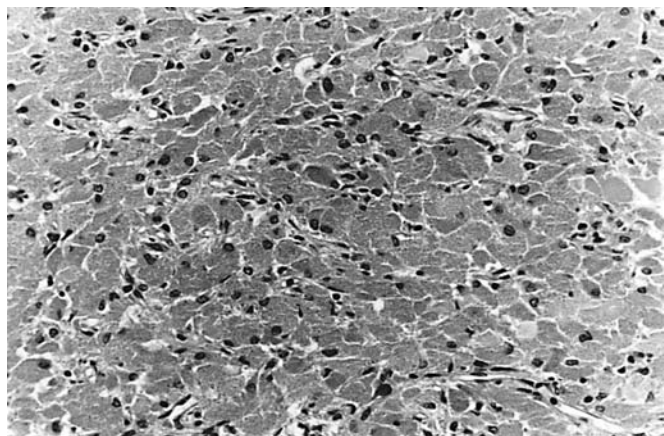


Fig. 24-8. Granular cell tumor comprised of polygonal cells with abundant granular cytoplasm.

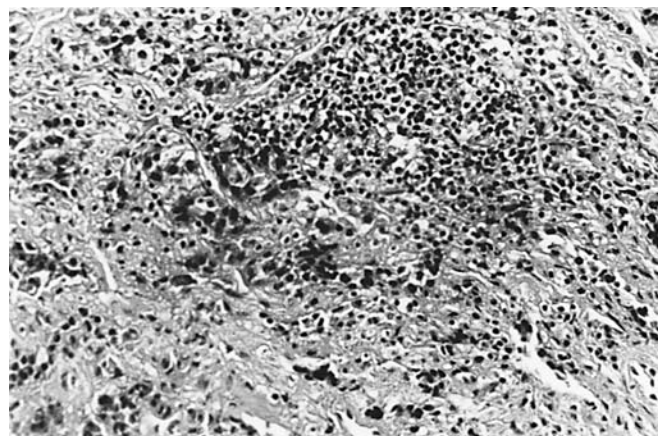


Fig. 24-9. Lymphocytic infiltrate and fibrosis in lymphocytic hypophysitis.

pituitary gland as well (21,22). From a histologic standpoint, there is generally little confusion between adenomas and these hematopoietic lesions. Immunohistochemistry very easily will resolve any potential differential diagnostic problems.

Rarely, one may encounter granular cell tumors in the pituitary gland region (23,24). The monomorphic, bland nature of most granular cell tumors may cause considerable confusion with pituitary adenomas. Most cases of granular cell tumor arise in the pituitary stalk or neurohypophysis region. Similar to granular cell tumors elsewhere in the body, these lesions are characterized by plump polygonal cells with abundant eosinophilic granular cytoplasm (Fig. 24-8). Cytoplasmic granules are PAS-positive and diastase-resistant. Ultrastructural demonstration of abundant cytoplasmic lysosomes is characteristic. Most cases of granular cell tumors arising in this location have an excellent prognosis with a good surgical resection.

Rarely, other primary central nervous system tumors, particular meningiomas and gliomas, may arise adjacent to the pituitary gland and secondarily involve it. Histologically, these lesions are seldom confused with adenoma. Occasionally, one may also encounter germ cell tumors, particularly germinoma, in this location (25). Focal extension of olfactory neuroblastoma to involve pituitary gland has also been described. Rare examples of hypothalamic neural hamartomas and adenohypophyseal neurochoristoma may also be seen (26). The neural hamartomas often consist of minute nodules of ectopic hypothalamic tissue. Most of these lesions are seen in young males and they present with signs and symptoms related to mass effect, autonomic dysfunction, or precocious puberty. Essentially, this lesion represents ectopic hypothalamic tissue. In contrast, the adenohypophyseal neuronal choristoma occurs within the pituitary gland itself, or is occasionally admixed with pituitary adenoma tissue, and histo-

logically consists of a neuronal or neuroglial tissue. Examples of neoplasms which morphologically resemble salivary gland-like tumors (pleomorphic adenoma, monomorphic adenoma, oncocytoma and low grade adenocarcinoma) have also been described (27). Rare examples of so-called pituicytomas arising from the neurohypophysis have been described (28). These low grade gliomas are marked by sheets or fascicles of spindled cells with fibrillar cytoplasm and oval to elongated nuclei with small nucleoli.

Rarely inflammatory conditions may also present in the pituitary gland. Neurosarcoidosis frequently involves the leptomeninges at the base of the brain, particularly in the region of the hypothalamus (29). A rare condition referred to as lymphocytic hypophysitis has been described, particularly during pregnancy or in the postpartum period (30,31). The lesion is thought to represent an autoimmune process and is characterized by infiltration of the adenohypophysis by chronic inflammatory cells including lymphocytes, plasma cells, and histiocytes (Fig. 24-9). Prominent fibrosis of the adenohypophysis is frequently seen. Clinically, most patients present with symptoms related to pituitary insufficiency.

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25 Primary Central Nervous System Lymphoma

WHILE REFERRING TO THE SHARP rise in the incidence of primary CNS lymphomas (PCNSLs) as an epidemic may be somewhat overstated, this tumor has made the transition from textbook and case report material to surgical pathology benches across America. While this is in part a result of the AIDS epidemic, an overall 10 fold increase in the incidence of PCNSL was seen between 1973 and 1991 (1).

As Epstein-Barr virus can be identified in most AIDS-associated PCNSLs (depending on the sensitivity of the assay), many investigators believe there is a direct relationship between EBV infection of B-lymphocytes, loss of CD4+ lymphocytes, and the development of PCNSL (3). EBV-driven lymphoproliferation does not, however, appear to underlie the increasing incidence of PCNSL in immunocompetent individuals (4,5). Nonbiologic influences such as better case finding, neuroimaging, and biopsy techniques also seem *not* to be responsible for this increase (6). Some investigators have postulated that the incidence of PCNSL will soon exceed that of meningiomas, so this is clearly an entity which should be on our minds as we embark on intraoperative consultations.

While PCNSL is the most common brain tumor in pediatric AIDS patients (7), most AIDS-associated PCNSL is seen in adult patients, with a mean age at presentation in the 30s. Immunocompetent individuals present considerably later in life, with a mean age in the 50s. Non-AIDS patients at increased risk for PCNSL are those with other immunodeficiency states, both congenital (e.g. Wiskott-Aldrich syndrome) and acquired (e.g., organ transplant recipients).

PCNSL usually presents as a periventricular mass; 75% are supratentorial. Their periventricular location favors subependymal spread and leptomeningeal seeding, which can be detected by CSF cytology in approximately 15%

of patients at presentation (8). Primary leptomeningeal lymphoma (without a parenchymal mass lesion) is rare, accounting for approximately 5% of cases. Extraaxial presentations are also being encountered with increased frequency (9,10). Radiographically, PCNSLs typically have indistinct borders, demonstrate homogeneous enhancement, and show little surrounding edema. Multiple lesions may be seen up to 50% of cases. Ring-enhancement, similar to that seen in glioblastomas, brain abscesses, and cerebral toxoplasmosis is seen more often in AIDS-associated PCNSL. Ocular disease is present at diagnosis in about 15% of patients. Conversely, the majority of patients who present with ocular lymphoma develop cerebral lymphoma, although this may take several years (11). As with other extranodal lymphomas in organs normally devoid of organized lymphoid tissue, the overwhelming majority of PCNSLs are diffuse large B-cell lymphomas (REAL classification) (8). This is true both for AIDS and non-AIDS associated PCNSLs, and there are no histopathologic features that allow one to determine whether the patient does or does not have AIDS.

This predominance of large, discohesive cells with relatively abundant cytoplasm and often prominent nucleoli underscores the utility of cytologic preparations in the intraoperative evaluation of CNS lesions (not to mention avoiding cryostat contamination in AIDS-associated lesions) (12). As PCNSL is not a surgical disease, it is important to distinguish these tumors from other malignant primary brain tumors, where resection will be attempted. While a good touch preparation usually provides an obvious answer, frozen sections may be more difficult to interpret, as artefactual nuclear angulation and loss of cytologic details may lead to a mistaken diagnosis of malignant glioma. Note also that this is one instance where touch preparations are often superior to smear prep-

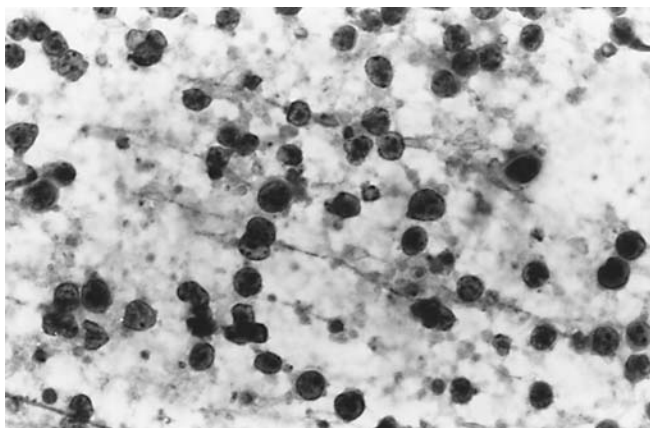


Fig. 25-1. Intraoperative touch preparation demonstrating discohesive cells with large nuclei and prominent nucleoli in a primary CNS lymphoma.

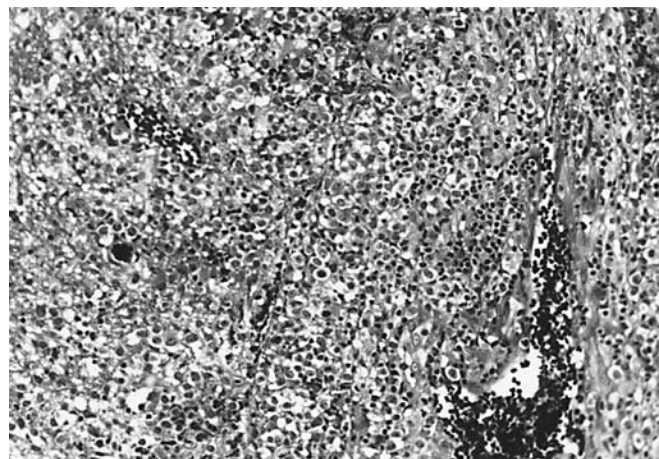


Fig. 25-2. Angiocentricity with angioinvasion in a primary CNS lymphoma.

arations, as the latter often disrupt the cytoplasm of neoplastic lymphoid cells. Cytologic preparations are also superior to frozen section in the diagnosis of non-neoplastic (inflammatory) AIDS associated lesions. In these cases, the overdiagnosis of atypical inflammatory infiltrates as PCNSL may be avoided by the use of well prepared touch preparations (Fig. 25-1). Diagnostic difficulties may be compounded in patients given steroids prior to biopsy, as this often results in massive tumor necrosis, leaving very little viable tissue for examination (13). While recommendations have been made in the literature to avoid steroids prior to biopsy (except in rare cases of incipient herniation) many clinicians more or less reflexively administer these agents to patients with brain tumors, making our job considerably more difficult than it needs to be. Once again, a well performed touch preparation may provide a diagnosis even in cases where the majority of the tumor is necrotic, as the premorbid cytology may be preserved, albeit in a rather mummified form. The importance of diagnostic conservatism in this situation cannot be overstated, however, as other malignant and nonmalignant CNS diseases may also demonstrate regressive responses to steroids. Immunohistochemical staining of necrotic tumor tissue must also be interpreted with caution, as LCA immunoreactivity has been seen in some necrotic carcinomas (14).

One of the histopathologic hallmarks of PCNSL is angiocentricity with angioinvasion (Fig. 25-2). The latter feature leads to the formation of multiple concentric layers of reticulin around blood vessels, which is responsible for the prior designation of PCNSL as “reticulin cell sarcoma.” When this angiocentricity is prominent within the cerebral cortex, it may resemble the “secondary structures of Scherer” seen in gliomatous cortical involvement (Fig. 25-3). A conspicuous difference is the absence of

perineuronal satellitosis in PCNSL and its presence in gliomatous permeation of the cortex.

At the opposite end of the differential diagnostic spectrum are benign vasculocentric lymphoid lesions such as primary CNS vasculitis and tumor-like demyelinating lesions resembling multiple sclerosis. Most PCNSLs contain an admixture of small, cytologically benign (usually T) lymphocytes. In addition, there may be a minor component of smaller, more indolent appearing B-cells within the lesions. It has been our experience that these benign appearing lymphocytes may comprise the entire neoplastic cell population as one moves radially away from the center of the lesion. Therefore, intraoperative clinicoradiologic correlation is imperative when confronted with a benign appearing, vasculocentric lymphoid infiltrate. If PCNSL is still a diagnostic consideration, additional biopsies should be requested to establish the diagnosis of large cell lymphoma.

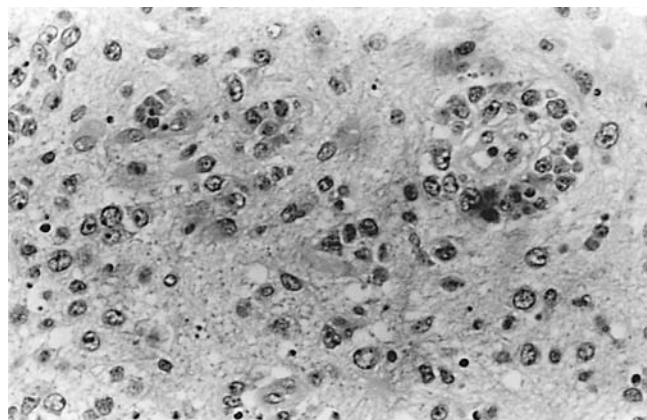


Fig. 25-3. Perivascular spread of primary CNS lymphoma within the cerebral cortex.

The pathogenesis of PCNSL remains controversial. The two leading theories are: (1) PCNSL evolves through malignant transformation of a chronic inflammatory process within the CNS, and (2) malignant transformation occurs outside the CNS, but growth is restricted to a subset of cells which enter and thrive within the brain microenvironment. Arguments for and against each of these hypotheses have been made in the literature and the question remains unresolved at present. In immunocompetent patients, PCNSL is virtually never associated with systemic lymphoma at diagnosis or at autopsy, and staging does not need to be performed in such patients (11). As patients with AIDS may harbor multiple extranodal large cell lymphomas, these immunocompromised patients should be evaluated for systemic disease.

Without treatment, the median survival for patients with PCNSL is 2–3 months. Aggressive regimens utilizing combined chemotherapeutic and radiotherapeutic modalities have markedly extended this median survival (up to several years) (15). However, the disease remains a fatal affliction.

Other lymphoid lesions which may involve the central nervous system include:

1. Angiocentric immunoproliferative lesions (“Lymphomatoid granulomatosis”) (16), T-cell lymphomas (17), and anaplastic large cell lymphomas (18). While these are distinctly uncommon within the CNS, they resemble their systemic counterparts.
2. Epidural/bone lymphomas presenting as spinal cord compression (20). While still mostly composed of B-cell lymphomas, a broader spectrum of histologies is seen in patients with lymphomatous cord compression.
3. Intravascular lymphomatosis (IVL, or angiotropic large cell lymphoma) may involve the CNS with or without evidence of extraneural IVL or systemic lymphoma (Fig. 25-4) (19). These patients present with a variety of neurologic syndromes, and cerebral angiography may demonstrate “classic” vasculitic changes.
4. Posttransplant lymphoproliferative disease (PTLD). While involvement of the CNS is unusual in patients with PTLD, we must be cognizant of this disorder, as CNS involvement may either accompany systemic disease, or rarely represent its presenting manifestation. As the therapeutic approach to PTLD differs dramatically from that taken with patients suffering from PCNSL, we must always keep this entity in mind when evaluating lymphoid lesions in the central nervous system (21).

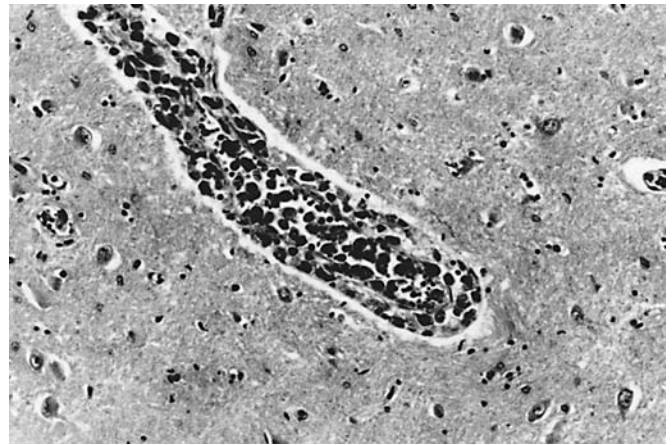


Fig. 25-4. Intravascular lymphoma within an intraparenchymal arteriole.

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26 Schwannoma

PERIPHERAL NERVE SHEATH TUMORS, including schwannomas, are well known to the surgical pathologist (1). In neuropathologic practice, schwannomas are encountered frequently in the cerebellopontine angle, occasionally in the spinal cord, and rarely in an intraparenchymal location within the cranial cavity.

Schwannomas comprise at least 75% of cerebellopontine angle tumors, where they generally arise from the vestibular portion of the eighth cranial nerve (hence the move to replace “acoustic neuroma” with “vestibular schwannoma” as the accepted designation for these tumors). Meningiomas run a distant second, representing approximately 10% to 15% of tumors in this region. Although exophytic brainstem gliomas may also rarely be encountered in the cerebellopontine angle, differential diagnosis operationally lies between the first two entities. When the classic spindle cell (Antoni A) and microcystic (Antoni B) areas of schwannoma can be identified, there is little doubt as to the correct diagnosis (Figs. 26-1 and 26-2). The difficulty lies in distinguishing Antoni A predominant schwannomas (which tend to occur in this location) from fibroblastic meningiomas. Both share a predominantly spindled morphology, an overall benign appearance, thick-walled hyalinized blood vessels, and perivascular whorl formation. Indeed, during intraoperative consultation, the prudent diagnosis may on occasion be “benign spindle cell lesion - defer to permanents.” Clues which we have found helpful in difficult cases are scattered degenerative atypical nuclei (“ancient change”) and perivascular hemosiderin in schwannomas (Figs. 26-3 and 26-4), and foci of more epithelioid syncytia in meningiomas (Table 26-1). While neither S-100 nor EMA immunoreactivity will specifically differentiate these tumors (2), strong diffuse S-100 immunoreactivity with focal, cytoplasmic EMA positivity is characteristic of schwannomas.

Schwann cells are the glia of the peripheral nervous

system, and frozen sections of schwannomas may, at first glance, look astrocytic. If careful examination does not reveal eosinophilic perinuclear cytoplasm and fine fibrillary cytoplasmic extensions seen in astrocytic tumors, one is likely to be dealing with a schwannoma. While distinctly unusual, exophytic pilocytic astrocytomas may present as cerebellopontine angle masses, and their classic biphasic pattern may mimic Antoni A and B differentiation. Awareness of this entity, along with careful attention to the aforementioned cytoplasmic details, will allow correct intraoperative diagnoses in these rare instances. While the presence of Rosenthal fibers and eosinophilic granular bodies in pilocytic astrocytomas is a helpful diagnostic clue, similar features have recently been reported in an otherwise classic intracranial schwannoma (3). Malignant schwannomas rarely occur in the cerebellopontine angle (4,5). As they figure more prominently in the differential diagnosis of spinal schwannomas, they will be discussed later.

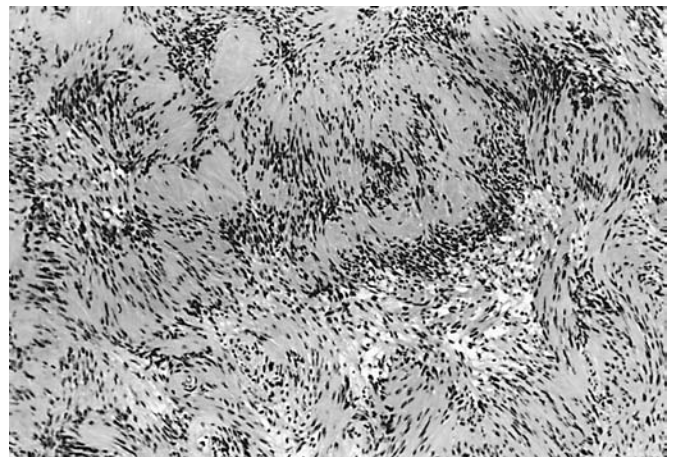


Fig. 26-1. Area of predominantly spindle (Antoni A) differentiation in a schwannoma.

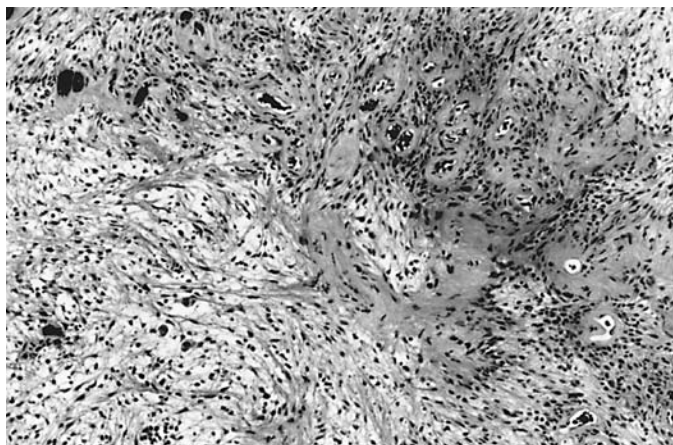


Fig. 26-2. Area of predominantly microcystic (Antoni B) differentiation in a schwannoma.



Fig. 26-4. Perivascular hemosiderin in a schwannoma.

The differential diagnosis of extramedullary, intradural spinal tumors usually also revolves around the distinction between schwannoma and meningioma. Meningiomas, however, are relatively more common in this location than in the cerebellopontine angle, especially in the cervical and upper thoracic spinal cord. The histopathologic differential tends to be somewhat easier in that Antoni B differentiation is usually more prominent in spinal schwannomas.

At the caudal end of the spinal cord, we need to distinguish schwannomas arising within the cauda equina from myxopapillary ependymomas arising from the filum terminale. While the surgical anatomy often provides helpful diagnostic information, either tumor may arise in association with the conus medullaris/filum terminale. Although these two entities are rather easily distinguished on permanent sections, intraoperative consultation may, at times, prove difficult. Confusion arises predominantly due to the presence of thick-walled blood vessels within

the myxopapillary ependymoma, as this vascular morphology is usually associated with extraaxial tumors, such as schwannomas and meningiomas. The tapering cytoplasmic processes characteristic of ependymomas will usually appear finer and more eosinophilic than the cytoplasm of neoplastic Schwann cells. While such cytologic differences are better seen on touch preparations, frozen sections may reveal characteristic perivascular and subcapsular pseudorosettes in the myxopapillary ependymoma. Besides avoiding a bit of embarrassment when the permanent sections come out, an intraoperative diagnosis of myxopapillary ependymoma will usually prompt the surgeon to search proximally for additional tumor, as skip lesions are known to occur with this entity.

While peripheral nerve sheath tumors other than schwannoma are rare within the intracranial cavity, we must consider a variety of these entities when examining spinal schwannomas. Cellular schwannomas and malig-

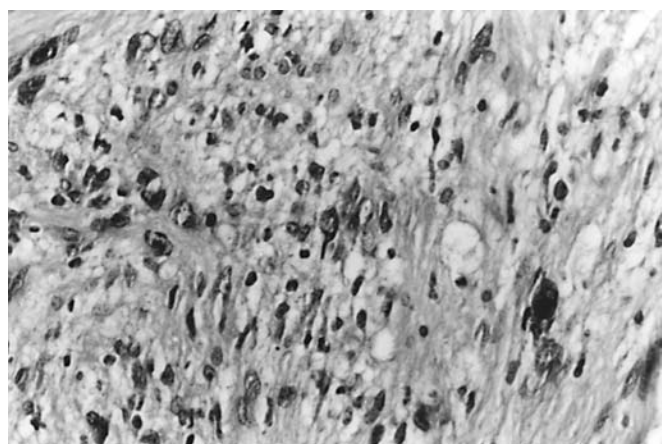


Fig. 26-3. Degenerative atypical nuclei (‘‘ancient change’’) in a schwannoma.

Table 26-1
Schwannoma Versus Meningioma

	<i>Schwannoma</i>	<i>Meningioma</i>
Intracranial location	Cerebellopontine angle	Cerebral convexity, sphenoid ridge, other
Spinal location	Lumbar > cervical	Cervical > lumbar
Attachment	Nerve root	Meninges
Spindle cells	+	+
Microcystic change	+	±
True pallisading	+	±
Scattered atypical nuclei	+	±
Hyalinized vessels	+	+
Perivascular hemosiderin	+	Rare
Epithelioid syncytia	Rare	±
Psammoma bodies	Rare	±
S-100 protein	Strong	±
EMA	Focal	Diffuse

nant peripheral nerve sheath tumors each comprise a few percent of spinal peripheral nerve sheath tumors (6–8). Neurofibromas are also unusual within the spinal canal, and generally occur in patients suffering from von Recklinghausen's disease (neurofibromatosis, type I). Perhaps the most unusual variation of peripheral nerve sheath tumor encountered in this location is the psammomatous melanotic schwannoma, which looks like it sounds and may be associated with cardiac myxomas and endocrine overreactivity (Carney's complex) (9). In addition to S-100 protein immunoreactivity, these tumors may react with HMB-45 antibodies (10). Psammomatous melanotic schwannomas are more prone to multiplicity, recurrence, and metastasis than classical schwannomas.

"Intraparenchymal" schwannomas are extremely rare, with less than 40 reported cases as of this writing (11,12). These have preferentially affected males, and have occurred in relatively young individuals, including children. Once considered, the diagnosis is usually not difficult at permanent section, although the appearance of Antoni B differentiation may lead to the diagnosis of glioma during intraoperative consultation, re-emphasizing the need for circumspection when dealing with circumscribed CNS tumors.

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27 Benign Epithelial Lesions— Craniopharyngiomas and Cysts

WHILE OLDER LITERATURE placed significant emphasis on distinguishing craniopharyngiomas from other cystic epithelial lesions, and more recent literature has stressed the importance of subclassifying craniopharyngiomas into adamantinomatous and papillary subtypes, the amalgamated experience with this group of lesions indicates that they behave in a fairly homogeneous and predictable manner: if they are totally removed, the patient is cured. If not, they will continue to grow, leading to clinical “recurrence.”

Although comprising less than 5% of CNS neoplasms, craniopharyngiomas are the most common non-neuroepithelial CNS tumors in childhood (1). While this statistic, along with embryologic/pathogenetic theories, has led to the notion of craniopharyngioma as a tumor nearly exclusively encountered in children, approximately half of all craniopharyngiomas present in adulthood.

Craniopharyngiomas present in the sellar region or third ventricle. Two histologic variants have been described (Table 27-1): the classic adamantinomatous variant composed of tooth-bud like basaloid squamous epithelium usually containing cysts, “wet keratin,” and calcifications (Fig. 27-1); and the more recently described papillary variant, resembling a typical squamous papilloma (Fig. 27-2) (2,3). Adamantinomatous craniopharyngiomas may occur at any age; the papillary variant is virtually confined to adulthood. In practice, two common difficulties are encountered in subclassification: the distinction between squamous and adamantinomatous epithelium, and the presence of both patterns within a single tumor. Recent studies indicate that the extent of resection rather than the histologic subtype determines the prognosis and therefore the management of these tumors (4). Extravasation of cyst contents with an associated foreign body giant cell reaction is much more common with the

adamantinomatous craniopharyngioma (Fig. 27-3), however, and may complicate or even preclude gross total resection. While xanthogranulomatous tissue obtained from the sellar region, even in the absence of epithelium, has traditionally been considered evidence of an adamantinomatous craniopharyngioma, a recent study suggests that xanthogranuloma of the sellar region may be a distinct clinicopathologic entity with a more favorable outcome (5,6).

The differential diagnosis of craniopharyngioma includes two very different types of lesions: pilocytic astrocytomas of the third ventricular region and hypothalamus, and other suprasellar cysts. Adamantinomatous craniopharyngiomas often incite a dense astrocytic response with abundant Rosenthal fiber formation (Fig. 27-4). If only this reactive tissue is sampled (for instance, during intraoperative consultation), the resemblance to pilocytic astrocytoma can be striking. Careful examination, however, usually fails to reveal a delicate microcystic component typically seen in pilocytic astrocytomas. Awareness of this potential pitfall, along with attention to the radiographic appearance of the tumor, will usually prevent misdiagnoses.

Table 27-1
Craniopharyngiomas

	<i>Adamantinomatous</i>	<i>Papillary</i>
Age	Children, adults	Adults
Location	Supra/para sellar	Third ventricle
Stellate reticulin	+	—
Calcifications	+	—
“Wet keratin”	+	—
Foreign body giant cell reaction	±	—

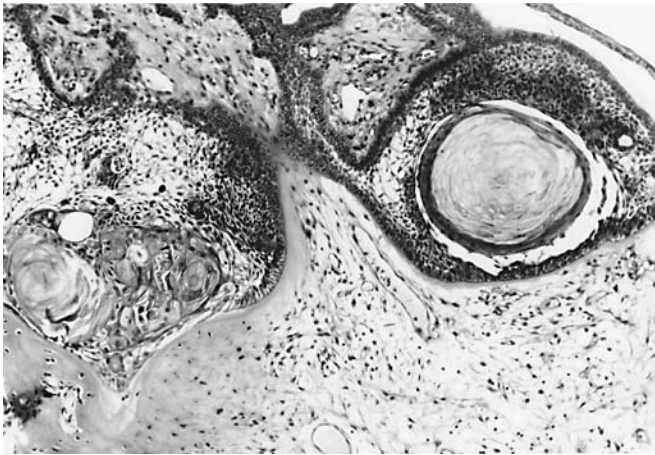


Fig. 27-1. Adamantinomatous craniopharyngioma demonstrating basaloid squamous epithelium, stellate reticulin, and "wet keratin."

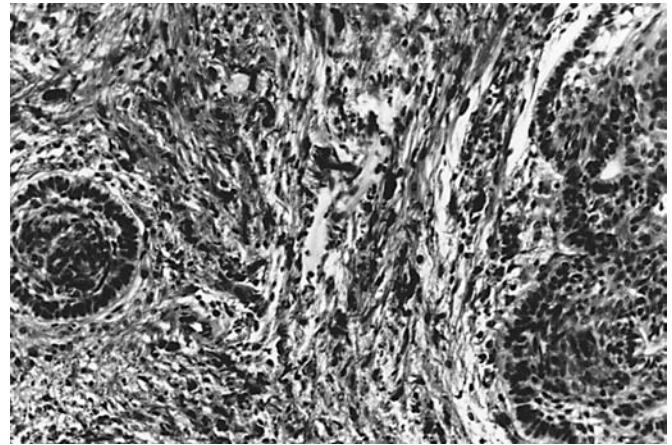


Fig. 27-4. Chronic reactive astrocytosis with prominent Rosenthal fiber formation associated with an adamantinomatous craniopharyngioma.

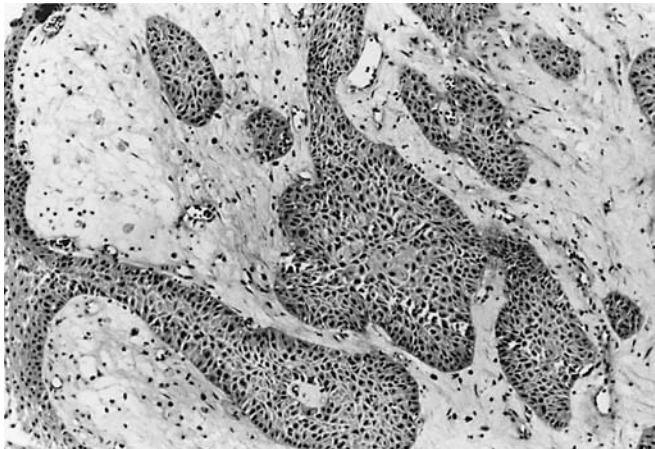


Fig. 27-2. Papillary craniopharyngioma resembling an inverted squamous papilloma.

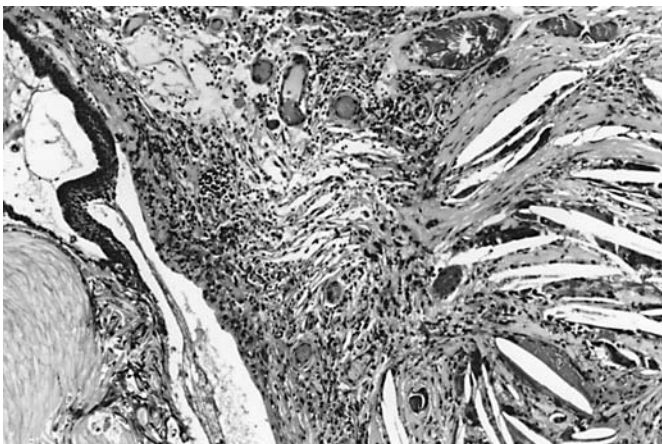


Fig. 27-3. Extravasation of cyst contents with accompanying foreign body giant cell reaction in an adamantinomatous craniopharyngioma.

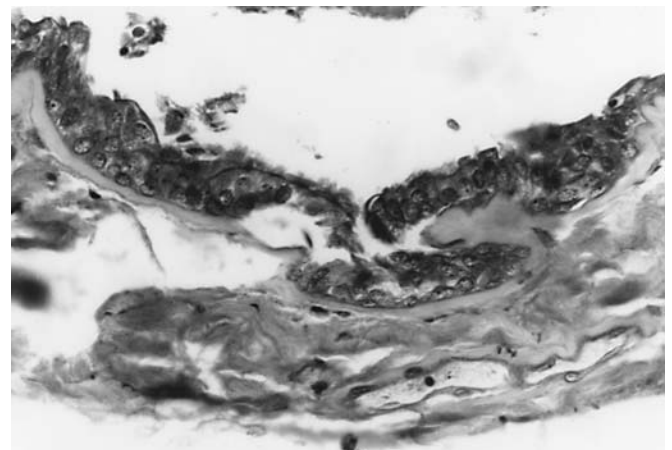


Fig. 27-5. Columnar ciliated cyst lining in a Rathke's cleft cyst.

Other cystic lesions which may occur in the sellar region include the classic Rathke's cleft cyst, with its columnar, sometimes ciliated epithelial lining (Fig. 27-5); and the squamous lined epidermoid and dermoid cysts. While the main histologic difference between squamous-lined cysts and craniopharyngiomas is architectural complexity, the distinction can also often be made even on small biopsy specimens, as craniopharyngiomas often lack the well-developed keratohyaline layer characteristic of epidermoid and dermoid cysts (Fig. 27-6).

Rathke's cleft cysts are usually easily distinguished from these other lesions by virtue of their columnar lining. However, squamous metaplasia may develop in these cysts, which then may complicate the diagnosis. Interestingly, the rarity of Rathke's cleft cysts obscures their recurrence rate, which is fairly similar to that seen with craniopharyngiomas. Similarly, incompletely resected epidermoid tumors also tend to regrow after varying peri-

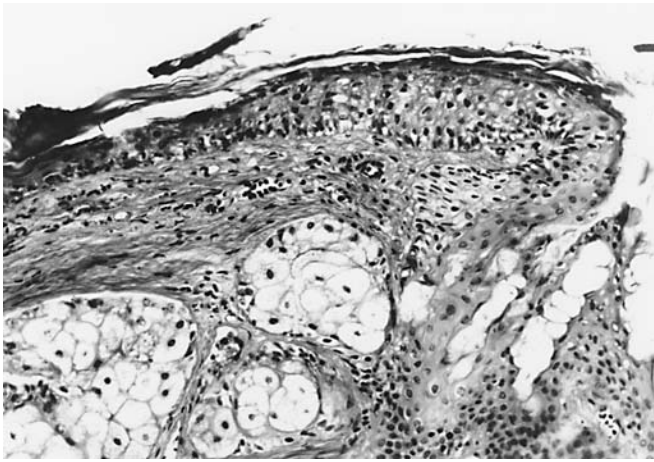


Fig. 27-6. Dermoid cyst demonstrating a well developed keratohyaline layer and dermal adnexa.

ods of time. Thus, these benign epithelial lesions seem to demonstrate roughly similar biologic behaviors (7).

Two other endodermally derived cysts may be encountered within the central nervous system (Table 27-2). Like Rathke's cleft cysts, these are lined by columnar epithelium resting on a thin basement membrane (8). Colloid cysts are, by definition, restricted to the third ventricle (9). Their radiographic appearance is virtually diagnostic, and the only challenge the pathologist may face is locating some epithelial lining cells in an aspirated or fragmented specimen. Endodermally derived columnar lined CNS cysts occurring in locations other than the sellar or third ventricular regions are referred to as neurenteric or enterogenous cysts (10). The former designation emphasizes the relationship of these cysts to neurenteric canal formation and regression. Indeed, most neurenteric cysts occur

anterior to the spinal cord in the region of the posterior mediastinum, and may be associated with anterior vertebral defects. "Enterogenous" emphasizes the derivation of these cysts from primitive foregut without reference to a specific embryologic event. Although these cysts may be encountered throughout the neuraxis, they rarely present diagnostic difficulties.

Arachnoid, ependymal, and choroid plexus cysts are very rarely seen in surgical practice, and the reader is referred elsewhere for a discussion of these entities (11).

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Table 27-2
Epithelial Cysts of the Neuraxis

	<i>Location</i>	<i>Lining</i>
Rathke	Sellar	Cuboidal/columnar
Colloid	Third ventricle	Cuboidal/columnar
Enterogenous	Spinal	Cuboidal/columnar
	Posterior fossa	
Epidermoid	Cerebellopontine angle	Squamous
	Skull	
Dermoid	Fontanelle	Squamous
	Spinal	(+ adnexa)

28 Melanocytic Lesions

WHILE METASTATIC MALIGNANT melanomas are the most common pigmented lesions encountered in the nervous system, their histopathologic features are well known to the surgical pathologist. This chapter will focus on two distinctive, but rarely encountered melanocytic CNS lesions: (1) meningeal melanocytoma and (2) meningeal melanocytosis. As the names imply, the former lesion presents as a meningeal mass, while the latter involves the meninges in a more diffuse fashion.

Meningeal melanocytomas were originally classified as pigmented or melanotic meningiomas, to emphasize their leptomeningeal location and to clearly distinguish them from malignant melanomas. Subsequent ultrastructural studies demonstrated that the proliferating cells were melanocytic rather than meningothelial, and the name “meningeal melanocytoma” was introduced (1). While the former appellation persists in some areas, review of these cases generally demonstrates ultrastructural and immunocytochemical features more consistent with melanocytic derivation. Thus, the majority of benign, pigmented, meningeal-based tumors are best designated as meningeal melanocytomas.

While the distinction from malignant melanoma may in some cases be difficult, awareness of this benign entity is usually all that is needed to arrive at a correct diagnosis (2). A whorling pattern of variably-pigmented spindle cells surrounded by heavily pigmented tumor cells is felt to be most characteristic of the (low-grade) melanocytoma (Figs. 28-1 and 28-2) (3). These tumors also demonstrate bland cytologic features and very low mitotic rates, without necrosis or CNS invasion. The presence of cytologic atypia, increased mitotic activity ($>3/10$ hpfs), coagulative tumor necrosis, and CNS invasion is characteristic of primary leptomeningeal melanoma (3). A small number of cases may show some of those features of malignancy, but not others. These rare tumors have been designated “melanocytic neoplasms of intermediate grade” (3). It is

noteworthy that even those tumors falling into the “malignant” category neither look nor behave as aggressively as cutaneous malignant melanomas, with long term disease-free survivals following total resection. It has been suggested that the behavior of these tumors more closely resembles ocular melanocytic neoplasms, which are also frequently cured with total resection (3). Any age group may be affected, as meningeal melanocytomas have been reported in children as young as nine and in adults in their eighth decade of life (4). Approximately half arise intracranially, with most of these occurring in the posterior fossa. The other half arise within the spinal canal, generally as intradural, extramedullary masses in the cervical and thoracic regions, often attached to nerve roots. Females predominant in both regions by about 2:1 (5). While most meningeal melanocytomas occur without cutaneous stigmata, some patients have pigmented skin lesions, which raises the possibility of metastatic malignant melanoma and/or a neurocutaneous syndrome. Once again, it is the relatively benign cytologic and architectural features that distinguish primary meningeal melanocytic tumors from malignant melanomas.

While melanotic meningiomas probably don’t exist as a separate entity, melanocytic schwannomas probably do (Fig. 28-3) (6). As Schwann cells are individually enveloped by basal laminae, laminin immunohistochemistry and/or ultrastructural examination for these basal laminae can distinguish melanocytic schwannomas from menin-

Table 28-1
Melanocytic Neoplasms

Melanocytoma
Malignant melanoma
Melanocytic schwannoma
Psammomatous melanocytic schwannoma
Meningeal melanocytosis

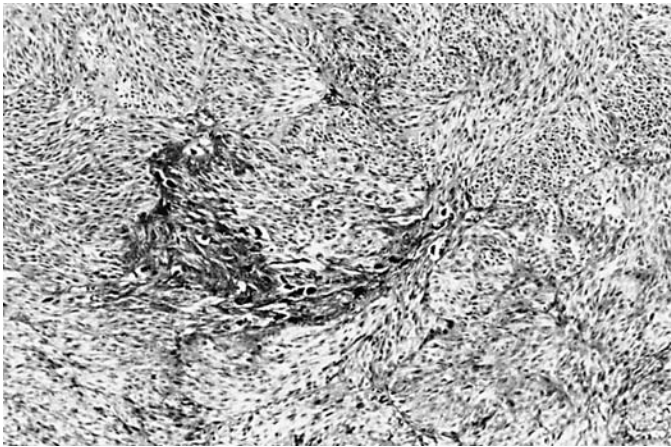


Fig. 28-1. Spindle cell nests with variable pigmentation in a meningeal melanocytoma.

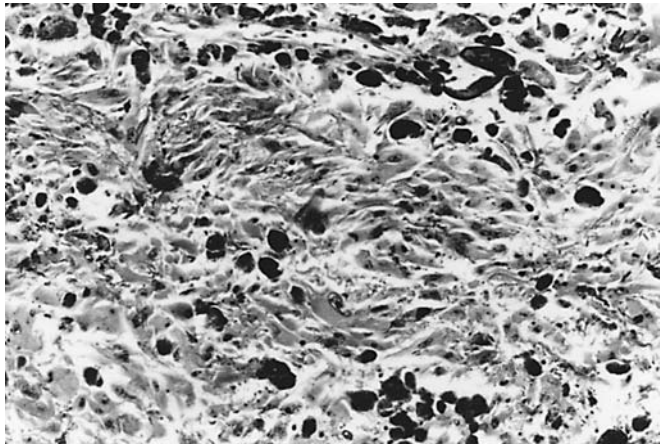


Fig. 28-4. Dense melanin pigmentation in a psammomatous melanocytic schwannoma.

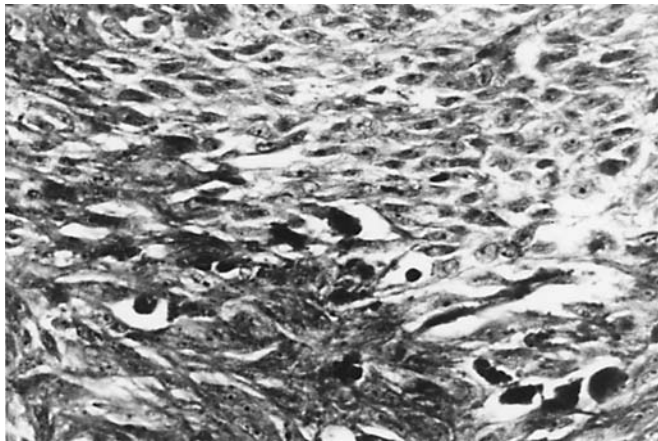


Fig. 28-2. Lack of cytologic atypia in a meningeal melanocytoma.

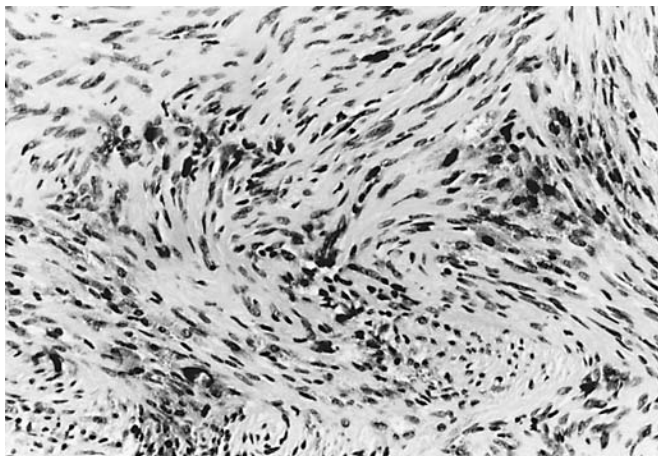


Fig. 28-3. Focal melanin production in an otherwise typical schwannoma.

geal melanocytomas. The rare, but distinctive, psammomatous melanocytic schwannoma is more easily recognized (Fig. 28-4), and may be associated with Carney's complex (myxomas, spotty pigmentation, endocrine overactivity, and sometimes multiple psammomatous melanotic schwannomas). These tumors often demonstrate more aggressive behavior, with a tendency to recur and metastasize (7).

Meningeal melanocytosis defines a set of lesions characterized by a diffuse proliferation of melanocytic cells within the leptomeninges without a dominant mass lesion (8). Presentation is generally in childhood, and manifests as increased intracranial pressure with hydrocephalus. Neuroimaging studies often demonstrate diffuse meningeal enhancement, and CSF cytology is often positive. While the initial impression of the CSF cytology may be large cell lymphoma or "atypical mononuclear cells," the presence of numerous irregular cytoplasmic projections and/or intracellular pigment will usually divulge the true nature of the abnormal cells (Fig. 28-5). Immunocyto-

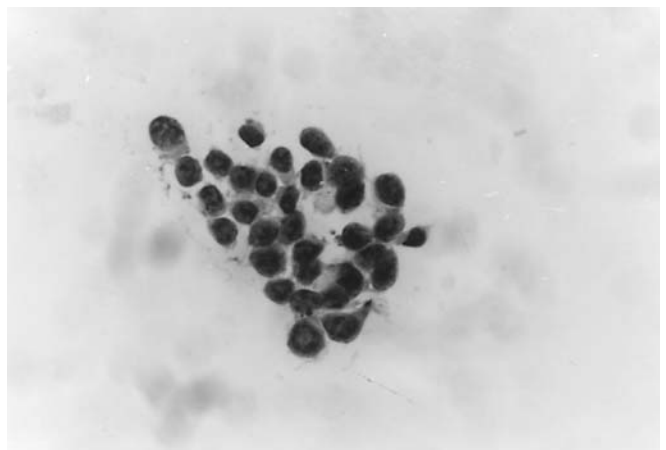


Fig. 28-5. Cerebrospinal fluid in meningeal melanocytosis.

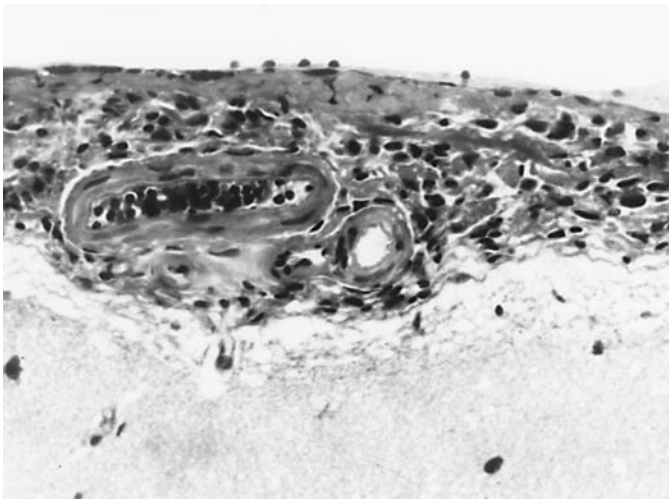


Fig. 28-6. Proliferation of abnormal melanocytic cells within the subarachnoid space in meningeal melanocytosis.

chemical staining may also be useful, as melanocytic cells will usually react with antibodies to S100 protein, and are also often reactive with HMB-45 antibodies.

On brain biopsy, meningeal melanocytosis characteristically appears as a band of pigmented cells within the meninges, sometimes tracking along Virchow-Robin spaces (Fig. 28-6). The main differential diagnostic consideration is superficial siderosis due to chronic leakage of blood into the CSF, which may (ironically) accompany meningeal melanocytomas (9). Histochemical stains for iron and melanin easily resolve this differential. Additional support for the diagnosis of meningeal melanocytosis can be obtained by immunocytochemical reactivity for S100 protein and/or HMB-45. If the proliferative nature of the biopsied lesion is in question (are these just normal pial melanocytes?), positive MIB-1 immunostaining may be helpful.

While the proliferating cells may appear cytologically benign, meningeal melanocytosis is a lethal disorder, with death often occurring within a year of diagnosis (8). While the possibility of leptomeningeal metastasis from a cutaneous melanoma should always be considered, this is particularly important in case of melanocytosis with more overtly malignant appearing cytologic features, also referred to as primary leptomeningeal melanoma (10).

Leptomeningeal melanocytosis may occur either as an isolated entity or as part of neurocutaneous melanosis, which includes multiple or vary large congenital nevi. In these patients, metastatic malignant melanoma must be excluded based on the histologic and cytologic features seen within either the leptomeningeal or cutaneous biopsy specimens.

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29 Paranganglioma

PARAGANGLIOMAS ARE NEUROENDOCRINE neoplasms which can arise in multiple locations throughout the body, including the adrenal gland, head and neck region, respiratory tract, genitourinary system, mediastinum, and rarely the central nervous system. The vast majority of paragangliomas involving the central nervous system arise in the intradural space of the spinal cord and in the filum terminale region (1–5). Less frequently, paragangliomas have been described involving the intracranial region, sellar, and suprasellar locations (6–8). Most patients with paragangliomas present in the fourth to sixth decades of life with signs and symptoms related to lower back pain, motor and sensory deficits, or urinary and/or fecal incontinence (1,2). Radiographically, paragangliomas appear somewhat discrete, with areas of contrast enhancement (9). Tumors grossly are often well-circumscribed and frequently encapsulated.

The most classic pattern encountered in paraganglioma is the nested or zellballen architectural pattern (Fig. 29-1). Cellular nests are separated by delicate fibrovascular septa. Cells are generally rounded in contour with clear to slightly eosinophilic cytoplasm and round to oval nuclei (Fig. 29-2). Occasionally, prominent nuclear pleomorphism may be observed (Fig. 29-3). Cells may be arranged in ribbon-like, adenomatous, or spindle cell configurations. Vessels may show prominent perivascular, hyalinized sclerosis (Fig. 29-4). Focal areas of pseudopapillary formation with perivascular myxoid change, somewhat reminiscent of the myxopapillary ependymoma, can also be encountered (Fig. 29-5). A subset of tumors may show definite evidence of ganglionic differentiation (10). Rarely oncocytic change or melanin pigmentation has been described (2,11).

The vast majority of the paragangliomas stain positively for markers of neuroendocrine differentiation including neuron specific enolase, synaptophysin, and chromogranin. Classically, they demonstrate argyrophilia

on a Grimelius stain. The sustentacular cells of the tumor stain positively for S-100 protein (Fig. 29-6) and also demonstrate glial fibrillary acidic protein (GFAP) positivity. Less commonly, focal staining with a variety of substances including somatostatin, serotonin, leu-enkephalin, and neurofilament protein have been observed. The circumscription of most paragangliomas makes the tumor amenable to surgical resection. Those patients whose tumors are completely resected do well clinically. Cases which are not completely resected may recur; rare cases of metastasis and fatality have been described (1,2).

The major differential diagnostic consideration, given the typical central nervous system clinical presentation and location of paraganglioma, is myxopapillary ependymoma. These two lesions are compared and contrasted in Table 29-1. There is considerable clinical overlap between the two lesions and both do well clinically following gross total excision. Histologically, paraganglionic cells are more commonly arranged in a nested pattern as opposed to myxopapillary ependymomas. Mucoid

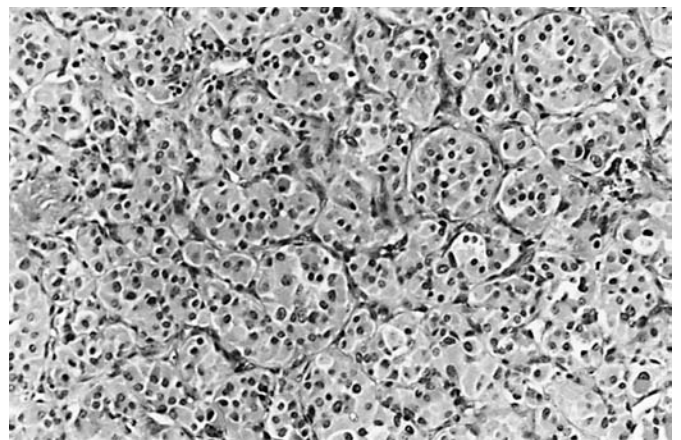


Fig. 29-1. Nested or zellballen architectural pattern of a paraganglioma.

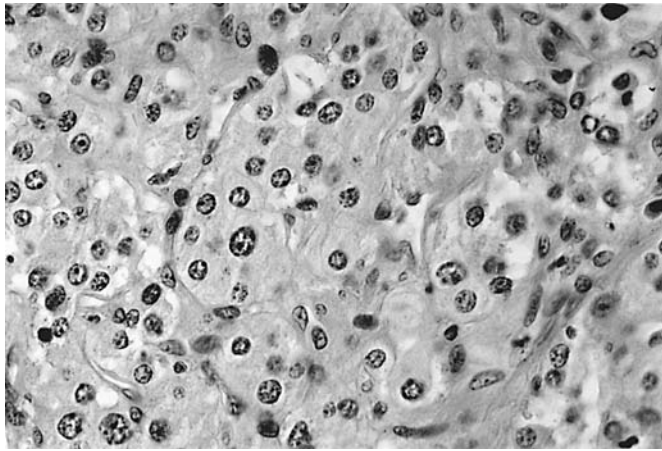


Fig. 29-2. Abundant cytoplasm and generally round to slightly oval nuclei in a paraganglioma.

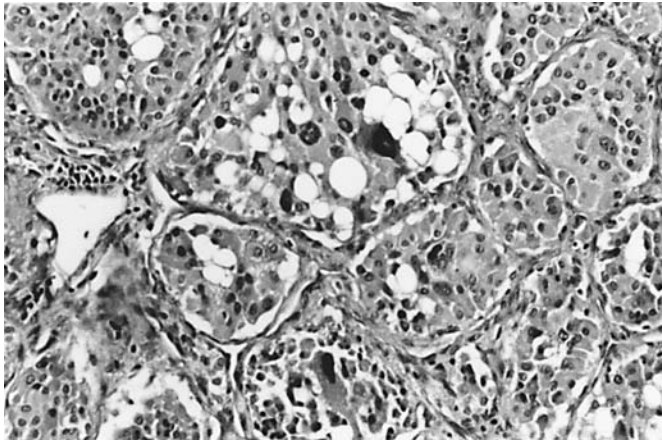


Fig. 29-3. Scattered cells demonstrating prominent nuclear pleomorphism in a paraganglioma.

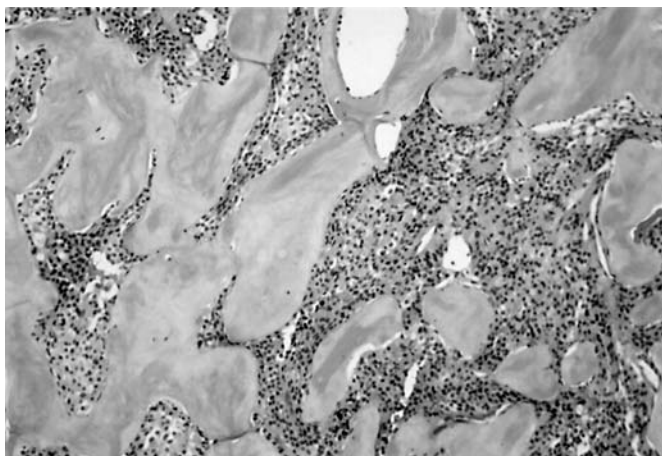


Fig. 29-4. Prominent perivascular, hyalinized sclerosis in a paraganglioma.

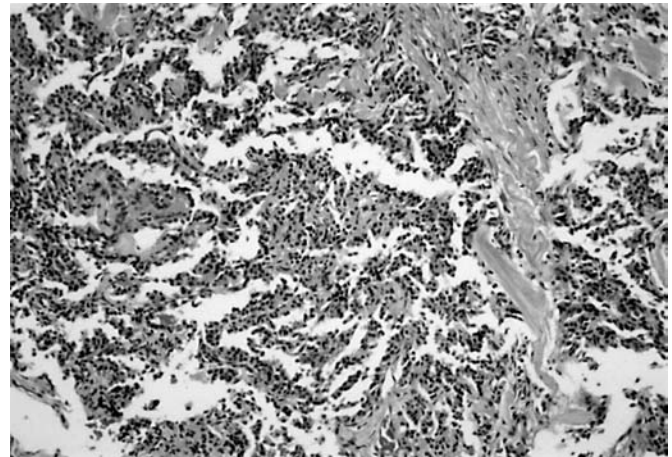


Fig. 29-5. Pseudopapillary architectural pattern in paraganglioma.

stroma, which is very characteristic of myxopapillary ependymoma, is only rarely encountered in paraganglioma. Ganglionic differentiation, when evident histologically, is a feature of paraganglioma as opposed to myxopapillary ependymoma. Immunohistochemical and ultrastructural studies can very easily resolve the difference. Only the sustentacular cells in paraganglioma stain positively for GFAP and S-100 protein, in contrast to the diffuse positive staining observed with GFAP in a myxopapillary ependymoma. Grimelius staining, staining for neuroendocrine markers by immunohistochemistry and electron microscopic evidence of neuroendocrine differentiation also allow for the distinction. In contrast to ordinary types of ependymoma, paragangliomas lack perivascular pseudorosettes or true ependymal rosettes. Rarely, other lesions may be entertained in the differential diagnosis such as meningioma or a peripheral nerve sheath tumor. In both of these cases, the immunohistochemical profile of paraganglioma should be characteristic enough to allow the distinction.

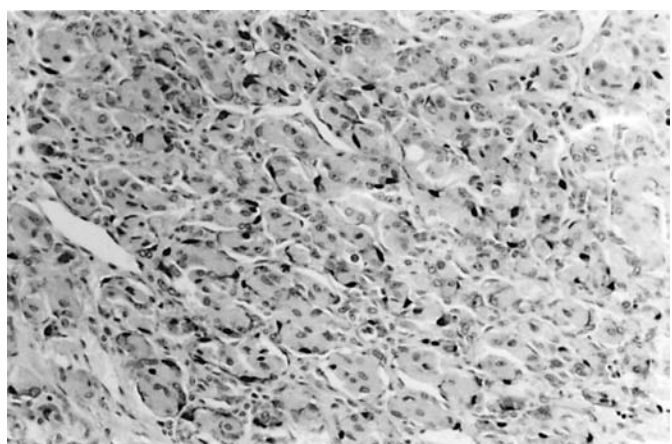


Fig. 29-6. S-100 protein positive staining sustentacular cells in a paraganglioma.

Table 29-1
Paraganglioma Versus Myxopapillary Ependymoma

	<i>Paraganglioma</i>	<i>Myxopapillary Ependymoma</i>
Peak age	4–6 th decades	Young adults
Location	Cauda equina	Cauda equina
Presentation	Lower back pain	Lower back pain
Papillary architecture	– (rarely pseudopapillary)	±
Zellballen architecture	+	–
Rosettes/pseudorosettes	–	–
Vascular hyalinization	±	±
Mucoid stroma (mucin +)	Rarely +	+
Nuclear pleomorphism	±	±
Mitoses	±	±
CSF protein	Increased	Increased
Encapsulated	+	±
Ganglionic differentiation	±	–
Neurosecretory granules on electron microscopy	+	–
GFAP	– (sustentacular cells +)	+
S-100	– (sustentacular cells +)	+
Grimelius	+	–
Neuron specific enolase	+	–
Prognosis	Good	Good

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30 Chordoma

AS THE NAME IMPLIES, the notochord is a cord of cells originating from the (ectodermally derived) primitive node. The notochord arises during early embryogenesis and is responsible for inducing neuralization of adjacent ectoderm (to form the primitive neural tube) and chondrification of adjacent mesoderm (to form the spinal column). Once these tasks are accomplished, the notochord is supposed to regress without leaving a trace. It has long been recognized, however, that remnants of the notochord may persist, especially at its rostral (skull base) and caudal (coccyx) ends (1). Small masses of notochordal remnants (called *ecchordoses physaliphora*) (Fig. 30-1) may then give rise to tumors of low malignant potential, appropriately named chordomas. Not surprisingly, these tumors are virtually confined to the midline of the body and occur most frequently in the sacrococcygeal region (approximately 50% of cases) and skull base (approximately 30% of cases) (2). It is in this latter location where the chordoma usually comes to the attention of the surgical neuropathologist, as it is one of the most commonly encountered skull base tumors (3,4). While intracranial chordomas generally present in adults (most series report an average age of around 40 years), they may also be seen in children, where they tend to pursue a more aggressive course (5,6). We must, therefore, always consider chordomas when examining midline skull base (clival) tumors, particularly in young and middle-aged adults. Typical chordomas are composed of lobules of cohesive polygonal cells arranged in nests and cords embedded in a mucopolysaccharide matrix (Fig. 30-2). Cells with numerous intracytoplasmic vacuoles (*physaliferous cells*) may be conspicuous, both on histologic and cytologic preparations (Fig. 30-3). Mitotic activity is variable, and has not been correlated with clinical behavior (although a recent small study of intracranial chordomas showed a significantly higher labeling index with the cell-cycle marker MIB-1 in chordomas which subsequently recurred within the

study period) (7). Coagulative tumor necrosis is unusual, and may portend a more aggressive course. Similarly, rare tumors may show sarcomatous transformation, and have been referred to as “dedifferentiated” chordomas, analogous to the terminology used for similarly afflicted lipomatous and cartilaginous tumors (8,9).

Approximately 10–20% of skull base chordomas show “chondroid” areas consisting of single lacunar-like cells in a bluish, hyaline extracellular matrix (Fig. 30-4). Such areas may be seen focally or compose up to 90% of the tumor. While it was initially felt that such tumors, termed “chondroid chordomas,” comprised a distinct entity with a more favorable prognosis, subsequent immunocytochemical studies have demonstrated (10):

1. Chondroid appearing areas within typical chordomas are immunocytochemically identical to non-chondroid areas (cytokeratin and S-100 positive).
2. Chordomas with chondroid appearing areas need to be distinguished from skull base chondrosarcomas (cytokeratin negative, S-100 positive) which are

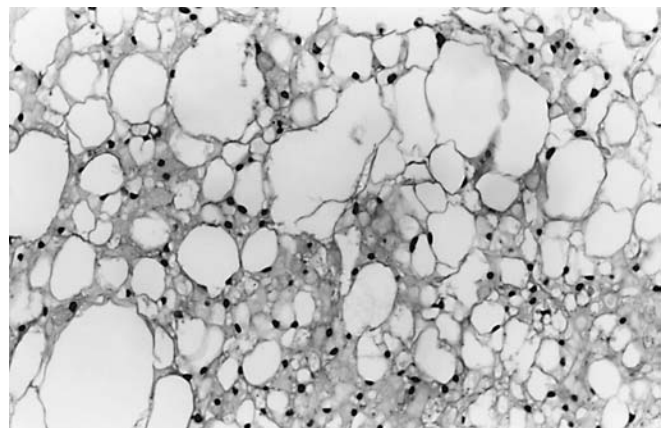


Fig. 30-1. Benign notochordal remnant (*ecchordosis physaliphora*).

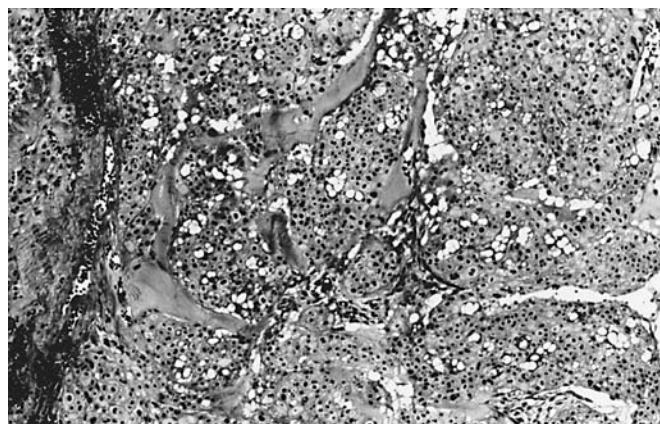


Fig. 30-2. Nests of epithelioid cells within a mucopolysaccharide matrix in a chordoma.

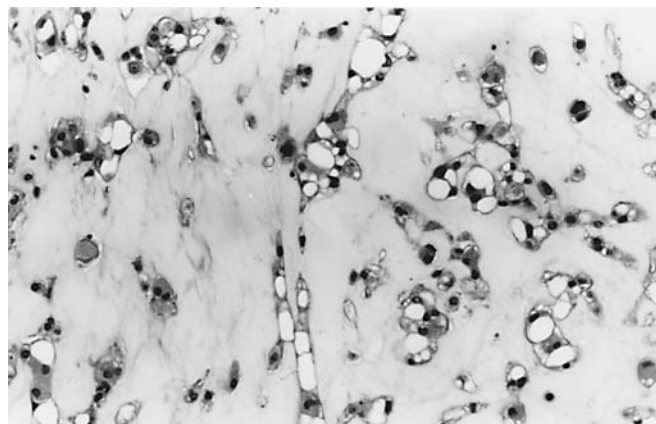


Fig. 30-4. Hyalinized areas within a chordoma resembling chondrosarcoma.

felt to have a more favorable prognosis (Table 30-1).

In the hopes of clearing up some of the confusion regarding these tumors, it has been proposed that chordomas containing cytokeratin positive areas resembling cartilage be referred to as “hyalinized chordoma” (10).

Meningiomas may rarely possess a chordoid appearance (“chordoid meningioma”). Chordoid meningiomas present in younger individuals, and may be associated with polyclonal gammopathy and/or anemia (Castleman syndrome) (11). Compared with chordomas, chordoid meningiomas typically behave in a benign fashion, and thus do not generally require post-operative radiation therapy. Careful histopathologic analysis usually reveals areas recognizable as meningioma within this variant. In difficult cases, cytokeratin immunocytochemistry may be useful, as tumor cells are positive in the vast majority of chordomas and only rarely and focally so in meningiomas (11,12).

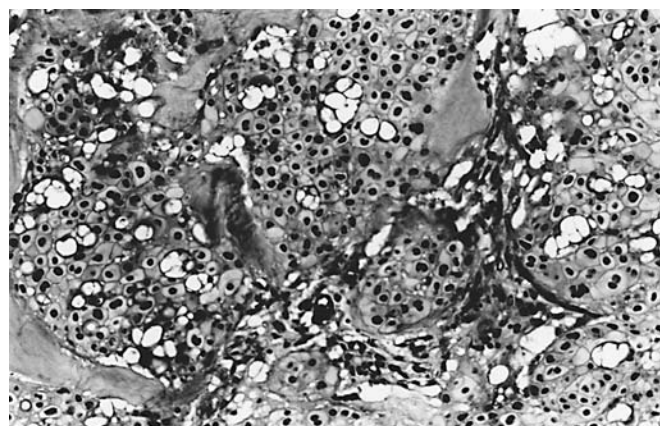


Fig. 30-3. Physaliferous cells in a chordoma.

Another rare, benign entity which must be kept in mind when examining skull base tumors is the chondromyxoid fibroma. These tumors consist of lobules of chondroid or myxoid tissue delineated by relatively hypocellular bands of fibrous tissue. Chondromyxoid fibromas lack the large epithelioid cells typical of chordomas, and do not react with cytokeratin antibodies (13). Therefore, as is the case in so much of surgical pathology, the differential diagnosis is not usually difficult, as long as it is considered.

While not a “skull base tumor”, the recently described third ventricular chordoid glioma is a midline tumor which may closely resemble a chordoma (hence its name) (14). These generally present as suprasellar or hypothalamic masses in adults. They are sharply delineated from the surrounding brain and are composed of epithelioid cords and nests of cells arranged in a somewhat basophilic vacuolated extracellular matrix. Lymphoplasmacytic infiltrates are scattered throughout the tumor. Chordoid gliomas are strongly and diffusely immunoreactive with antibodies to glial fibrillary acidic protein, and weakly to nonimmunoreactive with antibodies to epithelial membrane antigen, thus allowing ready distinction from classic chordomas.

Table 30-1
Chordoma Versus Chondrosarcoma

	<i>Chordoma</i>	<i>Chondrosarcoma</i>
Matrix	Usually myxoid	Chondroid
Epithelioid cords	+	±
Cytoplasmic vacuolation	+	±
S-100 protein	+	+
Cytokeratin	+	—
EMA	+	—

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31 Tumor-Like Demyelinating Lesion

WHILE THERE ARE PLENTY OF diagnostic pitfalls to avoid during neurosurgical intraoperative consultation, opportunities to really screw up are, thankfully, few and far between. Perhaps the prototype for this rather unpleasant situation is, for lack of a better name, the tumor-like demyelinating lesion (TLDL).

Beginning in the late 60's, reports of tumor-like presentations of multiple sclerosis began to emerge in the literature (1). Codification of this entity was not forthcoming until 1993, when Dr. John Kepes added to his catalog of landmark articles a study of 31 patients with tumor-like demyelinating lesions of the brain (2). Patients with TLDLs vary widely in age (from the 2nd to 8th decades), although most present between the ages of 20 and 50. So far, there appears to be a moderate female predominance. The majority of biopsied patients present with single focal lesions, although a small number may be biopsied in the face of multiple lesions, depending on the clinical and radiographic features of the lesions. Most of these solitary lesions are seen in the subcortical white matter (similar to gliomas), although any region of the central nervous system, including the spinal cord (3), may be involved. TLDLs may show a broad spectrum of imaging characteristics, including many felt to be characteristic of malignant neoplasms (peripheral edema, mass effect, ring enhancement and central "necrosis") (4).

The clues to correct pathologic diagnosis of demyelinating disease versus tumor have been eloquently enumerated by Dr. David Zagzag (5). His analysis centered on permanent sections, which emphasizes the level of difficulty which may be encountered with many of these lesions. Five pathologic findings in TLDLs may create difficulties (Figs. 31-1 and 31-2):

1. Hypercellularity
2. Astrocytic pleomorphism
3. Microcystic change

4. Astrocytic mitoses
5. Necrosis

The first three features paint a typical picture of an astrocytic glioma. The presence of mitoses would upgrade that to anaplastic astrocytoma, and the presence of necrosis could lead to the erroneous diagnosis of glioblastoma multiforme.

Four histopathologic features suggest that a clinically diagnosed "tumor" is not a neoplasm (Table 31-1):

1. Abundant lipid-laden macrophages
2. Evenly spaced astrocytes with well developed processes
3. Sharp demarcation
4. Perivascular chronic inflammation

While the presence of perivascular chronic inflammation would appear to be an obvious tip-off that the lesion is nonneoplastic, it is a cruel irony that the tumor for which demyelinating plaques are most often mistaken (the

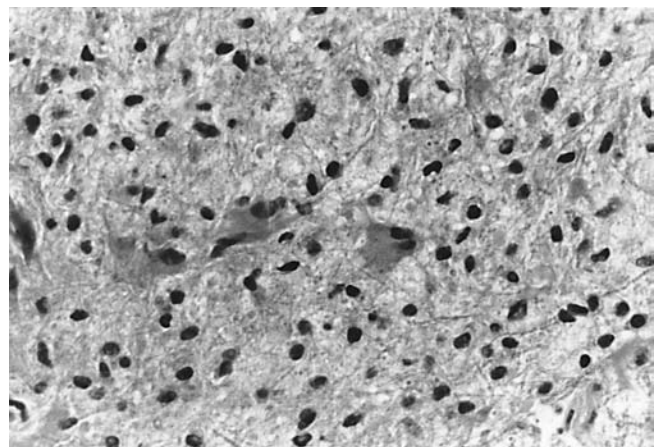


Fig. 31-1. Hypercellularity with astrocyte pleomorphism in a tumor-like demyelinating lesion.

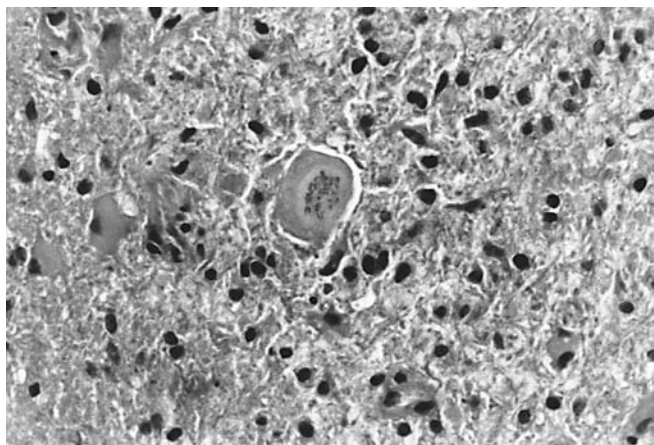


Fig. 31-2. Astrocyte mitosis ("Creutzfeldt cell") in a tumor-like demyelinating lesion.

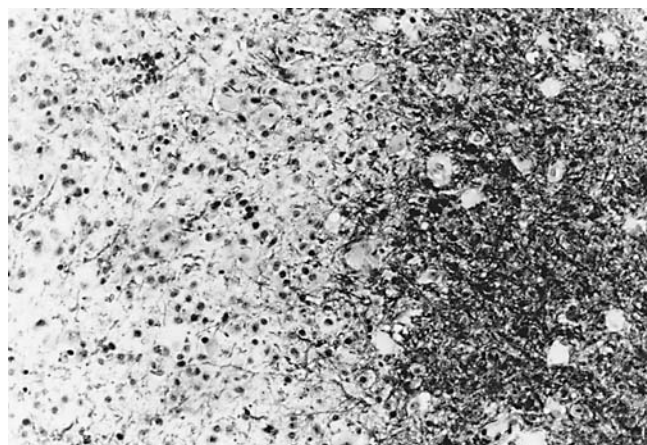


Fig. 31-3. Sharp demarcation between a tumor-like demyelinating lesion and adjacent brain (Luxol fast blue stain).

gemistocytic astrocytoma) is one of the few CNS tumors in which abundant perivascular lymphocytic infiltrates are characteristic. A sharp border between the hypercellular lesion and the surrounding normal appearing brain parenchyma is extremely helpful when present (Fig. 31-3). The unusual gliomas that tend to show similar demarcation are usually otherwise histologically dissimilar from those confused with demyelinating plaques, with the exception of the lipid-rich epithelioid glioblastoma multiforme (6). Distinguishing reactive gemistocytes from neoplastic gemistocytes is an inexact science to say the least, and considerable experience is required to acquire even a moderate degree of confidence in this endeavor. Our most reliable differentiating feature is, therefore, the presence of lipid-laden macrophages - or more saliently, the *recognition* of lipid-laden macrophages within the lesion (Fig. 31-4). As astrocyte lipidization may be encountered in both low- and high-grade gliomas (6), we must take a few moments to be sure the lipid-laden cells we are examining are, in fact, macrophages. On permanent sections, immunohistochemical staining (e.g., HAM56) may be used for confirmation (7). Intraoperatively, careful examination of cytologic preparations, particularly with regard

to nuclear morphology and the presence or absence of eosinophilic glial filaments will usually reliably differentiate lipid-laden macrophages from lipidized astrocytes (Fig. 31-5) (8). We must also keep in mind that macrophages can infiltrate the site of a previous biopsy, so awareness of this possibility is paramount during intraoperative consultation.

Although it has frequently been stated that foamy macrophages are never seen in gliomas, we and others have rarely encountered this difficulty. As with other intraoperative consultative work, when in doubt we should err on the conservative side. If permanent sections support a malignant brain tumor, it is a relatively simple matter to go back and resect the lesion (particularly if an approach has already been made). It is considerably more difficult to replace inappropriately resected brain tissue. As in other branches of surgical pathology, no diagnosis is occasionally preferable to a wrong diagnosis. It is equally important that the appropriate diagnosis be made on per-

Table 31-1
Tumorlike Demyelinating Lesion (TLDL) Versus Glioma

	TLDL	Glioma
Pleomorphism	+	+
Microcystic change	+	+
Mitotic figures	±	±
Lipidized astrocytes	±	±
Lipidized macrophages	+	Rare
Perivascular lymphocytes	+	±
Reactive astrocytes	+	±
Sharp demarcation	+	Rare
Response to preoperative steroids	Often marked	Mild to moderate

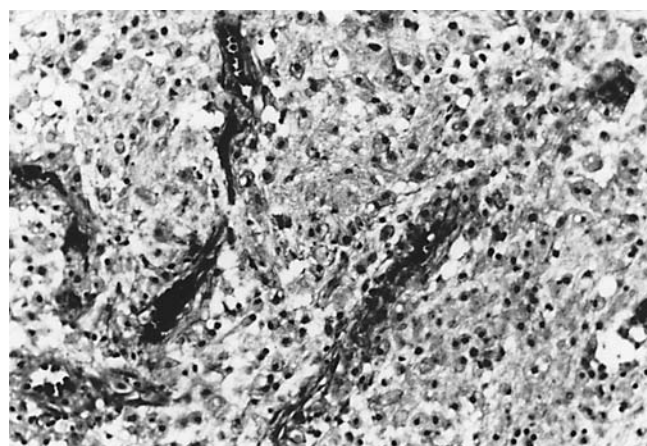


Fig. 31-4. Abundant lipid laden macrophages in a tumor-like demyelinating lesion.

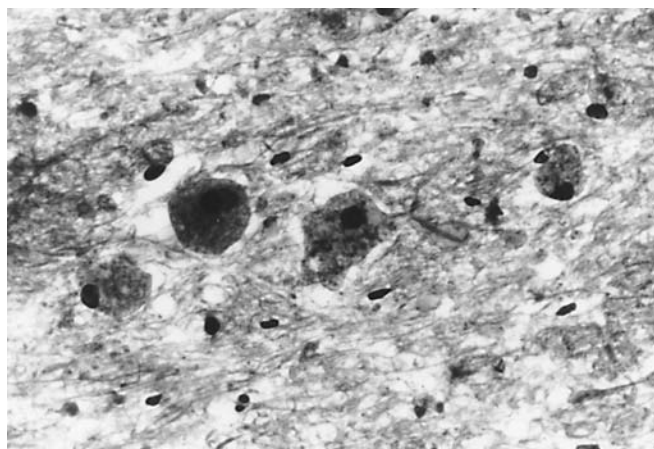


Fig. 31-5. Intraoperative smear preparation demonstrating lipid laden macrophages in a tumor-like demyelinating lesion.

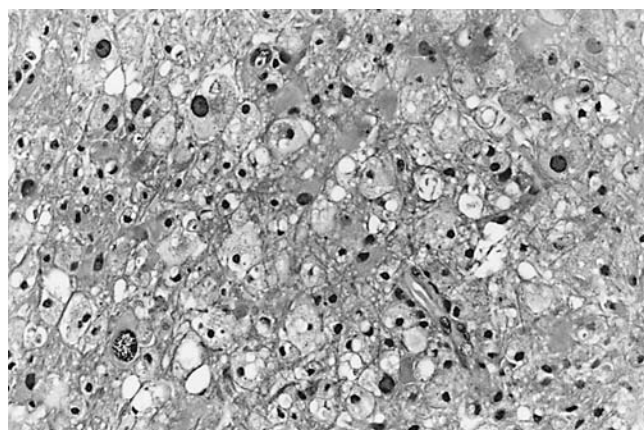


Fig. 31-6. Demyelination with enlarged oligodendroglial and astrocyte nuclei in progressive multifocal leukoencephalopathy.

manent sections, as radiation therapy appears to be detrimental in patients with demyelinating lesions (9).

A benign lesion which needs to be considered in the differential diagnosis of TLDLs is an organizing cerebral infarct. Although distinguishing these two nonneoplastic lesions is not imperative at the time of operation, the presence of a cerebral infarct generates a different array of diagnostic and therapeutic options. It is important therefore, to resolve these two lesions on permanent sections. Histochemical or immunohistochemical staining for axons may be useful in distinguishing these possibilities. However, it must be kept in mind that axons are only relatively spared in demyelinating diseases. We know from studies of multiple sclerosis patients that significant axonal damage may occur, particularly in severe, acute lesions (10). TLDLs probably represent the pinnacle of acuteness and severity in demyelinating lesions. Therefore, considerable axonal damage may be encountered. Nevertheless, distinguishing between TLDLs and organizing infarcts is usually relatively easy (even without special stains) as the latter demonstrate virtually total absence of astrocytes and axons within the central portion of the lesion. Progressive multifocal leukoencephalopathy due to infection with the polyoma JC virus must be considered in the differential diagnosis of TLDLs in immunosuppressed and elderly patients (11). In these instances, a careful search for oligodendroglial and/or astrocytic cells with enlarged, virally infected nuclei is usually rewarding (Fig. 31-6) (12). In recalcitrant cases, immunohistochemical (13) and/or molecular biologic methods (14) may be employed to secure a definitive diagnosis.

Interestingly, it appears that many, if not most, patients with TLDLs do not go on to develop further demyelinating lesions. In other words, they do not have multiple sclerosis. The pathogenesis of these lesions is currently poorly understood. Patients treated with a combination of levami-

sole and fluorouracil may develop multifocal inflammatory demyelinating lesions similar to multiple sclerosis (15). TLDLs may rarely be associated with systemic malignancies, raising the possibility of a paraneoplastic etiology (16). In addition, a rare complication of these lesions is subsequent development of primary CNS lymphoma, often in a different location within the brain (17). For the most part, however, we have the rare opportunity to provide the surgeon (and patient) with two pieces of good news: it's not a tumor, and it probably is not multiple sclerosis.

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32 Vascular Malformations

DESPITE THE RECENT ONSLAUGHT of publications dealing with “mixed” vascular malformations (1–3), four basic types of vascular malformation are recognized (4): arteriovenous malformations (AVMs), cavernous malformations (CMs), venous malformations (VMs) and capillary telangiectases (CTs). AVMs and CMs are commonly encountered surgically, while VMs and CTs are nearly exclusively seen incidentally at autopsy. However, as VMs and CTs may rarely present surgically, and as these latter lesions are often included in descriptions of mixed vascular malformations, all four of these malformations will be discussed and illustrated in this chapter.

By far the most commonly encountered vascular malformation in surgical neuropathology is the AVM. These generally present as hemorrhages or seizures in young adults (5). While most AVMs arise within the territory of the middle cerebral artery, they may be seen anywhere within the neuraxis. Angiographic examination is usually diagnostic. However, AVMs may be angiographically “occult,” presumably due to thrombosis of arterial feeding blood vessels.

AVMs consist of a complex mass of blood vessels and gliotic neural parenchyma (Figs. 32-1 and 32-2). At least some of the blood vessels contain a well-defined (but often abnormal) internal elastic lamina. The vascular media may be replaced by a collagenous scar, or markedly thinned with aneurysmal dilatation. Due to pulsatile arterial flow within the malformation, the neural parenchyma adjacent to the abnormal vessels usually demonstrates reactive astrocytosis (Fig. 32-1). Occasionally, this intervening parenchyma may show a predominance of oligodendroglial-like cells. This pattern may either be a degenerative change due to tissue condensation or represent a related developmental disturbance. Although AVMs have rarely been reported in association with gliomas, the neoplasm in such cases is adjacent to, but not admixed with, the abnormal vessels (6).

Aside from distinguishing AVMs from the other vascular malformations discussed below, care must be taken not to over interpret clusters of normal leptomeningeal blood vessels as evidence of a vascular malformation. Such clusters often occur when the meninges retract as superficial cortical specimens are removed during surgery. While this produces an architectural resemblance to the tangled mass of vessels seen in AVMs, the blood vessel walls appear either normal, show arteriosclerotic vascular disease, or (in the elderly population) demonstrate evidence of amyloid deposition. This last consideration is an important one, as amyloid angiopathy is a common cause of lobar hemorrhage in the older population. We regularly obtain a Congo red stain on any patient over the age of 60 with an unexplained intraparenchymal hemorrhage.

The complex of histopathologic features seen in AVMs may be augmented by prior attempts at therapy via pre-operative embolization and/or stereotactic radiosurgery. Embolization of AVMs with polyvinylalcohol (PVA)

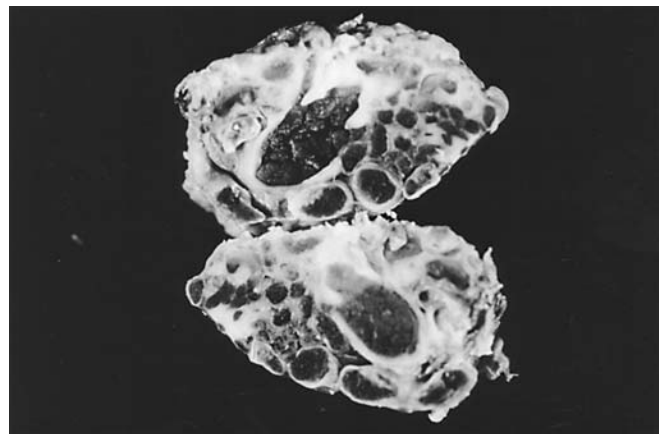


Fig. 32-1. A tangled complex of blood vessels with intervening neural parenchyma characterizes the arteriovenous malformation.



Fig. 32-2. Abnormal arteries and veins with intervening gliotic neural parenchyma forming an arteriovenous malformation.

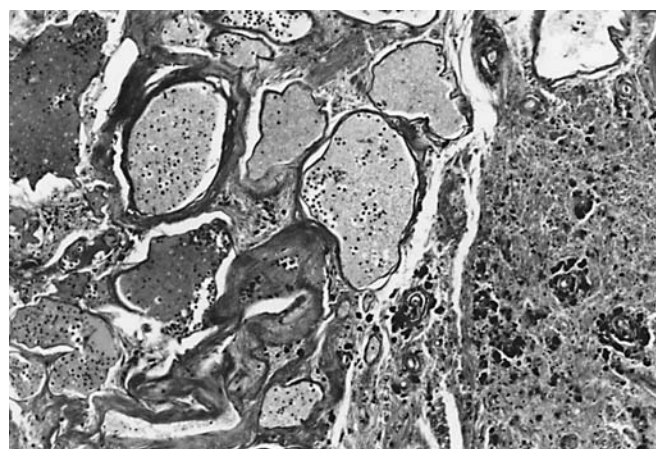


Fig. 32-4. Back-to-back hyalinized vascular spaces with evidence of prior hemorrhage in a cavernous malformation.

induces a foreign body giant cell reaction within embolized vessels. Giant cells may be seen as early as 2 days after embolization. Injury to vessel walls may result in aneurysm formation leading to vascular rupture. This usually takes several weeks to develop, so it has been recommended that the interval between embolization and surgery be kept as short as possible (7). Stereotactic radiosurgery has become the treatment of choice for many AVMs, with obliteration of 75% of cases within about 2 to 3 years. Histopathologically, the procedure induces endothelial damage with intimal smooth muscle proliferation and fibrosis ultimately leading to luminal obliteration. The proliferative/sclerotic changes involve all or nearly all of the circumference of the vessel wall, which allows this process to be distinguished from the usual focal mural proliferations seen in untreated AVMs (8).

The only other vascular malformation encountered with any frequency in surgical neuropathology is the cavernous malformation (also referred to as cavernous angoma).

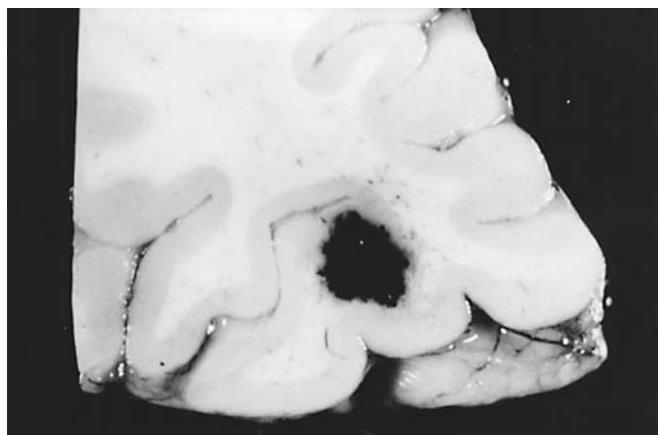


Fig. 32-3. Well circumscribed mulberry appearance of a cavernous malformation.

These are classically angiographically occult vascular malformations which may present with hemorrhage, seizures, or as a mass lesion, usually in adolescents and young to middle-aged adults. CMs are distinguished from the other types of malformations on the basis of a central “nidus”, where the cavernous vascular spaces are separated only by collagenous tissue, without intervening neural parenchyma (Figs. 32-3 and 32-4) (9). When this nidus is obtained surgically, there is little difficulty with the diagnosis. If only the periphery of the lesion is obtained, the presence of the malformation/parenchymal interface may lead to some confusion (10). While the vessels comprising CMs may rarely contain a few elastin fibers, a well defined elastic lamina is never present, nor is a well defined muscular media part of the malformation. Although arterial feeders, and thus pulsatile flow resulting in parenchymal gliosis, are also not present in CMs, these malformations have often bled repeatedly prior to surgery, resulting in hemosiderin and calcium deposition with reactive astrocytosis in the adjacent neural parenchyma. CMs are more often multiple and/or familial than AVMs, underscoring the importance of correctly diagnosing surgically removed vascular malformations (Table 32-1) (11).

Table 32-1
Arteriovenous (AVM) Versus Cavernous (CM) Malformation

	AVM	CM
Angiographic appearance	Usually obvious	Usually occult
Abnormal arteries	+	—
Intervening parenchyma	+	Peripherally
Gliosis	+	±
Calcification	±	±
Hemosiderin	Unusual	Usual
Multiple	Rare	Common
Familial	Rare	Common



Fig. 32-5. Thickened, dilated veins separated by normal neural parenchyma in a venous malformation.

Cerebral venous malformations are usually asymptomatic, and consist of a cluster of abnormally thickened and dilated veins separated by normal appearing neural parenchyma (Fig. 32-5). These “malformations” usually occur secondary to failure of formation of normal regional venous drainage, necessitating an abnormally large amount of blood be drained through too few venous channels. VMs demonstrate a classic angiographic appearance and are not resected except in rare instances of life threatening hemorrhage. In these unusual cases, some authors believe that the hemorrhage derives from an associated CM and not from the venous malformation itself (12). Venous angiomas may also occur within the subarachnoid space of the lower thoracic spinal cord (Fig. 32-6). Such patients may present with paraparesis due to secondary parenchymal cord damage (subacute necrotizing myelopathy of Foix and Alajouine) (13). Spinal vascular malformations may also reside entirely within the cord parenchyma, in which case they present clinically and radiographically as spinal cord neoplasms (14).

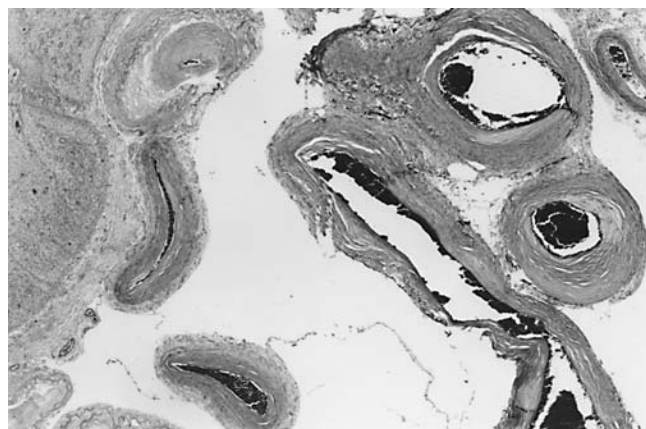


Fig. 32-6. Spinal subarachnoid venous malformation in the Foix-Alajouine syndrome.

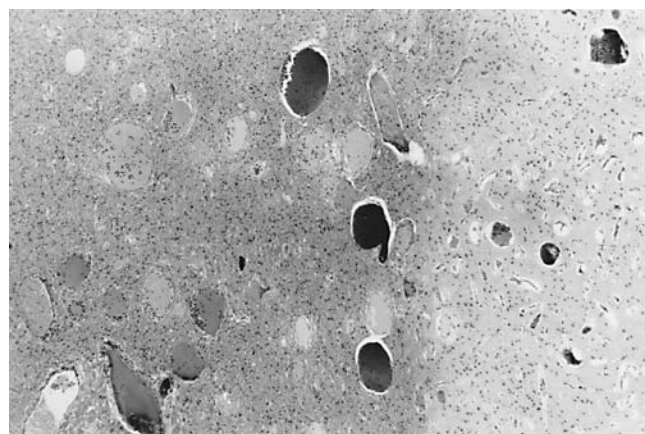


Fig. 32-7. Dilated capillary spaces at the gray/white interface in a capillary telangiectasis.

Last, and least, is the capillary malformation (or telangiectasis). These are identical to VMs with the exception that the vessel walls of capillary telangiectasias are composed of a single layer of endothelial cells devoid of muscle or elastin fibers (Fig. 32-7). As with VMs, clinical symptomatology is currently blamed on coexisting CMs, and is not felt to be related to the telangiectasis itself.

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33 Central Nervous System Vasculitis

P RIMARY ANGIITIS OF THE NERVOUS SYSTEM (PACNS) is a relatively rare disorder, with fewer than 200 pathologically documented cases reported (1). Brain biopsies for PACNS are somewhat less rare, with one large medical center averaging 10 such biopsies per year (2). With the recent and increasing realization that the “classic” angiographic pattern of CNS vasculitis is neither sensitive nor specific for PACNS, it is likely that the number of patients biopsied will increase, as current treatment regimens for PACNS carry significant morbidity and even mortality compared with modern neurosurgical interventions (3).

While in many cases our role may be limited to reading the biopsy, we should be prepared to aid our clinical colleagues in the selection of a biopsy site. Biopsy of the non-dominant temporal tip has been recommended, as alternative processes often involve the basilar meninges (4). However, if the patient demonstrates a focal abnormality on neuroimaging, Sutton’s law (“go where the money is”) is always preferred, except in the rare situation in which the surgeon feels that biopsy of such an area would carry too much risk to the patient. We should always try to insist on a sample from a radiographically abnormal area.

Then comes the great unanswerable question: “How much do you need?” The recommendation in the literature is for a cubic centimeter of cerebral cortex with underlying white matter and overlying meninges (or several healthy stereotactic biopsy cores) (4). In addition, material should be procured in the operating room for microbiologic studies. Due to morphologic difficulties engendered when freezing such specimens, intraoperative diagnostic consultation is generally not a good idea unless the surgeon is willing to keep providing tissue until a diagnosis of vasculitis is clear (we have yet to encounter such an offer). The pathologic specimens should be fixed, thinly sliced perpendicular to the cortical surface, carefully embedded

so as to keep all the specimens oriented and flush with the surface of the block, and serially sectioned.

Despite the initial designation “granulomatous angiitis of the central nervous system,” fewer than 50% of surgically diagnosed cases of PACNS demonstrate granulomatous inflammation (5). It is not clear, at present, whether this represents a sampling problem, a different time point in the evolution of the disease process, or varying pathogeneses. As pathologists, our job is to look for any evidence of vasculitis—inflammation of the vessel wall accompanied by structural injury (Figs. 33-1 and 33-2). The majority of positive biopsies demonstrate a predominantly lymphocytic vasculitis involving small leptomeningeal or intracortical blood vessels, or both. Although veins and venules may be involved, arteritis is much more common. While clinical correlation is required to definitively classify the vasculitis as primary, involvement of small caliber (~50µm) blood vessels is characteristic of PACNS (and the reason why the cerebral angiogram *should* be negative).

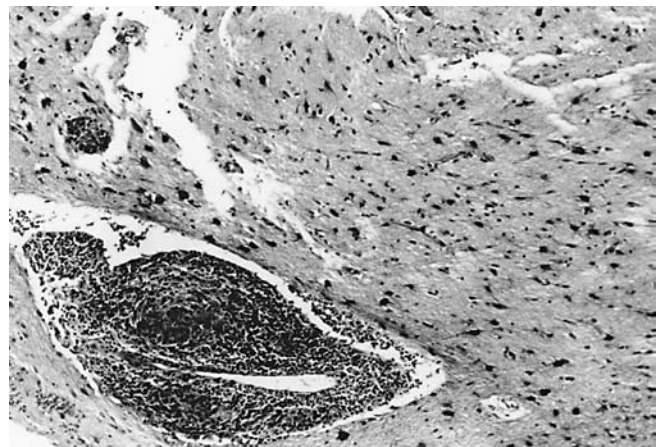


Fig. 33-1. Vasculitis involving a small intracortical arteriole with prominent surrounding astrocytosis.

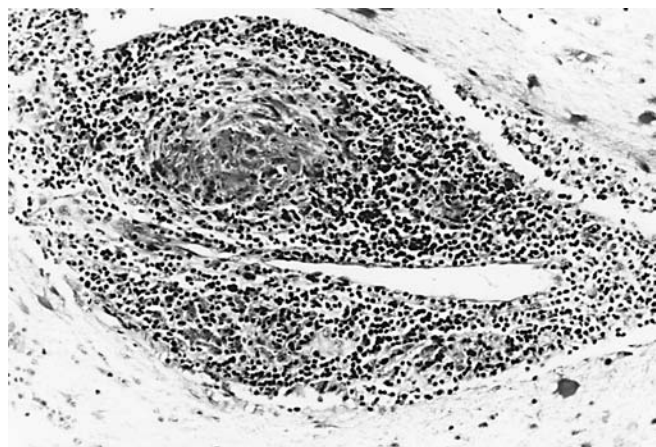


Fig. 33-2. Mural granuloma in primary angiitis of the central nervous system.

Although the histopathologic differential diagnosis of perivascular lymphocytic inflammation is broad, that of true vasculitic involvement is fairly narrow, including lymphoma, infection, and (in cases of granulomatous arteritis) sarcoidosis.

Angiocentric immunoproliferative lesions (AIL), also known as lymphomatoid granulomatosis, are uncommonly encountered in the CNS, although the incidence may be increased in patients with AIDS (6). As in extraneural sites, the distinction between PACNS and AIL is largely cytologic. In problematic cases, molecular diagnostic evaluation of the infiltrates for monoclonality may provide an answer.

Varicella zoster vasculitis may be histologically inseparable from PACNS, either in its granulomatous or non-granulomatous form (7), and may be responsible for apparent associations between PACNS and leukemias, lymphomas, and Hodgkin's disease (8). The clinical history may provide valuable clues, particularly in AIDS and other immunosuppressed patients, where the virus may be disseminated within and outside of the CNS. In problematic cases, molecular diagnostic evaluation for the VZV genome may be performed on CSF or paraffin embedded tissue (9). In the distinctly rare cases of arboviral infection, vasculitis will be accompanied by histopathologic features of encephalitis (parenchymal inflammation with microglial nodules).

While sarcoidosis may present purely within the CNS, such cases nearly always demonstrate granulomatous inflammation unassociated with blood vessels (particularly granulomatous meningitis) in addition to vasculitic involvement (when present) (10). Although it is distinctly unusual to find foreign material, acid-fast bacilli, or fungi within such lesions, each is capable of inducing granulomatous inflammation, and we would be remiss not to search for the former (with and without polarization

microscopy) and stain for the latter. A recent study indicates that patients with pathogen-free granulomatous inflammation of the CNS without clinical or laboratory evidence of pulmonary sarcoidosis are much more likely to follow an aggressive course, including the development of typical CNS vasculitis (11).

Diseases within the clinical differential of PACNS (but with distinctive pathologic features) may be seen within the biopsy specimen. These include arteriosclerotic vascular disease with or without infarction, Alzheimer's disease with or without amyloid angiopathy, and rarely other conditions such as Creutzfeldt-Jakob disease, demyelination, or neoplasia. Interestingly, angiographic abnormalities previously thought to be diagnostic of PACNS are more likely to be encountered in this group of patients (3,6). Among these, the only pathologically problematic cases are those which demonstrate amyloid angiopathy with vascular inflammation. While mild chronic inflammation, including giant cells, may be seen incidentally as a "foreign body" response to the amyloid, patients with cerebral amyloid angiopathy associated with transmural inflammation and a clinical course consistent with PACNS should be treated, as responses to therapy have been documented in such cases (12).

All too often, however, we are left with a normal looking biopsy. While a conscientious attempt at serially sectioning and examining all of the available material is warranted in such cases, herculean efforts are usually unrewarding, especially in the absence of reactive astrogliosis within the brain parenchyma. Fragments of normal appearing, non-reactive brain are usually just that. While the patient may still have PACNS, we can obviously only do the best we can with what we have. In the absence of a competing histopathologic diagnosis, clinicians will often, depending on the severity of the situation, opt to treat empirically and assess the patient for a clinical response.

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34 Granulomatous Inflammation

A LIST OF CONDITIONS THAT are associated with granulomatous inflammation in the central nervous system is somewhat limited and is summarized in Table 34-1. The majority of cases of granulomatous disease are infectious in etiology or represent sarcoidosis. In some of these conditions, such as rheumatoid arthritis and histiocytosis X, granulomatous inflammation is not commonly encountered. Foreign body giant cell reaction does not generally present a diagnostic dilemma. Polarizable suture material, particularly in patients with a prior history of surgery, or foreign material in the case of head trauma, should be recognized in association with the granulomas. A number of a parasites can also result in a granulomatous inflammatory response. Occasionally, a ruptured dermoid cyst can establish a foreign body granulomatous response to extruded keratin material. The presence of small granulomas and giant cells in the setting of a pineal gland tumor should cause one to consider germinoma as a likely diagnosis; occasionally, cases in which biopsy material is comprised entirely of granulomatous inflammation may be encountered (1). Granulomatous vasculitis, outside the setting of an infection or sarcoidosis, is relatively uncommon in the central nervous system. Occasionally Wegener's arteritis can involve the central nervous system or orbit by contiguous spread.

In most instances, the differential diagnosis of granulomatous inflammation concerns infection, particularly mycobacterial infection, and sarcoidosis. Although several mycobacterial organisms can presumably produce granulomatous inflammation, *Mycobacterium tuberculosis* is probably the most commonly recognized. An increasing incidence of extrapulmonary infections, an association with acquired immunodeficiency syndrome, and the fairly recent development of drug resistant strains continues to make tuberculosis of the central nervous system a clinical problem. There are two major pathologic manifestations of tuberculosis infection in the central ner-

vous system: 1) infection involving the leptomeninges with or without secondary ventriculitis, and 2) inflammation confined primarily to the parenchyma, corresponding to a tuberculous abscess or so-called tuberculoma.

Tuberculous meningoencephalitis (2-7) is histologically characterized by a subarachnoid exudate consisting of a mixed acute and chronic inflammatory cell infiltrate. Grossly, the exudate and disease process, when leptomeningeal based, is most prominent at the base of the brain around the interpeduncular fossa. Granulomas seen in this setting may be either necrotizing or non-necrotizing in nature (Fig. 34-1). The cortex subjacent to the leptomeninges frequently shows a prominent reactive astrocytosis, microglial cell proliferation, and variable degrees of perivascular inflammation. Often, there is a vasculitic component associated with the tuberculous meningitis, with inflammation involving both small and medium-sized vessels. Vascular subendothelial proliferation with occlusion of vascular lumina and subsequent infarction are common. Secondary involvement of the ventricular system with hydrocephalus, resulting from impeded cerebrospinal fluid reabsorption or blockage of cerebrospinal fluid flow, may also occur. Unless there is an obvious cause for the granulomatous inflammation (such as foreign body),

Table 34-1
Causes of Granulomatous Inflammation
in the Central Nervous System

Mycobacterial infection
Fungal infection (e.g., Aspergillosis, cryptococcosis)
Sarcoidosis
Foreign body giant cell reaction (such as to suture material, parasites, dermoid cyst rupture)
Granulomatous vasculitis
Germinoma
Rheumatoid arthritis
Histiocytosis X

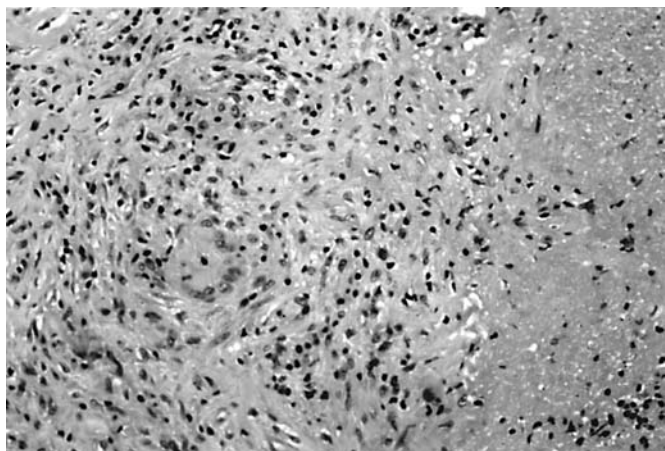


Fig. 34-1. Leptomenigeal necrotizing granulomatous inflammation due to *Mycobacterium tuberculosis*.

stains for microbacterial or microorganisms such as acid fast (Ziehl-Neelsen) or Fite stain, as well as a fungal stain such as a Gomori methanamine silver, should be routinely performed (Fig. 34-2). Unfortunately, the yield on tissue sections for such stains is fairly low and the gold standard for diagnosis still remains culture. Recent advancement in the molecular biology arena may allow for a more timely diagnosis utilizing polymerase chain reaction on cerebrospinal fluid (8). Staining cerebrospinal fluid for organisms generally yields a positive result in less than 25% of cases. In a number of series, mycobacteria were isolated from less than 50% of patients presumed to have disease by clinical criteria. Nevertheless, identification of organisms in tissue specimens may allow for more timely intervention. Identification of granulomas during intraoperative consultation should also prompt recommendation for culture and an appropriate triage of tissue.

Tuberculomas or tuberculous abscesses (9–14) are relatively rare in the United States. The lesions are classically

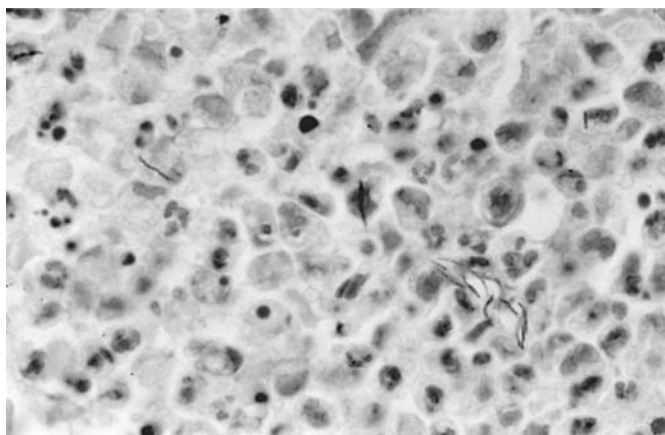


Fig. 34-2. Mycobacterial organisms (*M. tuberculosis*) identified on a Ziehl Neelsen stain in the leptomeninges.



Fig. 34-3. Tuberculous abscess with necrosis, granuloma, and fibrosis.

nodular and fairly discrete in appearance with central chalky caseous material, corresponding to necrosis, and an outer rim of granulation tissue often accompanied by granulomas (Fig. 34-3). Interestingly, tuberculous abscesses frequently are not coexistent with tuberculous leptomeningitis. Most cases of tuberculomas have been described in the first three decades of life and there appears to be a relatively increased frequency of cerebellar involvement by tuberculomas. Additional stains for microorganisms may yield higher positive results in as many as 60% of cases, as compared with the lower positive staining rate encountered in tuberculous meningitis.

The distinction of tuberculous infection in the central nervous system from sarcoidosis is important from a therapeutic standpoint. The diagnosis of neurosarcoidosis (15–19) is often difficult because of the varied and often nonspecific neurological manifestations and presentations. Cerebrospinal fluid abnormalities are quite variable and nonspecific. Involvement of the central and peripheral nervous system in sarcoidosis occurs in approximately 5% of patients with the disease. Cases in which the primary presentation of sarcoidosis has been in the central nervous system have been described. Similar to tuberculous meningitis, sarcoidosis has an affinity for involving the base of the brain, particularly the region of the optic chiasm (Fig. 38-4) and hypothalamus. The most frequent site of involvement in the central nervous system by sarcoidosis is the leptomeninges, but occasional cases may be predominantly parenchymal based or a mixture of parenchymal and leptomeningeal disease. Histologically, sarcoidosis is generally characterized by non-necrotizing granulomatous inflammation, although occasional small foci of necrosis may be seen in association with some granulomas. In general, the granulomata are preferentially perivascular in location and are often associated with a chronic inflammatory cell infiltrate consisting primarily

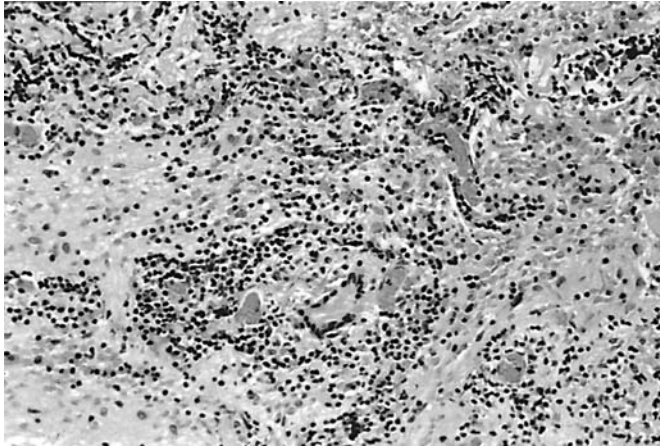


Fig. 34-4. Optic nerve involvement by nonnecrotizing granulomatous inflammation in sarcoid.

of both B and T lymphocytes and monocytes (Fig. 34-5). Vessels may show focal infiltration by inflammatory cells, constituting a non-necrotizing vasculitis. Typically, there is no evidence of mycobacteria or other organisms either by culture or on tissue staining, which should be routinely performed in such cases. Interestingly, a number of studies using polymerase chain reaction have found evidence of mycobacterial DNA in some patients with sarcoidosis, raising interesting questions with regard to the potential relationship of these entities (20–21). The clinicopathologic features of tuberculous infection and sarcoidosis are compared and contrasted in Table 34-2.

The routine evaluation of granulomatous inflammation often starts with a biopsy and intraoperative consultation. Identification of granulomas at the time of intraoperative consultation, without an obvious explanation for their presence i.e. foreign body giant cell reaction or neoplasm, should prompt recommendation for culture, particularly for fungal and mycobacterial organisms. Depending on

Table 34-2
Clinicopathologic Features of Tuberculous Meningitis Versus Sarcoidosis

	<i>Tuberculosis</i>	<i>Sarcoidosis</i>
Age	Any	Usually young adults
Multisystem involvement	+	+
Base of brain	+	+
Meningeal disease	Primary	Primary
Parenchymal disease	+	+ (less frequent)
Acute inflammation	+ (early)	—
Granulomas	+	+
Extensive caseous necrosis	±	—
Hydrocephalus	±	±
Vasculitis	+	± (perivascular inflammation and granulomas)
Cultures	Positive	Negative
AFB/FITE stain	Positive up to 50–60%	Negative

the amount of material available, one may elect to freeze a small piece of tissue for potential molecular biologic identification of mycobacterial organisms, if such technology is readily available (22). Such identification may provide a far quicker diagnosis than waiting up to six weeks for a microbiologic culture result. Tissue processed routinely for light microscopic examination should be carefully evaluated. Routinely, polarization to look for foreign material should be performed. Again, in cases in which there is no obvious etiology for the granulomas, additional stains for mycobacterial and fungal organisms should be routinely performed.

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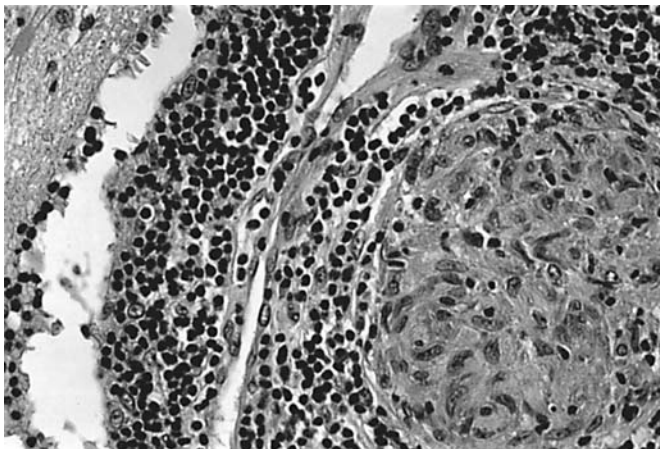


Fig. 34-5. Perivascular nonnecrotizing granuloma in sarcoidosis.

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35 Meningitis, Abscess, and Encephalitis

LEPTOMENINGITIS (PACHYMEMINGITIS, MENINGITIS) is an inflammatory condition involving the leptomeningeal coverings of the brain and spinal cord. The process may be suppurative or nonsuppurative, depending upon the causative organism. Clinically, patients present with fever, headaches, nausea, vomiting, neck stiffness, photophobia, and confusion. The number of routes by which organisms reach the leptomeninges and cause meningitis are several and include hematogenous dissemination, direct implantation due to surgery or trauma, local extension from an adjacent site, structural abnormalities such as neural tube defects, and retrograde ascending infection (usually via the peripheral nervous system as in rabies).

In general, bacterial meningitis (1–5) results in a predominantly neutrophilic response. Bacteremia may be present in anywhere between 29% and 90% of cases. Cerebrospinal fluid may have a cloudy appearance and contain numerous inflammatory cells, frequently decreased glucose and increased protein levels. Certain organisms are more commonly encountered in certain age groups. In the neonatal period extending from birth to one month, commonly isolated organisms include group B *Streptococcus*, gram negative bacilli including *E. coli* and less commonly *Listeria* species and *Staphylococcus* (Fig. 35-1). During childhood, *H. influenza*, *N. meningitidis*, and *S. pneumoniae* are the most commonly encountered agents. Among adults, *S. pneumoniae* becomes the most commonly encountered organism. *N. meningitidis* may also be seen, particularly in young adults, in the setting of epidemic-type outbreaks. *Streptococcus*, *Staphylococcus*, *Listeria*, and gram-negative bacilli are seen in a smaller percentage of adults. The spectrum of likely encountered organisms is significantly broader in hospital acquired or iatrogenic related cases of meningitis, as opposed to community acquired forms.

The term *acute leptomeningitis* is generally used when referring to an infection of hours to days duration and is

characterized by a predominantly neutrophilic infiltrate. *Subacute leptomeningitis* refers to an inflammatory process of days to weeks duration and is characterized by a mixture of acute and chronic inflammatory cells. The term *chronic meningitis* implies an inflammatory reaction of several weeks to months duration and is characterized by a prominent chronic inflammatory infiltrate, meningeal fibrosis, and granulation tissue formation (6). In general, the histologic features seen in any given case of meningitis, are dependent upon the organism involved, the various toxic substances generated by the organism, the immune status of the patient, and extent, duration, and appropriateness of the therapeutic agents employed to treat the meningitis.

From a gross pathologic standpoint, meningitis is characterized by cerebral edema and vascular congestion. The subarachnoid space may become extended by an inflammatory exudate. Most cases of bacterial meningitis are preferentially centered in the region of the basal cistern and sylvian fissure, due to the effects of gravity and positioning.

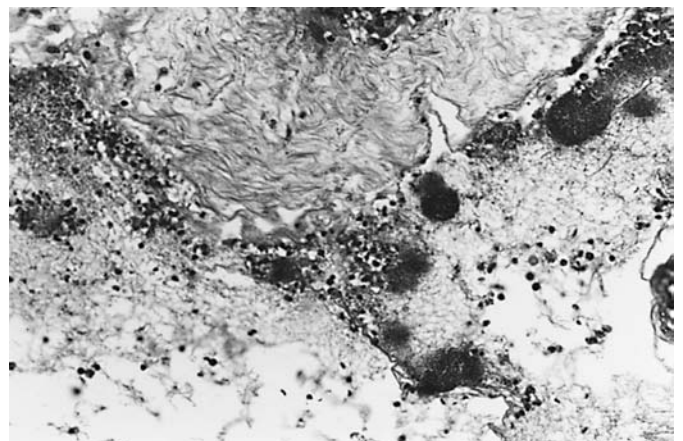


Fig. 35-1. Colonies of group B Streptococcal organisms in the leptomeninges of a neonate with leptomeningitis.

Microscopically, bacterial meningitis is characterized early on by an acute inflammatory cell infiltrate, consisting primarily of neutrophils and smaller numbers of macrophages, lymphocytes, and plasma cells. The inflammatory infiltrate may extend to involve the perivascular Virchow-Robin spaces and may produce an adjacent cerebritis. Edema of the brain parenchyma underlying the leptomeninges is common. Mortality associated with meningitis is usually related to edema with herniation and concomitant brainstem ischemia or problems related to cerebrospinal fluid obstruction. Over time as the inflammatory process runs its course or with therapeutic intervention, the predominant cell types in the exudate change from acute to chronic. Fibroblastic proliferation, capillary proliferation, and granulation tissue formation then ensue.

In general, most cases of acute bacterial meningitis are diagnosed based on clinical history and presentation along with cerebrospinal fluid studies including culture. It is rare that biopsy is required or performed to confirm a diagnosis of acute meningitis. Certainly, in cases in which acute meningitis is encountered during intraoperative consultation, recommendations should be made for cultures. Tissue section stains for micro-organisms including a gram stain, fungal stain such as Gomori methanamine silver, and a mycobacterial stain such as Zeil-Neelsen, or Fite should be performed. Occasionally, what one encounters in a surgical neuropathologic case is tissue manifesting the sequelae of meningitis, such as vasculitis with vascular necrosis, hemorrhage due to vascular necrosis, or thrombosis resulting in infarct.

Viral meningitis, in contrast to bacterial meningitis, tends to be more often a benign condition, and in most cases resolves spontaneously. Again, many cases are diagnosed based on clinical presentation, cerebrospinal fluid studies and serologies. Histologically, one typically sees infiltration of the leptomeninges by a chronic inflammatory cell infiltrate consisting primarily of lymphocytes (Fig. 35-2). Perivascular cuffing by lymphocytes, macrophages, and plasma cells may be seen in the superficial cortical layers. Infection may spread to involve the parenchyma, in which case a meningoencephalitis picture may be seen. The most common causative agents of viral encephalitis include Cocksackie virus, echovirus, mumps virus and herpes virus. The term aseptic meningitis has been used by some to refer to viral meningitis. In its proper usage, the term simply refers to cases in which bacteriologic cultures were negative. Many of such cases turn out to be viral in origin, however, unusual bacterial organisms, fungal organisms, and parasitic entities may on occasion cause a case of so-called aseptic meningitis. Unlike most forms of bacterial meningitis, which are often fairly easily diagnosable with a culture, identification of a precise viral organism as etiologic in meningitis is much

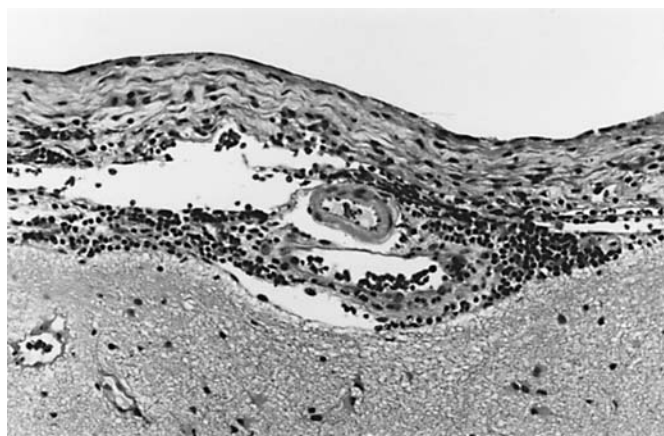


Fig. 35-2. Viral leptomenigitis with chronic inflammatory cell infiltrate.

more difficult and challenging. Identifiable classic viral inclusions are the exception rather than the rule. As a result, some of these cases are more likely to mimic other conditions such as sarcoidosis, vasculitis, connective tissue disease, or neoplasm and end up resulting in a biopsy. If adequate material is available, tissue should be sent for specific viral culture of agents that are deemed most likely, if such culturing techniques are available. Tissue fixed in glutaraldehyde for electron microscopic evaluation may be useful on occasion in identifying a viral organism. Likewise, fresh/frozen tissue may ultimately be useful for immunofluorescent or molecular biologic studies (8). Certain organisms (such as cytomegalovirus and herpes simplex virus) can also be identified by immunohistochemistry using routine formalin-fixed, paraffin-embedded tissue. Table 35-1 summarizes the clinicopathologic features of bacterial and viral meningitis.

An abscess is defined as a focal suppurative process involving the brain parenchyma (9–16) (Fig. 35-3). The incidence of brain abscesses is variable and the lesion is still associated with significant morbidity and mortality.

Table 35-1
Clinicopathologic Features of Bacterial Versus Viral Meningitis

	<i>Bacterial</i>	<i>Viral</i>
Age	Any	Any
Clinical symptoms	May be similar	
CSF glucose	Decreased	Normal-decreased
CSF protein	Increased	Normal-increased
Cultures	Often positive	Often negative
Cause of aseptic meningitis	Rare	Common
Neutrophilic exudate	+(early)	—
Lymphocytic exudate	+(late)	+
Vasculitis	±	±
Thrombosis	±	—
Complications	Frequent	Rare

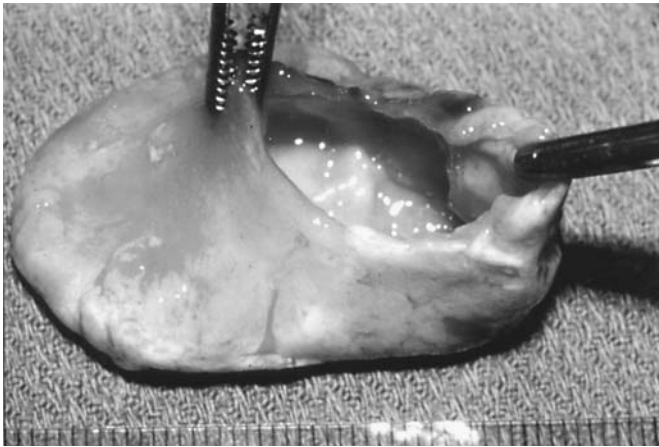


Fig. 35-3. An organizing bacterial abscess.

Due to improved imaging studies and earlier antibiotic intervention, the organisms responsible for abscess formation have changed over time. Currently, the most commonly identified organisms include *Streptococcus* species, gram negative bacilli, *S. aureus*, and anaerobic organisms. In an immunocompromised individual, the types of organisms one may encounter in this setting are much broader and organisms such as *Nocardia*, *Mycobacterium*, and fungi become more prevalent. The radiographic appearance of an abscess may closely mimic the ring enhancing configuration that one most commonly associates with a glioblastoma multiforme. Distinction of abscess from tumor is critically important, even in the context of intraoperative consultation where triaging tissue for culture is important.

The histologic evolution of an abscess is a well outlined process. The earliest changes involve a cerebritis picture, in which one sees perivascular acute and chronic inflammation, foci of necrosis, and surrounding edema (Fig. 35-4). These earliest changes are seen most prominently in

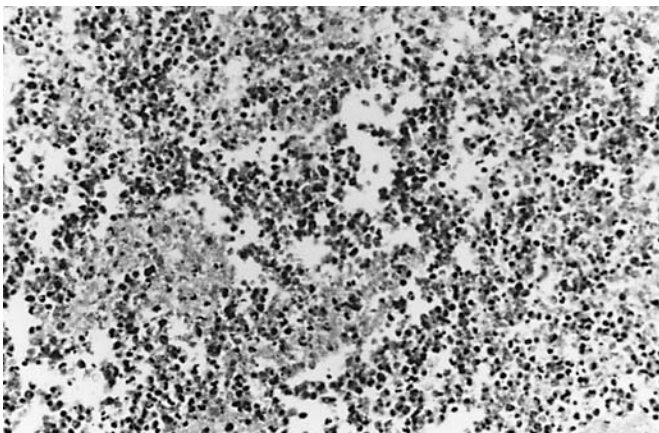


Fig. 35-4. Central necrosis and acute inflammation of an early bacterial abscess.

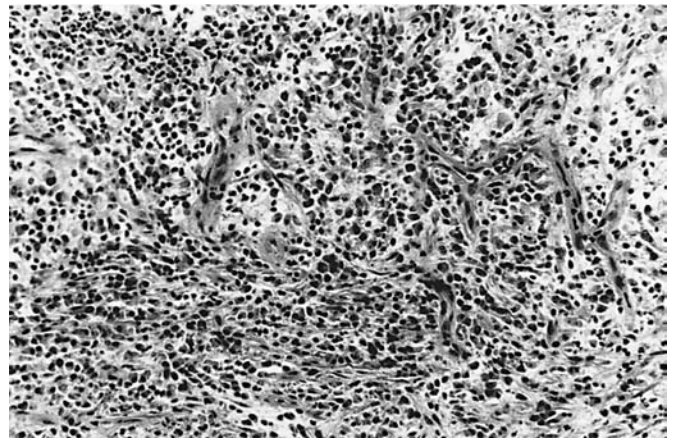


Fig. 35-5. Chronic inflammation and vascular proliferation in the wall of an organizing abscess.

the first few days. By a week to ten days, the necrotic foci have expanded and one begins to see some degree of fibroblastic proliferation and neovascularization at the edge of the lesion, which forms a recognizable layer around the central area of necrosis by two weeks. In the rim of fibroblastic proliferation, one sees increased vascular proliferation and predominantly chronic inflammatory cells (Fig. 35-5). Reactive astrocytosis begins developing outside this fibroblastic layer.

Histologic features that may be helpful in delineating an abscess from a malignant glioma are several. First, vascular necrosis associated with petechial hemorrhages and a fibroblastic proliferation are more suggestive of abscess than tumor. Certainly, tumors may hemorrhage and elicit a fibroblastic response. In general, abscesses contain a greater degree of inflammation as compared with glioblastoma multiforme. Large numbers of neutrophils seen in association with necrosis would be unusual in glioblastoma multiforme-associated necrosis. Likewise, the number of lymphocytes seen in capsule region of the abscess also far exceed those typically encountered in a glioblastoma multiforme. In general, the degree of nuclear pleomorphism is a more prominent feature of tumor rather than abscess. Mitotic figures may be encountered in either process, but an atypical mitotic figure, if identified, is a feature of tumor and not abscess. Although there are several differences between these two processes, their similarity may be quite striking, particularly in a small, stereotactic biopsy.

Although yield from special stains for microorganisms may be relatively low, such stains are still worth routinely performing in rare cases of abscess encountered histologically. Certain organisms such as *Nocardia* and fungi may be readily identifiable by light microscopy with stains (Fig. 35-6). Rare parasitic associated abscesses tend to be more readily evident by careful routine light microscopic

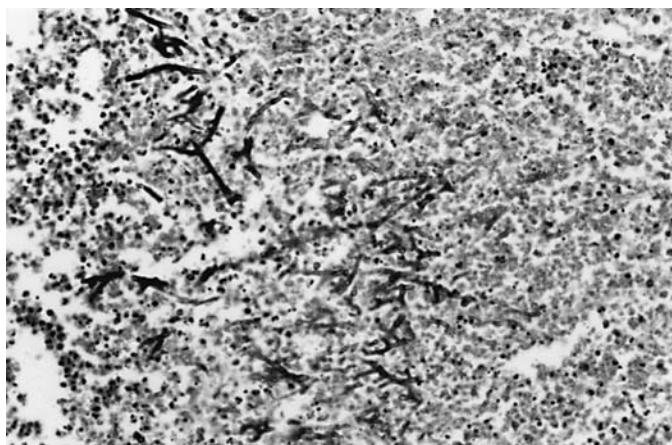


Fig. 35-6. Aspergillus hyphal forms in an abscess center.

examination (Fig. 35-7). Most cases of fungal or parasitic infection, however, are suspected clinically and usually do not result in a biopsy.

Encephalitis is defined as inflammation involving the brain parenchyma. Most cases have a definite infectious etiology; however, there are occasional presumably non-infectious causes of encephalitis. Rasmussen's encephalitis is one such condition which has been associated with chronic epilepsy (17). Histologically, Rasmussen's encephalitis demonstrates many of the typical features of viral type encephalitis but appears to be immune mediated (18). With current antiviral therapy, there has been an increased amount of attention focused on prompt and specific diagnoses. Again, clinical presentation, serologic, cerebrospinal fluid findings, and molecular biologic studies are the mainstay approaches. Obtaining tissue via biopsy is generally not part of the routine evaluation, but may be done occasionally to rule out other lesions or in a particularly unusual or difficult case. Clinically, the typical encephalitis presents as an acute onset febrile illness which may be accompanied by headaches, altered

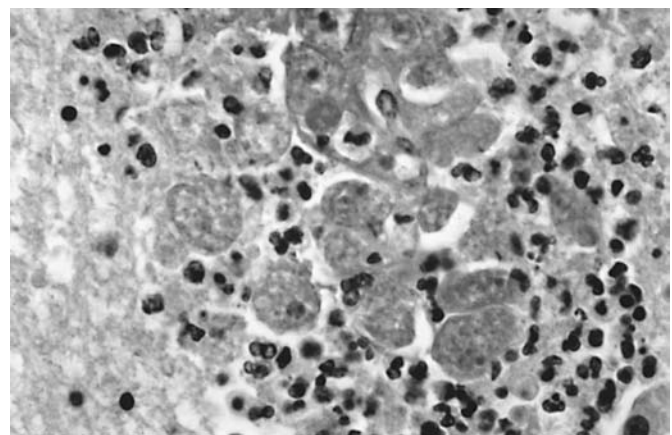


Fig. 35-7. Amebic organisms in an abscess.

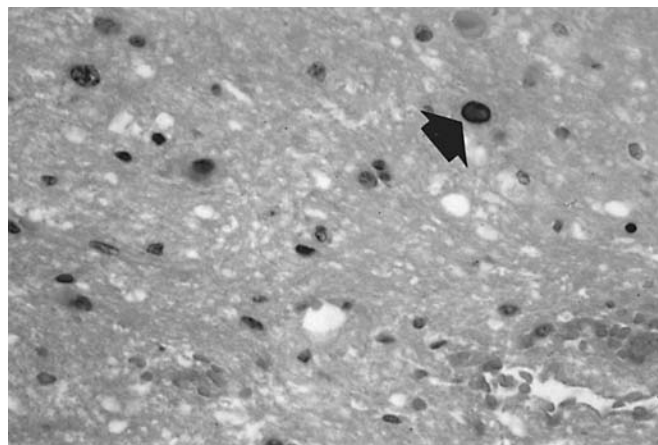


Fig. 35-8. Intranuclear Cowdry type A viral inclusion (arrow) in herpes encephalitis.

levels of consciousness, behavioral and speech disturbances, and variety of a neurologic signs which may be focal or more commonly diffuse such as seizures or hemiparesis. As with viral meningitis, the etiology is often somewhat obscure on biopsy and ancillary studies including electron microscopy, immunohistochemistry, molecular biology, and culture become important if a definitive diagnosis is to be arrived at.

The list of viral agents that have been associated with encephalitis are quite extensive and beyond the scope of this review to cover in detail. A few types are worth brief mention. Herpes virus (19–24) accounts for approximately 10% of all cases of encephalitis in the United States. The majority of cases occur in patients who are older than 50 years of age or younger than 20 years. It is thought that approximately one-third of cases of herpes encephalitis are related to primary infection and the remaining two-thirds are the result of a reactivation of a latent infection. The classic histopathologic finding in herpes encephalitis is that of a necrotizing, hemorrhagic encephalitis. Phagocytosis of neuronal cells by microglial cells (neuronophagia), diffuse microglial cell proliferation, and intranuclear Cowdry type A inclusions may be present (Fig. 35-8). Most commonly, the temporal lobes, insular cortex, and orbital surfaces of frontal lobes are involved. Emphasis in recent years has turned away from the brain biopsy as gold standard for diagnosis toward detection of the herpes virus antigen in the cerebrospinal fluid or viral DNA from cells in cerebrospinal fluid by polymerase chain reaction. If tissue is obtained by biopsy, cultures should be sent in cases in which the index of suspicion is high. Tissue should be routinely processed for electron microscopy for identification of the characteristic hexagonal 92–100 nm viral particles. Immunohistochemical, immunofluorescent, or molecular biologic studies may also be useful in confirming the diagnosis. In cases



Fig. 35-9. Cytoplasmic inclusions (Negri bodies) in hippocampal neurons in rabies.

in which an encephalitis is suggested on biopsy by the presence of perivascular inflammation, microglial proliferation and/or nodules, and viral inclusions, this may provide the basis for immediate therapeutic intervention with antiviral agents.

The other common endemic cause of encephalitis in the United States is rabies virus. The classic pathologic lesion is the cytoplasmic Negri body inclusion which involves neurons in the hippocampal and cerebellar regions (Fig. 35-9). Cytomegalovirus (CMV) encephalitis (25) generally occurs in the setting of immunocompromised individuals, although it has been rarely described in the immunocompetent person. The classic histopathology is that of microglial nodules which are variably associated with the classic intracytoplasmic and/or intranuclear inclusions. Occasionally, focal parenchymal necrosis, necrotizing ventriculoencephalitis, and focal demyelination may be seen in association with CMV (Fig. 35-10). Occasionally, nonviral organisms may also present with

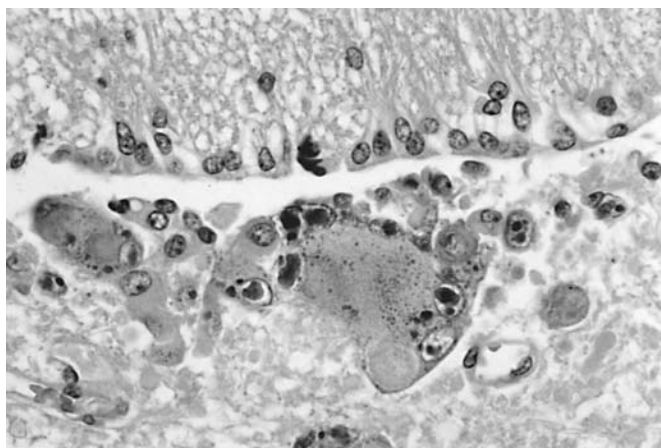


Fig. 35-10. Cytomegalovirus intranuclear and cytoplasmic inclusions in the setting of a ventriculitis.

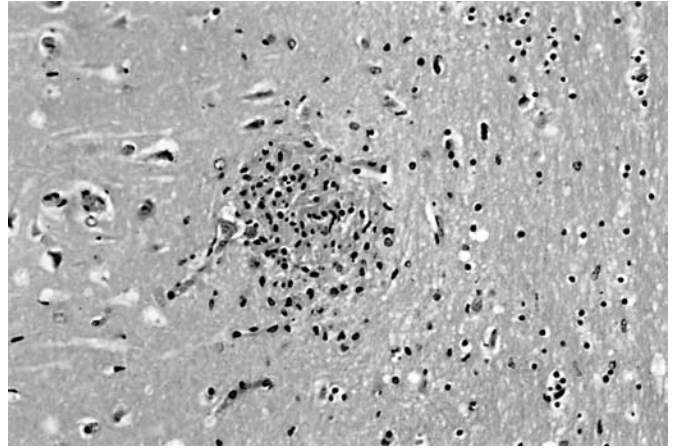


Fig. 35-11. Microglial nodule formation in a liver transplant patient with toxoplasmosis encephalitis.

a viral encephalitis type picture with microglial nodules, gliosis, and perivascular chronic inflammation. More commonly, toxoplasmosis presents as an abscess; however, occasionally toxoplasmosis may cause pathology more reminiscent of a viral encephalitis (25) (Fig. 35-11).

No discussion of viral infections of the central nervous system would be complete without at least a brief mention of human immunodeficiency virus (27–32) (HIV). The pathologic findings that have been described in association with HIV infection are myriad. Many of these findings are secondary to opportunistic infections. HIV infection can manifest itself by a whole variety of pathologic patterns including meningitis, viral type encephalitis with microglial nodules often characterized by multinucleated giant cells, demyelination, and vasculitis to name a few (Fig. 35-12). In general, patients with HIV infection are not biopsied indiscriminately. In many cases there are specific questions related to a mass lesion or white matter lesion in these patients that press for a tissue diagnosis.

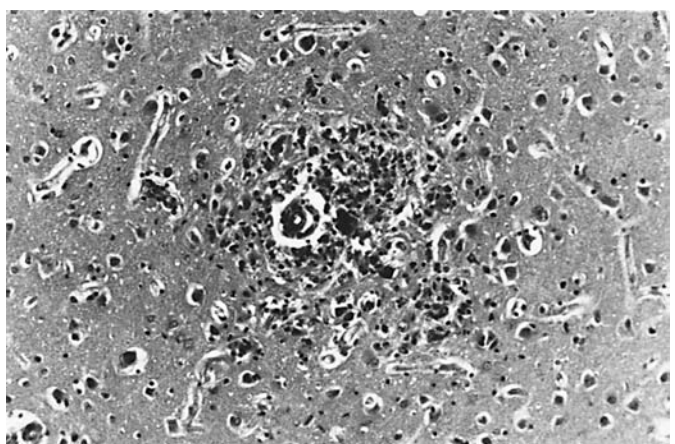


Fig. 35-12. Microglial nodule with rare giant cells in an HIV encephalitis.

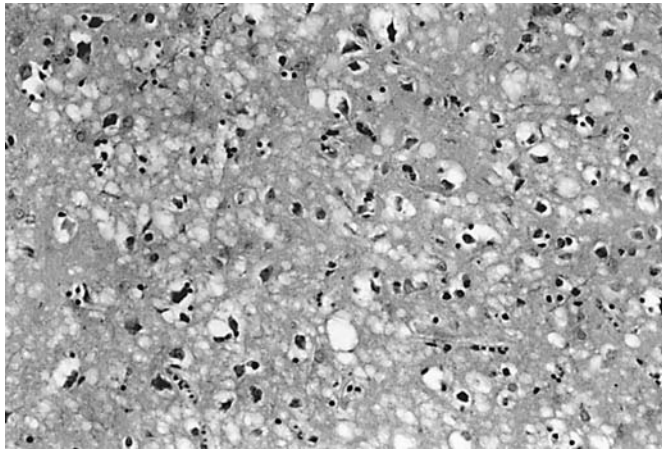


Fig. 35-13. Spongiform degeneration in Creutzfeldt-Jakob disease.

Although seldom encountered, the subject of prion protein disease, particularly Creutzfeldt-Jakob disease, is one that often generates anxiety and a lot of questions (33,34). The typical clinical presentation of Creutzfeldt-Jakob disease is that of a middle-aged to elderly individual who presents with a rapidly progressive dementia associated with myoclonus. In general, a biopsy is not typically employed in the diagnosis which is generally made based on clinical presentation and electroencephalogram (EEG) findings. More recently, an immunoassay to detect the 14-3-3 protein in cerebrospinal fluid has proven to be a fairly sensitive marker for Creutzfeldt-Jakob disease (35). Nevertheless, there may be circumstances in which a biopsy is performed, more commonly to exclude other causes of dementia. If this is the case, there is absolutely no indication for frozen section or intraoperative consultation in this scenario. Due to the artifacts associated with the frozen section procedure and because of the issues of contamination of equipment, an intraoperative consultation should not be performed and the diagnosis would be virtually impossible to make with any degree of certainty in this context. In cases where there is a suspicion of Creutzfeldt-Jakob disease, tissue should be archived frozen for a more definitive Western blot analysis (36).

Histologically, Creutzfeldt-Jakob disease is characterized by a triad of findings including spongiform degeneration, loss of neurons, and reactive astrocytosis (Fig. 35-13). These findings may be quite focal, and may not necessarily be prominently seen in a biopsy taken from a single site. Inflammation, microglial nodules or microglial cell proliferation, and inclusion bodies are not present. In a minority of cases and in some variant types, one may also observe so-called kuru plaques, which consist of amyloid material that is arranged in a starburst-like configuration.

Although actual cases of Creutzfeldt-Jakob disease are

fairly infrequent, protocols should be in place for handling such specimens and for decontamination (37–40). Unfortunately, formalin and other routinely used fixatives do not inactivate the agent. In cases of suspected Creutzfeldt-Jakob disease, all persons who will be potentially handling material should be advised of the potential infectivity of the case. In general, the disease does not appear to be transmitted by aerosolization of contaminated material. All instruments that come in contact with the tissue need to be decontaminated. Effective means of decontamination involve sterilization via steam autoclaving for at least 1 hour at 130°C or use of 5% sodium hypochlorite (household bleach). Use of phenol-saturated formalin and/or formic acid in the processing of paraffin blocks may also help in reducing but not entirely eliminating the titers of infectivity.

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