26 Brain

The pathology of the central nervous system is an intimidating area for pathologists. In part this is because we have virtually no role in the gross examination, just processing shreds of white pulp on gauze, and in part because of the feeling that "it could be anything at all," including a long list of exotic zebras that look just like the common things except behave completely differently. The fact that we are often asked to make our diagnoses on frozen section does not help matters. However, even in the brain, the list of likely diagnoses is still reasonably short if you have three pieces of key information: the age of the patient and the location and radiographic appearance of the tumor. Table 26.1 lists differential diagnoses that should at least put you in the right ballpark.

A strategy often proposed is to start by asking if your "lesion" could be normal tissue (i.e., the surgeon has missed). To answer this question you have to know a little normal histology, which is reviewed below. Second, you should ask if your lesion is neoplastic or nonneoplastic. The nonneoplastic lesion that many pathologists worry most about is the demyelinating lesion, which can look like a tumor by radiology. Abundant foamy macrophages, and an absence of obvious tumor cells, should make you think of a possible demyelinating lesion. Gliosis, a reactive proliferation of astrocytes, can also simulate a glioma histologically (see next section). However, once you have decided you have a neoplasm, the real work begins.

General Principles I

First, as in any organ, there are a finite number of cell types in the brain, and each cell type can give rise to a spectrum of neoplasms. In the brain, the cells and their common neoplasms are the following:

Native Cells	Tumors
Astrocytes	Astrocytoma and variants
Oligodendroglia	Oligodendroglioma
Ependyma	Ependymoma and variants
Neurons and precursors	Neurocytoma and gangliocytoma
Meninges (arachnoid cells)	Meningioma and variants, hemangiopericytoma
Choroid plexus	Choroid plexus papilloma/carcinoma
Pituitary	Pituitary adenoma
Schwann cells (in nerves)	Schwannoma
Stromal or vascular cells	Hemangioblastoma
Embryonal (immature) cells	Medulloblastoma/peripheral neuroectodermal tumors, neuroblastoma, others
Pharynx remnants*	Craniopharyngioma, Rathke's cleft cyst
Germ cell remnants*	Germinoma, teratoma, etc.
Notochord remnant*	Chordoma

Table 26.1. Differential diagnoses.

	Infants and young children	Adolescents and young adults	Adults to elderly
Cerebellum (infratentorial)	Pilocytic astrocytoma/ Medulloblastoma	Pilocytic astrocytoma/ Ependymoma/ Medulloblastoma	Diffuse astrocytoma/ Hemangioblastoma/ Metastases
Cerebellopontine angle (cranial nerves)			Schwannoma/ Meningioma
Cerebrum (supratentorial)	Neuroblastoma (rare in this location, more often an abdominal tumor)	Pilocytic astrocytoma/ Diffuse astrocytoma/ Ependymoma/ Pleomorphic xanthoastrocytoma	Diffuse astrocytoma, especially glioblastoma multiforme/ Meningioma/ Oligodendroglioma/ Mets/ Lymphoma
Sella	Craniopharyngioma	Pituitary adenoma/ Craniopharyngioma/ Germ cell tumors	Pituitary adenoma/ Craniopharyngioma (papillary type)
Pineal	Pineoblastoma	Germ cell tumors/ Pineoblastoma/ Pineal tumors/cysts	Pineal tumors/cysts
Ventricles (in or adjacent to)	Ependymoblastoma/ Choroid plexus papilloma/ carcinoma	Choroid plexus papilloma/ Ependymoma/ Pilocytic astrocytoma/ Neurocytoma/ Subependymal giant cell astrocytoma	Subependymoma
Dural based			Meningioma/ Hemangiopericytoma and solitary fibrous tumor

**Remnants* are those cell lines that do not anatomically belong in the brain but sometimes get left behind in some developmental fluke. They create midline tumors.

General Principles II

There is a broad grading system used for most central nervous system (CNS) neoplasms, the World Health Organization (WHO) tumor grade, which ranges from I (most indolent) to IV (most aggressive). In this system, grade I is equivalent to "benign," but in the CNS something cytologically benign may be clinically devastating depending on where it is growing. For this reason, CNS tumors are not described as benign versus malignant but are graded according to the WHO scale. The grade I and II tumors are sometimes referred to as "low grade," whereas grade III and IV lesions are considered "high grade." There is no TNM staging for primary brain tumors; margin status and tumor size are also not usually determined by the pathologist.

Many neoplasms are assigned to a grade by definition, but some types have a spectrum of grades based on certain histologic features. For most tumors, the following features are used to assign a higher grade to the lesion:

- Cytologic atypia (a subjective observation requiring some experience)
- Increasing cellularity relative to lowest grade tumor (again, subjective)
- Increasing numbers of mitoses (usually quantitative)
- Microvascular proliferation (objective: either present or absent)
- Necrosis (objective)

These features need to be searched for in every tumor (Table 26.2).

Table 26.2. Morphologic features in increasing order of concern.

Morphologic features in increasing order of concern							
EGBs or RFs	No atypia	No mitoses	Atypia	High cellularity	High mitoses	MVP	Necrosis
Pilocytic astrocytoma, grade I						occ. in pilocytic astrocytoma, I	
		Astrocytoma, grade II		Anaplastic astrocytoma, grade III		GBM, grade IV	
		Oligodendroglioma, grade II		Oligodendroglioma, grade III*		Oligo, IV**	
		Ependymoma, grade II		Ependymoma, grade III			
	Subependymoma, grade I						

EGBs, eosinophilic granular bodies; GBM, glioblastoma multiforme; MVP, microvascular proliferation; Occ, occasionally or rarely; RFs, rosenthal fibers.
*Microvascular proliferation is required to diagnose grade III oligodendroglioma
**Grade IV oligodendroglioma is very unusual and requires extreme malignant features.

General Principles III

Central nervous system tumors are usually initially sent for frozen section, to guide intraoperative management, and should also be evaluated with a smear or touch preparation, along with the frozen. The smear highlights some features that also narrow your differential diagnosis; on a smear it is easy to detect the fibrillary processes that identify most glial tumors, and nuclear detail is preserved. You can also get a feel for how cohesive (cell-to-cell adhesion) the tumor cells are, from very cohesive tumors (usually metastasis, schwannoma, or meningioma) to very noncohesive tumors (lymphoma, pituitary adenoma, and oligodendroglioma).

The general aim of the frozen section diagnosis is to verify that lesional tissue is present, classify the tumor into a major category (such as glioma vs. meningioma vs. carcinoma), and approximate a grade (low or high). It is often difficult and/or unwise to get more specific than this at the time frozen.

Overall, the tumors discussed in this chapter are organized based on location and age. However, astrocytomas, oligodendrogliomas, and meningiomas are discussed first, as they are so common and can arise almost anywhere along the neural axis. These are mainly tumors of adults. Note that metastases are actually the most common brain tumors in adults but are often diagnosed clinically (no biopsy, no pathologist).

Astrocytoma

Astrocytes, in their nonneoplastic form, are stellate cells with long processes that support the neurons. There are several variants of astrocytoma; the first split in categorization is between diffuse (infiltrating) types and circumscribed variants. Diffuse astrocytomas creep out into the surrounding brain so subtly that it is hard to tell where tumor ends and reactive brain begins. They come in three grades: *well differentiated* (II), *anaplastic* (III), and *glioblastoma multiforme* (IV). The distinction is by the criteria listed earlier. Hypercellularity and mitoses bump the tumor to grade III, while the presence of microvascular proliferation or necrosis is diagnostic of a glioblastoma multiforme.

Histologically, the cells of a diffuse astrocytoma are scattered in and among the normal cells of brain, with no visible architecture or cell borders (Figure 26.1). The key is in recognizing (1) that there are too many nuclei, distributed too unevenly, and (2) that many of the nuclei are hyperchromatic, coarse in texture, irregularly shaped, and large. In this sense, the astrocytomas follow the rules of other organs—you just have to learn to recognize the features of a "bad cell."

The higher the grade of tumor, the more obvious it becomes. Finding significant numbers of mitoses will generally push you to grade III. The glioblastoma multiforme, while classically shown with pseudopalisading necrosis (tumor cells lining up around a necrotic focus), can be diagnosed just by identifying a combination of malignant astrocytes, focal necrosis not associated with prior therapy, and/or microvascular proliferation, which is a characteristic expanding capillary population (Figure 26.2).

A circumscribed (nondiffuse) and very indolent form of astrocytoma is the *pilocytic astrocytoma* (grade I). It occurs in children and young adults and is usually associated with the

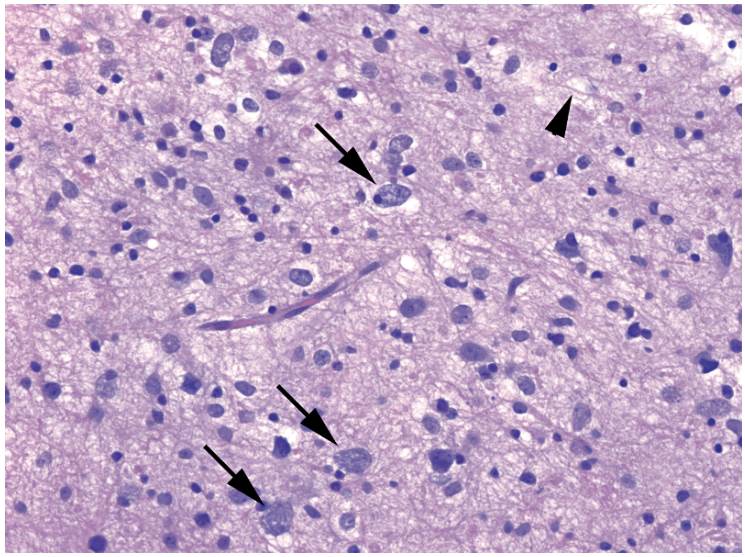

FIGURE 26.1. Astrocytoma, grade II. This field of tissue is hypercellular relative to normal brain. There are scattered large nuclei with irregular shapes and coarse chromatin (arrows); these are malignant astrocytes. The background is fibrillary (arrowhead), meaning there is a diffuse network of native neuropil and the processes of the malignant astrocytes.

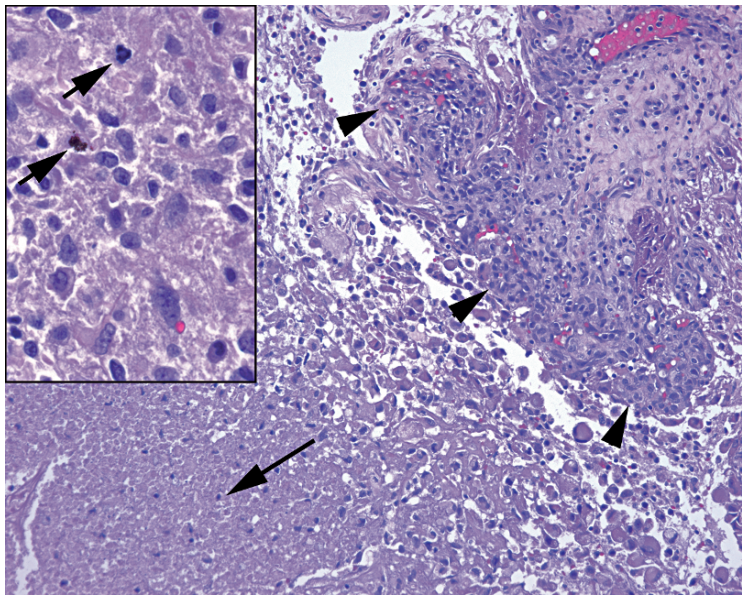

FIGURE 26.2. Glioblastoma multiforme. In this example, there is both necrosis (arrow) and microvascular proliferation (outlined by arrowheads). The microvascular proliferation is an expanding tangle of capillaries, some of which make glomeruloid forms. Many of the malignant astrocytes in this field have a gemistocytic morphology (eccentric nuclei and abundant pink cytoplasm). **Inset**: A high-power view of malignant astrocytes with enlarged and irregular nuclei and multiple mitoses (arrows).

cerebellum, optic nerve, hypothalamic region, or ventricles. The "pilo" means hair, because the fine processes create a matted-hair–like background (Figure 26.3). These tumors also show the hallmarks of a slow-growing glial process: Rosenthal fibers and eosinophilic granular bodies, both types of pink concretions seen among the tumor cells. Other, more rare, circumscribed astrocytic lesions include the *pleomorphic xanthoastrocytoma*, a seizure-causing tumor of young adults often found in the cerebral cortex, and the *subependymal giant cell astrocytoma* of tuberous sclerosis.

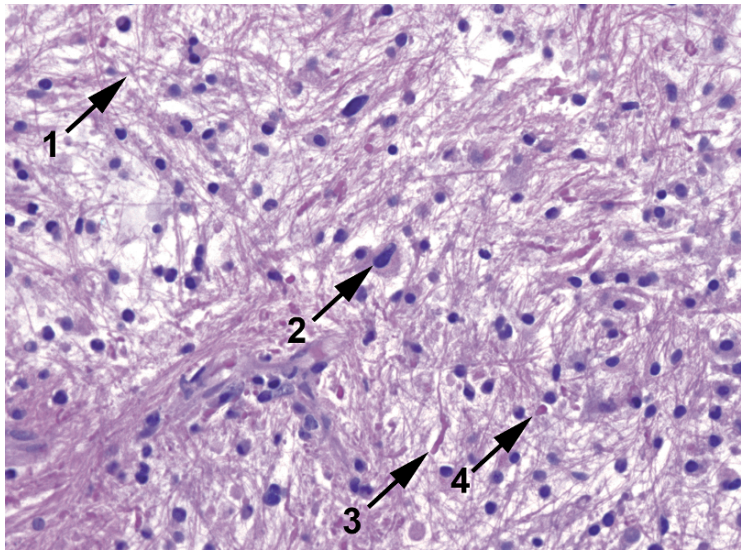

Figure 26.3. Pilocytic astrocytoma. The classic features shown here are a fibrillary or hair-like background (1), scattered large dark nuclei (2), Rosenthal fibers (3), and eosinophilic granular bodies (4).

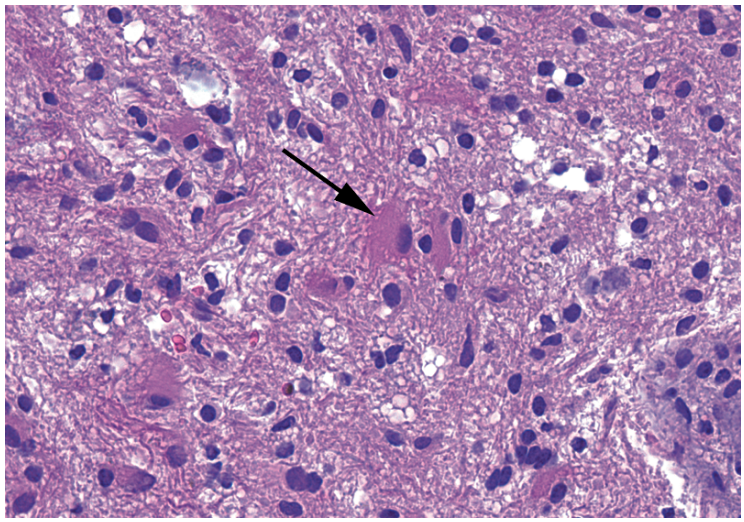

Figure 26.4. Reactive astrocytes. Normal resting astrocytes generally do not have visible cytoplasm. When responding to inflammation or injury, they become compact in shape, with dense pink cytoplasm and stubby processes (arrow).

Astrocytes can become reactive, in which their processes shorten and become more clearly visible, emphasizing their stellate shape (Figure 26.4). This nonspecific reaction to injury is called *gliosis*, and it can make nonneoplastic brain appear hypercellular. The key differential is with a well-differentiated astrocytoma, which can also resemble a subtle hypercellularity, especially around the edges. However, although some glioma cells can develop a prominent "gemistocytic" or abundant pink cytoplasm, they usually lack the multiple well-defined processes of reactive astrocytes. *Other features that favor glioma* over gliosis include the following:

- Microcystic pattern
- Calcifications
- Mitoses
- Clustering of glial cells around neurons or vessels or below the pia (satellitosis)
- Irregular distribution and crowding of glial cells

Oligodendroglioma

The oligodendroglioma is typically in the frontal/temporal lobes of adults. Usually it is a grade II tumor, although vascular proliferation and mitotic activity can push it to grade III. Histologically, it is characterized by a population of tumor cells that look like normal oligodendroglia: small round nuclei surrounded by clear halos (a retraction artifact seen only in formalin-fixed tissues). The chromatin is a little clumpy, like a plasma cell, but overall it is uniform (Figure 26.5). Architecturally, they tend to cluster around existing neurons (satellitosis). Other helpful features include a net-like capillary array, a microcystic pattern (as though torn apart by expanding bubbles), and calcifications. On a smear, these cells are not fibrillary like the astrocytoma but instead sheet out as discohesive round cells.

All useful tips, but in reality the oligodendroglioma is evolving from a morphologic diagnosis to a molecular one. "Pure" oligodendrogliomas are almost always characterized by a chromosomal deletion of 1p and/or 19q, and this same population tends to respond well to therapy. As a result, cases with anything other than classic features are often sent for cytogenetics. The idea of a mixed glioma (an oligoastrocytoma) is controversial but is included in the WHO classification.

Meningioma

The meningioma arises from arachnoid-type cells associated with the dura and is therefore almost always dural based, which may include tumors on the cerebral convexities, tumors of the falx, or tumors around the brain stem or spinal cord. It is common in adults, rare in children. The usual meningioma is a grade I tumor, but certain features or subtypes can raise the grade to II (atypical) or III (malignant).

Histologically, meningioma is one of the most protean tumors in the CNS. It has 16 subtypes and counting, very few of which have clinical significance but that must be recognized for their benign selves and not called carcinoma, sarcoma, and so forth. For this reason, before you start trying to learn subtypes, become very comfortable with the basic cytologic features of *meningothelial cells*—these do not vary much across types. The classic meningothelial cell

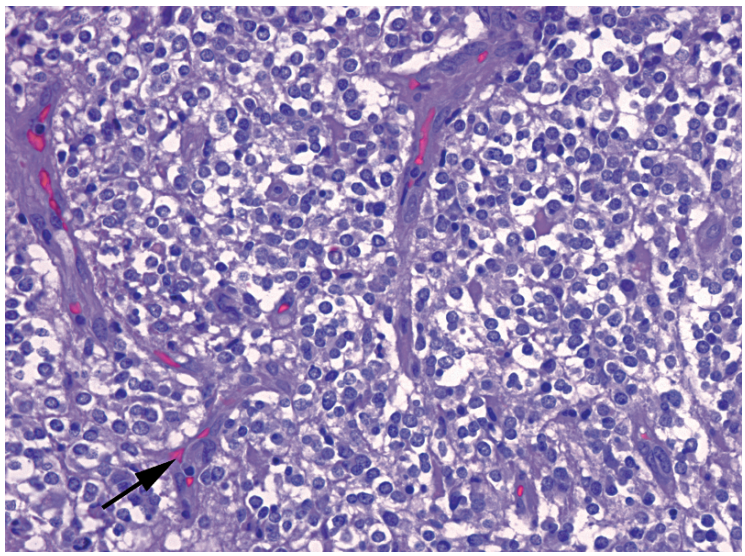

Figure 26.5. Oligodendroglioma. This is a very cellular example of an oligodendroglioma. The closely packed oligodendroglia have very round nuclei which are surrounded by clear halos. The tumor cells are suspended in a network of fine capillaries (arrow).

occurs in a syncytium with its neighbors, so cell borders are invisible. The nuclei are small, oval, and regular, with a very fine powdery chromatin, and they tend to stream in parallel in their syncytial groups (Figure 26.6). Nuclear inclusions may be seen. Meningiomas of all types often have whorls, which are spiral-shaped streams of nuclei, similar to the whorl of a fingerprint. Finally, psammoma bodies are frequently present.

The "classic" meningioma is called the *syncytial type*, but it can differentiate along more mesenchymal lines (fibrous, angiomatous) or more epithelial lines (secretory, clear cell). Important subtypes are the following:

- Clear cell (grade II): glycogen-filled cells, which therefore lose their syncytial appearance, resembling instead a clear cell carcinoma (Figure 26.7)
- Chordoid (grade II): resembles a chordoma, with a myxoid background and cords of cells

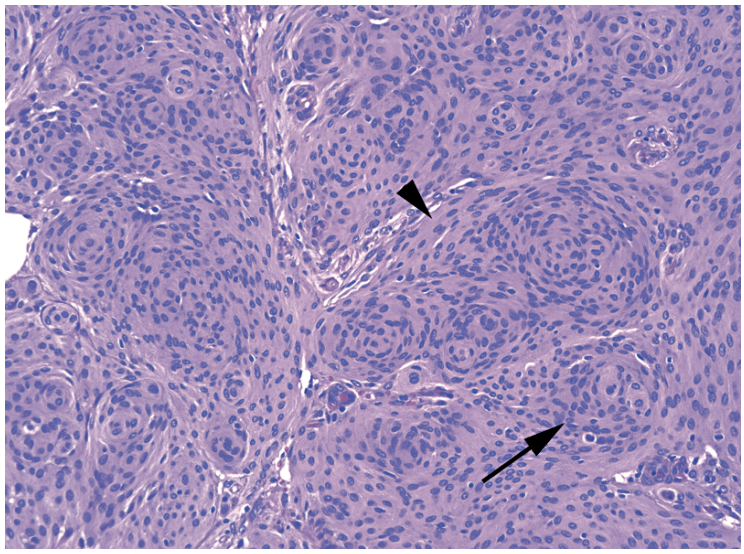

Figure 26.6. Syncytial meningioma. The meningioma nuclei are small and oval and tend to cluster in syncytial groups (arrowhead) without visible cell borders, or make whorls (arrow).

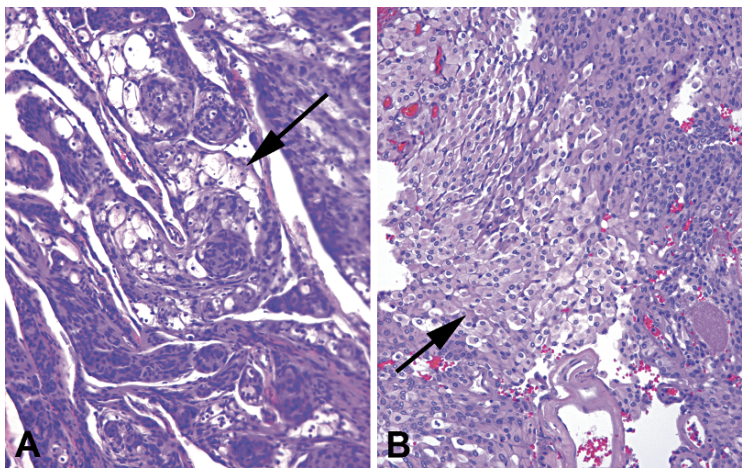

Figure 26.7. Aggressive variants of meningioma. **(A)** Clusters of distended clear cells (arrow) are visible in this meningioma, indicative of clear cell meningioma. **(B)** Rhabdoid meningioma has plump eosinophilic cells (arrow) with rhabdoid (resembling immature skeletal muscle) morphology.

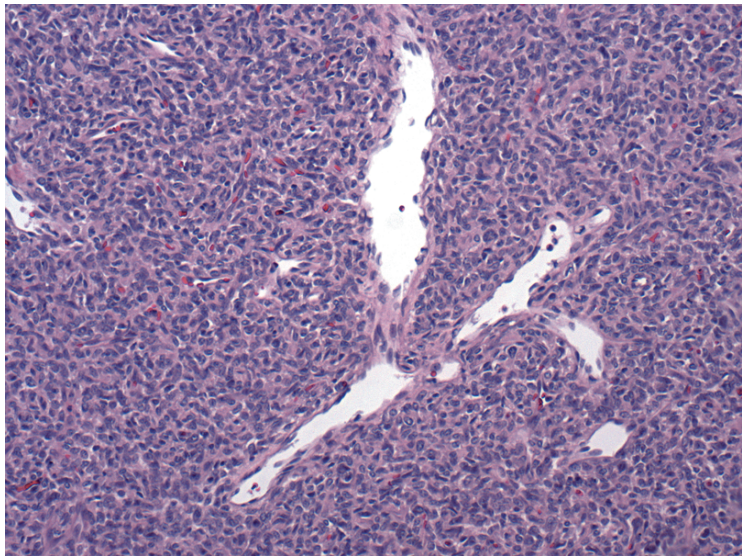

Figure 26.8. Hemangiopericytoma. A typical staghorn vessel in a background of small blue cells that are somewhere between epithelioid and spindled.

- Rhabdoid (grade III): plump pink cells with discrete cell borders, similar to rhabdomyoblasts (see Figure 26.7)
- Papillary (grade III): syncytial, meningothelial cells on arborizing fibrovascular cores

A meningioma can also be upgraded based on cytologic criteria, including cellularity, pleomorphism, mitotic rate (over 4 per 10 high-power fields [hpf]), and necrosis. Brain invasion (true infiltration into brain parenchyma) is a poor prognostic sign that previously resulted in the diagnosis of a malignant meningioma. The current WHO classification assigns these tumors a grade II "atypical" designation. Skull invasion, on the other hand, does *not* affect the tumor grade, although invasion of the skull base can be surgically problematic.

Related but much less common lesions are the *hemangiopericytoma (HPC)* and *solitary fibrous tumor*. The cell of origin is probably the same, and these are also dural-based, enhancing, well-circumscribed lesions. However, the hemangiopericytoma is the more aggressive tumor of the two. It is a blue and cellular tumor with prominent and stereotypical gaping vessels called *staghorn vessels* (Figure 26.8). The nuclei are oval but have nucleoli and more coarse chromatin than the meningioma.

Lesions of the Posterior Fossa (Infratentorial)

The main structure of the posterior fossa is the cerebellum. Never forget where you are; the granule cells of the cerebellum look tumor-like on smear if you are not expecting them. Within the cerebellum of adults, your differential usually includes gliomas, metastases, and the *hemangioblastoma*. Infratentorial tumors are much more commonly seen in children, and in this age group the big players are low-grade gliomas (*pilocytic astrocytoma* and *ependymoma*) and *medulloblastoma*: fortunately difficult to mix up on frozen section.

A special infratentorial location is along the eighth nerve, the most common site of *schwannoma* in adults. Named the *acoustic neuroma* because of its position on the auditory nerve, the schwannoma is a tumor of peripheral nerve, made up of the myelinating nonneural Schwann cells.

Hemangioblastoma is an uncommon tumor often associated with the von Hippel-Lindau syndrome (VHL). It looks a little like a renal cell carcinoma, with packets of lipidized clear tumor cells surrounded by a delicate capillary network (Figure 26.9). This is unfortunate,

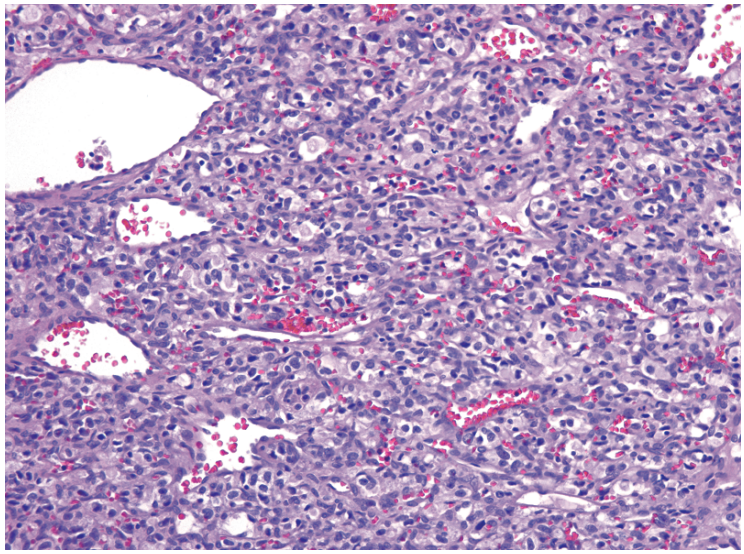

Figure 26.9. Hemangioblastoma. Clear (lipidized) cells with bland nuclei in a background of interlacing and dilated capillaries.

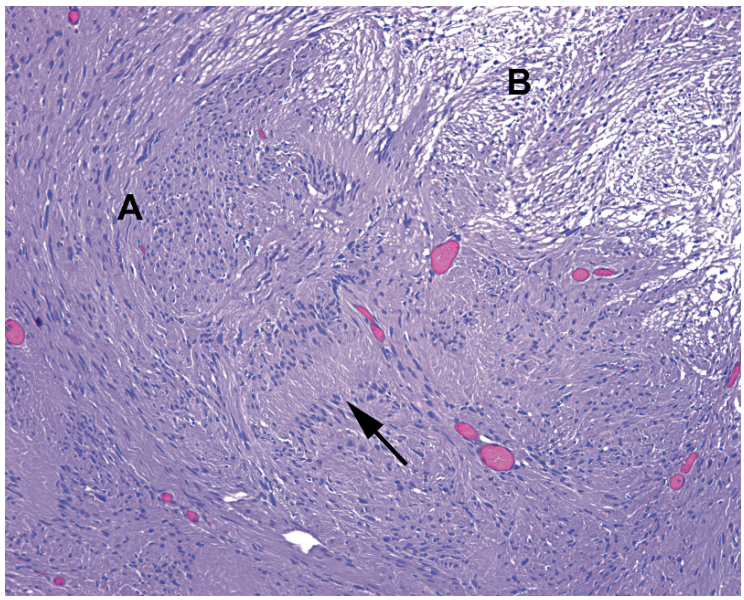

Figure 26.10. Schwannoma. This lesion shows alternating areas of high and low cellularity, called Antoni A **(A)** and B **(B)** areas. The elongated Schwann cells tend to stream in parallel groups and form opposing parallel arrays, called Verocay bodies (arrow).

because VHL patients also get renal cell carcinoma metastases. Oil Red O (a stain for fat performed only on frozen sections) and some immunostains can sort out the ambiguous cases.

Pilocytic astrocytomas (arising from the fourth ventricle) are described above in the section on astrocytomas. *Ependymoma*s (also from the ventricle) are described below, with other ventricular tumors.

Schwannoma is a benign fibrillary tumor consisting of a streaming mass of elongated nuclei (Figure 26.10). It often has alternating areas of high and low cellularity (Antoni A and B areas) and tends to make little palisaded arrays called Verocay bodies. Hyalinized (thick, pink)

vessels are common. *Medulloblastoma* is one of the aggressive small round blue cell tumors of childhood (discussed later).

Lesions of the Midline

Tumors arising from embryologic remnants tend to occur in the midline. *Germ cell tumors* include the *germinoma*, which is essentially a primary CNS seminoma, and the *teratoma*, more often found in a sacrococcygeal location than in the head. Other germ cell tumors, such as yolk sac tumor and choriocarcinoma, are rare but do occur in the CNS.

Craniopharyngioma and Rathke's cleft cyst both derive from pharyngeal tissues occurring in the sellar region. The craniopharyngioma, most common in young people, classically has an "adamantinomatous" appearance, meaning it looks like a developing tooth. The nests of cells are bounded by dark palisaded cells, with central areas of stellate cells in a myxoid stroma (Figure 26.11). There is also keratin and debris. Adults, when they get craniopharyngiomas, more often get the papillary type, resembling a nonkeratinizing squamous papilloma.

Chordomas are tumors of the notochord remnant, hence the name; note that they have nothing to do with "chondroid" or cartilage. They are most often found at the top and bottom of the spine—the clivus and the sacrum. Like intervertebral discs, another notochord remnant, they have a bluish, mucinous background. The "physaliphorous" tumor cells are typically full of clear bubbles and grow in cords.

Other sources of midline tumors include the pituitary and pineal. *Pituitary adenoma* is a common tumor of the sella. Remember that the pituitary is a very heterogenous mass of cell types, arranged in lobular nests. Therefore, cellular monotony and loss of the normal pattern of small nests of cells is the key to differentiating between an adenoma and normal pituitary (Figure 26.12). The pituitary adenoma looks similar to a neuroendocrine tumor in other sites, both cytologically and architecturally. The *pineocytoma* is the pineal adenoma. It can be very difficult to tell a pineal tumor from normal pineal, mainly because so few pathologists have actually seen a normal pineal. Tumors that are midline because they are associated with the third or fourth ventricle are discussed in the next section.

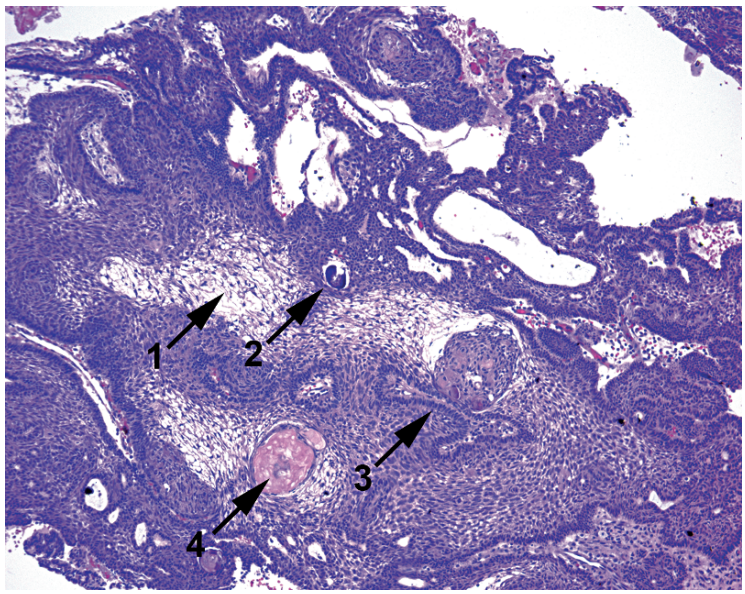

Figure 26.11. Craniopharyngioma, adamantinomatous type. There are areas of stellate reticulum (1), calcification (2), peripheral palisading (3), and accumulated "wet" keratin (4).

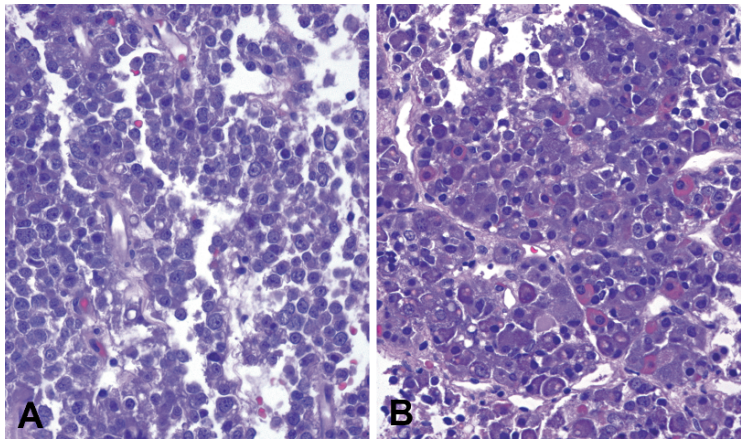

Figure 26.12. Pituitary adenoma versus normal. **(A)** In a pituitary adenoma, there is a monomorphic population of neuroendocrine-type cells. A collagen or reticulin stain would show sheets of cells no longer encircled by reticulin. **(B)** Normal pituitary is a mix of many different cell types, both eosinophilic and basophilic, and a reticulin stain would show the tissue divided into small discrete nests.

Lesions of the Ventricular/Periventricular Areas

Ependymoma

The ependymoma is a usually low-grade (II) lesion of children and young adults. Grade III anaplastic ependymomas also exist, but in most studies this pathologic distinction is not clinically meaningful. It arises from a population of cells that line the ventricles, called *ependymal cells*. When they become neoplastic, they retain this affinity for making boundaries or lumens and tend to encircle vessels.

Histologically, this is a circumscribed lesion composed of cells with pale oval nuclei that align themselves around blood vessels, sending processes down to the vessel like spokes of a wheel (Figure 26.13). The resulting structure is called a *pseudorosette*. When the cells make an array around a tiny open lumen, it is called a *true rosette*. These rosettes are the signature feature of the ependymoma.

A special type of ependymoma is the *myxopapillary ependymoma*, occurring almost exclusively at the filum terminale. It has a myxoid background and ependymal cells radiating off of papillary structures, so it was well named (Figure 26.14). A *subependymoma* is an even lower grade lesion (I) which typically occurs as a nodule on the ventricular wall.

Other Tumors

Pilocytic astrocytomas are commonly associated with ventricles, especially in children. The subependymal giant cell astrocytoma of tuberous sclerosis is a tumor of the lateral ventricles consisting of very large cells with a somewhat ganglionic appearance.

Central neurocytoma is a low-grade lesion of neural origin, typically occurring in the lateral/third ventricle area. Like other neuronal tumors, it is uncommon and mainly occurs in children and young adults. It may be mistaken for an ependymoma.

Choroid plexus papilloma is an intraventricular tumor of young children and can even be congenital. It resembles normal choroid plexus but grows in large arborizing fronds to make a mass. The bland columnar cells form a single-to-pseudostratified layer on the fibrovascular cores. When these tumors become more solid, mitotically active, and invasive, they are known as *choroid plexus carcinomas*.

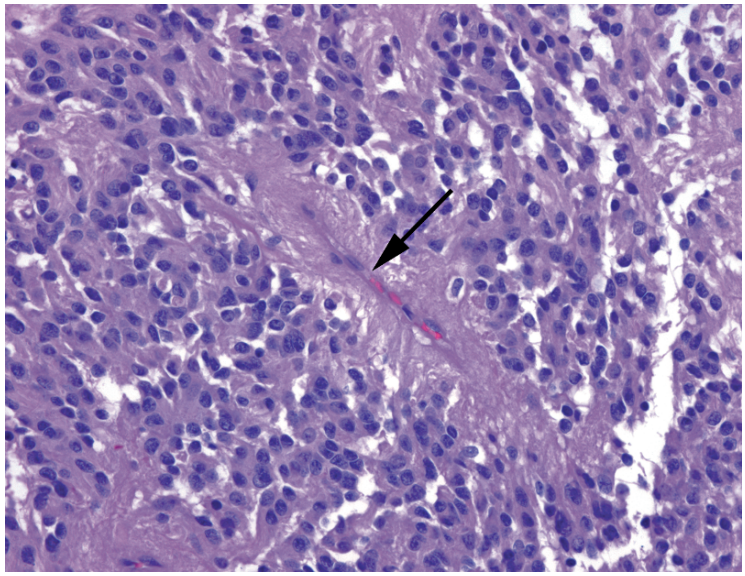

Figure 26.13. Ependymoma. There is a fibrillary background and a tendency for the cells to line up around vessels (arrow), with the ependymal cell processes extending to the vessel and the nuclei around the perimeter. This is actually an example of a pseudorosette; true rosettes have a lumen, not a vessel, at the center.

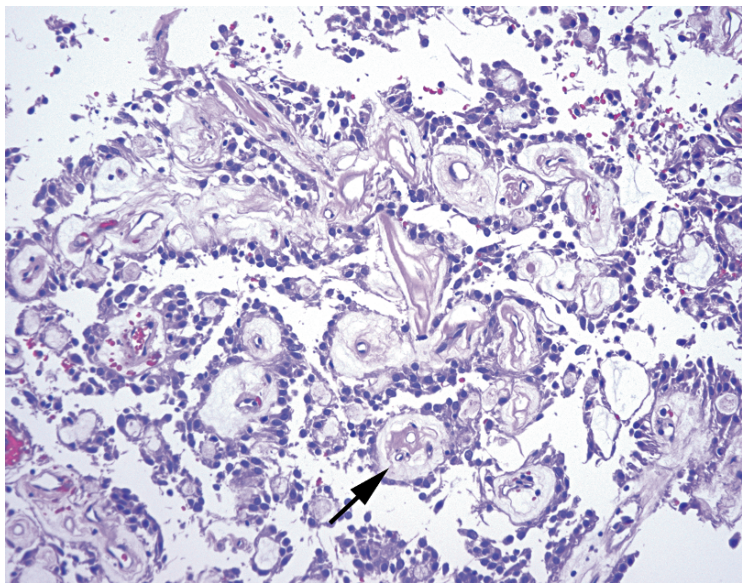

Figure 26.14. Myxopapillary ependymoma. The tumor is a papillary neoplasm with vascular cores surrounded by a myxoid stroma (arrow) and lined by ependymal cells.

Embryonal Lesions (Blastomas)

Blastomas are the small blue cell tumors of infancy and childhood, high grade and aggressive. They arise from immature stem cells. A feature they have in common is the tendency to form rosettes, similar to fetal neural tissue. This category does not include hemangio*blastoma*, or glio*blastoma* multiforme, or olfactory neuro*blastoma* (a sinonasal tumor of adults, arising from the olfactory membrane, unrelated to other things called neuroblastoma).

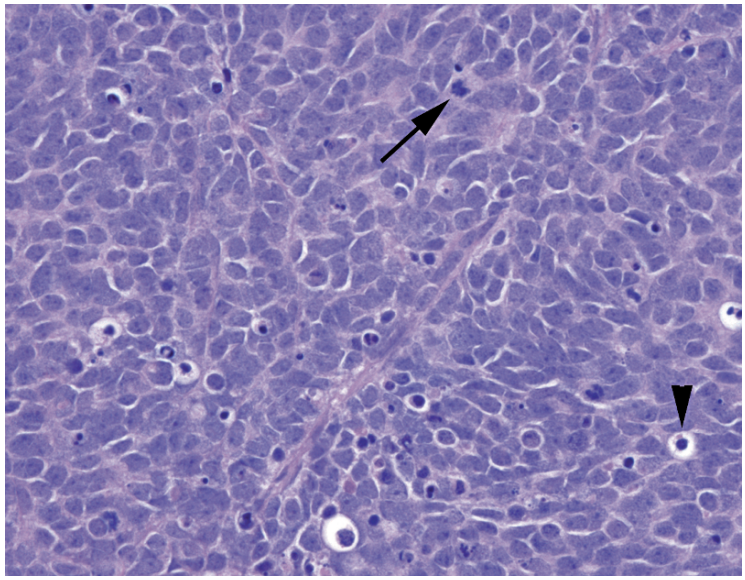

Figure 26.15. Medulloblastoma. A small round blue cell tumor composed of cells that are not actually round but more wedge-shaped or even spindly. The chromatin is very fine in texture, and there are frequent apoptoses (arrowhead) and mitoses (arrow).

Medulloblastoma is the most common of these tumors. When an identical tumor arises in the CNS outside of the cerebellum, it is called a *peripheral neuroectodermal tumor* (PNET; note that the PNET/Ewing's sarcoma tumors described outside the CNS are cytogenetically distinct from the CNS PNET see Chapter 28). These tumors are sheets of small blue cells of high nuclear to cytoplasmic ratio, high mitotic rate, and necrosis (Figure 26.15). The chromatin of the cells is fine and granular like small cell carcinoma, but the nuclei tend to be somewhat wedge or carrot shaped, especially when molded into rosettes. Unlike small cell carcinoma, there is often a fibrillary background due to the neural lineage of this tumor. Like neural stem cells, these tumors retain the ability to differentiate into neurons and glia, so these more differentiated cellular elements may be seen in the tumor.

Other tumors in this category, all rare, all grade IV, include ependymoblastoma, medullomyoblastoma, pineoblastoma, retinoblastoma, and neuroblastoma. Neuroblastoma is typically an abdominal neoplasm arising in the adrenal, but it can occur in the CNS as well, whereas retinoblastoma arises in the eye.