1 NORMAL ANATOMY AND HISTOLOGY OF THE CNS

ANATOMY

Knowledge of nervous system anatomy is essential for success in surgical neuropathology. Familiarity with native cellular elements will often predict the appearances of diverse tumors within the brain but, perhaps more importantly, recognition of normal or reactive processes will help avoid the pitfall of diagnosing malignancy when, in fact, a nonneoplastic reactive process or even normal tissue is present. Many surgical neuropathology specimens originate in the brain and spinal cord coverings, cranial and spinal nerve roots, blood vessels, and bone and soft tissue surrounding the nervous system; thus recognition of the normal brain is not enough. As with general surgical pathology, knowledge of diseases common to these locations and the ages at which they typically occur is essential.

The human brain can be described in many ways. However, for the purpose of surgical neuropathology, this description will emphasize different surgical compartments and cytoarchitectural areas that are especially associated with tumors or other pathological processes (Figure 1.1). The central nervous system (CNS) is often divided into the *supratentorial* and *infratentorial* compartments by the dural tentorium, which separates the cerebral hemispheres from the brainstem and cerebellum. The *spinal cord*, *roots*, and distalmost *cauda equina* and *filum terminale* (Figure 1.2) are often considered separately, especially in view of the paraspinal soft tissue pathology, which can affect the integrity of the spinal cord.

Brain tissue is divided into *gray* and *white matter*. This distinction may be useful in the differential diagnosis of neoplasms, but is more important in other pathological processes such as infection or neurodegeneration. The surgical neuropathologist is often interested in the relation of a tumor to the *ventricles*, including the ventricular spaces themselves and their periventricular regions. The base of the skull, including the pituitary gland-bearing *sella turcica*, is another particular region defined by the propensities of certain tumors for this region, both sellar and suprasellar.

The gross anatomy of the nervous system also reflects a level of complex and interrelated structure and function enviable to say the least of visceral organs.

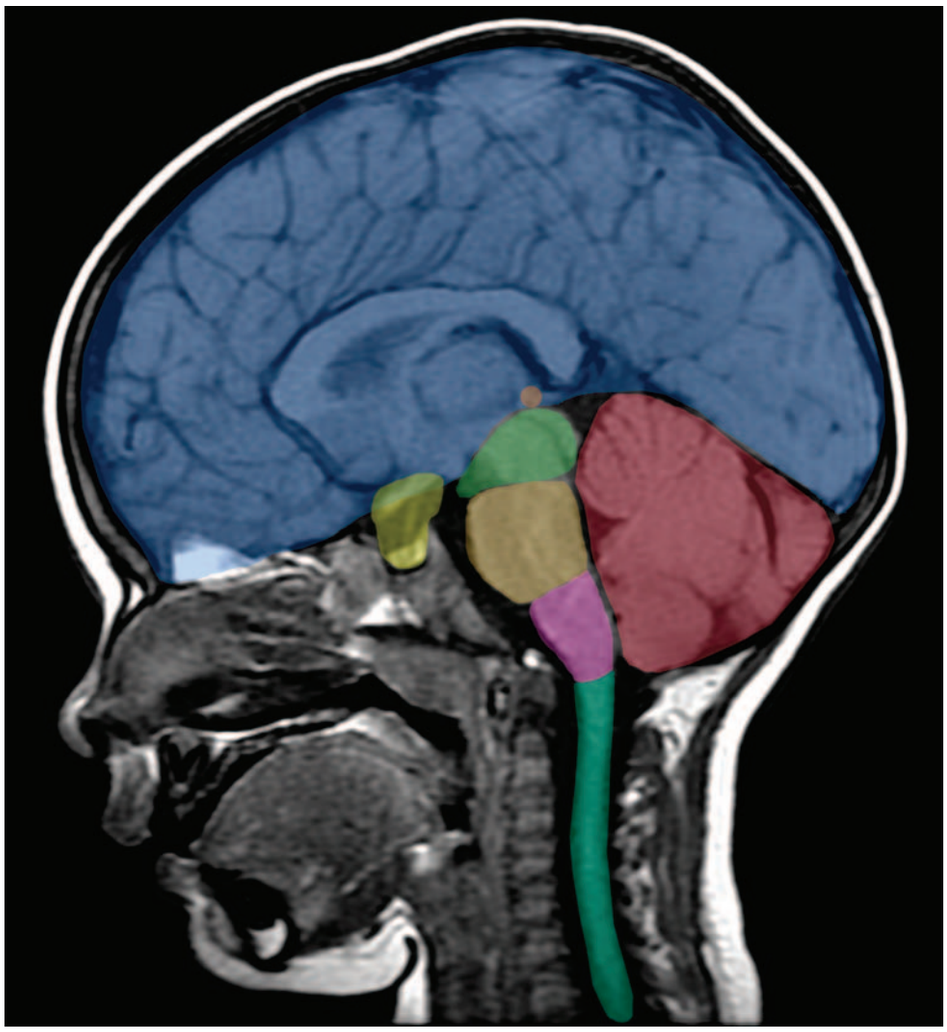


Figure 1.1. Midsagittal magnetic resonance imaging of the brain with regions often associated with particular neuropathological processes. Blue = supratentorial hemispheres with lateral and third ventricles. Red = cerebellum. Brainstem = midbrain (light green) pons (tan) and medulla (pink). Yellow = sella turcica and optic pathways. Dark green = spinal cord. Brown = pineal gland region.

The nervous system possesses a wide array of sometimes overlapping but clinically distinct functions, thus forming the basis of a vast array of clinical symptoms attributable to the regions affected, not to mention their pace of onset. Thereby, seizures imply injury to gray matter; lesions involving given white matter tracts cause neurological deficits reflecting the normal function of the tract, including weakness, altered sensation, visual deficits, cranial neuropathies, or other motor and sensory deficits.

Mass lesions first compromise local blood supply, then intrude into ventricular spaces, sometimes causing obstruction of flow of cerebrospinal fluid at various narrow passages such as the foramina of Munro, cerebral aqueduct, or fourth ventricle, and finally compression of brain tissue via paths of least resistance. Expanding lesions are ultimately confronted by the rigid resistance of the dura and skull. These cerebral herniations cause clinical symptoms that herald the serious effects of mass lesions from the supratentorial compartment as they press the medial temporal lobes against the edge of the tentorium. A greater or diffuse swelling of the supratentorial brain will cause the brainstem to herniate downward, often resulting in hemorrhages within the pons, termed Duret hemorrhages

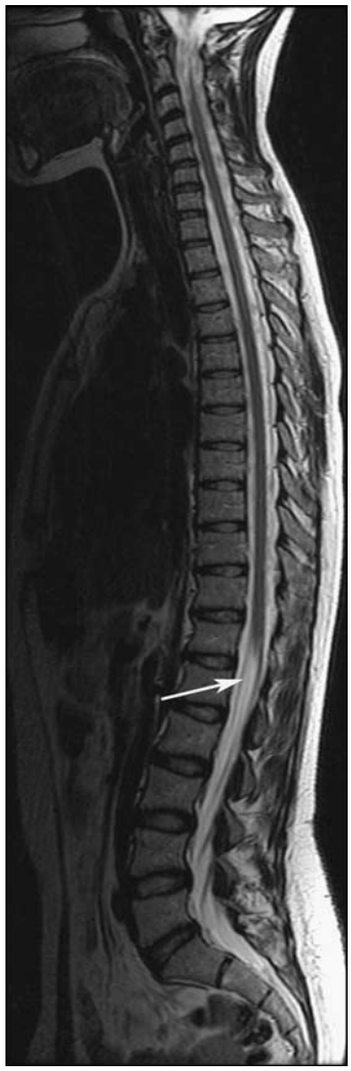


Figure 1.2. The spinal cord, roots, and distalmost cauda equina and filum terminale (arrow) are often considered separately, especially in view of the paraspinal soft tissue pathology, which can affect the integrity of the spinal cord.

representing the rupture of penetrating blood vessels that are otherwise tethered to the basilar artery. The most serious and life-threatening herniation involves downward pressure of the contents of the posterior fossa leading to compression of the medulla and vital respiratory control centers by the cerebellar tonsils.

Vascular pathology is inextricably related to virtually the entire spectrum of neuropathology. While the brain may only account for 2 percent of body weight, it accounts for 20 percent of oxygen consumption and thus normally receives 20 percent of cardiac output. The *circle of Willis* is an interconnected structure supplying arterial blood to the brain through the merging of paired sources in the carotid arteries and vertebral arteries at the base of the brain. The branching of the brain's arterial blood supply has been likened to that of an oak tree with right angles whereas that of the venous drainage is like the tapering confluence of elm branches. This is of more than botanical significance, since metastatic tumors, infections, or other arterial microemboli have a propensity to become lodged at a point of critical narrowing and angulation occurring at the grey–white junction such that this is often the location of the smallest of such lesions.

The brain is covered by successive layers. The most intimately associated is the pia mater, which tightly adheres to the entire surface of the brain and invests large penetrating blood vessels. Investing the pia mater is the arachnoid membrane, which is so intimately associated as to be combined through the term pia-arachnoid. The arachnoid membrane divests from the pia in the lower spinal canal, resulting in an expanded subarachnoid space that is amenable to lumbar puncture below lumbar vertebral body L2, which corresponds to the lower extent of the cauda equina.

HISTOLOGY

Surgical neuropathology requires the knowledge of normal histology in the immature, adult, and aged brain and how the cellular constituents vary accordingly.

Neurons are the functional unit of the nervous system and display a number of different and distinctive morphologies, which are of both functional and anatomical significance. Neurons of all types generally contain a round nucleus with a prominent nucleolus and a cell cytoplasm or perikaryon with Nissl substance. Motor neurons tend to be large trapezoidal or triangular cells (Figure 1.3) while sensory neurons have a more globular shape (Figure 1.4). A third type of neurons that are abundant in the cerebellum and dentate gyrus of the hippocampus are granular cell neurons (Figure 1.5). These are significantly smaller than most cortical neurons and do not show obvious cell processes in routine sections. The importance in recognizing normal neuronal morphology for the surgical neuropathologist lies in distinguishing normal ganglionic or neuronal cells from dysplastic or neoplastic ganglion cells, to recognize their appearance in gray matter structures or spinal or cranial nerve ganglia that are infiltrated by neoplasms, and to carefully distinguish normal granular cell neurons from "small blue cell" neoplasms or lymphocytes.

Neurons may be identified immunohistochemically with either one or a combination of three different antibodies. *Synaptophysin* is a useful marker of the neuronal cell surface or cytoplasm (Figure 1.6a), although the immunostaining results in infiltrative tumors or other processes can be difficult to interpret because of background normal staining for synaptophysin. *Neurofilament* is the characteristic intermediate filament of neurons. Antibodies to the nonphosphorylated neurofilament of the neuronal cell body (perikaryon) and to the phosphorylated neurofilament of neuronal processes can be used to distinguish these compartments accordingly. However, mixed neurofilament antibodies are commonly used in current surgical neuropathology and label both the cell body and its neurites (Figure 1.6b). A third marker of neuronal differentiation is anti-*neuN*, which offers the advantage of nuclear staining (Figure 1.6c). Not all neurons stain positively for neuN, including Purkinje cells, most neurons of the internal nuclear layer of the retina, and the sympathetic chain ganglia.

Neurons are the most quintessential cellular component of the CNS. However, *astrocytes* are the most plentiful cell type and exhibit the broadest range

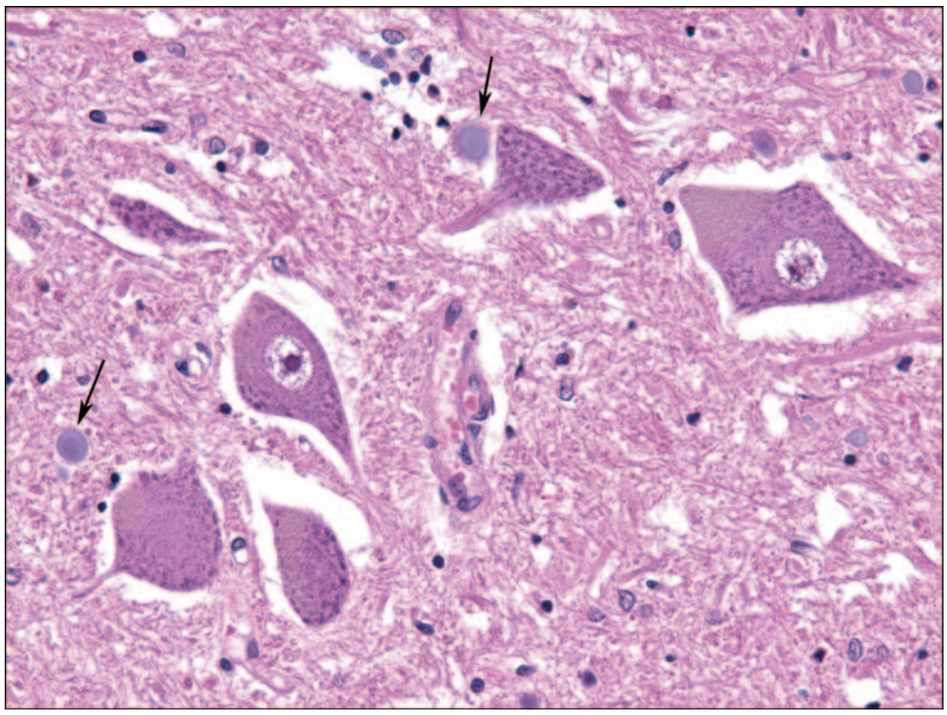


Figure 1.3. Large motor neurons tend to be large trapezoidal or triangular cells. Note cytoplasmic Nissl substance and eccentric aggregation of golden brown lipofuscin pigment. Corpora amylacea (arrows) are within slender glial cell processes not discernable in H&E sections.

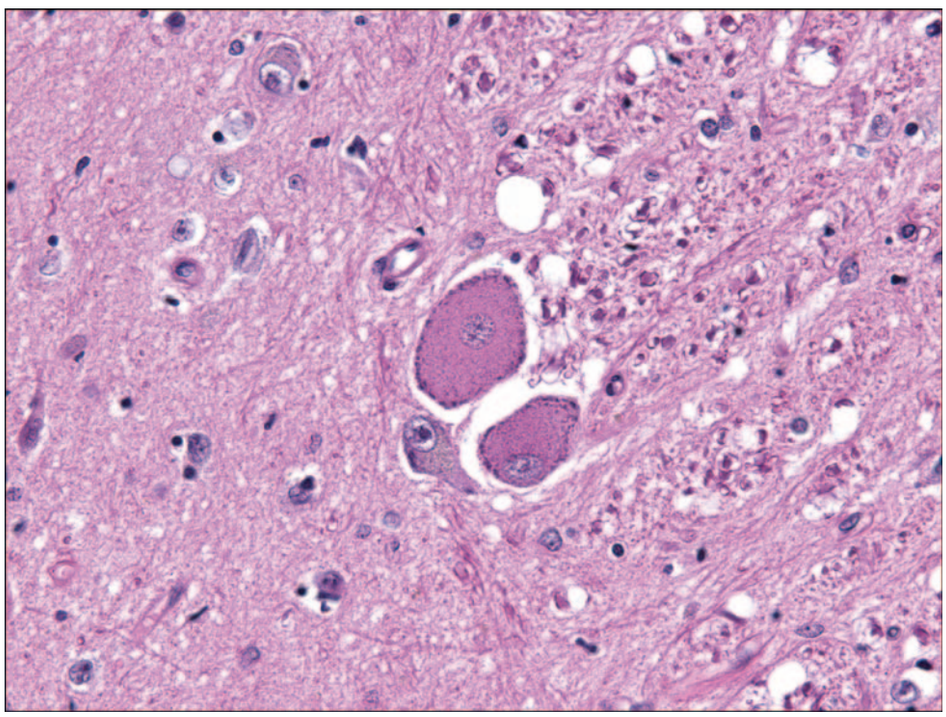


Figure 1.4. Sensory neurons have a more globular shape.

of normal and reactive morphologies. Two predominant types of astrocytes may be found in the brain: *fibrous astrocytes* in white matter and subpial and perivascular gray matter, which are detectable by glial fibrillary acidic protein (GFAP) immunohistochemistry, and *protoplasmic astrocytes* in gray matter, which contain little detectable GFAP. Reactive astrocytes often show eosinophilic cytoplasm and profusion of delicate cell processes detectable

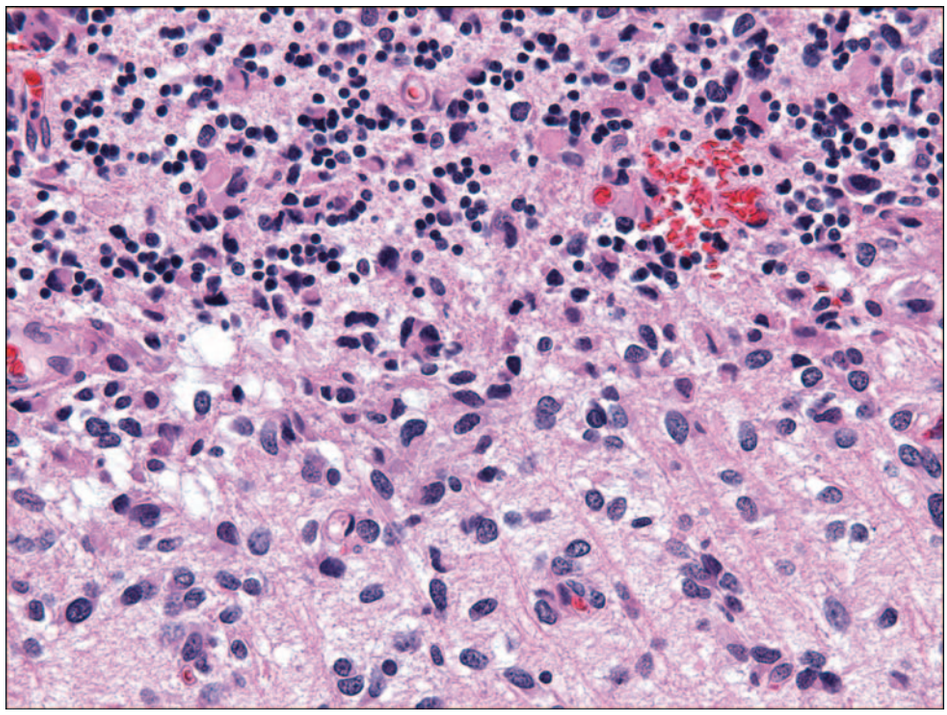


Figure 1.5. Granular cell neurons of the cerebellum are seen in the upper field. Infiltrating neoplastic cells in this medulloblastoma are seen to be considerably larger, although cytological preparations and cryosections of cerebellar tissue in which granule cells predominate may be mistaken for a "small blue cell" tumor.

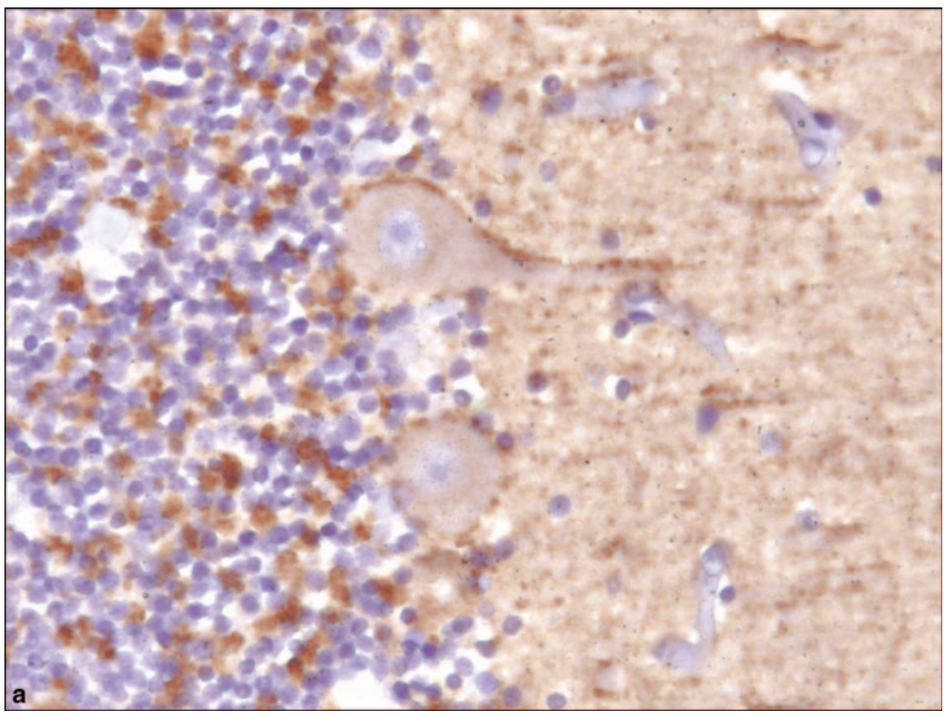
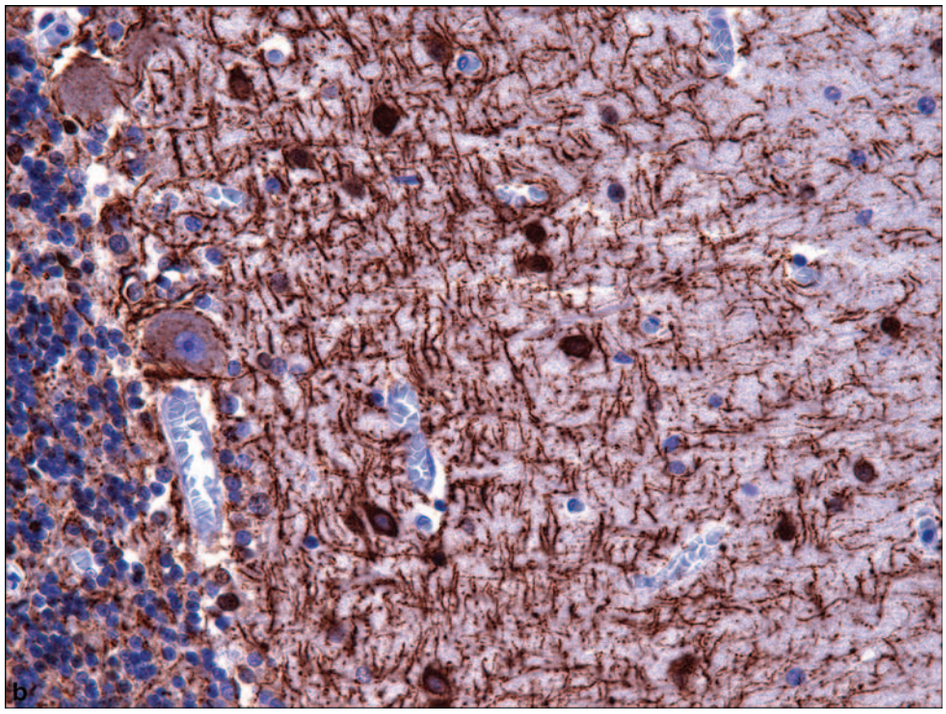


Figure 1.6. Immunohistochemistry for neuronal differentiation: (a) synaptophysin; (b) neurofilament; (c) *neuN*.

by hematoxylin – eosin defined (H&E) stain or especially by GFAP immunohistochemistry (Figure 1.7). This may be useful in distinguishing white matter astrocytes from oligodendrocytes. A particular type of chronic gliosis is recognizable as dense subpial gliosis often seen in chronic epilepsy resection specimens, known as Chaslin's gliosis (Figure 1.8). Distinguishing reactive



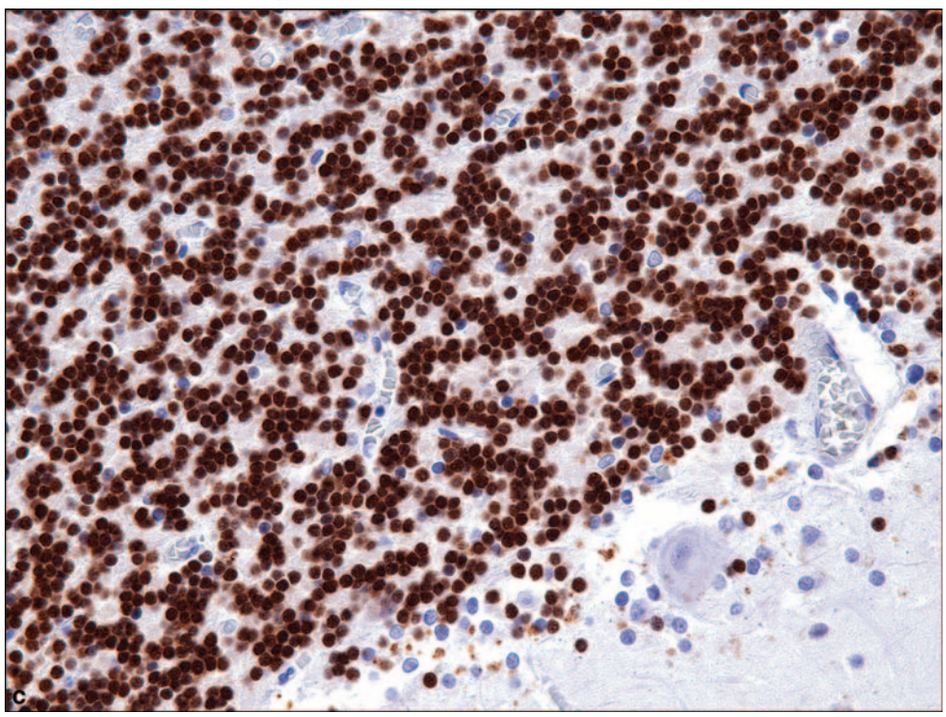


Figure 1.6. *continued.*

from neoplastic astrocytes may represent a significant challenge, and this challenge is discussed under ''Astrocytic Tumors.''

Corpora amylacea are age-related inclusions in astrocytes, which should not be confused with other pathological inclusions or microorganisms such as fungi. These are easily identified with a periodic acid – Schiff (PAS) stain and

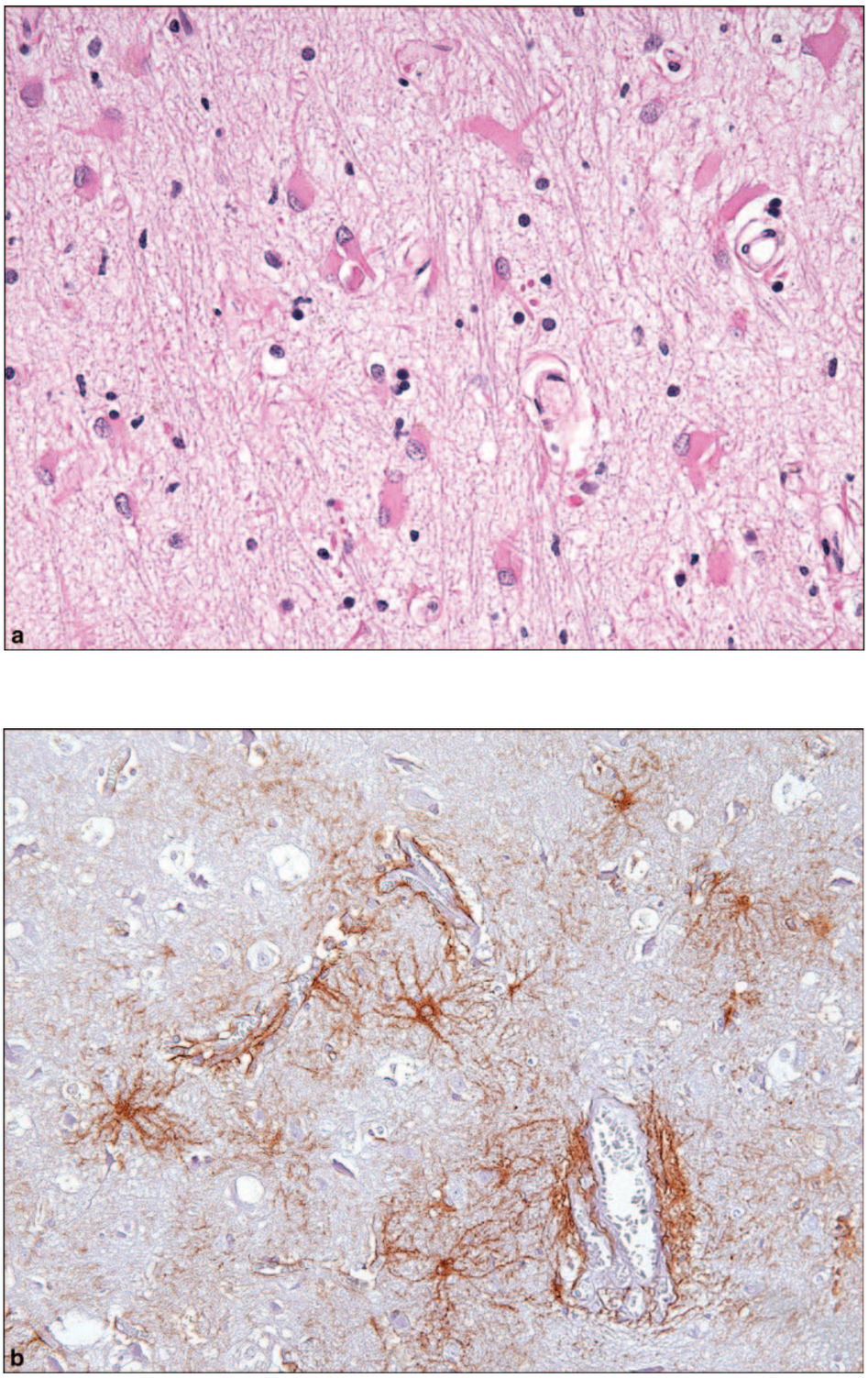


Figure 1.7. Immunohistochemistry for glial differentiation: (a) reactive fibrillary astrocytes; (b) GFAP immunohistochemistry.

usually signify chronic gliosis (Figure 1.9). Another feature of reactive, and especially indolent and chronic gliosis are Rosenthal fibers. These are brightly eosinophilic elongated or beaded structures, which are also intracellular inclusions in astrocytes although they appear as solitary structures within the brain background (Figure 1.10).

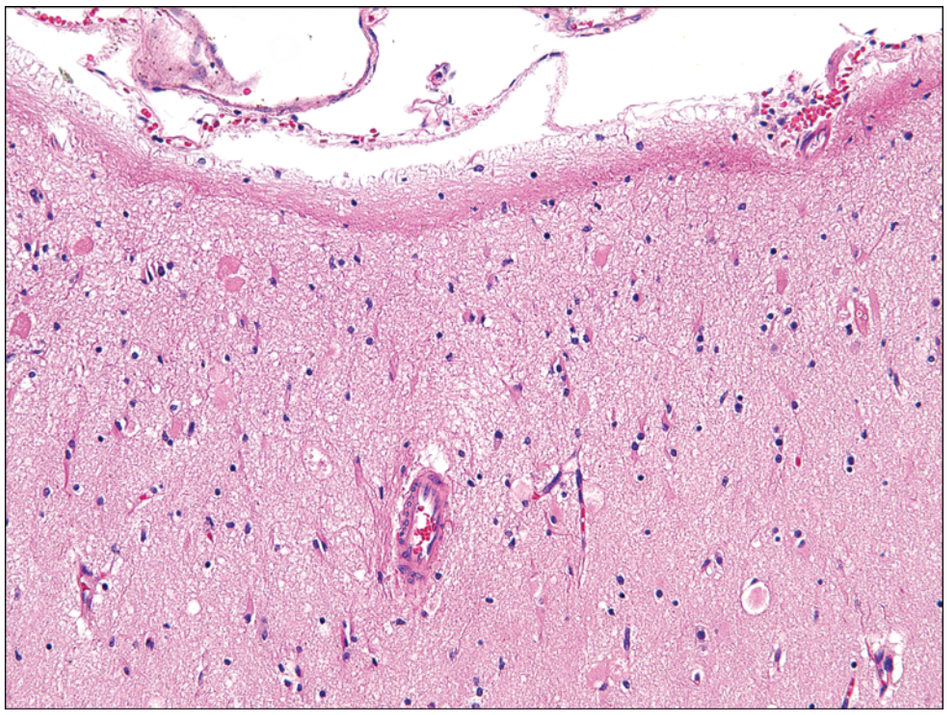


Figure 1.8. Dense subpial or interface (Chaslin's) gliosis.

Reactive astrocytes may undergo mitotic activity and one feature is the multinucleated Creutzfeldt astrocyte with its characteristic "micronuclei." These may be a conspicuous feature of demyelinating disease (Chapter 6, Figure 6.1). The *gemistocytic astrocyte* is one with abundant eosinophilic cytoplasm causing nuclear displacement. This may be a striking feature of reactive processes, such as that seen in the wall of a cerebral infarction or abscess, and is sometimes difficult to distinguish from a neoplastic gemistocytic astrocyte.

Perhaps one of the most striking examples of abnormal cellular morphologies among reactive astrocytes may be seen by the surgical neuropathologist in examples of progressive multifocal leukoencephalopathy. These are markedly enlarged cells with bizarre nuclei (Figure 1.11).

Another more subtle form of reactive astrocytosis is in the form of metabolic astrocytes, the most typical of which are designated the Alzheimer Type 2 astrocytes (Figure 1.12). This is not usually a primary diagnostic issue in surgical neuropathology; however, they should not be confused with other types of infiltrating, particularly neoplastic cells such as there in oligodendroglioma in gray matter.

Oligodendrocytes are especially plentiful in CNS white matter being the myelinating cell of the CNS, which includes the optic nerves. Their inconspicuous round nuclei are scattered evenly or in vague rows throughout white matter, a tendency that can become more pronounced in the atrophic process that affects the aged brain (Figure 1.13). This may create an unsettling degree of hypercellularity that may even be misdiagnosed as a diffuse glioma. Oligodendrocytes may also be noted in gray matter as innocuous cells loosely arranged

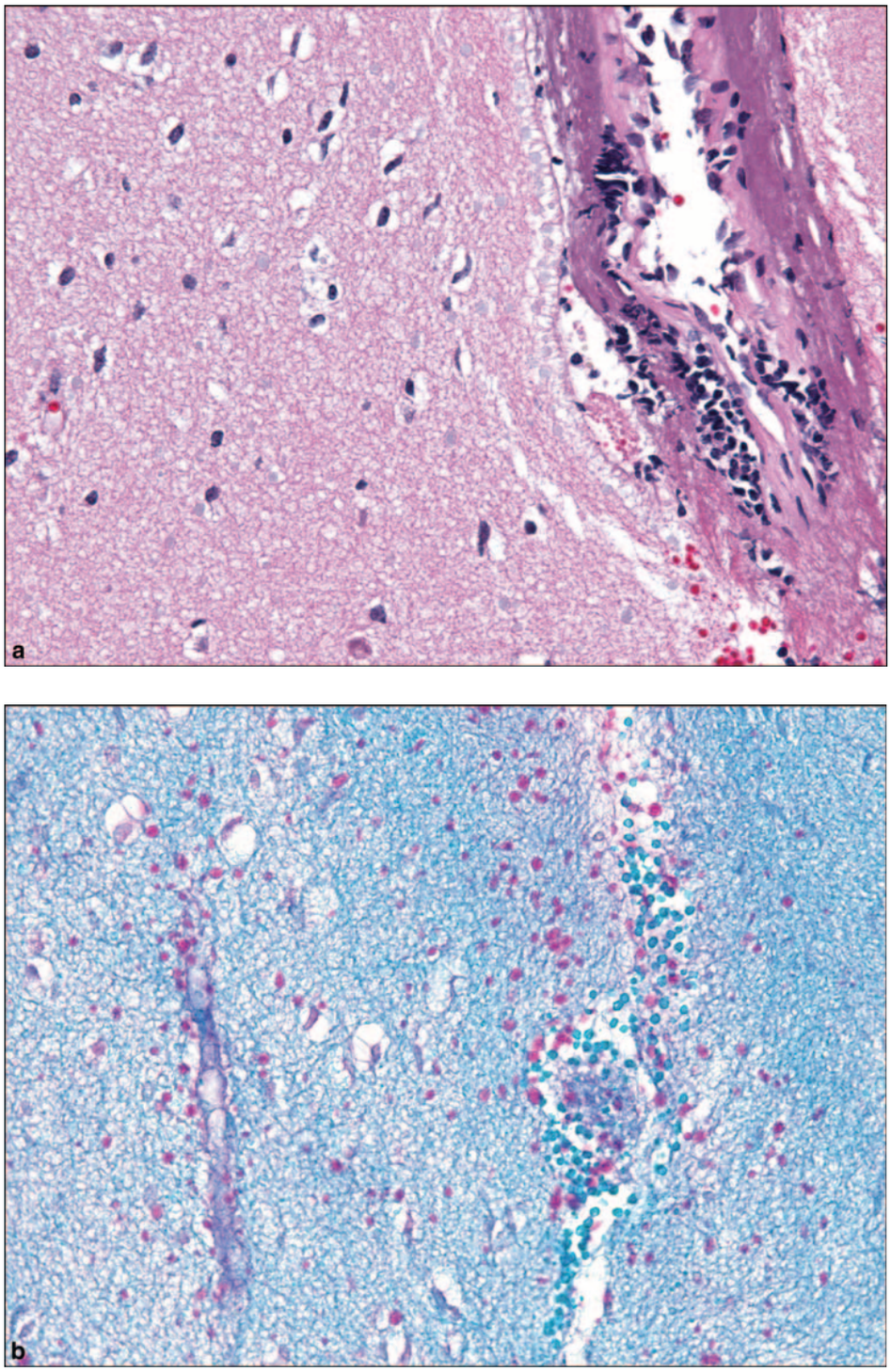


Figure 1.9. (a) Corpora amylacea may be inconspicuous in H&E-stained sections, but (b) are easily identified with a PAS stain.

around neuronal cell bodies. Unfortunately, there are no immunostains that reliably and specifically distinguish oligodendrocytes from astrocytes.

Ependymocytes are cuboidal or columnar ciliated cells that line ventricles (Figure 1.14). *Choroid plexus epithelium* is a specialized form of ependymal cell. The hypocellular and fibrillary zone immediately subjacent to the ependymal lining is known as the subependymal plate. In this location, clusters of ependymal