Chapter 19
Non-neoplastic Disorders

There are a large number of non-neoplastic processes of inflammatory, vascular, degenerative, metabolic, malformative, traumatic, toxic, or simply unknown origin affecting the CNS, but here we will only cover those that lend themselves to intraoperative consultation. These processes may be grouped together into the four categories that we saw in the algorithm for non-neoplastic disorders: benign cystic lesions, and "solid" lesions with predominance of acute inflammatory cells, chronic inflammatory cells, and macrophages. Benign cystic lesions were covered in the previous chapter, which is why we will cover the three remaining ones together with an independent section on inflammatory lesions in AIDS patients because of their special features.

Non-neoplastic Disorders of the CNS: Algorithmic Approach (Fig. 19.1)

CNS lesions with predominance of inflammatory cells and/or macrophages may suggest a neoplasia, both clinically and radiologically. During the intraoperative consultation, clinical and radiologic information usually is not very helpful because the picture may be very confusing to both, the radiologist and the neurosurgeon. This presents a major challenge to the pathologist, who can only count on the microscope to answer a very concrete question: neoplastic or non-neoplastic? In this compromising situation, the cytologic

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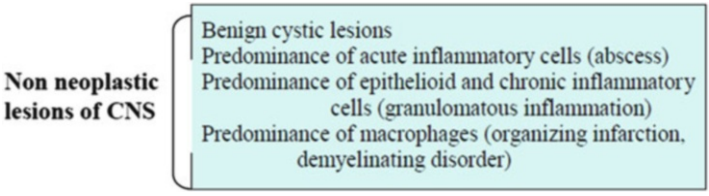

FIG. 19.1. Non-neoplastic disorders of the CNS: algorithmic approach.

method can be a good ally, because the characteristic features of macrophages and inflammatory cells, obscured in frozen sections, are nicely preserved in smears. Thus, the unequivocal identification of large numbers of inflammatory cells or abundant macrophages in smears virtually rules out the diagnosis of neoplasia and guides the diagnosis toward an inflammatory lesion, a non-neoplastic necrotizing process, or a demyelinating disease.

Acute Inflammatory Cell-Rich Lesions

Acute pyogenic encephalitis starts as a focus of cerebritis corresponding to an ill-defined area of parenchyma with acute inflammatory changes, necrotic foci, and surrounding edema. Without adequate treatment, the lesion progresses in about 2 weeks, and turns into an abscess with purulent content surrounded by a granulation tissue-like zone of fibroblastic and angioblastic activity (*pyogenic abscess*). At this stage, the lesion has the distinctive ring enhancement and may be approached surgically to drain it, or because the radiologic image was confused with that of a malignant glioma. Smears from the purulent content show abundant neutrophils, fibrin strands, and necrotic debris (Fig. 19.2). If the biopsy specimen is taken from the outer zone of the lesion, one may encounter predominantly chronic inflammatory cells, macrophages, proliferating vessels, and prominent gliosis (beware of mistaking it for glioma). Triaging tissue for aerobic and anaerobic culture for bacteria and fungi is essential, the most commonly identified organisms being aerobic gram-negative bacilli, *Streptococcus sp.*, *Staphylococcus aureus*, and anaerobic organisms, but mixed infections

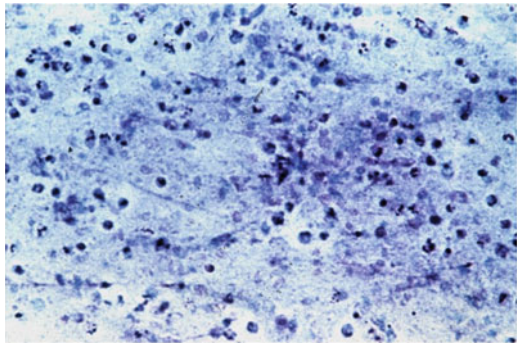

Fig. 19.2. Pyogenic abscess. Purulent content with abundant neutrophils (pyocytes) and fibrinonecrotic debris. Smear, Papanicolaou.

are common. In immunocompromised patients *Mycobacterium*, *Nocardia*, and fungi become more prevalent.

Epithelioid-Cell and Lymphoid-Cell-Rich Lesions

Even though we should take into account all processes that can cause granulomatous inflammation (Table 19.1); in most instances granulomatous disease is a result of sarcoidosis or infection, particularly mycobacterial infection.

Thus, the identification of epithelioid and lymphoplasmacytic cells in intraoperative consultation should prompt triaging of tissue for culture. Additional stainings for mycobacterial and fungal organisms should be performed on permanent sections.

Neurosarcoidosis

In the course of a sarcoidosis, involvement of the central or peripheral nervous system occurs with a certain frequency (about 5 %), in some cases being the first symptom of the disease. The preferential location in the CNS is basal and medial, affecting mainly the leptomeninges (granulomatous basilar meningitis), but the parenchyma of the hypothalamic region and pituitary gland

Table 19.1. CNS inflammatory granulomatous lesions.

Sarcoidosis
Infections (mycobacterial, fungal)
Secondary to germinoma
Secondary to foreign body
Suture material
Textiloma
Parasites
Granulomatous vasculitis

(Modified from Prayson RA, Cohen ML. Practical Differential diagnosis in Surgical Neuropathology, New Jersey: Humana Press, 2000.)

may also be involved, whether by extension of the meningeal lesion or in an isolated manner. Smears show a chronic inflammatory cell infiltrate and tight clusters of epithelioid cells (granulomas). Occasional multinucleated giant cells can be seen, but necrosis is absent (Fig. 19.3). Microorganisms should be ruled out subsequently by special staining and culture, even if their absence does not mean with absolute certainty that this is a case of sarcoidosis. This should be based on ancillary serologic tests and clinico-radiologic examination.

Mycobacterial Infections

Tuberculous mycobacterial infection is common in immunocompromised patients particularly in HIV-seropositive individuals and in developing countries. Immunosuppresion also predisposes to infection with atypical mycobacteria (*M. avium–intracellulare*, *M. africanus*). In addition to tuberculous meningitis, with its classic location in the basal cisterns, tuberculosis may cause intraparenchymal abscesses and tuberculomas, which may be mistaken for an aggressive glial neoplasia. Tuberculomas are nodular and discrete lesions, with central caseous chalky material and an outer rim of a granulation tissue-like zone with granulomatous inflammation (Fig. 19.4a). Depending on the biopsied zone, the cytologic smears may be purely necrotic, or display loosely formed granulomas with admixed necrosis and inflammatory cells (Fig. 19.5). Smears from a tuberculous abscess are similar to those

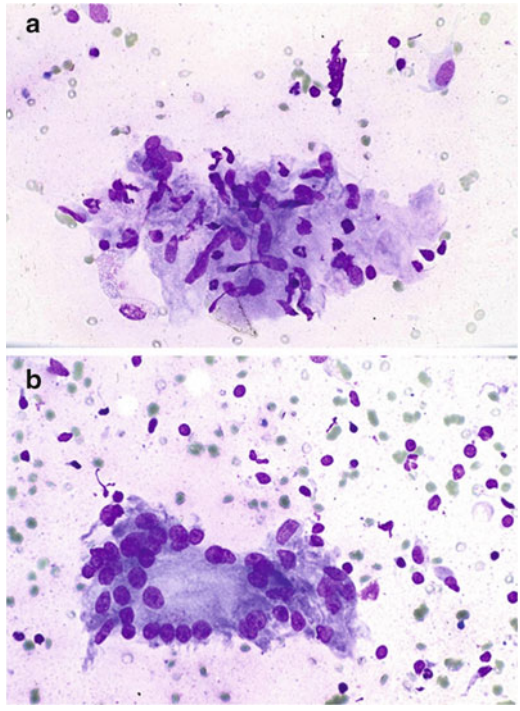

FIG. 19.3. Sarcoidosis. (**a**) Tight cluster of epithelioid histiocytes (granuloma). (**b**) Multinucleated giant cell and chronic inflammatory infiltrate ((**a**, **b**) Smears, Romanowsky).

of a pyogenic abscess and typically lack epithelioid granulomas and giant cells. Again, the definitive diagnosis must be performed with the aid of acid-fast stains, polymerase chain reaction assay, or culture (Fig. 19.4b).

Macrophage-Rich Lesions

There are a large number of CNS lesions, of a very different nature, that share a conspicuous component of lipid-laden or foamy macrophages. Some are authentic rarities which is why we

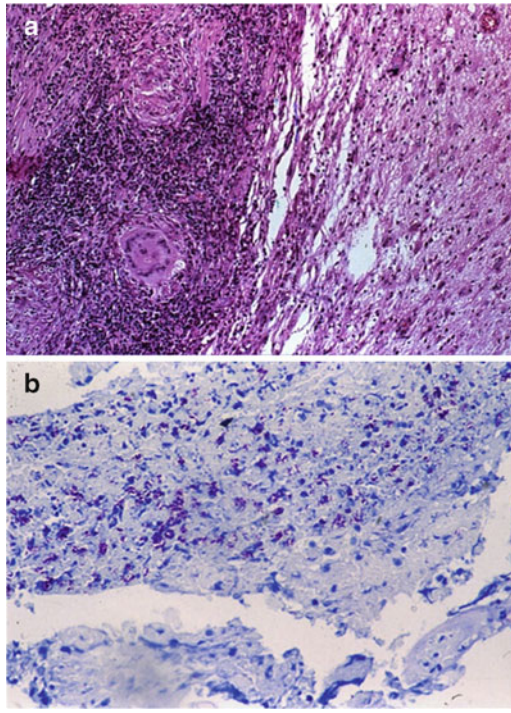

FIG. 19.4. Tuberculosis. (**a**) Well-demarcated cerebral tuberculoma with an outer rim of granulomatous inflammation. (**b**) Brain biopsy from the wall of a tuberculous abscess showing abundant Zhiel-Neelsen-positive mycobacterial organisms.

have listed only those amenable to occasional neurosurgical intervention for purposes of definitive diagnosis in Table 19.2.

Histiocytosis and xanthogranulomatous reaction in cysts have already been covered in their corresponding chapters. We discuss progressive multifocal leukoencephalopathy (PML) in the special section on inflammatory lesions found in AIDS.

Tumor-Like Demyelinating Lesion

The multicentric foci of demyelination of classic multiple sclerosis usually does not present a diagnostic problem. However, isolated

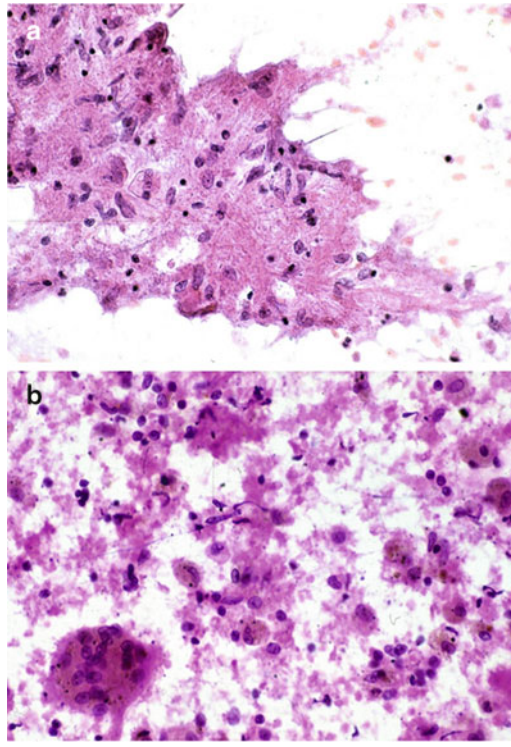

FIG. 19.5. Tuberculosis. (**a**) Loose cluster of epithelioid histiocytes (granuloma). (**b**) Multinucleated giant cell, histiocytes, and inflammatory cells in a necrotic background ((**a**, **b**) Smears, H&E).

lesions, which are well-correlated with the initial phase of multiple sclerosis or some other demyelinating variant, may show as space-occupying lesions associated with edema, a mass effect, and evidence of disruption of the blood–brain barrier on CT/MR scans, which is why they may be mistaken for an aggressive glial neoplasia. These so-called tumor-like demyelinating lesions (TLDLs) may involve any region of the central nervous system, the spinal cord included, but most are located in the subcortical or periventricular white matter. They affect mainly young and adult patients, even though the age at diagnosis extends from 20 to 80 years of age. In many cases of these TLDLs, a biopsy is performed, which gives rise to a serious diagnostic problem, because

Table 19.2. Macrophage-rich lesions.

Tumor-like demyelinating lesion (TLDL)
Organizing infarction
Progressive multifocal leukoencephalopathy (PML)
Histiocytosis
Xanthogranulomatous reaction in cysts

the abundant macrophages and reactive astrocytes, characteristic of this process, may be confused with neoplastic oligodendrocytes and astrocytes in frozen sections (TLDLs are the most common conditions misdiagnosed as gliomas). This panorama, so confusing, may be made clearer by use of the cytologic technique, thereby easily ruling out the possibility of neoplasia. Smears show a granular-vacuolated background with foamy, sometimes lipid-laden macrophages and prominent reactive astrocytes. Some astrocytes may display an "exploded" nucleus that either resembles scattered chromosomes or multiple micronuclei (Creutzfeldt cells) that are quite characteristic of TLDL. Occasionally, a dense chronic inflammatory cell component of bland-appearing lymphocytes may be seen, but a fibrillary background with neoplastic astrocytes (diffuse astrocytoma) or round oligodendrocytes with scant and wispy cytoplasm (oligodendroglioma) are absent (Fig. 19.6).

Cerebral Infarction

The range of cytomorphologic changes in CNS infarction is variable, depending on the severity of tissue injury, but changes that are sufficiently intense to be confused with a malignant glioma display well-developed and noticeable changes during the intraoperative consultation. After an initial phase of edema and acute inflammatory infiltrate, starting on the 4th to 7th days, the changes progress to obvious tissue necrosis with intense infiltration by foamy, lipid-laden macrophages. This macrophage infiltration is joined progressively by a proliferation of reactive astrocytes and neoformed microvessels. Smears show a picture very different from that of

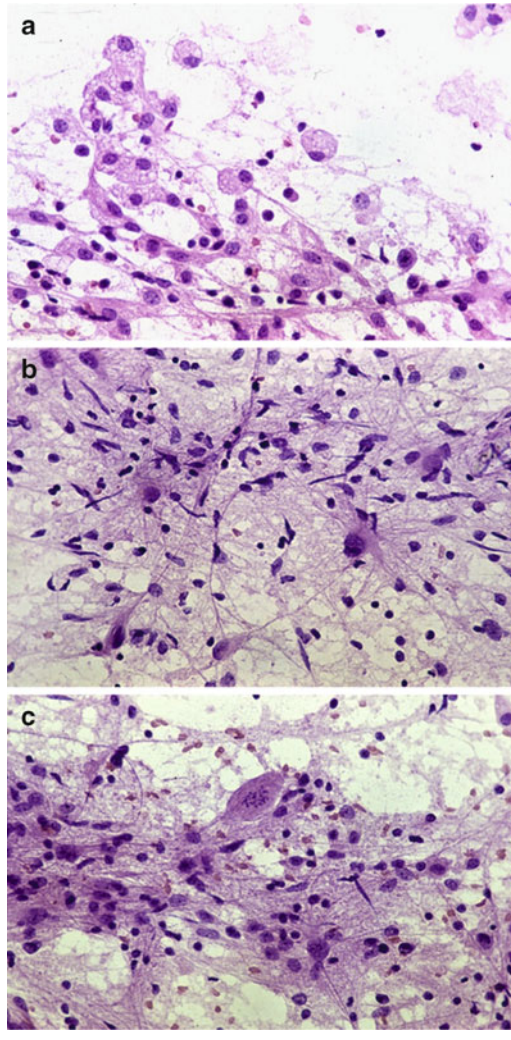

FIG. 19.6. TLDL. Smears consist of abundant well-defined foamy macrophages (**a**) admixed with reactive astrocytes and inflammatory cells (**b**) in a granular-vacuolated background. Some astrocytes show "exploded" nuclei (Creutzfeldt cells) (**c**) ((**a**– **c**) Smears H&E).

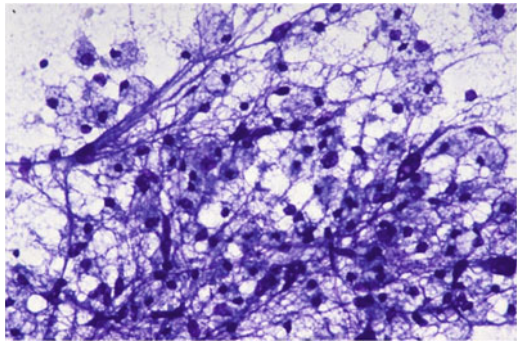

FIG. 19.7. Cerebral infarction. Smear displaying well-defined lipid-laden macrophages and some reactive astrocytes with coarse processes. The background shows abundant lipid droplets. Romanowsky.

glioma with abundant, isolated, and well-defined macrophages. Occasionally, proliferating capillaries and reactive astrocytes may be observed, even though reactive astrocytes are not as abundant as in TLDLs. The background may be granular-vacuolated (necrotic debris and lipids droplets), but not fibrillary (Fig. 19.7).

Inflammatory/Infectious Lesions in AIDS

A subset of AIDS patients develop neurologic symptoms related to the presence of a cerebral, rounded mass lesion in CT/MR scans. The most common causes of such lesions are toxoplasmosis and primary CNS lymphoma, although other etiologies cannot be ruled out clinically or radiologically. What should be done in these cases is to treat the lesion as if it were toxoplasmosis (the most frequent cause), and to biopsy only those that do not respond to pharmacologic treatment. In spite of this, it is not uncommon to find cases of toxoplasmosis (resistant to empirical treatment) in the biopsied cases. Other infectious diseases with CT/MR scan abnormalities, occasionally biopsied and sent for intraoperative consultation, are PML and cytomegalovirus encephalitis.

Toxoplasmosis

Up to the explosive spread of AIDS in the 1980s, cerebral toxoplasmosis used to be a rare process related to immunosuppression or affecting newborns. Since then, its incidence has increased to the point of becoming a common disease and the most frequent cause of intracranial masses in AIDS patients (almost half of seropositive patients develop the disease). The causative agent is an obligate intracellular protozoan (*Toxoplasma gondii*), which remains immunologically inert (bradyzoites) for an indefinite time in the interior of intracellular pseudocysts and true cysts. When the immunodeficiency state of the carrier favors its release, it causes a rapid proliferation and full development of its pathogenic action (tachyzoites). At first, the lesion is of the acute inflammatory type, with areas of necrosis and edema, progressing rapidly to the *Toxoplasma* "abscess." This consists of a necrotic central nucleus surrounded by inflamed and edematous tissue. The inflammatory infiltrate is polymorphic with segmented leukocytes, lymphocytes, histiocytes, and macrophages. In more peripheral areas, it is common to find vascular lesions with thrombosis and fibrinoid necrosis. It is in this external zone where "free" tachyzoite- and bradyzoite-filled cysts are most numerous. The intraoperative cytologic diagnosis is based on the identification of these specific elements (tachyzoites and cysts) in an unspecific inflammatory-necrotic background. Cysts are spherical bag-like structures with abundant bradyzoites in their interior. Also, "free" tachyzoites may be recognized in the form of small aggregates, but it is easy to confuse them with cellular debris. The organisms measure 4–8 mm and exhibit a crescentic profile with a hyperchromatic, eccentric nucleus. Cysts should not be confused with "explosive" mitotic figures whose chromosomes vaguely resemble bradyzoites. Differentiation is simple, because chromosomes, as against what happens in bradyzoites, remain confined to the center of the cell and do not reach the external cell border (Fig. 19.8).

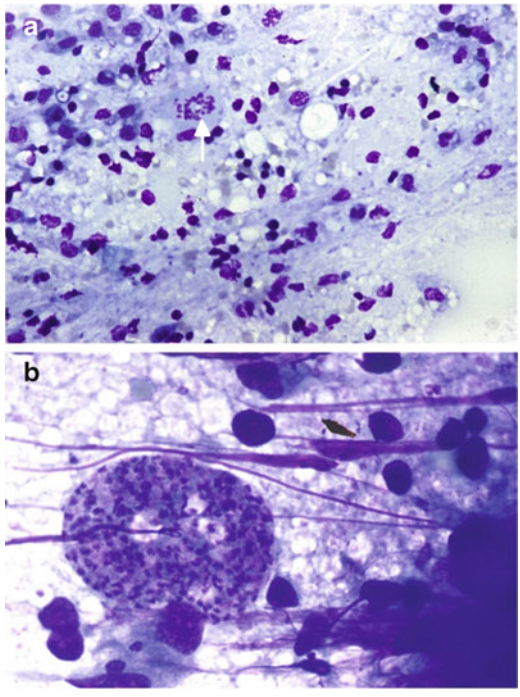

FIG. 19.8. Toxoplasmosis. Smears consist of polymorphous inflammatory infiltrate with histiocytes and astrocytes, some displaying "explosive" mitosis (*arrow*) (**a**), and bradyzoites-filled cysts (**b**). These mitotic figures should be not mistaken for toxoplasma cysts ((**a**, **b**) Smears, Romanowsky).

Progressive Multifocal Leukoencephalopathy

Described by Astrom et al. (1958) as a neurologic complication in tumors in terminal stage, leukemias, and Hodgkin's disease, PML used to be a rare disease until the expansion of the AIDS pandemic. However, in HIV-seropositive patients, the incidence is high (about 2–5 %) and may be the presenting manifestation of the disease. The cause is an opportunistic virus of the polyoma group (JC virus) that shows a marked tropism for

oligodendrocytes. The reactivation of its pathogenic effect in immunosuppressed patients determines the progressive development of multiple foci of demyelinization with infiltration by lipid-laden macrophages and atypical astrocytic hyperplasia. The findings of neuroimaging studies are quite characteristic, displaying scattered nonenhancing foci of white-matter hypodensity, preferentially located in the cerebral hemispheres, and the corpus callosum, although any level of the neuraxis may be affected. In such cases, PCR amplification of JC virus DNA sequences from CSF is the diagnostic method of choice, but occasionally a biopsy is performed, especially in tumefactive variants associated with a mass effect on CT/MR scan, or PCR negative cases. Smears show an appearance very similar to that observed in TLDL, with a granular-vacuolated background, lipid-laden macrophages, and reactive astrocytes, but with two highly significant differences: the presence of infected oligodendrocytes and of very large, pleomorphic bizarre-appearing astrocytes. Infected oligodendrocytes display intense nuclear anlargement and changes of three types: coarse hyperchromatism with clearings, chromatin effacement ("ground-glass" appearance), and well-defined inclusion bodies. The first of these is the most frequent type and may be compared with the nuclear changes of the polyomavirus in urine ("decoy cells"). On the other hand, atypical astrocytic hyperplasia is especially conspicuous, with enlarged astrocytes exhibiting a worrisome appearance very similar to that of neoplastic cells (Fig. 19.9).

CMV Encephalitis

Another opportunistic virus, cytomegalovirus, causes chronic and subacute encephalitis cases with periventricular predominance that are difficult to distinguish, clinically and radiologically, from the pictures of dementia associated with HIV. PCR tests of CSF only identify CMV successfully in one third of the cases. Additionally, given the high sensitivity of this technique, confu-

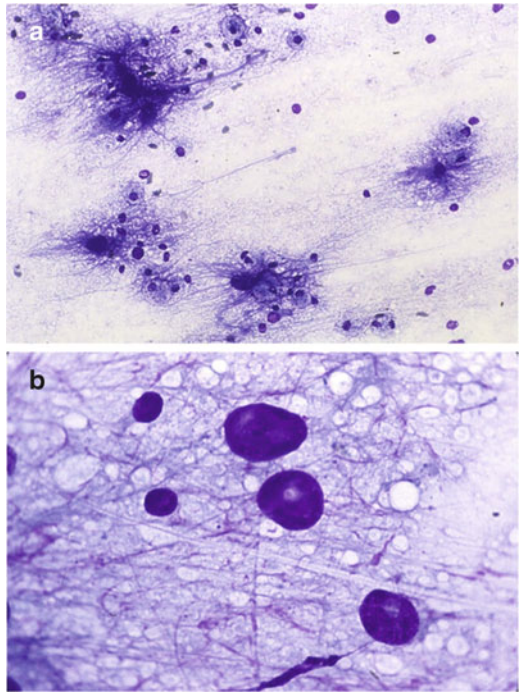

FIG. 19.9. PML. (**a**) Lipid-laden macrophages, atypical reactive astrocytes, and large, infected oligodendrocytes. (**b**) Higher magnification showing enlarged infected oligodendrocytes with nuclear "ground-glass" appearance and clearings (*holes*). Compare the nuclear size with that of the two normal oligodendrocytes ((**a**, **b**) Smears, Romanowsky).

sion of latent with truly active infections is possible. That is why it is useful to recognize this type of lesion in stereotactic biopsies, based on the identification of the cytopathic changes that are characteristic of the virus. The cells, of large size, display a voluminous nuclear basophilic inclusion surrounded by a clear halo due to the margination of chromatin (an "owl's eye" nucleus). At the same time, less well-defined small intracytoplasmic inclusions

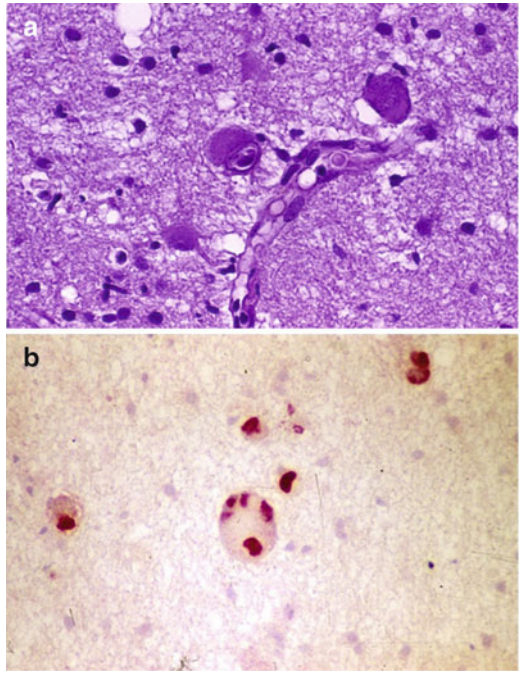

FIG. 19.10. CMV encephalitis. (**a**) Brain biopsy showing enlarged infected astrocytes. One of them exhibits a typical voluminous nuclear inclusion. (**b**) Immunostain for viral antigen displaying many positive cells not seen with conventional stains.

may be seen. This cytopathic action is ubiquitous and may involve the whole range of brain tissue cells: neurons, astrocytes, oligodendrocytes, ependymal cells, endothelial cells, and even macrophages. The identification of these infected cells is made much easier by specific immunostaining, revealing positive immunoreactivity even in cells in which the viral cytopathic effect is not fully developed (Fig. 19.10).

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