Clinical Features. Since the virus enters the CNS by ascending along the peripheral nerves from the wound site, the incubation period (usually between 1 and 3 months) depends on the distance between the wound and the brain. The disease begins with nonspecific symptoms such as malaise, headache, and fever, but the conjunction of these symptoms with local paresthesias around the wound is diagnostic. As the infection advances, the affected individual exhibits extraordinary CNS excitability; the slightest touch is painful and produces violent motor responses or even convulsions. Contracture of the pharyngeal musculature on swallowing produces foaming at the mouth, which may create an aversion to swallowing even water (hydrophobia). There are signs of meningeal irritation and, as the disease progresses, flaccid paralysis. Alternating periods of mania and stupor progress to coma and eventually death from respiratory failure.

Human Immunodeficiency Virus

In the period before the availability of effective antiretroviral therapy, neuropathologic changes were demonstrated at postmortem examination in as many as 80% to 90% of cases of AIDS. These changes stem from direct effects of virus on the nervous system, opportunistic infections, and primary CNS lymphoma, a high fraction of which were EBV-positive B cell tumors. There has been a decrease in the frequency of these secondary effects of HIV infection thanks to the efficacy of multidrug antiretroviral therapy.

HIV aseptic meningitis occurs within 1 to 2 weeks of seroconversion in about 10% of patients; antibodies to HIV can be demonstrated and the virus can be isolated from the CSF. The neuropathologic studies of the early, acute phases of HIV invasion of the CNS have shown mild lymphocytic meningitis, perivascular inflammation, and some myelin loss. Among CNS cell types only microglia express both the CD4 coreceptor and the chemokine receptors (CCR5 or CXCR4) that are required in combination for efficient infection by HIV. During the chronic phase, HIV encephalitis is commonly found when symptomatic individuals come to autopsy.

An "immune reconstitution inflammatory syndrome" (IRIS) has been identified in patients with AIDS after effective treatment; the syndrome is recognized as a paradoxical deterioration after starting therapy, and consists of an exuberant "reconstituted" inflammatory response while on antiretroviral therapy (Chapter 6). In the CNS, IRIS has caused paradoxical exacerbation of symptoms from opportunistic infections. Neuropathologic studies confirm intense inflammation with an influx of CD8+ lymphocytes.

Cognitive changes, some mild and others florid enough to be termed *HIV-associated dementia*, appear to have persisted in the era of effective anti-HIV treatment regimens. Rather than having a specific pathologic lesion as its correlate, this disorder is most closely related to inflammatory activation of microglial cells, not all of which are necessarily HIV-infected. A wide range of possible mechanisms for neuronal dysfunction and injury in this setting have been proposed, including the actions of inflammatory cytokines and a cascade of toxic effects of HIV-derived proteins; in all probability, both have contributory roles in the pathogenesis of brain injury (Chapter 6).

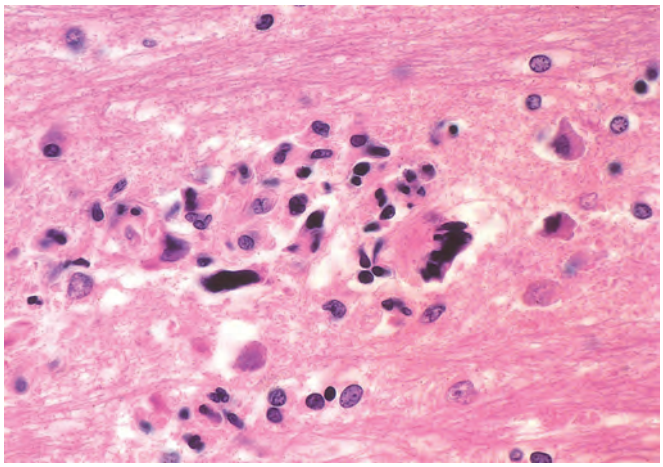

Figure 28-26 HIV encephalitis. Note the microglial nodule and multinucleated giant cells.

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HIV encephalitis is a chronic inflammatory reaction associated with widely distributed **microglial nodules**, often containing macrophage-derived **multinucleated giant cell**s; foci of tissue necrosis and reactive gliosis are sometimes seen together with these lesions (Fig. 28-26). Some of the microglial nodules are found near small blood vessels, which show abnormally prominent endothelial cells and perivascular foamy or pigment-laden macrophages. These changes are especially prominent in the subcortical white matter, diencephalon, and brainstem. In some cases there is also a disorder of white matter characterized by multifocal or diffuse areas of myelin pallor, axonal swelling and gliosis. HIV can be detected in CD4+ mononuclear and multinucleated macrophages and microglia.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an encephalitis caused by the JC polyomavirus; because the virus preferentially infects oligodendrocytes, demyelination is its principal pathologic effect. The disease occurs almost exclusively in immunosuppressed individuals in various clinical settings, including chronic lymphoproliferative or myeloproliferative illnesses, immunosuppressive chemotherapy including monoclonal antibody therapy targeting integrins, granulomatous diseases, and AIDS.

Although most people have serologic evidence of exposure to JC virus by the age of 14 years, primary infection is asymptomatic. PML results from the reactivation of virus in the setting of immunosuppression. Clinically, affected individuals develop focal and relentlessly progressive

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The lesions consist of patches of irregular, ill-defined white matter injury that range in size from millimeters to near confluent involvement of large regions of the brain (Fig. 28-27). Microscopically, individual lesions show an area of demyelination, most often in a subcortical location, in the center of which are scattered lipid-laden macrophages and a reduced number of axons. Particularly at the edge of the lesion are greatly