Pathologic Quiz Case

Progressive Fatal Encephalopathy in an Immunosuppressed Patient With a History of Discoid Lupus Erythematosus

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The patient was a 70-year-old white woman with a progressive mental deterioration during a period of 3 months. Her initial complaint was passing out at home. She had some balance problems for 6 months prior to this event with frequent falls along with some intermittent night sweats and inflammatory red nodular changes on her legs and arms, which gradually faded. The patient had been diagnosed with antinuclear antibody–negative cutaneous lupus for which she was taking prednisone and had a history of deep venous thrombosis but without documented evidence of lupus anticoagulant. Also, she had carried a diagnosis of myelodysplastic disorder with anemia for 4 years, leading to splenectomy. She had not traveled nor had any other history of specific exposure or ingestion. She had a healthy cat. Initial computed tomographic scan and magnetic resonance imaging (MRI) were suspicious for acute cerebral vascular insult. During the next month, the patient started having frequent seizurelike symptoms and intermittent fevers, becoming increasingly somnolent and confused. She also developed syndrome of inappropriate antidiuretic hormone secretion. She did not respond to treatment with prednisone or broad-spectrum antibacterial and antiviral medications. A repeated MRI of the head demonstrated a fairly intense contrast-enhanced area in the right temporal lobe (Figure 1) and was followed by another MRI 2 months after the initial presentation that was consistent with encephalitis within bilateral insular cortex, basal ganglia, temporal lobe, and left occipital lobe involvement. A positron emission tomographic scan was interpreted as ''suggestive of lupus involvement.'' A cerebrospinal fluid (CSF) analysis revealed high protein and low glucose levels with cytology showing occasional atypical cells suggestive of neoplasm (see Figure 4, inset). All viral, bacterial, and fungal etiologies were excluded by negative cultures and serology. A brain biopsy showed a meningoencephalitis along with re-canalization of several arterioles, but no vasculitis, demyelination, or neoplasm. Her condition precipitously deteriorated to the state of being virtually unresponsive. Plasma exchange therapy was attempted as the last treatment resort with no success.

The brain autopsy performed after the patient's death revealed extensive necrosis and softening of the basal portions of the brain. On coronal sections (Figure 2), necrosis extended deeper into the brain parenchyma, involving cortical, subcortical, and limbic structures such as bilateral hippocampus, globus pallidus, right anterior cingulate gyrus, bilateral orbital gyrus, and basal portions of the occipital lobe. There were also round, well-demarcated necrotic masses noted within both insular cortices. Additional significant gross findings were florid bilateral pleural infusions and atelectasis.

Microscopic sections from different necrotic brain areas demonstrated numerous protozoan trophozoites and cysts admixed with extensive necrotic debris, reactive gliosis, and mixed inflammatory infiltrate in a granulomatous pattern. Encysted organisms characterized by a wrinkled outer membrane (exocyst) and small, round inner membrane (endocyst) were scattered throughout the affected areas (Figure 3). Trophozoites have pale eosinophylic karyosomes and are predominantly found in perivascular cuffs (Figure 4) or, less frequently, in the necrotic brain. The inflammatory infiltrate is composed primarily of mononucleated inflammatory cells admixed with polymorphonuclears, eosinophils, and occasional giant cells. The inflammatory cells tend to be angiocentric, associated with fibrinoid necrosis of the blood vessel wall. The mononuclear inflammatory infiltrate is present in the overlying leptomeninges.

What is your diagnosis?

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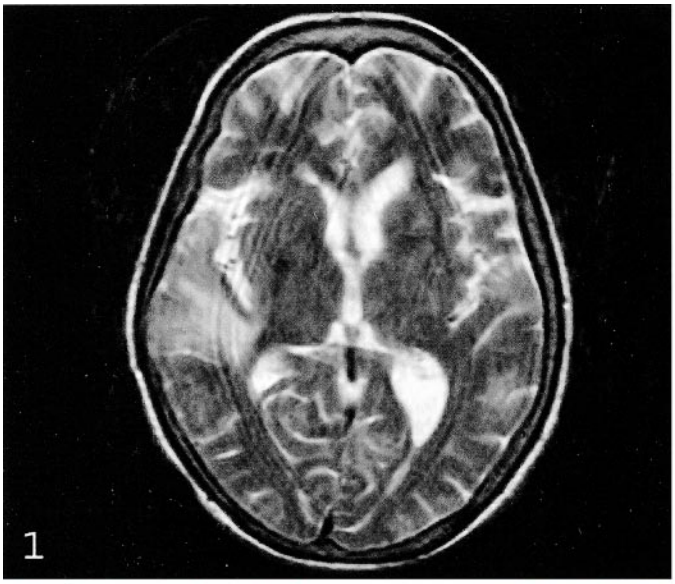

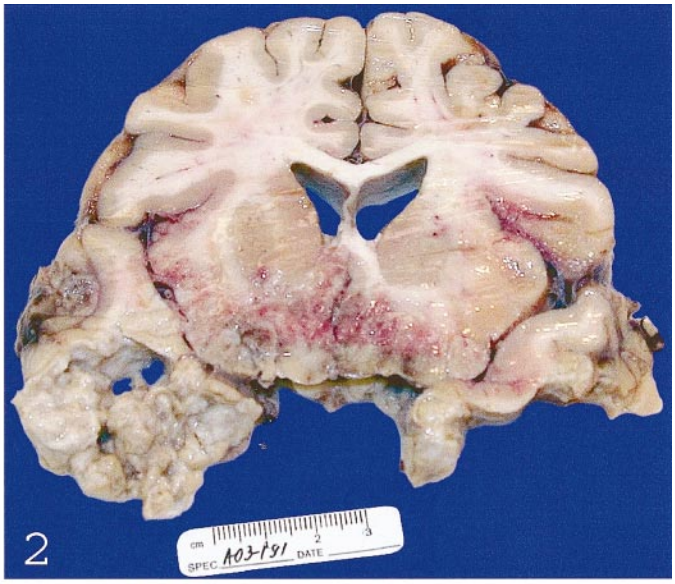

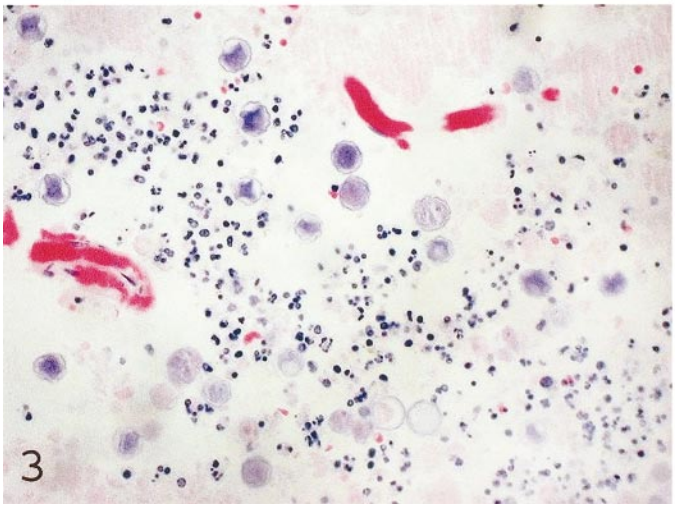

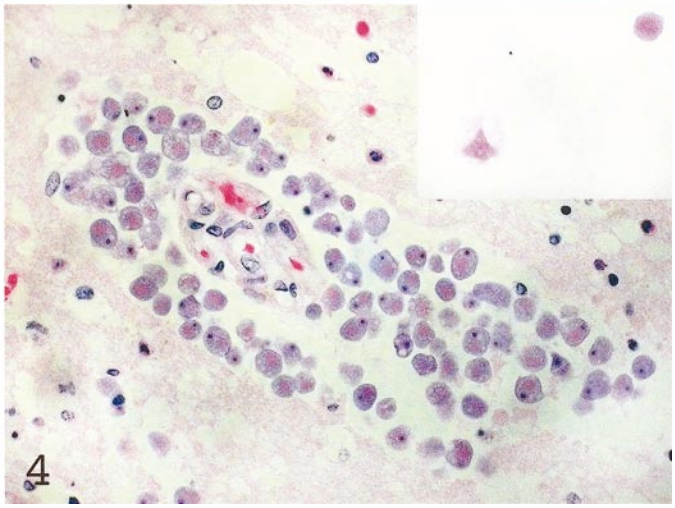

Pathologic Diagnosis: Subacute Granulomatous Meningoencephalitis (*Acanthamoeba culbertsoni*)

Amoebas belonging to the genera *Naegleria*, *Acanthamoeba*, and *Balamuthia* are free-living, amphizoic, and opportunistic protozoa that are ubiquitous in nature. They are widely distributed in fresh water, soil, and dust throughout the world, thus providing a potential source of infection for man and other animals. Specifically, *Acanthamoeba* spp live in ponds, lakes, bottled mineral water, air, and even in dialysis machines and air conditioning units. These amoebae can also act as nonopportunistic pathogens. Human infection has increased significantly during the past 15 years. The epidemiology, immunology, protozoology, pathology, and clinical features of the infections produced by these protozoa differ strikingly. The amoeba's life cycle includes an active feeding trophozoite stage and a dormant cyst stage. Trophozoites feed on bacteria, yeast, and algae. However, both trophozoites and cysts can retain viable bacteria and may serve as reservoirs for bacteria with human pathogenic potential.[1]

Acanthamoebic meningoencephalitis is a slowly progressive infection of the central nervous system (CNS) with an insidious onset. *Acanthamoeba* spp are a well-known cause of a nonfatal, but vision-threatening subacute keratitis of the human eye in healthy individuals, particularly in contact lens wearers.[2] Also, it has been associated with cutaneous lesions, pulmonary disease, otitis, and sinusitis. The infection occurs mostly in patients undergoing immunosuppressive therapy or other immunocompromised patients, such as acquired immunodeficiency syndrome patients, chronic alcoholics, and debilitated and malnourished individuals. There are very few case reports in immunocompetent individuals.[3,4] A case similar to ours with prednisone treatment for systemic lupus erythematosus has been described.[5] The usual portal of entry into the body is through the upper respiratory tract or an ulceration of skin, reaching the CNS through a hematogenous route or via direct spread from an ocular source.[2]

Naegleria fowleri is a thermophilic amoeba that grows well in tropical and subtropical climates. *Naegleria fowleri* generally causes the primary amoebic meningoencephalitis, which is usually purulent and characterized by an acute fulminant course with rapidly progressing obtundation but without localizing signs, leading to death 3 to 7 days after exposure. The victims are usually healthy, young individuals with a history of recent water-related sport activities.[6] It can penetrate through the cribriform plate via the olfactory nerves.

In contrast, the infection caused by *Acanthamoeba* spp or *Balamuthia mandrillaris* is termed *granulomatous amoebic encephalitis*. In immunocompromised individuals, the granulomatous component is negligible. The granulomatous inflammatory masses, resulting in hemorrhagic necrosis, have a predilection for diencephalon, thalamus, brain stem, and posterior fossa structures and are usually multiple.[7]

Imaging findings are striking but nonspecific. A computed tomographic scan can show multiple small-to-large low-density areas in cerebral cortex and underlying white matter, with mild mass effect. An MRI shows areas of high signal on T2-weighted images that enhance heterogeneously or in a ringlike manner.[7] Differential diagnosis includes infarcts from septic emboli, abscesses, tuberculous or fungal granulomas, and primary or metastatic neoplasms. The infection has a chronic or subacute course and may mimic bacterial leptomeningitis, tuberculous meningitis, or viral encephalitis. Common signs include mental status abnormalities, seizures, hemiparesis, ataxia, aphasia, and visual disturbances. Nausea, vomiting, fever, and meningism are often present. Some patients present with symptoms suggesting a brain abscess or neoplasm. The usual natural history is progression to coma and death, the most frequent immediate cause of death being bronchopneumonia.[8]

Neuropathologically, the infection is characterized by brain edema and subacute necrotizing hemorrhagic encephalitis. Trophozoites and cysts mingled with macrophages and other inflammatory cells are usually present within perivascular spaces and also in the necrotic CNS parenchyma. Focal chronic leptomeningitis and vasculitis may be seen in areas near the parenchymal lesions.

Diagnosis of infection includes direct microscopy of wet mounts of CSF or stained smears of CSF sediment, light or electron microscopy of tissues, in vitro cultivation of *Acanthamoeba*, and histological assessment of frozen or paraffin-embedded sections of brain or cutaneous lesion. Immunocytochemistry, chemifluorescent dye staining, polymerase chain reaction, and analysis of DNA sequence variation also have been employed for laboratory diagnosis.[1] In our case specifically, the immunohistochemical tests were performed on multiple sections of the CNS and were positive on a rabbit anti–*A. culbertsoni* antibody.

It is necessary to have a high index of suspicion to recognize this infection, especially when CSF examination is negative for routine organisms and conventional antimeningitis therapy has failed.[3] There is no known therapy for this disease. Various drugs have been tried in the treatment of this condition, with very little therapeutic success. Very few survivors have been described in the literature.[3,9,10]

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References

1. Marciano-Cabral F, Cabral G. Acanthamoeba spp. as agents of disease in humans. *Clin Microbiol Rev.* 2003;16:273–307.
2. Martinez AJ. Free-living amebas: infection of the central nervous system. *Mt Sinai J Med.* 1993;60:271–278.
3. Hamide A, Sarkar E, Kumar N, Das AK, Narayan SK, Parija SC. Acanthameba meningoencephalitis: a case report. *Neurol India.* 2002;50:484–486.
4. Rodriguez R, Mendez O, Molina O, et al. Central nervous system infection by free-living amebas: report of 3 Venezuelan cases [in Spanish]. *Rev Neurol.* 1998;26:1005–1008.
5. Koide J, Okusawa E, Ito T, et al. Granulomatous amoebic encephalitis caused by Acanthamoeba in a patient with systemic lupus erythematosus. *Clin Rheumatol.* 1998;17:329–332.
6. Martinez AJ, Visvesvara GS. Free-living, amphizoic and opportunistic amebas. *Brain Pathol.* 1997;7:583–598.
7. Sell JJ, Rupp FW, Orrison WW Jr. Granulomatous amebic encephalitis caused by acanthamoeba. *Neuroradiology.* 1997;39:434–436.
8. Ma P, Visvesvara GS, Martinez AJ, Theodore FH, Daggett PM, Sawyer TK. Naegleria and Acanthamoeba infections: review. *Rev Infect Dis.* 1990;12:490–513.
9. Sharma PP, Gupta P, Murali MV, Ramachandran VG. Primary amebic meningoencephalitis caused by Acanthamoeba: successfully treated with cotrimoxazole. *Indian Pediatr.* 1993;30:1219–1222.
10. Seijo Martinez M, Gonzalez-Mediero G, Santiago P, et al. Granulomatous amebic encephalitis in a patient with AIDS: isolation of acanthamoeba sp. group II from brain tissue and successful treatment with sulfadiazine and fluconazole. *J Clin Microbiol.* 2000;38:3892–3895.