A Case of Balamuthia mandrillaris Meningoencephalitis

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Balamuthia mandrillaris is a newly described pathogen that causes granulomatous amebic encephalitis, an extremely rare clinical entity that usually occurs in immunosuppressed individuals. We report a case of pathologically proven Balamuthia encephalitis with unusual laboratory and radiologic findings. A 52-year-old woman with idiopathic seizures and a 2-year history of chronic neutropenia of unknown cause had a subacute illness with progressive lethargy, headaches, and coma and died 3 months after the onset of symptoms. Cerebrospinal fluid (CSF) glucose concentrations were extremely low or unmeasurable, a feature not previously described (to our knowledge). Cranial magnetic resonance imaging scans showed a single large temporal lobe nodule, followed 6 weeks later by the appearance of 18 ring-enhancing lesions in the cerebral hemispheres that disappeared after treatment with antibiotics and high-dose corticosteroids. The initial brain biopsy specimen and analysis of CSF samples did not demonstrate amebae, but a second biopsy specimen and the postmortem pathologic examination showed Balamuthia trophozoites surrounded by widespread granulomatous inflammation and vasculitis. The patient's neutropenia and antibiotic use may have caused susceptibility to this organism. Amebic meningoencephalitis should be considered in cases of subacute meningoencephalitis with greatly depressed CSF glucose concentrations and multiple nodular lesions on cerebral imaging. Arch Neurol. 2000;57:1210-1212

REPORT OF A CASE

A 52-year-old woman with chronic idiopathic neutropenia had a generalized seizure. Six years earlier, she had infrequent generalized clonic seizures and the results of cranial magnetic resonance imaging (MRI) were normal. In the 5 years preceding her present illness, she had taken numerous antibiotics for intermittent sinus infections, and during the year prior to her illness she was treated with filgrastim (granulocyte colony-stimulating factor) (300 µg twice a day). Three weeks before the acute illness, she had seen a physician for an ulcerated lesion on her malleolus that was no longer apparent at hospital admission. She awoke from the seizure with slurred speech and left hemiparesis that improved over 3 days, but there was persistent word-finding trouble and marked fatigue. A cranial MRI scan showed a single 1-cm-diameter nodule in the right temporal lobe that did not enhance with gadolinium. For several weeks after the seizure, she slept from Friday night to Monday morning, and also napped uncharacteristically...
each day on returning from work. When awake she had normal cognition. Six weeks later a second MRI scan showed approximately 18 ring-enhancing lesions, measuring 0.5 to 2.5 cm in diameter, distributed throughout both cerebral hemispheres, sparing the cerebellum and brainstem (Figure 1). Analysis of the CSF sample revealed the following values: white blood cell count, $0.4 \times 10^9/L$ (0.90 mononuclear lymphocytes); protein, 2.6 g/L; and glucose, 1.6 mmol/L (28 mg/dL). Treatment with intravenous dexamethsone, vancomycin, and ceftazidime was initiated. A biopsy specimen from a right frontal lobe lesion showed extensive inflammation, with sheets of lymphocytes and plasma cells in a roughly perivascular distribution, and epithelioid cells consistent with granulomatous inflammation. Acid-fast and silver stains were negative for organisms. Cultures obtained from swabs of the biopsy site were negative for bacteria, mycobacteria, and fungi.

In the following 10 days, the patient began having headaches, fevers, episodes of extreme agitation, and intractable vomiting, and over the next 2 weeks she became progressively incoherent, agitated, and lethargic. Cranial computed tomographic scans showed hydrocephalus, and a ventricular drain was inserted. She grimaced in response to noxious stimuli and weakly withdrew all limbs except the left arm from nail bed pressure. Her pupils were 2.5 mm and unreactive, and corneal, oculocephalic, and gag reflexes were absent. Her limbs were flaccid, with normal deep tendon reflexes and bilateral Babinski signs.

During the next 2 weeks, she remained comatose despite the addition of multiple antimicrobial agents to her regimen, including amphotericin, fluconazole, sulfamethoxazole-trimethoprim, meropenem, isoniazid, rifampin, ethambutol, pyrazinamide, and metronidazole). A second CSF analysis showed a white blood cell count of $0.002 \times 10^9/L$, a protein level of 10.8 g/L, and unmeasurably low levels of glucose. A third MRI scan, which was obtained approximately 3 weeks after the previous MRI scan showing multiple ring-enhancing lesions, demonstrated severe hydrocephalus with dilation of the cerebral aqueduct (despite the presence of a functioning drain), irregular ependymal enhancement, and periventricular T2 hyperintensity extending into the caudate, thalami, and midbrain (Figure 2). The original right temporal lesion was seen, but the other ring-enhancing lesions were no longer present (Figure 3).

A biopsy specimen from the right temporal lobe showed diffuse necrosis, marked perivascular lymphocytic infiltrates with acute and chronic inflammation throughout the brain parenchyma and leptomeninges, and marked diffuse gliosis. The patient became completely unresponsive to noxious stimuli, and, at the family’s request, further medical care and mechanical ventilation were withdrawn and she died 12 days after admission. The postmortem pathology report showed widespread chronic inflammation of the leptomeninges and brain parenchyma in a perivascular distribution, with areas of necrosis in the basal ganglia, temporal lobe, and pons. Amoebae were seen throughout the cortex, leptomeninges, and basal ganglia (Figure 4). Indirect immunofluorescent tests on sections of cortex using rabbit antisera against Naegleria, Balamuthia mandrillaris, and 5 species of Acanthamoeba were positive only for Balamuthia. Reexamination of the temporal lobe biopsy specimen showed amebae that had been initially interpreted as macrophages.

**COMMENT**

While GAE typically occurs in the setting of immune suppression, *Balamuthia* is capable of infecting immunocompetent hosts, although immune compromise or al-
Alcohol abuse is seen in approximately 50% of the reported cases.1,3 The use of broad-spectrum antibiotics precedes infection in roughly 60% of cases of GAE caused by Acanthamoeba and may be considered a risk factor.4 Involvement of the central nervous system is thought to occur through hematogenous spread from a lesion in the lungs or skin, although in most cases a primary site of infection is not identified.

Granulomatous encephalitis has few differentiating clinical features from other types of subacute meningoencephalitis except for the prominence of sleepiness and a somewhat higher frequency of focal neurologic signs. Antemortem diagnosis without a brain biopsy specimen is difficult because free-swimming amebae are rarely observed or cultured from CSF, and the typical lymphocyte-predominant pleocytosis and elevated protein levels are more commonly seen with mycobacterial or fungal infection. Previous reports of GAE describe mildly low or normal CSF glucose concentrations, generally well above the range seen in bacterial meningitis.1,3-5 The exceptionally low CSF glucose level in our case is a feature that, to our knowledge, has not been previously described. The disappearance of almost all the ring-enhancing lesions was another unusual feature. Death within 6 to 8 weeks of diagnosis is the rule, although symptoms often date back several months. The 6-year history of seizures in our patient might suggest that the initial infection occurred years earlier, but previous literature does not support the possibility of illness of this duration. Balamuthia encephalitis has few features that distinguish it from the more common Acanthamoeba encephalitis. Acanthamoeba infection may preferentially involve posterior structures of the brain (cerebellum, thalamus, and brainstem), as described in a series of 12 pathologically confirmed cases described by Martinez.4 Reports suggest that Balamuthia perhaps more frequently involves the cortex.1 In our patient, the initial lesion was in the temporal lobe, and the distribution of subsequent ring-enhancing lesions was isolated to the cerebral hemispheres; posterior structures were involved only toward the end of her illness.

Previous pathologic reports of GAE describe multifocal necrotizing granulomas, often with multinucleated giant cells around visible trophozoites, and moderate to severe angiitis with perivascular lymphocytic cuffing. The pathologic examination in our patient demonstrated these findings.

No effective treatment for GAE has been found, but several case reports suggest a sensitivity of amebae to pentamidine and ketoconazole. Slater et al6 report a case of successful treatment of a skin lesion caused by Acanthamoeba with this combination. Earlier diagnosis in our patient would probably not have altered the outcome, but it would have provided the opportunity to attempt treatment with pentamidine and ketoconazole. While Balamuthia encephalitis is rare, it should be considered in a patient with a subacute granulomatous meningoencephalitis, even if CSF glucose concentrations suggest a bacterial or mycobacterial pathogen.

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REFERENCES