12-Year-old Boy With Fever, Headache and Vomiting

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CASE

A 12-year-old previously healthy boy presented to our hospital with headache and vomiting for 1 month and fever, drowsiness, and behavioral changes for 1 week. He lived in a rural area in Kyrgyzstan, where his family was engaged in livestock. On admission, he was lethargic and confused. Neurologic examination was significant for neck stiffness and right-sided hemiparesis. There was no skin lesion. Laboratory studies revealed a white blood cell count of 7.8×10^3/uL with 52% neutrophils, 42% lymphocytes, 5% monocytes and 0.3% eosinophils; hemoglobin of 13.6 g/dL; platelets of 298×10^3/uL; C-reactive protein of 3.5 mg/L; and erythrocyte sedimentation rate of 11 mm/h. The blood chemistry panel was normal. Serologic tests for human immunodeficiency virus, *Toxoplasma gondii* and *Bartonella henselae* were negative. *Brucella* tube agglutination and interferon-gamma release assay tests were negative. Cranial magnetic resonance imaging (MRI) revealed an invasive-appearing, calcified herniating mass with ill-defined borders (Fig. 1). Chest radiography, abdominal ultrasonography and echocardiogram were all normal.

With the preliminary diagnosis of a brain tumor, the patient underwent diagnostic and therapeutic surgery with the removal of a 5-cm necrotic mass. Stains of the tissue biopsy did not reveal any bacteria, but hyphae-like structures were detected. There was no evidence of malignancy.

Empiric antimicrobial therapy with vancomycin (60 mg/kg/day), ceftriaxone (100 mg/kg/day), metronidazole (40 mg/kg/day) and liposomal amphotericin B (5 mg/kg) was initiated for presumed central nervous system (CNS) infection. The patient was given steroids (prednisone 1 mg/kg/day) for cerebral edema. External ventricular drainage (EVD) was placed due to the development of hydrocephalus. Cerebrospinal fluid (CSF) obtained from EVD showed no leukocytes, erythrocytes of 130/mm^3, glucose of 61 mg/dl (blood glucose was 80 mg/dl) and protein of 118 mg/dl. Multiple bacterial and fungal cultures from blood and CSF were negative. Serum and CSF galactomannan were negative. The results of fungal and bacterial cultures of the brain biopsy specimen were negative, as was the result of the *Mycobacterium tuberculosis* polymerase chain reaction (PCR) test. Histopathologic examination of the brain biopsy revealed the diagnosis.

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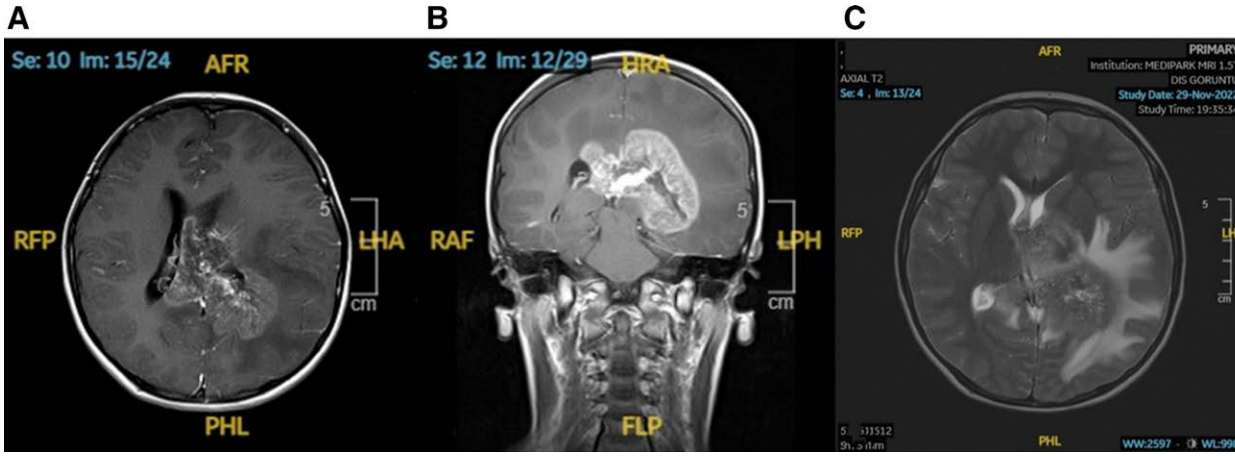


FIGURE 1. Magnetic resonance imaging of the brain: axial (A) and coronal (B) T1-weighted images showing invasive-appearing, calcified mass with unclear borders. T2-diffusion-weighted image (C) shows hyperintensity of the giant lesion in midline.

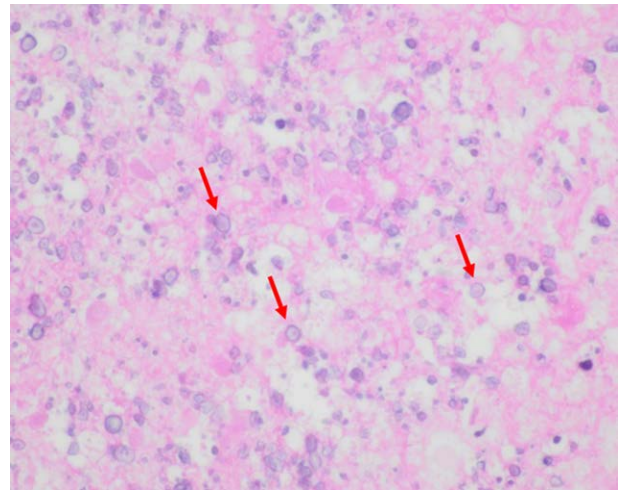


FIGURE 2. Ameba trophozoites (arrows) in brain tissue (hematoxylin and eosin stain, original magnification x600).

DENOUEMENT

Histopathologic examination of the brain tissue showed diffuse necrosis, inflammation, and the presence of microorganisms compatible with amebic trophozoites (Fig. 2). Therefore, while vancomycin and ceftriaxone were discontinued, liposomal amphotericin B and metronidazole were continued. Since the species of ameba had not yet been identified, treatment with intravenous azithromycin (500 mg once daily) and trimethoprim-sulfamethoxazole (12 mg TMP/kg/day) was initiated for coverage of amebic encephalitis.[1] Miltefosine or pentamidine treatment was also considered, but neither drug was available in our country. The amebas were eventually identified as *Balamuthia mandrillaris* by real-time PCR of the biopsy specimen. The patient was diagnosed with granulomatous amebic encephalitis (GAE) caused by *B. mandrillaris.*

The patient's fever did not recur in the postoperative period, but his clinical status progressively deteriorated. On postoperative day 6, he became unconscious with a Glasgow coma score of 7 (eye-opening to pain 2, verbal response none and motor response 4). On postoperative day 10, he developed status epilepticus, requiring intubation and mechanical ventilation. A noncontrast computed tomography (CT) of the brain on postoperative day 14 revealed a partially removed calcific mass located in the midline and slightly to the left. Diffuse gyral edema was evident in both cerebral hemispheres. Brain death occurred 11 weeks after admission to the hospital. The patient died 3 days later.

B. mandrillaris is a free-living ameba naturally found in the environment. It can cause rare cases of human disease, including cutaneous and CNS disease called GAE.[1,2] The true incidence of this infection is unknown and data about the epidemiology of *Balamuthia* infections have been derived from small case series and individual case reports.[2,3] More than 200 cases of *Balamuthia* disease have been reported worldwide since 1989.[4] Infection can occur in both immunocompetent and immunocompromised patients and has been associated with agricultural exposure and activities such as swimming and gardening.[2,4] Balamuthia enter the human body through a lesion in the skin or via the lungs by inhalation of cysts. The incubation period of *Balamuthia* GAE is unknown but is believed to range from several weeks to months.[1]

Balamuthia infection can present with a local skin lesion, isolated brain involvement or disseminated disease

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affecting the brain, skin and other organs.[2,4] Although not common, some patients with *Balamuthia* GAE may develop an initial skin lesion 1 month to 2 years before the development of neurologic symptoms.[1,4] *Balamuthia* encephalitis has an insidious onset and develops as a subacute or chronic disease. Initial symptoms may include fever, headache, vomiting, stiff neck, personality changes, confusion, lethargy, seizures, hemiparesis, aphasia, cranial nerve palsies, diplopia and/or dizziness.[1–4] Fever often is low grade and intermittent.[1] CNS symptoms are generally related to bleeding, infarction and necrosis.[5] Signs of increased intracranial pressure may be present, followed by meningeal symptoms and progressive loss of consciousness. The clinical course may resemble that of a brain tumor or a brain abscess.[3]

CSF indices may demonstrate lymphocytic pleocytosis and increased protein concentration, with normal to low glucose concentration, but *Balamuthia* organisms are rarely seen in the CSF.[1,2,4] In our patient, lumbar puncture was not performed due to the risk of cerebral herniation. CSF samples were obtained from EVD during the postoperative period, and therefore, CSF cell count and chemistries could not be interpreted clearly. CT or MRI of the brain may show single or multiple space-occupying or ring-enhancing lesions. Hydrocephalus or edema may also be present.[1,4,6] These findings may cause patients to be initially misdiagnosed as having a brain tumor, as in our patient.

Confirmation of *Balamuthia* species can be made by direct immunofluorescence, immunoperoxidase staining or real-time PCR in a reference laboratory.[4] Brain biopsy typically shows granulomas with foamy macrophages, multinucleated giant cells accompanied by lymphocytes. Amebae tend to settle in the vascular walls of capillaries and venules, and vascular damage may be present as tissue bleeding. Neutrophils may predominate, and amebae may be seen.[7]

The optimal treatment regimen and duration for *B. mandrillaris* infection have not been established;[1,2,4] experience is based on a limited number of case reports[2,8–11] and in vitro drug activity.[12] The Centers for Disease Control and Prevention currently recommends the following multidrug regimen: pentamidine, sulfadiazine, flucytosine, fluconazole plus either azithromycin or clarithromycin.[4] Additionally, miltefosine has shown good *in vitro* activity against *B.mandrillaris,*[12] and has been used successfully in combination therapy of *Balamuthia* infection.[2,11] Unfortunately, our patient died shortly after the diagnosis of *Balamuthia* GAE was confirmed, so the treatment regimen recommended by the Centers for Disease Control and Prevention could not be applied. Surgical resection of the CNS lesions can also play a critical role in the rapid diagnosis and treatment of *Balamuthia* GAE.[13] Despite treatment, mortality is high for *Balamuthia* infections and patients generally die several weeks to months after the onset of symptoms.[1,14]

In conclusion, *Balamuthia* GAE should be kept in mind in patients presenting with subacute or chronic meningoencephalitis and intracerebral lesions resembling brain tumors. However, even with early diagnosis, the prognosis remains quite poor.

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