Case Report

*Acanthamoeba* encephalitis: A Case Report and Review of Therapy

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**Abstract**

**Background:** *Acanthamoeba* is a rare cause of encephalitis yet is associated with high mortality. Treatment protocols vary greatly and generally include combination therapy across a wide spectrum of antiinfective classes.

**Case Description:** A 63-year-old male who underwent renal transplantation presented 6 months after transplantation with depressed level of consciousness. Imaging of the head with computerized tomography showed an enhancing lesion suspicious for brain abscess. Biopsy of the lesion showed *Acanthamoeba* cysts.

The patient was treated with sulfadiazine, fluconazole, flucytosine, azithromycin, and miltefosine but without success. We review recently published cases of *Acanthamoeba* encephalitis with an emphasis on treatment protocols and outcomes.

**Conclusion:** Free-living protozoans such as *Acanthamoeba* are ubiquitous in the environment and should be suspected in immunosuppressed persons who present with central nervous system findings and brain abscess. Biopsy is critical to establish the etiology so that appropriate combination therapy can be deployed.

**Key Words:** *Acanthamoeba*, brain abscess, encephalitis, miltefosine

**INTRODUCTION**

*Acanthamoeba* was discovered in 1930 and since then at least 24 species have been described.¹⁹,²² It is ubiquitous in nature and has been isolated from soil, fresh and brackish water, bottled mineral water, cooling towers of power plants, heating, ventilating and air conditioning units, and just about any surface that comes in contact with water, including medical and laboratory devices.²² Here we report a case of cerebral *Acanthamoeba* infection in an immunocompromised host, which was unsuccessfully treated with combination therapy including miltefosine.

**CASE REPORT**

A 63-year-old male with a history of kidney transplantation presented to the Emergency Department for altered mental status. His wife observed the patient to have intermittent confusion for the previous 2 weeks and also noted that he was sleeping more than usual. She denied fever, nausea, vomiting, neck rigidity, photophobia, or any gross motor or sensory deficits in the patient. The patient had not traveled outside Mississippi since his transplant 6 months prior to the onset of symptoms. He was taking mycophenolate and tacrolimus for his renal allograft. On the night of admission the patient was found unresponsive in his bed. Emergency responders found the patient with marked bradycardia and a temporary pacemaker was placed en route to the hospital.

Upon arrival to the hospital the patient was arousable but unable to answer questions or follow commands.
DISCUSSION

Granulomatous amoebic encephalitis (GAE) is an infection of the central nervous system with a mortality rate over 50% and is increasingly recognized as an opportunistic infection of immunocompromised hosts. Reported cases of amoebic encephalitis are increasing as awareness of these pathogens and the population of immunosuppressed patients grows. GAE is caused primarily by free-living amoebae species of *Acanthamoeba*, *Sappinia*, or *Balamuthia*. Most cases are diagnosed postmortem and a limited number of cases have reported successful treatment using various combinations of antimicrobial agents.\(^3,7,14\) Mortality from central nervous system (CNS) amoebic infections remains extremely high and may exceed 90%.\(^5\) Currently, there is no recommended standard therapeutic regimen for CNS infections with these amoebae.

The life cycle of *Acanthamoeba* consist of two stages, a vegetative trophozoite stage and a dormant cyst stage. Under optimal conditions of nutrients, pH and temperature, trophozoites predominate, however, under stressful conditions, a double-walled cyst is formed. The route of entry into the human body is postulated to be primarily through the lungs or breaks in the skin. The organism then disperses via blood to the brain. The most common manifestations of *Acanthamoeba* infection are related to CNS involvement. Common signs and symptoms are nonspecific and consist of headache, stiff neck, alterations in mental status or cognitive abilities, nausea, vomiting, low-grade fever, gait or coordination disturbances, visual disturbance, focal motor deficits, seizures, or coma.\(^3,22\)

Definitive diagnosis is made by examination of tissue and, rarely, by cerebrospinal fluid (CSF) analysis. CSF may show mild pleocytosis, moderately elevated protein,
and low glucose, however, amoebae are frequently seen by any staining or microscopic technique. Serology for amoeba-specific antibodies is available, however, these assays are not widely available and their specificity for active disease is low since most people have been exposed to this organism at one or more times in their life. The most expeditious and common way to make the diagnosis of GAE is to demonstrate trophozoites or cysts in tissue samples. A unique characteristic feature of Acanthamoeba sp. is the presence of fine, tapering, thorn-like acanthopodia protruding from the cell. Trophozoites are 15-50 \( \mu \text{m} \) in size with a centrally located nucleus and a densely staining nucleolus. Cysts are 10-25 \( \mu \text{m} \) with two cell walls usually discernible and also demonstrate a nucleus with a dense nucleolus. The organism can also be cultivated quite readily in vitro in special media.

Currently, there is no reliably effective drug therapy for Acanthamoeba infection of the CNS. Most published cases have used multiple drug combinations with varying success. A review of the English language literature for cases of CNS infection with Acanthamoeba diagnosed antemortem since 2000 and which described treatment protocols is summarized in Table 1.

Of the 18 cases in the literature, 83% (15/18) were males and 61% (11/18) had identifiable underlying immunosuppressive conditions. Mortality was 44% (8/18) and the survivors were evenly divided by the concurrence of an immunosuppressive condition. The number of cases is too small to draw any reliable conclusions about efficacy and there is a large overlap of drugs used between patients who survived and those who succumbed to infection. The Infectious Diseases Society of America (IDSA) guidelines for Acanthamoeba CNS infection have a III-level recommendation for either trimethoprim-sulfamethoxazole + rifampin + ketoconazole or fluconazole + sulfadiazine + pyrimethamine. Recently, the Centers for Disease Control and Prevention (CDC) announced the availability of miltefosine as an investigational drug to treat amoebic CNS infection. Two cases included in Table 1 used miltefosine as part of combination therapy and both patients survived. Although the patient presented in this report was also treated with miltefosine, this drug should be strongly considered as part of combination therapy for amoebic infections of the CNS.

**CONCLUSION**

Because of the rarity of amoebic encephalitis, it is unlikely there will be randomized clinical trials to rigorously test treatment options. Case reports and small series will remain important for identifying trends in epidemiology, natural history, and treatment of amoeba infections of the CNS. As human population demographics shift, and the number of immunosuppressed patients rises, this information will be critical to provide clinicians and laboratory workers with the most effective diagnostic and therapeutic options.

| Case (age, sex) | Underlying medical condition | Treatment regimen | Outcome | Reference |
|----------------|------------------------------|------------------|---------|-----------|
| 25 months, male | Acute lymphoblastic leukemia | TMP/SMX<sup>1</sup>, Flu<sup>2</sup>, PTD<sup>3</sup> | Survive | 6 |
| 53 years, male | HIV | SFZ<sup>4</sup>, PYR<sup>5</sup>, Flu | Death | 7 |
| 79 years, male | Autoimmune hepatitis | PTD, Vor<sup>6</sup>, AZM<sup>7</sup> | Death | 8 |
| 38 years, male | Immunocompetent | Vor, MFS<sup>8</sup> | Survive | 9 |
| 51 years, male | Systemic lupus erythematosus | Flu, IMiB, MTZ<sup>9</sup>, intrathecal AmB<sup>10</sup> | Death | 10 |
| 17 years, male | Immunocompetent | TMP/SMX, Flu, Rif<sup>12</sup> | Survive | 11 |
| 13 years, male | Fragile X syndrome | AmB, Vor | Death | 12 |
| 25 year, male | Disseminated tuberculosis | AN<sup>13</sup>, MFS<sup>14</sup> | Survive | 13 |
| 25 years, male | Seizure disorder | Rif, TMP/SMX, Flu | Survive | 14 |
| 63 year, female | Hypertension | AmB, Rif | Death | 15 |
| 42 years, male | Liver transplant | Rif, TMP/SMX | Survive | 16 |
| 51 years, male | Renal transplant | AmB, PTD, Rif, AZM, 5-FC<sup>14</sup>, SFZ, MTZ | Death | 17 |
| 24 year, female | Unknown | AmB | Death | 18 |
| 33 years, male | HIV | SFZ, PYR, Flu | Survive | 19 |
| 45 year, female | Immunocompetent | ABZ<sup>15</sup>, CFX<sup>16</sup>, Flu | Survive | 20 |
| 8 years, male | Mandibular tuberculosis | TMP/SMX | Death | 21 |
| 8 years, female | Immunocompetent | TMP/SMX, Ket<sup>17</sup>, Rif | Survive | 21 |
| 3 years, male | Immunocompetent | TMP/SMX, Ket, Rif | Survive | 21 |

<sup>1</sup>Trimethoprim/sulfamethoxazole, <sup>2</sup>Fluconazole, <sup>3</sup>Pentamidine, <sup>4</sup>Sulfadiazine, <sup>5</sup>Pyrimethamine, <sup>6</sup>Voriconazole, <sup>7</sup>Azithromycin, <sup>8</sup>Miltefosine, <sup>9</sup>Imipenem, <sup>10</sup>Flucytosine, <sup>11</sup>Amphotericin B, <sup>12</sup>Rifapentine, <sup>13</sup>Amikacin, <sup>14</sup>S-Flucytosine, <sup>15</sup>Albendazole, <sup>16</sup>Ceftriaxone, <sup>17</sup>Ketoconazole, HIV: Human immunodeficiency virus.
Acanthamoeba Granulomatous Amebic Encephalitis: A Challenging and Often Fatal Diagnosis

In the article “Acanthamoeba encephalitis: A case report and review of therapy”, the authors describe a classic case of Acanthamoeba granulomatous amebic encephalitis (GAE) in an immunocompromised patient. Given its rarity and the specific expertise needed to make the diagnosis, Acanthamoeba GAE remains a challenging diagnosis. The differential diagnosis is usually that of a space-occupying brain lesion and includes more common infections like bacterial brain abscess, tuberculosis, fungal infection, neurocysticercosis, and toxoplasmosis as well as noninfectious etiologies such as malignancy or stroke. The incubation period of Acanthamoeba GAE is unknown although, in disseminated infections with preceding cutaneous involvement, several weeks or months may elapse between the appearance of skin lesions and the recognition of central nervous system (CNS) disease. Patients with Acanthamoeba GAE are usually immunocompromised and frequently present with an insidious and protracted onset of low-grade fever, headache, fatigue, weakness, and nausea. Patients will then progress to neurologic symptoms that may include altered mental status, hemiparesis, seizures, blurred vision, and diplopia. Other neurologic symptoms can also occur later in the course of illness such as cranial nerve palsies, dizziness, ataxia, confusion, and personality change. Delayed diagnosis is common because of the slowly progressive and nonspecific nature of early disease as well as a lack of awareness of this infection among clinicians. Over the course of a week to several months from the onset of neurologic symptoms, the disease almost universally progresses to coma and death from increased intracranial pressure and brain herniation. Cerebrospinal fluid (CSF) from patients with Acanthamoeba GAE typically demonstrates a moderate

by correlation of results of sequential magnetic resonance imaging, biopsy, in vitro culture, immunofluorescence analysis and molecular analysis. J Clin Microbiol 2006;44:4265-9.

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lymphocytic pleocytosis. Protein may be elevated and glucose may be normal or low. Acanthamoeba organisms are rarely seen in the CSF. Computed tomography and magnetic resonance imaging scans of the brain frequently reveal single or multiple hypodense, ring-enhancing, space-occupying lesions. The diagnosis of Acanthamoeba GAE is usually made once affected brain tissue is obtained, whether via premortem biopsy as in the case presented here or postmortem, and amebic cysts and trophozoites are directly visualized in the tissue with hematoxylin and eosin (H and E) staining by an experienced pathologist. The diagnosis of Acanthamoeba infection can be confirmed with immunohistochemical techniques that detect amebic antigen in the tissue or polymerase chain reaction (PCR) testing to detect Acanthamoeba DNA in the tissue.\(^5\) Confirmatory testing is only available at selected reference diagnostic laboratories including at the U.S. Centers for Disease Control and Prevention (CDC).

More often than not, Acanthamoeba infection is a fatal disease. Among 94 cases of Acanthamoeba infection reported to CDC from 1955 through 2013, mortality was 85% (CDC unpublished data). The rarity of this infection precludes the use of rigorous studies to examine effective treatment regimens; therefore, treatment recommendations rely solely on individual case reports of successful outcomes. Survivors were given multidrug regimens consisting of various combinations of pentamidine, sulfadiazine, fluocytosine, fluconazole, itraconazole or voriconazole, trimethoprim-sulfamethoxazole, and miltefosine. The drug miltefosine has shown particular promise in treating free-living ameba infections, including those caused by Acanthamoeba and Balamuthia mandrillaris (a free-living ameba similar to Acanthamoeba that also causes GAE). Although the number of B. mandrillaris and Acanthamoeba infections treated with a miltefosine-containing regimen is small, it appears that a miltefosine-containing treatment regimen does offer a survival advantage for patients with these often fatal infections.\(^1\)

Finally, this patient’s immunocompromised status was the result of an immunosuppressive regimen prescribed following a kidney transplant 6 months prior to symptom onset. In addition to the resulting immunosuppression, the patient’s organ transplant also represented a possible route of exposure to Acanthamoeba. While there has not yet been a documented case of Acanthamoeba infection transmitted via solid organ transplant, the related free-living ameba, Balamuthia mandrillaris, has caused three clusters of organ transplant-transmitted infection when an infected donor’s organs were transplanted into multiple recipients.\(^2\) In the case presented here, transplant transmission was investigated and donor testing was negative for Acanthamoeba. However, the potential for transplant transmission remains and clinicians should be aware of the possibility when considering the diagnosis of Acanthamoeba infection.

With increasing populations of immunocompromised patients, the diagnosis of Acanthamoeba GAE should be considered in an immunosuppressed patient with encephalitis and aggressively treated with a combination of antimicrobials. In solid organ transplant patients, the possibility of transplant-transmitted infection should be investigated so that other recipients can be prophylactically treated to prevent this deadly infection.

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