

# Fatal Granulomatous Amoebic Encephalitis Caused by *Acanthamoeba* in a Patient With Kidney Transplant: A Case Report

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**Granulomatous amoebic encephalitis (GAE) due to *Acanthamoeba* is almost a uniformly fatal infection in immunocompromised hosts despite multidrug combination therapy. We report a case of GAE in a female who received a deceased donor kidney graft. She was treated with a combination of miltefosine, pentamidine, sulfadiazine, fluconazole, flucytosine, and azithromycin.**

**Keywords.** *Acanthamoeba*; encephalitis; granulomatous amoebic; immunosuppression; transplantation.

## CASE REPORT

A 64-year-old woman underwent deceased donor kidney transplantation due to diabetic nephropathy with uneventful recovery postoperatively and who had no known episodes of rejection. Seven months after transplantation, she presented with an episode of confusion that was attributed to a recurrent urinary tract infection and after treatment she was discharged home. A noncontrast computed tomography (CT) head scan and magnetic resonance imaging (MRI) of the brain at this time were normal. She returned 10 days later with intermittent confusion and word-finding difficulty. A physical examination was notable for a nontoxic-appearing woman with stable vital signs. She was awake and alert but oriented to person only. Speech was intact: language evaluation revealed expressive

aphasia with impaired naming, intact repetition, and ability to follow simple commands. Cranial nerves and motor function were intact: deep tendon reflexes were 2+ and symmetric. She had downgoing toes bilaterally. Sensory function was intact except for decreased vibration bilaterally in the distal lower extremities. Cerebellar function was intact and gait was normal. Home transplant-related medications included tacrolimus, mycophenolate mofetil, prednisone, and valganciclovir for cytomegalovirus prophylaxis. Noncontrast CT head scan revealed hypodensity with mild mass effect in the left temporal lobe and insular cortex with the radiological differential diagnosis including encephalitis and acute stroke. An MRI of the brain with contrast showed diffuse, T2 hyperintense lesion of the left temporal lobe, and insular cortex. This was associated with patchy cytotoxic edema and focal, subtle enhancement with a tiny single focus of necrosis. There were multiple microhemorrhages within and remote from this region. Appearances were of atypical infectious encephalitis with microhemorrhages secondary to either a necrotizing vasculitis or arising from a central embolic source (Figure 1A). Treatment with acyclovir was initiated empirically for concerns of herpes simplex virus (HSV) encephalitis. On follow-up neurologic examinations, her mental status continued to fluctuate with speech impairment and hallucinations, which prompted electroencephalography that demonstrated diffuse slowing and a lumbar puncture with cerebrospinal fluid (CSF) analysis showing 12 white blood cells (80% lymphocytes, 14% monocytes, and 6% neutrophils), protein of 53 mg/dL, and glucose of 61 mg/dL. Acyclovir was later discontinued after CSF HSV polymerase chain reaction (PCR) testing resulted in negative findings. On hospital day 10, her mental status continued to deteriorate and repeat MRI of the brain (Figure 1B) showed interval progression of cerebritis with more areas of the brain involvement and increased mass effect with midline shift; in addition, there was an increased number of the microhemorrhages and increased peripheral lesion enhancement. An Infectious Diseases consultation was requested. The following day, she underwent stereotactic left craniotomy with left temporal lobe brain biopsy. With disease progression, the patient's mental status progressively deteriorated: she became more lethargic and developed right arm weakness. Microscopy of the biopsy specimen showed necrotizing granulomas with acute inflammation, with microorganisms morphologically consistent with amoeba. Photomicrographs were sent to the Centers for Disease Control and Prevention (CDC) for telediagnosis. The Centers for Disease Control and Prevention experts reviewed the images on day 13, and it was their opinion that the images showed free-living amoebae of the *Acanthamoeba/Balamuthia*

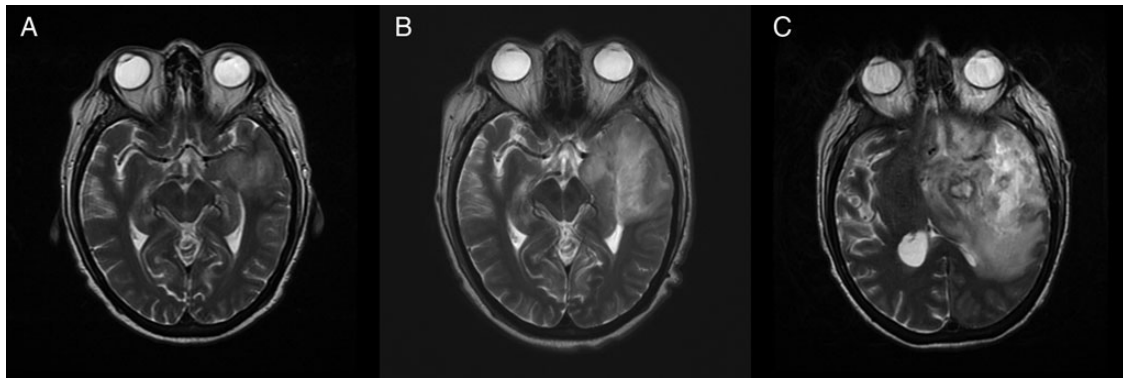
Received 19 March 2015; accepted 6 July 2015.

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### Open Forum Infectious Diseases

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DOI: 10.1093/ofid/ofv104



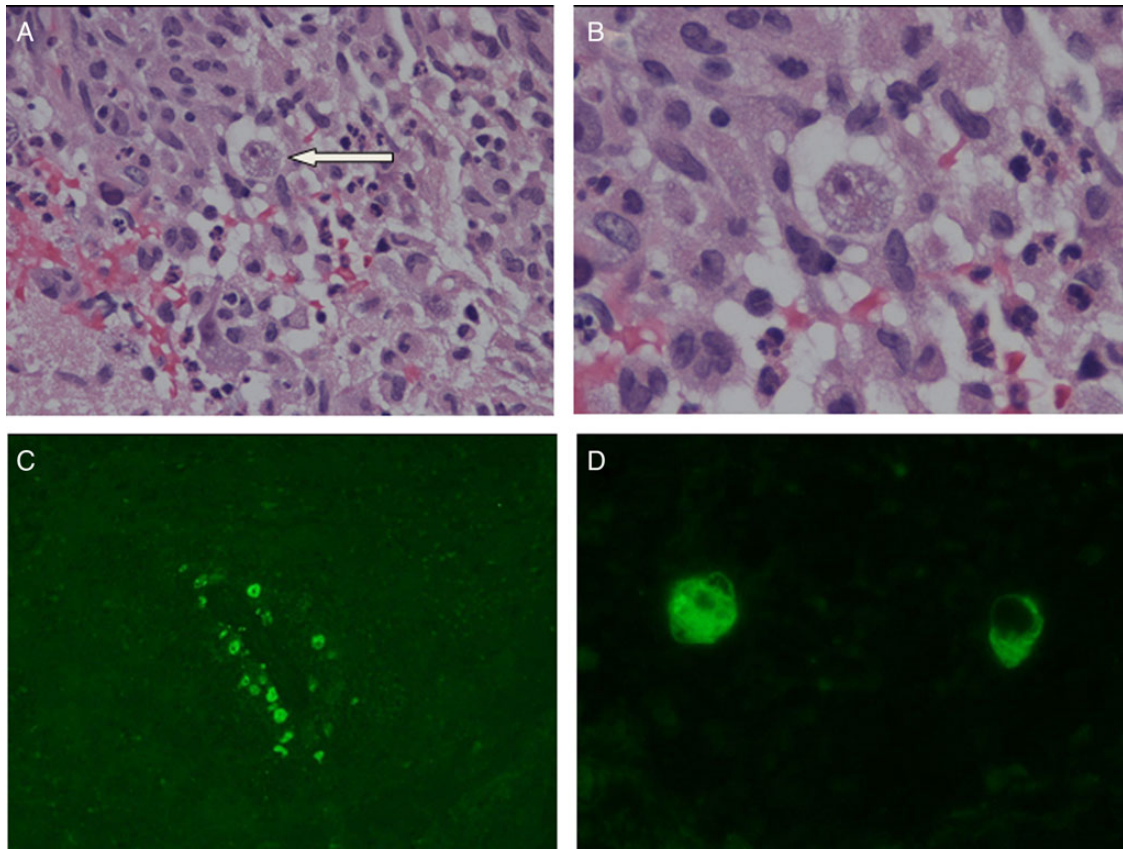
**Figure 1.** (A–C) T2 brain magnetic resonance imaging of the patient with granulomatous amoebic encephalitis caused by *Acanthamoeba*. Brain imaging demonstrates progressive changes of cerebritis visible as T2 hyperintensity with mass effect that initially involves the anterior temporal lobe progressing to affect most of the left cerebral hemisphere, with increased mass effect and multiple areas of necrosis.

type. Hematoxylin and eosin (H&E) and unstained slides were sent to the CDC laboratory for immunohistochemical confirmation, which was consistent with *Acanthamoeba* species (Figure 2A–D). A multidrug regimen was initiated that included miltefosine, pentamidine, sulfadiazine, flucytosine, fluconazole, and azithromycin. Methicillin-resistant *Staphylococcus aureus* was grown from brain tissue biopsy; therefore, treatment with parenteral vancomycin was initiated. Both tacrolimus and mycophenolate were discontinued, and prednisone was tapered off over several days. *Acanthamoeba* serology sent to the CDC laboratories to monitor response of therapy was negative. John Cunningham (JC) virus PCR was reported as positive with 51 copies/mL, but there was no evidence of progressive multifocal leukoencephalopathy features on brain biopsy. Patient kidney function deteriorated, and antimicrobials were adjusted for renal function. Unlike *Balamuthia*, *Acanthamoeba* has not been documented to be transmitted by solid organ transplant, and to exclude this possibility, further investigation and contact to transplant centers, including examination of donor samples, revealed that our patient’s infection was not a donor-derived infection and was most likely acquired by environmental exposure. The patient’s condition deteriorated despite being on combination antimicrobial therapy, and she eventually developed right-sided hemiplegia then coma. Repeat MRI of the showed further interval progression with worsening cerebritis, now involving most of the left cerebral hemisphere and left midbrain. There was significantly increased mass effect (Figure 1C). Hospice care was initiated at the family’s request and the patient died 3 days later.

## DISCUSSION

*Acanthamoeba* is a genus of amoebae, and it is a free-living opportunistic protozoan ubiquitous in nature. It has been isolated from soil, dust, sand, nasal swab samples, feces, vegetables, fish,

reptiles, birds, mammals, and various water samples including fresh water, seawater, tap water, bottled mineral water, indoor/outdoor swimming pools, aquariums, and sewage [1]. Trophozoites are small, usually 15–35  $\mu\text{m}$  in length, and oval to triangular in shape when moving. Smaller, 10–15  $\mu\text{m}$  in diameter, double-walled cysts form under unfavorable conditions of high temperature and osmolarity and low pH, especially in nutrient-poor environments [1,2]. The clinical syndromes associated with *Acanthamoeba* infections remain rare. Aside from the well known *Acanthamoeba* keratitis associated with the use of contaminated contact lenses in the presence of microabrasions of the cornea, granulomatous amoebic encephalitis (GAE) is being recognized more frequently, especially with the growing population of immune-compromised hosts [3]. As such, GAE is now being diagnosed at the time of acute illness presentation, rather than at post mortem examination [4,5]. Up to 80% of the population is seropositive to various *Acanthamoeba* spp [6], but only a minority develop clinically significant illnesses. Early clinical diagnosis can be difficult with symptoms often mimicking ischemic stroke or other infectious encephalitides [5]. Imaging findings in the early stages of infection are often nonspecific. Lesions are either multifocal, with discrete focal lesions at the grey/white matter junction, or present as a larger solitary mass-like lesion. Depending on the location of the lesion(s) within the brain, there is a wide differential diagnosis that often includes infectious etiology, low-grade glioma, lymphoma, or demyelinating disease [5]. *Acanthamoeba* is traditionally described as affecting the posterior structures of the brain [7]. However, as in our case, which initially affected the left temporal lobe, reported cases have been described in various brain lobes and brainstem structures often with an associated meningoencephalitis [7–9]. With worsening infection, eventually the signs of raised intracranial pressure develop invariably leading to coma and death. Diagnosis is usually only confirmed with brain biopsy. This can delay the diagnosis and commencement of



**Figure 2.** (A) Brain biopsy sections of the same patient stained with hematoxylin and eosin showing a dense granulomatous infiltrate accompanied by microorganisms morphologically consistent with free-living amoeba (arrow). (B) Higher magnification of (A) showing the characteristic nuclear appearance of the amoeba. (C) Indirect immunofluorescence labeling of brain biopsy sections performed using a rabbit serum (1:100, R150, exposed to *Acanthamoeba castellanii* whole-cell lysate) followed by 1:200 fluorescein isothiocyanate-conjugate goat anti-rabbit immunoglobulin G (F6005; Sigma-Aldrich): at low magnification, the photomicrograph shows fluorescent microorganisms around blood vessels. (D) High magnification photomicrograph showing 2 *Acanthamoebae* fluorescing bright green after indirect immunofluorescence.

treatment and may contribute to the subsequent fatal outcome, particularly in the immune-compromised patients [2, 4, 6].

There are no reported cases of donor-derived infections with *Acanthamoeba* unlike *Balamuthia mandrillaris*, another free-living amoeba that has been reported to result from donor-derived infections in organ recipients. Our patient's donor had negative tissue examination for *Acanthamoeba* [10]. Cerebrospinal fluid analysis in GAE demonstrates lymphocytic pleocytosis, low glucose, and high protein. Careful examination of CSF cytology may rarely reveal the trophozoites [8]. *Acanthamoeba* serology can potentially be used to follow disease activity [11, 12]. Histologic examination of tissue specimens such as skin or brain biopsies with the regular (H&E) staining can be diagnostic. Antigen detection of *Acanthamoeba* using indirect immunofluorescence testing in tissue specimens and molecular diagnostics with PCR are available in some laboratories, including US CDC laboratories [4].

As our patient's clinical condition deteriorated, all the cerebral lesions enlarged with the appearance of multiple new

microhemorrhages. The volume of affected brain tissue and necrosis increased in size. The enhancement pattern of the largest lesion evolved over time: initially focal and asymmetric eventually becoming a peripheral thin rim. This would confirm an inflammatory zone that has been previously shown histologically to correlate with an inflammatory response secondary to amoebic trophozoite infiltration of the pial vessels and a border zone encephalitis [9].

Multiple antimicrobials have been used in the treatment of GAE in various combinations that include, but are not limited to, trimethoprim/sulfamethoxazole, pentamidine, sulfadiazine, pyrimethamine, azithromycin, rifampin, flucytosine, albendazole, miltefosine, metronidazole, ketoconazole, fluconazole, voriconazole, and amphotericin B. Polymicrobial therapy is potentially more effective if combined with resection of the lesions to better control the infection. Among all the solid organ transplant recipients, there was only 1 case report in the English literature of a survivor with liver transplant who was on cyclosporine monotherapy as an immunosuppressant at the time of

diagnosis. He underwent resection of the brain lesion followed by trimethoprim/sulfamethoxazole and rifampin treatment [13]. Minimal immunosuppression can also provide a favorable outcome if coupled with effective surveillance and increased awareness of such infections.

## CONCLUSION

Although rare, *Acanthamoeba* infection is associated with several clinical presentations such as keratitis, skin infections, sinusitis, and pneumonitis. Disseminated infections are being reported more frequently, especially in the immune-suppressed hosts that include GAE. Disseminated infections used to be a post mortem diagnosis, but with the increased index of suspicion of such infections and the newer methods of diagnosis, earlier detection and treatment can be achieved. Unfortunately, the disseminated disease is usually fatal in 85% of cases (94 cases reported to CDC from 1955 to 2013) [4]. The few survivors of GAE received combination antimicrobial therapy. Regimens that include miltefosine have shown efficacy to treat both *Balamuthia* and *Acanthamoeba* infections, but that is based only on case reports, given the rarity of these infections [11].

## Acknowledgments

We thank Naomi Rance for providing explanation of histopathology figures. We thank Jennifer Cope for her contributions, reading the manuscript, and giving valuable comments.

**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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