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CASE REPORT



Granulomatous amoebic encephalitis caused by *Acanthamoeba* in a patient with AIDS: a challenging diagnosis

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ABSTRACT

Introduction: *Acanthamoeba* spp. is a ubiquitous free-living amoeba that causes human infections affecting predominantly the cornea and central nervous system. The diagnosis and treatment of *Acanthamoeba* encephalitis is very challenging. **Case summary:** A 53-year-old male with HIV/AIDS was admitted for altered mental status and fever. On initial examination, he had left hemianopia with left-sided weakness and numbness. MRI revealed an inflammatory and enhancing parenchymal mass associated with leptomeningeal enhancement in the occipitoparietal lobe containing multiple punctate hemorrhages. He was treated with empiric antibiotics for presumptive toxoplasmosis, brain abscess, fungal infection and tuberculosis with an unremarkable lymphoma work up. Initial brain biopsy studies were unremarkable except for non-specific granulomas and adjacent necrotic tissue. The patient passed away 2.5 months after initial presentation with no diagnosis. Post-mortem testing by the Centers for Disease Control and Prevention (CDC) confirmed the diagnosis of granulomatous amoebic encephalitis (GAE) by visualization with immunohistochemistry staining and PCR. Recovery is rare from GAE likely due to delay in diagnosis. **Conclusions:** This case illustrates the importance of including GAE into the differential diagnosis of brain mass. We advocate early molecular testing of tissue specimen by the CDC to achieve an appropriate diagnosis, and a multidisciplinary approach for the management of this condition.

KEYWORDS

Granulomatous amoebic encephalitis; *Acanthamoeba*; AIDS; HIV; biopsy

Introduction

Acanthamoeba spp. is a ubiquitous amoeba in the environment and can survive in a wide range of temperature, pH and, osmolarity. It can be found in water, airborne dust, and soil with frequent asymptomatic human exposure [1]. *Acanthamoeba* spp. can exist in trophozoite or the more resilient cyst form. Human entry is primarily through skin, lung, or sinuses with hematogenous spread and a predilection for brain and vascular tissue. The incubation period is difficult to determine since it is generally unknown what specific exposure led to infection, but may be prolonged (weeks or months).

Acanthamoeba spp. disease can present as granulomatous amoebic encephalitis (GAE), keratitis, dermatitis, pneumonitis, sinusitis, and disseminated infections in patients with immunodeficiencies (HIV/AIDS (human immunodeficiency virus/acquired immune deficiency syndrome), chemotherapy and organ transplantation) [1]. Several free-living amoebas can cause GAE. GAE by *Acanthamoeba* spp. is primarily seen in immunocompromised individuals, while *Balamuthia mandrillaris*, another

pathogenic free-living amoeba (FLA) can affect both immunocompromised (<40% of cases) and immune competent individuals [2]. The diagnosis is established post-mortem in the large majority of reported cases. Several hundred cases of GAE have been documented with a higher incidence in men [3]. The difficulty in diagnosis is likely multi-factorial; the rarity of GAE, limited availability of diagnostic studies, and non-specific clinical and radiologic presentations. Here, we present a fatal case of *Acanthamoeba* GAE in a patient with AIDS with a post-mortem diagnosis.

Case report

A 53-year-old African American male with HIV/AIDS (non-compliant with antiretroviral therapy, CD4 count of 82 cells/mm³), untreated hepatitis C, poorly-controlled diabetes mellitus type 2, hypertension, newly diagnosed non-ischemic cardiomyopathy, poly-substance abuse, and history of multiple incarcerations presented to the emergency department from jail with

fever and altered mental status for several days. Prior to admission, he had multiple admissions for diabetic ketoacidosis, medication non-compliance, complaints of headaches, and ambiguous left sided weakness. History was limited due to altered mental status.

On examination, vital signs were remarkable only for fever of 39.4 °C. Initial positive physical exam findings included: somnolence, oral thrush, 3/6 systolic murmur, alert and orientation only to self, 4/5 strength in the left upper and lower extremities, and decreased sensation in the left hemibody and bilateral feet. Complete blood count and metabolic panel were unremarkable except for mildly elevated transaminases (AST 75 IU/L, ALT 45 IU/L). Computed tomography (CT) scan of the brain without contrast showed a right occipitoparietal hypodensity (2.1x3.3x3.6cm) with associated vasogenic edema and mass effect (Figure 1(a)).

He was empirically treated with vancomycin and cefepime for a presumptive brain abscess. Given his low CD4 count, toxoplasmosis was considered as one of the possible causes, for which he received treatment with sulfadiazine, pyrimethamine and leucovorin. Fluconazole was also added for oral thrush. Several days later, brain magnetic resonance imaging (MRI) with and without contrast re-demonstrated a right occipitoparietal enhancing lesion with low T1 and high T2 signal measuring approximately 4 cm, with

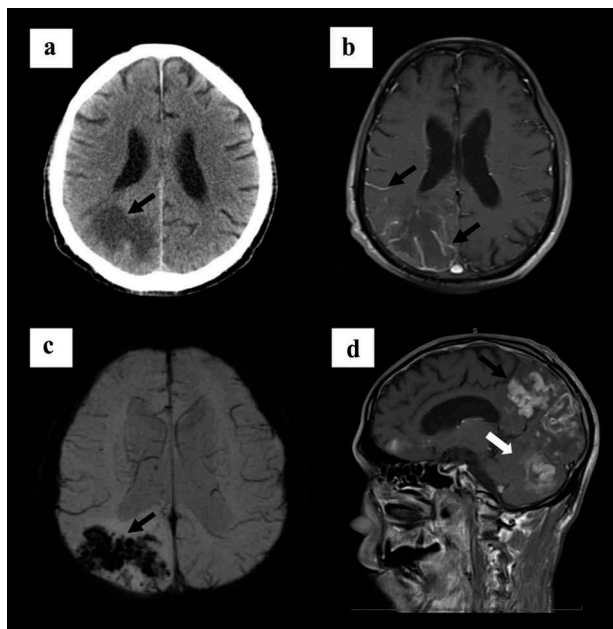


Figure 1. Initial presentation CT brain scan without contrast demonstrating: (a) right occipitoparietal hypodensity with associated vasogenic edema (arrow) and mass effect. Subsequent repeated MRI brain scans with and without contrast demonstrating: (b) right occipitoparietal enhancing lesion with low T1 and high T2 signal measuring approximately 4 cm with significant edema, leptomeningeal enhancement (arrows); (c) multiple punctate hemorrhages (arrow). (d) two months later, worsening of the occipitoparietal lesion, contralateral dissemination of supra (arrow) and infratentorial regions (white arrow).

significant edema, leptomeningeal enhancement (Figure 1(b)), and multiple punctate hemorrhages (Figure 1(c)). Further work up for tuberculosis with interferon gamma releasing assay (IGRA) was indeterminate. Additional laboratory studies showed positive CMV (cytomegalovirus) IgG and syphilis IgG titers, with a non-reactive serum RPR (rapid plasma reagin). The remaining work-up that included toxoplasma IgG and PCR (polymerase chain reaction), histoplasma urine antigen, hepatitis serology, *Cryptococcus* antigen, and blood cultures were all negative. Cerebral spinal fluid (CSF) showed 236 white blood cells with lymphocytosis of 94%, no red blood cells, normal glucose, and elevated protein > 600 mg/dl. CSF studies were negative for toxoplasma PCR, VDRL (Venereal Disease Research Laboratory test), *Cryptococcus* antigen, MTB (*Mycobacterium tuberculosis*) PCR, viral encephalitis panel, and cultures; however, EBV (Epstein-Barr virus) PCR was non-negligible with 488 IU/ml. Cytology showed increased lymphoid cells with no evidence of lymphoma. Flow cytometry was unremarkable.

Two weeks after initial presentation, a repeat MRI demonstrated enlargement of the cerebral lesion, now measuring 4.4 × 4.5x4.7cm. All initial cultures and serologies for common infectious etiologies of brain lesions associated with HIV/AIDS (reported above) were negative and antibiotics and anti-toxoplasma treatment were discontinued. Due to the concern for a metastatic malignancy, we obtained a pan CT scan, which was unremarkable. Three weeks after initial presentation, a brain biopsy of the right occipitoparietal lobe was attained through a stereotaxic bur hole. The biopsy stains were negative for fungus, acid fast bacilli, CMV, *Toxoplasma*, *Treponema*, and *Cryptococcus*. Immunologic staining for B and T cell infiltration patterns were inconsistent with malignancy; however, there were non-specific findings of granulomatous inflammation and necrosis (Figure 2(a)). At this point, our consult services (Infectious diseases, Neurology and Oncology) did not pursue further work-up, and the diagnosis remained unclear. Post-biopsy, the patient improved clinically despite the worsening radiologic findings. He was able to ambulate and discharged back to jail approximately one month after admission.

While incarcerated, he clinically deteriorated with bowel/bladder incontinence and weakness, and he was eventually readmitted for altered mental status two months later. MRI showed worsening of the occipitoparietal lesion with contralateral spread and involvement of supra and infratentorial regions (Figure 1(d)). Laboratory studies on readmission showed leukopenia, anemia, and a CD4 count of 57 cells/mm³ with a HIV viral load of 38,784 copies/mL. Repeat lumbar puncture findings showed lymphocytosis and elevated protein consistent with the initial lumbar puncture. He was treated empirically for tuberculous meningitis with rifampin, isoniazid, pyrazinamide, ethambutol, and steroids.

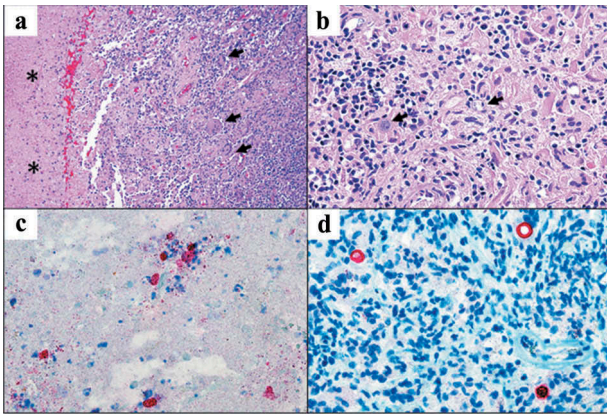


Figure 2. Brain biopsy from patient with granulomatous amoebic encephalitis. (a) Necrosis (*) and granulomatous inflammation with prominent multinucleated giant cells (arrows); H&E, x100. (b) Two amoebic cysts (arrows) within the granulomatous inflammatory infiltrate; H&E, x400. (c and d) Staining of amoebas by immunohistochemistry (red) for *Acanthamoeba* spp. within areas of necrosis (c) and inflammation (d); naphthol fast red substrate with hematoxylin counterstain, x400.

Subsequently, ADA (adenosine deaminase) from CSF was 6.1 IU/L and repeat IGRA was negative. Further work-up for malignancy with a single-photon emission computed tomography (SPECT) scan was consistent with an inflammatory/infectious process rather than malignancy. The patient later developed tonic-clonic seizures requiring endotracheal intubation. He was started empirically on antifungal coverage with amphotericin. Unfortunately, the patient's condition deteriorated with loss of brain stem reflexes. Repeat CT brain scan showed impending uncal herniation and obliteration of subarachnoid cisterns 2 days before death (Figure 3(a-d)). His family was contacted and withdrawal of care was initiated. Formalin-fixed paraffin-embedded (FFPE) biopsy specimens were sent to the CDC (Centers for Disease Control and Prevention) Infectious Diseases Pathology Branch (IDPB) for evaluation for tuberculosis. IDPB reported necrotizing and granulomatous encephalitis with intralesional amoebic trophozoites and cysts (Figure 2(b)) that labeled by immunohistochemistry for *Acanthamoeba* spp. (Figure 2(c and d)). Real-time PCR performed on deoxyribonucleic acid (DNA) extracts from the FFPE tissue block by CDC's Waterborne Disease Prevention Branch confirmed *Acanthamoeba* spp., but genotyping was not possible.

Discussion

Here we present a case of GAE in a patient with HIV/AIDS with non-specific clinical presentation, imaging, laboratory studies and brain biopsy. His course was complicated by poor follow-up, health care proxy designation and communication. In most reported cases, clinical presentation and neuroimaging of GAE were non-specific, presenting with location-specific symptoms of a cerebral mass lesion later identified peri-mortem.

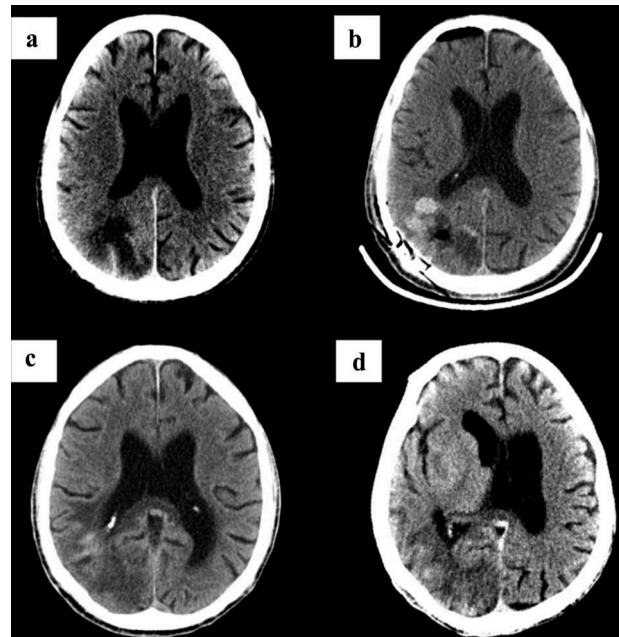


Figure 3. Chronological deterioration on transverse CT brain scans over 6 weeks. Initial presentation CT brain scan without contrast demonstrated an occipitoparietal hypodensity (a), evolution with blood and pneumocephalus 23 days from presentation (b), hydrocephalus 5 weeks from presentation (c) and finally uncal herniation 6 weeks from presentation (d), almost 2 weeks before the patient passed away.

There are no commercially available serologic tests for *Acanthamoeba* spp. infections and positive titers are common due to the ubiquitous nature of *Acanthamoeba* spp [4]. Some case studies reported that amoebic trophozoites can be seen on wet mount or Giemsa stain after low-speed centrifugation of CSF [5,6]. However, CSF diagnosis of GAE is problematic as amoebas are rarely seen and can be mistaken for macrophages [7]. In our patient, both CSF studies showed lymphocytosis and elevated protein which were non-specific findings. In the setting of brain lesions in immunocompromised individuals, toxoplasmosis and lymphomas are the two most common causes [8]. Although we found mild elevation of EBV PCR in CSF, this is not helpful and commonly attributed to asymptomatic viral shedding in the context of an acute process.

In neuroimaging of GAE, lesions are often found in the diencephalon, thalamus, brainstem and posterior fossa. T2 weighted images show heterogeneous hyperintensity, restricted diffusion, enhancement, inflammation and hemorrhage [5,9]. Our neuroradiologic findings with punctate hemorrhages could have been suggestive of herpetic and fungal etiologies but these were ruled out by serology and cultures. Despite radiographic worsening of the cerebral lesions, our patient had a brief clinical improvement, which could have been from *Toxoplasma* and fungal treatment that included medications with partial activity against *Acanthamoeba* spp [7].

In GAE, brain biopsy with immunohistochemistry and PCR studies are the gold standard diagnostic tools and both are available at the CDC [10]. *Acanthamoeba* spp. can be visualized with common stains (e.g. trichrome, hematoxylin and eosin (H&E)) and immunohistochemistry stains in brain tissue [7]. Unfortunately sectioning of the brain tissue while the patient was admitted at our institution did not reveal amoeba but showed non-specific granulomatous inflammation and necrosis. We did not see any monoclonal B or T cell infiltration, making malignancy unlikely. At that point, it was unclear whether this was an atypical presentation of a common disease, such as central nervous system lymphoma or tuberculosis, vs a rare disease. Due to this inconclusive work-up and the patient's clinical improvement despite the lack of definitive treatment, he was discharged without a clear diagnosis from his first hospital admission. In retrospect, we believe that a second brain biopsy and an early neuropathology evaluation of tissue specimens by an advanced institution should have been pursued before discharge. It was only until his second hospital admission that the brain tissue was sent to the CDC, where additional sectioning of the specimen was performed. This led to identification of amoebas in H&E-stained sections and immunohistochemistry. Unfortunately, the final diagnosis was achieved after the patient's death.

There is no universally effective treatment for GAE, in part, due to the small number of cases and delay in diagnosis. There have been more reports treating *Balamuthia* GAE compared to *Acanthamoeba* GAE. These studies suggest a combination of four to five antimicrobials such as pentamidine, cotrimoxazole, propamidine isethionate, azoles, amphotericin B, flucytosine, sulfadiazine, rifampin, azithromycin, amikacin, miltefosine, and phenothiazines plus/minus neurosurgical resection [7,11]. Voriconazole and miltefosine have *in vitro* efficacy for *Acanthamoeba* spp. with good penetration into the CSF [12,13]. Although miltefosine is no longer available from the CDC, it is commercially available and data from 26 case reports have suggested increased survival [6,14]. There is poor efficacy of traditional anti-parasitic drugs, such as metronidazole and albendazole. Initiation of anti-retroviral therapy has been helpful in some cases and immune reconstitution inflammatory syndrome has not been described. The role of steroids is unclear. The clinician must weigh the positive anti-inflammatory effects (to relieve compression of the brain) vs the negative immunosuppressive effects of steroids. As of 2012, a review of published case reports showed less than 10 cases (out of several hundred documented cases) of both immunocompetent and immunocompromised patients with *Acanthamoeba* GAE survived [15]. Prognosis remains poor, in part due to late diagnosis [6].

Here we describe an interdisciplinary approach to the diagnosis of amoebic infection in a patient with compatible radiologic and histopathologic features, with confirmation of *Acanthamoeba* spp. by immunohistochemistry and molecular testing performed on formalin-fixed paraffin-embedded tissue. In our case, amoebas were seen in tissues only after deeper sectioning of the specimen, and then only few organisms were identified by H&E stain. If diagnosis remains unclear after extensive work-up as in our case, thinner sections at multiple levels should be pursued at a more advanced institution because lesions may be few and focal in amoebic infections. Further utilization of new technologies such as next generation sequencing may also identify more cases of GAE to facilitate earlier diagnosis and provide a wider therapeutic window for treatment.





Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent those of the Centers for Disease Control and Prevention.

Disclosure statement

No potential conflict of interest was reported by the authors.

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