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Acanthamoeba castellanii encephalitis in a patient with AIDS: a case report and literature review

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Summary

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Contributors

AH, AW and GD wrote the manuscript. AH, AW, GD and NM performed the literature review. SN provided the histopathology images. IA and JC provided the CDC data. AH, AW, GD, IA and JC had access to the data. All authors reviewed, commented on, and contributed to the final version of the manuscript.

Conflicts of Interest

We have no potential or real conflicts of interest to disclose.

Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Amoebic encephalitis is a rare cause of central nervous system (CNS) infection for which mortality exceeds 90%. We present the case of a 27-year-old man with Acquired Immunodeficiency Syndrome (AIDS) who presented to a hospital in Atlanta with tonic-clonic seizures and headache. His clinical condition deteriorated over several days. Brain biopsy revealed lymphohistiocytic inflammation and necrosis with trophozoites and encysted forms of amoebae. Immunohistochemical and polymerase chain reaction (PCR) testing confirmed *Acanthamoeba castellanii* encephalitis, classically described as granulomatous amoebic encephalitis (GAE). No proven therapy for GAE is available, although both surgical and multi-agent antimicrobial treatment strategies are often employed. Most recently, these include the antileishmanial agent miltefosine. Here we review all cases of GAE due to *Acanthamoeba* in persons with HIV/AIDS identified in the literature and reported to the CDC. We describe this case as a reminder to the clinician to consider protozoal infections, especially free-living amoeba (FLA), in the immunocompromised host with a CNS infection refractory to traditional antimicrobial therapy.

Case Description

A 27-year-old man with human immunodeficiency virus (HIV) infection presented to our hospital in Atlanta, Georgia, in September 2018 with a two-day history of holocephalic, throbbing headache with photosensitivity and tonic-clonic seizures. He reported one week of subjective fevers, chills, and lethargy but denied focal weakness or sensory deficits. He described intermittent compliance with antiretroviral therapy. Past medical history was notable for esophageal candidiasis, late latent syphilis, and anal low-grade squamous intraepithelial lesions. He denied any recent travel or fresh-water exposure.

On admission, physical exam was notable for lethargy without disorientation or focal neurological deficits. CD4+ T-lymphocyte count was 5/μL and HIV-RNA viral load was 1·9 million copies/mL. Magnetic resonance imaging (MRI), revealed a right frontoparietal 2*2 cm lesion with internal and peripheral enhancement without restricted diffusion, mild surrounding edema, and associated mass effect and a smaller hyperintense focus in the left subcortical white matter (Figure 1). Serum cryptococcal antigen and galactomannan, *Toxoplasma* and *Coccidioides* antibodies, rapid plasma reagin, interferon gamma-release assay and urine *Histoplasma* antigen were negative. Bacterial, fungal, and acid-fast bacilli (AFB) blood cultures were unrevealing. Cerebrospinal fluid (CSF) studies demonstrated an opening pressure of 25 cm of H_2O, 217 leukocytes/μL (29% neutrophils, 30% lymphocytes, 40% monocytes, and 1% eosinophils); protein and glucose levels were 61 and 41 mg/dL, respectively. CSF bacterial, fungal and AFB cultures, India ink stain, cryptococcal antigen, VDRL, *Toxoplasma* IgM and IgG, and viral PCR for cytomegalovirus, herpes simplex, and JC virus were negative. Epstein-Barr virus PCR was not obtained, and CSF cytology was negative.

The patient was initially treated with ampicillin, ceftriaxone, vancomycin, acyclovir, rifampin, isoniazid, pyrazinamide, ethambutol, pyrimethamine, and clindamycin to include coverage for common aerobic and anaerobic bacterial infections, viral meningitis or encephalitis, tuberculosis, and toxoplasmosis. Despite this multidrug treatment, the patient developed worsening lethargy and focal neurological findings, including tongue paresthesia,

left hemineglect, and right gaze deviation. Repeat MRI on hospital day six revealed interval enlargement of prior lesions (Figure 2) and new left inferior frontal lobe and right postcentral gyrus peripherally enhancing lesions (not depicted in figure). A transesophageal echocardiogram was negative for endocarditis. As his condition deteriorated, antibacterial therapy was broadened to imipenem with vancomycin, trimethoprim and sulfamethoxazole were added for empiric treatment of nocardiosis, and liposomal amphotericin B was initiated.

Brain biopsy was performed on hospital day eleven. Histopathology revealed necrotic brain tissue in the right parietal lesion containing mixed inflammatory infiltrate, encysted forms of amoebae (Figure 3), and necrotic trophozoites. Due to the multifocal nature and magnitude of necrosis, aggressive resection was not pursued. Multidrug treatment with miltefosine, flucytosine, pentamidine, sulfadiazine, fluconazole, and azithromycin was initiated according to Centers for Disease Control and Prevention (CDC) recommendations. Upon consultation with the patient's family and due to lack of improvement in his clinical condition after three days, hospice care was initiated and the patient passed away on day fifteen.

Immunohistochemical (IHC) and real-time PCR testing performed postmortem at CDC confirmed *Acanthamoeba* spp., and amplification and sequencing of 18S ribosomal RNA genes was consistent with *Acanthamoeba castellanii* (T1 genotype).

Review and Discussion

FLA are unicellular, aerobic, mitochondriate, eukaryotic protists, also called amphizoic amoebae for their ability to exist as both a parasite and free-living organism.[1] Four amoebae capable of causing CNS infections in humans have been described: *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappinia pedata*. *N. fowleri* causes a rapidly progressive and almost uniformly lethal CNS infection referred to as primary amebic meningoencephalitis (PAM). *Acanthamoeba,* and *B. mandrillaris* cause granulomatous amoebic encephalitis (GAE), a subacute CNS infection that portends a very poor prognosis. *Sappinia pedata* has only been described once as a non-granulomatous subacute encephalitis. Our discussion focuses on features of *Acanthamoeba* spp. CNS infection relevant to the clinician.

Epidemiology

Acanthamoeba was first discovered by Castellani as a contaminant in yeast culture in 1930 and reported to cause a fatal encephalitis in experimental primate models in 1958.[2–4] *Acanthamoeba* spp. are ubiquitous in the environment and have been isolated from both soil and aqueous settings, including swimming pools, tap water, sewage, freshwater, seawater, ventilation ducts, air conditioning units and numerous other locations.[2,5,6] Serologic evidence of exposure to *Acanthamoeba* is almost universally prevalent in some populations.[7,8] Unlike PAM, which has an association with warmer climates and spring and summer months, GAE infections occur with no clear seasonal or geographic predominance.[9]

Pathogenesis

Acanthamoeba exhibits a two-stage life cycle consisting of a vegetative trophozoite stage and a dormant cyst stage. The trophozoite represents the form of the amoebae under favorable environmental conditions during which mitotic replication takes place and is also the primary infectious form.[6,10] Hypothesized routes to invasion of the CNS include hematogenous spread following inoculation of the respiratory tract or broken skin, as well as migration to the olfactory neuroepithelium following inoculation of the sinonasal epithelium.[11] Hematologic spread may also lead to disseminated disease. Meanwhile, ophthalmologic exposure may manifest as keratitis and is mostly associated with use of contact lenses.

Acanthamoeba is believed to cross the blood brain barrier at the capillary endothelium via one or more mechanisms involving paracellular transit (through the disruption of tight junctions) or a transcellular migration with or without disruption of endothelial cell function.[12] A recent review of 86 case reports revealed the cerebral cortex as the primary site of CNS seeding with any lobe potentially involved, consistent with a mechanism capable of diffuse spread.[5] In contrast, *N. fowleri* infection is observed to predominantly affect the frontal lobe (suggestive of invasion via olfactory neuroepithelium).

The immune response remains incompletely understood, particularly in the immunocompromised host. Upon transit into the CNS in the presence of a competent immune system, the initial reaction is thought to be a type IV hypersensitivity reaction suggesting prior sensitization of the host.[13,14] This reaction correlates with perivascular cuffing in some histopathologic studies.[13,14] Granulomatous inflammation follows over 2–3 weeks.[13,15] The slow nature of this process and the resulting sequestering of the organism may explain the clinical latency of several weeks observed in animal models of GAE.[13] Within the context of this granuloma formation, macrophage-derived epithelioid cells release lytic agents resulting in tissue destruction.[14]

Clinical Features and Diagnosis

Acanthamoeba CNS infection in patients with AIDS typically presents with non-specific, variable features of encephalitis, including headache, altered mental status, seizures, and focal neurologic deficits, depending on the site of infection. For this reason, the clinician must maintain a degree of suspicion for *Acanthamoeba*, especially in the immunocompromised patient with suggestive lesions who is seronegative for toxoplasmosis. We identified sixteen cases of GAE in AIDS patients in which CD4 T lymphocyte count was available through literature review (Table 1) and review of the Centers for Disease Control and Prevention (CDC) free-living amoeba infections database (Table 2). Including our case, the mean and median CD4 counts were 39 and 24 (IQR 6–74), respectively. Other features of *Acanthamoeba* in patients with AIDS include diffuse cutaneous lesions which have been reported with and without GAE, as well as nasal ulcers.[30]

Radiographic findings described in all patients with GAE are highly variable. A review of 29 cases reported single (40%) or multiple (60%) lesions that are most frequently hypodense on CT (48%), hypointense on T1-weighted MRI (34%), and hyperintense on T2-weighted

MRI (45%).[37] Meanwhile, contrast enhancement was described as uniform or patchy in 41% and peripheral or ring-enhancing in 34%.[37] Examination of the CSF may show lymphocyte-predominant pleocytosis with increased protein and decreased glucose, although the blunted immune response in an immunocompromised state may result in atypical findings.

The 2012 CDC surveillance case definition for GAE and *Acanthamoeba* disease other than keratitis requires laboratory confirmation through detection of the organism, nucleic acid, or antigen in CSF, biopsy or tissue specimens in the presence of a clinically compatible illness.[38] Trophozoite or cystic forms of *Acanthamoeba* have been observed by direct microscopic examination of the CSF.[39,40] In most cases, definitive diagnosis of GAE depends on histologic examination of tissue samples.

The samples obtained from our patient's biopsy demonstrated necrotic brain tissue with mixed inflammatory infiltrate consisting of degenerating neutrophils and mononuclear cells. Encysted forms of amoebae were observed throughout necrotic brain tissue (Figure 3). A previous report of histopathologic findings in amoebic CNS infections described three cases of *Acanthamoeba* encephalitis including one in which the patient had AIDS. In these cases, trophozoites (2 of 3 cases), cysts (3 of 3), and granulomatous inflammation (3 of 3) were observed.[41]

Granulomas were not identified in the samples of brain tissue obtained from our patient. *Acanthamoeba* infections of the CNS are often indiscriminately described as GAE; however, patients with AIDS and other T-lymphocyte depleted conditions may be unable to mount the immune response necessary for granuloma formation.[13] Since the presence of granulomatous inflammation is dependent on host immune status, such infections in the immunocompromised host without histologic evidence of true granuloma may be referred to as "granulomatoid" so as not to obscure the pathophysiology involved in the disease process.[15]

Although not widely available in clinical laboratories, molecular diagnostics for CNS *Acanthamoeba* infections have been described in the literature and may offer advantages over histologic diagnosis, including the ability to detect the organism directly from CSF – although this may still lack sensitivity. The triplex real-time PCR assay used in the case presented here was developed by CDC and can detect *Acanthamoeba*, *B. mandrillaris*, and *N. fowleri* DNA extracted directly from brain or CSF specimens.[42] Meanwhile, the emergence of mass spectrometry offers new opportunities for rapid and precise identification of *Acanthamoeba* spp. Recent literature has demonstrated the ability of matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) assays for genotype discrimination.[43,44]

Treatment

There is no proven treatment for GAE. Table 1 summarizes treatment regimens and outcomes reported in the literature for cases of *Acanthamoeba* CNS infection in HIV-positive individuals. These cases were found through searches in Medline and SCOPUS databases for the terms "*Acanthamoeba* + HIV" and "*Acanthamoeba* + AIDS" followed by review of all titles for case reports. Details in the table were gleaned from original

text. Additional data were obtained from CDC's free-living amoeba infections database which uses a detailed case report form to collect clinical and epidemiologic information on laboratory-confirmed free-living amoeba cases. The database was queried for *Acanthamoeba* cases occurring in HIV-positive patients from which an additional sixteen unpublished cases of CNS *Acanthamoeba* infection were identified (Table 2). These cases employed surgical and/or antimicrobial treatment modalities but overwhelmingly resulted in death. In only two recent cases was survival reported; in both, the anti-microbial regimen included miltefosine.

Current investigational therapies for GAE include surgical resection of lesions, hyperbaric oxygen, and combination drug therapy.[45] Many plant-derived substances have also been described.[46] Infectious Diseases Society of America (IDSA) guidelines propose use of trimethoprim-sulfamethoxazole (TMP-SMX), rifampin, sulfadiazine, pyrimethamine, and ketoconazole or fluconazole in the treatment of GAE but with poor evidence (grade C-III) to support these recommendations.[47] A recent review identified 13 selected cases (not limited to HIV-positive hosts) of patients who survived the infection.[5] Among these, the most frequently-employed agents included rifampin (8), amphotericin B (5), fluconazole (4) and TMP-SMX (4) in regimens ranging from 2–5 total antimicrobials. Treatment of one of the surviving patients employed miltefosine monotherapy.[48] Two case reports of HIV-infected survivors reported starting antiretroviral therapy concurrently with GAE-directed antimicrobials, suggesting that early initiation of ART could be beneficial.[2,19,25]

Miltefosine, an anti-cancer drug that acts as an inhibitor of protein kinase B, has emerged as an additional treatment for both encephalitis and keratitis caused by *Acanthamoeba*. Miltefosine has also been used – and is FDA-approved – for treatment of leishmaniasis but can be used off-label for treatment of *Acanthamoeba* infections. Based on a review of 26 case reports, miltefosine might offer a mortality benefit in the treatment of GAE.[49] In another review of 123 patients, miltefosine offered a mortality benefit in both non-keratitis *Acanthamoeba* and *Balamuthia mandrillaris* infections; the exact mechanism of action of miltefosine in treatment of protozoal infections remains unknown, but perhaps relates to the inhibition of metabolism of phospholipids in parasite cell membranes.[50]

Conclusion

Various free-living amoebae have been implicated in CNS disease, including *Naegleria fowleri*, *Balamuthia mandrillaris*, *Sappinia pedata*, and *Acanthamoeba* spp. Limited data exist regarding the clinical characteristics, radiographic findings, and effective treatment of *Acanthamoeba* encephalitis, as fewer than 200 cases (regardless of HIV status) have been described in the literature since the condition was first described in humans in the 1960s. However, cases of CNS infection by *Acanthamoeba* may be unrecognized and underreported. Because symptoms and imaging can mimic other causes of CNS infections in the immunosuppressed patient with HIV, the clinician must maintain a degree of suspicion and pursue investigation early in the course of a patient with suspicious CNS lesions, lack of response to empiric antimicrobials, and negative diagnostic testing for more common organisms. CSF cytology is encouraged but has poor sensitivity, therefore early brain biopsy should be strongly considered to facilitate a histopathologic diagnosis.

Once the diagnosis of *Acanthamoeba* is confirmed, clinicians should consider assessing exposures that might have led to infection including water, soil, and other environmental exposures including how those may be related to the patient's occupation, hobbies and other activities. Although the organism is ubiquitous, reporting the case to public health authorities with this exposure information can aide in identifying trends in infections that inform guidance offered to immunosuppressed patients. The prognosis of *Acanthamoeba* encephalitis is exceptionally poor with a mortality rate exceeding 90%.[51] Delayed diagnosis and treatment likely contribute to such poor outcomes, and therefore *Acanthamoeba* must be considered in all immunocompromised patients presenting with a meningoencephalitis syndrome, particularly those with a space-occupying lesion and negative *Toxoplasma* serologies.

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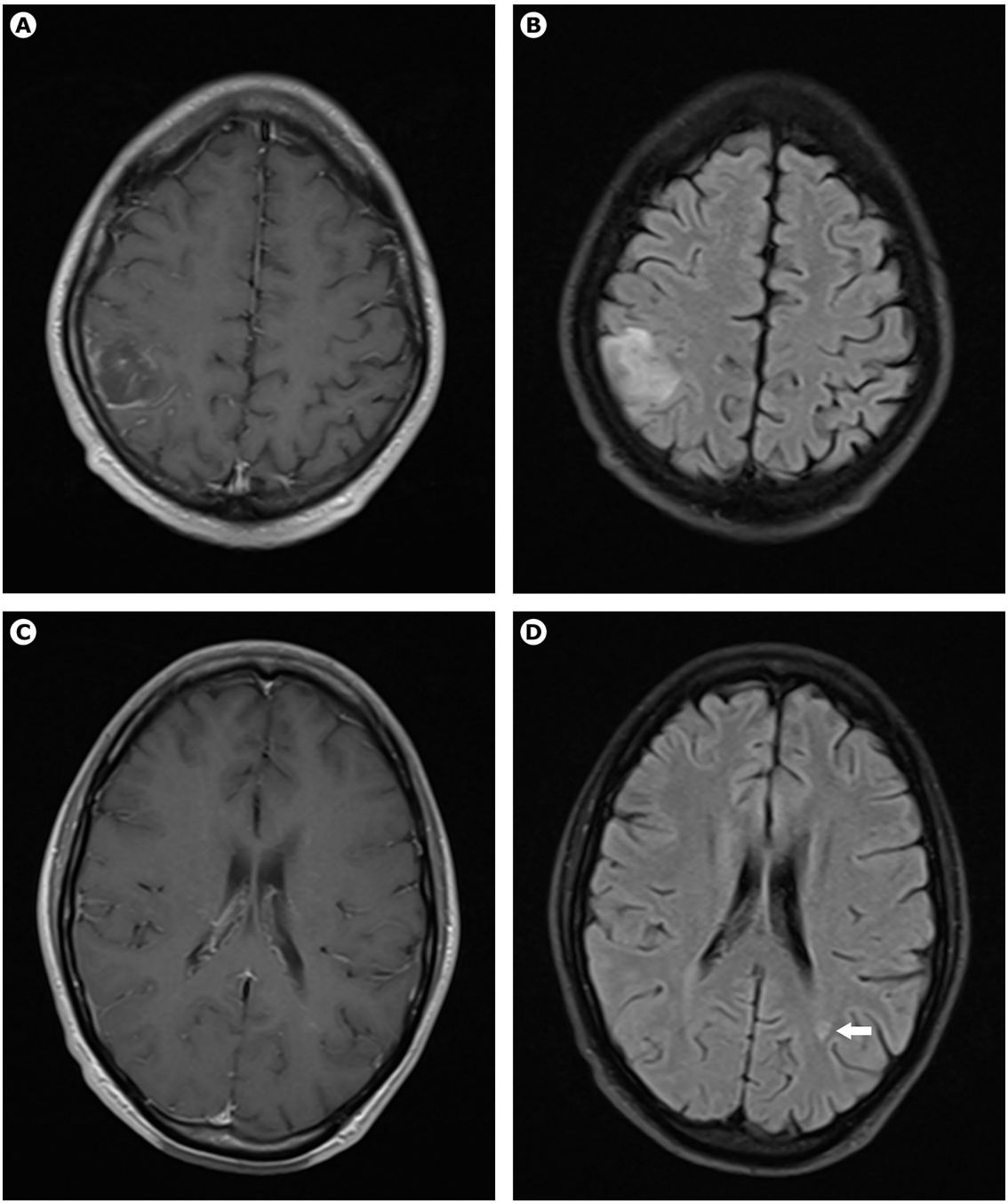

Figure 1: MRI brain obtained on admission

Axial post-contrast T1 (A) and T2 FLAIR (B) sequences demonstrate right frontoparietal 2*2 cm lesion with minimal surrounding edema with mass effect. Post-contrast T1 image (C) and corresponding T2 FLAIR (D) best demonstrated the smaller lesion in the left subcortical white matter.

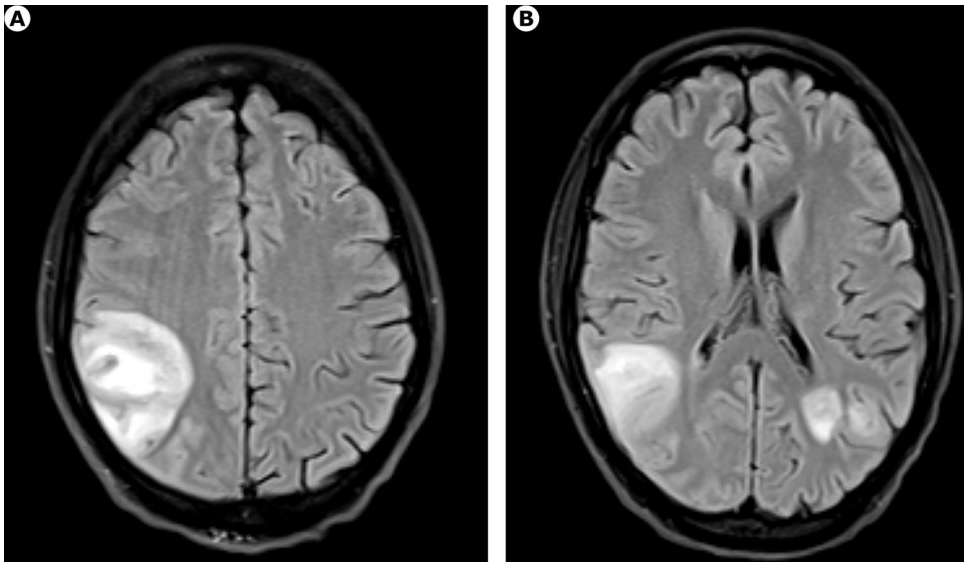

Figure 2: MRI brain on hospital day 6

T2 FLAIR axial MRI brain demonstrates (A) interval enlargement of right frontoparietal peripherally enhancing lesion (now measuring 6*4 cm) with significant edema and mass effect and (B) edematous and peripherally enhancing lesions new compared to admission MRI, illustrating diffuse disease consistent with multifocal cerebritis.

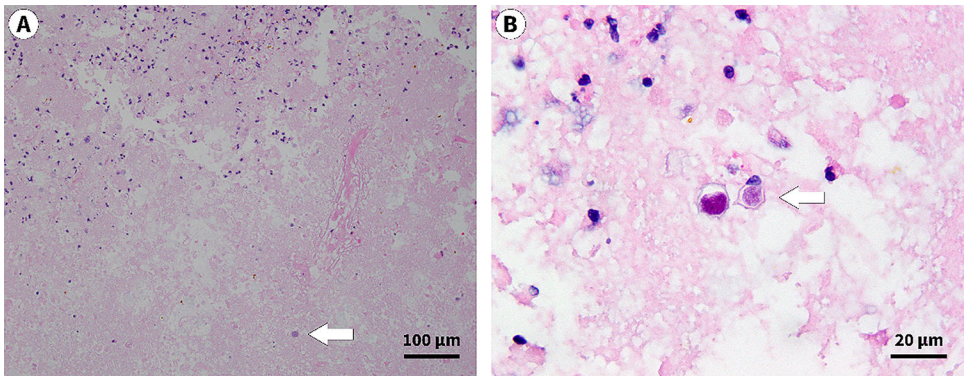

Figure 3: Brain biopsy of GAE due to *Acanthamoeba*

Brain biopsy demonstrates cystic amoebae within necrotic brain tissue; (A) 20x, H&E; demonstrates a necrotizing encephalitis with evident scattered cyst forms (example indicated by arrow). (B) 100x, H&E; demonstrates cyst forms (indicated by arrow) in a background of necroinflammatory debris.

Table 1:

Published reports of *Acanthamoeba* CNS infections in HIV-positive patients

	Sex	Age	Location	CD4 count (cells/μL)	CSF WBC (cells/μL)**	CSF Protein (mg/dL)	CSF Glucose (mg/dL)	Presenting features	Medical treatment	Surgical treatment	Outcome
***Damhorst* et al. (2020)** *	*M*	*27*	*USA*	*5*	*217 (40% M)*	*61*	*41*	*Headache, seizures*	*Miltefosine, flucytosine, pentamidine, sulfadiazine, fluconazole and azithromycin*	··	*Death*
Monogue, *et al.* (2019) [16]	M	35	USA	30	420† (84% N)†	266†	34†	Headache, fever and altered mental status†	Albendazole, azithromycin, fluconazole, flucytosine, miltefosine, pentamidine, rifampin, sulfadiazine and TMP-SMX	··	Survival
Lau, *et al.* (2019) [17]	M	53	USA	82	236 (94% L)	> 600	Normal	Hemianopia, focal weakness, sensory loss, altered mental status	Amphotericin, ethambutol, fluconazole, isoniazid, sulfadiazine, pyrimethamine, rifampin, steroids, vancomycin, cefepime, pyrazinamide and leucovorin	··	Death
Geith *et al.* (2018) [18]	M	54	Germany	··	··	··	··	Progressive focal weakness	Pyrimethamine, fluconazole, acyclovir, clindamycin, ceftriaxone and meropenem	··	Death
El Sahly *et al.* (2017) [19]	M	38	USA	19	26 (85% L)	347	11	Headaches, generalized weakness	Miltefosine, fluconazole, TMP-SMX and flucytosine	··	Survival
Dowell *et al.* (2015) [20]	M	41	USA	4	10	79	72	Malaise, night sweats, confusion	Pentamidine, sulfadiazine, and voriconazole followed by pentamidine, fluconazole, flucytosine and azithromycin	··	Death
Pietrucha *et al.* (2012) [21]	M	53	USA	25	··	··	··	Weakness, confusion, seizure	Sulfadiazine, pyrimethamine and dexamethasone	··	Death
Ravula *et al.* (2010) [22]	F	8	USA	0	16 (80% L)	47	36	Fevere, headache	Vancomycin, ceftazidime, amphotericin, sulfadiazine and pyrimethamine	··	Death
MacLean *et al.* (2007) [23]	M	41	USA	6	1	127	79	Focal weakness, seizure	Dexamethasone	··	Death

	Sex	Age	Location	CD4 count (cells/μL)	CSF WBC (cells/μL)**	CSF Protein (mg/dL)	CSF Glucose (mg/dL)	Presenting features	Medical treatment	Surgical treatment	Outcome
Kumar *et al.* (2007) [24]	M	24	India	151	240 (90% L)	460	36	Fever, headache, altered sensorium	Amphotericin B and rifampin	··	Death
Seijo Martinez *et al.* (2000) [25]	M	33	Spain	82	··	··	··	Headache, confusion, visual field deficit	Sulfadiazine, pyrimethamine, TMP-SMX and fluconazole	Resection	Survival
Kim *et al.* (2000) [26]	M	42	USA	··	··	··	··	Nasal congestion	Itraconazole, metronidazole and pentamidine	Resection	Death
Bonilla *et al.* (1999) [27]	M	37	USA	6	··	··	··	Facial pain, sinusitis	Vancomycin, ceftazidime and amphotericin	··	Death
Calore *et al.* (1997) [28]	M	46	Brazil	··	169 (75% L)	415	10	Amnesia, ptosis	TB and toxoplasmosis therapy	··	Death
Khalife *et al.* (1994) [29]	M	44	USA	37	··	··	··	Forgetfullness	Erythromycin and clarithromycin	··	Death
Tan *et al.* (1993)[30,31]	NA	38	USA	··	··	··	··	Confusion	Amphotericin B, broad-spectrum antibiotics and TB therapy	··	Death
Gordon *et al.* (1992) [32]	M	34	USA	24	··	··	··	Headache, fever, chills, confusion	Sulfadiazine and pyrimethamine	··	Death
Gordon *et al.* (1992) [32]	M	34	USA	··	0	50	47	Fever, slurred speech, focal motor signs	Sulfadiazine and pyrimethamine	··	Death
Di Gregorio *et al.* (1992) [33]	M	24	Italy	11	··	··	··	Fever, asthenia	Amphotericin, chloramphenicol and ceftizoxime	··	Death
Gardner *et al.* (1991) [34]	M	39	USA	··	0	62	48	Lightheadedness, headache	Clindamycin, pyrimethamine and dexamethasone	··	Death
Wiley *et al.* (1987)[30,35]	M	34	USA	··	129 (83% N)	145	89	Skin lesions, focal weakness	TMP-SMX, gentamicin, amphotericin and clindamycin	··	Death
Robinson *et al.* (1987) [36]	M	34	USA	··	1†	30†	89†	··	··	Resection	Death

*Current report

**Predominant cell type and percent listed when available

†Details not present in referenced article but reported to CDC

TMP-SMX = trimethoprim-sulfamethoxazole, TB = tuberculosis, L = lymphocytes, M = monocytes, N = neutrophils

Table 2:

Acanthamoeba CNS infections in HIV-positive patients reported to CDC.

Year*	Sex	Age	CD4 (cells/ μL)	CSF WBC (cells/ μL)†	CSF Protein (mg/dL)	CSF Glucose (mg/dL)	Presenting features	Medical treatment	Surgical treatment	Outcome
2018	M	54	66	28	176	45	Paresthesias	Acyclovir, ceftriaxone, metronidazole, trimethoprim/ sulfamethoxazole, cefepime, penicillin G, vancomycin, dexamethasone	Resection	Death
2016	F	59	97	··	··	··	Headaches, blurry vision	Amphotericin, ceftriaxone, fluconazole, mannitol, metronidazole, pyrimethamine, rifampin, miltefosine, sulfadiazine, vancomycin, leucovorin	··	Death
2015	M	66	23	6.9 (88% N)	··	136	··	Acyclovir, azithromycin, ceftriaxone, ethambutol, rifampin	··	Death
2009	M	42	··	··	··	··	··	··	Resection	Death
2000	M	42	··	28 (80% N)	219	51	··	··	··	Death
1996	M	41	··	··	··	··	··	··	Resection	Unknown
1995	F	36	··	··	··	··	··	··	Resection	Death
1995	M	43	··	··	··	··	··	··	Resection	Unknown
1994	M	0	··	··	··	··	··	··	Resection	Death
1994	M	31	··	··	··	··	··	··	Resection	Death
1994	M	43	··	··	··	··	··	Sulfadiazine, pyrimethamine	Resection	Death
1993	M	41	··	··	··	··	··	··	Resection	Death
1992	M	57	··	··	··	··	··	Pyrimethamine, sulfadiazine	Resection	Death
1991	F	29	··	··	··	··	··	··	Resection	Death
1991	M	30	··	··	··	··	··	··	Resection	Death
1991	M	35	··	··	··	··	··	Pyrimethamine, dexamethasone, clindamycin	Resection	Death

Excludes published cases presented in Table 1.

*Year of clinical care as reported to CDC (does not reflect date of reporting to CDC)

†Predominant cell type and percent listed when available

N = neutrophils