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A Surviving Case of Acanthamoeba Granulomatous Amebic Encephalitis in a Hematopoietic Stem Cell Transplant Recipient

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Patient: Male, 32-year-old
Final Diagnosis: Granulomatous amebic encephalitis
Symptoms: —
Medication: —
Clinical Procedure: —
Specialty: —

Objective: Challenging differential diagnosis

Background: *Acanthamoeba* are free-living amoebae with potential to infect immunocompromised hosts. The mortality rate of granulomatous amebic encephalitis (GAE) due to *Acanthamoeba* exceeds 90% and there are currently no reports of survival of this infection in recipients of hematopoietic stem cell transplant.

Case Report: We report herein the case of a 32-year-old man presenting to our service with abrupt neurological deterioration and seizures 5 months after allogeneic stem cell transplantation for Hodgkin lymphoma. Clinical and imaging findings were non-specific at presentation. Multiple circumscribed, heterogenous, mass-like lesions were identified on MRI. Brain biopsy was performed and revealed multiple cysts and trophozoites suggesting a diagnosis of granulomatous amebic encephalitis. PCR testing confirmed *Acanthamoeba*. Treatment with miltefosine, metronidazole, azithromycin, fluconazole, pentamidine isethionate, and co-trimoxazole was instituted and the patient survived and shows continued improvement with intensive rehabilitation.

Conclusions: We report the first successful outcome in this setting. The diagnosis would have been missed on cerebrospinal fluid analysis alone, but was rapidly made by histological analysis of brain biopsy. This diagnostically challenging infection is likely under-recognized. Early brain biopsy and commencement of a prolonged miltefosine-containing anti-ameba regimen can be curative.

MeSH Keywords: Acanthamoeba • Amoeba • Central Nervous System Protozoal Infections • Hematopoietic Stem Cell Transplantation

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Background

Granulomatous amebic encephalitis is a rare central nervous system infection that is usually rapidly fatal [1,2]. Symptoms are myriad, and reflect the area of brain infected. Typically, the onset of symptoms is insidious until overwhelming infection results in rapid severe neurological decline, including seizures, altered levels of consciousness, coma, and death. Diagnosis is challenging due to the non-specific clinical presentation and radiological features. Brain biopsy is generally required for diagnosis, with cerebrospinal fluid analysis and culture yielding false-negative results in the majority of cases [2]. The optimal treatment for this infection has not been described. Herein, we report a case in which diagnosis was promptly made by early brain biopsy and a prolonged combination anti-amebic treatment approach was instituted with successful outcome.

Case Report

A 32-year-old male engineer presented 5 months after allogeneic hematopoietic stem cell transplant for chemotherapy-refractory Hodgkin lymphoma with a 4-day history of headache, difficulty finding words, and unable to read back cell phone texts which he had just completed. Collateral history confirmed he had driven through a red light he did not notice, and noted episodes of staring with speech arrest. Neurological examination confirmed anomic aphasia with compensatory circumlocution, and alexia without agraphia (unable to read despite retaining the ability to write). Visual field testing revealed right homonymous superior quadrantanopia.

He was diagnosed 2 years prior to this presentation with stage IVB classical Hodgkin lymphoma and international prognostic score (IPS) of 5. Interim positron emission tomography (PET) following 2 cycles of Adriamycin, Bleomycin, Vinblastine, and Dacarbazine (ABVD) chemotherapy was Deauville score 4, and treatment was intensified to the dose-escalated Bleomycin Etoposide Adriamycin Cyclophosphamide Oncovin Procarbazine Prednisolone (BEACOPP) regimen for 2 cycles, resulting in a persistent Deauville 4 score. The patient received salvage therapy with Brentuximab vedotin and Ifosfamide Carboplatin Etoposide (ICE) for 3 cycles, achieving a complete remission (Deauville score 1) which was consolidated with a matched unrelated allograft using Carmustine/BCNU Etoposide Cytarabine Melphalan (BEAM) and Alemtuzumab conditioning. He engrafted on day 12 and his post-transplant course was complicated by steroid-responsive grade 3 skin graft versus host disease. The patient was PET-negative and a 100% total and CD3 donor chimera on day 100.

At the time of this acute neurological presentation on day 160, he remained profoundly immunosuppressed. His medication consisted of valaciclovir 500 mg once daily, atovaquone 750 mg twice daily, phenoxymethylpenicillin 333 mg twice daily, prednisolone 10 mg once daily (for skin graft versus host disease), and ciclosporin 50mg twice daily. He reported adherence to all medications. His absolute lymphocyte count was 0.1×10^9/L with absolute CD4+ T cell count 51×10^6/L.

MRI brain revealed multiple circumscribed heterogenous mass-like lesions in the left occipital and right frontal lobes, with further areas of edema in the splenium of the corpus callosum and left temporal lobe, which correlated with his alexia without agraphia and right superior quadrantanopia, respectively (Figure 1A). Cerebrospinal fluid (CSF) analysis revealed elevated white cell count of 42/mm^3 (reference 0–5 WBC/mm^3) and elevated protein 1.49 mg/dL (reference 0.15–0.45g/L) (Table 1). CSF microscopy was negative. The patient was rapidly deteriorating neurologically, and electroencephalogram was not possible, but an urgent brain biopsy was performed. The histological features were consistent with GAE, with *Acanthamoeba* spp. favored as the most likely causative organism based on morphological grounds (Figure 2), in the context of immunosuppression and due to the presence of intra-axial mass lesions. CSF PCR was negative for *Acanthamoeba, Naegleria,* and *Balamuthia*, but PCR of brain tissue was positive for *Acanthamoeba* species.

The *Acanthamoeba* trophozoites and cysts noted on brain biopsy led to a change in treatment from initial empiric antimicrobial cover to fluconazole 12 mg/kg once daily po, pentamidine isethionate 4 mg/kg 4 times daily iv, metronidazole 500 mg 3 times daily iv, azithromycin 250 mg once daily po, co-trimoxazole 5 mg/kg twice daily IV, and miltefosine 50 mg 3 times daily po.

The patient deteriorated abruptly on day 9 of admission (day 5 of anti-amoebic therapy). Episodes of speech arrest became more frequent and he became disoriented to place and time. On day 8 of admission, serum sodium had been 139 mEq/L (139 mmol/L) (reference range 136–145 mEq/L, 136–145 mmol/L). On the evening of day 9, this fell to 129 mEq/L (129 mmol/L) in tandem with worsening symptomatology. Eslicarbazepine 400 mg qd and clobazam 5 mg bid anticonvulsant therapy was added, but on day 10, the patient had a generalized tonic-clonic seizure associated with a precipitous fall in serum sodium to 110 mmol/L. He was treated with hypertonic (3%) saline with temporary omission of other infusions, including pentamidine isethionate, given its potential to aggravate hyponatremia. Repeat MRI brain revealed significantly worsened vasogenic edema with resultant mass effect (Figure 1B). Risk of transforaminal herniation was deemed to be high based on the imaging, and dexamethasone 8 mg tid IV was instituted to ameliorate edema. Clinical and laboratory parameters were consistent with Syndrome of Inappropriate Anti-Diuretic Hormone secretion (SIADH) as a

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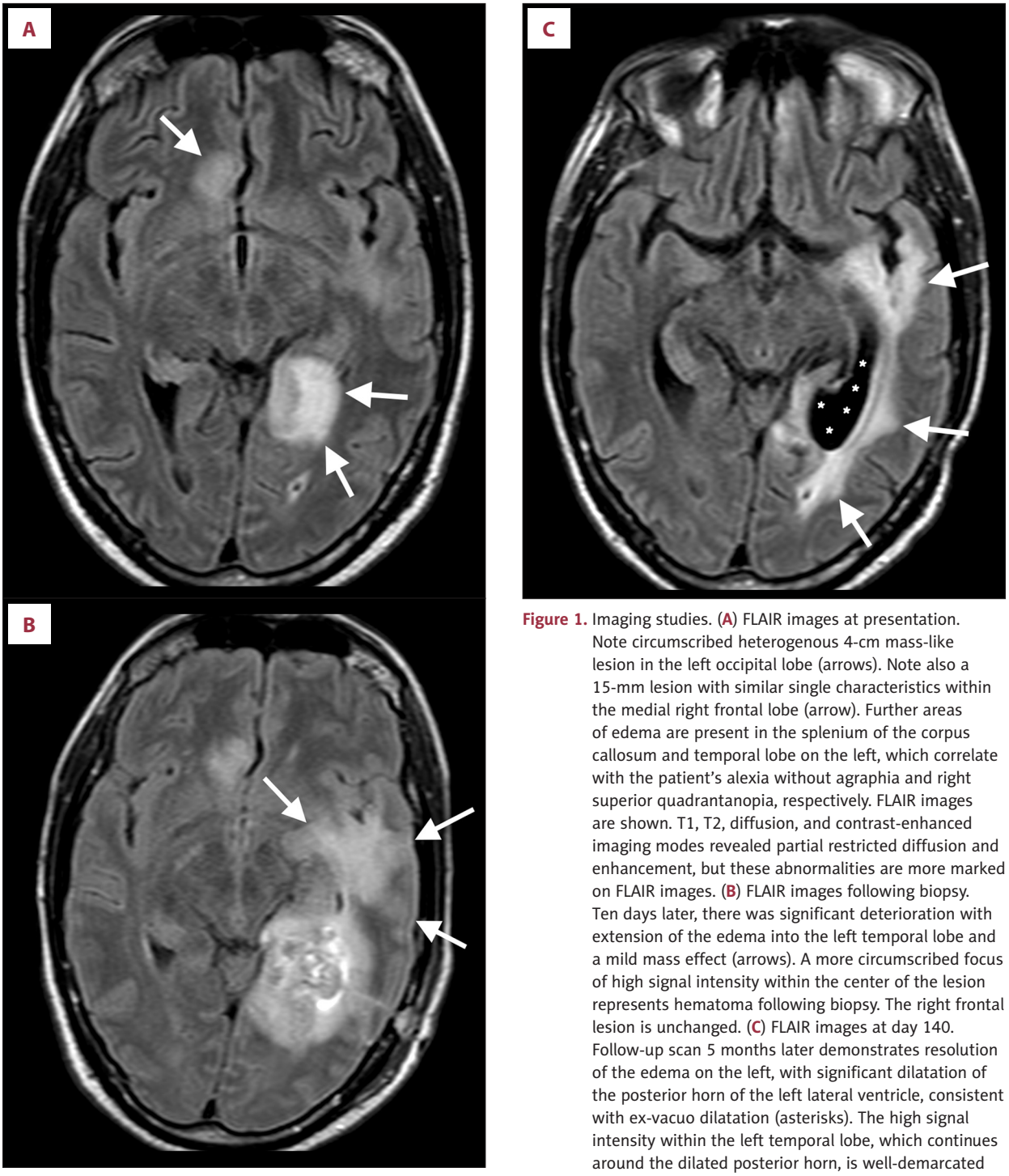

Figure 1. Imaging studies. (**A**) FLAIR images at presentation. Note circumscribed heterogenous 4-cm mass-like lesion in the left occipital lobe (arrows). Note also a 15-mm lesion with similar single characteristics within the medial right frontal lobe (arrow). Further areas of edema are present in the splenium of the corpus callosum and temporal lobe on the left, which correlate with the patient's alexia without agraphia and right superior quadrantanopia, respectively. FLAIR images are shown. T1, T2, diffusion, and contrast-enhanced imaging modes revealed partial restricted diffusion and enhancement, but these abnormalities are more marked on FLAIR images. (**B**) FLAIR images following biopsy. Ten days later, there was significant deterioration with extension of the edema into the left temporal lobe and a mild mass effect (arrows). A more circumscribed focus of high signal intensity within the center of the lesion represents hematoma following biopsy. The right frontal lesion is unchanged. (**C**) FLAIR images at day 140. Follow-up scan 5 months later demonstrates resolution of the edema on the left, with significant dilatation of the posterior horn of the left lateral ventricle, consistent with ex-vacuo dilatation (asterisks). The high signal intensity within the left temporal lobe, which continues around the dilated posterior horn, is well-demarcated and is consistent with gliosis (arrows).

cause of this abrupt severe hyponatremia – the onset was 9 days after brain biopsy; serum osmolarity was 280 mmol/kg and urinary osmolarity and sodium were both inappropriately high at 556 mmol/kg and 178 mmol/L, respectively. The patient responded to hypertonic saline, with normalization of serum sodium and correction of both urinary osmolarity and sodium over the course of 11 days.

In total, our patient was hospitalized for 53 days. Increasing nausea limited tolerance of the anti-amebic regimen and in total he completed 21 days of pentamidine isethionate, 28 days of co-trimoxazole and azithromycin, 60 days of metronidazole, 120 days of fluconazole, and 150 days of miltefosine. Maintenance therapy of miltefosine 50 mg 3 times weekly was planned but

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Table 1. Cerebrospinal fluid (CSF) analysis.

	Parameter	Result
Peripheral blood	White cell count (cells/mm^3)	2.3
	Neutrophils (cells/mm^3/%)	2/87%
	Lymphocytes (cells/mm^3/%)	<0.1/4%
	Glucose (mg/dL)	162
	Protein (g/dL)	5
Cerebrospinal fluid	White cell count (cells/mm^3)	42
	Neutrophils (cells/mm^3/%)	1/3%
	Lymphocytes (cells/mm^3/%)	37/88%
	CD8 (cells/mm^3/%)	32/88%
	CD4 (cells/mm^3/%)	2/6%
	NK (cells/mm^3/%)	3/7%
	Glucose (mg/dL)	72
	Protein (mg/dL)	149
Microbiology CSF results	Bacterial culture	Negative
	TB GeneXpert	Negative
	Viral PCR*	Negative
	Toxoplasma gondii PCR	Negative
	Microsporidia PCR	Negative
	PCR for Acanthamoeba, Balamuthia, Naegleria	Negative

* PCR of CSF for HSV1, HSV2, EBV, CMV, VZV, JCV, HHV6 and enterovirus were all negative.

discontinued because of gastrointestinal intolerance. CSF reanalysis on day 40 indicated normalization of cell count and protein. Repeat MRI at this time showed persistent decreased gyral enhancement, widespread edema, and areas of parenchymal necrosis. Repeat imaging on day 140 demonstrated resolution of edema and ex-vacuo dilatation of the posterior horn of the left lateral ventricle with surrounding gliosis, consistent with the natural history of treated necrotic areas (Figure 1C).

Persistent language deficits, including anomic aphasia and alexia, on discharge from hospital reflected left temporoparietal and callosal injuries. He underwent an outpatient neuro-rehabilitation program, with significant improvement in attention and recall. At 12 months after presentation, he is performing well in language and reading, with minor residual difficulty in naming low-frequency items, but improved fluency and fewer word-finding pauses. He displays excellent procedural memory for complex skills learned previously including engine repair, which he has resumed as a hobby. Our patient shows ongoing improvement and remains in complete remission 1 year after transplant for Hodgkin lymphoma.

Discussion

Granulomatous amoebic encephalitis (GAE) is a rare central nervous system infection caused by free-living amoebae and is associated with a high mortality rate. Three genera of pathogenic free-living amoebae are known to infect human hosts: *Acanthamoeba* spp., *Balamuthia mandrillaris, and Naegleria fowleri* [1,2]. Only the former 2 genera cause GAE and have 2 distinct life-cycle stages – the infectious trophozoite and dormant cyst stages [1,2]. Although *Acanthamoeba* are found ubiquitously in the environment, there are fewer than 50 reported cases of acanthamebic GAE in the literature, although it is likely that the true incidence is underestimated due to a failure to recognize and diagnose the infection. At the time of writing, we are aware of only 10 reported cases of acanthamebic GAE in patients after hematopoietic stem cell transplant [3–11]. In each of these cases, the infection proved fatal, and in 8 of the 10 cases the diagnosis was established only following histologic examination of autopsy specimens [3–9].

The source of the Acanthamoeba infection was not obvious in the case reported herein. Our patient previously used disposal contact lenses for correction of myopia but ceased using them prior to undergoing hematopoietic stem cell transplantation and had no symptoms or signs of keratitis. *Acanthamoeba* spp. are thought to enter the host via the lower respiratory tract or olfactory epithelium and spread hematogenously to the central nervous system [2] and this is the most likely mode of infection in our patient. The amoebae induce an inflammatory response and adhere to endothelial cells in the microvasculature via mannose binding protein to disrupt tight junctions and permeate the blood brain barrier [12,13]. *Acanthamoeba* spp. also produce proteases and toxins that damage tight junctions, connective tissue, and neurons [1,14]. The onset of clinical symptoms is insidious. Typical features include headache, nausea, irritability, and low-grade fever. Other clinical features depend on the area of brain affected, with a literature review indicating that the frontal and temporal lobes are the most commonly affected areas in *Acanthamoeba* GAE [15]. GAE is progressive, resulting in seizures, raised intracranial pressure, altered mental status, coma, and death. Diagnosis is challenging, with culture or isolation of *Acanthamoeba* from CSF of

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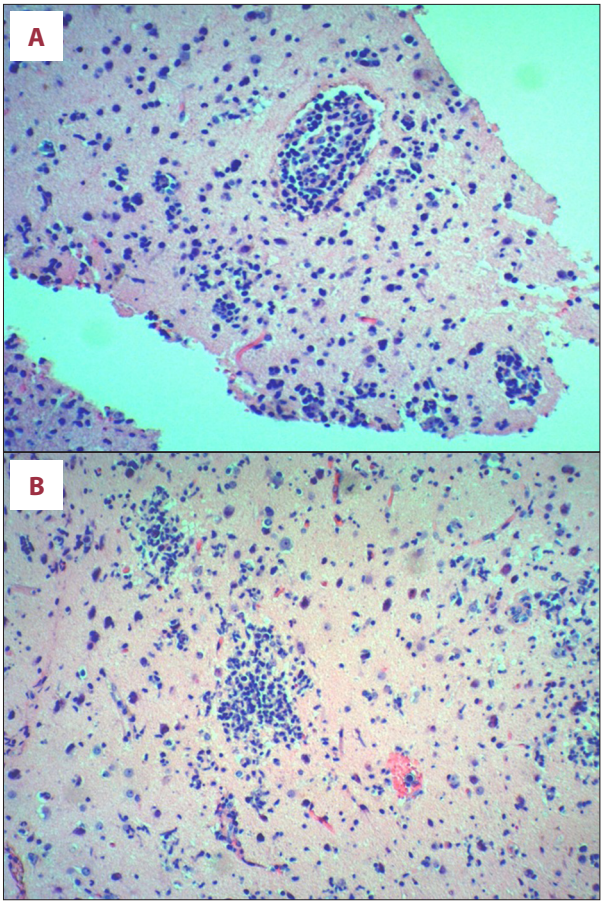

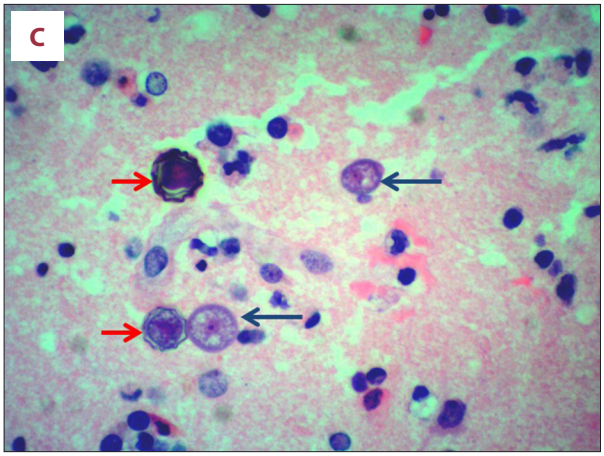

Figure 2. Histopathology. (**A**) Low-power magnification H&E photomicrographs of brain histology. Fragments of grey and white matter showing perivascular and parenchymal chronic inflammation, composed of lymphocytes, macrophages, and microglial cells. Rare multinucleated giant cells are seen (H&E ×10 objective). (**B**) Low-power magnification H&E photomicrographs of brain histology. Several variably sized aggregates of microglial cells forming microglial nodules are seen (H&E ×10 objective). (**C**) High-power magnification H&E photomicrographs of brain histology. Multiple rounded organisms are seen. The majority have a well-defined capsule with abundant granular/vacuolated cytoplasm, a round nucleus, and prominent central karyosome, consistent with amoebic trophozoites (blue arrows). Smaller ones have dark nuclei with a wrinkled and rather refractile outer capsule, consistent with amoebic cysts (red arrows) (H&E ×40 objective).

affected individuals proving difficult [2] and, in this case, had biopsy not been performed, the diagnosis would have been missed based on CSF analysis alone.

The optimal approach to the management of *Acanthamoeba* GAE is unknown. Drugs with *in vitro* activity that have resulted in successful outcomes for a small number of patients include rifampicin, azole anti-fungal drugs, pentamidine isethionate, sulfadiazine, flucytosine, azithromycin, caspofungin, and miltefosine. The Center for Disease Control and Prevention recommend a combination approach with miltefosine, pentamidine isethionate, and fluconazole. Miltefosine is an alkylphosphocholine drug that was initially developed as an anticancer drug but found a niche in the treatment of parasitic infections, in particular leishmaniasis [16]. Later, *in vitro* activity against *Acanthamoeba* was observed [17]. The mechanism of activity is thought to be the disruption of lipid-dependent cell signalling pathways in the parasite cell membrane. The introduction of miltefosine-containing combinations for the treatment of acanthamebic GAE is thought to have improved survival, at least in immunocompetent patients [18,19] and a case of successful treatment of a heart transplant recipient is reported [20]. In general, miltefosine is well tolerated, with manageable gastrointestinal symptoms constituting the chief adverse effect reported. As yet, there has been no clear guidance regarding the optimal duration of therapy, but continued treatment until radiological evidence of the absence of active disease and a normal CSF examination is advisable. It is likely that, as in our patient's case, several months of treatment will be required to secure a successful outcome.

Our patient is the first reported case of survival following acanthamebic GAE in the setting of profound immunosuppression after hematopoietic stem cell transplantation. Prompt biopsy and institution of an appropriate miltefosine-containing regimen led to a successful outcome following a prolonged treatment course and intensive rehabilitation.

Conclusions

This case illustrates the importance of early brain biopsy in a profoundly immunosuppressed patient with unexplained neurological deterioration, as the diagnosis would not have been made if relying on CSF analysis alone. Granulomatous

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amebic encephalitis is a rapidly fatal infection that is likely under-recognized. Early recognition and prompt institution of appropriate miltefosine-containing anti-amebic regimen can secure a successful outcome, even in profoundly immunosuppressed patients.

References:

1. Siddiqui R, Khan NA: Biology and pathogenesis of Acanthamoeba. Parasit Vectors, 2012; 5: 6
2. Schuster FL, Visvesvara GS: Opportunistic amoebae: Challenges in prophylaxis and treatment. Drug Resist Updat, 2004; 7(1): 41–51
3. Anderlini P, Przepiorka D, Luna M et al: Acanthamoeba meningoencephalitis after bone marrow transplantation. Bone Marrow Transplant, 1994; 14(3): 459–61
4. Feingold JM, Abraham J, Bilgrami S et al: Acanthamoeba meningoencephalitis following autologous peripheral stem cell transplantation. Bone Marrow Transplant, 1998; 22(3): 297–300
5. Castellano-Sanchez A, Popp AC, Nolte FS et al: Acanthamoeba castellani encephalitis following partially mismatched related donor peripheral stem cell transplantation. Transpl Infect Dis, 2003; 5(4): 191–94
6. Peman J, Jarque I, Frasquet J et al: Unexpected postmortem diagnosis of Acanthamoeba meningoencephalitis following allogeneic peripheral blood stem cell transplantation. Am J Transplant, 2008; 8(7): 1562–66
7. Akpek G, Uslu A, Huebner T et al: Granulomatous amebic encephalitis: An under-recognized cause of infectious mortality after hematopoietic stem cell transplantation. Transpl Infect Dis, 2011; 13(4): 366–73
8. Doan N, Rozansky G, Nguyen HS et al: Granulomatous amebic encephalitis following hematopoietic stem cell transplantation. Surg Neurol Int, 2015; 6(Suppl. 18): S459–62
9. Coven SL, Song E, Steward S et al: Acanthamoeba granulomatous amoebic encephalitis after pediatric hematopoietic stem cell transplant. Pediatr Transplant, 2017; 21(8): e13060
10. Kaul DR, Lowe L, Visvesvara GS et al: Acanthamoeba infection in a patient with chronic graft-versus-host disease occurring during treatment with voriconazole. Transpl Infect Dis. 2008;10(6): 437-41.
11. Abd H, Saeed A, Jalal S, Bekassy AN, Sandstrom G. Ante mortem diagnosis of amoebic encephalitis in a haematopoietic stem cell transplanted patient. Scand J Infect Dis, 2009; 41(8): 619–22
12. Alsam S, Kim KS, Stins M et al: Acanthamoeba interactions with human brain microvascular endothelial cells. Microb Pathog, 2003; 35(6): 235–41
13. Khan NA, Siddiqui R: Acanthamoeba affects the integrity of human brain microvascular endothelial cells and degrades the tight junction proteins. Int J Parasitol, 2009; 39(14): 1611–16
14. Sissons J, Alsam S, Goldsworthy G et al: Identification and properties of proteases from an Acanthamoeba isolate capable of producing granulomatous encephalitis. BMC Microbiol, 2006; 6: 42
15. Ong TYY, Khan NA, Siddiqui R: Brain-eating amoebae: Predilection sites in the brain and disease outcome. J Clin Microbiol, 2017; 55(7): 1989–97
16. Dorlo TP, Balasegaram M, Beijnen JH, de Vries PJ: Miltefosine: A review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. J Antimicrob Chemother, 2012; 67(11): 2576–97
17. Schuster FL, Guglielmo BJ, Visvesvara GS: *In-vitro* activity of miltefosine and voriconazole on clinical isolates of free-living amebas: *Balamuthia mandrillaris*, *Acanthamoeba* spp., and *Naegleria fowleri*. J Eukaryot Microbiol, 2006; 53(2): 121–26
18. Aichelburg AC, Walochnik J, Assadian O et al: Successful treatment of disseminated *Acanthamoeba* sp. infection with miltefosine. Emerg Infect Dis, 2008; 14(11): 1743–46
19. Webster D, Umar I, Kolyvas G et al: Treatment of granulomatous amoebic encephalitis with voriconazole and miltefosine in an immunocompetent soldier. Am J Trop Med Hyg, 2012; 87(4): 715–18
20. Brondfield MN, Reid MJ, Rutishauser RL et al: Disseminated Acanthamoeba infection in a heart transplant recipient treated successfully with a miltefosine-containing regimen: Case report and review of the literature. Transpl Infect Dis, 2017; 19(2): e12661

Conflicts of interest

None.

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