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Case Report

Non-granulomatous meningoencephalitis with *Balamuthia mandrillaris* mimicking a tumor: First confirmed case from Pakistan

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ABSTRACT

Background: Free-living amoebae rarely instigate intracranial infections that may resemble neoplastic conditions on imaging. *Naegleria fowleri* precipitates an acute, swiftly fatal meningoencephalitis, whereas *Acanthamoeba* and *Balamuthia* species typically manifest with a less aggressive onset but carry equally dire consequences.

Case Description: The case describes a 33-year-old woman with subacute encephalitis caused by *Balamuthia mandrillaris*. She experienced 2 months of back pain, 1 month of headaches, and 2 weeks of vomiting without fever, recent travel, aquatic activities, or animal exposure. Brain magnetic resonance imaging revealed a sizable, heterogeneous enhancing mass in the right temporal and frontal lobes, accompanied by vasogenic edema and midline shift. Histopathology showed marked inflammation and damage to blood vessels with amoebic trophozoites present. The trophozoites displayed specific characteristics, leading to the diagnosis of amoebic meningoencephalitis. Polymerase chain reaction and Sanger sequencing confirmed *B. mandrillaris* infection while testing for *N. fowleri* and *Acanthamoeba* was negative. Despite antibiotic treatment, the patient's condition deteriorated rapidly, resulting in death within 2 weeks of presentation.

Conclusion: This is the first confirmed case of *B. mandrillaris* central nervous system (CNS) infection from Pakistan. The incidence of this disease is expected to rise due to increasing temperatures due to climate change and the deteriorating quality of the water supply. *Balamuthia* meningoencephalitis should, therefore be on the differential for non-neoplastic CNS lesions. Furthermore, an atypical histopathologic picture, including the absence of granulomatous inflammation, needs to be recognized.

Keywords: *Acanthamoeba*, *Balamuthia*, Meningoencephalitis, Polymerase chain reaction, Sanger sequencing

INTRODUCTION

Intracranial infections are an uncommon cause of intracranial mass lesions where they can mimic a neoplastic process. Although bacterial abscesses are more common, occasionally, free-living amoebae can also cause central nervous system (CNS) infections. The amoeba causing human infections are normal inhabitants of soil and water, where they feed on bacteria. A few members can become facultative parasites when an opportunity to enter a vertebrate exists. They are termed "amphizoic" as they can live as free-living organisms and also as endoparasites. Five

amoebic species are known to cause CNS infections; *Naegleria fowleri* causes primary amoebic meningoencephalitis. *Acanthamoeba* spp. and *Balamuthia mandrillaris are* usually present with granulomatous amoebic infection and, much less commonly, *Sappinia pedata*. Rare cases of *Entamoeba histolytica* infection have also been known, usually presenting as an abscess.[6] We present a case of subacute granulomatous encephalitis caused by *Balamuthia* spp. in a young woman.

CASE DESCRIPTION

A 33-year-old woman presented with a history of intermittent vomiting for about 2 weeks. On further probing, she revealed a history of back pain for about 2 months and headaches for 1 month. There was no history of fever, recent travel, history of recent exposure to animals, fresh water swimming, etc. No history of tuberculosis or any other significant medical condition. The review of systems was unremarkable. On examination, the patient was awake, alert, and oriented with no apparent pallor, jaundice, edema, cyanosis, or clubbing. She was afebrile, with blood pressure, heart, and respiratory rates all within normal limits. The cranial nerve examination was normal. There were no gastrointestinal, pulmonary, or cardiovascular signs and symptoms. Magnetic resonance imaging (MRI) brain showed a large heterogenous enhancing lesion involving the right temporal and frontal lobes with surrounding vasogenic edema and midline shift, as shown in Figure 1.

Considering the impression of a neoplastic lesion, neuro-navigation-guided right temporal awake craniotomy was performed, and maximum safe resection of the lesion was done. She developed no new postoperative deficits, postoperative MRI showed gross total resection of the lesion [Figure 1], and she was shifted out of the special care unit. On postoperative day 2, she developed drowsiness and decreased responsiveness, and she was shifted back to special care and computed tomography head repeated, which showed an increase in cerebral edema. And she had developed hyponatremia, and was managed appropriately. She continued to worsen with vital instability and was electively intubated and shifted to the intensive care unit.

Meanwhile, her histopathology revealed hippocampal formation, cortex, and white matter with overlying leptomeninges with marked lymphoplasmacytic and histiocytic inflammation. Several vessels showed mural necrosis and transmural inflammation with large cells with foamy cytoplasm with Periodic acid-Schiff+/diastase resistant granules large nuclei with prominent nucleoli suggestive of amebic organisms. Rare red blood cell engulfment was noted. No cyst forms were present, and only rare multinucleate giant cells were seen without a prominent granulomatous reaction. The final histopathology diagnosis was amebic meningoencephalitis; however, speciation was not possible based on morphology alone. There was no evidence of fungal infection or any neoplasm. The larger size of the putative organism favored *Balamuthia* or *Acanthamoeba* as the culprit, as shown in Figure 2.

After this diagnosis, infectious disease service was urgently consulted and an antibiotic regimen was initiated that included intravenous azithromycin, meropenem, metronidazole, fluconazole, co-trimoxazole, rifampicin, miltefosine, and intrathecal amphotericin. A cerebrospinal fluid (CSF) tap was also conducted and sent for *N. fowleri* polymerase chain reaction (PCR), which was negative. Cytology was similarly negative. CSF studies showed low glucose (21 mg/dL), raised proteins (427 mg/dL), and WBC counts (8.7 × 107 with 80% lymphocytes). Culture studies showed no bacterial or fungal growth.

Her MRI brain was repeated, which revealed multifocal areas of infarction and abnormal patchy hyperintensities with tonsillar herniation [Figure 3]. She continued to decline and had developed absent brainstem reflexes. Her EEG showed extreme low-voltage theta activity, suggestive of severe encephalopathy. MRI perfusion scan was done, which showed multifocal cerebral infarcts and features suggestive of encephalopathy and impaired cerebral perfusion.

The family was counseled in detail regarding the poor prognosis, and they decided to withdrawal from ventilatory support. Once extubated, she passed away shortly. The medical autopsy was not performed as per the family's wish.

PCR, as well as Sanger sequencing was positive for *B. mandrillaris*.

DISCUSSION

Pathogenic free-living amoebas cause two distinct clinical forms of encephalitis: primary amebic meningoencephalitis (PAM) and granulomatous amebic encephalitis (GAE). *N. fowleri* causes a rapidly progressive and almost uniformly lethal CNS infection referred to as PAM. *Acanthamoeba* spp. and *B. mandrillaris* cause GAE, a subacute CNS infection that has a very poor prognosis. *S. pedata* has been described only once as a non-granulomatous subacute encephalitis.[3]

Centers for Disease Control and Prevention first discovered *B. mandrillaris* in the brain of dead pregnant mandrill baboon (a type of primate) in 1986. After extensive research, *B. mandrillaris* (Previously known as a leptomyxid ameba) was determined to be a new species of amoeba in 1993. Its lifecycle has two morphological forms (trophozoite and cyst). Two hundred cases of *Balamuthia* disease have been reported worldwide. Those at high risk for this infection include people with human immunodeficiency virus/acquired immunodeficiency syndrome, cancer, liver disease, or diabetes mellitus, people receiving immunosuppressive

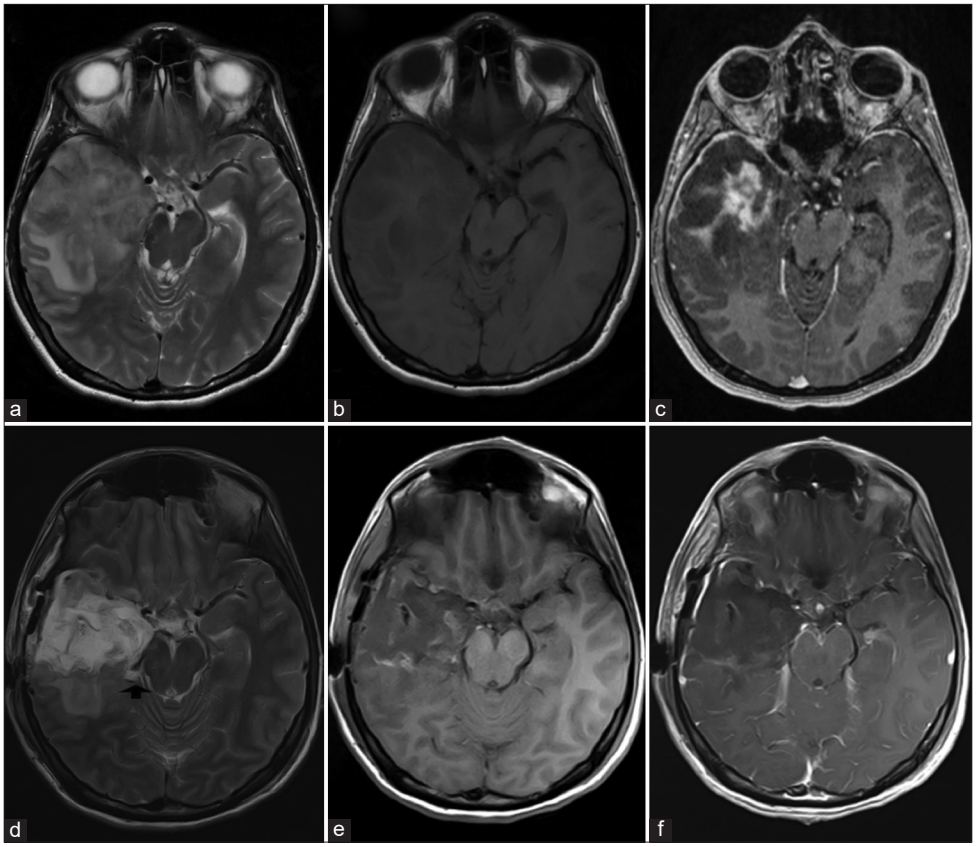

Figure 1: Radiologic findings: (a-c) Pre-surgery magnetic resonance imaging (MRI); (d-f) MRI postoperative. (a-c) Preoperative MRI: (a) T2 axial, (b) T1 axial, and (c) T1 post-contrast axial (A large heterogenous appearing lesion involving the right temporal and frontal lobe with surrounding vasogenic edema. The lesion is iso- to hypointense on T1 and hyperintense on T2, with heterogeneous enhancement noted on the contrast sequence. The lesion is also causing a mass effect and midline shift to the contralateral side). (d-f) MRI status post-surgery: (d) T2 axial, (e) T1 axial, (f) T1 post-contrast axial status post-surgery (right temporal resection cavity is evident with vasogenic edema in the right temporal region extending into the right parieto-occipital lobe. On T1 post-contrast, no enhancing residual component of the lesion was noted).

drugs, and alcoholics, although 40% of infected patients are immune-competent.[1,16] The life cycle of *B. mandrillaris* consists of two stages: a vegetative trophozoite stage and a dormant cyst stage.[10]

The pathogenesis might begin with skin injuries, persistent sinus infections, or pneumonia before disseminating hematogenously to the CNS and triggering GAE. Typically, the skin lesion manifests as a painless patch or sore in the central face or limb (particularly the knee). Recognizing this skin abnormality is crucial, as it enables early diagnosis weeks or even months before CNS symptoms emerge. However, like the current case, most patients initially exhibit neurological symptoms without any visible skin manifestations.[16]

Recent studies have shown that the human brain microvascular endothelial cells produce interleukin-6 in response to *B. mandrillaris* infection, and this may play a role in the traversal of the blood-brain barrier (BBB). Human-to-human disease transmission of the pathogen can occur through organ transplantation, and thus, brain-dead victims of *Balamuthia* encephalitis are not suitable organ donors.[4] Symptoms of *Balamuthia* infection typically manifest over weeks to a few months and often include general clinical signs such as fever (39%), headache (39%), vomiting (30%), and lethargy (28%). Common neurological symptoms on presentation include altered mental status (30%), seizures (21%), and weakness (19%). While *Balamuthia* infection usually presents with manifestations in a single organ system, such as in cases of GAE or cutaneous balamuthiasis, autopsy findings have revealed the presence of amebae in other organs like the kidneys, lungs, and adrenal glands in patients with GAE.[2]

Diagnosis of GAE is challenging. MRI typically shows multiple enhanced mass-like lesions with ring enhancement,

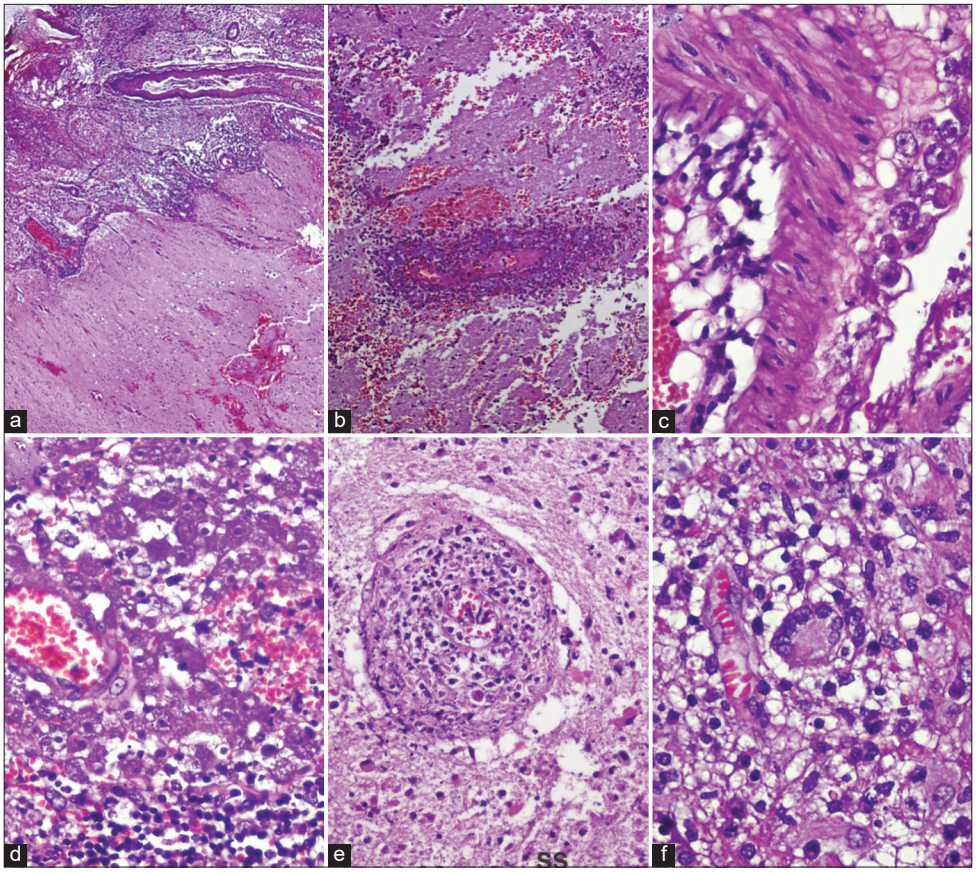

Figure 2: Histopathologic findings: (a and b) leptomeningitis and encephalitis, (c and d) necrotizing vasculitis with aggregation of amebic organisms around the blood vessel, (e) vasculitis, (f) rare multinucleated giant cells.

edema, and hydrocephalus mimicking brain abscess, brain metastasis, or intracerebral hematoma. A few cases reported solitary mass lesions which mimicked a brain tumor, similar to our case. An important hallmark is hemorrhage into the mass lesion. In patients with GAE due to *B. mandrillaris*, any cortical lobe can be involved: temporal (51%), frontal (41%), occipital (31%), and parietal (21%). Among extra cortical sites, the cerebellum, thalamus, and basal ganglia, including the caudate nucleus and the brainstem, are the most favored sites. As in our patient, angiitis secondary to amoebic invasion can cause small vessel occlusions, resulting in cerebral infarction, as was seen in the second postoperative MRI of our case.[8,12]

In cases of GAE caused by *Acanthamoeba* or *Balamuthia*, wet mount examinations of CSF often reveal few or no trophozoites, unlike in PAM caused by *N. fowleri*, where abundant trophozoites are typically observed in CSF samples. Therefore, CSF examination is not the preferred method for ruling out GAE infections. CSF studies typically indicate lymphocytic-predominant pleocytosis, elevated protein levels, and normal or reduced glucose levels, consistent with findings in our patient. However, PCR tests for CSF are not widely available, leading to delayed diagnosis. Consequently, a biopsy is often necessary, and obtaining a pathological diagnosis may be time-consuming. This contributes to the challenge of achieving a definitive diagnosis before the patient's demise.[12]

Histopathological examination usually reveals granulomatous inflammation characterized by the clustering of foamy macrophages, multinucleated giant cells, and lymphocytes. Trophozoite stages of the parasite are frequently misidentified as macrophages or necrotic keratinocytes. Trophozoites of *B. mandrillaris* typically exhibit a three-layered structure: an outer irregular or wrinkled thin ectocyst, a middle amorphous or fibrillar mesocyst, and a smooth thick endocyst.[12]

Since *B. mandrillaris* shares a phylogenetic relation with *Acanthamoeba* spp., morphological differentiation between these two amoebas is not feasible. In addition, GAE induced by either *Acanthamoeba* spp. or *B. mandrillaris* displays similar clinical progression, neuroimaging features, and pathological characteristics. Hence, confirmation of diagnosis relies on serological or molecular assays, with

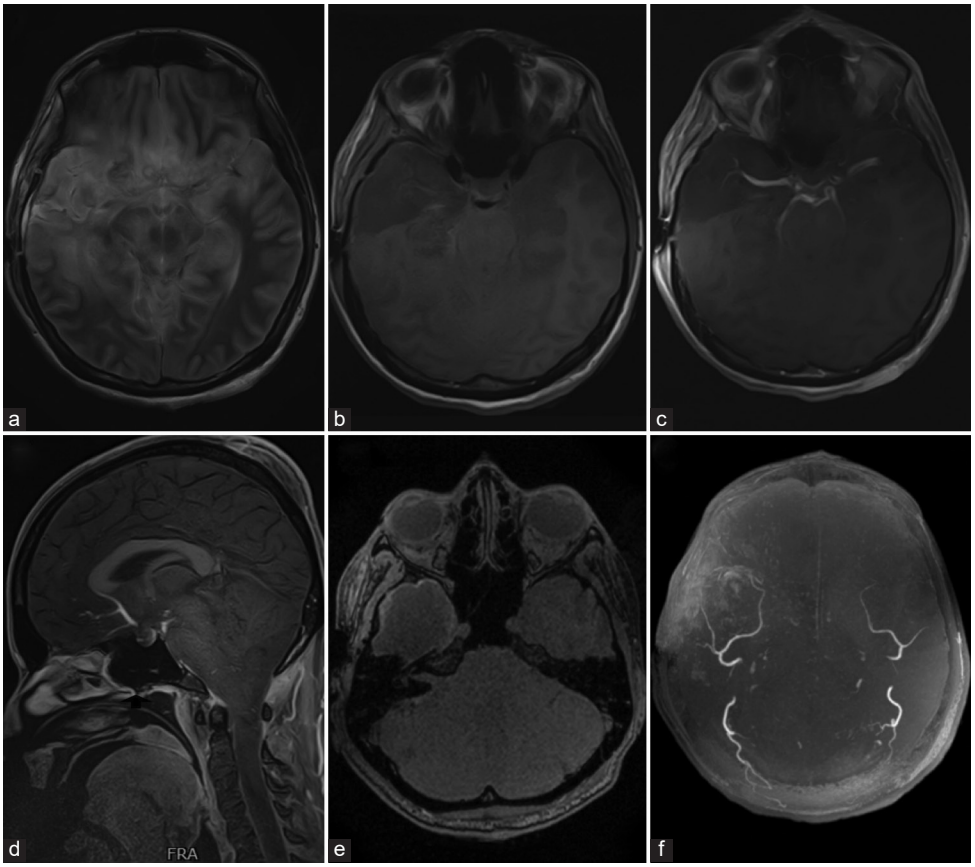

Figure 3: (a) Multiple patchy T2 hyperintensity along areas involving the cerebellum, bilateral temporal lobes, frontal lobes and left parietal lobe, posterior margins of resection cavity, brainstem, and right basal ganglia showing patchy diffusion restriction. (b and c) There is also interval development of basal meningeal enhancement noted. (d) On T1 contrast sagittal view, tonsillar herniation is evident with resultant mass effect on the brainstem. (e and f) Heterogeneous perfusion signals were noted in the brain parenchyma. Most of the areas of the brain were showing significantly reduced blood volume and flow, there was elevated time to peak and mean transit time.

molecular techniques emerging as the most promising diagnostic approach. PCR-based methods, which analyze ribosomal RNA gene sequences (16s ribosomal RNA [rRNA] or 18s rRNA), offer heightened sensitivity and specificity in detecting *B. mandrillaris*, necessitating minimal pathogen-specific expertise. Furthermore, analysis of nuclear and mitochondrial 18S ribosomal DNA of *Balamuthia* has unveiled a singular genotype responsible for human infections globally, in contrast to *Acanthamoeba*, which exhibits 18 genotypes.[19]

There are currently no established treatment guidelines for GAE. Surgical removal of the lesion may help decrease the parasite load. An effective antimicrobial therapy necessitates a novel drug possessing amoebicidal properties capable of penetrating the BBB with minimal toxicity. Challenges in treatment arise from the limited penetration of antimicrobial agents into the CSF and the thick cell wall of the amebic cyst. In rare instances, a combination therapy including flucytosine, pentamidine, fluconazole, sulfadiazine, and either azithromycin or clarithromycin has demonstrated effectiveness. Miltefosine, previously utilized for leishmaniasis treatment, has shown potential and has been endorsed by the U.S. Food and Drug Administration as an investigational treatment for *Balamuthia*, which was also administered in this case.[8,15,19]

The mortality rate for *Balamuthia* GAE exceeds 95%, with only a limited number of documented cases showing survival. Krasaelap *et al*. have reported a mere ten cases of individuals overcoming this fatal CNS infection. Interestingly, males appear to be more vulnerable, with a male-to-female ratio of 2.5:1, likely due to increased exposure to outdoor activities. However, among survivors, an equal number of males and females were observed, suggesting a potential role of the female gender in enhancing survival rates. Skin lesions often precede neurological symptoms, occurring in about a quarter of cases, yet up to half of survivors develop them. The absence

of cutaneous manifestations in our patient contributed to delayed diagnosis, underscoring the importance of skin symptoms in early recognition and timely treatment, ultimately improving the chances of patient survival.[8]

In our case as the patient had no preoperative clinical signs of infection, comorbidities, immune-compromised status, or any other relevant past medical history, the presence of a lesion being of infectious etiology was a lesser differential. There are anecdotal accounts of a few case reports that had shown worsening of patient's condition after surgical excision or biopsy,[17] while few cases recovered after resection of amoebic mass.[11] The previous cases of *Balamuthia* misdiagnosed as having tuberculous encephalitis have been reported.[18]

Similar to our case, previous anecdotal accounts have suggested pathogenesis as dissemination of granulomatous inflammation following surgical resection, leading to severe reactionary vasculitis and subsequent cerebral perfusion limitation.[11,17]

N. fowleri infections caused by inadequately chlorinated domestic water supply and associated with nasal irrigation using neti pots and ablution practices (ritual nasal cleansing) have also been diagnosed. *N. fowleri* has also been found in the piped water supply in Karachi.[13] It has been showed that swimming pool for fresh pond water exposure is found in only a small minority of *Naegleria* cases in Pakistan (1/19 cases in Ghanchi *et al.*).[5] Given the ubiquity of such exposures, risk factors for severe disease need to be studied. The majority of cases have not shown any indication of immunocompromise and were in young, healthy individuals.[13] Similarly, the majority of Balamuthia amoebic encephalitis (BME) have been found in immunocompetent individuals, although cases with immunocompromise have also been reported. Suggested risk factors for BAE include contact with contaminated soil, habitation in warmer environments, and Hispanic origin, indicating a possible genetic component to its predisposition.[7] The prevalence of *Balamuthia* in Pakistan and the most common mode of transmission remains unknown.

Better diagnostic methods need to be identified for the diagnosis of amoebic infections. Ghanchi *et al*. showed the utility of the PCR-based diagnosis of the amoeba for the early diagnosis and management of the disease.[5] Compared to the other diagnostic methods such as microscopic examination of the wet film preparation of CSF, CSF culture, and amebic antigen detection, PCR is more sensitive and specific. Ghanchi *et al*.[5] showed a sensitivity of around 40% for wet mount for PCR positive cases. Recently, metagenomic approaches have been used which allow identification of species without apiori suspicion of the organism.[20]

In this case, the long interval between symptoms favored against *Naegleria* which has the mean ± standard deviation time from symptom onset to death was 6.38 ± 3.15 days (range 3–15 days).[13] With up to 65% of water samples collected from filtration plants being positive for *Acanthamoeba* spp. and up to 5% of water samples were positive for *B. mandrillaris*.[20] While it has been suggested that the prevalence of *Naegleria* may be increasing due to rising temperatures due to climate change and deterioration of water distribution and chlorination systems,[5,13] whether the same is true for *Balamuthia* is not clear. It has also been suggested that *B. mandrillaris* is difficult to isolate and culture, which may contribute to under detection of this organism in the environment. The route of entry of *Balamuthia* is not clear but may include penetration through the olfactory neuroepithelium through the nasal route. However, hematogenous dissemination from a primary lung or skin has also been suggested. The absence of orbitofrontal lobe involvement in our case also supports a possible hematogenous route of entry into the CNS. Invasion into the CNS likely occurs at the sites of the BBB, but the precise mechanisms how *B. mandrillaris* penetrates the BBB is still unclear.[5,13]

Systemic involvement with amoebae in the lungs and liver[14] as well as other organs has been found in autopsy cases. Rare cases have resulted in successful treatment.[9]

CONCLUSION

We report a rare case of amoebic infection presenting with tumor-like characteristics, later confirmed to be caused by *B. mandrillaris*. Consistent with prior research, this patient unfortunately did not survive the illness. Clinical suspicion for *Balamuthia* should be heightened in patients presenting with subacute granulomatous meningoencephalitis and negative results on viral, bacterial, and fungal infection tests. Despite attempts with various antimicrobial combinations, the prognosis for GAE remains bleak. At present, the condition is largely fatal, and our understanding of its pathogenesis and management is limited. It is hoped that future advancements will provide better therapeutic strategies for treating primary amebic CNS infections. Further studies are crucial to identify novel drugs capable of penetrating the BBB and treating GAE more effectively.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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