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Case report

A case report of *Balamuthia mandrillaris* encephalitis

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ABSTRACT

Balamuthia amoebic encephalitis (BAE) is a rare and severe parasitic infection of the central nervous system. Its delayed diagnosis and treatment are often due to the lack of specific clinical manifestations and its poor prognosis. Reported mortality rates reach around 95%. The Balamuthia mandrillaris is also known as the "brain-eating amoeba." Recently, the use of metagenomic next-generation sequencing (mNGS) in clinical settings has led to an increase in BAE diagnoses. A case report detailing the use of mNGS to diagnose granulomatous encephalitis caused by the Baramsi amoeba has improved clinicians' understanding of this disease and helped reduce misdiagnoses and missed diagnoses.

1. Introduction

Amoebas, belonging to the genera *Naegleria*, *Acanthamoeba*, and *Balamuthia*, are free-living, amphizoic, and opportunistic protozoa found ubiquitously in nature. These conditional pathogens can cause human infections by invading the brain, skin, lungs, and eyes [1].

The first reported case of *Balamuthia mandrillaris* encephalitis occurred in 1986, following the death of a pregnant mandrill baboon at the San Diego Wild Animal Park. The causative agent was isolated and characterized from the animal [2]. *B. mandrillaris* encephalitis is a rare infectious disease of the central nervous system. The difficulty in diagnosing *Balamuthia* amoebic encephalitis (BAE) and the resultant delay in initiating antimicrobial therapy, results in extremely high mortality rate. We present a case report of a 77-year-old woman diagnosed with BAE using next-generation sequencing (NGS).

2. Case report

A 77-year-old Chinese woman with a seven-year history of chronic gastritis was admitted to a local hospital for a one-day history of dizziness and unsteady walking. Upon arrival, her temperature was 37.8 °C, and a physical examination revealed dysarthria and ataxic gait.

The patient's complete blood count was normal, but her blood chemistry analysis showed a low sodium level (121 mmol/L). A non-contrast brain computed tomography (CT) scan displayed an area of high attenuation in the left temporal lobe. Brain magnetic resonance imaging (MRI) identified an abnormal signal in the left temporal lobe, and a new infarction in the left occipital lobe. Consequently, antiplatelet aggregation therapy was initiated on the second day of hospitalization.

Her neurological status worsened on the third day of admission, with progressive confusion and language difficulties. After eight days in the local hospital, she was transferred to our institution for further treatment.

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Physical examination upon arrival revealed dysarthria, unsteady gait with truncal ataxia, and poor postural control. Her Glasgow Coma Score was 9, with normal eye movements, and no diplopia or eye tremors. Scattered ecchymosis was observed on her skin. Her temperature was 38.5 °C, and laboratory findings showed leukocytosis (9960 cells/mm^3) with lymphopenia (410 cells/mm^3), mild anemia (hematocrit 33.9%), and normal platelet count (45,000 cells/mm^3). Tumor markers, antinuclear antibody profile, and anti-neutrophil antibody tests were negative.

Given the low platelet count and scattered ecchymosis, we initiated supportive therapy involving nutritional supplements and vasodilators (betahistine hydrochloride and acetoglutamine). However, these interventions did not improve her symptoms after two days.

Over the following days, the patient experienced progressive obtundation and limb muscle weakness. On the third day of hospitalization, she required endotracheal intubation and hyperventilation due to airway obstruction. One day later, she developed signs of a progressive cerebral hernia, exhibiting anisocoria (pupil diameters of 3 mm and 5 mm on the left and right eyes, respectively), with diminished pupillary light reflex and horizontal nystagmus. An MRI brain scan on the fifth day revealed multiple areas of abnormal signals in the pia mater, ependymal area, and brain parenchyma (Fig. 1). Abdominal and chest CT scans performed the following day were unremarkable.

Based on the patient's imaging findings, we suspected a central nervous system infection. On the fifth day of hospitalization, we initiated empirical antibacterial therapy with moxifloxacin (0.4 g intravenously daily), minocycline (0.1 g intravenously every 12 hours), and ganciclovir (0.25 g intravenously every 12 hours). A lumbar puncture was also performed.

Cerebrospinal fluid (CSF) analysis revealed a cell count of 25 cells/mm^3 (4% neutrophils and 96% monocytes), protein level of 724

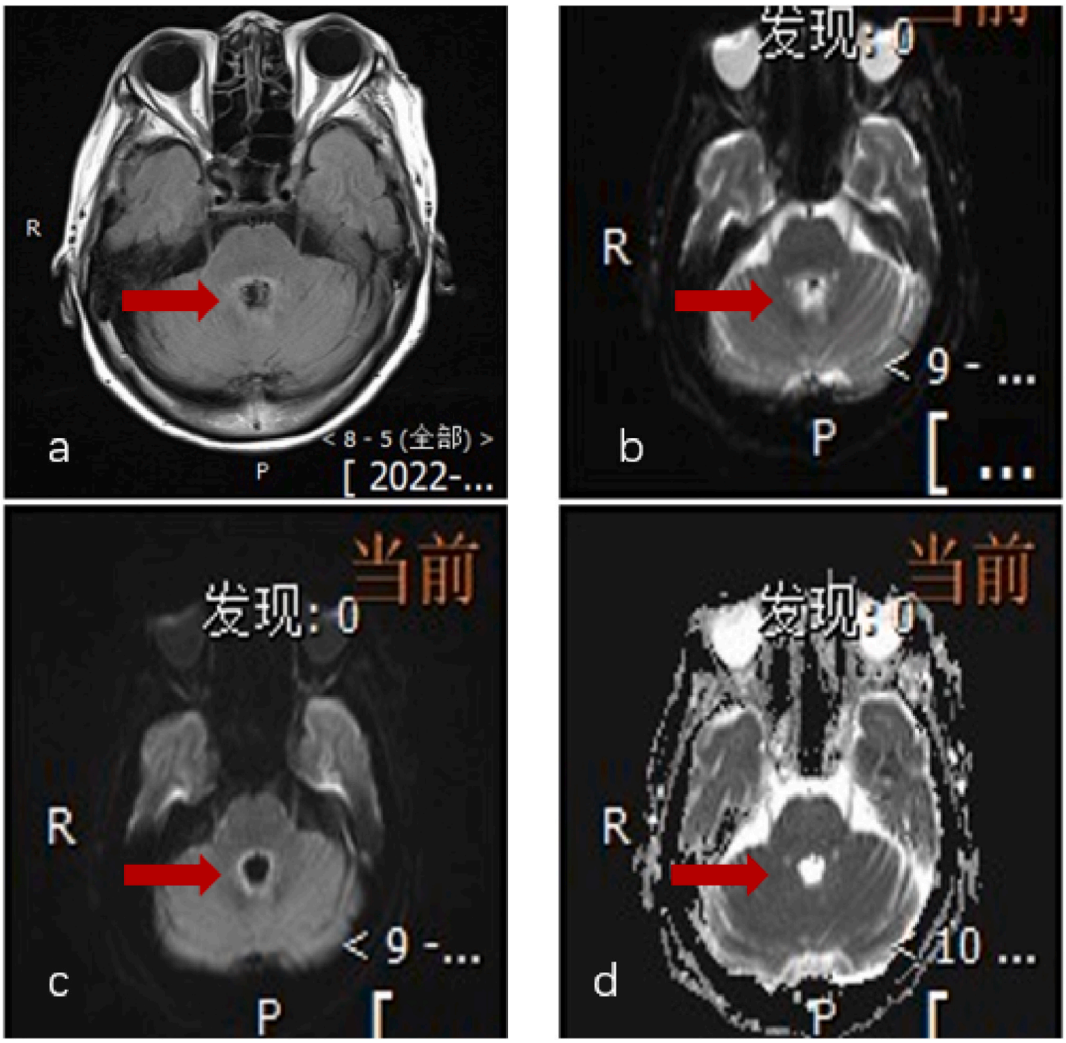

Fig. 1. Proton density magnetic resonance imaging of the brain on November 27, 2022.(a)The fourth ventricle exhibits a peripheral hypersignal shadow on T2-FLAIR imaging. (b) there is a slightly increased signal surrounding the fourth ventricle on T2-weighted imaging. (c) On diffusion-weighted imaging (DWI) (b = 1000), there is a slight elevation in signal intensity around the fourth ventricle. (d) The apparent diffusion coefficient (ADC) map demonstrates a slightly decreased signal around the fourth ventricle.

mg/dL, and glucose level of 80.82 mg/dL. Cultures of the CSF did not identify any bacteria, fungi, or viral elements, and *Cryptococcus* testing was negative. T-cell tests for *Brucella* antibodies in the blood and tuberculosis infection were also negative. Two days later, a second lumbar puncture was performed to identify the pathogen using high-throughput NGS. This analysis revealed 162 cells/mm^3 (9% neutrophils and 91% monocytes), a protein level of 1285 mg/dL, and a glucose level of 10.08 mg/dL. NGS examination of the CSF identified 724 *B. mandrillaris* sequences (Fig. 2), leading to the diagnosis of *B. mandrillaris* encephalitis on the ninth day of hospitalization.

Despite aggressive treatment measures, the patient's condition worsened. Unfortunately, before the NGS results were available, the patient's family chose to forgo further treatment, and she passed away during the discharge process. Throughout her treatment, we maintained open communication with the patient's family members, ensuring they understood the treatment process and the course of the disease.

3. Discussion

B. mandrillaris is a free-living amoeba. It thrives in various environments, having been isolated from freshwater, soil, and dust in many countries [3,4]. Transmission likely occurs through respiratory tract or skin lesions, followed by dissemination via the bloodstream. *B. mandrillaris* can disrupt the blood-brain barrier, directly invade the central nervous system through the olfactory neuroepithelium, or potentially even enter through the gastrointestinal tract, as recent animal studies suggest [5]. This diverse array of entry points highlights its ability to cause central nervous system infection in multiple ways.

The case presented here involved a patient residing in rural Shandong Province, China, with frequent contact with local ponds and mountainous environments. This reinforces the potential exposure risk associated with natural surroundings.

A literature review across major databases (EMBASE, MEDLINE, and Web of Science) for *B. mandrillaris* intracranial infections revealed only 10 survivors among over 150 cases reported worldwide [6]. While *B. mandrillaris* typically leads to widespread and fatal central nervous system dysfunction, a rare presentation known as granulomatous amoebic encephalitis (GAE) can occur [7]. Notably, this infection can affect both immunocompromised and immunocompetent individuals of any age. According to a 2019 report by Cope et al., the most common initial clinical features include fever, headache, vomiting, and lethargy, while altered mental state, seizures, and weakness are frequent neurological presentations [8]. Due to the amoeba's resistance to detection through CSF examinations, diagnosis often relies on specific neuroimaging findings. Typical neuroimaging findings of *Balamuthia* GAE include ring-enhancing lesions, multifocal lesions, space-occupying lesions, and edema [9]. Unfortunately, the non-specific nature of these clinical and imaging manifestations contributes to delayed diagnosis in most patients.

Currently, brain tissue and skin biopsies remain the gold standard for diagnosis. However, advancements in technology have highlighted the role of NGS in amoebic encephalitis diagnosis. Compared to traditional methods like polymerase chain reaction, NGS offers significantly higher throughput but involves a more complex operational workflow.

Optimal treatment for GAE remains unclear, with combination therapy involving miltefosine, fluconazole, and pentamidine isethionate currently recommended by several authorities [10]. In certain cases, surgical excision of isolated brain lesions may prove effective. We identified a documented case of successful BAE treatment involving a combination of surgery and medication [10].

4. Conclusion

The patient in this case presented with a typical subacute course and multiple enhancing intracranial mass lesions on imaging. Given these findings, we initially suspected a metastatic tumor and subsequently performed chest and abdominal CT scans to rule out a primary malignancy. No tumor was identified. We ultimately employed NGS on the patient's CSF and detected the presence of *B. mandrillaris* in the CSF. Unfortunately, the disease progressed rapidly, and the patient did not receive effective treatment.

BAE is a rare and challenging diagnosis, often resulting in an extremely high mortality rate. Therefore, understanding the natural history of this deadly infection and developing effective treatment strategies are crucial. Considering BAE in the differential diagnosis of encephalitis of unknown origin, especially when imaging suggests mass lesions, is key. Early diagnosis through metagenomic NGS can buy valuable time for implementing prompt treatment and potentially improving patient outcomes.

Ethical compliance statement

The authors confirmed that patients provided written informed consent for the publication of the literature.

List of parasites

Genus		Species		Relative abundance
name	sequence number	name	sequence number	
巴拉姆希阿米巴 *Balamuthia*	724	弗弗巴拉姆希阿米巴 *Balamuthia mandrillaris*	724	91.60%

Fig. 2. Metagenomics next-generation sequencing of the cerebrospinal fluid revealed 724 *Balamuthia mandrillaris* sequences.

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Data availability statement

The data are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Zhen Li: Writing – original draft. **Wenqiang Li:** Conceptualization. **Yuanyuan Li:** Investigation. **Fubing Ma:** Project administration. **Guangjuan Li:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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