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CASE REPORT

Fatal Primary Amoebic Meningoencephalitis in Coastal Areas of North China in an Immunocompetent Patient: A Case Report and Literature Review

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Purpose: Primary amoebic meningoencephalitis (PAM) is a rapidly fatal infection caused by *Naegleria fowleri* (*N. fowleri*) with a mortality rate exceeding 95%. This study presented the clinical course, diagnosis, treatment, and outcome of a confirmed PAM case in an adult female. Additionally, we analyzed the epidemiology of PAM in China and review the therapeutic regimens of surviving cases worldwide, aiming to enhance disease awareness and improve clinical outcomes.

Case Presentation: The patient was a 50-year-old immunocompetent woman with a history of hot spring bathing before symptom onset, which was not initially disclosed. Moreover, her early infectious symptoms, particularly fever following a tick bite in an orchard, directed clinical suspicion toward tick-borne disease. Four days later, she was hospitalized with generalized convulsions and coma. Clinical examination suggested a bacterial intracranial infection, and treatment with meropenem and vancomycin was initiated. However, her condition deteriorated rapidly. The presence of *N. fowleri* was identified by cerebrospinal fluid (CSF) metagenomic next-generation sequencing (mNGS) and smear. The etiology was clarified only after retrospective confirmation of hot spring contact, which was later confirmed by blood mNGS. Despite intensive therapy with amphotericin B (AmB), the patient unfortunately died. To provide insights into PAM management in China, we also conducted a systematic analysis of 15 domestic cases and 18 global survivors.

Conclusion: PAM is characterized by rapid progression, underscoring the importance of early diagnosis. In cases of rapidly advancing meningoencephalitis, clinicians should maintain a high index of suspicion for rare pathogens such as *N. fowleri*, with thorough and repeated assessment of recent environmental exposures such as hot spring immersion or freshwater swimming. Early application of mNGS is essential for timely pathogen identification. While AmB remains the first-line therapy, its dosing and duration should be tailored to individual patient factors, and combination therapy should be considered to enhance efficacy. Overall, improved clinical vigilance, advanced pathogen diagnostics, and standardized anti-amoebic therapy form the cornerstone of enhancing outcomes in PAM. As the first documented PAM case in Shandong Province, China, this report highlights the need for heightened awareness in coastal regions while contributing valuable epidemiological insights into this devastating disease.

Keywords: *Naegleria fowleri*, primary amoebic meningoencephalitis, metagenomic next-generation sequencing, diagnosis, coastal areas of North China

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Introduction

Primary amoebic meningoencephalitis (PAM) is a rare but always fatal infectious disease of the central nervous system caused by *Naegleria fowleri* (*N. fowleri*). *N. fowleri*, as a thermophilic and free-living organism, can be found in warm freshwater environments or moist soil, including lakes, ponds, rivers, untreated swimming pools, hot springs, and muddy puddles.[1–3] Exposure to these environments is a high risk factor for infection, especially for previous healthy young males, which showed a estimated mortality rate of 95–98%.[2,4] PAM progresses rapidly, with an incubation period of 2–15 days, and death usually occurs within 3–7 days after the onset of symptoms.[2] The initial manifestations of PAM are generally nonspecific (eg, fever, headache), mimicking more prevalent neurological infections like viral/bacterial meningitis, frequently resulting in diagnostic delays or missed cases. Consequently, prompt and definitive diagnosis is critical for initiating timely treatment and implementing effective containment measures.

Currently, there is no consistently effective treatment regimen for PAM. The standard of care, as recommended by the US Centers for Disease Control and Prevention (CDC) and based on published survivor case series, involves a combination therapy centered on amphotericin B (administered intravenously, with intrathecal delivery in cases of elevated intracranial pressure). This is combined with dexamethasone, miltefosine, azithromycin, rifampin, and an azole antifungal agent (typically posaconazole, although fluconazole has also been utilized in survivors), alongside meticulous neurocritical care support.[4,5]

Since the first report of PAM in 1965, an increasing number of new cases have been reported worldwide.[4,6] Nevertheless, such infection remain relatively rare in China, especially in females.[6] This case report describes a patient with PAM whose diagnosis was initially delayed due to a misleading presentation of post-tick-bite fever, which diverted the initial clinical suspicion toward other infectious etiologies. This is the first case of PAM in an immunocompetent adult female from northern coastal China. The diagnosis was confirmed by detecting *N. fowleri* via metagenomic next-generation sequencing (mNGS) of both cerebrospinal fluid and blood. Although hot spring exposure was identified as the probable source, the patient's initial report of a tick bite only, which initially delayed the etiological diagnosis. Additionally, we summarized the clinical characteristics of Chinese PAM cases to provide epidemiological evidence for PAM in China, and compiled treatment information from global survivors to optimize clinical management of this disease.

Case Presentation

This report describes a PAM case in which early diagnostic efforts were initially misleading due to fever occurring after a tick bite. The disease continued to progress. Guided by pathogen detection findings, a thorough exposure history was re-evaluated, which subsequently led to the identification of hot spring bathing as the likely infection source. The timeline of diagnosis is as follows.

A previously healthy 50-year-old woman was admitted to our hospital on June 7, 2024, presenting with fever and headache for four days, followed by the acute onset of confusion and seizures. Her symptoms began on June 3 following a tick bite in an orchard. Initial evaluation at a local hospital in Weihai showed negative severe fever with thrombocytopenia syndrome virus (SFTSV) antigen testing, along with normal peripheral white blood cell (WBC) count, C-reactive protein (CRP), and procalcitonin (PCT) levels. On June 6, 20:00, she developed acute limb weakness and fell. Cranial computed tomography (CT) was unremarkable. During transfer to our hospital on June 7, the patient experienced generalized convulsions and coma, received invasive mechanical ventilation, sedation, antiepileptic treatment immediately upon ICU admission.

Upon admission, her respiratory rate was 38 breaths/min, blood pressure was 152/107 mmHg, and she showed signs of neck stiffness and meningeal irritation. No tick mouthparts or abnormal secretions were found at the bite site. The patient was preliminarily diagnosed with "intracranial infection", and treated with ceftriaxone (2.0 g, qd). On the morning of June 8, lumbar puncture was performed and CSF was collected for bacterial culture and metagenomic next-generation sequencing (mNGS) to further clarify the cause of infection. The cerebrospinal fluid (CSF) was pale yellow and turbid (Figure 1A), with pressure > 330 mmH_2O, WBC 8530×10^6/L, polymorphonuclear cells at 77.6%, protein concentration of 7628.7 mg/L, and glucose concentration < 0.28 mmol/L. Blood routine showed a WBC count of

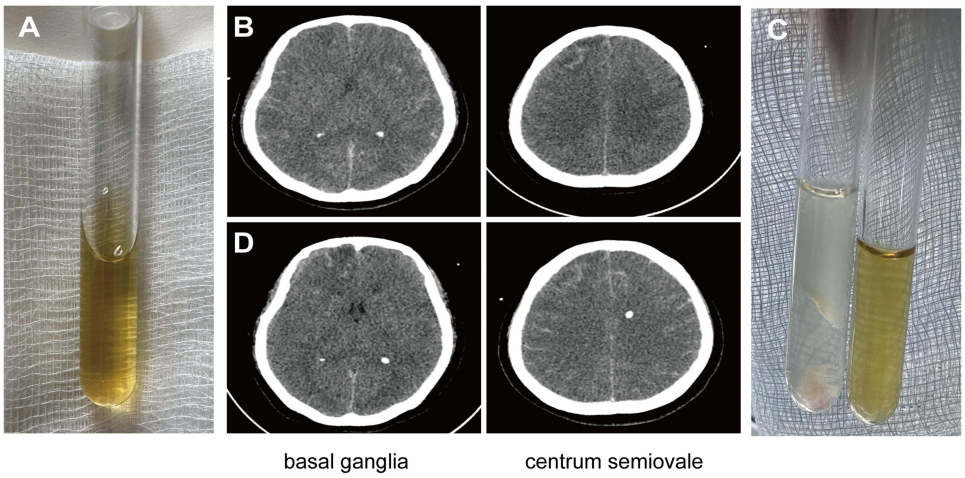

Figure 1 CSF profiles and brain CT findings at different time points. (**A**) On the morning of June 8, the CSF was light yellow and slightly turbid. (**B**) On the afternoon of June 8, the cranial CT scan showed decreased density of the brain parenchyma, narrowed ventricles and sulci, indicating diffuse brain swelling. Left: Basal ganglia level; Right: Centrum semiovale level. (**C**) On June 10, the cerebrospinal fluid was collected again, which was more turbid than before. (**D**) On the June 9, the postoperative cranial CT suggested that the brain tissue swelling is still severe, and the left EVD tube can be seen. Left: Basal ganglia level; Right: Centrum semiovale level.

14.92×10^9/L, neutrophil percentage 93.6%, lymphocyte percentage 2.3%, procalcitonin (PCT) 0.206 ng/mL, and glucose of 10.1 mmol/L, indicating a high likelihood of intracranial bacterial infection. Broad-spectrum antibiotic therapy with meropenem (2g q8h) and vancomycin (1g q12h) was initiated empirically.

However, the patient's condition continued to deteriorate. On the afternoon of June 8, the patient's pupils were unevenly dilated, and a cranial CT scan showed diffuse brain swelling with non-visualization of cerebral sulci and cisterns (Figure 1B). On June 9, her CSF was collected again for bacterial culture, which was more turbid than before (Figure 1C). On June 10, cranial CT after external ventricular drain (EVD) showed diffuse brain tissue swelling and subarachnoid hemorrhage (Figure 1D). The patient's condition continued to deteriorate, CSF mNGS got a positive result. Briefly, the DNA and RNA in the CSF sample were extracted using PathoXtract® Basic Pathogen Nucleic Acid Kit (WYXM03211S, WillingMed Corp, Beijing, China) and PathoXtract® Virus DNA/RNA Isolation Kit (WYXM03009S, WillingMed Corp, Beijing, China), respectively, according to the manufacturer's protocol. Equal amounts of the extracted DNA and RNA were mixed and RNA was reverse-transcribed into complementary DNA (cDNA) before library preparation. NGS was performed on the MGISEQ200RS platform. A total of 2891 reads which uniquely aligned with the *N. fowleri* genome were identified, with a coverage of 2.44% of the *N. fowleri* genome (Figure 2A). This result suggests PAM. An inquiry with the patient's family revealed that the patient had bathed in a local hot spring five days (May 29) before the onset of symptoms. This exposure history is highly consistent with the infection route of PAM. Further microscopic examination of CSF revealed amoebic trophozoites (Figure 3), and microscopy of nasal swab secretion did not reveal amoebic trophozoites. Given the exposure history, a definitive diagnosis of PAM was made, and immediate treatment with AmB (5 mg/day, q12h) was initiated, and continues to provide full support for life. A blood sample was also collected and sent for mNGS.

However, the patient's condition continued to worsen, brain edema is progressively worsening, accompanied by brain herniation; both pupils were dilated, and spontaneous breathing ceased. The patient was declared clinically dead on June 11. On June 12, an *N. fowleri* DNA sequences occupied 1.22% of the whole genome was identified from the blood mNGS (Figure 2B), further confirmed the infection. All CSF cultures were reported negative after the patient's death.

Discussion

The present case describes the first confirmed PAM case in Shandong Province—a mid-latitude coastal city in northern China. Currently, there are still relatively few PAM cases reported in China. The discovery of this case extends the known northern geographical distribution of PAM in China, revealing the potential risk of *Naegleria fowleri* in temperate coastal climate zones. Furthermore, detailed documentation of cases across diverse age groups and genders is crucial for

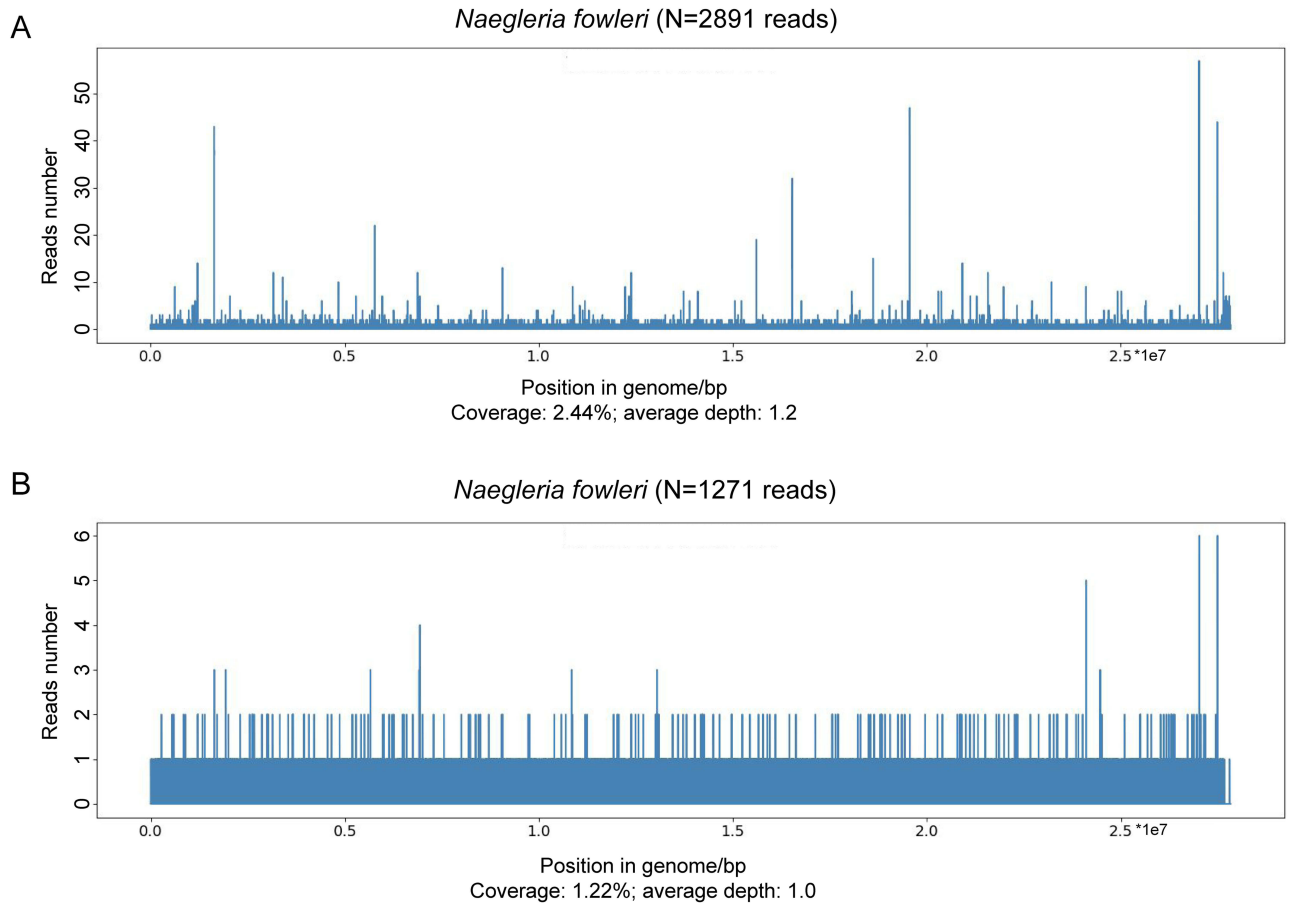

Figure 2 Diagnosis of *N. fowleri* infection using the NGS method in CSF and blood sample. (**A**) Mapping results of *N. fowleri* reads on the genome in the CSF sample on June 10. (**B**) Mapping results of *N. fowleri* reads on the genome in the blood sample on June 12.

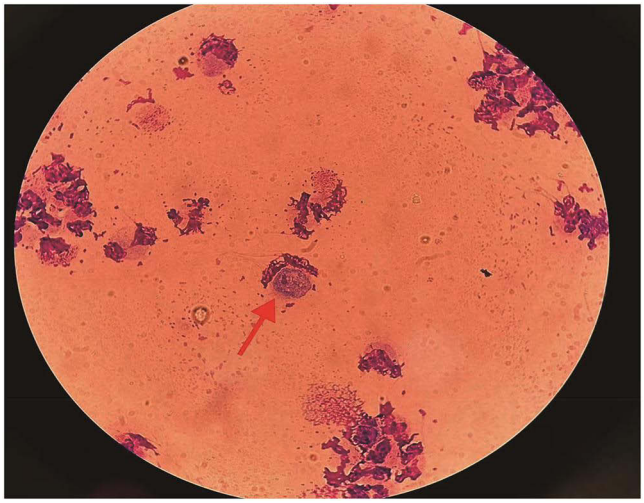

Figure 3 The image of *N.fowleri* on the Wright-Giemsa stained CSF smear (1,000x, oil immersion). The arrow indicates the *N.fowleri* trophozoite (scale bar: 20 μm).

understanding the disease's epidemiological patterns. Therefore, we provide a comprehensive analysis of this case's clinical characteristics and management, and supplemented by a systematic review of both Chinese cases and global survivors, in order to enrich China's epidemiological database and lay a foundation for the treatment and prevention of this disease.

Naegleria fowleri, a thermophilic, free-living, unicellular organism of the phylum Percolozoa, is commonly known as the "brain-eating amoeba". Since its first identification in 1962, this pathogen has caused 488 documented cases of PAM worldwide. Geographically, these cases span 39 countries, with the highest incidence reported in the United States, Australia, Pakistan, India, Mexico, and the Czech Republic.[7] These regions share common ecological characteristics: warm freshwater environments and low- to mid-latitude climates that provide optimal conditions for *N. fowleri* proliferation.[8] The primary transmission route involves inhalation of contaminated water during recreational activities (eg, swimming, bathing) or practices (eg, nasal cleansing, ablution).[8] Demographically, PAM predominantly affects immunocompetent children and young adults, with a notable male predominance.[9,10]

The clinical manifestations of PAM typically emerge 5–7 days after initial exposure, though onset may also occur as early as 24 hours.[10,11] Initial symptoms characteristically include headache, fever, altered mental status, nausea, vomiting, and seizures, which are very similar to the presentation of viral or bacterial meningitis.[8,9] As the infection progresses, patients may develop neurological signs indicative of parenchymal invasion, including cranial nerve deficits, nuchal rigidity, and photophobia.[10] The disease course is marked by rapidly escalating intracranial pressure and distinctive cerebrospinal fluid (CSF) abnormalities: pleocytosis (predominantly neutrophilic), markedly elevated protein levels, and hypoglycorrhachia. Neuroimaging typically reveals cerebral edema, sulcal effacement, and diffuse meningeal enhancement, with histopathological examination demonstrating characteristic hemorrhagic necrosis and perivascular amoebic infiltration in the olfactory bulbs and basal brain regions. Notably, some patients may present with an initially asymptomatic phase.[9,10]

The diagnosis and treatment process of this case highlights the extreme difficulty in the early diagnosis of PAM. Initially, the patient's history of a "tick bite" and subsequent fever led the clinical reasoning toward tick-borne diseases, constituting a classic example of "anchoring bias." Although the patient was admitted to our hospital with generalized seizures and coma, examinations revealed neck stiffness and positive meningeal irritation signs. CSF analysis showed typical purulent changes—such as significantly elevated WBC, extremely high protein concentration, and low glucose levels—providing a basis for diagnosing intracranial infection. These atypical early manifestations, combined with the plausible alternative diagnosis of tick-borne disease, significantly delayed the definitive diagnosis. Crucially, the retrospectively obtained history of "hot spring bathing" served as decisive epidemiological evidence supporting the mNGS findings and ultimately confirming the diagnosis of PAM. This case conveys an important clinical consideration: for immunocompetent patients clinically suspected of having "bacterial or viral meningitis" with rapid disease progression, clinicians must consciously overcome the constraints of the initial diagnostic impression, systematically and repeatedly inquire about all possible environmental exposures, especially recreational activities in freshwater or warm water, and include PAM in the differential diagnosis. When the clinical course does not align with the initial diagnostic assumption, mNGS should be considered as early as possible. It should be regarded as a critical diagnostic tool when conventional microbiological tests cannot promptly identify the pathogen.

Through a systematic review of PubMed, Web of Science and China National Knowledge Infrastructure (CNKI) databases using keywords "N. fowleri" and "Primary Amoebic Meningoencephalitis", we identified 15 PAM cases reported in China (Supplementary Table 1), not including this case. The search time was up to May 31, 2025. Duplicate reports were excluded, and no language restrictions were applied. Among them, 9 cases occurred in coastal cities, including 4 in Zhejiang, 1 in Fujian, 1 in Guangdong, and 1 in Guangxi. Six cases occurred in cities in warm areas near the Qinling-Huaihe line, including 2 in Henan, 2 in Hubei, 1 in Hunan, and 1 in Sichuan. Among these 15 patients, 4 were pediatric cases, including a girl. All adult cases were male, this study is the first case of a female patient in China, and also the first case in Shandong Province. Headache and fever were the most common symptoms of infection. CSF routine indicators were abnormal. Microscopy (7/15) and NGS (7/15) were commonly used methods for pathogen identification. Except for one patient whose final outcome was moderate disability, all the other patients died. 14/15 had a history of contact with water sources. The present case had a definite history of hot spring exposure. Following the receipt of the mNGS results, an epidemiological investigation was immediately launched. We contacted the hot spring facility visited by the patient and mandated strengthened water disinfection procedures. Public health advisories were also issued, recommending that individuals protect their nose and mouth while bathing to prevent choking or aspiration, with the aim of reducing the risk of additional infections.

Before the advent of mNGS, most patients could only be diagnosed by observing amoebic trophozoites or protozoa in CSF under a microscope, and some patients were even diagnosed through autopsy.[12] Due to the rarity of PAM, most microbiologists in China are not skilled in microscopic smear detection techniques. Additionally, PAM needs to be differentiated from granulomatous amoebic encephalitis, which usually occurs in individuals with weak immune systems or poor general health conditions and progresses more slowly than PAM.[13] Therefore, relying solely on microscopic examination may lead to confuse the two diseases. With the advent of mNGS, clinical microbiological testing has gained an additional layer of assurance. It can be seen that since the widespread implementation of mNGS in mainland China in 2018, the diagnosis rate of PAM has significantly increased. However, compared with CSF microscopy, it takes longer, which may seriously delay the treatment of PAM. Therefore, CSF microscopy remains an important skill, and laboratory physicians need to improve their awareness of this disease. But mNGS has also become an important auxiliary means to diagnose the disease.

Despite the characteristically high mortality rate exceeding 90% in PAM, our systematic review identified 18 documented survival cases (Supplementary Table 2)—a significantly higher number than previously reported in the literature (7 cases[10] or 11 cases[14]), reported in previous studies. Notably, the majority of survivors (n=11) were pediatric patients, with the youngest case being a 25-day-old neonate. This phenomenon may be associated with several factors. Firstly, physiological differences: the blood–brain barrier in children exhibits relatively higher permeability compared to adults.[15,16] This may facilitate better distribution of hydrophilic drugs, such as amphotericin B, within the central nervous system, thereby enhancing their efficacy in eliminating amoebic trophozoites. Secondly, immune response intensity: the relatively mature immune system in adults may trigger a more severe "inflammatory storm" after infection,[17,18] leading to more extensive secondary brain tissue damage and refractory intracranial hypertension. Additionally, the timeliness of diagnosis cannot be overlooked. Due to more limited daily activities, children's exposure history (eg, swimming) is often clearer, which may prompt clinicians to consider PAM earlier and initiate targeted investigations and treatment. In contrast, the adult patient in this case experienced critical diagnostic delay, as the initial presentation was confounded by other exposure history (tick bite).

Currently, AmB is considered the first choice for the treatment of PAM. The US Centers for Disease Control and Prevention (CDC) recommends a standardized protocol consisting of intravenous AmB at a dose of 1.5 mg/kg/day, divided into 2 doses, for 3 days, followed by 1 mg/kg/day for another 11 days. Conventional intrathecal administration of AmB (1.5 mg/d for 2 days, 1 mg/d for another 8 days) can also be combined with intravenous AmB.[19] All 18 surviving patients received AmB therapy, with treatment durations ranging from 3 to 35 days. Combination therapy was common, with 15 patients (83.3%) receiving adjunctive antimicrobials including Rifampin, Fluconazole, azithromycin, Miltefosine, or miconazole. By contrast, although AmB was administered immediately following mNGS suggestion in the present case, therapeutic intervention occurred during the end-stage of disease progression, with the patient having already developed irreversible cerebral herniation, thus missing the treatment window. This underscores the critical dependence of successful PAM treatment on the intervention opportunity provided by early diagnosis. However, our patient's failure to respond to therapy, which precluded the accumulation of definitive clinical experience. The optimal treatment duration and combination regimen remain need to explore.

This study has several limitations. First, due to the rapid progression of the patient's condition, more aggressive combination regimens or intrathecal administration of AmB were not attempted, limiting the opportunity to accumulate further treatment experience in this case. Second, while the pathogen was successfully identified via mNGS, the prolonged sample turnaround time compromised the timeliness of the result. Moreover, the information provided regarding pathogen drug resistance remains insufficient. Future efforts should aim to shorten the mNGS testing time and incorporate in vitro susceptibility testing to better guide individualized treatment.

Conclusion

This case starkly illustrates the significant risks associated with anchoring bias in clinical diagnosis. The initial history of a tick bite served as a powerful diagnostic anchor, prematurely narrowing the diagnostic focus. This led to the attribution of rapidly progressive neurological symptoms to a tick-borne disease, while failing to promptly identify the more fulminant PAM, ultimately resulting in a catastrophic diagnostic delay. This sobering lesson underscores that when a

patient deteriorates rapidly despite treatment based on an initial diagnosis, clinicians must possess a high degree of reflective awareness and error-correction capability. They must proactively question and break free from the constraints of the initial diagnosis to conduct a systematic and critical re-evaluation of the clinical picture. To achieve early diagnosis of PAM, two key clinical measures should be advanced and implemented: First, a thorough inquiry into water exposure history must be integrated into the etiological assessment of every patient with acute severe encephalitis, regardless of other suspected causes, and should be pursued repeatedly. Second, advanced pathogen detection technologies, such as mNGS, should be actively and early utilized to overcome the limitations of conventional diagnostic methods. Cultivating sustained vigilance for PAM and enhancing rapid pathogen identification capabilities are crucial prerequisites for managing such rare yet fatal infections and improving patient outcomes in the future.

Ethics Statements

The study was conducted in accordance with the Declaration of Helsinki. All procedures performed in the study involving human participants were in conformity to the ethical standards of the Ethics Committee of Yantai Yuhuangding Hospital Affiliated to Qingdao University. Ethics approval was not required by the local ethics committee, as this is a case report with anonymized details. Written informed consent was obtained from the patient's daughter for the publication of any potentially identifiable images or data included in this article.

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Disclosure

The authors declare that they have no competing interests in this work.

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