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Neuroinfectious diseases - case report collection 2022

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CASE REPORT
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Influenza A H3N2-Associated Meningoencephalitis in an Older Adult With Viral RNA in Cerebrospinal Fluid: Case Report

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Influenza-associated encephalopathy (IAE) is most frequently observed in young children, but less reported in adults. Diagnosis of IAE is difficult, as clinical presentations vary significantly and the influenza virus is rarely detected in cerebrospinal fluid (CSF). Herein, we described the case of an older adult presenting with acute meningoencephalitis due to an influenza A (H3N2) infection and the influenza A (H3N2) RNA is detected in cerebrospinal fluid. To the best of our knowledge, this is infrequently reported in the literature. We emphasize that, in adults presenting with acute viral encephalitis, clinicians should consider an influenza infection as part of the differential diagnosis and that metagenomic next-generation sequencing of CSF for IAE may help establish an accurate diagnosis. It must be emphasized that the administration of steroids in a timely manner following the onset of symptoms may yield a better outcome in patients.

Keywords: influenza A H3N2, adult, influenza associated encephalitis, metagenomic next-generation sequencing, cerebrospinal fluid

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INTRODUCTION

Influenza-associated encephalopathy (IAE) is more common in young children than in adults. The most severe category of IAE is acute necrotizing encephalopathy (ANE), first described in Japan in 1995, and is characterized by the sudden onset of fever, convulsions, coma, and even death. Symmetric inflammatory brain lesions are generally noted on neuroimaging (1, 2). Since the global pandemic of novel influenza A H1N1 in 2009, there has been a sustained rise in the number of cases of IAE (3). While influenza A H1N1-associated encephalopathy is reported more than others, the prevalence of H3N2 associated encephalitis has been increasing in recent years (4). However, only a small number of cases have been reported in China. Here, we describe a rare case of a 70 year old male patient presenting with meningoencephalitis due to an influenza A H3N2 infection.

CASE REPORT

A 70 year old male patient with a history of sinusitis and nasal polyps presented to the emergency department with a 2 day history of headache and without an of prodromal respiratory symptoms in the prior 2 weeks. He had no history of influenza virus vaccination.

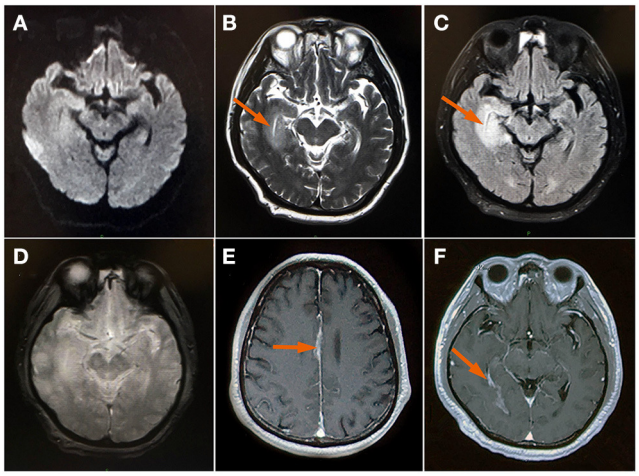

FIGURE 1 | MRI brain **(A)** Axial DWI and **(D)** GRE sequence showed insignificant findings; **(B)** axial T2WI showed bright signal axial (arrow); **(C)** FLAIR image showed an edematous swollen temporal lobe (arrow); **(E,F)** Contrast-enhanced images demonstrated a fine linear enhancement of cerebral falx and bilateral choroid (arrow). DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion-recovery; GRE (gradient echo); T2WI, T2 weighted image.

Upon arrival to the emergency department, the patient presented with severe persistent headache, no vomiting, no disturbance of consciousness and no limb convulsions. Neurological examination revealed clear consciousness, fluent speech, equal pupils, pupil light reflex is positive, full eye movement, no diplopia or nystagmus, bilateral facial symmetry, positive neck stiffness, negative Kerning sign, Brudzinski sign and bilateral Babinski signs. The muscle strength and tension of limbs are normal. His chest CT, routine blood and biochemical analyses showed insignificant findings. Brain magnetic resonance imaging (MRI) revealed right temporal lobe lesions (shown in **Figure 1**) and he was given treatment with gabapentin for his headache. The gadolinium enhanced brain MRI demonstrated a fine linear enhancement of the bilateral frontal sulcus, cerebral falx, bilateral choroid, and bilateral ventricular ependyma (shown in **Figure 1**). Broad-spectrum antimicrobial agents, intravenous ceftriaxone and ganciclovir, were initiated for presumed infectious meningoencephalitis.

On the 3rd day of admission to the emergency department, the patient developed a fever up to 39°C and was transferred to the Department of Neurology. There were no disturbing symptoms after hospitalization. Neurological examination revealed clear consciousness, fluent speech, equal pupils, pupil light reflex is positive, full eye movement, no diplopia or nystagmus, bilateral facial symmetry, positive neck stiffness, negative Kerning sign, Brudzinski sign and bilateral Babinski signs. The muscle strength and tension of limbs are normal. Laboratory data showed a normal white blood cell count (8.69×10^9/L), but excessively elevated levels of aspartate aminotransferase (80 U/L) and alanine aminotransferase (157 U/L). A CSF analysis showed elevated total protein levels of 163 mg/dL, elevated total cell count of 720×10^6/L, CSF white blood cell count of 650×106/L (42% polymorphonuclear leukocytes, 58% lymphocytes), elevated CSF immunity (IgG = 221 mg/L, IgA = 42.7 mg/L, albumin = 750 mg/L, IgM = 1.16 mg/L), decreased glucose of 2.28 mmol/L, decreased chlorides of 118 mmol/L, and Gram-staining results were negative, with no microbial growth.

Influenza A H3N2 was detected in the CSF from metagenomic next-generation sequencing and the SARS-Co-2 and Herpes simplex was not detected in the CSF, spectrum of autoimmune diseases and Spectrum of demyelinating disorders of the central nervous system test was negative from the CSF. Therefore, a diagnosis of influenza A (H3N2) associated meningoencephalitis was made based on the MRI findings, clinical presentation, and CSF analysis and treatment with oral oseltamivir at 75 mg twice a day was initiated on the second day of admission to the Department of Neurology. Simultaneously, intravenous methylprednisolone pulse therapy (at 80 mg a day for 5 days) was started, followed by a slow tapering of oral methylprednisolone. After a 5-day course of oseltamivir and methylprednisolone, the patient began to gradually recover and was completely recovered by day thirteen. The control examination of the CSF before discharge from the hospital showed total protein levels of 52 mg/dL, total cell count of 40×10^6/L, CSF white blood cell count of 30×10^6/L (13.3% polymorphonuclear leukocytes, 86.7% lymphocytes), CSF immunity (IgG = 62.7 mg/L, IgA = 9.2 mg/L, albumin = 283 mg/L, IgM = 0.88 mg/L), normal glucose at 2.28 mmol/L, and normal chlorides at 123 mmol/L, and Gram-staining results were negative, with no microbial growth. The above results are better than before. He was discharged without any subsequent encephalitic or neuropsychiatric manifestations. He was prescribed a slow tapering of oral methylprednisolone.

One month later, the patient developed a fever and headache again. Upon inquiry, the patient had stopped methylprednisolone on his own and did not comply with the doctor's order. A brain MRI DWI image and T2-W image demonstrated an abnormal signal in the right temporal occipital lobe, which showed an increase in the range of the lesion (shown in **Figure 2**). A contrast-enhanced coronal T1-W image demonstrated obvious abnormal enhancement in the right temporal occipital lobe and bilateral choroid (shown in **Figure 2**).

A lumbar puncture showed an elevated total protein of 1,030 mg/dL, elevated total cell count of 220×10^6/L, white blood cell count of 190×10^6/L (32% polymorphonuclear leukocytes, 68% lymphocytes), elevated CSF immunity (IgG = 113 mg/L, IgA = 17.8 mg/L, albumin = 560 mg/L, IgM = 3.27 mg/L), normal glucose at 2.82 mmol/L, and normal chlorides at 122 mmol/L. Additionally, the Gram-staining results were negative, with no microbial growth. The CSF metagenomic next-generation sequencing and CSF neuronal/inflammatory antibody test were insignificant. Non-specific autoimmune encephalitis caused by viral infection was considered and intravenous methylprednisolone pulse therapy (500 mg daily for 3 days) was started, followed by a slow tapering of oral methylprednisolone. The subject had completely recovered by day nine and he was discharged without any symptoms. He was given instructions to continue the slow tapering of oral methylprednisolone and to follow-up after 3 months so long as he was without any discomfort.

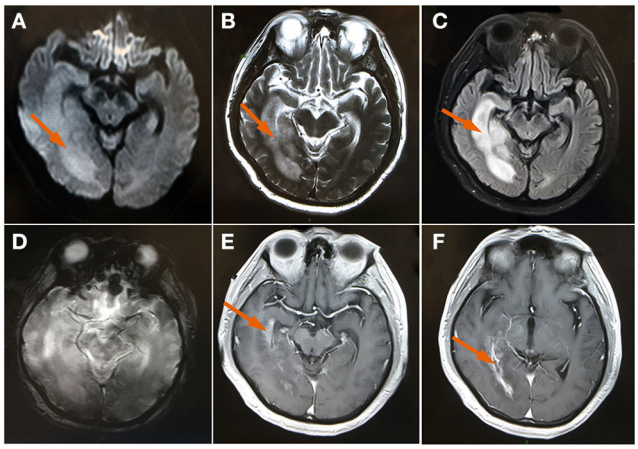

FIGURE 2 | MRI brain **(A)** Axial DWI and **(B)** axial T2WI showed a high signal and the size of the edematous area showed a marked increase at the right temporal occipital lobe (arrow); **(C)** FLAIR image showed a swollen, edematous temporal occipital lobe (arrow); **(D)** axial GRE sequence at the same level with the high signal of T2WI; **(E,F)** A contrast-enhanced image demonstrated an abnormal enhancement of the right temporal occipital lobe and bilateral choroid (arrow). DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion-recovery; GRE, gradient echo image; T2WI, T2 weighted image.

DISCUSSION

IAE is a serious complication of influenza infection and frequently begins with a prodrome of respiratory symptoms, followed by a disturbance of consciousness and seizures. In young children, altered consciousness tends to be the most frequent neurological manifestation, while respiratory symptoms are also commonly present at admission (5). The interval between the onset of respiratory symptoms and IAE ranges from 1 to 14 days (6). Influenza is rarely detected from the CSF, which may be due to a low viral load or the clearance of the virus from the CSF prior to sampling (7). Since the world pandemic of influenza A (H1N1) in 2009, there have been a few reports of IAE in various countries, which generally focus on the cases with severe neurological complications, with fewer reports of mild cases (8).

Here we describe a rare case of an older adult patient with acute meningoencephalitis associated with an H3N2 influenza infection. Different from previous reports, this case is characterized by an older adult with no prodromal respiratory symptoms or mild neurological complications, and the influenza was detected within the CSF.

On an MRI, the lesions of IAE are typically multifocal bilateral symmetric and primarily involve the thalami, cerebral periventricular white matter, brainstem tegmentum, or pons and cerebellum, and can also be manifested as diffuse cortical involvement and diffuse cerebral edema, however, meningeal enhancement has been rarely reported (9). This patient's neuroimaging findings were different from those in previous reports, in that the lesion was found primarily in the unilateral temporal lobe with no necrosis. Interestingly, the meninges showed significant enhancement, which has only been limitedly reported previously.

Until now, the pathogenesis of IAE has not been clear; previous studies suggested that the lack of a detectable influenza in CSF suggest that IAE is likely due to post-infection inflammation or immune-mediated responses rather than the direct effect of the virus (10). CSF cytology, protein, and glucose levels are normal in most cases, but mild pleocytosis or elevated protein levels are occasionally observed (11).

While previous reports differ, in this patient, influenza was detected in the CSF and a CSF analysis showed pleocytosis, elevated protein levels, and elevated IgG and IgA. This suggests that a nervous system injury may be related to an inflammatory or immune-mediated response and therefore may also be a direct effect of virus.

Currently, there is no recommendation for standard of care for this disease. Treatment is primarily supportive and may involve intensive care. Antiviral therapy with oseltamivir is recommended, particularly in patients who present within 48 h of the onset of symptoms, to reduce viral replication (6). The administration of steroids within 24 h after the onset of symptoms tends to yield a better outcome in those patients without brainstem lesions (12). Given his symptoms, neuroimaging, and laboratory tests, the patient described here received antiviral medication and corticosteroids, which could explain the therapy failure at the beginning in our case. due to a delay in the diagnosis with the subsequent start of steroid therapy and the patient's failure to follow the doctor's order to take oral steroids.

In summary, the findings on the neuroimaging and CSF examination in this case vary from previous reports. A molecular analysis of the CSF supports the hypothesis that adult IAE may be caused by a direct invasion of the brain by the influenza virus and is also the result of the immune response to the virus, but further research is still needed. Furthermore, it must be emphasized that timely steroid treatment in the early stages of the disease is extremely important.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Tianjin Huanhu Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-cD and Y-qL collected data and drafted and revised articles. Both authors contributed to the article and approved the submitted version.

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CASE REPORT
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Human Encephalitis Complicated With Ocular Symptoms Associated With Pseudorabies Virus Infection: A Case Report

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Pseudorabies virus (PRV) is an alpha herpesvirus found in many wild and domestic animals, and causes neurological diseases in humans. Several cases of PRV-induced human encephalitis accompanied with severe visual impairment have been reported. There is currently no effective treatment for severe visual impairment caused by PRV. We report a case of PRV encephalitis with severe visual impairment. The diagnosis and treatment experience of this patient is summarized to improve the awareness of clinicians. We present a 42-year-old man with PRV infection who was admitted due to intermittent fever for 5 days and unconsciousness for 1 day. He subsequently developed severe visual impairment during hospital stay. Empirical antiviral treatment with ganciclovir and sodium foscarnet was started on the day of admission and continued for > 50 days, which had significant treatment effect. Eye complications caused by PRV infection have been frequently reported in patients with PRV encephalitis. In this patient, based on the patient's condition, antiviral therapy was initiated on admission day, and according to the results of the next-generation sequencing of the cerebrospinal fluid, the duration of antiviral therapy was prolonged, which improved treatment efficacy and alleviated neurological symptoms and eye vision damage. To the best of our knowledge, this is the first report that describes partial restoration of acute vision loss associated with PRV infection after aggressive treatment. Our experience suggests that although prompt treatment cannot prevent the acute vision loss associated with PRV infection, timely anti-viral and anti-inflammatory treatment can alleviate ocular complications.

Keywords: viral encephalitis, next-generation sequencing, severe visual impairment, case report, antiviral therapy

INTRODUCTION

Pseudorabies virus (PRV), namely porcine herpes virus type 1, is a double-stranded DNA virus belonging to the alpha herpesvirus subfamily (1, 2). Since 2018, with the detection of PRV nucleic acids by next-generation sequencing (NGS), several reports from China have shown that PRV can infect humans. In addition, these patients had a very poor prognosis, despite receiving systematic antiviral treatment (3). According to a study, 17.4% (4/23) of patients

with PRV infection died, 17.4% (4/23) developed blindness, 21.7% (5/23) patients experienced severe visual impairment, and 65.2% (15/23) patients had severe central nervous system symptoms such as persistent vegetative status, and memory loss (4). In order to improve clinician's understanding of the disease, we report a case of PRV encephalitis with severe visual impairment and analyze and summarize the diagnosis and treatment experience of this patient. To the best of our knowledge, this is the first documented case of PRV infection in which antiviral therapy was started on the day of admission and the duration of therapy prolonged based on NGS results, leading to significant alleviation of encephalitis and ocular symptoms. Here, we report a patient with PRV encephalitis with severe visual impairment who showed significant improvement with anti-viral and anti-inflammatory treatment.

A 42-year-old man was admitted to the Second Hospital of Hebei Medical University (Hebei, China), with convulsions for 1 day and headache and fever for 5 days (peak temperature: 39.5°C), accompanied by nausea and vomiting. One day before admission, patient had an episode of altered sensorium and facial twitch. The patient became unresponsive looking at the mobile phone and stopped communicating with his family. Soon, the patient had urinary and stool incontinence. His past medical history was unremarkable. Based on the clinical condition, empirical antiviral therapy were started on the day of admission. Occupational history revealed that his daily work involved close contact with swine and selling pork. Prior to the onset of his symptoms, a large numbers of pigs had died on his farm for no apparent reason. Lumbar puncture (**Table 1**) was performed and cerebrospinal fluid analysis showed high cerebrospinal pressure with increased white blood cell count, monocyte ratio and absolute monocyte count. NGS of the cerebrospinal fluid detected PRV. Electroencephalography (EEG) showed abnormal findings (**Figure 1A**). Brain magnetic resonance imaging (MRI) revealed intense T1 and T2 signal changes in the anterior cingulate gyrus, insula, and frontotemporal lobes (**Figures 1B,C**). On the second day of hospitalization, the patient became comatose and showed signs of respiratory distress with decrease in oxygen saturation. Therefore, he was admitted to the intensive care unit for endotracheal intubation and ventilator-assisted breathing. Ophthalmological examination on 6th day showed no obvious hyperemia in the conjunctiva, but the reflection of light was slow and the fundus was unclear. He developed blurred vision in both eyes gradually, but we did not focus on the condition due to his poor general condition. After treatment for 41 days, NGS of the cerebrospinal fluid detected PRV with 2 unique sequence reads, relative abundance 0.15% and 0.09 % coverage. Forty-one days after admission, the patient complained of lack of light perception (**Table 1**). Fundus examination showed sluggish light reflex in both eyes (**Figure 1D**). Ophthalmic ultrasound showed severe vitreous opacity in both eyes (**Figures 1E,F**). Based on the patient's condition and the results of NGS of the cerebrospinal fluid, antiviral therapy was continued till the NGS of cerebrospinal fluid turned negative (**Table 1**). Fifty-one days after admission, the patient's family members noticed that the patient was able to see objects within 1 m and could read text (**Table 1**). On the 57th day after admission, the patient was discharged home for recuperation. Seventeen days after discharge, the patient's level of consciousness was better than that at the time of discharge; however, the patient showed difficulty in communicating with and recognizing people. He was able to walk for a few steps with support. His eyesight visibility was 3.5 m, and he was able to read simple text symbols (**Table 1**). Follow-up examination at 27 days after discharge showed that the patient's consciousness had improved compared to the last follow-up visit. The patient was still not able to speak fluently and had difficulty in recognizing people. He was able to walk with support. His eyesight visibility was 5 m. Repeat ophthalmological ultrasound showed moderate vitreous opacity in both eyes (more obvious in the left eye), mild thickening of the posterior wall of both eyes, and total retinal detachment in the right eye (**Figure 2**). Ophthalmology wide-angle lens examination was performed to assess the risk of surgery (**Figure 2**). Visual acuity examination (left: 0.15, right: $0.1 \times 0.5/5 = 0.01$) (**Figures 3D–F**). On follow-up examination 48 days after discharge, the patient was able to walk slowly on his own without support (**Figure 3A**). The eyesight visibility was 15 m. Repeat head MRI (**Figures 3B,C**) showed few changes compared with the previous MRI; the local swelling was reduced, and the degree of brain atrophy was aggravated.

Abbreviations: CSF, Cerebrospinal fluid; PRV, Pseudorabies virus; LS, Lumbosacral; T, Thoracic; L: Lumbar.

DISCUSSION AND CONCLUSIONS

The patient was admitted to the hospital for fever and headache. Based on the clinical experience, empirical antiviral therapy was initiated on the day of admission. However, timely antiviral and immunoglobulin therapy does not seem to stop the progress of panencephalitis. A previous article reviewed 23 cases of encephalitis caused by pseudorabies virus, all of whom had a history of close contact with pigs or pork. In that report, "flu-like" symptoms were observed in the early stage of infection (usually within 7 days), including fever (100%, 23/23), respiratory symptoms (72.7%, 16/22), and headache (57.9%,11/19). Subsequently, these cases showed rapid onset of neurological symptoms, including seizures/convulsions (95.7%, 22/23) and altered consciousness (95.7%, 22/23); 60% (12/20) of the patients showed severe visual impairment, and at the time of publication of this literature review, 65.2% (15/23) of the patients still had severe central nervous system symptoms such as persistent vegetative status, memory loss, and/or ability to only follow simple instructions (4). Lumbar puncture of all cases reviewed showed increased intracranial pressure and lymphocytosis (3–7, 9–11, 14, 15). The present case is in line with the general manifestations of most cases of porcine herpes encephalitis. History of contact with sick pigs is a key pointer toward infection with this pathogen (4). NGS of the cerebrospinal fluid plays an important role in diagnosis. NGS has a high sensitivity and specificity for diagnosis of unknown pathogen infections (3,

TABLE 1 | Temporal changes in the findings of cerebrospinal fluid examination and evolution of the patients' ocular involvement during treatment and follow-up.

Time-point	Patient's condition	CSF: Routine examination	CSF: Biochemistry	CSF: Cytology	CSF: Next-generation sequencing
0d	The family members did not report any vision-related problem and the patient was using his mobile phone.				
2d		Cerebrospinal fluid pressure: 210 mmH_2O Gross appearance: colorless and transparent.	Chlorine 122.6 mmol/L, protein 0.18 g/L, glucose 3.71 mmol/L.	White blood cell count: 25×10^6/L, mononuclear cell ratio: 96%, absolute monocyte value: 2410×10^6/L; protein: negative.	Pseudorabies virus was detected on next-generation sequencing of cerebrospinal fluid. The type was dsDNA, the number of specific sequences was 13996, the relative abundance was 85.79%, and the coverage was 86.02%.
4d		Cerebrospinal fluid pressure: 160 mmH_2O Gross appearance: colorless and transparent.	Chlorine 128.7 mmol/L, protein 0.14 g/L, glucose 5.26 mmol/L.	White blood cell count: 23×10^6/L, monocyte ratio: 95.7%, absolute monocyte value: 2410×10^6/L, protein: negative.	
6d	The intraocular pressure in both eyes was normal; there was no conjunctival congestion, the cornea was clear, the anterior chamber was normal, the pupil diameter was approximately 3 mm. The patient was in coma.				
41d	Light reflex was sluggish; the fundus of ophthalmoscope was unclear, and the patient complained of lack of light perception. Color ultrasound of the eyes: severe vitreous opacity in both eyes, thickening of the posterior wall of the eyes, and thickening of all four rectus muscles of the eyes.	Cerebrospinal fluid pressure: 120 mmH_2O Gross appearance: colorless and transparent.	Chlorine 109.6 mmol/L, protein 0.58 g/L, glucose 3.32 mmol/L.	White blood cell count: 7×10^6/L, mononuclear cell ratio: 100%, absolute monocyte value: 710×10^6/L; protein: weakly positive.	Pseudorabies virus was detected on next-generation sequencing of cerebrospinal fluid; the type was dsDNA, the number of specific sequences was 2, the relative abundance was 0.15%, and the coverage was 0.09%.
49d	The patient was able to see things.				
51d	The patient's visibility was 1 m and he was able to read text.				
54d		Cerebrospinal fluid pressure: 160 mmH_2O Gross appearance: colorless and transparent.	Chlorine: 109.6 mmol/L, protein: 0.58 g/L; glucose 3.32 mmol/L.	White blood cell count: 3×10^6/L; protein: weakly positive.	Next-generation sequencing of cerebrospinal fluid showed no clear pathogenic prokaryotic microorganisms, viruses, or eukaryotic microorganisms.
55d	Ophthalmic ultrasound: severe vitreous opacity in both eyes, slight thickening of the posterior wall of both eyes, and thickening of the inner rectus muscle of the right eye.				
73d	The patient's visibility was 3.5 m. He was able to read simple text symbols.				
83d	The patient's visibility was 5 m. Repeat ophthalmological ultrasound: moderate vitreous opacity in both eyes (more obvious in the left eye), mild thickening of the posterior wall of both eyes, and total retinal detachment in the right eye. Improvement in the ophthalmology wide-angle lens examination (picture: J left eye). Visual inspection: the patient's left eye visual acuity was 0.15, and the right eye was $0.1\times0.5/5=0.01$.				
124d	The patient's visibility was 15 m.				

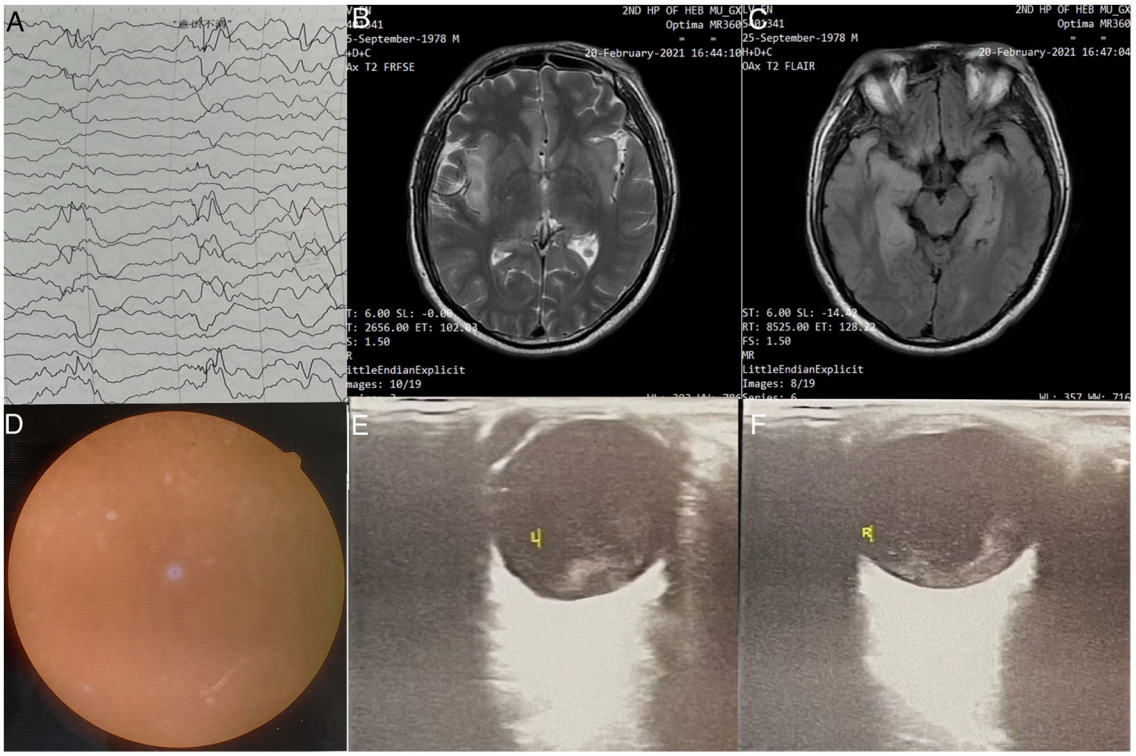

FIGURE 1 | (A) Electroencephalography findings: Severe abnormal diffuse mixed slow waves with a lot of fast waves, intermittent low-voltage waves, lasting about 1s, diffuse 1-2Hz irregular s activity, left sharp waves and sharp slow waves are emitted from the front side of the head; **(B)** Head MRI - T2 FRFSE: Bilaterally symmetrical abnormal signals are observed in the anterior cingulate gyrus; **(C)** Head MRI - T2 FLAIR sequence: Symmetrical abnormal signals of insula and fronto temporal lobes; **(D)** Fundus examination: Both eyes have clear cornea with no hyperemia, anterior chambers, pupil diameter of ∼3mm, slow reflection of light; **(E)** Ophthalmic ultrasound-L: (1) Severe vitreous opacity; (2) Thickening of the posterior wall of eyeball; (3) Thickening of the four rectus muscles of the eyes; **(F)** Ophthalmic ultrasound-R: (1) Severe vitreous opacity; (2) Thickening of the posterior wall of eyeball; (3) Thickening of the four rectus muscles of the eyes. The ring of the right eye is intact, the lens wave is visible, and the dark area can be seen in the vitreous body. There is medium to high amount of diffuse flocculent weak echo and cluster echo. The posterior wall of the ball is thickened and slightly rough. The thickness of the superior rectus, external rectus, inferior rectus, and medial rectus is ∼5.9, 5.6, 5.6, and 6.4mm, respectively.

16–25). With improvement in the patient's condition, the number of virus copies on NGS gradually decrease, which can facilitate further treatment decision-making (24). Based on the results of NGS, we extended the course of antiviral treatment until the NGS results showed 0 PRV reads in the CSF.

Early and accurate diagnosis of CNS virus infection can help improve the prognosis. Recently, many diagnostic methods for PRV detection have been developed, which can be categorized as serological techniques to detect PRV-specific antibodies and molecular biological methods to detect PRV nucleic acids (16, 25). The Pseudorabies Virus (PRV) g E antibody ELISA detection kit has been widely used, especially in the breeding industry (26).

We reviewed previously published case reports and identified a total of 26 patients with PRV encephalitis. In all 26 patients, the diagnosis was confirmed by metagenomic sequencing of cerebrospinal fluid (**Table 2**). Plasma antibody test results or cerebrospinal fluid antibody test results were available for 16 patients. Twelve patients (12/16) tested positive for antibodies in plasma or cerebrospinal fluid, 6 patients (6 /16) tested positive for the cerebrospinal fluid antibody, and 5 patients (5/16) tested positive for both plasma and cerebrospinal fluid antibodies. Positive antibody results were measured between days 7 to 46 of disease onset. There were no reports of positive antibody tests in plasma or cerebrospinal fluid within the initial 5 days of disease onset (**Table 2**). The cerebrospinal fluid NGS test of all 26 patients with PRV encephalitis was found to be positive, and in 9 case reports, the detection time was recorded. All the positive results were tested within 5 days after onset. The detection time of the remaining 17 cases was unknown (**Table 2**). Based on the literature review, CSF NGS detection seems to be more sensitive than antibody detection in the early stages of PRV encephalitis.

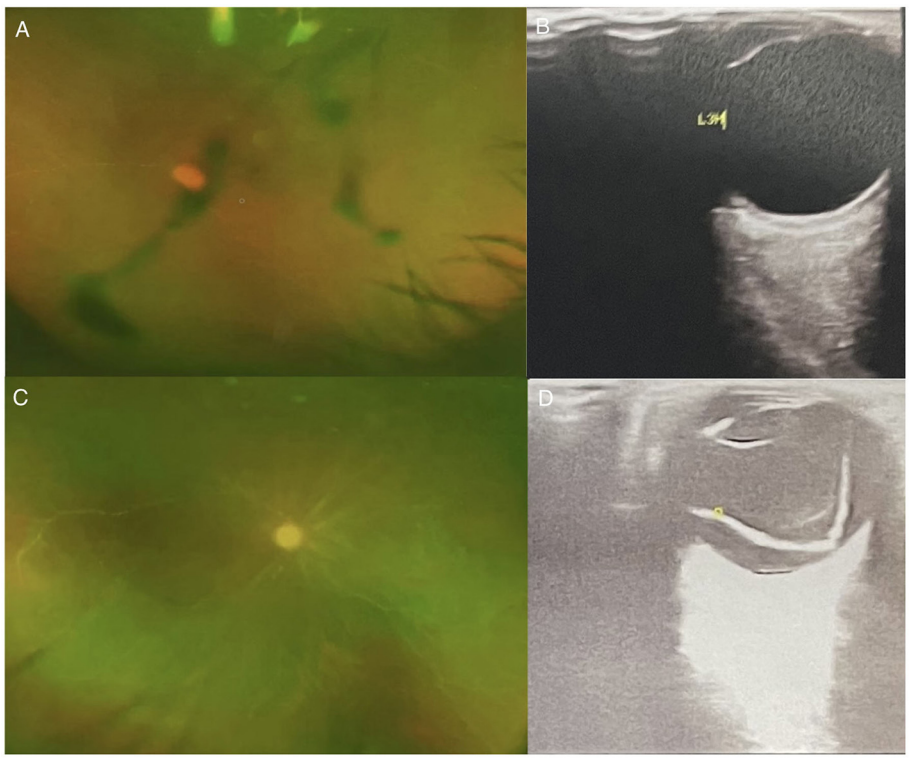

FIGURE 2 | (A) Ophthalmology wide-angle lens examination-L; **(B)** Ophthalmic Ultrasound-left: The left eye ring is intact, the lens wave is visible, and the dark area of the vitreous body is moderately diffuse. Spot flocculent weak echo and mass echo, and the posterior wall of the ball is slightly thickened. There is no obvious thickening of the four rectus muscles. **(C)** Ophthalmology wide-angle lens examination-R; **(D)** Ophthalmic Ultrasound-right: The right eye ring is intact, the lens wave is visible, and low and medium amount of diffuse spot flocculent weak echo and cluster echo are seen in the dark area of the vitreous body. Both the horizontal axis and the vertical axis can be detected in the vitreous "shaped echo" band echo. The tip is connected with the optic papilla, and the two ends are connected with the peripheral spherical wall.

In our patient, there were no ophthalmological symptoms at the onset. The patient quickly developed altered sensorium. Forty-one days after admission, the patient showed recovery of disturbed consciousness and complained of lack of light perception. According to recent reports, it is not uncommon for PRV viral encephalitis to cause bilateral necrotizing retinitis (3, 11, 15). In the review of 23 cases of encephalitis caused by PRV, 17.4% (4/23) developed blindness, and 21.7% (5/23) patients experienced severe visual impairment (4). Visual impairment can appear in the early stage or in the late stage (3, 11, 15, 24). Close attention should be paid to visual impairment in these patients, as the symptoms may be masked by altered consciousness. At present, pars plana vitrectomy and silicone oil injection are the main treatment measures for the ocular complications of PRV such as retinal detachment, acute retinal necrosis syndrome, and severe visual impairment (24, 25). Despite active treatment, the prognosis of patients with the ocular complications of PRV is poor.

A total of 19 cases of PRV encephalitis patients were retrieved for the antiviral treatment regimens after evaluation of the case reports (**Table 2**). Seven patients were treated with acyclovir alone, 9 patients were treated with a combination of acyclovir and potassium phosphate, and 2 patients were treated with ganciclovir; none of the cases was treated with sodium phosphate alone. Moreover, 1 patient was prescribed empirical treatment with acyclovir, which was subsequently changed to ganciclovir after definitive diagnosis (**Table 2**). Among the reviewed case reports, two reports described treatment with a combination of ganciclovir and foscarnet. In the first case, the consciousness and cognitive function of the patient with PRV encephalitis were significantly improved (7). Another patient had decreased visual acuity in both eyes and disappeared vitreous opacity in the left eye (12). By reviewing the 19 cases, it is difficult to compare the efficacy of the different antiviral regimens. Fan S. reported treatment of 17 patients with PRV encephalitis with acyclovir monotherapy, 4 of whom died, and the remaining patients had severe residual neurological deficit (9). In one particular case, after 24 days of acyclovir combined with foscarnet, the patient was still in deep coma and on mechanical ventilation (13). The above reports suggest that PRV encephalitis may not respond well to acyclovir. Presently, there is no relevant controlled drug trial and the effectiveness of antiviral drugs for PRV encephalitis still needs to be evaluated further.

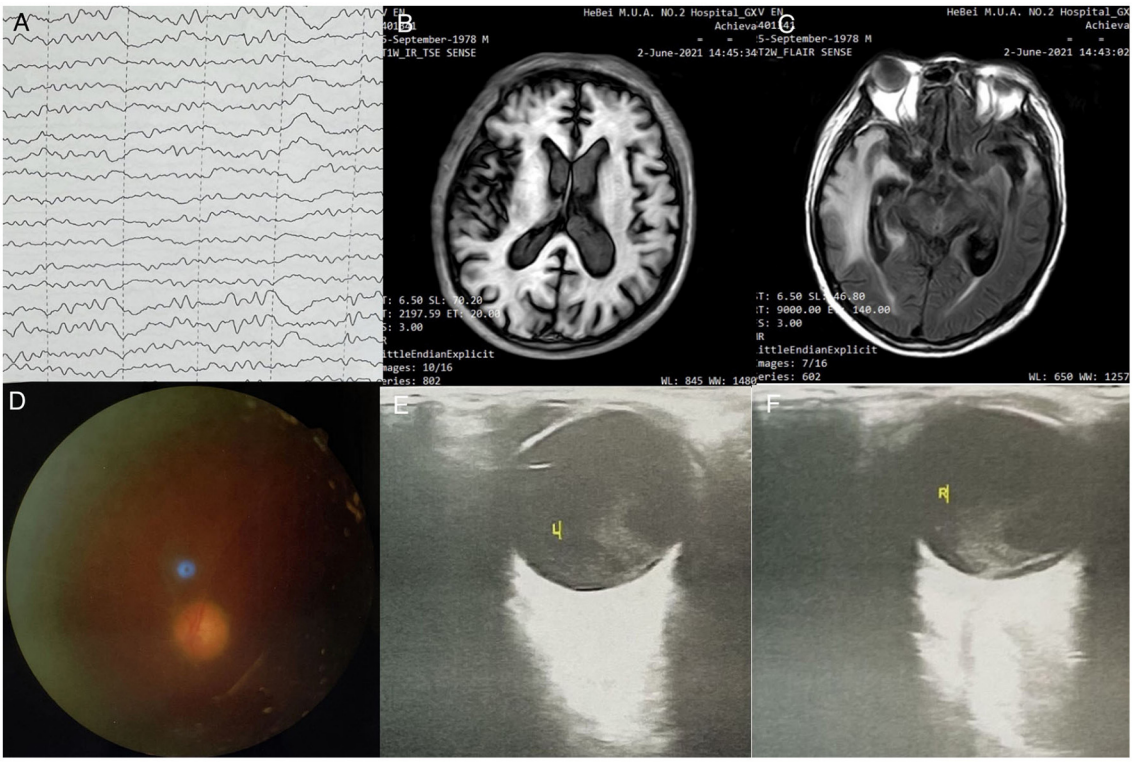

FIGURE 3 | (A) EEG examination: moderate to severe abnormal EEG, background diffuse 0, 6 slow wave bursts, 7-8 Hz slow rhythm bursts in the occipital lobe; **(B)** Head MRI - T1IR-TSE: normal head size, bilateral frontal lobe, temporal lobe, insula, bilateral hippocampus, bilateral thalamus, bilateral cingulate gyrus, flaky T1 low signal; **(C)** Head MRI - T2 FLAIR sequence: head size is normal; temporal lobe, insula, and bilateral hippocampus present high signal in T2 FLAIR, high signal in FLAIR; local sulci are clearer than before; **(D)** Fundus examination-left eye; **(E)** Ophthalmic ultrasound-L: severe vitreous opacity, mild thickening of the posterior wall of the eyes; **(F)** Ophthalmic ultrasound-L: severe vitreous opacity, mild thickening of the posterior wall of the eyes, thickening of the inner rectus muscle of the right eye.

Based on our literature review, a total of 19 patients who received specific treatment regimens were identified. Six PRV patients (6/19) were treated with glucocorticoids alone, 10 patients (10/19) received intravenous immunoglobulin (IVIg) in combination with glucocorticoids, while 3 PRV patients (3/19) were not treated with intravenous immunoglobulin (IVIg) or glucocorticoids (**Table 2**). According to one article, once a PRV patient is diagnosed, treatment should be started immediately, including human immunoglobulin, glucocorticoids, antiviral drugs, along with symptomatic and supportive treatments. In severe cases, intravenous immunoglobulin and glucocorticoid therapy can save the life of the patient (27, 28). A study suggested that severe visual impairment can be avoided with antiviral and corticosteroid therapy (11). Immunotherapy was used in most previously reported cases. Nonetheless, there is no relevant controlled drug trial. Thus, there is a lack of robust evidence of the effectiveness of human immunoglobulin and glucocorticoids in PRV patients.

In this case, we initiated the empirical antiviral therapy on the day of admission. Subsequently, based on the patient's condition and the result of NGS, antiviral therapy was continued to more than 50 days until the NGS results showed 0 PRV reads in the CSF. The consciousness, motor function and vision of the patient were improved gradually. On day 48 after discharge, the patient was able to walk slowly on his own without support and his visibility was 15 m. Forty-eight days after discharge, the patient was able to walk slowly on his own without support and his visibility was 15 m. In this case, early and long-term antiviral therapy and early immuno therapy may be the reasons for the better curative effect. In this case, the patient's visual function improved but retinal detachment occurred in the right eye later. This suggests that although the vision loss in the acute phase can improve with antiviral and anti-inflammatory treatment, the risk of subsequent retinal peeling cannot be ignored. Therefore, during follow-up, regular fundal examination should be conducted to monitor for potential retinal detachment. Our case may provide new insights for the treatment of patients with PRV encephalitis and can help reduce the disability rate and improve the quality of life of patients to a certain extent.

TABLE 2 | Summary of human cases of PRV infection reported.

Case	Diagnosis						Treatment details					Clinical outcomes	References
	Cerebrospinal fluid (NGS)		Antibody (ELISA)				Ganciclovir	foscarnet	Acyclovir	immunotherapy	steroids		
	±	Onset to sampling	CSF+/-	Onset to sampling	Serum+/-	Onset to sampling	±	±	±	±	±		
1	+	3d	+	23d	+	23d	+	−	+	−	+	The patient can follow instructions, perform eye movements and simple body movements	(5)
2	+	NA	NA	NA	+	>10d	−	−	+	+	+	The patient remained in light coma after 7 weeks of treatment. Consciousness returned at week 12.	(3)
3	+	NA	NA	NA	+	>10d	−	−	+	−	+	The patient was in coma and was kept on a ventilator when he left the hospital, and died after being transferred back to the local hospital.	
4	+	NA	NA	NA	+	>10d	−	−	+	−	+	The patient remained in coma with intermittent convulsions at week 8; slightly improved at week 16.	
5	+	NA	NA	NA	NA	NA	−	−	+	−	+	After one year of follow-up, the patient was blind in both eyes and took care of himself.	
6	+	1d	−	−	+	21d	−	−	+	−	−	1 month after treatment, patient was still dependent on tracheostomy and gastrostomy tube	(6)
7	+	NA	−	−	−	−	+	+	−	−	−	The patient's consciousness and cognitive function improved significantly. At 190-day follow-up, the patient remained blind.	(7)
8	+	1d	+	40d	+	23d	NA	NA	NA	NA	NA	Blindness	(8)
9	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	mild memory impairment	
10	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Minimally conscious status	
11	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Persistent vegetative status	
12	+	NA	−	−	gB+	10d	−	−	+	+	+	Patient died after 2 week	(9)
13	+	NA	gE+	10d	−	−	−	+	+	−	+	mRS 3	

(Continued)

TABLE 2 | Continued

Case	Diagnosis						Treatment details					Clinical outcomes	References
	Cerebrospinal fluid (NGS)		Antibody (ELISA)				Ganciclovir	foscarnet	Acyclovir	immunotherapy	steroids		
	±	Onset to sampling	CSF+/-	Onset to sampling	Serum+/-	Onset to sampling	±	±	±	±	±		
14	+	NA	gB+	46d	gE + gB+	46d	–	+	+	+	–	mRS 3	
15	+	NA	–	–	–	–	–	+	+	–	–	Died 2 months later	
16	+	NA	gE + gB+	36d	gE + gB+	36	NA	NA	NA	NA	NA	Died	
17	+	NA	gE + gB+	29d	gE + gB+	10d	NA	NA	NA	NA	NA	Died	
18	+	NA	–	–	gB+	7d	NA	NA	NA	NA	NA	mRS 5	
19	+	3d	NA	NA	NA	NA	–	–	+	+	+	Visual acuity in the right eye of the patient decreased to 2/20.	(10)
20	+	1d	NA	NA	NA	NA	–	+	+	+	+	Slow responses, occasional seizures, mRS	(11)
21	+	2d	NA	NA	NA	NA	–	+	+	+	+	Ventilator-dependent. Follows simple instructions, mRS 3	
22	+	NA	NA	NA	NA	NA	–	+	+	+	+	Follows simple instructions, mRS 3	
23	+	NA	NA	NA	NA	NA	–	+	+	+	+	Ventilator-dependent Slow responses, mRS 3	
24	+	1d	NA	NA	NA	NA	–	+	+	+	+	Blindness, mRs 3	
25	+	5d	NA	NA	NA	NA	+	+	–	–	+	The vitreous opacity of the left eye disappeared, and the occluded retinal vessels remained unchanged.	(12)
26	+	2d	–	2d	–	2d	–	+	+	+	+	The patient's prognosis is very poor, and mechanical ventilation is still required.	(13)

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LYu: data collection and analysis, manuscript writing, and literature research. LYi: decision making of patient's diagnosis and treatment, contributed ideas to the article, and supervision of the work. LM and WL: patient follow-up. ZY: cytological examination and cerebrospinal fluid examination. DJ: assessment of the patient's ophthalmic condition. BH and HJ: diagnosis and treatment experience sharing and guidance. TF and TM: treatment of patients in the ICU. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Guillain-Barré Syndrome in Patient With SARS-CoV-2 PCR Positivity Treated Successfully With Therapeutic Exchange Plasma: A First Case Report From Vietnam

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Since the first case of Guillain-Barré syndrome (GBS)-associated SARS-CoV-2 (COVID-19) infection reported in 2020, a series of cases have been published in some countries. In this case report, we present a young patient with GBS, whose clinical and laboratory data were appropriate for the diagnosis of GBS due to COVID-19 infection. Neurological examination revealed the muscular weakness of lower limbs with Medical Research Council (MRC) scale of 2/5 associated with diminished reflexes. Laboratory studies showed the positive nasal swab RT-PCR test for COVID-19, leukopenia, increased ferritin and LDH levels, normal electrolyte and liver and kidney function, and normal chest X-ray. The result of cerebrospinal fluid showed the albuminocytologic dissociation. The patient was treated with remdesivir, dexamethasone, anticoagulation, and therapeutic plasma exchange (TPE). Patient's muscle weakness was significantly improved after 1 week of admission. He was discharged at 23rd days of hospitalization and followed-up in the out-patients department.

Keywords: Guillain-Barré syndrome, SARS-CoV-2, COVID-19, MRC scale, therapeutic plasma exchange

INTRODUCTION

Since the first COVID-19 patient reported in March 2020, until now, Vietnam has experienced four waves of COVID-19 with more than 2 million confirmed cases and nearly 36 thousand deaths due to COVID-19. During this outbreak of COVID-19 pandemic (September–October 2021), Ho Chi Minh City and Binh Duong Province, located in the South of Vietnam, were two main regions where the number of people who contracted COVID-19 and were hospitalized due to COVID-19 was highest. During this time, the national mortality rate from COVID-19 was 2.4% compared with 1.7% currently.

Although the main symptoms of patients with COVID-19 have been well described previously, COVID-19 patients can present with diverse neurological symptoms such as headache, dizziness, loss of smell and taste, inflammatory polyradiculoneuropathy or Guillain-Barré Syndrome (GBS) (1, 2). Since the first case of GBS-associated SARS-CoV-2 (Covid-19) infection reported by Zhao H. et al. (3), a series of cases have been published (4–9).

Here, we present a patient with GBS, whose clinical and laboratory data were appropriate for the diagnosis of GBS due to COVID-19 infection. The patient was treated successfully by therapeutic plasma exchange (TPE) in combination with standard treatment for Covid-19. This is the first case of GBS associated with the COVID-19 case in Vietnam treated by TPE. It appears that the intervention with TPE made a significant difference compared to most other previously

TABLE 1 | Characteristics of laboratory parameters of reported patient.

Parameters	At admission	Day 5th–7th	After day 7th	Institutional normal range
RT-PCR SARS-CoV-2	Positive	*(non realized)*	Negative	Negative
White blood cell (10^9/L)	2.66	16.4	10.1	4.0–11.0
Neutrophil (%)	37.9	88.07	61.4	45–75
Lymphocyte (%)	40·1	6·17	28.1	20–45
Platelet (10^9/L)	61	325	271	140–500
CRP (mg/dL)	0.26	0.46	0.03	<1·0
Lactate (mmol/L)	2.47	2.13	-	0·5–2·2
Ferritin (ng/mL)	686.3	295.1	256.5	23·9–336·2
Fibrinogen (g/L)	2.67	2.78	0.61	1·5–4·0
TP (%)	99	75	75	>70
APTT (second)	44.5	29.5	15.5	20–40
Arterial Blood Gas				
pH	7·41	7.34	7·35	7.35–7.45
PCO_2 (mmHg)	38	35	42	35–45
HCO_3^- (mmol/L)	24.1	18.9	23.2	18–23
Base Excess$^-$ (mmol/L)	−0.4	−6.1	−2.4	−2– +3
PO_2 (mmHg)	93	92	100	80–100
A-aDO_2	9	14	-	5–20
PaO_2/FiO_2	442	406	476	
Sodium (mmol/L)	136	135	139	135–145
Potassium (mmol/L)	2.7	3.8	3.8	3.5–5.0
Calcium (mmol/L)	1.11	1.2	1.26	1.1–1.6
Magnesium (mmol/L)	0.83	0.92	0.99	0.73–1.06
Urea (mmol/L)	3.68	5.11	6.15	2.8–7.2
Creatinine (mmol/L)	95.04	70.04	55.69	72–127
eGFR-MDRD (mL/m/m^2)	95.15	135.32	176.3	≥60
AST (U/L)	46.97	51.47	89.58	0–50
ALT (U/L)	12.81	21.69	77.63	0–50
LDH	351.06	260.53	252.8	<247
Glucose (mmol/L)	4.9	4.5	-	4.1–5.9
Total protein (g/L)	64.4	63.7	-	66–83
Albumin (g/L)	34.7	34.2	-	35–52
Cerebrospinal fluid		*(non realized)*	*(non-realized)*	
Protein (g/L)	0.89	-	-	0.15–0.45
Glucose (mmol/L)	3.65	-	-	NA
Lactate (mmol/L)	1.53	-	-	1.1–2.4
Pandy's test	Positive	-	-	Negative
Cells	0	-	-	0

CRP, C-reactive protein; LDH, Lactate Dehydrogenase; eGFR, estimated Glomerular Filtration Rate; PT, Prothrombin Time; APTT, Activated Partial Thromboplastin Time; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase.

reported patients with Covid-19 induced GBS worldwide during the pandemic outbreak.

CASE REPORT

An 18-year-old man admitted to an intensive care unit (ICU of COVID-19 Unit of Phu Chanh, Binh Duong General Hospital, Binh Duong Province–Vietnam) during the middle of October 2021 because of fever, cough, sore throat, weakness, and pain of his legs for 4 days. He was otherwise in good health prior to this hospitalization. However, his roommate was diagnosed with COVID-19 and hospitalized two days before his admission. At the time of admission, his temperature was 38·6 °C, pulse was 80/min, respirations were 20/min, blood pressure was 120/80 mm Hg, and SpO_2 was 95% with room air. He had no symptoms of chest pain or shortness of breath. Neurological examination revealed the muscular weakness of lower limbs with Medical Research Council (MRC) scale of 2/5 (vs 5/5 for upper limbs), diminished reflexes of lower limbs, normal sensation, no abnormal cranial nerve symptoms, and no meningeal signs. The rest of his clinical examination was normal.

Laboratory studies demonstrated a positive nasal swab RT-PCR test for COVID-19, leucopenia, increased ferritin and LDH levels, normal electrolyte and liver and kidney function, and normal chest X-ray. The result of cerebrospinal fluid showed the albuminocytologic dissociation (without an elevation in white blood cells; **Table 1**). The result of magnetic resonance imaging (MRI) of the spine was normal. The diagnosis of Guillain Barré Syndrome induced by COVID-19 was confirmed in this patient according to the hospital's medical experts. Some other differential diagnosis such as compressive myelopathy, transverse myelitis, and other infectious causes of acute myelitis were also eliminated due to lack of medical history and clinical features.

The patient was then treated with antiviral drug (remdesivir 200 mg loading dose on the first day and 100 mg in the next 4 days), intravenous corticosteroids (dexamethasone 9 mg/day in 3 days and 6 mg/day in the next 7 days), and anticoagulation. He was also treated with the therapeutic plasma exchange (TPE) for 5 alternating day cycles by using 5% human albumin replacement (3.200 ml/cycle). The patient's muscle weakness of the lower limbs improved at day 7 and 14 from 2/5 to 3/5 and then 4/5, respectively, according to the Medical Research Council (MRC) Scale. He also benefited from early rehabilitation to improve muscle strength during his hospitalization in the ICU. At day 7th, he developed a nosocomial lung infection, confirmed by chest X-ray and was treated successfully with short period of antibiotic (intravenous levofloxacin 750 mg/day for 5 days) and conventional oxygen therapy (nasal cannula 3 L/min). His RT-PCR for SARS-COV-2 (COVID-19) were negative at day 14th and 21th. Other laboratory tests were normalized at day 14th. The patient was discharged after 23 days from his hospitalized stay (**Figure 1**). He has been followed-up regularly at the outpatient Department for Long Covid-19 for his GBS and rehabilitation. At the 3rd month, the patient had a total recover from his

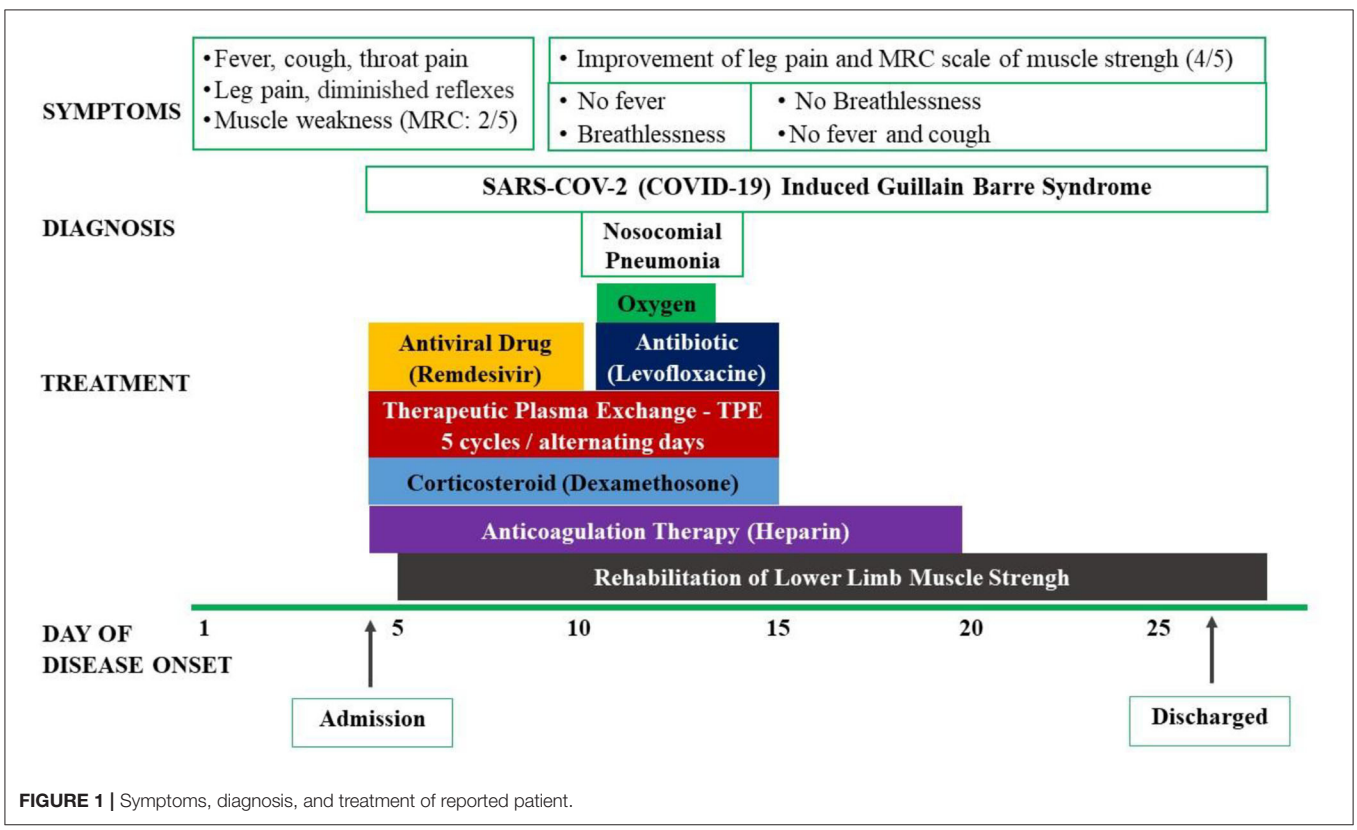

FIGURE 1 | Symptoms, diagnosis, and treatment of reported patient.

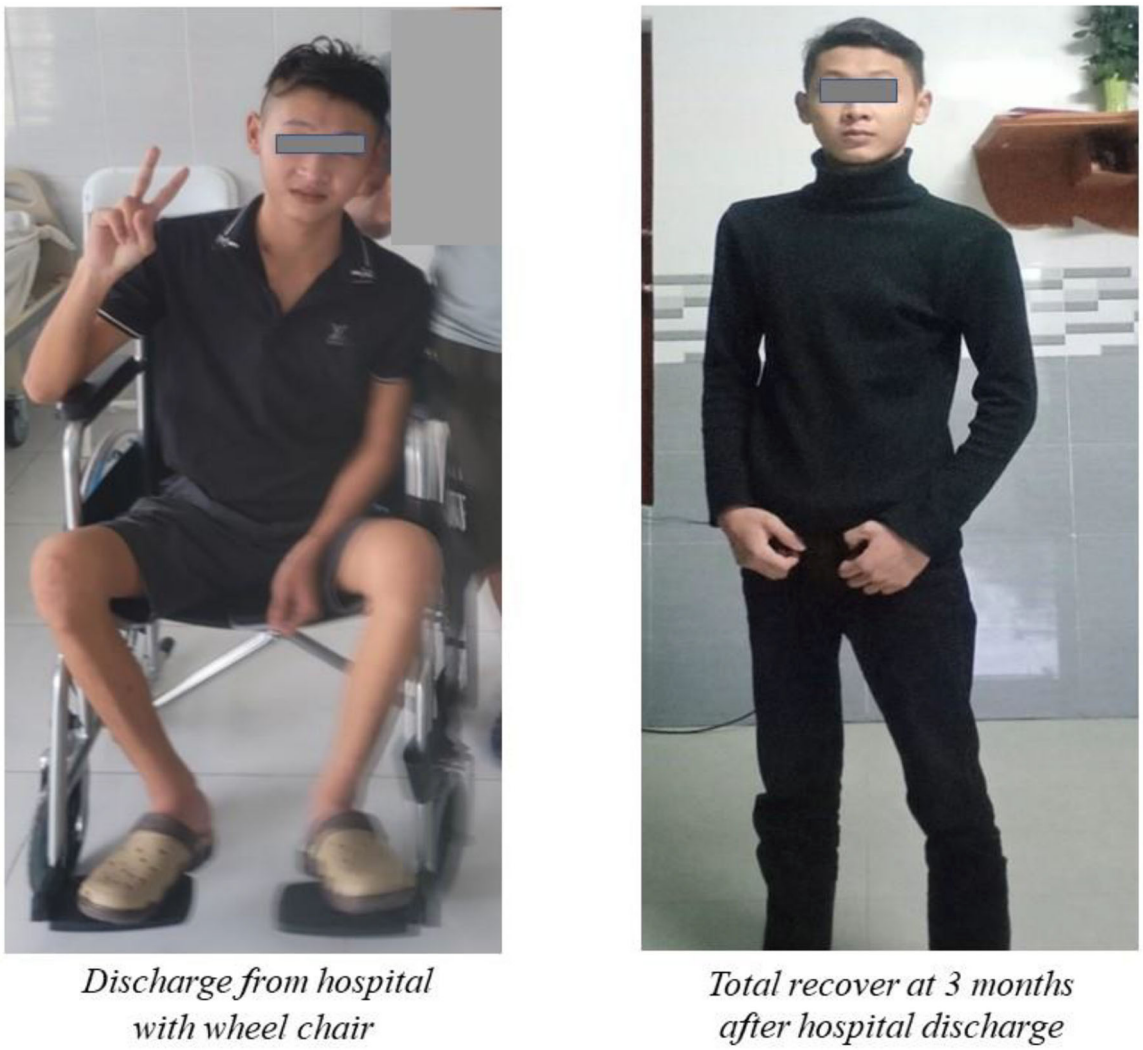

FIGURE 2 | Clinical status of reported patient at post-COVID status.

GBS with MRC scale of 5/5 and he started to go to work (**Figure 2**).

DISCUSSION

Guillain-Barré Syndrome (GBS) is an acute inflammatory polyradiculoneuropathy that results in muscle weakness and diminished reflexes. GBS may occur after immunization or viral infection, including the SARS-COV-2 (COVID-19) (9–14). After one of the first cases of GBS -associated SARS-CoV-2 infection presented by Zhao et *al.* in 2020 (3), other cases have been reported in the world literature during the COVID-19 pandemic (5–8, 10–14).

In 2020, Caress et *al.* analyzed 37 cases of GBS (mean age: 59 years and 65% of male gender), associated with COVID-19 and showed that the mean time from COVID-19 infection to GBS symptoms was 11 days. All 37 patients were free of severe acute respiratory distress syndrome. Albuminocytologic dissociation in cerebrospinal fluid was positive in 76% of cases. Most patients were treated with a single course of intravenous immunoglobulin and improved within 8 weeks. The authors also demonstrated the similar clinical manifestation and severity between non-COVID-19 and COVID-19 induced GBS in the study patients (15).

In 2021, Rumeileh et al. reviewed 73 patients reported in 52 publications, which demonstrated similar results to include the mean age of reported patients being 55 years old and the males accounting for 68.5% of cases (16). In this series of cases, cerebrospinal fluid albuminocytologic dissociation was found in 71 and 100% was negative for SARS-CoV-2. The treatment for GBS in this case series was intravenous immunoglobulin and more than 70% of cases had a good prognosis (16). The first case of GBS with severe acute respiratory distress syndrome induced

by coronavirus-2 (SARS-CoV-2) was reported in a 50-year-old male in 2021. In this case report, the patient's cerebrospinal fluid was positive for SARS-CoV-2 (Covid-19), confirmed by RT-PCR (17).

In this case report, we presented a patient with acute progressive and symmetric muscle weakness of lower limbs associated with Covid-19 infection. The results of the clinical examination and laboratory data were appropriate for the diagnosis of Covid-19-induced GBS. It appears to be the first case of GBS associated with COVID-19 reported in Vietnam. Our patient was younger than most other patients in previous reports described above. Besides the treatment with antiviral therapy, anticoagulation and corticosteroids, our patient also received TPE (therapeutic plasma exchange). Although TPE is the treatment of choice for patients with GBS before COVID-19 pandemic, the use of TPE for COVID-19-induced GBS is still rare. The majority of the patients with COVID-19-associated GBS patients noted above were mainly treated with intravenous immunoglobulin. Fortunately, our patient had a total recover from his GBS with MRS scale of 5/5 at 3rd month after hospital discharge.

Both intravenous immunoglobulin and TPE are indicated to treat GBS within 2–4weeks after the onset of neuropathic symptoms to prevent further nerve damage, and both treatments have similar efficacy (16, 18–21). In GBS patients, TPE helps to remove antibodies and other potentially detrimental factors from the blood. TPE might be more effective when starting the treatment within seven days after symptoms onset, but data suggest it is still beneficial in patients treated up to 30 days after disease onset (19).

In addition, TPE is effective in decreasing inflammatory cytokines (including IL-6), acute phase proteins (ferritin, CRP), and improving tissue oxygenation and as such could be considered as an additional therapy to reduce the risk of cytokine storm-induced acute respiratory distress syndrome (ARDS) in COVID-19 patients (22). Moreover, in patients with COVID-19, TPE may help to repair coagulopathy and to restore endothelial membrane by decreasing blood viscosity (20, 23). The association between blood hyperviscosity and the tendency of thrombosis is also considered as a risk of COVID-19 infection.

However, it has been proven in various epidemiological studies, particularly from the United Kingdom, that the incidence of Guillain-Barre syndrome did not increase during the pandemic (24–26). In fact, GBS related COVID-19 is also a rare complication. Definitely, it has been currently more than 10 million people contracted COVID-19 in Vietnam but this case report is the first and only one which has been diagnosed by local experts and declared officially in the country.

One of the limitations of our case report is the lack of electromyography and nerve conduction studies to support the diagnosis of GBS during the acute phase. This was secondary to the lack of access to these tests in our COVID-19 ICU. However, similar to us, we suspect that during the COVID-19 pandemic many health care systems had limited procedures and transportation of patients for testing to decrease health care worker's exposure to COVID-19. In addition, another limitation was also related to the lack of negative results of other infectious test for supporting the diagnosis of GBS during COVID-19 pandemic.

CONCLUSION

Guillain-Barre Syndrome (GBS) is an acute inflammatory and demyelinating polyradiculoneuropathy disease. GBS may occur in young patients with COVID-19 as a main symptom of Covid-19 infection. The early management of Covid-19 induced GBS with therapeutic plasma exchange in combination with standard treatment improved the patient's prognosis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) and/or minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

The literature search was done by SD-Q, DH-T-A, QT-X, and CN with significant contributions from TN-T-K, VN-N, and TC. Data collection was done by SD-Q, DH-T-A, TN-Q, TN-T-K, and TN-C. All authors contributed equally to analyzing and interpreting the data of case report. SD-Q, QT-X, and DH-T-A drafted the manuscript, with editing by TC and significant contributions by CN, VN-N, TN-C, and CN. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Concurrent Tuberculous Meningoencephalitis and Anti-NMDAR Encephalitis: A Case Report

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Background: Cases of tuberculosis triggering the development of anti-*N*-methyl-*D*-aspartate receptor (NMDAR) encephalitis are absent.

Case Presentation: Herein, we report, for the first time, the case of a patient who developed anti-NMDAR encephalitis likely due to tuberculosis. The patient, a 33-year-old man, experienced weight loss during the previous 2 years, along with acute headache, fever, cognitive deficits, and right ophthalmoplegia. Based on these findings and on data from magnetic resonance imaging and cerebrospinal fluid antibody analysis, tuberculous meningoencephalitis combined with anti-NMDAR encephalitis was diagnosed. Marked clinical and brain imaging improvement were observed after antituberculosis and high-dose corticosteroid treatment initiation, which persisted during the 3 months of follow-up.

Conclusions: This case suggests that anti-NMDAR encephalitis may arise after tuberculosis infection. Therefore, clinicians must be aware of this possibility, especially when cognitive and new neurological symptoms suddenly occur.

Keywords: anti-NMDAR antibody, autoimmune encephalitis, case report, *Mycobacterium tuberculosis*, tuberculosis meningoencephalitis

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INTRODUCTION

Encephalitis caused by antibodies against the *N*-methyl-*D*-aspartate receptor (NMDAR) is a well-described dysimmune entity of the central nervous system (CNS) and the most frequent form of autoimmune encephalitis (AIE) (1). Frequently idiopathic, anti-NMDAR encephalitis can occur as a paraneoplastic manifestation and post-infection neurological complication (2). In particular, the herpes simplex virus (HSV) is the most frequently identified virus associated with this disorder (3). This study describes the case of a patient presenting with anti-NMDAR encephalitis after a *Mycobacterium tuberculosis* (MTB) infection.

Case Presentation

The patient, a 33-year-old man, was hospitalized with complaints of headache, fever, unresponsiveness, irritability, and neck pain. The patient was reported to have lost 35 kg during the last 2 years (**Figure 1**). Twenty days before admission, the patient experienced persistent acute headaches, primarily in the front of the ear, temporal and posterior occipital part of the right side, without any distinct cause. These headaches were mainly characterized by unbearable distending pain, occasionally accompanied by dull, tingling, throbbing pain,

which led to prolonged insomnia. Moreover, the patient experienced loss of appetite, but without nausea, vomiting, fever, diplopia, limb movement disorder, chest tightness, or shortness of breath. Eighteen days before admission, the patient sought medical help to manage the headaches. At that time, brain computed tomography (CT) scans were normal and the patient was given analgesic drugs, including rotundine (60 mg, orally three times per day), which relieved the headaches for 4 h and partly ameliorated the insomnia. Gradually, the degree of the headaches reduced, only occurring three to four times a day for approximately 4 h. However, 3 days before admission, the patient developed a low-grade fever when a headache occurred, accompanied by irritability and neck pain. Brain MRI was normal, but chest CT images revealed that the upper lobe of both lungs had lesions secondary to tuberculosis, and the left pleura was thickened and had encapsulated effusion (**Figures 2A,B**). The patient had no history of chronic disease, smoked for 20 years (10 cigarettes per day), occasionally drank a small amount of alcohol, and denied to have a family history of genetic disease. At admission, the patient was irritable and unresponsive, and upon examination, verbal reduction (unable to express full sentences), mild loss of comprehension, decreased calculation ability, and poor spatial learning and memory were confirmed. The eyeballs were in place on both sides, and horizontal nystagmus to the right was observed. The patient also showed signs of meningeal irritation, with nuchal rigidity (neck flexion angle of approximately 5°), positive bilateral Kernig's sign, and negative Brucella's sign. According to the Clinical Assessment Scale in AIE (CASE) (4), modified Rankin scale (mRS), Glasgow coma scale, mini-mental state examination (MMSE), and the Montreal Cognitive Assessment Test (MoCA) the patient scored 6, 3, 13 (E3M4V6), 9, and 8, respectively.

Laboratory tests showed that the erythrocyte sedimentation rate was 56 mm/h, and serum blood cell counts and C reactive protein levels were within normal range. Lumbar puncture showed an increased opening pressure, and cerebrospinal fluid (CSF) analysis revealed elevated white blood cell (WBC) count and protein levels (**Table 1**). Based on these findings, the initial clinical diagnosis of possible viral meningoencephalitis was achieved. The patient was treated empirically with intravenous acyclovir 10 mg/kg three times per day. However, his health status continued to gradually worsen, with the highest body temperature reaching 39°C, with confusion, occasional nonsense, and partial third cranial nerve palsy, on day 3 (**Figure 1**). The CASE and mRS scores were 13 and 4. Furthermore, CSF and serum analyses revealed the presence of anti-NMDAR antibody IgG, determined by cell-based assay (CBA) and tissue-based assay (TBA). The result of tuberculin-purified protein derivative (PPD) skin test was positive (++), and that of the T-SPOT.TB assay was positive. CSF was positive for the MTB complex DNA assay; however, the modified acid-fast staining and metagenomic next-generation sequencing (mNGS) result was negative. Moreover, MRI showed nodules and ring enhancement in the right lateral ventricle, left temporal and left cerebellar hemisphere, abnormal signal foci were observed in the right temporal lobe and basal ganglia, as well as enhancement of the pia mater of the right frontotemporal area (**Figures 2C,D**). Furthermore, the patient was negative for anti-MBP, anti-AQP4, anti-MOG, anti-GFAP, and anti-GQ1b IgGs, and neuron antibodies in serum and CSF. Tumor markers, blood cultures, and autoantibodies associated with other autoimmune diseases were also negative. Moreover, color Doppler ultrasound of lymphatic, reproductive, urinary, and digestive systems, and of the heart were all normal. The lungs were also normal as per bronchoscopy analysis.

Diagnosis of tuberculosis meningoencephalitis combined with anti-NMDAR encephalitis was achieved, and a standard antituberculosis regimen (rifampicin 0.45 g/day, ethambutol 0.75 g/day, isoniazid 0.6 g/day, and pyrazinamide 1.5 g/day) and intravenous 1,000 mg/d glucocorticoid pulse therapy (halved every 3 days, and switched to oral after 12 days) was initiated. Thereafter, the consciousness status of the patient and irritability gradually improved, and the head and neck pain was substantially ameliorated. On day 8, despite the health improvements noticed, the comprehension, calculation ability,

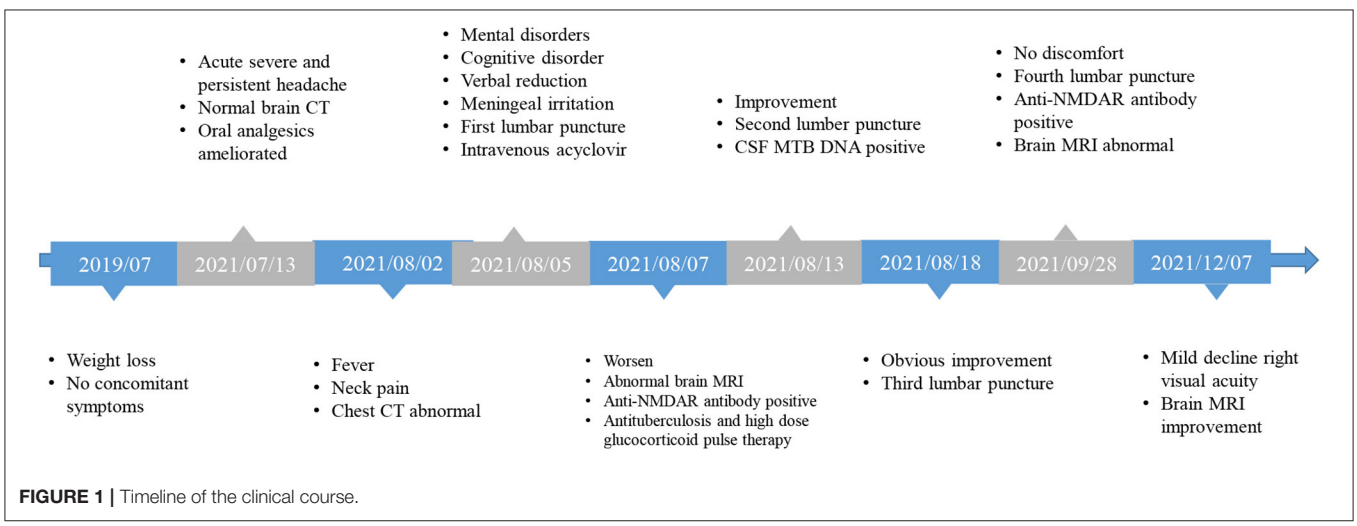

FIGURE 1 | Timeline of the clinical course.

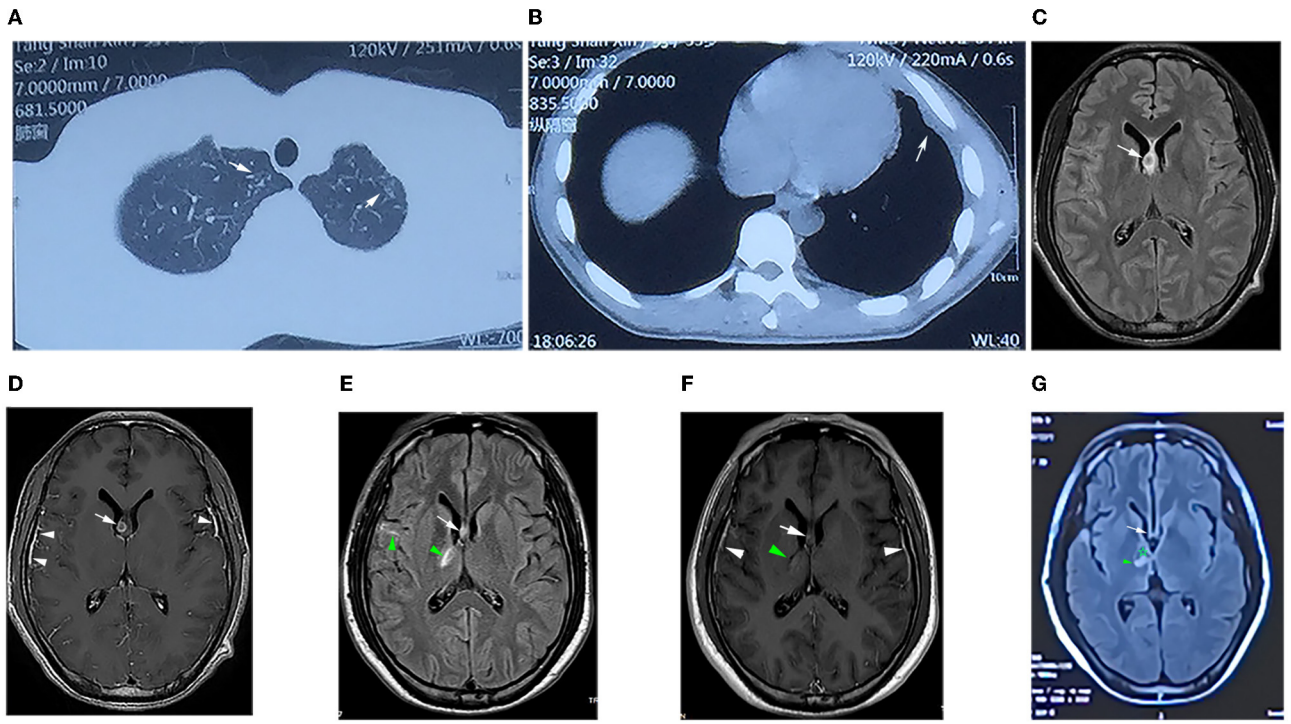

FIGURE 2 | (A) Computed tomography (CT) of the chest showing patchy high-density shadows in the upper lobes of both lungs (white arrow), suggesting secondary to tuberculosis. **(B)** CT scan revealed thickening of the left pleura and encapsulated effusion (white arrow). **(C)** T2-weighted magnetic resonance imaging (T2WI) FLAIR showing small circular isointense, slightly long hyperintense in the right lateral ventricle subependymal (white arrows). **(D)** Contrast-enhanced T1WI showing that the lesion was ring-enhancing (white arrows) and significant enhancement of the bilateral temporal leptomeningeal (white triangle). **(E)** T2WI FLAIR image showing that the right subependymal lesion (arrow) was smaller than that in **(C)**, and the right basal ganglia and right temporal lobe were patchy and line-like hyperintensity (green triangles). **(F)** Contrast-enhanced T1WI showing that the lesion in the right subependymal was smaller than that in **(D)** (white arrow), the lesion in the right basal ganglia was slightly enhanced (green triangle), and the meninges were thicker as before (white triangle). **(G)** T2WI FLAIR image showing that the subependymal lesion had basically disappeared (white arrow), the right basal ganglia lesion was slightly smaller (green triangle), and softening could be seen inside (☆).

spatial learning, and memory impairments remained unchanged, and depression manifestations appeared. The pain symptoms disappeared, but neck resistance increased to 15°C. On day 13, a lumbar puncture was performed with intrathecal isoniazid (0.1 g) and dexamethasone (5 mg). CSF analysis revealed evident improvements (**Table 1**), and the comprehension, mood, verbal reduction, and partial oculomotor nerve palsy showed some improvements. The neck flexion angle of 25° remained. The CASE and mRS scores were 6 and 3. The patient was discharged with an oral standard antituberculosis regimen combined with prednisone (60 mg/day) for 2 weeks, which was tapered to 50 mg/day until the following medical examination.

After 1 month of follow-up, the patient had gained 8 kg without any discomfort. Physical examination showed only right ptosis and diplopia. Moreover, the CASE, MMSE, MoCA, and mRS scores were 3, 29, 27, and 1, respectively. The CSF anti-NMDAR antibody titer remained unchanged. Noteworthily, the serum anti-NMDAR antibody titer, and protein and WBC of CSF were significantly reduced (**Table 1**). Brain MRI revealed significant shrinkage of the primary nodules. Nevertheless, the lesion in the right basal ganglia was larger than before, new lesions appeared in the right pontine and right-sided temporal lobe, and the right frontotemporal leptomeninges showed more evident enhancement than before (**Figures 2E,F**). The patient continued to receive the antituberculosis treatment regimen along with regular tapered prednisone. Additional evaluations revealed that the patient was still experiencing mild visual acuity decline in the right eye but without impact on his daily life, and the ptosis and memory disorders disappeared without further complaints. Physical examination remarkably improved after 3 months of discharge. The CASE and mRS scores were 2 and 1. The lesions on the CT chest and brain MRI (**Figure 2G**) showed evident improvements.

DISCUSSION AND CONCLUSION

Although no direct evidence for tuberculosis-induced anti-NMDAR encephalitis, our patient was diagnosed with tuberculosis meningoencephalitis associated with anti-NMDAR encephalitis (5). According to the clinical symptoms, basic laboratory data, thickened meninges and granuloma in MRI, and MTB DNA detection in the CSF, the patient met the criteria for tuberculous meningoencephalitis and pleurisy diagnosis (6). However, it remains unclear why the mNGS failed to identify the MTB. It is possible that small populations of non-replicating MTB may persist in granulomatous foci (7), almost few MTB may be contained in CSF and serum. In addition, mNGS has

TABLE 1 | Some data of laboratory tests.

Items	2021-8-5	2021-8-13	2021-8-18	2021-9-28
Opening pressure (mm H_2O)	325	280	170	140
CSF WBC (10^6/ mm^3)	12	480	80	34
CSF Protein (mg/dL)	1,650	1,000	720	540
CSF Glucose (mg/dL)	43.02	19.98	37.98	68.76
CSF Chlorine (mmol/L)	115	116.7	124.7	127.1
Blood glucose (mg/dL)	90	107.82	93.6	172.98
CSF Modified acid-fast staining	(–)	(–)	(±)*	(–)
CSF mNGS	(–)	–	–	–
CSF MTB complex DNA assay	–	(+)	(–)	(–)
CSF NMDAR-ab	1:3.2	–	–	1:3.2
Serum NMDAR-ab	1:1,000	–	–	1:32

**Found one MTB;–, none tested.*

limited sensitivity for the detection of intracellular bacteria; indeed, a meta-analysis of mNGS for MTB diagnosis revealed a comprehensive sensitivity was 61% (8). Notably, at early disease onset, irritability, cognitive dysfunction (comprehension, orientation, and calculation), and verbal reduction observed in our patient could not be explained by intracranial lesions on MRI. Furthermore, TBA and CBA methods positively detected anti-NMDAR antibodies in the blood and CSF, whereas neoplastic disorders, viral encephalitis, rheumatologic disorders, bacterial endocarditis, and other disease were excluded (5). Importantly, as tuberculous meningoencephalitis could not be ruled out, possible anti-NMDAR encephalitis was diagnosed.

In various animal models of tuberculosis, bacterial growth is rapid during the first 3 weeks of infection and reaches a plateau when adaptive immunity develops (9, 10). In addition, tuberculous granuloma formation requires adaptive immunity (11). Our patient experienced headaches only in the first 20 days; thus, we believe that the MTB infection occurred before the anti-NMDAR encephalitis was developed.

As no such case had been previously reported, and the etiology and pathogenesis of anti-NMDAR encephalitis are not fully understood, we questioned the probability of other causes of anti-NMDAR encephalitis. First reports on anti-NMDAR encephalitis described a close relationship with tumors (2). However, in this case, the patient was negative for serum tumor markers and CSF anti-tumor-associated neuron antibodies, and symptoms or imaging data of lymphatic, hematopoietic, reproductive, urinary, digestive, or respiratory cancers were not observed. Moreover, tumor-related manifestations were noted during the follow-up period. Interestingly, some cases of non-tumor-associated anti-NMDAR encephalitis were described to be related to infections (12, 13), in particular, HSV infection (14). Our patient presented with headache, fever, and signs of meningeal irritation, which strongly suggested CNS infections. Viral meningoencephalitis was the first diagnosis; however, 26 days after disease onset, the symptoms and signs were further exacerbated, and the antiviral therapy was ineffective. Moreover, CSF and brain MRI data failed to support this initial diagnosis. To date, anti-NMDAR encephalitis has been rarely associated with multiple sclerosis (15) and vaccines (16, 17); nevertheless, our patient was negative for anti-MBP, anti-AQP4, anti-MOG, and anti-GFAP IgGs in the serum, and CSF, or had clinical signs or symptoms of such etiology. Moreover, the patient had not been vaccinated in 10 years. Therefore, common autoimmune demyelinating diseases of the CNS or vaccine-triggered pathology were excluded from the differential diagnosis.

The mechanisms connecting anti-NMDAR encephalitis with MTB infection remain unclear. Although we could not obtain a direct proof of the relation between these two conditions, there are some possible explanations. Tuberculosis infection itself triggers immune responses, which in turn may establish a potential background that favors autoimmunity. In the case of our patient, the MTB infection may have led to anti-NMDAR encephalitis development.

The MTB bacteria are phagocytosed by macrophages, which in turn produce large amounts of signaling molecules (such as TNF-α, IL-6, and IL-12p40) that recruit other immune cells (18). Moreover, lipids of the bacterial cell wall can destroy the mitochondrial membrane, which affects the cellular energy metabolism, while bacterial lipids and proteins can induce delayed hypersensitivity, leading to tissue necrosis and systemic symptoms, activation of the $CD4^+$/$CD8^+$ T cells, and enhanced secretion of cytokines (11). These strong immunities and inflammatory responses can derange the intracranial immune microenvironment, directly damaging the nerve tissue and promot leakage of NMDAR antigens; they can impair the blood-brain-barrier, increasing its permeability and allowing for the peripheral analogs of the NMDAR antigen to enter the intracranial space; then trigger the production of anti-NMDAR antibodies (19). Nevertheless, other unknown immunological triggers may have been involved in this case, and the tuberculosis infection may have appeared coincidently with anti-NMDAR encephalitis.

Anti-NMDAR encephalitis patients usually present with abnormal behavior and mental, speech dysfunction, dyskinesias, memory deficits, autonomic instability, and a decrease in the level of consciousness (5). Neither oculomotor nerve palsy nor neck resistance has been associated with anti-NMDAR encephalitis. Moreover, non-specific lesions on MRI were identified in 33–50% of anti-NMDAR encephalitis patients. To date, no intracranial granuloma was reported in an anti-NMDAR encephalitis patient, and only one case report described microglial nodules in the frontal lobes and basal ganglia (20). Nonetheless, oculomotor nerve palsy, neck resistance, and intracranial granuloma on MRI are characteristic features of MBT meningoencephalitis (14). As Bickerstaff's brainstem encephalitis (BBE) is characterized by abnormal mental status, bilateral external ophthalmoplegia and ataxia, and presence of anti-GQ1b antibodies, this disorder could have also been considered as differential diagnosis in our case. Despite 32% of patients do not have detectable antibodies (21), our patient had unilateral external ophthalmoplegia and not ataxia, so he did not meet the BBE criteria.

Tuberculosis combined with anti-NMDAR encephalitis is a rare event; nonetheless, it should be considered when patients with tuberculosis present with atypical symptoms. Furthermore, tuberculosis should be considered when patients with anti-NMDAR encephalitis present considerable weight loss pre-onset and/or brain granulomas; various laboratory methods should be employed to detect tuberculosis and prevent its

spread after using immunosuppressants. Follow-up and restaging MRI assessments are a good strategy to diagnose such cases and evaluate treatment efficacy. In summary, the present case suggests that tuberculosis may trigger or aggravate anti-NMDAR encephalitis, an association that should be recognized to avoid misdiagnosis and ensure adequate patient care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CX: data acquisition and drafting the manuscript. WQ: data acquisition. LJ and YH: revision of the manuscript. CS: data interpretation and critical revision of the manuscript. All authors read and approved the final version of the manuscript.

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Case report: First case of neuromelioidosis in Europe: CNS infection caused by *Burkholderia pseudomallei*

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Neuromelioidosis is a rare CNS infection caused by *Burkholderia pseudomallei* and is characterized by high morbidity and mortality. Our report presents the diagnostic and therapeutic approach of the first case of neuromelioidosis confirmed in Europe. A 47-year-old man with a medical history of recurrent otitis with otorrhea and fever after tympanoplasty and radical cavity revision operation on the left ear was admitted with headache, decreased level of consciousness, dysarthria, left-sided hemiparesis, and urinary incontinence. After extensive investigations including MRI, microbiological, serological, and CSF analyses, and, ultimately, brain biopsy, a diagnosis of neuromelioidosis was established. Despite antibiotic treatment, the patient showed no clinical improvement and remained in a severely compromised neurological state under mandatory mechanical ventilation. Neuromelioidosis can pose a diagnostic challenge requiring an extensive diagnostic evaluation because of its uncommon clinical and radiological presentations.

KEYWORDS

neuromelioidosis, Europe, case report, MRI, *Burkholderia pseudomallei*

Introduction

Melioidosis is a rare infectious disease caused by *Burkholderia pseudomallei*, a Gram-negative, aerobic, and non-spore-forming, soil saprophyte. The disease is endemic to tropical regions such as northern Australia and Southeast Asia (1). According to growing evidence, melioidosis may also be endemic in the Indian subcontinent and the Caribbean (2, 3). Typical manifestations of the disease include abscess formation especially in the lungs, liver, spleen, skin, and skeletal muscle. The involvement of the central nervous system is rare (1–5%) but statistically associated with higher case mortality up to 25% (4, 5).

Here, we present the first case of neuromelioidosis confirmed in Europe based on detection of the bacterium in cerebrospinal fluid, brain bioptic sample, and smear of the left ear.

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Case presentation

A 47-year-old man presented to an external department of otolaryngology with deterioration of general condition and fever. The diagnostic investigation did not identify any infectious source. Regarding the medical history of the patient, antibiotic treatment had been repeatedly administered because of recurrent otitis with otorrhea and fever after tympanoplasty and radical cavity revision operation on the left ear approximately 6 months before the current presentation. The patient works as exhibition organizer and therefore often travels internationally. However, in the preceding 2 years, he did not travel outside Europe and was mainly located in Germany or Italy according to his family. Two days after hospital discharge, the patient presented again in the emergency department of the same clinic with headache, decreased level of consciousness, dysarthria, left-sided hemiparesis, and urinary incontinence. The brain CT-scan was normal. One week after admission, the patient was transferred to our hospital for the purpose of a neurological assessment.

Upon arrival, the patient showed decreased level of consciousness, left-sided hemiparesis, and urinary incontinence. The lumbar puncture revealed signs compatible with CNS infection (glucose 19 mg/dl, lactate 3.9 mmol/l, protein 206 mg/dl, and leukocytes 103/µl), whereupon treatment with empiric intravenous triple therapy with acyclovir, ampicillin, and ceftriaxone was initiated. The new CT scan of the brain revealed partial compression of the right lateral ventricle. Subsequently, the patient was admitted to our general neurology ward for further diagnostic investigation. The Brain MRI showed FLAIR-hyperintense bihemispheric lesions (significantly more on the right than on the left) in the area of the thalamus and the internal capsule, and extensive brainstem involvement with faint contrast enhancement in the posterior limbs of the internal capsule along with the parapontine region. The progressive deterioration of the patient's level of consciousness resulted in transfer to our intermediate care unit and subsequently to our intensive care unit because of further worsening with a score of 6 on the Glasgow Coma Scale. Upon admission to the intensive care unit, the patient was hemodynamically stable, free of vasopressor support, and received 2 L of oxygen per minute *via* nasal cannula. Protective endotracheal intubation was performed within a short timeframe as a result of the prolonged comatose state with limited protective brainstem reflexes. Because the X-ray confirmed bilateral pneumonia, presumably triggered by microaspiration, the antibiotic regimen was switched to piperacillin/tazobactam and clarithromycin.

An extensive differential diagnostic, including cerebrospinal fluid (CSF) analysis, was carried out with regard to encephalitis of infectious, autoimmune, or malignant etiology. PCR testing for HSV 1/2, VZV, JCV, and HHV-6 was negative, and no organisms were isolated by culture. Anti-Zic4 antibodies were weakly positive in the CSF. A tumor search, including a chest and abdomen CT scan, showed no evidence of neoplasy. A smear culture of the drainage deriving from the left ear isolated *B. pseudomallei*. The supplementary imaging of the mastoid and the otolaryngological examination did not provide any evidence of mastoiditis or abscess. However, the antibiotic regimen was switched to ceftazidime in accordance with the antibiogram. The follow-up MRI imaging of the brain on day 4 showed an increasing size of the cerebral lesions and radiological features of elevated intracranial pressure. Consequently, an external ventricular drain system (EVD) was placed for intracranial pressure monitoring and management. For diagnostic clarification, stereotactic brain biopsy was performed. The histopathological assessment revealed an inflammatory process that could not be further specified. With a provisional diagnosis of an autoimmune/inflammatory encephalitis, intravenous methylprednisolone pulse treatment was initiated. In the further course, plasma separation was also initiated because of suspicion of an autoimmune inflammatory etiology. However, from both the CSF and brain biopsy samples, which were sent for a supplementary examination to the Bundeswehr Institute of Microbiology in Munich, *B. pseudomallei* was isolated. Based on the radiological and microbiological findings as well as the clinical presentation, which strongly indicated the presence of neuromelioidosis, the antibiotic treatment was escalated to meropenem. The re-evaluation of the mastoid CT-imaging revealed an exposed bone defect in the mastoid cavity of the left ear, which might have been the entry point of the detected pathogen to the CNS. Therefore, an uncomplicated radical cavity revision with bone reconstruction was carried out in collaboration with our otorhinolaryngology department. Another follow-up MRI imaging of the brain on day 25 revealed regression of the inflammatory changes but with significant residual florid inflammatory supra- and infratentorial lesions. Due to stable intracranial pressure in the range of normal standards, the EVD could be removed and the dexamethasone treatment gradually tapered. Nevertheless, no improvement in the neurological condition could be observed during the entire in-patient stay. In the further course, tracheostomy was performed as a result of the prolonged comatose state with mandatory mechanical ventilation due to lack of spontaneous breathing. Furthermore, a port system was placed for further administration of meropenem (6 weeks in total) followed by a maintenance phase with oral antibiotic treatment with cotrimoxazole for 6

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; CT, computer tomography; EVD, external ventricular drain; FLAIR, fluid-attenuated inversion recovery; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus; HSV-1/HSV-2, herpes simplex virus type 1/type 2; IV, intravenous; JCV, John Cunningham virus; MRI, magnet resonance imaging; PCR, polymerase chain reaction; and VZV, varicella zoster virus.

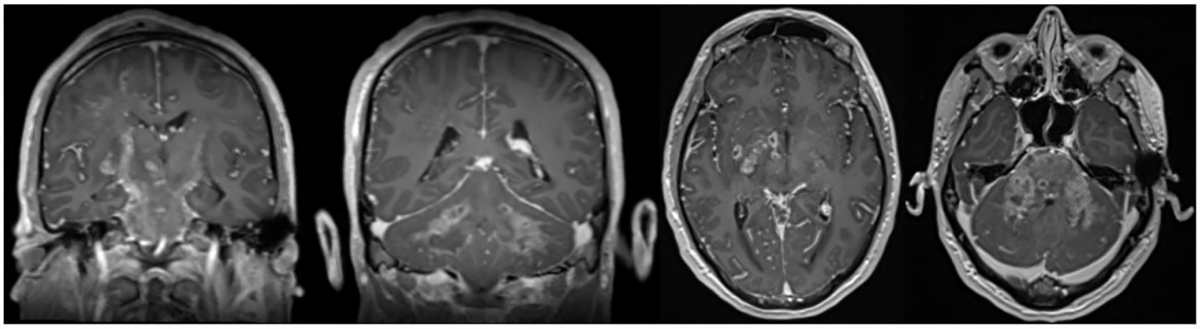

FIGURE 1
Axial and coronal contrast-enhanced T1-weighted images showing typical rim-enhancing microabscesses spreading along white matter tracts.

months. At discharge, the patient showed no further clinical improvement and remained in the comatose state under mandatory mechanical ventilation. The patient was transported to a post-acute care facility for the purpose of further antibiotic administration.

The differential diagnosis for this presentation was wide. It included infectious, primary autoimmune, and malignant etiologies. The group of infectious causes included central nervous system (CNS) toxoplasmosis, tuberculous encephalitis, viral meningoencephalitis, listeriosis, and brucellosis. None of these organisms were isolated. Malignant differential diagnoses included CNS lymphoma. No malignant cells were identified on CSF cytology and cerebral biopsy.

Discussion

Neuromelioidosis is a rare infection of the nervous system caused by *Burkholderia pseudomallei*. It accounts for approximately 3% of all melioidosis cases and is statistically associated with much higher morbidity and mortality rate. The transmission of melioidosis is by direct inoculation, inhalation, or ingestion (6). Our case demonstrates an additional mechanism of accessing the CNS *via* possible entry of the detected pathogen through an exposed mastoid bone defect. Extensive involvement of the brainstem in MRI imaging is common. This could be observed in our case, whose brain-MRI revealed bihemispheric distinctly right-sided accentuated FLAIR hyperintensities as well as rim-enhancing microabscesses spreading along white matter tracts predominantly in corticospinal tracts and cerebral peduncles (Figure 1). Bearing this typical pattern in mind, the rare disease might get diagnosed more often, and initiating therapy in early phases might save patients from persistent disability and death. However, whether the initial immunosuppressant therapy in our case was beneficial by limiting CNS immunoreaction or detrimental by weakening the antimicrobial response remains speculative. An additional frequent radiological feature of neuromelioidosis is thickening of trigeminal nerves, which could also be observed in the brain MRI scans of our patient. This radiological finding may contribute to the identification of the pathogen's entry mechanisms into the CNS potentially through direct axonal transport in cranial nerves (7). Our patient provided a diagnostic predicament as the initial clinical presentation, MRI and, negative cultures delayed the identification of the pathogen and thus the early initiation of appropriate antibiotic treatment. We present the first case of neuromelioidosis in Europe with a severe neurological outcome.

Conclusions

Neuromelioidosis presentation can mimic other inflammatory or infectious conditions. Bearing the typical MRI pattern with typical rim-enhancing microabscesses spreading along white mater tracts in mind, this rare disease might get diagnosed more often, and initiating therapy in early phases might save patients from persistent disability and death.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation

and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ND and MG: acquisition of the data and drafting of the manuscript. GF, SZ, and BT: acquisition and interpretation of the data. AA: acquisition of the data and revision of the manuscript. SGM and H-PH: revision of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Meningitis and intracranial aneurysm caused by mixed infection of oral microflora dominated by anaerobes

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Introduction: Meningitis caused by oral anaerobic bacteria is rare, especially when complicated with an infected intracranial aneurysm. This paper has described an extremely rare case of bacterial meningitis caused by a mixed infection of oral microflora dominated by anaerobes, which developed cerebral infarcts, brain abscess, intracranial aneurysm, and severe hydrocephalus during treatment.

Case report: We describe a 65-year-old male patient who was presented with fever and headache as the initial symptoms and then developed left ophthalmoplegia, right hemiplegia, and disturbance of consciousness. Brain imaging showed that intracranial lesions were increased progressively, and cerebral infarcts, brain abscesses, intracranial aneurysm, and severe hydrocephalus were appeared gradually. Eventually, we diagnosed it as anaerobic meningitis by making deoxyribonucleic acid sequencing from the brain abscess pus. After using an anti-microbial regimen that can sufficiently cover anaerobes, the patient's condition was effectively controlled.

Conclusion: Anaerobic meningitis can cause a series of intracranial complications. Among them, the intracranial aneurysm is extremely rare. When evidence shows that the infection originates from oral flora, physicians should consider the possibility of this type of encephalitis. An early diagnosis and timely treatment are crucial to improving the prognosis.

KEYWORDS

oral microflora, anaerobes, meningitis, intracranial aneurysm, case report

Introduction

The oral cavity harbors a diverse and abundant microflora. As part of the Human Microbiome Project, culture-independent molecular approaches have identified nearly 1,200 taxa of microbes in the human mouth (1). Under normal conditions, these organisms do not exhibit pathogenicity. However, in patients predisposed to infection

or immunocompromised, it may act as an infectious pathogen to cause a series of diseases, such as intracranial invasion and serial intracranial complications (2, 3). The oral anaerobes, such as Prevotella, Fusobacterium, Bacteroides, and Peptostreptococcus, have been regarded as the opportunistic pathogen (3). Abscesses, bacteremia, and bone infections are the most common clinical presentation (2, 4). However, meningitis is rare, especially when complicated with an infected intracranial aneurysm. In this paper, we reported an extremely rare case of bacterial meningitis caused by a mixed infection of oral microflora dominated by anaerobes, which developed cerebral infarcts, brain abscess, intracranial aneurysm, and severe hydrocephalus during treatment.

Case report

A 65-year-old male patient was admitted to the hospital because of fever and headache lasting for 5 days. The patient long had poor oral hygiene and 4 years ago, the patient underwent implantation of mandibular dentures. Fever usually occurred at noon and was generally under 38°C. In addition, the patient was presented with persistent heartburn, anorexia, asthenia, and night sweats. Blood routine examination revealed that the white blood cell (WBC) count was 12.08 $\times$ 10^9/L (normal range, 4–10 $\times$ 10^9/L) with neutrophil leukocytosis of 71.1%. No significant abnormality was found in the heart or lungs of the patient. Then the patient was admitted to the Department of Infectious Diseases.

On admission, physical examination showed poor mental status and subtle abduction limitation in the left eye without other neurological signs or symptoms. The patient underwent a lumbar puncture on the day of admission. Cerebrovascular fluid (CSF) showed a normal WBC count (4/μl, reference range 0–8/μl), mildly increased protein level (0.6 g/L, reference range 0.15–0.45 g/L), reduced chloride levels (114.6 mmol/L, reference range 118–132 mmol/L), and normal glucose levels (3.97 mmol/L, reference range 2.5–4.2 mmol/L; Table 1). Pre-antibiotic blood culture was taken with a negative result. Additional laboratory examinations, such as serology testing for HIV, hepatitis B/C, syphilis, rheumatic diseases, and tumor markers, were normal. Cranial magnetic resonance imaging (MRI) was normal (Figure 1A), and there was no evidence of intracranial aneurysm on brain magnetic resonance angiography (MRA; Figure 1B). The diagnosis of viral encephalitis was considered and treatment with intravenous acyclovir (10 mg/kg) was initiated and continued every 8 h. However, with frequent low fever, the illness was not well-controlled. Considering the likelihood of bacterial infections, ceftazidime (2 g every 12 h) was given on the third day of admission. On hospital day 7, the patient developed significant diplopia and weakness in the right upper extremity with a brain MRI showing acute multiple cerebral infarcts in the left cerebral hemisphere (Figures 1C,D). On the same day, the patient underwent a lumbar puncture once more, and the macroscopic appearance of the CSF was slightly yellow with a pressure of 190 mmH_2O (normal range, 80–180 mmH_2O). CSF results are shown in Table 1. The patient was diagnosed with intracranial infection and transferred to the Department of Neurology.

Neurological examination showed drowsiness, left abducens nerve palsy, degree 4 muscle strength in right upper limb, and neck rigidity (+). The culture of bacteria and mycobacterium tuberculosis and the detection of viral nucleic acid for retrovirus, herpes virus 1 and 2, rhinovirus, Epstein-Barr (EB) virus, and cytomegalovirus in CSF were negative. Additionally, the brucellosis agglutination test, Japanese encephalitis virus antibodies detection, T cell spot test for tuberculosis (T-SPOT), tuberculin test, and mycobacterium tuberculosis/rifampicin resistance test (X-pert) were also negative. Since our patient had such signs, the diagnosis of tuberculous meningitis was considered. The patient was administered an anti-tuberculous therapy that included isoniazid (0.6 g once daily), rifampicin (0.45 g once daily), ethambutol (0.75 g once daily), and pyrazinamide (0.5 g three times daily). In the following days, the body temperature returned to normal, but the patient still had intermittent headache. Compound codeine phosphate and ibuprofen sustained release tablet (0.2 g/13 mg two times daily) were added to control the headache. On hospital day 16, the patient developed frequent nausea and vomiting. The mental state of the patient also became very poor yet no fever, abdominal pain, or blurred vision were observed. Physical examinations, laboratory tests, and abdominal computed tomography (CT) scans could not reveal the cause of the patient's deterioration. We suggested that it might be the side effects of anti-tuberculosis drugs. Ondansetron (8 mg) and metoclopramide (10 mg) were intravenously utilized for anti-emesis. His gastrointestinal symptoms were improved. However, the mental state was getting even worse. On hospital day 25, the patient was presented with near-complete left oculomotor nerve palsy with blepharoptosis and dilated pupils on the left side. CSF results showed an increased WBC count (300 $\times$ 10^6/L) with 63% mononuclear cells (Table 1). Cranial CT revealed significantly increased low-density shadow in the left frontal, temporal, and parietal lobes (Figures 1E–G). As a result of the disease progression, the patient was transferred to a superior hospital.

Detailed neurological examinations and evaluations were performed on this patient again. The MRI (Figures 1H,I) and MRA (Figure 1J) re-examination demonstrated that the lesions in the left cerebral hemisphere were increased significantly, and a cerebral aneurysm was formed in the intracavernous segment of the left internal carotid artery (ICA). In addition, the sphenoid sinus mucosa was thickened. Taking the possibility of bacterial infection into consideration, the patient was treated with ceftriaxone (2 g every 12 h). On hospital day 28, the patient underwent a lumbar puncture examination again. CSF results

TABLE 1 Dynamic cerebrovascular fluid (CSF) analysis throughout hospitalization.

CSF-Variable	Day 1	Day 7	Day 25	Day 28	Day 58	Day 63
CSF opening pressure (cm of water)	17.5	19	12	13.5	22	13
General appearance	Colorless	Slightly yellow	Colorless	Colorless	Colorless	Colorless
White cell count (10^6/L)	4	238	300	50	80	8
Mononuclear cells percentage (%)	–	42	63	94	–	–
Protein (g/L)	0.6	1.27	1.33	0.76	2.01	0.32
Glucose (mmol/L)	3.97	3.18	3.58	2.94	2.01	4.01
Chloride (mmol/L)	114.6	114.8	120.7	114.9	113.7	119
Microbiological testing	–	–	–	–	–	–

are shown in Table 1. Metagenomic sequencing of viral and bacterial genomes from this patient's CSF sample was performed with a negative result. Unfortunately, the patient fell into a coma the following day and was admitted to the intensive care unit (ICU). Head MRI showed a markedly enlarged size of the left temporal lesions with abscess formation and bleeding, accompanied by peripheral ring-shaped enhancement (Figures 1K,L). Due to the patient's poor condition, the anti-infection regimen was adjusted to an intravenous drip of biapenem (0.3 g every 12 h) and vancomycin (1 g every 12 h). The patient was gradually recovered consciousness within the next 7 days. On hospital day 37, brain MRI showed a decreased size of the left temporal lesions but with perifocal evident edema (Figure 1M). To further clarify the nature of the intracranial lesions, the patient was transferred to the Neurosurgical Department to perform the needle biopsy with the assistance of real-time neuro-navigation on hospital day 38. The next day, this patient underwent the procedure, and the surgical specimen was sent for smear, culture, and deoxyribonucleic acid sequencing. According to the sequencing results, the patient was diagnosed with bacterial meningitis caused by a mixed infection of oral microflora dominated by anaerobes, such as *Fusobacterium nucleatum* (69.79% relative abundance), *Prevotella intermedia* (20.77% relative abundance), *Bacteroides uniformis* (1.35% relative abundance), *Campylobacter rectus* (1.26% relative abundance), *Oral peptostreptococcus* (0.08% relative abundance), *Streptococcus constellatus* (0.02% relative abundance), *Torque teno* virus 15, and *Treponema socranskii*. The anti-microbial regimen (biapenem combined with vancomycin), which could sufficiently cover anaerobe, was used continuously. For the poor oral hygiene, the patient received a detailed oral examination and nursing intervention. In the following days, the overall condition of the patient was significantly improved, but there was still a loss of appetite. However, the clinical symptoms worsened from the hospital day 53. The patient was presented with severe lethargy, headache, nausea, and vomiting. Repeat brain MRI showed that the lesions and edema of the left temporal lobe were improved, but hydrocephalus became even worse (Figures 1N,O). The patient was transferred to the Department of Neurosurgery of our hospital at the insistence of family of the patient on hospital day 58.

Neurological examination revealed consciousness disturbance with a Glasgow Coma Scale (GCS) of 9 (E2V2M5), right hemiplegia, left eyeball fixation, pupil dilation with ptosis on the left side, and stiffness in the neck. Cranial CT showed intraventricular extension and hydrocephalus (Figure 1P). We considered that the aggravation of this patient's disease might be related to the progressive hydrocephalus. Then, the patient underwent ventriculostomy on hospital day 59. The anti-infection therapy regimen previously described was changed to the combination of meropenem (2 g every 8 h) and linezolid (0.6 g every 12 h). The clinical symptoms of the patient were improved significantly, and the patient gradually regain consciousness. On hospital day 85, this patient underwent a ventriculoperitoneal shunt operation, and then the mental state of the patient improved further. On hospital day 97, when the patient was discharged, patient was able to walk with assistance and engage in simple conversation but showed a loss of appetite and significant weight loss.

In the 1-month follow-up, the patient could walk without the assistance of a cane or brace. However, severe neurological deficits, such as diplopia and right hemiplegia, still existed. To prevent disease recurrence, we suggested that the patient should maintain good oral hygiene and regular follow-up at the stomatology clinic. Because of the high risk of rupture and mortality of the patient's intracranial aneurysm, surgical treatment was advised. However, the patient refused further examination and treatment for financial reasons. Regular follow-ups will be carried out for our patients. The clinical course is summarized in Figure 2.

Discussion

Adult bacterial meningitis (ABM) caused by anaerobic bacteria infection is a rare condition and is often overlooked or under-diagnosed (5–7). The clinical outcome is usually more severe. With mastoiditis and acute or chronic otitis

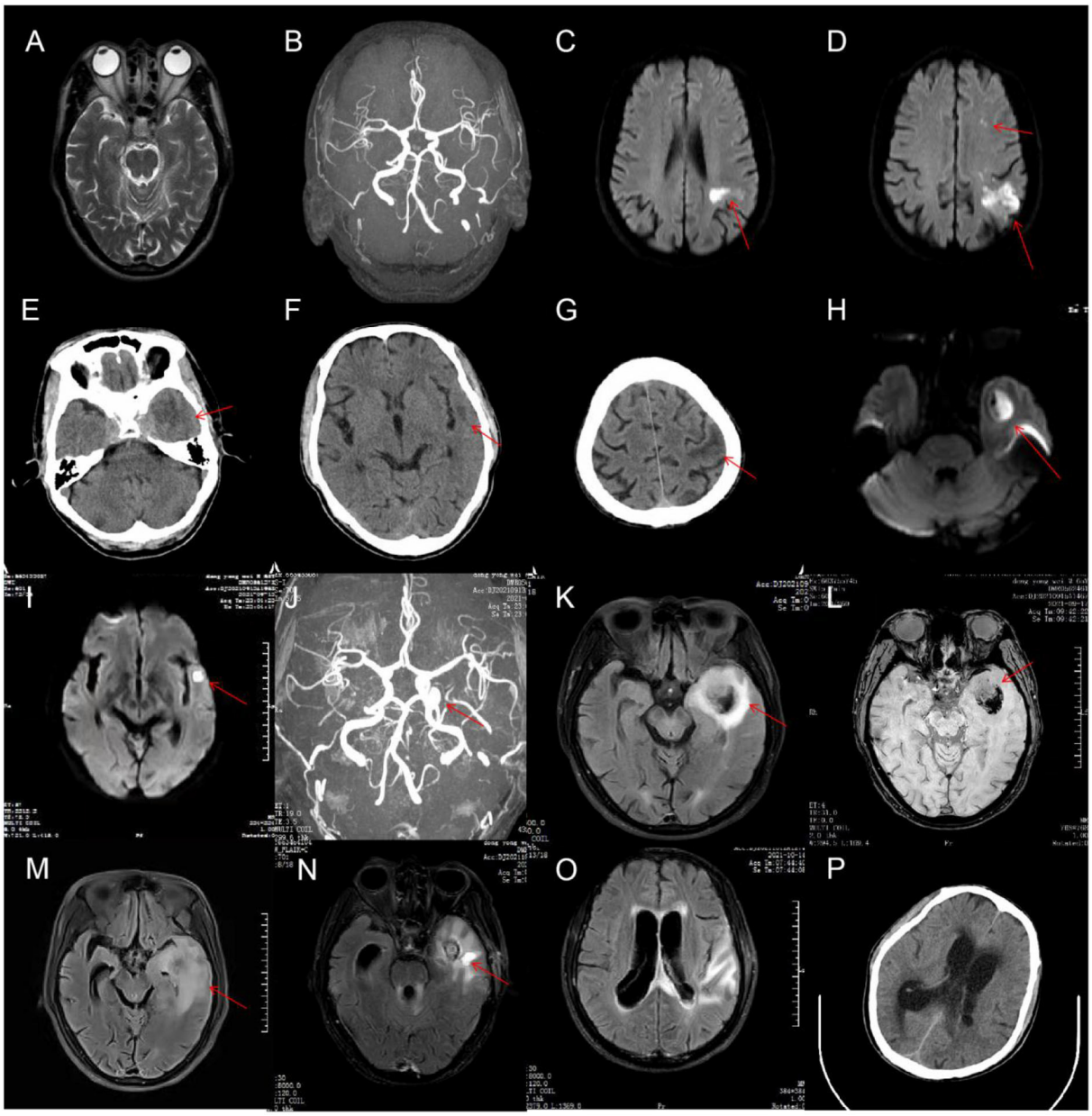

FIGURE 1
On admission, cranial magnetic resonance imaging (MRI) of the patient was normal **(A)**, and there was no evidence of intracranial aneurysm on brain magnetic resonance angiography (MRA) **(B)**. On hospital day 7, a brain MRI was done again and showed acute multiple cerebral infarcts in the left cerebral hemisphere **(C,D)**. On hospital day 25, cranial CT revealed significantly increased low-density shadow in the left frontal, temporal, and parietal lobes **(E–G)**. The MRI **(H,I)** and MRA **(J)** re-examination demonstrated that the lesions in the left cerebral hemisphere were increased significantly, and a cerebral aneurysm formed in the intracavernous segment of the left internal carotid artery (ICA). On hospital day 29, a repeat head MRI showed markedly enlarged size of the left temporal lesions with abscess formation and bleeding **(K,L)**. On hospital day 37, brain MRI showed a decreased size of the left temporal lesions but with perifocal evident edema **(M)**. On hospital day 55, a repeat head MRI showed that the lesions and edema of the left temporal lobe was improved, but hydrocephalus became even worse **(N,O)**. On hospital day 58, cranial CT showed intraventricular extension and hydrocephalus **(P)**.

media being the most common triggers, other triggers include oropharyngeal infection, sinusitis, craniotomy, poor oral hygiene, head trauma, tumors of the head and neck regions, and sacrococcygeal dermal sinus (2, 8–16). Our patient was presented with fever and headache as the initial symptoms and then developed left ophthalmoplegia, right hemiplegia, and disturbance of consciousness. Brain imaging showed that cerebral infarcts, brain abscesses, intracranial aneurysm, and

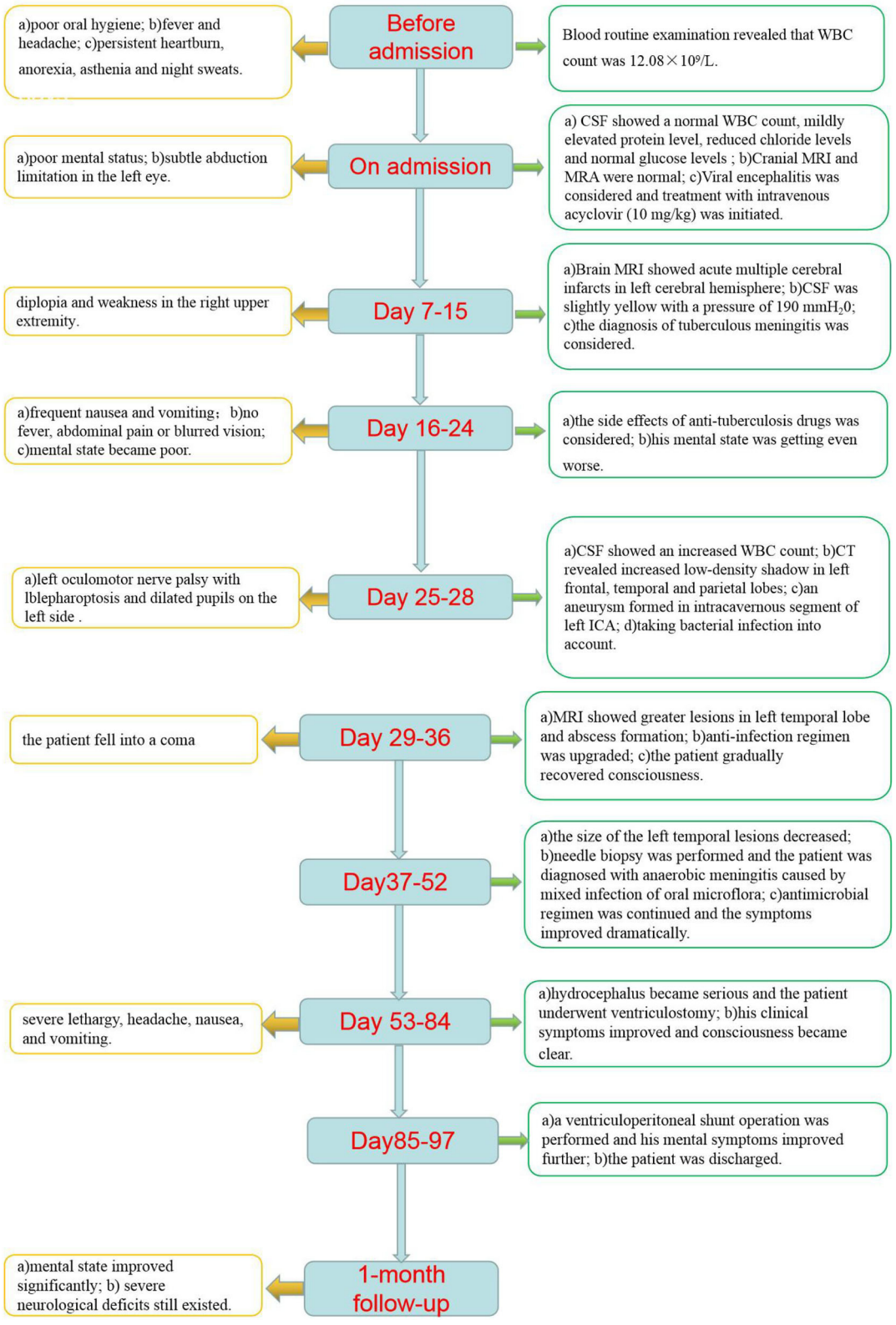

FIGURE 2
Clinical course of the case.

severe hydrocephalus were appeared gradually. CSF showed a significantly increased WBC count. Eventually, the diagnosis of anaerobic meningitis was made by deoxyribonucleic acid sequencing from the brain abscess pus. According to the sequencing results, this was a mixed infection of various oral microorganisms, mostly anaerobic bacteria. These bacteria are commonly found in the mucosal surfaces of the mouth and upper respiratory tract. As our patient long had poor oral hygiene, we speculated that chronic oral inflammations might be the predisposing factor of anaerobic meningitis in this patient. Oral flora can theoretically enter the brain through the following ways (3): (a) systemic hematogenous bacteremia; (b) direct venous drainage *via* the two main venous networks leading to the cavernous sinus, the facial, and the pterygoid vein systems; (c) inoculation *via* contiguous extension or by the introduction of foreign objects; and (d) lymphatic drainage. Our patient had no symptoms of bacteremia, the results of blood cultures and echocardiography were all negative. The D-dimer test was within normal ranges. Brain imaging showed that intracranial lesions, such as cerebral infarcts, brain abscess, and intracranial aneurysm, were all on the left side of the cerebral hemisphere. Based on this, we excluded systemic hematogenous bacteremia diagnosis. Although cranial imaging showed sphenoid sinusitis, we saw no evidence of osseous destruction. From the considerations above, we thought that the most likely route of infection in our patient was hematogenous dissemination *via* venous pathways. The spread of bacteria through the blood led to the left cavernous sinus involvement, which resulted in near-complete left oculomotor nerve palsy with blepharoptosis and dilated pupils on the left side (palsy of the oculomotor, trochlear, or abducens cranial nerves). A possible explanation for why all the intracranial lesions occurred in the left cerebral hemisphere was that the left implantation of mandibular dentures could increase the probability of the destruction of the anatomical barrier of the left oral mucosa.

Bacterial aneurysms, also known as infective or microbial aneurysms, are rare inflammatory neurovascular lesions that account for 0.7–6.5% of all intracranial aneurysms (17, 18), most of which are secondary to infectious endocarditis (19–21). They often exhibited multiple lesions, hemorrhagic presentation, and septic cerebral embolism (22–24). Among these, septic embolism was likely the cause of multiple cerebral infarcts in our patient. Currently, there are two hypotheses that explain the pathogenesis of bacterial aneurysms that include the vasa vasorum hypothesis or embolic (25–28). The former is the most widely accepted mechanism of pathogenesis. It proposes that bacteria from septic emboli escape through the vasa vasorum and cause severe inflammation of the adventitia. The infection then spreads inwardly. The arterial pulsation against the weakened vessel wall eventually results in aneurysm formation and enlargement. The embolic hypothesis posits the centrifugal spread of inflammation and proposes that septic emboli occlude the arterial lumen and that destruction spreads outward from the intima to the adventitia (28). During the initial admission, there were no intracranial aneurysms observed on cranial MRA for our patient. With the progression of the disease, a cerebral aneurysm of the intracavernous segment in the left ICA was discovered on hospital day 25. We considered that this aneurysm was occurred according to the vasa vasorum theory *via* cavernous sinus phlebitis. The possible mechanisms of oral pathogens affecting inflammatory remodeling in the wall of the intracranial aneurysm are macrophage infiltration, activation of toll-like receptors by lipopolysaccharide (LPS), activation of the complement system, endothelial dysfunction, and so on (29). So far, bacterial intracranial aneurysms caused by oral anaerobes are very rare. At present, only two cases were reported. Park et al. (9) reported a case of intracranial mycotic aneurysm caused by *P. intermedia* associated with chronic sinusitis and successfully identified the bacteria by 16S rRNA sequencing. In Kyoya's case (30), a 62-year-old man displayed multiple infectious intracranial aneurysms, intracerebral hemorrhage, and epistaxis after tooth extraction. By culturing the aspirate of the abscess, the pathogenic bacterium was ultimately identified as oral bacteria, such as Gram-negative anaerobic rods (*Fusobacterium sp.*) and Gram-positive anaerobic cocci (*Parvimonas micra*). Combined with appropriate anti-infective treatment and surgical intervention, the patient finally achieved a good result. A previous study found that earlier and adequate antibiotic therapy may have increased the chance of improved aneurysmal outcomes (31). The aneurysms with a high risk of rupture, such as saccular morphology, may correlate with unfavorable aneurysmal outcomes, which need to be treated more aggressively than with antibiotics alone (31, 32). After effective anti-anaerobes treatment, there was no further enlargement or rupture of the intracranial aneurysm in our patient based on the subsequent re-examination. However, the patient refused further surgical intervention for financial reasons.

According to the sequencing results from the brain abscess pus, anaerobes associated with intracranial infection in our patient included *F. nucleatum*, *P. intermedia*, *B. uniformis*, and *O. peptostreptococcus*. *F. nucleatum* is a Gram-negative anaerobic bacillus with species-specific reservoirs in the human mouth, gastrointestinal tract, and elsewhere. According to some studies, this bacterial is associated with meningitis or related complications that include acute cerebral infarction, brain abscess, cerebral sinus vein thrombosis (CSVT), and hydrocephalus (5, 33, 34). *F. nucleatum* is often found to be involved in polymicrobial infections (4). In a case series of five Fusobacterial brain abscesses, only one patient had a monomicrobic *F. necrophorum* infection, whereas all others had polymicrobic infections involving *F. nucleatum* (35). The authors suggested that the less virulent *F. nucleatum* requires synergy from other organisms (35). Prevotella is the second most abundant genus. Several studies have reported that Prevotella was associated with meningitis and was involved in

the formation of brain abscesses (3, 5, 9). In Mo's case, a 48-year-old man, with mixed infections caused by *P. intermedia* and *S. constellatus*, presented a large area of ischemic infarction and ultimately abandoned the treatment due to a worsening condition (36). *B. uniformis* is also a strict anaerobe, Gram-negative bacillus, and part of the normal oral cavity and gastrointestinal flora. Maj et al. (37) found that this bacterium was involved in the formation of brain abscesses as part of a mixed infection of multiple microorganisms. Moreover, some case reports or case series showed that *O. peptostreptococcus* was associated with intracranial infection or related complications (3). In the initial stage of the disease, although Ceftazidime was used to treat bacterial infections, a pitfall of this regimen was the incomplete coverage of the above anaerobes, which led to the fast progression of infection. After using a combination of biapenem and vancomycin, the patient's infection was effectively controlled. Currently, there is no consensus as to the best regimen for the anti-infection treatment of anaerobic meningitis, further study is still in need. The timely use of broad-spectrum antibiotics covering above different anaerobic flora is essential to improving the prognosis of the disease. The sensitivity and resistance to the drug and the difference in blood-brain barrier penetration of the anaerobic bacteria species should be considered comprehensively when selecting an appropriate antibiotic. Especially, when there is evidence that the infection may originate from oral flora, physicians should strongly consider requesting anaerobic culture and altering patient treatment to one that includes anaerobic anti-microbial coverage.

Anaerobic bacteria are usually difficult to detect, especially after the initiation of anti-microbial therapy (7). Alternatively, clinicians rarely use a scheduled specific anaerobic bacteria culture of CSF specimens in clinical practice (7, 38). All these factors made the diagnosis of anaerobic meningitis very difficult. When culture methods fail to yield an etiological answer, further microbiological evaluation is justified. Suitable molecular biologic approaches, such as high-throughput sequencing, may help to provide a diagnosis.

Conclusion

In summary, anaerobic meningitis caused by a mixed infection of oral microflora is rare, especially when complicated with an infected intracranial aneurysm, which is usually associated with underlying causes. This report illustrates the importance of considering oral anaerobes as a cause of meningitis and intracranial aneurysm. It underlines the usefulness of molecular techniques in the diagnosis of infections with anaerobic bacteria and the importance of early intervention for a good prognosis.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Jincheng People's Hospital Affiliated to Shanxi Medical University, Jincheng, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LJ and LX put forward research ideas. FY and CL took the responsibility of communicating with the patient's family and obtaining the authorization in this paper. HC and DZ responsible for drafting articles. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Multifocal brain abscesses caused by invasive *Streptococcus intermedia*: A case report

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Multifocal brain abscesses caused by invasive *Streptococcus intermedia* are relatively rare. Here, we present a 67-year-old male was admitted to the hospital for unconsciousness and fever. The computed tomography (CT) examination showed multiple intracranial space-occupying and "cavity-like" changes in the right lower lung. The examination of cerebrospinal fluid (CSF) was consistent with typical bacterial meningitis, CSF analyses revealed leukocytosis (10,300 $\times$ 10^6/L), elevated protein levels (140.39 mg/dL), decreased glucose levels (0.27 mmol/L), and normal chloride concentration level (120.2 mmol/L), however, pathogens were not detected in the cultures. Then, the CSF and sputum samples were analyzed using meta-genomic next-generation sequencing (mNGS), and *S. intermedia* was detected in both samples. We adjusted the use of antibiotics according to the results of mNGS in time. After anti-infective treatment, the patient achieved good treatment results in a very short time. This case highlights the mNGS can identify pathogens of brain abscess, and provide strong evidence for clinical diagnosis and treatment strategy.

KEYWORDS

multiple brain abscesses, *Streptococcus intermedia*, meta-genomic next-generation sequencing, case report, cerebrospinal fluid

Introduction

Brain abscess is often a localized brain infection caused by the spread of nearby infections, such as otitis, mastoiditis, sinusitis, neurosurgery or traumatic brain injury, and blood spread (1). It has a prevalence of ~0.9 per 10,000 people per year, with a 1-year mortality rate of ~20%. Common clinical symptoms of brain abscess include headache, fever, vomiting, cramps, and focal neurological deficits (2).

S. intermedia exists mainly exists in the human oral cavity, throat, and gastrointestinal tract. *S. intermedius* can cause gingival abscess and aspiration pneumonia, leading to sepsis, endocarditis, and lung abscesses. *S. intermedia* has been reported to cause brain abscesses and often coexist with anaerobic bacteria (3, 4). Herein, we present a case of multifocal brain abscess that showed the diagnosis and treatment of the patient.

Case presentation

A 67-year-old male was admitted to our hospital due to unconsciousness and fever. The patient had fever symptoms 3 days before admission, the highest temperature was 39.6°C, and no special treatment was given. The patient had a history of drunkenness and aspiration 1 week before admission. One day before admission, the patient suddenly lost consciousness with quadriplegia. Physical examination: the patient was in a deep coma; the diameter of the bilateral pupils was 2 mm; the Glasgow score was E1V1M3; and the muscle strength of the limbs was grade 2. Blood analyses revealed evidence of leukocytosis (33.6 $\times$ 10^9/L) and elevated C-reactive protein (CRP) levels (199.80 mg/L), neutrophils percentage (93.80%), and procalcitonin range (1.58 ng/ml). Head computed tomography (CT) showed multiple intracranial space-occupying edema, and chest CT showed a right upper lobe space occupying the cavity. Brain magnetic resonance imaging (MRI) showed multiple divergent intracranial abscesses, which were low signal on the T1 weighted image and high signal on the T2 weighted image and were significantly enhanced. On the day of admission, the patient had difficulty breathing and was given mechanical ventilation with tracheal intubation (Figure 1). On day 3, a tracheotomy was performed. The patient had no history of tuberculosis, sputum tuberculosis and tuberculosis infection T cell detection was negative.

To determine the patient's intracranial infection, we performed a lumbar puncture on the third day after admission. Cerebrospinal fluid (CSF) analyses revealed leukocytosis (10,300 $\times$ 10^6/L), elevated protein levels (140.39 mg/dL),

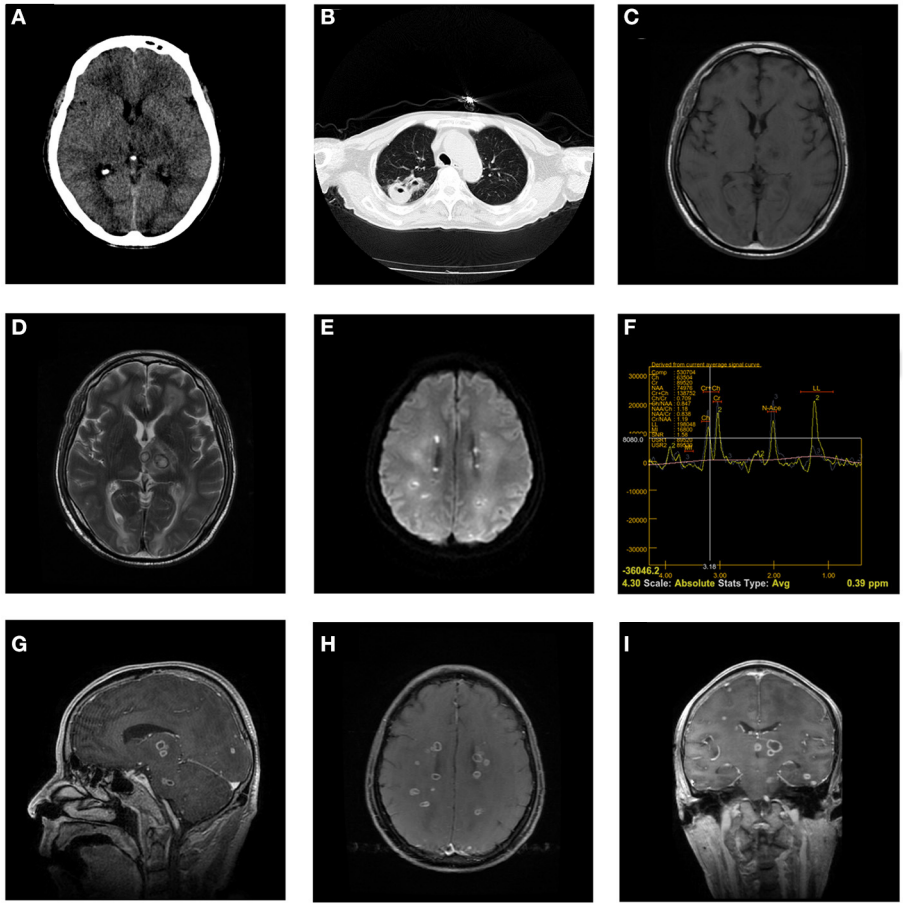

FIGURE 1
Head CT on admission shows multiple annular nodules in the left thalamus, and the edema is obvious **(A)**. The chest CT shows a space-occupying lesion in the cavity in the upper lobe of the right lung **(B)**. The head MRI on May 12 showed that scattered multiple signals can be seen in the bilateral cerebral hemispheres, thalamus, and brainstem, which were low signal on the T1 weighted image and high signal on the T2 weighted image and diffusion-weighted imaging **(C–E)**. Magnetic Resonance Spectroscopy (left thalamus) showed that the Cho peak, Cr peak, and NAA peak decreased, the Cho/Cr ratio was 0.709, the Cho/NAA ratio was 0.847, and the LL peak increased significantly **(F)**. Brain abscess was significantly enhanced **(G–I)**.

TABLE 1 List of macro genomic pathogens detected in alveolar lavage fluid and cerebrospinal fluid (CSF) samples on 5 days after admission.

Sample	Gram staining	Genera	Sequence number	Species	Sequence number	Relative abundance (%)	Coverage (%)
Alveolar lavage fluid	G^-	Burkholderia	15,266	*Burkholderia cenocepacia*	1,295	3.72	16.42
	G^+	Streptococcus	63,514	*Streptococcus intermedius*	10	0.0288	1.64
	G^-	Pseudomonas	37	*Pseudomonas aeruginosa*	8	0.0230	0.0689
CSF	G^+	Streptococcus	49	*Streptococcus intermedius*	24	39.34	0.19

TABLE 2 List of macro genomic pathogens detected in cerebrospinal fluid (CSF) samples at 4 weeks after admission.

Sample	Gram staining	Genera	Sequence number	Species	Sequence number	Relative abundance (%)	Coverage (%)
CSF	G^+	Streptococcus	11	*Streptococcus intermedius*	5	5.62	0.0403

decreased glucose levels (0.27 mmol/L), and normal chloride concentration level (120.2 mmol/L). However, pathogens were not detected in the cultures, and Gram staining assays were prepared from CSF, sputum, and blood samples. We used vancomycin (2 g every 12 h, ivgtt) combined with meropenem (1 g every 8 h, ivgtt) and ornidazole (0.5 g every 12 h, ivgtt) as an empirical anti-infection treatment. We used mNGS to identify pathogens in CSF and alveolar lavage fluid on 5th day after admission (Table 1). We stopped vancomycin and meropenem, then switched to ceftriaxone (2 g every 24 h, ivgtt) combined with amikacin (0.4 g every 12 h, ivgtt) for anti-infection treatment.

The patient's consciousness and limb muscle strength gradually improved during the subsequent treatment. Two weeks after admission, the patient's body temperature was normal, and no more than 39°C. Celsius Routine blood leukocyte count, neutrophil ratio, and procalcitonin levels decreased gradually to normal levels. We performed lumbar puncture during hospitalization at the third week after admission, which showed that the patient's intracranial pressure was 180 mmH_2O and the color of the CSF was light blood and clear; CSF analyses showed normal leukocyte count (15 × 10^6/L), elevated protein levels (72.3 mg/dL), and normal glucose levels (4.37 mmol/L) and chloride concentration level (119 mmol/L). We then sequenced the CSF again at 4 weeks after admission, suggesting that *S. intermedia* could still be detected, but its relative abundance decreased from 39.34 to 5.62% (Table 2). We continued to use ceftriaxone in the treatment of intracranial infection until the patient's body temperature was normal for 2 weeks, we stopped all antibiotics at 6 weeks after admission (Table 3).

After 8 weeks, the patient's consciousness became clear, and the muscle strength of the limbs recovered to grade 4. CT showed that the size of the lesion and the degree of edema improved significantly, the patient's upper right pneumonia was better than before, and the patient was discharged at the 10 weeks after admission (Table 3). The 3-month follow-up head MRI showed that the brain abscess had basically disappeared (Figure 2).

TABLE 3 Timeline.

3 days before admission	Presented with fever symptoms, no treatment was given.
1 days before admission	Lost consciousness with quadriplegia
The day of admission	Tracheal intubation
	Improve laboratory examinations
	Vancomycin combined with meropenem and ornidazole as an empirical anti-infection treatment
3 days after admission	Lumbar puncture: CSF leukocyte count was 10,300 × 10^6/L
	Tracheotomy was performed
4 days after admission	T-SPOT was negative
5 days after admission	The mNGS was used to in CSF and alveolar lavage fluid
7 days after admission	Changed antibiotics
2 weeks after admission	Fever symptoms improved
3 weeks after admission	Lumbar puncture: CSF leukocyte count was 15 × 10^6/L
4 weeks after admission	The mNGS was used to in CSF again, relative abundance decreased
6 weeks after admission	Stopped antibiotics, and moved out of ICU
8 weeks after admission	The patient's consciousness became clear
10 weeks after admission	Discharged

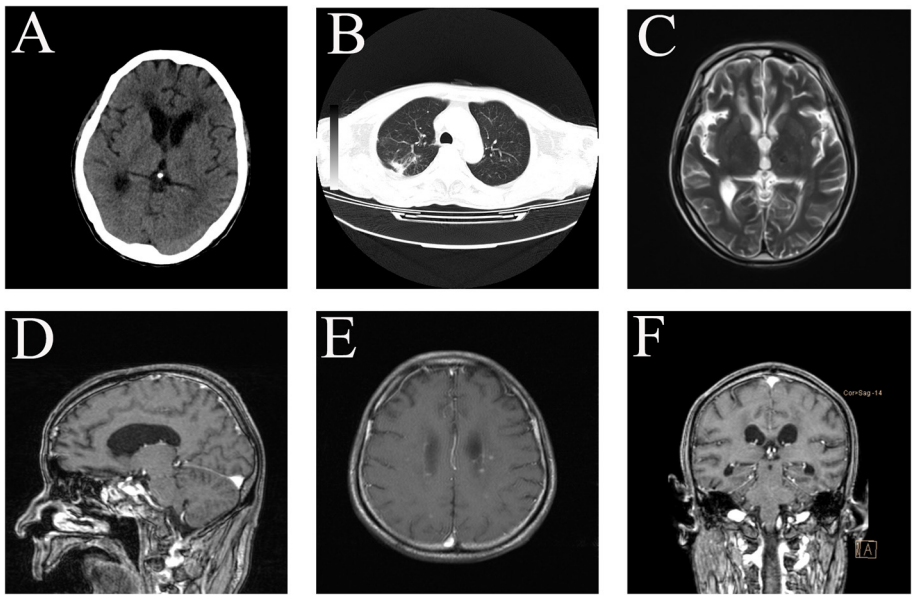

FIGURE 2
CT after 2 months of treatment. The size of the lesion and the degree of edema improved significantly **(A)**. The patient's upper right pneumonia is better than before **(B)**. The patient MRI in August 2021 showed that the abscess was significantly absorbed and improved **(C–F)**.

Discussion

Multiple intracranial lesions accompanied by cavitation changes in the lungs need to rule out lung cancer brain metastases and tuberculous brain abscesses. The main symptom of the patient was high fever. Combined with the patient's laboratory examination, the first consideration was inflammatory disease. Tuberculous brain abscesses and bacterial brain abscesses have similar clinical and conventional MRI findings, both manifest as ring-enhancing cystic space-occupying lesions, which require further differential diagnosis with the help of clinical manifestations, biopsy, pathology, etc (5). Combined with the patient's medical history, laboratory examination, and imaging examination, we considered that the patient had a bacterial brain abscess.

Regarding the choice of the treatment plan for brain abscess, it is necessary to comprehensively evaluate the patient's clinical status and abscess. In this case, most of the intracranial lesions were divergent, and most of the abscesses were <1 cm in diameter, most of which were in the functional area of the brain, and a stereotactic puncture and craniotomy could not be performed. Therefore, it is important to choose a targeted drug treatment.

According to the overall etiological characteristics of intracranial infection in recent years, the distribution is slightly different in different regions and years. The etiology of brain abscesses is still dominated by positive bacteria, and the most common pathogens are *Streptococcus* and *Staphylococcus*. In a retrospective study, 332 patients with brain abscess with positive cultures were counted, and it was found that the most common bacteria were *Streptococcus*, *Staphylococcus*, and *Proteus* (6).

The positive rate of bacteriological culture in patients with brain abscesses was low. In a 10-year retrospective study, the study found that only 34 cases were positive in pus culture, accounting for 25.76% of the total number of confirmed patients (7). Empirical antimicrobial therapy recommended vancomycin combined with cephalosporins or carbapenems against *Pseudomonas*. However, it should be noted that long-term use of vancomycin and meropenem may cause complications such as neutropenia and imbalance in the bacterial population. The current view is that mNGS has certain advantages over traditional methods in central nervous system infection, improves the positive rate, and shortens the time of diagnosis (8, 9). In this case, *Burkholderia cepacia*, *S. intermedia*, and *Pseudomonas aeruginosa* were detected in alveolar lavage fluid samples from patient with mNGS, and *S. intermedia* was detected in patient CSF samples. The relative abundance of *Burkholderia cepacia* in bronchoalveolar lavage was higher than in *S. intermedia*. However, *S. intermedia* was detected in the CSF and alveolar lavage fluid, so we determined that *S. intermedia* may be the pathogen, and *Burkholderia cepacia* may be the hospital-acquired infectious bacteria.

Bacteria can invade the brain through direct dissemination or hematogenous dissemination, direct dissemination accounts for 20–60% of intracranial infections, bacteremic dissemination usually causes multiple lesions (1, 10). *S. intermedia* is part of the normal microbiota and are found at various mucosal sites in the respiratory (11). Brain abscesses are frequently caused by oral cavity bacteria (12). The patient had a history of drunkenness and aspiration 1 week before admission. We speculate that the patient's pneumonia due to aspiration, and the *S. intermedia* entered the patient's brain through blood dissemination, resulting in multiple brain abscesses in the patient.

A review of brain abscesses caused by invasive *Streptococcus intermedia* pointed out that most commonly prescribed antibiotic regimens were a combination of ceftriaxone and metronidazole alone (11). Therefore, we stopped vancomycin and meropenem, and switched to ceftriaxone combined with amikacin (Anti-pulmonary infection) for anti-infection treatment.

According to meta-analysis and retrospective study, more central nervous system infections can be correctly treated by mNGS (13–15). Currently, the application of mNGS in central nervous system infections is mainly based on case reports, and there are few large-scale studies to be referred to (16–18).

In summary, we report a patient with multifocal brain abscesses caused by *S. intermedia*; the patient had multiple failed cultures of pathogens from the patient's blood and CSF samples, and the mNGS analysis approach was used, we adjusted the use of antibiotics in time, and finally, the patient achieved good treatment results in a very short time.

Conclusions

mNGS has certain advantages in identifying brain abscesses; it can effectively avoid delaying the diagnosis and treatment of patients due to the lack of pathogens in routine culture. We believe that mNGS will provide greater help to neurosurgeons in their future work.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Wannan Medical College (Yijishan Hospital). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the patient's legal representative for the publication of any potentially identifiable images or data included in this article.

Author contributions

SC and ZY participated in the collection of data and drafted the manuscript. LY collected the data for case presentation. TY reviewed the literature and participated in its design. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Central nervous system infection caused by *Mycobacterium houstonense*: A case report

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Background: *Mycobacterium houstonense* is a rapidly growing mycobacterium (RGM) that belongs to the unnamed third biovariant complex of the *Mycobacterium fortuitum* group, which is rarely responsible for human infection. Approximately 76% of infections caused by the *M. fortuitum* group occur after open fractures or skin, soft tissue, bone, or puncture wounds. To date, only a few cases of human infectious disease caused by *M. houstonense* have been reported worldwide.

Case presentation: We present a case of a 26-year-old man with a central nervous system (CNS) infection caused by *M. houstonense*. The patient was transferred to our hospital because of headaches and muscle strength changes. One month prior to presentation at our hospital, the patient was diagnosed with tuberculous meningitis at the other two hospitals, but his condition did not improve after anti-tuberculous treatment, antibiotics, and anti-viral treatment before admission to our hospital. Lumbar puncture was performed at both previous hospitals, as well as at our hospital; the results consistently indicated high cerebrospinal fluid (CSF) opening pressure. *M. houstonense* was detected in the CSF of the second hospital's lumbar puncture by metagenomic next-generation sequencing (mNGS) but was not identified at our hospital. The patient was discharged from our hospital after receiving non-tuberculous mycobacterium (NTM) treatment for 1 month according to the Chinese NTM guidelines. However, the patient died 20 days after discharge.

Conclusion: Since it is difficult to identify *M. houstonense*, this is the first case of human CNS infection caused by *M. houstonense* in China. This case may be considered by neurologists and infectious physicians when CNS infection does not respond to conventional treatment, especially in the uncommon type of NTM.

KEYWORDS

***Mycobacteria houstonense*, *Mycobacterium fortuitum* group, rapidly growing mycobacteria, central nervous system infection, next generation sequencing**

Introduction

Mycobacteria houstonense is an acid-fast, gram-positive, sorbitol-positive, pleomorphic bacillus. Long filamentous forms are often observed, but the organisms have no spores or capsules (1). Rapidly growing mycobacteria (RGM) account for half of the known mycobacterial species and are divided into six major groups, including *Mycobacterium fortuitum* group, *Mycobacteria chelonae/Mycobacteria abscessus* complex, *Mycobacteria smegmatis* group, *Mycobacteria mucogenicum* group, *Mycobacteria mageritense/Mycobacteria wolinskyi* complex, and pigmented RGM (2). Members of the *M. fortuitum* group can cause disease in fish and other animals including humans. This group includes *M. fortuitum*, *Mycobacteria peregrinum*, and the unnamed third biovariant complex (*Mycobacteria senegalense*, *Mycobacteria porcinum*, *Mycobacteria houstonense*, *Mycobacteria neworleansense*, *Mycobacteria boenickei*, *Mycobacteria conceptionense*, *Mycobacteria septicum*, and *Mycobacteria alvei*) (3, 4). Here, we report a case of central nervous system (CNS) infection in China. *M. houstonense* was first isolated from the facial wound of a patient who lived in Houston, Texas, that's how *M. houstonense* got its name (1). To the best of our knowledge, this is the first report of human CNS infection caused by *M. houstonense* in China.

Case presentation

A 26-year-old man was transferred to our hospital with complaints of dizziness, headache, insomnia for 1 month, and exacerbated limb weakness for half a month. One month ago, the patient first presented to the local hospital for these symptoms. Enhanced MRI of the brain showed a negative result while enhanced MRI of the cervical spine showed slight thickening of the cervical spinal cord. Upon lumbar puncture, the opening pressure was found to be more than 330 mmH_2O and the cerebrospinal fluid (CSF) was transparent yellow, with a glucose (GLU) level of 3.8 mmol/L (reference range, 2.5–4.4 mmol/L), a microprotein level of 3.4 g/L (reference range, 0.15–0.45 g/L), and a chloride ion level of 112 mmol/L(reference range, 120–130 mmol/L). There were 50 nucleated cells per μl (reference range, 0–10), of which 95% were monocytes and 5% were coenocytes (Table 1). Considering the results of the CSF analysis (mononuclear-predominant CSF pleocytosis and a high protein level), the high open pressure, symptoms of intracranial hypertension, the inflammatory lesion on MRI findings, and the high incidence of tuberculosis in China [age-standardized incidence of tuberculosis, 54.18 per 100,000 population from 1990 to 2007 (5)], the patient was initially diagnosed with tuberculous meningitis and myelitis. He then received empirical antituberculosis therapy (a standard four-drug regimen of isoniazid, linezolid, moxifloxacin, and tigecycline). However, empirical treatment with anti-tuberculous drugs, antibiotics, antiviral drugs, and drugs to reduce the intracranial pressure (Figure 4), did not improve his condition. Thereafter, the patient was transferred to another hospital and, a lumbar puncture was repeated, the opening pressure was more than 330 mmH_2O. The CSF was slightly yellow, with a GLU level of 5.35 mmol/L (reference range, 2.5–4.4 mmol/L), a microprotein level of 5.179 g/L (reference range, 0.08–0.43 g/L), a chloride ion level of 106.5 mmol/L (reference range, 120–130 mmol/L), there were 129 nucleated cells per microliter (reference range, 0–10), of which 94% were monocytes and 6% multinucleated cells (Table 1). The acid-fast staining, mycobacterium culture, Xpert MTB, and RT-PCR of the CSF samples were negative. *M. houstonense* was identified in the CSF by metagenomic next-generation sequencing (mNGS) in a company for gene sequencing named Smicere Diagnostics and the report is attached as a Supplementary material 1 which showed the reads of 264 (Supplementary material 1). The pathogen's data were aligned to the National Center for Biotechnology Information GenBank database and revealed sequence homology above 96.825 and 97.183% with *M. houstonense* (GenBank accession no. NZ_LT546208.1 and no. NZ_LT546207.1), respectively (Supplementary material 2). After 7 days, the CSF sample pathogen cultures in blood agar at 35°C from another lumbar puncture were negative. Despite empirical treatments with anti-tuberculous drugs (isoniazid, linezolid, moxifloxacin, and tigecycline) which are the same treatment in the previous hospital due to insufficient course (Figure 4), the patient's condition worsened (decreasing myodynamia of limbs and endorsed racing thoughts) and he was transferred to our hospital. This patient did not have any underlying diseases or past medical history, and he was employed in the field of information technology.

After being admitted to our hospital, the patient's neurological examination showed the myodynamia of the left limb was grade 2, the right upper limb was grade 4, and less than grade 4. The muscle tension on the left side was decreased and that on the right side was normal. Poor abduction of the eyes and tongue deviation to the left was observed. The symmetry of the tendon reflexes in the extremities was weakened, and the craniocervical flexion test and bilateral Kerning sign were positive. The finger-to-nose test, heel-knee-shin test, Romberg test, and other ataxic tests could not be performed. The laboratory tests showed that there were 6.11×10^9 erythrocytes per L, 312×10^9 platelets per L, and 23.11×10^9 leukocytes per L, of which 93.4% were neutrophils. His blood biochemistry was normal except for the raised glutamic-pyruvic transaminase level of 201 IU/ L (reference range, <40 IU/L) and glutamic oxalacetic transaminase of 53 IU/L (reference range, <35 international IU/L), and a mild reduced albumin level of 34.7 g/L (reference range, 40–55 g/L). His inflammatory biomarkers showed an elevated procalcitonin level of 4.03 n/ml (reference range, <0.046 ng/ml), C-reaction protein level of 15 mg/L (reference range, <5 mg/L), interleukin-6 level of 5.81 pg per ml (reference range, 0–7 pg per ml). His HIV antibody test was

TABLE 1 CSF findings.

Variable	Referrence range, The first hospital	The first hospital	Referrence range, The second hospital	The second hospital			Referrence range, Our hospital	Our hospital					
Date		Dec 25, 2021		Dec 29, 2021	Jan 5, 2022	Jan 12,2022		Jan 14, 2022	Jan 21, 2022	Jan 24, 2022	Jan 28, 2022	Feb 7, 2022	Feb 14, 2022
Opening pressure (mmH_2O)	80–180	>330	80–180	>330	>330	>330	80–180	150	>330	>330	>330	>330	>330
Appearance		Yellow		Light yellow	Light yellow	Light yellow		Yellow, slightly turbid	Light yellow, transparent	Light yellow, transparent	Light yellow, transparent	Yellow, transparent	Colorless, transparent
Nucleated cell count(cells/ul)	0–10	50		129	69	44	0–10	10	18	18	16	70	45
Proportion of mononuclear (%)		95		94	95	91		NA	NA	NA	NA	94	96
Microprotein (g/L)	0.15–0.45	3.400	0.08–0.43	5.179	4.964	4.827	0.15–0.45	11.480	9.160	7.740	6.560	6.500	7.150
CSF glucose (mmol/L)	2.5–4.4	3.80	2.5–4.4	5.35	3.53	4.26	2.5–4.4	5.04	4.05	4.24	4.41	2.74	4.24
Synchronous blood glucose (mmol/L)	3.9–5.9	NA	3.9–6.1	NA	NA	NA	3.9–5.9	8.42	5.51	6.37	7.00	5.57	8.72
CSF chloride ion (mmol/L)	120–130	112	120–130	106.5	107.5	96.8	120–130	108	104	101	110	112	105
Synchronous blood chloride ion (mmol/L)	99–110	NA	90–110	NA	NA	NA	99–110	98.6	91.8	94.8	96.7	100.8	100.1
IgG synthesis rate (mg/day)	0–5.81	NA	0–5.81	NA	NA	NA	0–5.81	NA	251.70	34.99	124.84	301.92	146.00
mNGS		NA		NA	*M. houstonense* was detected	NA		NA	Negative	Negative	NA	Negative	NA
Acid-fast staining		Negative		Negative	Negative	Negative		Negative	Negative	Negative	Negative	Negative	Negative
Mycobacterium culture		Negative		Negative	Negative	Negative		Negative	Negative	Negative	Negative	Negative	Negative
Xpert MTB		Negative		Negative	Negative	Negative		Negative	Negative	Negative	Negative	Negative	Negative
RT-PCR		Negative		Negative	Negative	Negative		Negative	Negative	Negative	Negative	Negative	Negative
Culture of *M. houstonense*		NA		NA	NA	Negative		NA	Negative	Negative	NA	Negative	NA

NA, not available.

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negative, but there were 502 $CD3^+$ T cells per μl (reference range, 941–2,226), 269 $CD4^+$ T cells per μl (reference range, 471–1,220), and 200 $CD8^+$ T cells per μl (reference range, 303–1,003) in blood. The first lumbar puncture in our hospital revealed the opening pressure was 150 mmH_2O, with a microprotein level of 11.8 g/L (reference range, 0.15–0.45 g/L), a chloride ion level of 108 mmol/L (reference range, 120–130 mmol/L), GLU was 5.04 mmol/L (reference range, 2.5–4.4 mmol/L). There were 10 nucleated cells per microliter (Table 1). The six subsequent lumbar punctures performed at our hospital revealed a high opening pressure and mononuclear-predominant CSF pleocytosis, hyperglycorrhachia, a high level of protein, and a low level of chloride ion. Nevertheless, the acid-fast staining, mycobacterium cultures, Xpert MTB and RT-PCRs of all CSF samples were negative (Table 1). Enhanced MRI of the brain and cervicothoracic region revealed abnormal enhanced meningeal pia and subarachnoid spaces with signs of communicating hydrocephalus (Figures 1, 2). Enhanced MRI of the lumbar spine (performed on 17 February 2022) revealed nodules and irregularly thickened meninges (Figure 3).

It is difficult to diagnose infections caused by NTM since these diseases are rare and their clinical manifestations lack specificity. Most patient with NTM-CNS has been diagnosed with an immunocompromised disease, such as HIV. Meanwhile, it is not helpful to distinguish nervous system infections caused by NTM from other infection types, such as tuberculous infections, on radiological images. Some NTM-CNS infections could present with hydrocephalus or brain atrophy, which is unexplained and not age-related (6, 7), radiological images may also show nodular basal enhancement in NTM-CNS infection (8). On the basis of these radiological and clinical manifestations, as well as the mNGS CSF result in the second hospital, this patient was considered to have a CNS infection caused by *M. houstonense,* which is an NTM. According to the Chinese NTM guidelines (9), amikacin, tigecycline, clarithromycin, and imipenem were administered (Figure 4). After 25 days of therapy, the patient still had intracranial hypertension (CSF pressure > 300 mmH_2O, the number of nucleated cells in the CSF ranged from 10 to 70/μl, and vision was impaired), and epileptic seizure occurred once. Therefore, we placed continuous lumbar cisterns to drain ∼200 ml/day, and the draining CSF was slightly flocculent. Levetiracetam was also administered. Imipenem was then replaced with meropenem on the 27th hospital day.

The patient's CSF culture and mNGS (performed three times in the Precision Medicine Center of our hospital) remained negative throughout the course of therapy in our hospital. The patient did not improve despite appropriate empirical treatment. Finally, the patient lost confidence and requested discharge. The patient still had poor visual acuity, intermittent headaches, and vomiting, and his condition gradually worsened after discharge. Unfortunately, he died 19 days after discharge.

Discussion

To the best of our knowledge, this is the first report to reveal a CNS infection caused by *M. houstonense* in China. Cases of humans infected with *M. houstonense* are rare throughout the world, and the mechanism of infection with this organism is unclear. Some studies have revealed that freshwater fish and other fish products, especially retail frozen fish, might be a source of NTM for humans (10). However, in this case, the patient was not an aquaculture worker and was not recently exposed to fish products.

The first report of *M. houstonense* infection in a human in the world was from the USA, the organism was found in a wound on the patient's face (1). In China, there were two reported cases of *M. houstonense* infection in humans, one was led to endophthalmitis and the other led to surgical wound infection following an open humeral fracture (11, 12). As for the respiratory system, one case report showed that infection with *M. houstonense* and *M. senegalense* would lead to greater difficulties in the nursing of patients with chronic moderate persistent asthma. According to the current works of literature, human infections induced by *M. houstonense* has mostly been reported as soft tissue infection in humans; CNS infection with RGM is rare. Most reported cases were caused by *M. fortuitum* in the *M. fortuitum* group, and meningitis mostly occurred after invasive operations or trauma (8, 13). This is the first study to report a CNS infection caused by *M. houstonense* without any suspected causes of infection, suggesting a new site of *M. houstonense* invasion.

As mentioned above, *M. houstonense* is an acid-fast, gram-positive, pleomorphic bacilli, and must be cultured in blood agar at 35°C for more than 2 days (1). In this case, the acid-fast staining, mycobacterium cultures, Xpert MTB, and RT-PCRs of all CSF samples, including the cultures of *M. houstonense*, were negative. *M. houstonense* was detected in the first mNGS. However, the following three times' mNGS were negative, the possible reason for this may be the first mNGS was tested in the initial phase of this disease and the following three time's results of mNGS may be affected by the follow-up treatment. As CSF is a sterile body fluid with a low bacterial load in an infected state, the results of conventional microbiological CSF assays may be negative (14, 15). Therefore, mNGS is a potential approach to diagnose infectious diseases that does not rely on a priori selection, because potential pathogens (viral, bacterial, fungal, and parasitic) can be identified by a single assay (16–18). In one study comparing the sensitivity of mNGS to other tests for diagnosing tuberculous meningitis, mNGS possessed the highest sensitivity (84.44%), followed by Xpert MTB /RIF (40%), RT-PCR (24.44%), MGIT960 culture (22.22%), and AFB smear (0%) (19). Another study found that mNGS detected the pathogen in all five prospectively collected body fluids from patients with potential infection, but the testing results

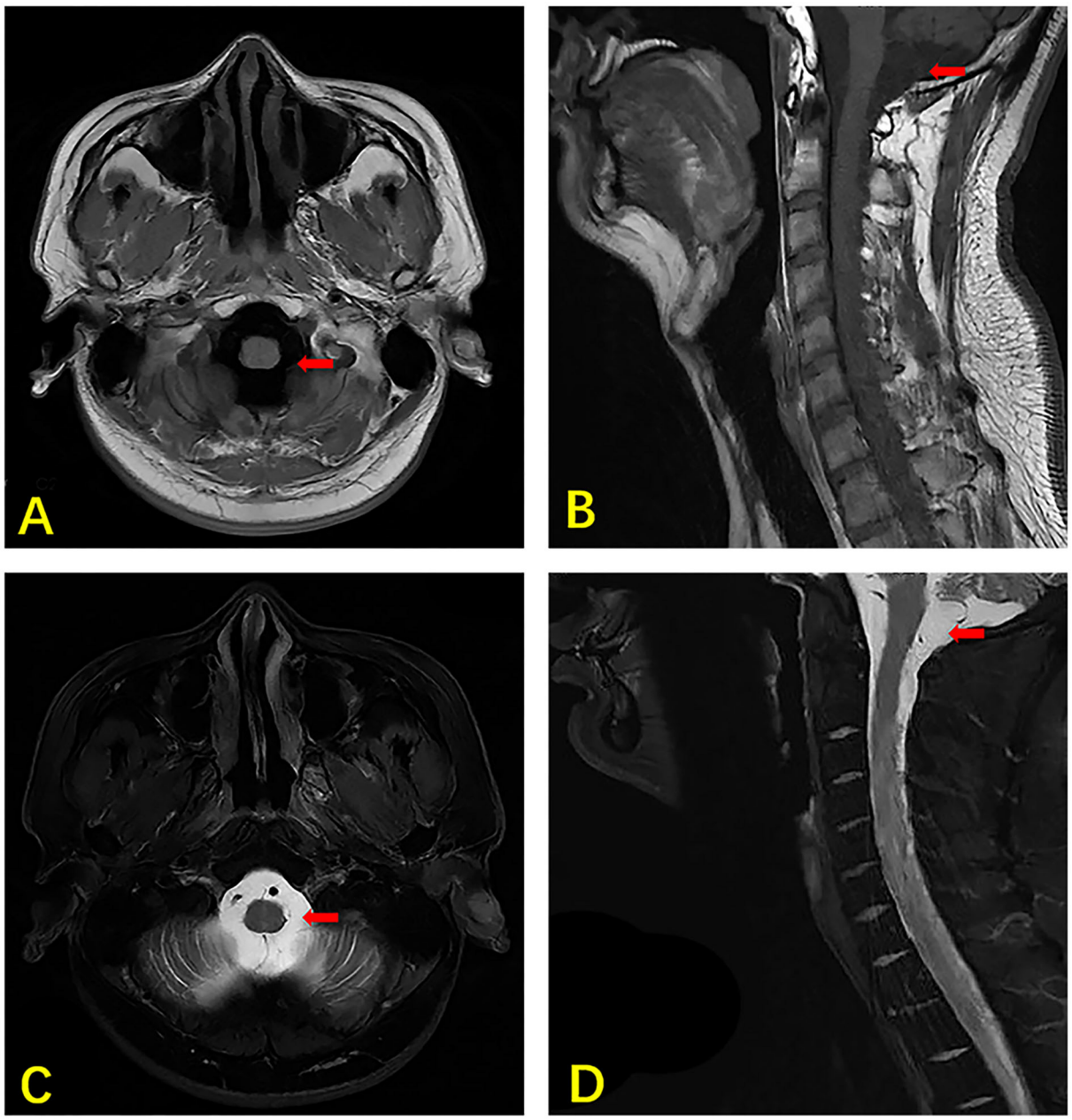

FIGURE 1
MRI of the brain and cervical vertebra of our case. The axial section T1 weighted image showing hydrocephalus (arrow) **(A)**. The sagittal section T1 weighted image showing hydrocephalus (arrow) **(B)**. The axial section T2 weighted image shows hydrocephalus (arrow) **(C)**. The sagittal section T2 weighted image showing hydrocephalus (arrow) **(D)**.

of all conventional microbiological assays (including culture) were negative (20). CNS infection caused by Mycobacteria is a paucibacillary infection, meaning that low numbers of bacilli are needed to cause infection (21), *M. houstonense* is a rare infectious disease in humans, especially in the CNS, and it is entirely possible to get negative results on conventional CSF tests. mNGS has a high potential value in accurate diagnosis, thus, we considered that *M. houstonense* is the pathogen that caused the CNS infection of our patient.

The patient in our case was a 26-year-old man without any underlying diseases (such as HIV, malignancy, or hematological system diseases) or a history of immunosuppressive therapy. However, there were 502 $CD3^+$ T cells/μl (reference range, 941–2,226), 269 $CD4^+$ T cells/μl (reference range, 471–1,220), and 200 $CD8^+$ T cells per microliter (reference range, 303–1,003) in the blood which showed an abnormal immune system. The reason why this young patient gets *M. houstonense* might be the following three reasons. Firstly, in China, the highest and

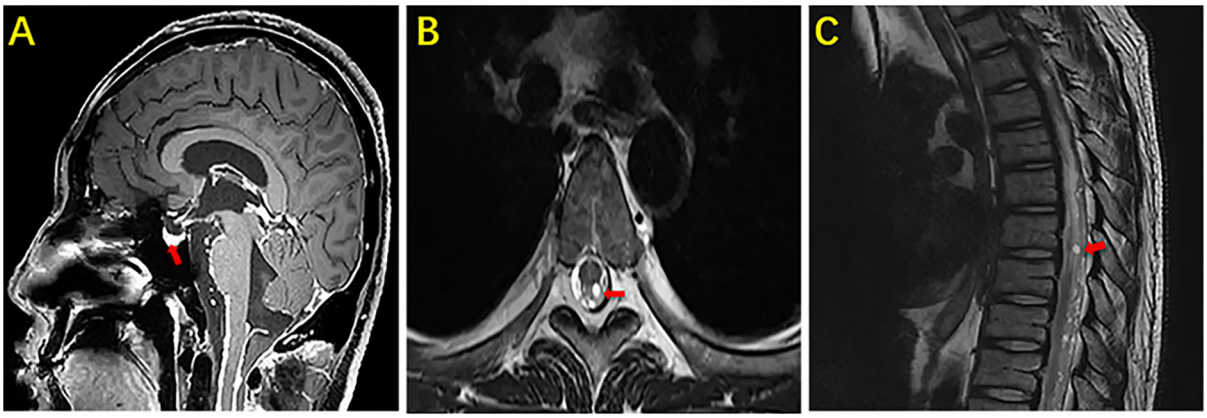

FIGURE 2
MRI of the brain and thoracic vertebra of our case. The sagittal section enhanced the image of the brain showing marked nodular enhancement under the pia mater (arrow) **(A)**. The axial section and sagittal section of the thoracic vertebra showing marked nodular enhancement in the spinal cord (arrow) **(B)**. The sagittal section of the thoracic vertebra showing marked nodular enhancement in the spinal cord (arrow) **(C)**.

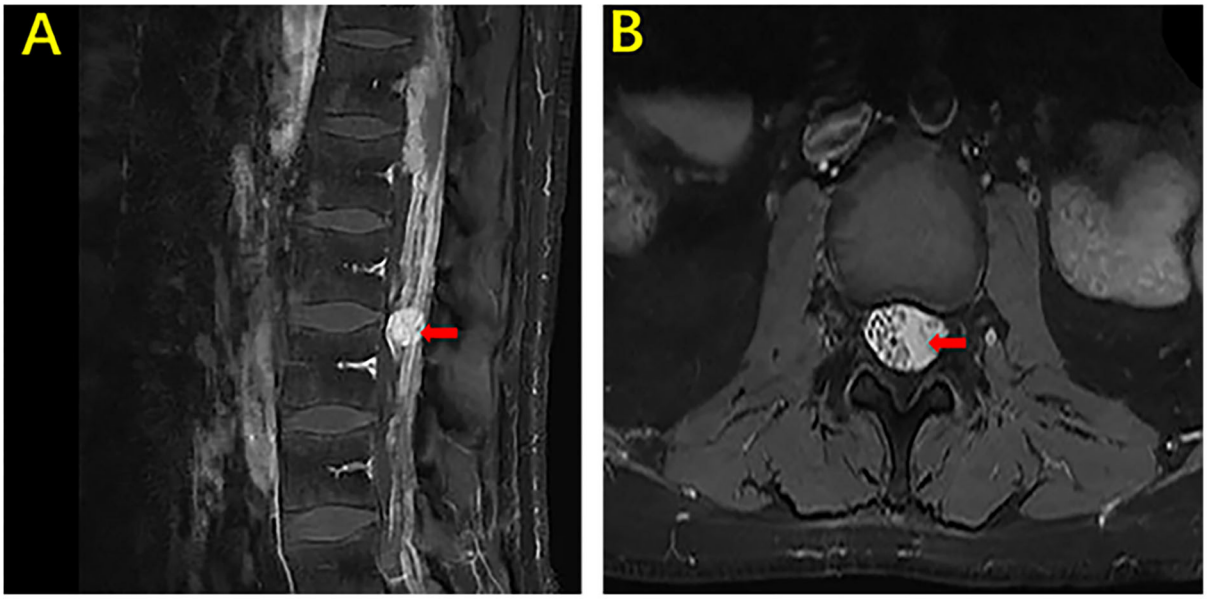

FIGURE 3
MRI of the brain and lumbar vertebra of our case. The sagittal section and axial section of the lumbar vertebra showing marked nodular enhancement in the spinal cord at the level of the second lumbar vertebra (arrow) **(A)**. The axial section of the lumbar vertebra showing marked nodular enhancement in the spinal cord at the same level in picture **(A)** (arrow) **(B)**.

lowest prevalence of NTM infections was 8.6% (7.1–10.5%) and 2.7% (2.1–3.4%) in southeastern and northeastern regions. The prevalence of NTM infections in Sichuan province was 7.7%, which was the third highest in China. Moreover, RGM constituted the major fraction in Southern China in contrast to Northern China (44.1 vs. 21.9%) (22). Our patient is a resident of Sichuan province, which is located in Southern China. Secondly, NTM disease is associated with suppressed T-cell-mediated response. Previous studies suggested that patients with NTM disease have lower counts of $CD4^+$ T cells, as well as a higher apoptosis rate on $CD4^+$ lymphocytes compared to healthy donors (23, 24). NTM are opportunistic human pathogens that colonize macrophages (25). Our patient has a severe decrease in $CD4^+$ T cells (<300 cells/μl), which would increase the risk of opportunistic infections and decrease the production of interferon (IFN)-γ, a macrophage activator produced by T cells or natural killer cells that could enhance the cooperation between dendritic cells and $CD4^+$ T cells (26–29). Thirdly, some

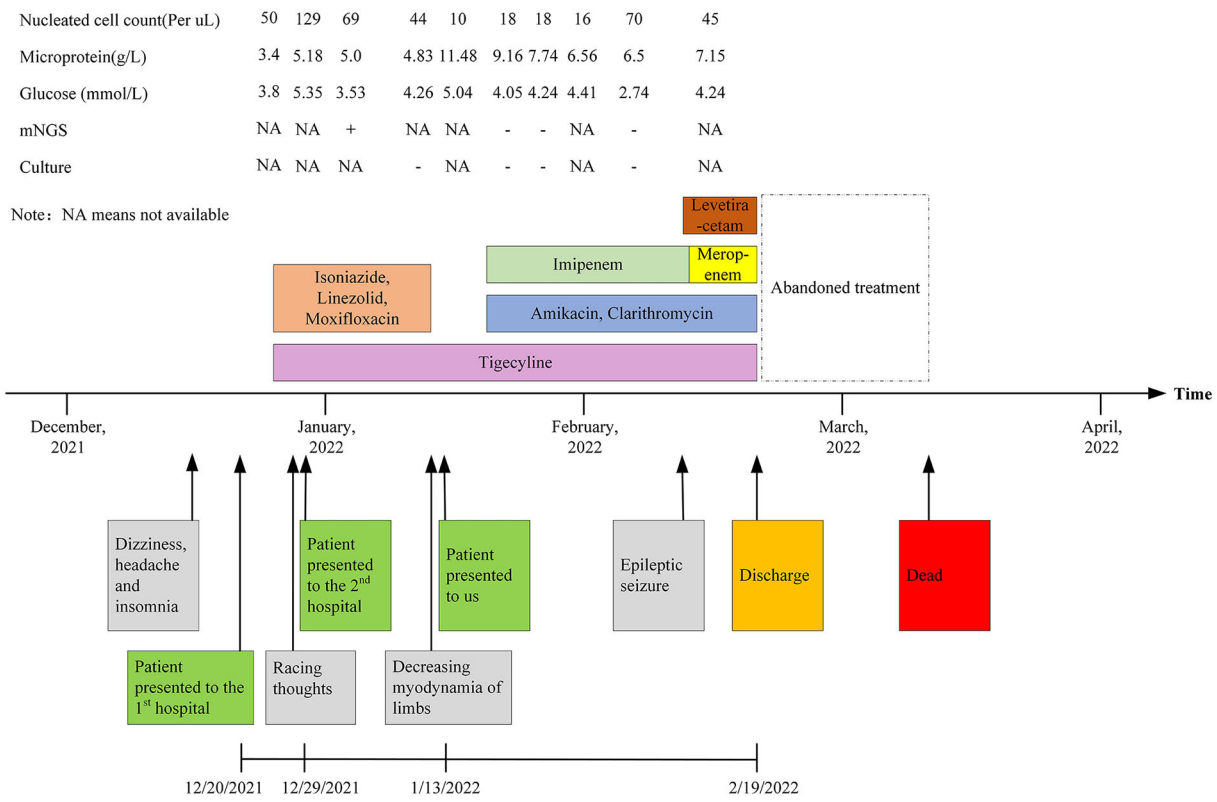

FIGURE 4
Clinical course, CSF findings, and antibiotic regimens for our case.

researchers have recently suggested that IFN-γ autoantibodies (AIGAs) may be a new form of late-onset immunodeficiency leading to severe mycobacterial infections (30). Patients infected by NTM commonly express high levels of AIGAs despite being previously healthy and mostly HIV negative, but they did not respond well to antibiotics (31, 32). A study from Thailand suggested that autoimmune disease caused by AIGAs is a major risk factor for extrapulmonary NTM infections (33). The presence of AIGAs might be one of the reasons why the patient was infected with *M. houstonense*. Unfortunately, the patient's family refused the test for AIGAs due to the shortage of cost. Therefore, according to the immune status (decreased $CD4^+$ T cells), the result of the first mNGS, and the resident of this patient, the patient got CNS infection caused by *M. houstonense*.

There are still large gaps in antimicrobial therapies for *M. houstonense* infections, and more research is needed to develop a standardized therapeutic regimen for *M. houstonense*. Some studies have suggested that for serious diseases caused by the *M. fortuitum* group, the aminoglycoside amikacin combined with a β-lactam (cefoxitin or imipenem, and imipenem is the most potent member of β-lactam according to current researches), inhibits 100% of *M. fortuitum* isolates (34). Another study found that the *M. fortuitum* group presented with >90% susceptibility to amikacin, cefoxitin, ciprofloxacin, gatifloxacin, imipenem, levofloxacin, linezolid, sulfamethoxazole or trimethoprim-sulfamethoxazole, as well as <90% susceptibility to clarithromycin, doxycycline, and vancomycin (13). Therefore, amikacin, cefoxitin, imipenem, sulfamethoxazole, and fluoroquinolones are usually recommended for *M. fortuitum* group (34). Some studies found that isolates of the unnamed third biovariant complex of the *Mycobacterium fortuitum* group were resistant to doxycycline and one-third were resistant to cefoxitin, all were susceptible to amikacin, ciprofloxacin, sulfamethoxazole, tigecycline, and imipenem also presented with >90% susceptibility to linezolid *in vitro*, the potential molecular mechanisms of linezolid resistance involved the presence of efflux pumps, and mutations in genes encoding for 23S rRNA and ribosomal proteins (35–38). Previous studies have shown tigecycline to be highly active (MIC $\leq$ 0.12 μg/ml) against the unnamed third biovariant complex of the *Mycobacterium fortuitum* group (sorbitol-positive) (39), and indicated that it could be a potential therapy to treat *M. houstonense*. One study suggested that only 9% of the *M. fortuitum* third biovariant (sorbitol-positive) is susceptible to clarithromycin (MIC,

≤4 μg/ml), however, the study did not indicate the specific strain. As for the potential clarithromycin resistance of *M. houstonense,* a possible mechanism could be the presence of erm genes. However, the data and clinical tests to support this conclusion are limited, and clarithromycin is still the cornerstone of management for NTM infectious diseases (40–42). Different sites and populations of *M. houstonense* infection may have different antimicrobial susceptibilities. A previous case report described an old man with surgical wound infection caused by *M. houstonense* that showed antimicrobial susceptibility of resistance to clarithromycin (11), however, it is not clear whether central *M. houstonense* infection is resistant to clarithromycin due to the negative culture. In this case, the treatment is based on drugs recommended in the Chinese NTM treatment guidelines, which didn't provide specific guidance for different strains (9).

This patient's condition did not improve after treatment with amikacin, tigecycline, clarithromycin, and imipenem(meropenem). We consider that one of the reasons for this might be inadequate treatment, as the patient was discharged after 1 month of treatment. The NTM guidelines state that the minimal treatment course is 4 months for skin and soft tissue infection, and 6 months for bone infection (9). A study of CNS infections caused by RGM showed that among survivors, the duration of treatment varies from 2.5 months to more than 16 months (8). Therefore, an inadequate treatment course might be the reason for the poor prognosis. Another reason may be the intracranial infection caused by *M. houstonense,* which is unknown to the medical field currently ease.

Conclusion

This is the first time that *M. houstonense* has been identified in CSF and has shown a poor prognosis after NTM treatments. Therefore, clinicians should pay more attention to CNS infections caused by the *M. fortuitum* group, more research is needed to explore the treatment for this group of infections, especially for *M. houstonense*.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The treatment for the patient is performed under the tenets of the Declaration of Helsinki. The patient reported in the study provided written informed consent for the treatment. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

LW drafted the manuscript. FW helped and revised the manuscript. CY was in charge of the data collection. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.908086/full#supplementary-material

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Case Report: Cryptococcal eosinophilic meningitis in a patient with Hodgkin lymphoma

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Cryptococcal meningitis is the most common fungal meningitis in clinical practice. It primarily occurs in immunocompromised people and is typically associated with human immunodeficiency virus (HIV) infection. In rare cases, it is associated with Hodgkin lymphoma (HL). Eosinophilic meningitis (EM) is characterized by increased eosinophils in the cerebrospinal fluid (CSF) and is often caused by a parasitic infection of the central nervous system (CNS). EM caused by cryptococcal infection is rare; only four cases have been reported in the past 30 years. Here, we report a case of cryptococcal meningitis in a patient with HL who presented with an atypical eosinophil-predominant CSF cytology response. The patient's eosinophil proportion reached 91%; a proportion this high has not been reported previously and may be associated with HL. After antifungal therapy and tumor chemotherapy, the proportion of eosinophils decreased significantly. This case shows that cryptococcal meningitis and HL may be simultaneously contributing to CSF eosinophilia. HL should be considered in patients with eosinophilic cryptococcal meningitis and multiple adenopathies.

KEYWORDS

cryptococcal meningitis, eosinophilic meningitis, eosinophilia, Hodgkin lymphoma, cryptococcal lymphadenitis

Introduction

Cryptococcal meningitis, caused by cryptococcal infection of the central nervous system (CNS), is the most common fungal meningitis in clinical practice. Most patients present with characteristic manifestations of meningitis, including headache, fever, and vomiting (1). The disease typically has a high mortality rate and a poor prognosis (2). Cryptococcal meningitis primarily occurs in immunocompromised patients and is typically associated with human immunodeficiency virus (HIV) infection. Hodgkin lymphoma (HL) is also considered a risk factor, but the association of both conditions is relatively rare (3, 4).

HL is a hematological malignancy, composed by large dysplastic mononuclear and multinucleated cells surrounded by a variable mixture of inflammatory cells. Peripheral adenopathies are usually the first manifestation of HL. The disease is categorized as classic HL (cHL) or nodular lymphocyte-predominant HL (NLPHL) (5). The former is subdivided into 4 histologic subtypes (Nodular sclerosis cHL, Mixed-cellularity cHL, Lymphocyte-rich cHL and Lymphocyte-depleted cHL). Over 90% of the cases are cHL, which behaves as an aggressive tumor; however, lymphocyte-rich cHL manifests with indolent biological nature in most instances and can be effectively treated with modern combination chemotherapy regimens (5). *Cryptococcus* infection in patients with HL occurs at ∼2.7% over 10 years and can lead to increased mortality (6).

Eosinophilic meningitis (EM), a disease characterized by increased eosinophils in the cerebrospinal fluid (CSF), is often caused by a parasitic infection of the CNS (7). EM caused by cryptococcal meningitis is rare. To our knowledge, only four cases have been reported in the past 30 years (8–11). A proportion of eosinophils as high as 91% presented in this case has not been reported, and such a high proportion may be associated with HL, which was reported to have a correlation with CSF eosinophilia as well (12–14).

Here, we report a case of cryptococcal meningitis in a patient with HL who presented with an atypical eosinophil-predominant CSF cytology response. After antifungal therapy and tumor chemotherapy, the proportion of eosinophils decreased significantly.

Case report

A previously healthy 20-year-old male patient presented with intermittent headaches, nausea and vomiting for 13 days, which had worsened in the previous 2 days. He also presented fever the day before the hospital admission. He took no regular medication. Physical examination revealed cervical rigidity, lymph node enlargements on the right side of the neck. Vital signs (body temperature, pulse rate, respiration rate, and blood pressure) were normal. Relevant laboratory tests and examinations were performed after admission. Complete blood count was normal (Hb 130 g/L, Leucocytes 3.9 × 10^9/L, with 1.4 × 10^9 lymphocytes/L, 1.6 × 10^9 neutrophils/L, 0.5 × 10^9 eosinophils/L, and 0.4 × 10^9 monocytes/L, and platelets 125 × 10^9/L), and the patient tested negative for HIV. Brain magnetic resonance imaging (MRI) revealed hyperintensity in the bilateral frontopolar and parietal cortex and sulcus. A lumbar puncture revealed elevated CSF opening pressure (>330 mmH_2O), decreased glucose (1.19 mmol/L), elevated protein (0.96 g/L), and pleocytosis of 358 × 10^6 leucocytes/L (91% eosinophils, 4% lymphocytes, 4% monocytes, and 1% plasma cells) (Figure 1A). Alcian blue staining revealed *Cryptococcus* (Figure 1B), and the CSF culture grew *Cryptococcus neoformans*

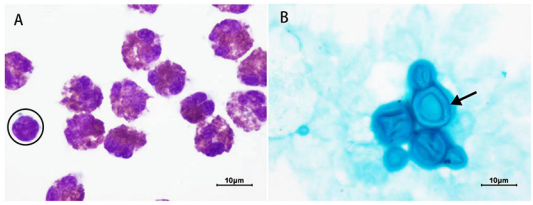

FIGURE 1
Results of cerebrospinal fluid (CSF) staining. **(A)** Wright-Giemsa staining (1,000 X). All cells are eosinophils except the one surrounded by a black circle, which is a lymphocyte. **(B)** Alcian blue staining (1,000 X). Black arrow = *Cryptococcus* with an intact capsule. The capsule of *Cryptococcus* is dark blue and the thallus is light blue.

resistant to fluconazole. To search for the cause of eosinophilia, metagenomic next-generation sequencing (m-NGS) of the CSF was performed, and only *Cryptococcus neoformans* (sequence number: 1427) was identified; no parasites or other pathogens were found. The patient was diagnosed with cryptococcal meningitis on the basis of his clinical symptoms and signs combined with the presence of *Cryptococcus* in the CSF. The following examinations were performed to identify the cause of lymph node enlargements. Color Doppler ultrasound of the superficial lymph nodes revealed multiple lymph node enlargements in the bilateral neck, axilla, and right groin. Chest computed tomography (CT) showed multiple lymph node enlargements on both sides of the neck, mediastinum, and lung hilum. A biopsy of the cervical lymph node was performed, and the pathological diagnosis was lymphocyte-rich cHL. An 18F-FDG PET-CT was performed and documented hypermetabolic activity on supra- and infra-diaphragmatic adenopathies, spleen and bone, corresponding to the stage IV of the Lugano classification (15). CSF analysis by flow cytometry showed no malignant cells.

Treatment for HL may suppress immunity and thus aggravate cryptococcal infection, and lymphocyte-rich cHL has an indolent biological nature; therefore, we first administered antifungal induction therapy (liposomal amphotericin B plus 5-flucytosine) and performed successive lumbar punctures to control the high CSF opening pressure. After 8 weeks, the symptoms of meningitis significantly improved. The CSF leukocyte count (8 × 10^6/L) and proportion of eosinophils (42%) were reduced, and a CSF culture was negative. The patient thus initiated antifungal consolidation therapy with voriconazole and was transferred to the hematology department to start chemotherapy with the ABVD protocol (doxorubicin, bleomycin, vinblastine, and dacarbazine). At the present moment, the patient has received antifungal consolidation therapy for 13 weeks and 4 cycles of ABVD and he is asymptomatic. CSF culture is still negative, and the leucocyte

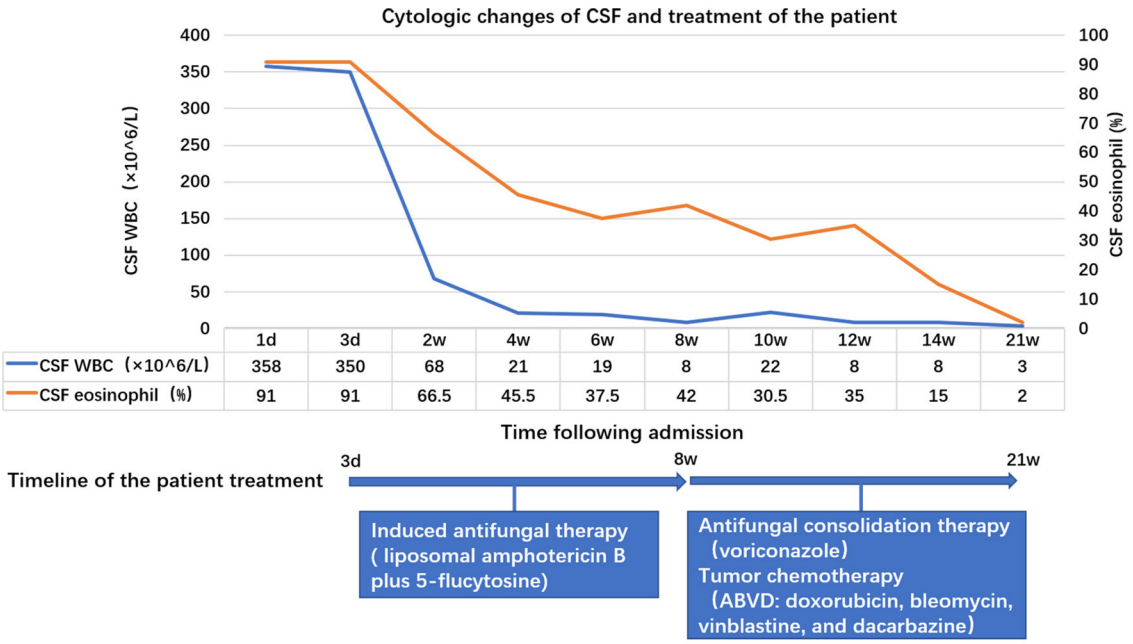

FIGURE 2
Changes in the leucocyte count and proportion of eosinophils in the cerebrospinal fluid (CSF) with treatment. On the first day of admission, the leukocyte count was 358 × 10^6/L (91% eosinophils), which decreased to 8 × 10^6/L (42% eosinophils) after about 8 weeks of antifungal induction therapy, and to 3 × 10^6/L (2% eosinophils) after 13 weeks of antifungal consolidation therapy combined with tumor chemotherapy.

count and proportion of eosinophils in the CSF have decreased gradually with treatment (Figure 2).

Discussion

Cryptococcal meningitis primarily occurs in immunocompromised hosts, most commonly HIV-infected patients. Other high-risk patient groups include patients receiving immunosuppressive therapies, patients with malignant tumors (including HL), solid organ transplant recipients, and patients with rheumatic diseases (3, 4). Our patient was HIV seronegative, with no history of immunosuppressive drugs, and had no other diseases. The immunosuppression associated to the HL contributed for the Cryptococcus infection. Studies have shown that ∼16–19% of cryptococcal meningitis patients without HIV have malignant neoplasms (16). A large retrospective review of 583 patients with cryptococcal infection associated with malignancies from 1970 to 2014 found that 52 (9%) cases were associated with HL (4).

Previous studies have shown that risk factors for cryptococcal infection in patients with HL include a history of HL of ≥12 months, stage IV disease, absolute lymphopenia in the peripheral blood, and extensive pretreatment with chemotherapeutic agents (6, 17). In this case, the patient had no history of malignancies, no decrease in lymphocyte count, and no chemotherapeutic treatment before infection. The only identified risk factor for cryptococcal infection was stage IV disease. Previous studies have also shown that the host's defense against cryptococcal infection mainly relies on T cell immunity (18). Compared with healthy individuals, the number of T cells in HL patients is reduced, and the proliferation ability of T cells is significantly decreased (19), which partially explains why HL patients present a higher risk to be infected with *Cryptococcus*.

In addition, it is critical to identify HL and cryptococcal lymphadenitis in patients with cryptococcal meningitis accompanied by multiple lymph node enlargements. The most common sites of *Cryptococcus* infection are the CNS and the lungs (20). However, many reports (20–22) have demonstrated that *Cryptococcus* can infect the lymph nodes and lead to cryptococcal lymphadenitis, of which the clinical manifestations are very similar to lymphoma, including lymph node enlargements in the neck, supraclavicular region, mediastinum, and groin as well as splenomegaly. Biopsy is the gold standard to distinguish these two diseases (21, 22). To exclude the presence of a HL or other malignancy, it is recommended to routinely perform a lymph node biopsy in all patients with cryptococcal meningitis and adenopathies.

Eosinophilic meningitis (EM) is defined by the presence of 10 or more eosinophils/uL in the CSF or eosinophilia of at least 10% of the total CSF leukocyte count (23). The etiology can be divided into infectious and non-infectious causes (7, 23). Parasitic infection is the most common form of infectious

TABLE 1 Summary of the clinical cases of cryptococcal meningitis with CSF eosinophilia published in the last 30 years.

References	Gender	Age (years)	Past medical history	Manifestations	CSF leukocytes ($\times 10^6$/L)	CSF eosinophils (%)	Treatment	Outcome
Schmidt et al. (8)	F	43	Thymectomy and multiple courses of combined irradiation and chemotherapy	Progressive waste, headache, fever, dysphagia and confusion	237	50	Fluconazole	Recovered well without neurological sequelae. CSF eosinophilia resolved after 11 months of therapy.
Grosse et al. (9)	F	64	Angioimmunoblastic T-cell lymphoma	Headache, fatigue and inattentiveness	582	12	Amphotericin, flucytosine and fluconazole	Recovered well without neurological sequelae. CSF eosinophilia resolved after 7 weeks of therapy.
Pfeffer et al. (10)	F	22	Asthma, perennial rhinitis, atopic dermatitis and high-dose steroid therapy	Headache, fever and encephalopathy	33	n.a.	Amphotericin, flucytosine and fluconazole	Recovered well without neurological sequelae. CSF eosinophilia resolved after 3 months of therapy.
Hadid et al. (11)	M	51	sarcoidosis	Headache, neck stiffness and photophobia	1,826	76	Amphotericin, flucytosine and fluconazole	Recovered well without neurological sequelae. CSF eosinophils reduced to 64% after 8 days of therapy.

F, female; M, male; n.a., Not available; CSF, Cerebrospinal fluid.

EM. Other rare pathogens include fungi, Streptococcus, coxsackieviruses, and Rickettsia. Among pathogenic fungi, *Coccidioides* is the most common, whereas *Cryptococcus* is relatively rare. Non-infectious factors include tumors, drugs, toxins, and ventriculoperitoneal shunts.

EM caused by cryptococcal meningitis is rare. As mentioned above, only four cases have been reported in the past 30 years (Table 1). All patients had a significant medical history: one patient had been submitted to thymectomy and combined irradiation and chemotherapy; one patient had had angioimmunoblastic T-cell lymphoma; one patient had asthma, perennial rhinitis, atopic dermatitis and high-dose steroid therapy; the other patient had sarcoidosis (8–11). The initial proportion of eosinophils in CSF of three patients was 50, 12, and 76%, respectively; exact data is not available for the other patient. Eosinophilia totally resolved after antifungal therapy alone in three patients. In the other case, the eosinophils in the CSF decreased from 76 to 64% after 8 days of antifungal therapy, but no further CSF data is available. In the case we now report, the eosinophils in the CSF decreased from 91 to 42% after antifungal therapy alone. No parasites or other pathogens were found, and the patient had no history of taking special drugs or toxins. Therefore, *Cryptococcus* infection was considered a possible cause of EM. In addition, the proportion of eosinophils was as high as 91% in our case, suggesting that other factors may have been involved in eosinophilia.

Current studies have shown that HL can cause peripheral blood eosinophilia with an incidence of ∼15% (24). However, few studies have investigated the association between HL and

CSF eosinophilia, except in the rare cases of HL meningeal invasion, which can present with EM (12–14). The diagnosis involvement of the meninges by HL relies on meningeal biopsy and detection of malignant cells in the CSF (13). In this case, the patient did not undergo any meningeal biopsy. Taking into account that the several CSF cytological examinations and the flow cytometry analysis did not reveal any malignant cells and that the symptoms of meningitis significantly improved without intrathecal chemotherapy, a meningeal involvement by HL was considered unlikely. However, the contribution of HL to the CSF eosinophilia cannot be excluded as the proportion of eosinophils was still high (42%) after 8 weeks of antifungal therapy alone, despite the negative CSF culture, and it decreased to 2% after the chemotherapy initiation. The specific mechanism requires further studies.

In conclusion, cryptococcal meningitis and HL may be simultaneously contributing to CSF eosinophilia. HL should be considered in patients with eosinophilic cryptococcal meningitis and multiple adenopathies. Early diagnosis and treatment of eosinophilic cryptococcal meningitis and the underlying immunodeficiency disease is essential for improving the clinical outcomes of these patients.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FZ, YL, HS, JT, and JW examined and treated the patient. FZ contributed to the conception and writing of the first draft of the manuscript. YL and HS collected the data. JW contributed to the critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Multiple brain tuberculomas after *in vitro* fertilization, embryo transfer, and abortion

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Background: Multiple brain tuberculomas (MBT), characterized by disseminated tuberculous granulomas in the brain, is a rare disease like tuberculosis encountered after *in vitro* fertilization, embryo transfer (IVF-ET), and abortion. This study aimed to investigate the clinical characteristics, diagnostic methods, and therapeutic strategies of MBT after IVF-ET and abortion.

Methods: A retrospective analysis was performed on the data of two patients who suffered from MBT after IVF-ET and abortion.

Results: Both patients manifested headache and vomiting, which are the common symptoms of intracranial hypertension, accompanied by tuberculous meningitis. Besides, case 1 was affected by fever and epilepsy. In terms of imaging characteristics, T2-weighted imaging (T2WI) displayed multiple intracranial punctate or patchy high-intensity signals, some of which were presented as "target sign" or enhanced-like disseminated nodules, similar to miliary tuberculosis. Regular anti-tuberculosis therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol was administered but failed to achieve a significant effect in the initial stage. The symptoms were gradually relieved, and the brain lesions in MRI were significantly alleviated after combining with intrathecal injections of isoniazid, dexamethasone, and chymotrypsin.

Conclusions: *In vitro* fertilization, embryo transfer (IVF-ET) may be a risk factor for MBT, the common manifestations of which are intracranial hypertension. In addition to multiple nodular enhancement on brain MRI, the "target sign" on T2WI is likely to be another typical feature of MBT. Provided that there is no obvious effect of regular anti-tuberculosis therapy (ATT), intrathecal injections of isoniazid, dexamethasone, and chymotrypsin are considered to produce a favorable prognosis, but further studies are still needed to confirm the efficacy.

KEYWORDS

multiple brain tuberculoma, *in vitro* fertilization, embryo transfer, anti-tuberculosis therapy, intrathecal injection, tuberculous meningitis

Introduction

With the popularization of technology, *in vitro* fertilization combined with embryo transfer (IVF-ET) has become widely used in fertility treatment worldwide (1). After IVF-ET, the levels of estrogen and progesterone, which inhibit T lymphocytes and cause an increased incidence of tuberculosis (TB) infection, increase in pregnant women. In patients undergoing IVF-ET, the peak serum estrogen levels are several times higher than those in normal individuals. In addition, the administration of progesterone and glucocorticoids, a routine treatment after IVF-ET, is applied to ensure the normal growth of embryos, which is conducive to the reproduction of *Mycobacterium tuberculosis*, resulting in the susceptibility of pregnant patients to TB after IVF-ET (2).

TB remains one of the most important global infectious diseases, affecting nearly every system in the body, including the central nervous system (CNS) (3). Brain tuberculoma, a rare tuberculous granuloma of CNS presenting as solitary or multiple, can affect any part of the brain. Hitherto, few cases of multiple brain tuberculosis (MBT) are available in the literature (4, 5). Herein, we reported two cases with MBT after IVF-ET and abortion and analyzed the diagnosis and treatment process to provide a reference.

Case presentation

Case 1

A 27-year-old woman with a history of IVF-ET 7 months ago was treated with glucocorticoid, namely, 10 mg of prednisone per day for 30 consecutive days before implantation, and spontaneous abortion occurred after 4 months of pregnancy. She was previously healthy and denied any previous history of TB and close family contacts. Several days later, symptoms such as headache, vomiting, and intermittent low-grade fever developed, and she received several symptomatic treatments in the first month without any effect. Therefore, she was admitted to the neurology department at the local hospital. Figures 1A,B show multiple lesions on her brain's magnetic resonance imaging (MRI). Chest radiography was normal, and the results of a human immunodeficiency virus (HIV) test was negative. In the absence of definite etiological evidence, empirical anti-TB drugs, including isoniazid, rifampin, ethambutol, and pyrazinamide, as well as some symptomatic treatments, were given. The patient was later transferred to the First Affiliated Hospital of Zhengzhou University after her condition worsened with paroxysmal coma and seizures. The signs of meningeal irritation were positive. Lumbar puncture showed the intracranial pressure exceeding 400 mmH_2O. CSF examination revealed low glucose (30–40 mg/dl), low chloride (119 mmol/L), WBC of 290*10∧9/L (65% lymphocytes and 27% neutrophils), and extremely high level of protein (297.5 mg/dl). Additionally, purified protein derivative (PPD)-positive cells accounted for 24% (reference value: <13.5%) and early secretory antigenic target (ESAT)-6 positive cells represented 23% (reference value: <9.5%) in the CSF. No mycobacteria were found in the CSF by stained smear and culture. Electroencephalogram (EEG) displayed paroxysmal spikes or sharp slow waves. No loss of consciousness with seizures occurred under the continuous administration of the previous anti-tuberculous therapy (ATT) combined with levofloxacin, prednisone, and partial symptomatic treatment, but her headache and intermittent fever were not relieved. Worse still, the patient developed herniation at the end of the first week of treatment, and she received continuous lumbar cerebrospinal fluid (CSF) drainage for one week. Based on routine treatment, intrathecal injections of isoniazid, dexamethasone, and chymotrypsin were performed every two days after removing the drainage tube. After another two months of treatment, the symptoms of fever, headache, and epilepsy were significantly relieved. The improvement of brain MRI is shown in Figure 1C. Her intracranial pressure decreased to 190 mmH_20. CSF examination showed reduced WBC of 30*10∧9/L (79% lymphocytes), significantly decreased protein (99.5 mg/dl), and normal glucose and chloride.

Case 2

A 27-year-old woman with a history of IVF-ET six months ago received 10 mg of prednisone per day for 20 days before embryo transfer. She suffered from spontaneous abortion one month ago and had a high fever immediately after the abortion. She was previously healthy and denied any previous history of TB and close family contacts. She was diagnosed with interstitial pneumonia and cured at a local hospital. Two weeks after the cure, she suddenly suffered from headaches, vomiting, and insanity. The signs of meningeal irritation were positive. In terms of auxiliary examination, CT showed no lung abnormalities, while brain MRI revealed multiple lesions (Figure 2A). The result of the HIV test was negative. The lumbar puncture showed an intracranial pressure of 110 mmH_2O. Examination of CSF demonstrated a low level of glucose (40–50 mmol/L), pleocytosis (WBC was 22*10∧9/L with 73% lymphocytes), and a high level of protein (121.2 mg/dl). Moreover, PPD-positive cells accounted for 26%, and ESAT-6 positive cells represented 25% of the CSF. No mycobacteria were found in the CSF by stained smear and culture. After 1 month of anti-tuberculous drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide), levofloxacin, and some symptomatic treatment, the patient still had severe headaches and vomiting. Brain MRI showed no significant changes compared with the previous scan (Figure 2B). Intrathecal

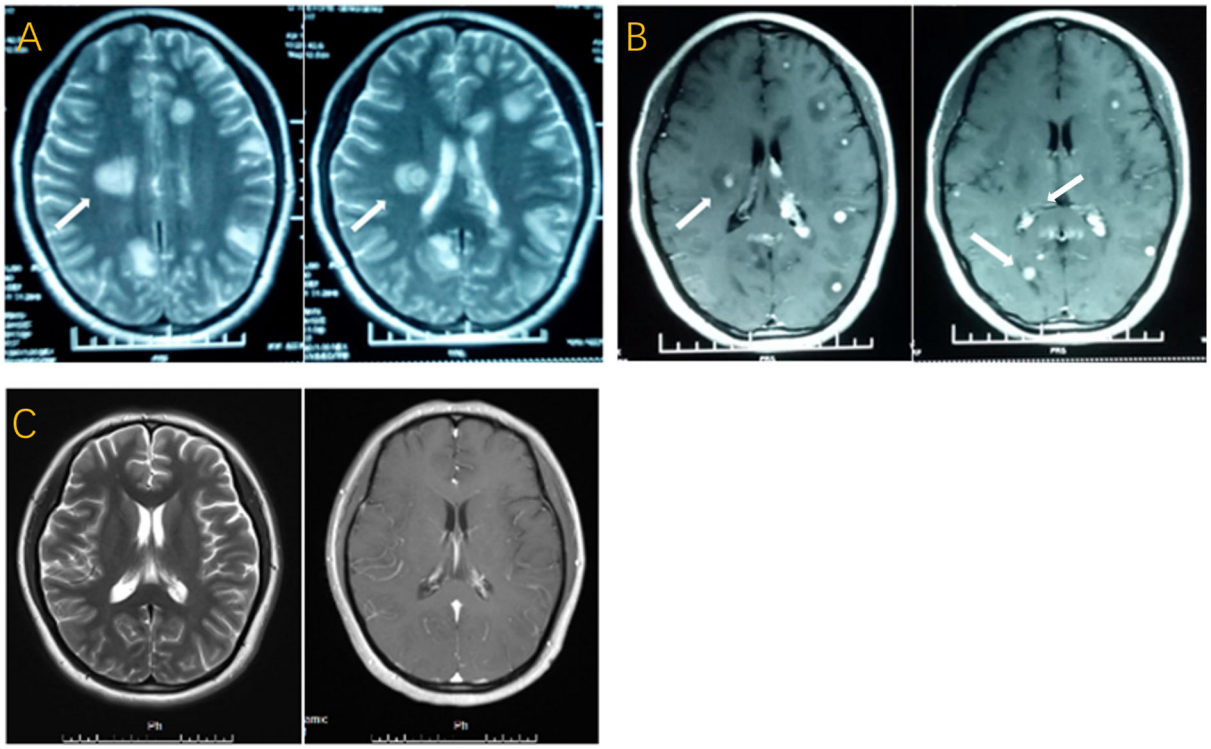

FIGURE 1
(A) T2-weighted image with multiple patchy high-intensity signals and "target sign". **(B)** T1-weighted post-gadolinium contrast image with multiple nodular lesions and peripheral oedema. **(C)** T2-weighted image and T1-weighted post-gadolinium contrast image done three months later with approximate disappearance of the lesions.

injections of isoniazid, dexamethasone, and chymotrypsin were performed to specifically prevent anti-TB and reduce arachnoid adhesion. Combined with the previous therapy for another month, her clinical symptoms were relieved. Moreover, the size and number of lesions were significantly reduced on brain MRI (Figure 2C).

Discussion

It is probably not a coincidence that both cases had a history of IVF-ET followed by spontaneous abortion. Pregnancy with miliary TB is reported to be not rare (1). However, since patients with TB may not show obvious symptoms during pregnancy and since radiographic examination is limited due to the patient's condition, the proportion of those who are not diagnosed with TB during pregnancy may be as high as 40% (6). It has been reported that the TB of the reproductive system is an important factor causing tubal infertility, and 20% of female primary infertility cases are caused by TB of the reproductive system (7). Unfortunately, whether these two patients suffered from occult TB before IVF-ET remains unclear.

Brain tuberculoma accounts for approximately 2% of CNS-TB, and brain tuberculoma with tuberculous meningitis accounts for only 10% (8). Both patients had concurrent MBT and tuberculous meningitis. Increased intracranial pressure is the most prevalent symptom among these manifestations (9, 10). In addition to high intracranial pressure, Case 1 was accompanied by fever and epilepsy, which was consistent with a larger lesion in her brain. The appearance of tuberculoma on MRI varies depending on whether the granuloma was noncaseating, caseating with a solid center, or a liquid center. Multiple hypointense on T2WI with annular or nodular enhancement on T1WI after gadolinium injection are the most common manifestations (11). However, the most characteristic lesion displayed a hyperintense core on T2WI, with a hypointense rim, and there was no obvious diffusion restriction on diffusion-weighted images, which can also be called "target sign" (4, 5). MRI of both patients displayed multiple nodules, typical target signs, and nodular enhancement. Additionally, several intraventricular tuberculomas were identified on the brain MRI in Case 1, which tended to be a factor in her later herniation.

The key to most CNS-TB diagnoses rests with the proper interpretation of the spinal CSF cellular characteristics

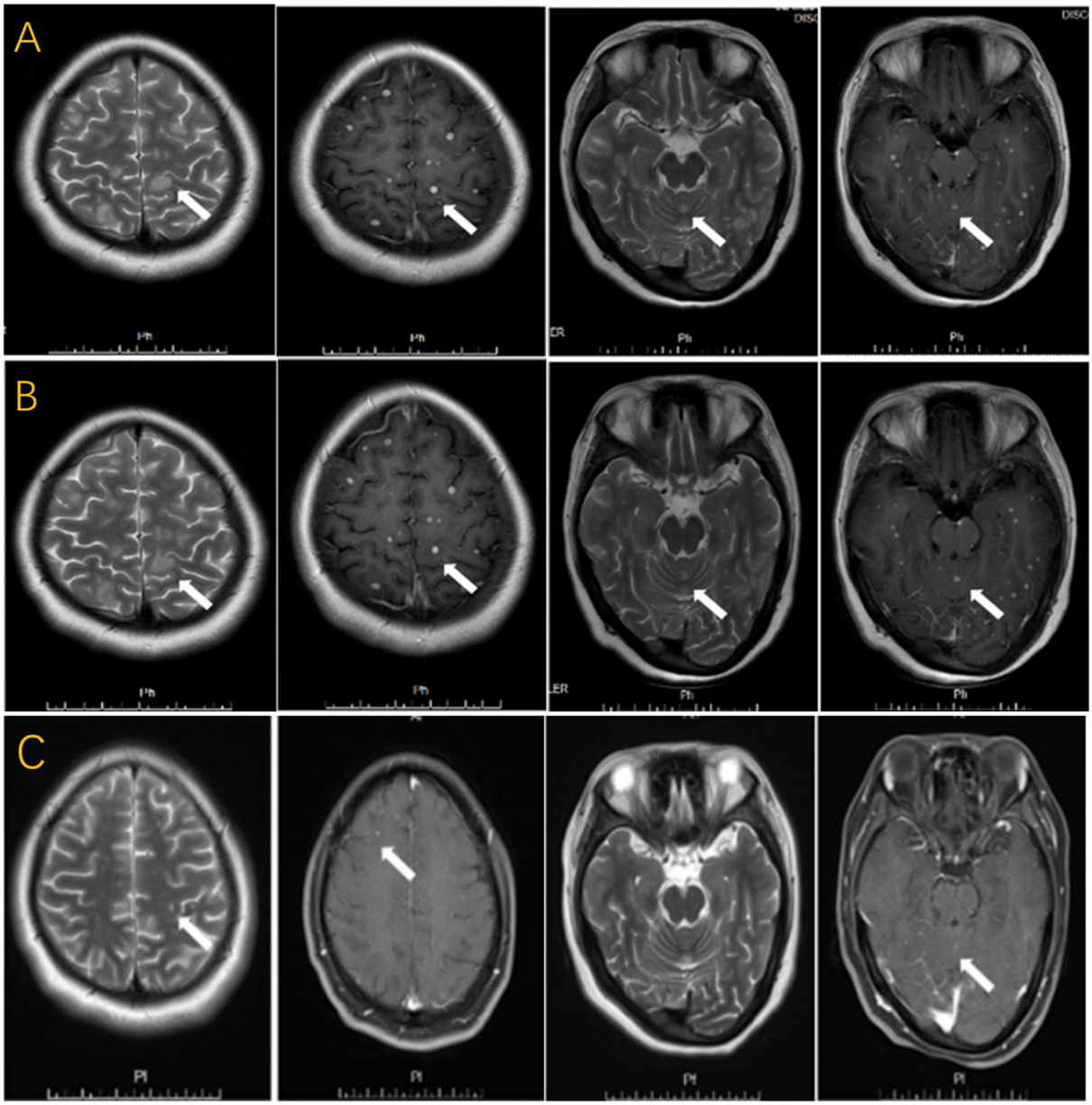

FIGURE 2
(A) T2-weighted image with multiple patchy hyper-intensity signals and "target sign". T1-weighted post-gadolinium contrast image with multiple nodular enhancing lesions, similar to military tuberculosis. **(B)** T2-weighted image and T1-weighted post-gadolinium contrast image done after regular ATT for a month with no significant improvement. **(C)** T2-weighted image and T1-weighted post-gadolinium contrast image done after intrathecal injections for one month with significant decreased lesions.

and the chemical composition of the CSF (CSF formula) combined with the visualization of mycobacteria in the CSF by stained smear or culture. During lumbar puncture, the opening pressure is usually elevated. Typically, the CSF formula shows mononucleosis with high protein and low glucose concentration (12). However, CSF examination can be completely normal in patients with MBT without tuberculous meningitis. Detection of mycobacterial DNA by polymerase chain reaction (PCR) has a sensitivity of 33–90% and a specificity of 88–100% for the diagnosis of tuberculoma, which is a promising noninvasive approach for rapid diagnosis of tuberculoma, even in the absence of meningitis and positive stained smear and culture (13, 14). We found typical examination results of the CSF formula in two cases due to

their coexistence with tuberculous meningitis. Unfortunately, no mycobacteria were found in the CSF by stained smear and culture in both cases. Moreover, they did not have access to the Next Generation Sequencing (NGS) due to their economic conditions.

Once the diagnosis of intracranial tuberculoma is suspected, routine ATT should be initiated. Failure to accept ATT immediately in Case 1 may have contributed to the greater lesion and deterioration. Additionally, both patients received oral prednisone for one month since low-dose corticosteroids are recommended to reduce brain inflammation and swelling in patients with tuberculous meningitis (15). Intrathecal injections of anti-tuberculosis drugs and anti-adhesion drugs are supposed to be beneficial for patients with MBT, especially those suffering from intraventricular tuberculoma, and MRI is a favorable approach to follow up the curative efficacy (16–18). The symptoms of the two patients did not improve significantly in the first 1 to 3 months, but the clinical conditions of the two patients improved remarkably after intrathecal injection of isoniazid against anti-tuberculosis, dexamethasone, and chymotrypsin against anti-adhesion.

Conclusion

In vitro fertilization combined with embryo transfer (IVF-ET) may be a risk factor for MBT, which is often manifested as intracranial hypertension. In addition to multi-nodule enhancement on brain MRI, the "target sign" on T2WI is likely to be another typical feature of MBT. Intrathecal injection of isoniazid, dexamethasone, and chymotrypsin has a favorable prognosis on the condition of ineffective conventional anti-tuberculosis therapy (ATT). However, the efficacy needs to be confirmed in further studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZS was the primary doctor of both cases and responsible for the writing of the manuscript and guided the completion of this article. YS contributed to the data collection and image processing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Dueling etiologies: Longitudinally extensive spinal cord lesion mimicking spinal cord infarct with simultaneous positive Lyme serology and amphiphysin antibody

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Background: Longitudinally extensive spinal cord lesions are challenging diagnostic entities as they are uncommon, but various etiologies can cause them.

Case report: We report a case of a 55-year-old man with a past medical history of hypertension. He is an ex-smoker. He presented with chest pain, followed by right lower limb weakness, preceded by 2 weeks of constipation and voiding dysfunction. The examination revealed right lower limb mild flaccid paresis, absent reflexes, reduced anal tone, and urinary retention. His symptoms deteriorated over 24 h, and he developed severe flaccid paraparesis with impaired pinprick sensation below the T4 level. MRI spine showed an abnormal, non-enhancing signal in the anterior aspect of the spinal cord extending from the T4 level to the conus without associated edema. He was commenced on intravenous steroids and had significant improvement after one dose. The imaging was felt to be consistent with spinal cord infarction, and aspirin was started. The cerebrospinal fluid analysis showed elevated protein (0.8 mg/ml). Investigations for stroke and autoimmune pathologies were negative. The Lyme immunoblot confirmed intrathecal production of IgG to Borrelia antigens. The patient was started on ceftriaxone. The paraneoplastic screen identified amphiphysin antibodies. CT-TAP and PET-CT did not identify occult malignancy. The patient had a significant improvement over 2 months, strength was almost fully recovered, and autonomic functions returned to normal.

Conclusion: We describe an unusual steroid-responsive, longitudinally extensive spinal cord lesion with radiological features of spinal cord infarct and a simultaneous finding of intrathecal Lyme antibodies and serum amphiphysin antibodies.

KEYWORDS

longitudinally extensive spinal cord lesion, transverse myelitis, spinal cord infarct, Lyme neuroborreliosis, amphiphysin antibody

Introduction

Myelopathy is defined as dysfunction of the spinal cord of any cause (1). It represents a heterogeneous group of disorders with distinct etiologies, clinical presentation, radiologic features, and prognoses (2). The clinical presentation and symptoms depend on the affected region of the spinal cord (3). The differential diagnosis is broad and includes metabolic, vascular, inflammatory, autoimmune, neoplastic, infective, traumatic, compressive, and idiopathic causes (4). Identifying the cause of myelopathy is critical, as delay in diagnosis and treatment could lead potentially to severe neurologic deficits (5).

Case presentation

A 55-year-old right-handed man presented to the emergency department with sudden-onset central chest pain while walking lasting 20 min and resolved spontaneously, followed by gradually worsening weakness of the right lower limb. He was able to drive and walk 1 h after the onset of symptoms. He also reported altered bowel habit, constipation, and difficulty passing urine over the previous 2 weeks.

He had a past medical history of hypertension well-controlled on a beta-blocker. He worked as a delivery driver and was an ex-smoker with a 30-pack/year history. He had no recent travel, vaccination, or unusual contact with animals. However, he reported an insect bite 6 months ago associated with an erythematous bullseye-like rash.

On admission, he was afebrile and had stable vital signs. The electrocardiogram showed normal sinus rhythm with T-wave inversion in leads aVL and V1. Cardiovascular, respiratory, and abdominal examination was unremarkable. On neurological examination, he was alert and orientated. There was no cranial neuropathy. In the right lower limb, he had reduced tone and weakness, with hip and knee flexion 3/5, hip extension 3/5, knee extension 2/5, ankle dorsiflexion 3/5, and plantarflexion 2/5. Reflexes were absent in the right lower limb but otherwise normal elsewhere, and plantars were downgoing bilaterally. He had a normal sensory examination. There was no limb ataxia.

Over the next 24 h, he developed bilateral severe flaccid paresis of the lower limbs (right side: hip flexion 2/5, extension 3/5, abduction 3/5, adduction 3/5; knee flexion 2/5, extension 2/5, ankle dorsiflexion 1/5, and plantarflexion 2/5; left side: hip flexion 3/5, extension 4/5, abduction 3/5, adduction 3/5, knee flexion 3/5, extension 3/5, ankle dorsiflexion 4/5, and plantarflexion 4/5). He had bilaterally absent knee and ankle reflexes with upgoing plantar responses. The repeat sensory exam showed patchy impairment to pinprick sensation on the upper chest, and intact sensation of proprioception, light touch, and temperature. The bladder scan revealed urinary retention (410 ml post-void volume), and there was reduced anal tone with intact sensation.

Laboratory results on admission showed a normal complete blood count except for macrocytosis (106 fl). Liver and renal functions were in the normal range. C-reactive protein was normal (<5 mg/l), Erythrocyte sedimentation rate was 18 mm/h. Troponin serial data and D-dimer were negative. Blood alcohol level was high (161 mg/dl). Lipid profile showed elevated LDL-cholesterol (4.9 mmol/l) and low HDL-cholesterol (1.3 mmol/l). Hematinics (including serum vitamin B12, folic acid level, and iron studies), thyroid function, hemoglobin A1c, and serum angiotensin-converting enzyme level were in the normal range. SARS-CoV-2 RNA from nasopharyngeal swab and serum anti-SARS-CoV2 IgG were negative.

Chest x-ray did not identify acute pathology. Computerized tomography (CT) of the brain showed mild cerebral atrophy and mild periventricular low density suggesting chronic microvascular disease. Magnetic resonance imaging (MRI) of the brain and the whole spine with contrast revealed an abnormal, increased T2 signal in the anterior aspect of the spinal cord beginning at the T4 level and extending to the conus without associated edema or contrast enhancement (Figures 1, 2). The additional diffusion-weighted imaging (DWI) of the spinal cord did not have a sufficient resolution.

The imaging findings were consistent with a longitudinally extensive transverse myelitis (LETM) of potential autoimmune, paraneoplastic, or infective etiology. Anterior spinal cord infarction was also considered within the differential diagnoses given the MRI characteristics (hyperintense T2 signal localized to the anterior and central portion of the cord with butterfly shaped appearance) and the acute symptom onset with associating chest pain.

On the 3rd day of his admission, he was started on daily 1 g intravenous (IV) methylprednisolone, and he had a noticeable improvement of his muscle strength after the first dose. He finished a 3-day course of IV methylprednisolone. He was also commenced on daily oral 300 mg aspirin on the 4th day of the admission.

The repeat MRI of the whole spine on day 10 of his admission showed interval resolution of the T2 signal hyperintensity in the lower cord and conus.

CT of the thorax, abdomen, and pelvis (CT-TAP) with contrast showed no abnormality; 24-h ECG, ambulatory blood pressure monitor (ABPM), and echocardiogram showed normal studies.

The cerebrospinal fluid (CSF) analysis showed normal leukocyte count (<5/ml), normal glucose (3.6 mmol/l, paired serum glucose 6.1 mmol/l), and elevated protein (0.8 g/L, normal range: 0.15–0.45 g/L). CSF oligoclonal band (OCB) with paired serum was negative. Polymerase chain reaction (PCR) assays of the CSF sample for bacterial (*Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitis*, beta-hemolytic *Streptococcus* Group B, and *Streptococcus pneumoniae*), viral (cytomegalovirus, enterovirus, herpes simplex viruses 1 and 2, human herpesvirus 6, human

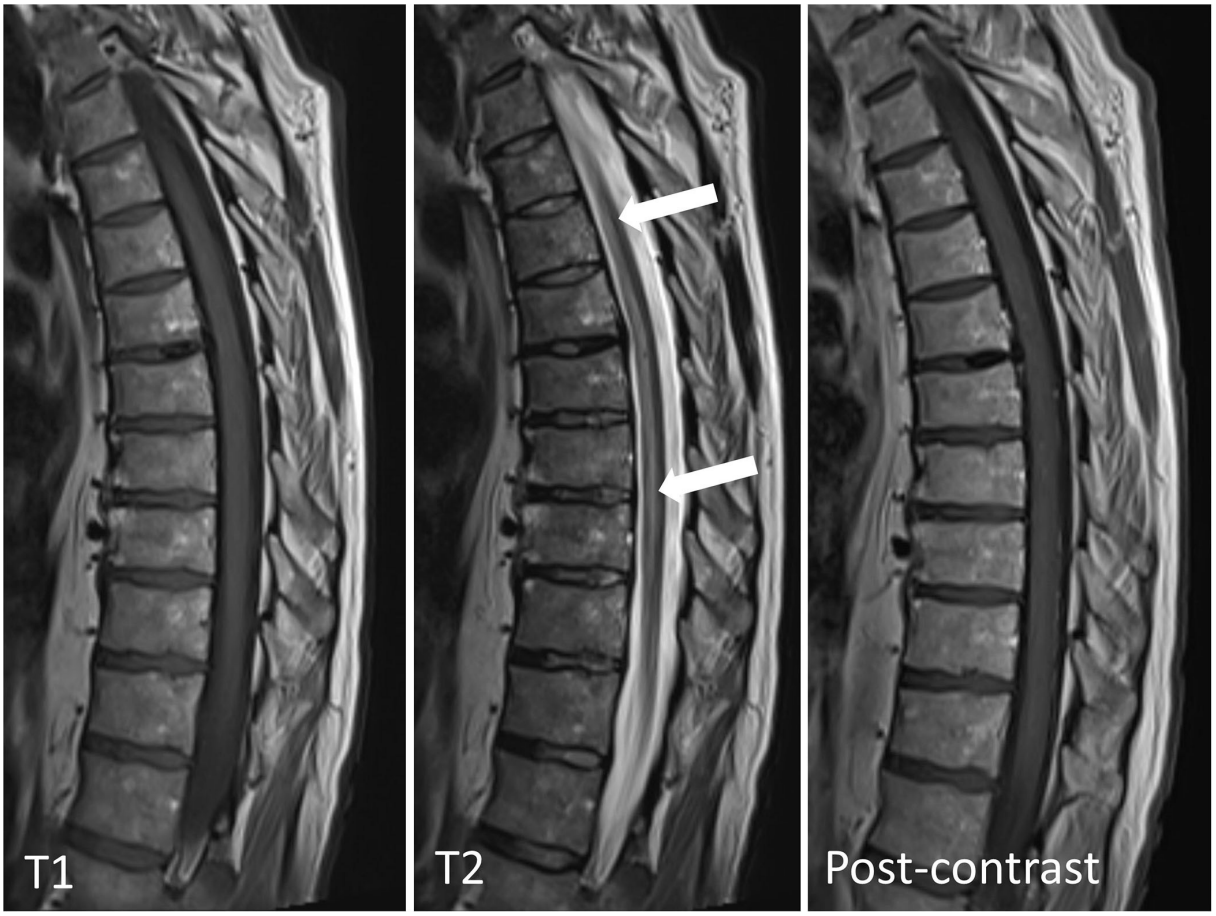

FIGURE 1
MRI of thoracic spine, sagittal view: non-enhancing high T2 signal in the anterior aspect of the spinal cord extending from T4 level to the conus without associated edema. The arrowheads point indicates the abnormal cord signal.

parechovirus, and varicella zoster), and yeast (Cryptococcus) neoformans/gattii infections were negative.

Vasculitis and autoimmune tests (including antinuclear, ANA, and antineutrophil cytoplasmic, ANCA), cardiolipin, beta-2-glycoprotein, anti-myelin oligodendrocyte glycoprotein (MOG), aquaporin-4, anti- CASPR2, NMDA- receptor, and anti- Lgil antibodies) were negative. Serology for different infectious diseases (human immunodeficiency viruses 1 and 2, syphilis, cytomegalovirus, Epstein-Barr virus, varicella zoster) returned negative except for the enzyme-linked immunosorbent assay (ELISA) for Lyme C6 antibody, which showed a strong positive result (3.02, normal 0–0.9), but the confirmatory serology immunoblot result was negative. As there was a high clinical suspicion for possible Lyme neuroborreliosis, he was started on 2 g ceftriaxone intravenously twice daily on day 12 of his admission, and a CSF sample was sent for Lyme immunoblot testing. Later, this identified the presence of intrathecal immunoglobulin G (IgG) against two specific Borrelia antigens, p21 and VlsE. He finished a 21-day course of IV ceftriaxone. A paraneoplastic neuronal screen was also carried out and revealed the presence of the amphiphysin antibody. Other onconeural antibodies (anti-Hu, Yo, Ri, Ma2, CV2/CRMP, Zic-4, Sox-1, Tr, titin, and Recoverin) were negative. He underwent positron emission tomography CT (PET-CT), but it did not identify any occult neoplasm.

The patient improved with rehabilitation and was discharged to a rehabilitation facility after 1 month of hospital admission. He was able to mobilize with a walking frame under supervision with minimal residual right lower limb weakness in 4 weeks. After 6 weeks, he was able to walk unaided with a stick, and bowel and bladder functions were fully recovered (Figure 3).

Discussion

Longitudinally extensive spinal cord lesions (LETMs) are defined as extensive involvement of the spinal cord where

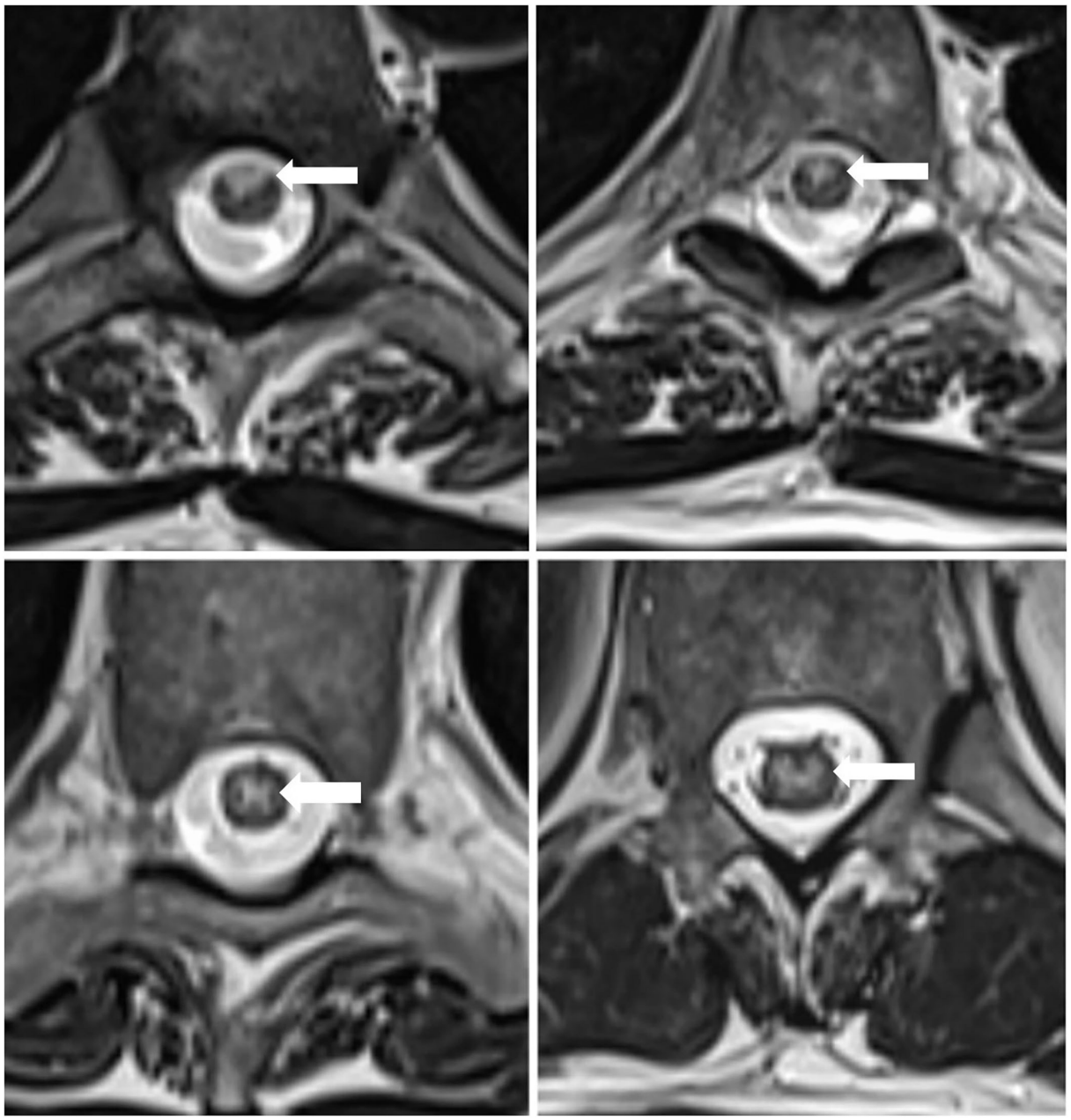

FIGURE 2
MRI of the thoracic spine, axial view: non-enhancing T2-hyperintensity in the anterior and centromedullar regions of the spinal cord. The arrowheads point indicates the abnormal cord signal.

an abnormal hyperintense T2-weighted signal affects at least three vertebral segments (6). The patient presented with symptoms, signs, and MRI scan features of an LETM. The clinical presentation was consistent with spinal cord infarction, autoimmune or idiopathic LETM. However, following extensive workup, several other possible causes were found, including infectious (Lyme neuroborreliosis), inflammatory and paraneoplastic etiologies.

Spinal cord infarction (SCI)

Two recent large retrospective studies showed that patients who were initially diagnosed with idiopathic transverse myelitis often had alternative myelopathy diagnoses, and vascular cause was found to be the second most common after inflammatory etiology (7, 8). Various vascular mechanisms can lead to myelopathies including arterial ischemia, venous ischemia or

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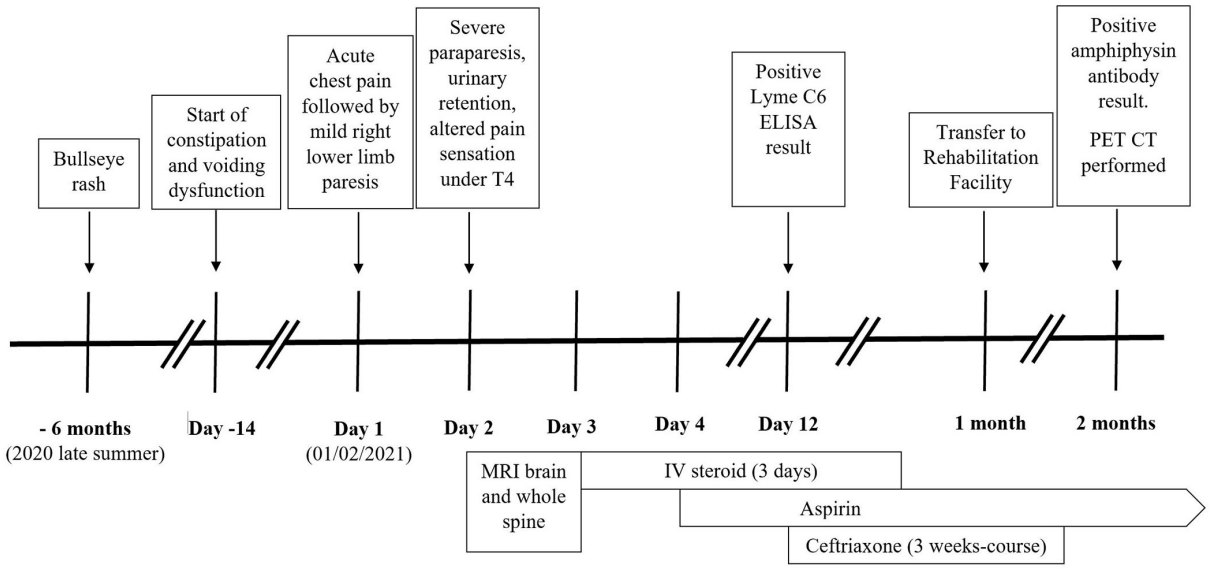

FIGURE 3
Case timeline.

congestion, hematomyelia, and extraparenchymal hemorrhage (9). Arterial ischemia can be divided into spinal cord transient ischemic attack, spontaneous spinal cord infarction, and periprocedural spinal cord infarction (9). SCI is a rare presentation due to the extensive collateral vascular supply of the spinal cord (10). The incidence is estimated at 3.1 per 100,000 people (9), representing 5–8% of acute myelopathies (11). Although SCI is more common in population with cardiovascular risk factors, it can also affect younger patients through various mechanisms (fibrocartilaginous embolism, coagulopathies, vertebral dissection, surfer's myelopathy, and cocaine use) (10). Rarely, systemic, infectious and paraneoplastic vasculitis can also affect the spinal cord vasculature leading to spinal cord infarction (12).

Symptoms of spinal cord infarction depend on the effected spinal cord region. Around 65% of spinal cord infarcts occur in the lower thoracic region (11). Insult of the anterior spinal artery territory can cause bilateral corticospinal tract deficit, lower motor neuron sign at the lesion level, loss of pain and temperature. Posterior spinal artery infarct results in dorsal column dysfunction (9).

Most commonly, patients have a sudden onset of symptoms (9). Around 70% of patients report acute back, chest, neck, or limb pain before the neurological deficit. This feature can be helpful to clinicians, because acute pain is atypical in myelitis (13). Patients usually develop flaccid muscle weakness with absent reflexes first. Upper motor neuron signs typically appear over time (11).

The typical MRI feature is T2 hyperintense signal in the territory of the effected artery. Most commonly, an anterior "pencil-like" lesion on sagittal sequences and an "owl/snake-eye" pattern on axial sequences are seen. These correspond to involvement of anterior horn cells, which are most vulnerable to ischemia (4). Significant spinal cord edema or contrast enhancement is unusual acutely (9). Diffusion-weighted imaging also recommended to be performed, but it has technical limitation, signal change can take days to evolve and its sensitivity is only 50% to 70% (9). Spinal cord infarction CSF analysis can show mild to moderate protein elevation (9).

This patient's MRI scan was suggestive of spinal cord infarction, and this was correlated with the initial clinical presentation. His CSF was also in keeping with this diagnosis. However, the clinical deficit seen in a spinal cord infarction would not typically improve with intravenous steroids, as what occurred in this patient (12).

Lyme neuroborreliosis and Lyme-associated myelitis

Lyme disease is an infectious disorder caused by tick-borne spirochetes of the *Borrelia burgdorferi sensulato* complex (*B. burgdorferi sensustricto*, *B. garinii*, *B. afzelii*, *B. spielmanii*, *B. bavariensis*, and *Candidatus B. mayonii*) (14, 15). Involvement of the nervous system is referred to as Lyme neuroborreliosis (LNB) (14). More than 95% of neurological presentations are considered as early Lyme neuroborreliosis with symptoms presenting <6 months after the infection. A minority (5%) of the cases count for late LNB with a disease duration between 6 months and

several years (16). Involvement of the central nervous system (CNS) in late LNB is rare and only occurs in 4% of cases, including myelitis, cerebral vasculitis, stroke-like signs due to occlusive vasculitis and cerebral infarction, chronic progressive encephalitis, encephalomyelitis with tetraspasticsyndrome, and spastic–ataxic gait disorder (16–18).

Most guidelines recommend a two-tiered testing protocol to confirm Lyme disease that relies on an initial sensitive screening test (commonly an ELISA) followed by a confirmatory immunoblot (IB) after a positive or equivocal ELISA result (17, 19).

Most frequently, LNB is associated with elevated CSF cell count (typically 10–1,000 leucocytes/ mm^3) and elevated CSF protein. A normal CSF cell count is rare, but it can be present (16).

CSF serology testing is also recommended by most guidelines. The presence of Bb-specific antibodies (in comparison to serum values and normalized for the state of the blood–brain barrier, called *Borrelia*-specific CSF/serum antibody index) is the evidence of intrathecal antibody production and considered the traditional diagnostic gold standard (17). The ESGBOR (the ESCIMID Study Group for Lyme borreliosis) guideline specifies that the diagnostic sensitivity of the intrathecal antibody synthesis is about 80% in a shorter disease duration (<8 weeks) and nearly 100% in a longer disease duration (20).

MRI findings in Lyme myelopathies show high variability. Lindland et al. (21) found that the cervical spinal cord is affected most frequently, lumbosacral myelitis is less common, and the majority is longitudinally extensive and centrally or slightly anteriorly located. Enhancement patterns ranged from no enhancement to nodular or diffusely extensive contrast enhancement (21).

A literature review by Kaiser et al. summarized the findings of published case reports of transverse myelitis secondary to Lyme disease from 1989 to 2018 with a total number of 48 (3). In this cohort, high variability of spinal cord lesion localization and degree of involvement was noted. The spinal MRI demonstrated spinal cord edema in 12 cases, and 1 case had a poliomyelitis pattern with anterior horn involvement. Seven of the cases discussed in their review had similar thoracic and lumbar longitudinally extensive spinal lesions similar to our patient.

In addition to the literature review by Kaiser et al., we found seven additional reported cases of Lyme-associated transverse myelitis in the adult population published in English literature (22–28). Our literature search involved articles on PubMed written in the English language.

It is recognized that an initial positive result of ELISA testing for Lyme disease may represent a false positive result, and this needs to be confirmed by immunoblot testing. In this patient's case, the confirmatory serology test was negative. In addition, the CSF white cell count was $< 5/mm^3$, and Lyme neuroborreliosis does not typically improve with steroid treatment (16). However, his CSF testing later identified intrathecal immunoglobulins directed against two *Borrelia*-specific antigens, which again raised the possibility of this being due to Lyme infection. A 21-day course of IV ceftriaxone was therefore started.

Myelopathy associated with amphiphysin antibody

The amphiphysin antibody is considered a well-characterized paraneoplastic antibody commonly associated with small cell lung cancer and breast cancer (29). Stiff person syndrome is the most well-known clinical presentation with amphiphysin antibody, but cases of rapidly progressive myelopathy and LETMs have been also reported (30). A comprehensive review of amphiphysinrelated neurological presentations by Pittock et al. (30) looked at the results of 120,000 patients who were tested for paraneoplastic antibodies. The amphiphysin antibody was detected, in total, 71 of the patients. The neurological presentations included, neuropathy, encephalopathy, myelopathy, stiff-man phenomenon, and cerebellar syndrome. Myelopathy was confirmed in 17 patients. Out of the 71 patients, cancer was found in 50 patients, proven histologically in 46 patients, and most of them had small cell lung carcinoma or breast cancer. The neurological presentation preceded cancer detection in 90% of the patients. In the case of 20 patients, cancer was not identified in the initial investigation but was detected during the 2 years of surveillance. Another retrospective study carried out by Flanagan et al. looked at the results of 31 patients who presented with isolated myelopathies and either had a known coexisting cancer or tested positive for paraneoplastic antibody with strong cancer association (31). All the patients presented with ether subacute or insidious onset. Nine of the patients had amphiphysin antibodies. Spinal MRI showed T2 signal abnormalities in 20 patients (65%), and 14 patients had a longitudinally extensive abnormality involving more than 3 vertebral segments. In 15 patients, it showed a symmetric tract or gray matter-specific signal abnormality, and gadolinium enhancement was present in 13 patients. Cancer was confirmed in 87% of the patients. Myelopathy preceded cancer diagnosis in 18 patients, and seven patients were initially considered to have primary progressive multiple sclerosis.

This patient was assessed for an occult malignancy, including CT and PET scanning, which was negative. Patients with a paraneoplastic disorder usually only show some improvement with treatment of the underlying malignancy; however, a temporary improvement may occur with immune therapy, including steroid treatment. This improvement would not usually be sustained, in the absence of definitive treatment of the malignancy (30, 31). It is possible for paraneoplastic neurological disorders to present some time before the causative malignancy can be identified. Therefore, continued interval

surveillance for malignancy is indicated in these cases, and that will be conducted in our patient, too.

Conclusion

Acute myelopathies represent a heterogeneous group of disorders with distinct etiologies and clinical and radiologic features (2). We describe the diagnostic challenges of a steroid-responsive longitudinally extensive spinal cord lesion with radiological features of anterior spinal infarct and a simultaneous finding of intrathecal Lyme and serum amphiphysin antibodies. According to our knowledge, no similar case has been described in the literature where all the rare myelopathy etiologies were found in the same individual and could explain the clinical presentation. The MRI findings (anterior involvement and butterfly-shaped T2 hyperintense signal), acute paresis, associated chest pain, and significant cardiovascular risk factors supported a diagnosis of spinal cord infarction. In parallel, our patient also reported a bullseye rash 6 months before his acute symptoms, complained of autonomic dysfunction 2 weeks prior to the acute symptoms, and presence of intrathecal IgG against two specific *Borrelia* antigens (p21 and VlsE), which confirmed Lyme neuroborreliosis. He had an excellent clinical response to steroids and ceftriaxone with steady recovery during his admission. These features are supportive for LETM caused by late Lyme neuroborreliosis or possible Lyme-associated vasculitic infarction of the spinal cord. Finally, the amphiphysin antibody was also detected in his serum sample, which can be associated with isolated LETM, and the presence of the amphiphysin antibody can precede cancer detection up to 2 years (30). Although the CT TAP and PET- CT during his admission did not identify any occult neoplasm, he will need a close follow-up in the future. In this man's case, it is not possible to say with absolute certainty whether there was one unique cause of his presentation, with the other possible causes being co-incidental or false positive, or whether in fact he had the most unusual coincidence of three different causes of his LETM. The improvement with intravenous steroids argues against this being solely due to isolated spinal cord infarction; the previous rash and CSF immunoglobulin findings are suggestive of Lyme etiology, which was treated with appropriate antibiotic therapy, and the amphiphysin antibody result means that he will need an ongoing follow-up and surveillance for an occult malignancy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

MK conceived of and drafted the manuscript. ED, MA, AM, and PB reviewed, revised, and edited the manuscript. All authors were involved in the care of the patient and read and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cross species transmission of pseudorabies virus leads to human encephalitis and visual impairment: A case report

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Pseudorabies virus (PRV) is a common pig infectious disease. There have been few reports of PRV infection in humans. The patient in this article had acute onset, which was manifested by fever, epilepsy, disturbance of consciousness, and other symptoms. The disease progressed rapidly and worsened in a short time so the ventilator had to be used to assist breathing. In the later stage of treatment, serious visual impairment also occurred. Pseudorabies virus was found in cerebrospinal fluid by second-generation gene sequencing (NGS). This indicates that the pseudorabies virus can spread across species, leading to human encephalitis and severe visual impairment. Therefore, attention should be paid to this disease, active prevention, and early detection are helpful to improve the treatment effect.

KEYWORDS

pseudorabies virus, viral encephalitis, secondary epilepsy, NGS, endophthalmitis, cerebrospinal fluid

Introduction

Pseudorabies virus (PRV) is also known as porcine herpes virus type I, infectious bulbar paralysis virus, and so on. PRV is very common in pig infection, but there are few reports on PRV-infected people (1, 2). We evaluated a case of encephalitis with unknown etiology, rapid onset, severe clinical manifestations such as fever, epilepsy, disturbance of consciousness and visual impairment, and detected pseudorabies virus by second-generation sequencing (NGS). The report is as follows to improve clinicians' understanding of the disease.

Case report

On the evening of 14 April 2021, a 54-year-old male did not know that his slipper had fallen while walking, and did not respond to the family's inquiries. At about eight o 'clock in the evening, the patient had a fever, with the highest temperature of 41°C. After the local hospital gave diclofenac sodium symptomatic antipyretic, the temperature gradually decreased to normal. During this period, the patient did not answer questions.

At about 10 o'clock in the evening, the patient began to lift the right upper limb involuntarily. The next morning, the patient was found to have a poor response. He could open his eyes when people called him, but did not respond, accompanied by involuntary twitching of the right limb. There was no nausea, vomiting, palpitation, shortness of breath, and incontinence during the course of the disease. To seek further diagnosis and treatment, he came to our hospital and was admitted to our department by the outpatient clinic with "consciousness disorder to be examined." Past history: found diabetes for half a month, denied any other special history. Physical examination: T 37.3°C, P 98 times/min, R 20 times/min, BP 129/95 mmhg, drowsiness, no obvious abnormalities found in skin, mucosa, lymph nodes and cardiopulmonary abdominal examination, equal size and equal circle of bilateral pupils with 3 mm in diameter, slow light reflex, involuntary twitching of right limb, negative meningeal irritation sign, and no positive signs found in other nervous systems physical examination. Initial diagnosis of consciousness disorder to be examined: intracranial infection, secondary epilepsy?

Improve related examinations, blood routine: WBC 8.7 g/L, NE 76.4%, HGB 163 g/L, PLT 111 G/L, blood biochemistry: TBil 53.4 umol/L, NCBil 43.3 umol/L, SAA 21.4 mg/L. There were no abnormalities in the electrolyte, liver function, renal function, blood glucose, high-sensitivity C-reactive protein, erythrocyte sedimentation rate and coagulation function, as shown in Table 1. Electroencephalogram (EEG): the main rhythm of each lead was 10 HZα with medium and low amplitude, and the parietal and occipital region was dominant, with left and right asymmetry and poor amplitude modulation. The left lead had more rhythm and activity of 4–7 HZθ with medium and low amplitude, and slightly more activity of 3–3.5 HZδ, and the front head was very biased. Brain magnetic resonance imaging (MRI): multiple spots and bands of abnormal signals were found in the left insula and temporal cortex, T2WI and T2 flair showed hyperintensity, T1 flair showed isointensity and hypointensity, and GD-DTPA enhanced scanning showed no obvious abnormal enhancement, as shown in Figure 1. Cranial MRA, MRV, neck vascular color ultrasound, chest CT, electrocardiogram, and heart color ultrasound showed no abnormalities. The patients were treated with epilepsy control, brain edema prevention, brain cell nutrition, anti-infection, water and electrolyte balance and liver protection, and closely monitor the changes of vital signs and mental pupils.

On 15 April, the patient was drowsy, still had intermittent twitching of the right lower limb, and coffee residue-like substances were extracted from the gastric tube. It was considered that stress ulcers occurred, and stomach protection drugs were added. In order to find out the cause, a lumbar puncture was performed to check the cerebrospinal fluid, and the pressure was 300 mm water column. The routine and biochemical results of cerebrospinal fluid are shown in Table 2. The diagnosis was considered viral encephalitis or autoimmune encephalitis, and antiviral combined with gamma globulin were added to the treatment. The serum and cerebrospinal fluid samples were sent to BGI for etiological second-generation sequencing examination, and the cerebrospinal fluid and serum were sent to kangshengda company for autoimmune encephalitis antibody detection. Dynamic monitoring of blood routine, electrolyte, liver and kidney function, blood glucose, CRP, and other related indicators during hospitalization are shown in Table 1. On 16 April, the patient was delirious, with a Glasgow (GCS) score of 3 points. He still had intermittent right limb twitching, intermittent fever, thick breathing sound, decreased blood oxygen saturation, and it was difficult to maintain stable vital signs. So he was urgently transferred to the central intensive care unit (ICU), and ventilator are assisted breathing was performed after endotracheal intubation.

On 19 April, the patient became drowsy. After people shouted, he could open his eyes and move according to the instructions. He still had an intermittent fever, the highest temperature was 38.6°C, there was no headache, the activity of the left limb was normal, the muscle strength of the right limb was grade 3, and there was no limb convulsion. Spontaneous breathing had been restored and the ventilator had been evacuated, but it is still in the state of endotracheal intubation. The second generation sequencing results of cerebrospinal fluid showed that it was infected with pseudorabies virus with a coverage rate of 1.86%, see Figure 2 for details. There was no abnormality in the second-generation sequencing of serum, and the antibodies of cerebrospinal fluid and serum to autoimmune encephalitis were negative. After inquiring about the medical history, we learned that the patient had been engaged in the pig industry for a long time. The patient had a clear diagnosis of viral encephalitis and continues to receive antiviral treatment. Considering that some of the patients were prone to retinitis leading to blindness, we invited ophthalmology to consult. Eye ophthalmologist examination: there was no congestion in the conjunctiva, the cornea was transparent, and the pupils of both eyes were very small, about 1.5 × 1 5 mm, direct and indirect light reflection existed, and it was difficult to peep into the fundus through ophthalmoscopy. On 22 April, the lumbar puncture was rechecked, the pressure was 220 mm water column, the routine and biochemical results of cerebrospinal fluid were not significantly changed. On 24 April, the patient's mind improved, the activity of the right limb was still poor, and the pupils on both sides were equal round, with a diameter of 3 mm. Re-examination of cranial MRI showed that the left frontotemporal insula had abnormal signals and meningeal changes, and the possibility of inflammatory lesions was high, which was better than before. On 27 April, the patient still had fever, the highest body temperature was 37.8°C, and the right muscle strength was grade 3. After pulling out the endotracheal intubation, the respiration was steady.

On 29 April, the patient could speak clearly, but the speech did not accord with the scene, and he was restless

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TABLE 1 Laboratory dynamic examination results of patients with pseudorabies virus encephalitis.

Test items	Apr 14	Apr 16	Apr 17	Apr 19	Apr 23	Apr 28	May 12	Jun 4
WBC (G/L)	8.7	13.1	8.9	5.6	8.7	9.4	4.5	4.7
NEU (%)	76.4	91.5	93.1	91.6	85.4	82.2	59.8	69.9
HGB (g/L)	163	152	146	148	137	120	117	111
PLT (G/L)	111	115	108	108	76	126	132	128
K^+ (mmol/L)	4.2	3.9	3.8	3.9	3.9	4.1	3.3	3.7
Na^+ (mmol/L)	136.5	140.6	147.4	152.4	144.1	139.1	138.1	139.4
ALT (U/L)	14.3	14.4	14.1	19.6	175.7	28.4	7.9	15.9
AST (U/L)	21.5	-	13.7	27.1	137.1	46.6	21.4	17.4
γ-GT (U/L)	25.9	19.9	22.4	29.7	76	51.1	50.1	39.1
ALP (U/L)	52.9	47.8	54.7	58.8	64.9	58.5	47.8	48.2
Alb (g/L)	40.7	36.2	33.7	31.3	31.1	38.2	37.1	38.9
A/G	1.3	1.4	0.8	0.6	0.6	1.1	1.3	1.6
Glu (mmol/L)	9.5	11.3	14.7	20.5	11.6	7.4	3.3	6.5
TBil (umol/L)	53.4	12.1	15.1	10.6	14.9	16.4	12.4	16.4
NCBil (umol/L)	43.3	0.8	11.4	7.2	9.8	11.7	10.3	13.3
CBil (umol/L)	10.1	11.3	3.7	3.4	5.1	4.7	2.1	3.1
Urea (mmol/L)	5.9	7.1	9.5	14.5	10.7	4.9	3.9	2.6
Cr (umol/L)	82.1	86.8	82.9	89.1	75.7	64.7	80.3	48.9
UA (umol/L)	328.7	158.7	262.6	411.8	317.5	214.1	268.3	258.2
NH3 (umol/L)	18.3	18.2	7.1	33.3	23.9	11.7	13.4	18.3
PA (mg/L)	436.2	78.3	149.2	195.1	215.6	222.8	195.3	204.1
Osm (mmol/L)	297	307	327	348	318	299	290	295
hsCRP (mg/L)	3.1	82.9	53.7	-	-	-	5.9	-
5-NT (U/L)	1.8	1.6	1.3	0.4	0.5	1.7	2.1	2.1

intermittently. Physical examination showed that memory and calculation ability were decreased, bilateral pupils were equal in size and circle, 5 mm in diameter, right muscle strength was grade 4, Risperidone was added for symptomatic treatment, and the rest remained unchanged. Therefore, we asked for ophthalmic consultation. Ophthalmic examination: VOD: 0.25, VOS: finger/2.5 m, fixed pupils in both eyes, mydriasis, 5 × 5 mm, fundoscopy showed that the retina at the posterior pole was flattened, no obvious hemorrhage or exudation was found. Therapeutically, antiviral eye drops and other local treatments were administered locally.

On 04 May, the patient was conscious, without irritability, and the muscle strength of the right limb was further improved, but the vision was still unclear. After reexamination of lumbar puncture, the cerebrospinal fluid pressure was 140 mm water column, the protein content increased, and there was no significant change in the rest. On 5 May, invited ophthalmology to consult again. Ophthalmic examination: VOD: 0.1 (+ 4.75d / + 1.25d × 155 corrections no response), VOS: 0.1 (+ 5.00d / + 1.50D × 180 corrections no response); Intraocular pressure: od 14 mmHg, os 14 mmHg; There was no congestion in the conjunctiva of both eyes, the cornea was transparent, the anterior chamber was deep, the crystal was transparent, the pupils of both eyes were fixed and dilated, 5 × 5 mm, the pupil margin was adhered to the front surface of the lens, pigmented keratic precipitates (KP) could be seen in the pupil area, fundus: vitreous cavity was turbid, the boundary of the optic disc could be seen faintly, and white linear changes could be seen in the peripheral omentum; The right eye macular OCT showed that the morphology of the right eye fovea was recognizable, the inner surface of the macular retina was still smooth, and the local ellipsoid structure was slightly disordered, see Figure 2 for details. The OCT of the left eye macular did not cooperate. B-ultrasound showed vitreous opacity in both eyes. It is necessary to continue to give eye drops to the patient for treatment.

On 12 May, the patient complained of transient dizziness when he got up and moving, which disappeared after standing. Both eyes were still blurred, bilateral pupils were dilated to the edge, the light reflex disappeared. The patient asked to be transferred to a superior hospital for treatment. On 3 June, the patient came to the hospital for follow-up visit, and the pathological changes in both eyes were no better than before. Reexamination of MRI showed that the range of inflammatory lesions was slightly smaller than before.

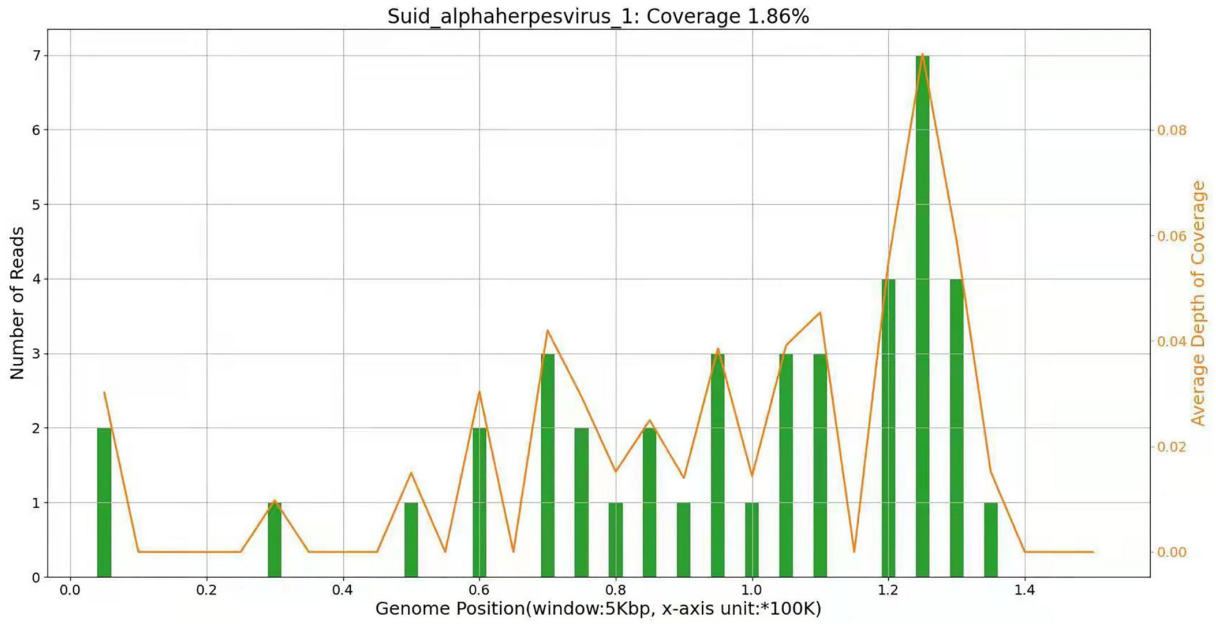

FIGURE 1
On 15 April, NGS results of cerebrospinal fluid showed that the pathogen of encephalitis in this patient was pseudorabies virus, and the genome coverage rate was 1.86%.

TABLE 2 Cerebrospinal fluid examination results of patients with pseudorabies virus encephalitis.

CSF test items	Apr 15	Apr 22	May 4	Jun 4
Pressure(mmH_2O)	300	220	140	130
Color	No	No	No	No
Transparent	Yes	Yes	Yes	Yes
Clot	No	No	No	No
WBC (10^6/L)	39	37	31	27
Monocytes (%)	89	96	98	
Multilobar nuclear cells (%)	11	4	2	
PRO (g/L)	0.23	0.29	0.45	0.39
Cl (mmol/L)	126.68	136.48	126.08	131.38
Glu (mmol/L)	6.21	5.41	2.75	3.89
LDH (U/L)	14.8	29.6	13.8	15.7
ADA (U/L)	1.5	1.5	0.3	4.7

Discussion

Pseudorabies virus belongs to a herpesvirus subfamily in Herpesviridae, which is round or oval in shape. It is composed of double-stranded DNA, 20 hedral nucleocapsid, envelope, and lipid bilayer from inside to outside. The size of double-stranded DNA is about 150 kb and the content of G + C is 74%; The envelope is located in the outermost layer of virus particles and consists of 11 glycoproteins and 4 non-glycoproteins. It plays an important role in the process of PRV infecting host cells. PRV is widely distributed all over the world, and pigs are the main natural host and source of infection. PRV is neurophilic and can retrogradely infect the nervous system from postsynaptic to presynaptic neurons, which can cause pseudorabies (PR). The clinical symptoms of sick pigs are very serious. The main pathological changes are encephalomyelitis, ganglionitis, hemorrhagic pneumonia, and necrotizing lymphadenitis, which can lead to death in severe cases (1, 2).

In recent years, studies have found that PRV can cause cross-species transmission and induce human infection. In Mravak et al. (3), reported three suspected PRV infection cases with positive serum antibodies. All three patients showed prodromal symptoms after close contact with livestock for 1–3 weeks, followed by self-limited multi-cranial nerve involvement, suggesting that PRV can infect humans (3). In 2018, a pig farmer developed fever, headache, and visual impairment. AI JW et al. detected the unique PRV gene sequence using NGS, and detected the presence of PRV DNA in the patient's vitreous humor using real-time PCR. PRV antibody was detected from the plasma 4 months after the patient's onset, confirming that PRV can spread and infect humans across species (4). In 2018, all four patients developed a high fever, headache and chills after occupational exposure to raw pork, and epilepsy, coma and respiratory failure occurred rapidly

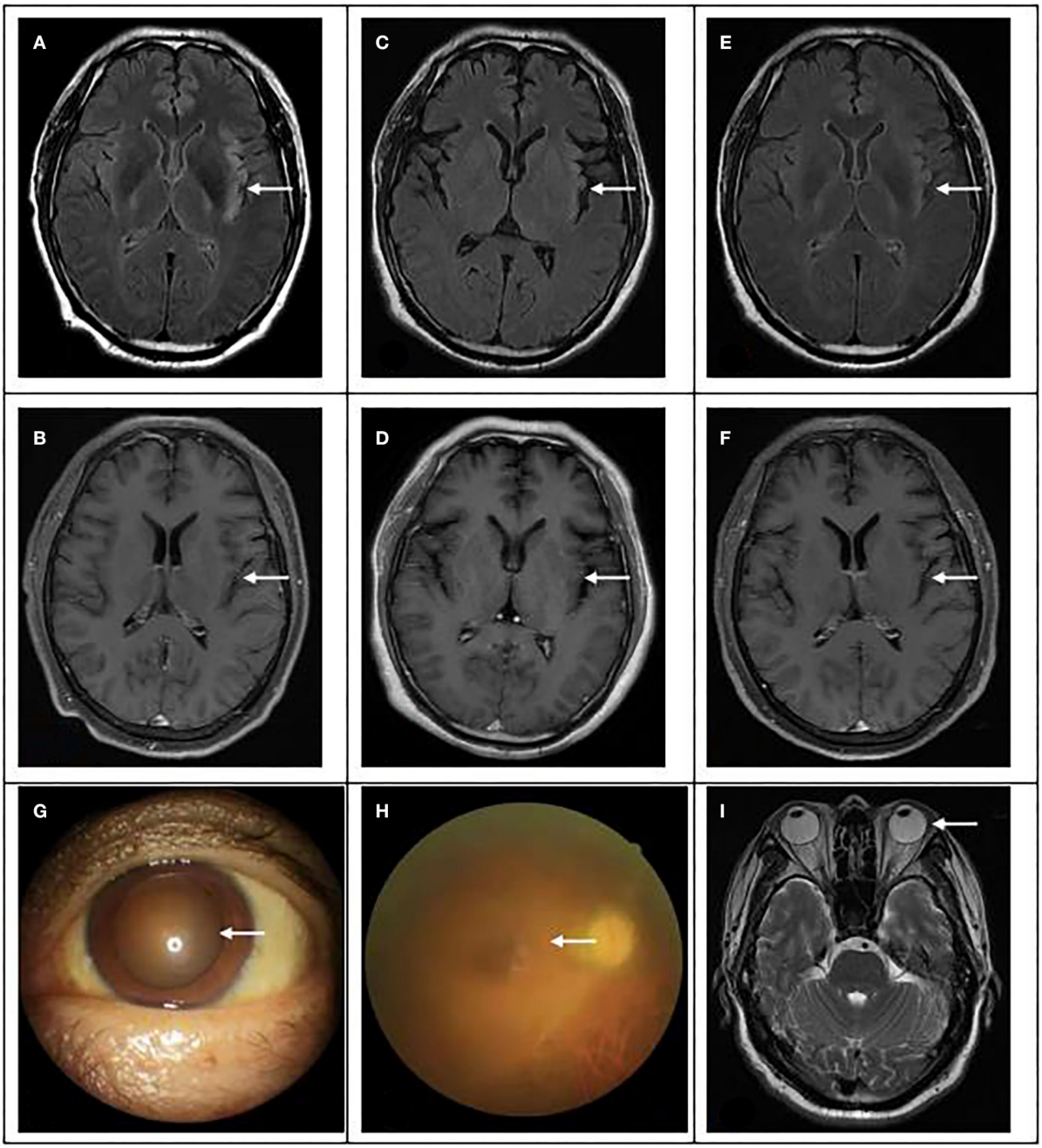

FIGURE 2
Brain magnetic resonance and eye examination results. **(A,B)** On 15 April, brain magnetic resonance showed multiple spots and bands of abnormal signals in the left insular and temporal cortex, high signal in T2WI and T2flair, and equal and low signal in T1flair. **(C,D)** On 24 April, MRI showed abnormal signal and meningeal changes in the left frontal temporal insula. **(E,F)** On 04 June, magnetic resonance imaging showed that the range of inflammatory lesions was slightly smaller than before. **(G)** The pupil of the patient was significantly enlarged, with a diameter of 5 × 5 mm. **(H)** Fundus lesions: vitreous cavity is turbid, the optic disc boundary is indistinctly seen, and white line changes can be seen in the peripheral momentum. **(I)**: No abnormality was found in eyeball magnetic resonance.

within 1–4 days. CSF analysis showed a slight increase in leukocyte count, and cranial MRI showed high T2 weighted values of bilateral temporal lobes and basal ganglia. PRV sequences were detected in cerebrospinal fluid samples of two patients through NGS. Therefore, Zhao et al. reported for the first time that PRV can cause human encephalitis (5).

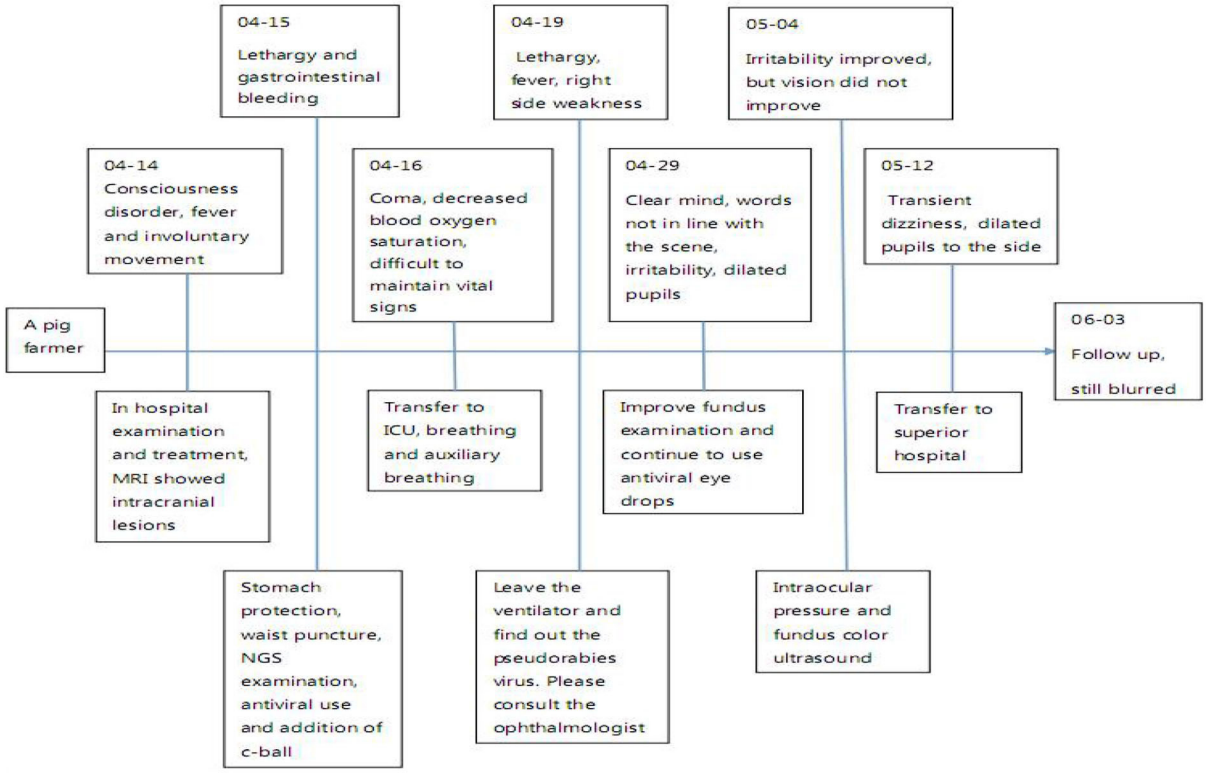

FIGURE 3
Timeline figure of the clinical information.

In 2019, Yang HN et al. reported a case of human PRV encephalitis in China. A 43 year old patient developed headache, convulsion, and coma within 3 days after contacting raw pork. Plain CT scan of the brain showed low density in the left marginal lobe, bilateral basal ganglia and occipital lobe. PRV nucleic acid sequence and PRV antibody were detected in the patient's cerebrospinal fluid, confirming PRV encephalitis (6). In addition, there were also cases reported that patients had acute fever, disturbance of consciousness, convulsions and respiratory failure, and some cases had retinitis, which worsens rapidly. Severe cases needed to be admitted to ICU to use mechanical ventilation to assist breathing (7–9). In conclusion, the cross species transmission of PRV to humans is gradually confirmed by research.

The current diagnostic criteria of viral encephalitis are as follows: 1) The change of mental state lasts for more than 24 h, except for other reasons; 2) Seizures, excluding previous history of epilepsy; 3) Body temperature $>$ 38°C before or within 72 h after onset; 4) Emerging focal clinical manifestations of the nervous system; 5) CSF leukocyte $>$ 5×10^6/L; 6) Imaging suggests encephalitis; 7) Abnormal EEG indicates encephalitis. If more than 3 items are met, encephalitis can be considered in clinical diagnosis. The main features of this case: having a history of contact with pigs, acute onset, fever, epilepsy, disturbance of consciousness and visual impairment, requiring ICU for treatment, and even using a ventilator to assist breathing. (Figure 3) The cerebrospinal fluid examination was consistent with the characteristics of viral encephalitis. Brain magnetic resonance imaging showed T2WI high signal. NGS detected pseudorabies virus from cerebrospinal fluid. Although the PRV coverage was relatively low, the mapped readings were evenly distributed in the whole PRV genome. Based on the above characteristics, it was diagnosed as pseudorabies virus encephalitis, whose clinical manifestations should be differentiated from autoimmune encephalitis, optic neuromyelitis, Vogt-Koyanagi-Harada syndrome (VKH), lymphoma, and other diseases (10).

In terms of treatment, previous research reports suggest that to avoid possible delays, antiviral treatment should be given as soon as possible. Delaying antiviral treatment for more than 48 h may lead to poor prognosis, including ocular complications—acute retinal necrosis syndrome (11). Although after onset, the patient was given Ganciclovir antiviral and

treated with Dexamethasone to resist inflammation and Gamma globulin to remove harmful antibodies at the first time, the condition was still aggravated and developed respiratory failure, and required ventilator to assist respiratory treatment. About half a month after the course of the disease, the patient had obvious visual impairment. Finally, although encephalitis was controlled, the visual impairment was difficult to reverse. In addition, the patient had obvious transient hyperbilirubinemia in the early stage of onset, it was not clear whether it was related to acute viral infection. Transient damage to liver function occurred in the course of the disease, which improved after liver protection treatment, and the mechanism needs to be studied.

Conclusion

PRV is a newly discovered cross-species transmission virus. It has the characteristics of acute onset, rapid progression, severe nervous system damage, prone to respiratory failure, visual impairment, etc., and the disease has high morbidity and mortality. Early diagnosis and timely treatment can achieve certain curative effects. NGS is a rapid and accurate method to detect PRV infection. Therefore, in clinical work, if a patient with similar clinical manifestations to the patient in this article is admitted, it is necessary to ask in detail whether there is a history of feeding pigs and pork processing, and to carry out serological tests, especially pathogenic NGS tests, in order to exclude pseudorabies viral encephalitis. At the same time, it also reminds employees engaged in animal husbandry that they need to raise their awareness of self-protection.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

YB and HH drafted the manuscript, sorted out the clinical data of patients, consulted the literature, and reviewed English grammar. NW, HA, WH, and YB conducted a follow-up visit to the patients before and after treatment, collected detailed clinical data, and reviewed the manuscript. YB and JC reviewed and proofread the whole article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Acute invasive mucormycosis rhinosinusitis causing multigroup cranial nerve injury and meningitis—A case report

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This study reported a case of a Rhino-Orbital-Cerebral Mycosis (ROCM) patient with multiple groups of cranial nerve damage as the primary clinical manifestation, confirmed by histopathology and cerebrospinal fluid metagenomic next-generation sequencing (mNGS) technology. Relying on the MRI3D-SPACE technology, we observed the location and extent of the cranial nerve damage in the patient. The results suggested that fungal meningoencephalitis caused by mucor may enter the skull retrograde along the cranial nerve perineurium. The patient was admitted to the hospital with a preliminary diagnosis of mucormycosis infection after 1.5 days of mouth deviation. We treated the patient immediately with intravenous amphotericin B liposomes. After 21 days of hospitalization, the clinical symptoms of the patient did not improve significantly. The patient was discharged due to financial difficulties and antifungal treatment at home, and his disease had stabilized at the 6-month follow-up.

KEYWORDS

Mucor, cranial nerve, 3D-SPACE technology, mNGS, infection

Introduction

Fungal infections of paranasal sinuses are common in the clinic and can be classified into invasive and noninvasive infections according to the progression of the disease (1, 2). Fungal infections of paranasal sinuses often require a differential diagnosis from chronic suppurative sinusitis, malignancy, sinus polyps, and necrotizing maxillary sinusitis (3–5). Early diagnosis of fungal sinusitis is usually critical, and most patients can be cured after early and timely diagnosis and reasonable treatment. Treatment is more complicated and prone to recurrence and poorer healing when delayed to a late stage (6, 7).

In 1969, Champion defined the simultaneous invasion of fungi into paranasal sinuses, eyes, and intracranial part of the brain as Rhino-Orbital-Cerebral Mycosis (ROCM), which belongs to acute invasive fungal rhinosinusitis (8). The main species responsible for invasive fungal rhinosinusitis infection are Mucor and Aspergillus, which belong to opportunistic pathogens (9, 10). The invasion routes can be divided into a direct spread and a transvascular invasion. Pathogens can enter the brain through the paranasal sinuses, orbit, extraocular muscles, ophthalmic artery, and optic nerve or drain to the cavernous sinus through the paranasal sinuses, orbital reflux veins, or intracranial infection.

Studies found that patients with ROCM may present with multiple cranial nerve palsy (function of the cranial nerves II, III, IV, V, and VI may be lost or impaired) (11, 12). The magnetic resonance 3D-SPACE sequence is a variation of the TSE sequence. Through reconstruction, the complex anatomical structure of the cranial nerve can be further clearly displayed at any level and direction, which is vital for observing the path, distribution, and injury of the cranial nerve (13). In this study, we reported a ROCM patient with multiple groups of cranial nerve damage as the primary clinical manifestation, confirmed by histopathology and cerebrospinal fluid mNGS technology. We used the MRI3D-SPACE technique to provide detailed observation and better assess the extent of ROCM patients with cranial nerve injury due to the fungal meningoencephalitis caused by Mucor.

Case description

A 36-year-old male patient was admitted to our hospital for mouth deviation for 1.5 days. The patient was admitted to the Department of Endocrinology 1 month ago due to diabetic ketoacidosis (10:00 a.m. on June 18, 2021). Physical examination showed that the patient had clear consciousness, less fluent speech, right peripheral facial paralysis, and a right deviation of the protruding tongue; his muscle strength and tension in four extremities were normal, and the bilateral Babinski sign was negative. Auxiliary urine routine examination revealed urine glucose of 4+, urine ketone body of 3+, urine protein of 1+, and glycosylated hemoglobin of 10.1%. No apparent abnormalities were observed on cranial MRI. Chest CT showed small solid nodules in the upper lobe of the right lung and the lower lobe of the left lung; ground-glass opacities in the medial segment of the right middle lobe indicated some inflammatory changes. Abdominal CT showed many colonic contents, which should be diagnosed based on clinical symptoms and regarded as minor bowel dysfunction. At admission, the random fingertip blood glucose and blood ketones were 20.1 mmol/L and 6.4 mmol/L, respectively. After admission, the patient's condition gradually worsened, with restricted right eye movement, hoarseness, occasional febrile headache, nausea, and vomiting. On the fourth day of admission, the patient had clear consciousness, a hoarse voice, right eyelid ptosis, and eye proptosis, which was fixed in the primary position. The patient's right frontal striae disappeared, the right nasolabial fold was shallow, and his tongue was extended to the right. The patient had hypoalgesia on the right side of the face, normal muscle strength in the extremities, and meningeal stimulation signs (+). The complete set of immune indexes and five preoperative indicators were normal. The lumbar puncture indicated the pressure of 150 mmH_2O, a yellowish color cerebrospinal fluid, white blood cells of 109×10^6/L ($0–8\times10^6$/L), protein of 1,003 mg/L (0.15–0.45 g/L), chloride of 111.2 mmol/L, and glucose of 5.54 mmol/L. Cerebrospinal fluid cytology tests showed a mixed cellular response. mNGS of *Rhizopus oryzae*'s sequence number was 19 (Total length was 1350 bp, 0.00334% coverage, and 1.00 X average depth). Repeated head MRI showed the inflammation of cerebellar infarction, right paranasal sinuses, and ethmoid sinuses. The plain and enhanced 3D-SPACE sequence scanning showed abnormal enhancement of the right hypoglossal nerve, the facial nerve, the cisternal segment of the trigeminal nerve, the posterior wall of the orbit, the periphery of the right maxillary sinus, and the oral maxillofacial spaces (Figure 1). Amphotericin B liposome (triamcinolone acetonide) was immediately intravenously administered at an initial dose of 5 mg/d, and no significant side effects were observed. Then, 5 mg of amphotericin B was added daily until the maintenance dose of 40 mg/day was reached. On the seventh day of admission, the specimen of the patient was taken for pathological examination with the assistance of the otorhinolaryngology and the Department of Stomatology. After 1 week, the patient was diagnosed with mucormycosis infection due to microscopic visualization of Molds hyphae (Figure 1). After 21 days of hospitalization, the clinical symptoms of the patient did not improve significantly. The patient was discharged due to financial difficulties and was provided antifungal treatment at home. During hospitalization, the patient was on antifungal medication (liposomal amphotericin B) for 17 days; after discharge, he was switched to oral antifungal (voriconazole) for 6 months. During the six-month follow-up, the condition of the patient was relatively stable.

Discussion

Mucor belongs to the class Zygomycetes, order Mucorales, and the most common pathogenic bacteria are Rhizopus, Mucor, and Oryzae in the family Mucoraceae (14). In this case, the patient was infected with *R. oryzae*. The patient had been admitted to the Department of Endocrinology due to diabetic ketoacidosis. Mucormycosis has a complex disease course, rapid progression, high mortality, and intricate clinical manifestations. It is divided into six types, of which the naso-orbital brain type accounts for 36.4%. This patient was finally diagnosed with ROCM when combined with the clinical characteristics of sinus, orbit, meninges, cranial nerve injury, and pathogen detection. The case was complicated due to the involvement of the cranial nerve, meninges, and infarction in the distribution area of the posterior inferior cerebellar artery, suggesting that both pathways were involved in the pathogenic process.

Studies showed that the prevalence of fungal sinus disease has been increasing in recent decades. This may be due to increased awareness of medical examinations, overuse of antibiotics, and increased use of immunosuppressive drugs (15). Common clinical manifestations of ROCM include headache,

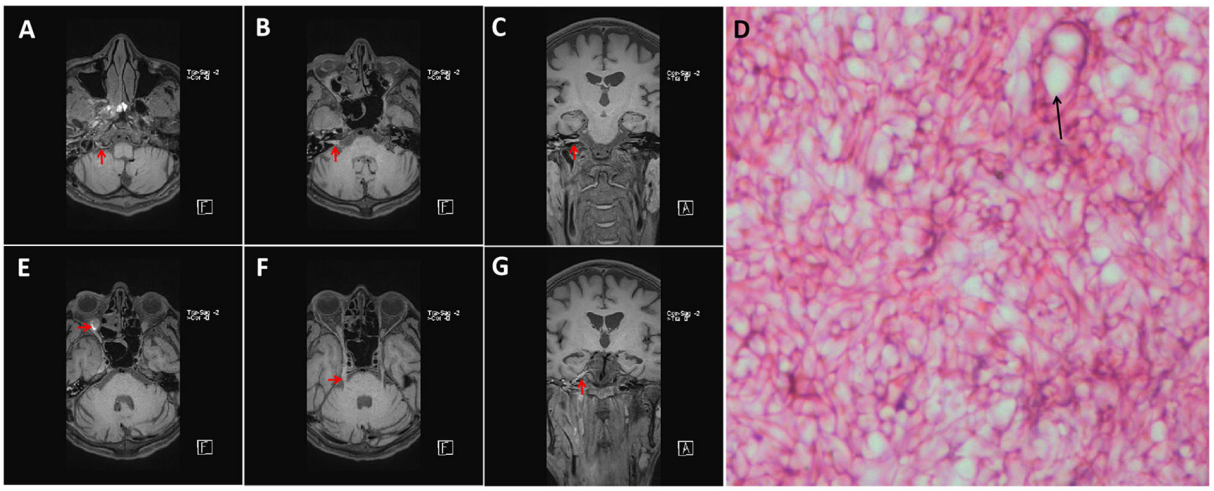

FIGURE 1
Enhanced MRI with 3D-T1-SPC sequence results of the patient (a standard dose of gadolinium). The MRI showed enhanced images of the right hypoglossal nerve **(A)**, the posterior orbital wall **(E)**, the facial nerve **(B,C)**, and the trigeminal nerve **(F,G)** slightly (Red Arrow). Microscopic photograph showing hyphae and Sporangium (Black Arrow) in HE staining [**(D)**, 400X].

fever, black nasal eschar, orbitofacial cellulitis, cranial nerve palsy, altered sensorium, and hemiparesis (16). However, in the present study, the patient was first admitted to the neurology department with a cranial nerve injury. His disease gradually aggravated to multiple groups of cranial nerve damage, leading to meningitis-like features that appeared successively. Early diagnosis is difficult because the patient has no nasal infection and other symptoms such as nasal congestion, runny nose, epistaxis, and typical ROCM imaging manifestations. Cranial nerves reach various parts of the head and the neck through the bony foramen of the skull base and meninges; hence, they are vulnerable to multiple local or systemic lesions throughout the process. Fungal infections such as mucormycosis can affect numerous cranial nerves and lead to fungal meningitis. ROCM is the most common clinical form of mucormycosis infection. Mucor can be transmitted *via* the nasal cavity, the paranasal sinuses, thje neck, and the orbit into the cranial cavity, causing brain infection and involvement of the cranial nerves (17). The definite diagnosis and treatment include a comprehensive analysis of the patient, finding the site of cranial nerve injury, and performing a lumbar puncture to find pathogens. Due to the slender anatomy, complex course, and overlapping surrounding structures of cranial nerves, standard radiographic methods cannot show their structures well. With the advancement of technology, 3D high-resolution body scanning technology can display the cranial nerve structure through 3D reconstruction and accurately measure each cranial nerve's course angle and brain cisternal segment length (13). The 3D-SPACE sequence has the best imaging effect on cranial nerves (especially the cisternal segment), and the scanning time is shorter. 3D-SPACE sequence enhancement showed abnormal enhancement of the right hypoglossal nerve, the facial nerve, and the trigeminal nerve's cisternal segment, which revealed the degree and location of cranial nerve injury. In addition, it was also found that the enhancement of cranial nerve was more pronounced at sites distant from the brainstem; no damage was found at the junction of cranial nerves and brainstem. The above two studies suggested that trichinosis can enter the skull retrogradely along the cranial nerves, adding to the etiological theory of intracranial infection. At the same time, relying on 3D-SPACE technology, it was also possible to assess the degree of mucormycosis cranial invasion and the effect of antifungal therapy. However, further studies with a large specimen size are still needed. The right eyeball of the patient was fixed without exophthalmos, and the possibility of incomplete orbital apex syndrome or superior orbital fissure syndrome was considered. The enhancement of the posterior wall of the eyeball could explain this clinical manifestation. Studies found that the appearance of orbital apex syndrome is highly suggestive of fungal infection, and the symptoms at this stage are typical of ROCM (18).

Cerebrospinal fluid testing showed that the patient was experiencing an inflammatory response. Therefore, screening for pathogens, in this case, becomes a critical adjunctive test to confirm the diagnosis of ROCM. An mNGS examination was performed directly to find the pathogen to confirm the diagnosis further. The mNGS technology has significant advantages in pathogen screening (19, 20), especially when suspected pathogen species are not identified. The patient was rapidly confirmed to have *R. oryzae* infection by mNGS and was given antifungal therapy. The diagnosis of ROCM in the patient was confirmed by analyzing the source of Mucor, which was

finally approved by histopathology. If patients with ROCM can be diagnosed early, they can receive active treatment. However, the rarity of ROCM leads to a high rate of misdiagnosis. Many cases are diagnosed before the end of life or even after the autopsy, so the mortality rate is also very high. Therefore, early lumbar puncture and rapid mNGS detection may indicate a better prognosis in patients with suspected fungal meningitis.

Conclusion

ROCM is easily misdiagnosed clinically and patients suffering from ROCM are susceptible to disability and death without timely treatment. In patients with a high clinical suspicion of ROCM, an MRI 3D-SPACE sequence is required to assess the extent of cranial nerve injury and to determine whether the pathogen has entered the skull. Cerebrospinal fluid mNGS technology offers tremendous advantages in pathogen screening. In patients with ROCM, signs of retrograde entry along cranial nerves and invasion of the meninges or brainstem should be promptly screened for pathogens from imaging by using cerebrospinal fluid mNGS technology. Fluconazole, itraconazole, and caspofungin are preferred for the prophylactic treatment of fungal infections. However, amphotericin B is widely accepted as an effective drug for treating Trichophyton. Its clinical application is limited due to its tendency to cause severe hepatic and renal side effects. Liposomal amphotericin B can be used preferentially in patients with ROCM because it has fewer therapeutic side effects than both amphotericin B. Besides, early aggressive and extensive surgical excision of fungal-infected inactivated tissue is also a preferred option. Early diagnosis and treatment are decisive for improving the prognosis of ROCM, and magnetic resonance 3D-SPACE sequence combined with mNGS technology may be of clinical application for early diagnosis of ROCM.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Harrison International Peace Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JH and TW organized and proofread the writing of the editorial. DC and TW wrote the manuscript draft. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Reversible encephalopathy associated with liposomal amphotericin B in a patient with cryptococcal meningitis

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Liposomal amphotericin B (L-AMB) is an anti-fungus medicine that has fewer side effects than traditional amphotericin B (AMB). Neurotoxicity of L-AMB has rarely been observed, and only one case of leukoencephalopathy during intravenous L-AMB has been reported. Herein, we described a patient with cryptococcal meningitis presenting with late-onset reversible encephalopathy associated with liposomal amphotericin B.

KEYWORDS

liposomal amphotericin B, leukoencephalopathy, encephalopathy, cryptococcal meningitis, neurotoxicity

Introduction

Amphotericin B (AMB) is an effective medicine for fungal infections. Side effects of AMB such as nephrotoxicity, hypokalemia, and fever are common, but neurotoxicity is rarely observed (1–3). Neurotoxic symptoms of AMB may include confusion, incoherence, delirium, psychological behavior, tremors, convulsions, loss of hearing, flaccid quadriparesis, akinetic mutism, and rapidly progressive leukoencephalopathy, while those have only be observed in a few cases (4). Additionally, the factors associated with the complications and the evolutions of the symptoms are still unclear.

Liposomal amphotericin B (L-AMB) is a unique lipid formulation with fewer side effects than traditional AMB. Currently, only one case with intravenous L-AMB was reported to present with leukoencephalopathy mimicking acute disseminated encephalomyelitis (ADEM) (5). In this study, we described a patient with cryptococcal meningitis presenting with late-onset reversible abnormality of white matter in the central nervous system during withdrawal of L-AMB.

Case report

A 39-year-old woman was referred to our department for headache and fever. On admission, brain magnetic resonance imaging (MRI) showed no abnormalities with white matter lesions or acute demyelinating lesions. The routine laboratory tests

including a complete blood count, liver and renal function, and myocardial enzymes were almost normal. HIV and hepatitis C were negative in the patient. Cerebrospinal fluid (CSF) examinations revealed increased intracranial pressure of 250 mmH_2O (normal 80–180 mmH_2O), an increased protein level of 510 mg/L (normal 150–450 mg/L), an elevated white cell count of 70 /μl (normal 0–10/μl), and a low glucose level of 2.38 mmol/L (normal 2.8–4.4 mmol/L). The ink stain of CSF was positive; cryptococcal polysaccharide capsular antigen in the CSF was positive; and CSF culture was also positive to cryptococcus neoformans. Collectively, the final diagnosis was cryptococcal meningitis. The weight of the patient was 40 kilograms. Consequently, the patient was treated with L-AMB (10–30 mg/d, gradually increasing in the induction phase), 5-flucytosine (25 mg/kg, 6-hourly), and fluconazole (400–800 mg/d) according to the guideline in China (6). Dexamethasone (1–5 mg/d) was also used to alleviate inflammation-induced edema intermittently (Figure 1). After 34 days of anti-fungal therapy, the headache and fever of the patient rapidly improved. In addition, CSF culture was negative for Cryptococcus, and she was discharged home after a 48-day course of anti-fungal therapy. Then, she was switched to consolidation therapeutic schedule shifting from L-AMB to fluconazole (400 mg orally, BID) and 5-flucytosine (25 mg/kg 6-hourly) (Figure 1).

L-AMB was discontinued after the patient was discharged home. However, 30 days after discharge, or on the 78th day after the initial anti-fungal therapy with a cumulative dose of 1,115 mg L-AMB therapy course, she suddenly presented with recurrent seizure attacks without any prodromal symptoms. She suffered an abrupt onset of upper extremities twitching; the episodes last for about 1 min without loss of consciousness and then complete recovery. On the second day, she showed hallucinations, altered moods, disorganized speech, aggressive behaviors, and other psychiatric behaviors. Subsequently, she developed a decreased level of consciousness from confusion to lethargy and to coma. On the third day, the patient began to recover following dehydration, rehydration, and sedation treatment, she gradually became awake with return of consciousness. On the fourth day, the central nervous system symptoms completely disappeared, and the patient recovered completely. During this episode, physical examination revealed disorders of consciousness, but pupillary light reflex, Babinski sign, and signs of meningeal irritation were negative. After the episode, she was conscious, and the other clinical neurologic examinations were normal. In addition, after 1 and 3 months of discharged follow-up, the patient was symptom free without any recurrence.

The routine examinations including complete blood count, liver and renal function, lactate dehydrogenase, creatine kinase, myocardial enzymes, and thyroid function tests were negative. Lumbar puncture was performed to exclude the recurrence of cryptococcal meningitis. However, the cryptococcal polysaccharide capsular antigen, ink stain, and culture of CSF did not support cryptococcal meningitis. The examinations of blood and CSF related to autoimmune encephalitis, demyelination, and metabolic diseases were negative.

Cerebral MRI showed bilaterally symmetric hyperintensity on DWI signal and abnormal hyperintensity on T2 weight image in the deep white matter and corpus callosum (Figure 2). The abnormal signals gradually reduced and disappeared 4 days later. A month after the encephalopathy, her brain MRI was almost normal (Figure 2). The electroencephalogram (EEG) was normal during the episode.

Discussion

We speculated the leukoencephalopathy of the patient might be related to the toxicity of L-AMB. First, there had not yet been any reports to present with the white matter lesions related to several other drugs that the patient had used, including fluconazole and 5-flucytosine. The fluconazole and 5-flucytosine had not been discontinued until the patient developed symptoms, and more importantly, they were still used between the episode and during recovery. However, some cases had reported that the leukoencephalopathy occurred with intravenous L-AMB (5). Therefore, we thought that it might possibly be related to the toxicity of L-AMB rather than fluconazole or 5-flucytosine. Additionally, the symptoms improved dramatically with non-specific treatment and the auto-antibodies relevant for demyelination and autoimmune encephalitis had not been found in the CSF and blood, thus the clinical and the imaging features did not support primary demyelinating disease or autoimmune encephalitis (7). Intriguingly, the leukoencephalopathy developed 30 days after the withdrawal of L-AMB. Bekersky et al. reported that the half-life of L-AMB elimination in tissues reached 1–4 weeks, which was longer than in plasma. In their study, rats received intravenous AMB for 91 days with a 30-day recovery. During recovery, the elimination of AMB from tissues was slower than its disappearance from plasma, and concentrations in liver and spleen greatly exceeded those in plasma (8). Therefore, it was reasonable to speculate that the half-life in brain tissue might be similar to liver and spleen tissues, and L-AMB might still be bio-available in the patient. Collectively, we thought that our patient might possibly have had one type of late-onset reversible leukoencephalopathy related to the toxicity of L-AMB. There were no similar reports of such cases, which could provide relevant reference for future clinical practice.

Cryptococcus meningitis could be associated with demyelinating leukoencephalopathy in a few cases. Wilcox et al. reported two cases of cryptococcus meningitis presenting with leukoencephalopathy prior to AMB therapy. They hypothesized that the lesions were induced by cryptococcal infection and parenchymal immune response (9). However, we thought that L-AMB, rather than cryptococcal infection itself,

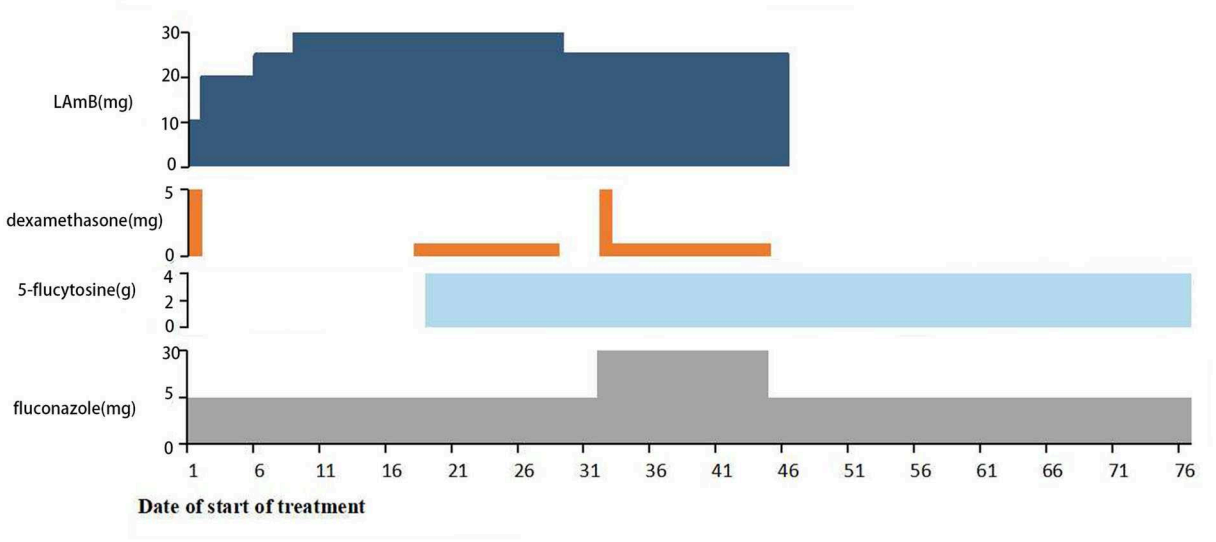

FIGURE 1
The medication of the patient during admission to our hospital. The patient first received induction therapy with L-AMB (10–30 mg/d) and fluconazole (400–800 mg/d), then followed by adding 5-flucytosine (25 mg/kg, 6-hourly) and intermittent use of Dexamethasone (1–5 mg/d).

was suspected as a cause of leukoencephalopathy because CSF examination excluded cryptococcal meningitis recurrence in our patient. Additionally, mild encephalitis/encephalopathy with a reversible splenial lesion (MERS) or reversible splenial lesion syndrome (RESLES) should be differentiated from the late-onset reversible leukoencephalopathy. MERS was a clinical-radiological syndrome proposed by Tada in 2004 (10), and usually triggered by viral infections and bacterial infections in children (11, 12). Prodromal symptoms included fever, cold-like reactions, digestive tract disturbances, abdominal pain, and headache (13), and fever was considered the most frequent prodromal symptom since it had been detected in most case series (10, 14–16). The characteristic clinical and imaging findings of the patient showed some similarities with MERS. However, our patient was a 39-year-old adult, which did not indicate MERS, and the patient had no prodromal symptoms such as fever, headache, and suspected infections. RESLES was a clinical imaging syndrome that involved the splenium of the corpus callosum, and a small part of lesions could spread to adjacent white matter (17). RESLES had various causes, including infections, high-altitude cerebral edema, seizures and antiepileptic drug withdrawal, and metabolic disturbances. However, there were no predisposing factors related to RESLES in our patient, such as blood pressure fluctuations and special drugs (17). Furthermore, the imaging features in our patient were characterized by the involvement of the genu of the corpus callosum as well as diffused and symmetrical white matter lesions, which was very rare in RESLES cases. Therefore, our patient should not be considered as MERS or RESLES.

The neurotoxic potential of AMB included confusion, incoherence, delirium, psychiatric behaviors, tremors, convulsions, hearing loss, flaccid quadriparesis, akinetic mutism, and rapidly progressive leukoencephalopathy (4, 18). Most previous cases with central nervous system symptoms were either immune-compromised or had a history of radiotherapy (4, 19–22). However, our patient was a 39-year-old woman with cryptococcal meningitis and had no significant medical history. The nervous side effects of L-AMB had rarely been reported. Sato et al. described the first case of cryptococcal meningitis showing progressive leukoencephalopathy that was associated with L-AMB (5). Previous studies had reported that the leukoencephalopathy occurred while receiving intravenous L-AMB (1, 5), and the symptoms were usually severe after treatment with a high dose of L-AMB or AMB. However, our patient was initially treated with L-AMB combinations of fluconazole and flucytosine, followed by a month after discontinuation of intravenous L-AMB, and then the patient showed transiently reversible encephalopathic features. It was interesting that the encephalopathy symptoms were dramatically alleviated with dehydration, rehydration, and sedation treatment. Of note, AMB-associated leukoencephalopathy predominantly showed the white matter lesions closely associated with primary lesions (4, 23), while our patient presented with white matter lesions widespread cerebral white matter, and corpus callosum T2 hyperintensities on MRI.

Previous studies demonstrated that the pathogenic mechanism of AMB-associated leukoencephalopathy was correlated with the AMB binding to myelin, which led to an

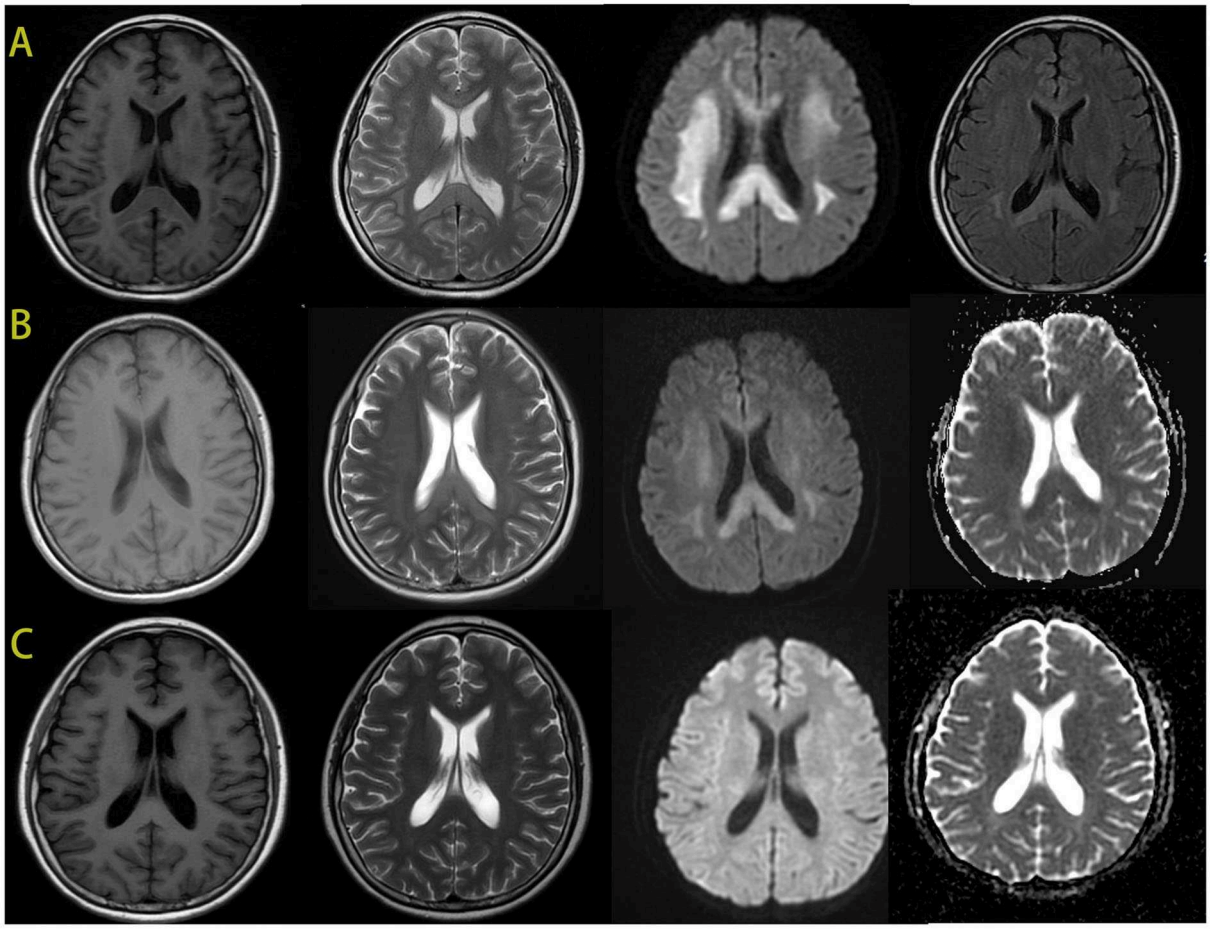

FIGURE 2
The brain MRI images of the patient. During the episode, the brain MRI showed hypointense signal in T1-weighted imaging and hyperintensity in T2-weighted imaging in the bilateral deep white matter and the corpus callosum. And there was an obviously bilaterally symmetric hyperintense DWI signal in the same region **(A)**. MRI after 4 days showed improvement of the abnormal signal in white matter, the hypointense ADC signal in the same region **(B)**. After 1 month, the images of her brain were almost normal **(C)**.

increase in membrane permeability and leakage of intracellular components, and eventually resulted in white matter lesion (4). The imaging characteristics of our patient showed hypointense signals on T1-weighted imaging and hyperintensity in T2-weighted imaging in the bilateral deep white matter and the corpus callosum and the hypointense ADC signal in the same region. Based on these characteristics, we also speculated that the pathogenesis might be due to L-AMB binding to myelin and leading to leakage of intracellular components, which then resulted in the cytotoxic edema and white matter lesions. However, the specific pathogenic mechanism needs to be confirmed by more cases.

Previous studies had reported that the leukoencephalopathy occurred while receiving intravenous L-AMB, and the symptoms were usually severe (1, 5). In contrast, our patient experienced acute encephalopathy during withdrawal of L-AMB, and the symptoms were mild, and the patient quickly showed dramatic improvement. This type of late-onset encephalopathy happening after withdrawal of L-AMB was very unusual, and had not been reported before. We speculated that the severity and onset of symptoms might be related to the dose and duration of L-AMB. More studies are warranted to confirm and better characterize these potentially important associations.

In summary, L-AMB had a significantly improved toxicity profile compared with AMB, while L-AMB-related leukoencephalopathy could be induced after withdrawal of L-AMB treatment. The late-onset reversible leukoencephalopathy might provide relevant reference for future clinical practice.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University. Written informed consent to participate in this study was provided by the patient. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

SL, HW, and CW were responsible for acquisition of data and drafting the manuscript. MZ was responsible for revising the manuscript. SL and DH were responsible for study concept or design, drafting, and revising the manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report and review of literature: Isolated intramedullary spinal neurocysticercosis

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Background: Cases of isolated intramedullary spinal neurocysticercosis are extremely rare. Only 25 cases have been reported before 2022. Due to its rarity, the diagnosis of spinal neurocysticercosis may be missed.

Case presentation: We describe a 37-year-old female patient who developed back pain and lower extremity weakness and was found to have an intramedullary thoracic spine cystic lesion. She was taken to the operating room for resection of the lesion. Pathology revealed a larval cyst wall consistent with neurocysticercosis. The patient was started on albendazole and dexamethasone. Her exam improved post-operatively, and she was able to ambulate with minimal difficulty at the time of follow up.

Conclusion: The case provides insights on the diagnosis and treatment of isolated intramedullary spinal neurocysticercosis. Review of the literature suggests that combined surgical and medical intervention results in significant improvement in the patient's neurological exam, and decreases morbidity associated with the disease. We propose a treatment paradigm for this rare manifestation of neurocysticercosis.

KEYWORDS

neurocysticercosis, spine, lesion, cyst, case report, resection, intramedullary

Introduction

Cysticercosis is the most common parasitic disease worldwide that affects the nervous system (1). It is caused by the cestode *Taenia solium* with pigs serving as an intermediate host. When humans ingest larvae in undercooked pork, the infection is limited to gastrointestinal tract, where mature worms develop. In neurocysticercosis, humans become intermediate hosts by ingesting the ova, not the larvae, usually from fecal contamination of water and contaminated vegetables, and develop disseminated disease (2). Cysts that form within the nervous system are primarily found in the brain, with only an estimated 1% of cases with spinal cysts (3).

Isolated intramedullary spinal neurocysticercosis is extremely rare, however, with few cases reported in literature before 2022. Given the non-specific presenting symptoms and increasing incidence, intramedullary spinal neurocysticercosis should be considered during the evaluation of suspicious cases with appropriate imaging. Here, the authors present a case of isolated intramedullary spinal neurocysticercosis and discuss the diagnostic evaluation, intervention, and current literature behind this disease process.

Methods

A PubMed search was performed for articles indexed through the Medline database. Keywords used included "spinal" AND "neurocysticercosis" AND "isolated." Fifty articles were identified, of which 16 were case reports of interest. Twenty-five patients were described within these 16 case reports published between 1993 and 2022 (Table 1). Thirty-four articles were excluded: fifteen articles were not about isolated intramedullary neurocysticercosis, eleven were not case reports, four were not isolated spinal cases, three articles were inaccessible and without abstract, and one article was not related to neurocysticercosis. A qualitative analysis was performed on the included cases, and findings are presented.

Case report/case presentation

A 37-year-old woman with no other medical history presented for evaluation of bilateral lower extremity weakness. She had been experiencing back pain for 3-weeks prior to presentation and was evaluated at an emergency department with initial onset of low back pain; she obtained a roentgenogram of her low back and was then discharged with a diagnosis of muscle strain. Three days after her initial evaluation, the patient began having lower extremity weakness, and presented for re-evaluation a week later; her weakness had progressed significantly. Patient was transferred from an outside emergency department to our institution. Her examination revealed bilateral lower extremity weakness, loss of sensation to the level of her umbilicus, urinary retention and constipation. When queried, she denied recent international travel: she had immigrated from Guatemala 15 years prior and has not returned since. She additionally denied ingestion of undercooked meats and being near livestock. She also denied headaches, seizures, or recent weight loss.

A magnetic resonance imaging (MRI) scan of her brain and entire spine demonstrated a ring-enhancing lesion at T8 with significant surrounding edema measuring 1.4 x 1.0 cm (shown in Figure 1). A small coma-shaped area of restricted diffusion is present eccentrically within the cyst. At this time, there was concern that this lesion represented an autoimmune demyelinating lesion (multiple sclerosis vs. transverse myelitis), and the patient was started on corticosteroids with moderate improvement in her strength over the course of 2 days. Despite a negative cystericus serum antibody test, there was growing concern that steroids were treating symptoms and not the underlying pathology, and the patient was therefore taken to the operating room for exploration and resection of the lesion.

In the operating room, a midline incision was made. Laminectomies were carried out from T7-T9 until the dura was adequately exposed. A midline durotomy was completed with localization through intraoperative ultrasound. Under high-intensity intraoperative microscopy, the posterior aspect of the spinal cord was observed to be extremely distorted due to the underlying lesion. A sharp incision was performed at the median sulcus and carried distally until a firmer portion of the lesion was encountered. A cystic component was then entered; purulence was noted on gross examination and suctioned away (shown in Figure 2). Multiple cultures, as well as portions of the capsule, were sent for pathological examination in both frozen and permanent sections. The preliminary pathological report returned as neurocysticercosis (shown in Figure 3). After removal of the capsule and cyst, the spinal cord was noted to be relaxed and pulsatile. A duraplasty was then performed utilizing an artificial dural graft material. The overlying muscle, fascia, subcutaneous tissue, and skin were then sequentially closed in a water-tight manner. The patient was extubated without complication and was admitted to the intensive care unit. Video highlights of the procedure are available in Supplementary materials.

In the following days, the patient was noted to have dramatic improvements in her bilateral lower extremity strength. She was started on albendazole (400 mg every 12 h) and dexamethasone (8 mg daily) for 14 days as per recommendations from Infectious Disease consultants. The remainder of her hospital course was uncomplicated. She was ultimately discharged to an Inpatient Rehabilitation Hospital and was noted to have full strength in her bilateral lower extremities and resolved urinary retention just prior to discharge, but remained with paresthesia in lower abdomen and lower extremities. She was then seen in the outpatient clinic 2 months later, where she stated that she had regained the majority of her strength in her lower extremities, and had significant improvements in her sensory complaints as well. An MRI was obtained demonstrating interval decrease in the size of lesion as well as decrease in the surrounding edema within the spinal cord (shown in Figure 4).

Ethics

Informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

TABLE 1 Literature review on cases of isolated intramedullary spinal neurocysticercosis.

References	PMID	Age	Location of lesion	Number of cysts	Clinical signs	Treatment	Resolution of symptoms
Yang et al. (4)	35193508	23	Thoracic	Single	Motor, sensory	Surgery	Yes
		24	Thoracic	Single	Back pain, motor	Surgery	Yes
		47	Thoracic/Lumbar	Multiple	Bowel/bladder, motor, sensory	Surgery, Albendazole, Decadron	Yes
		27	Lumbar/Sacral	Single	Back pain, motor	Surgery	Yes
		38	Thoracic	Single	Motor, sensory	Surgery	Yes
		35	Thoracic	Single	Motor, sensory	Surgery	Yes
Dhar et al., (5)	34926816	35	Lumbar	Multiple	Back pain, sensory	Surgery, Albendazole, Decadron	Yes
Vadher et al. (6)	34113502	20	Thoracic	Multiple	Motor, sensory	Surgery, Albendazole, Decadron	Yes, but not complete
Jobanputra et al. (7)	32123621	44	Cervical	Single	Sensory	Surgery	Yes
Maste et al. (8)	29492150	30	Thoracic	Single	Back pain, motor, sensory	Albendazole, decadron	Yes
Datta et al. (9)	28602886	70	Thoracic	Single	Motor, sensory	Albendazole, decadron	Yes
		23	Thoracic	Multiple	Motor, sensory	Surgery, Albendazole, Decadron	Yes, but not complete
		24	Thoracic	Single	Motor, sensory	None	Yes, but not complete
Salazar et al. (10)	25595849	43	Cervical/Thoracic	Single	Motor, sensory	Surgery, Albendazole, Decadron	Yes
Qazi et al., (11)	25540546	19	Thoracic/Lumbar	Single	Bowel/bladder, motor, sensory	Surgery	Yes
Agale et al. (12)	22870160	38	Thoracic	Single	Motor	Surgery, Albendazole	Yes, but not complete
Azfar et al. (13)	21977090	10	Thoracic	Single	Bowel/bladder, motor, sensory	Albendazole, decadron	Yes
Lambertucci et al. (14)	22146927	23	Cervical	Single	Back pain, motor	Surgery, Albendazole, Decadron	Unknown
Vij et al. (15)	22234147	25	Thoracic	Single	Back pain, bowel/bladder, motor, sensory	Surgery, Decadron	Unknown
Gonçalves et al. (16)	20147871	62	Thoracic	Single	Yes, but not defined	Surgery	Yes
Bouree et al. (17)	17153691	20	Thoracic	Single	Back pain, motor	Surgery	Yes, but not complete
Colli et al. (18)	15926788	15	Thoracic	Not stated	Yes, but not defined	Surgery	No
		24	Lumbar/Sacral	Not stated	Sensory	Surgery	Yes, but not complete
		51	Cervical	Not stated	Yes, but not defined	Surgery	No
Sheehan et al. (19)	15926780	16	Cervical	Single	Sensory	Surgery, Praziquantel, Decadron	Yes, but not complete

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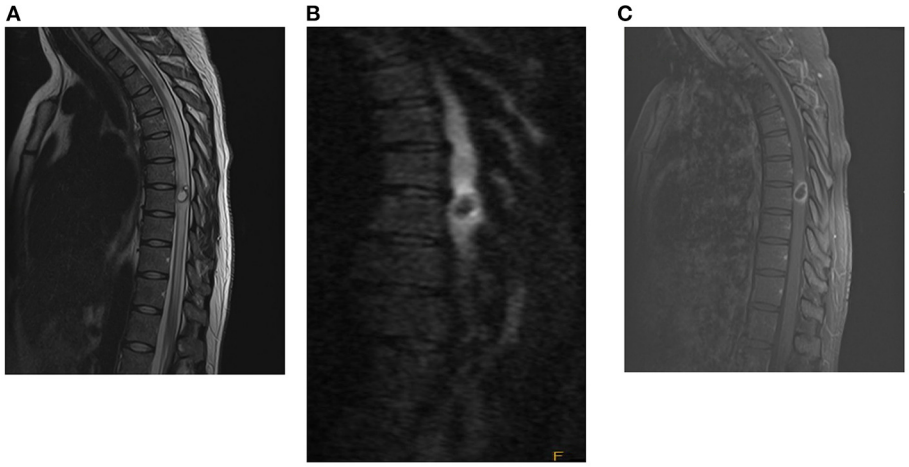

FIGURE 1
Pre-operative MRI with and without contrast of spine [**(A)**: T2, **(B)**: T1 wo contrast, **(C)**: T1 w contrast], demonstrating a rim-enhancing cystic lesion in the mid-thoracic spine with diffuse surrounding cord edema.

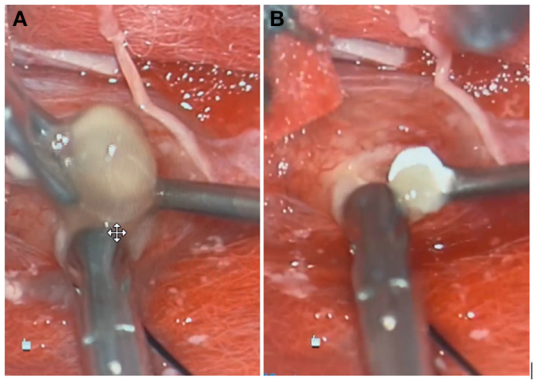

FIGURE 2
Gross specimen of lesions extracted during surgical intervention, one large **(A)** and one small **(B)**.

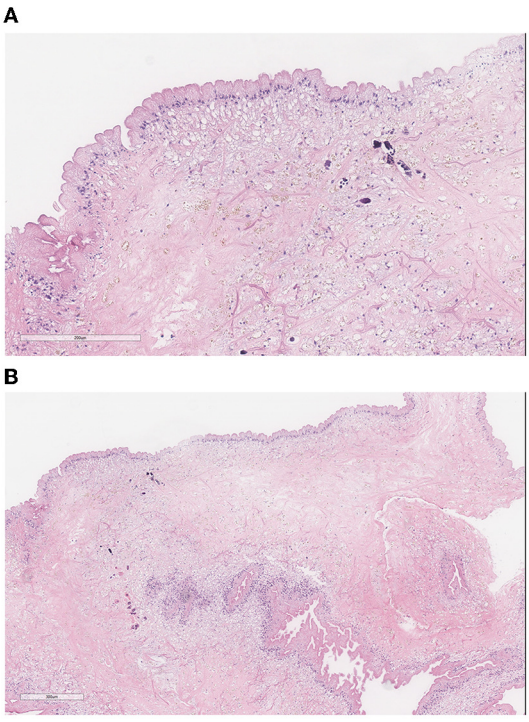

FIGURE 3
(A) Pathology demonstrates the characteristic three-layered wall of a **(B)** neurocysticercosis cyst: the undulating outer eosinophilic cuticular layer, the underlying cellular layer containing uniform small dark nuclei, and the inner reticular layer containing loosely arranged fibrils. Small amounts of calcification seen are consistent with the chronic nature of the infection.

Discussion

Cysticercosis occurs when *Taenia solium* ova are ingested by the patient. The ova hatch in the intestine, and the larvae penetrate into the bloodstream and eventually lodge in host tissue. When the tissue involved is either the brain or the spine, the disease is called neurocysticercosis. While symptoms may develop as a result of mass effect from the cyst, cysts may also remain asymptomatic for many years (20). This may be the result of parasite-linked anti-inflammatory factors which inhibit both humoral and cellular immune responses to the cyst (21). When the cysticercus dies (either due to treatment or due to the parasite's lifespan), parasite-linked immunosuppression ceases and lesions can become symptomatic. This is likely the case with our patient, who did not have a scolex noted on surgical pathology indicating a live organism, but did have calcification suggestive of a long-standing lesion (22).

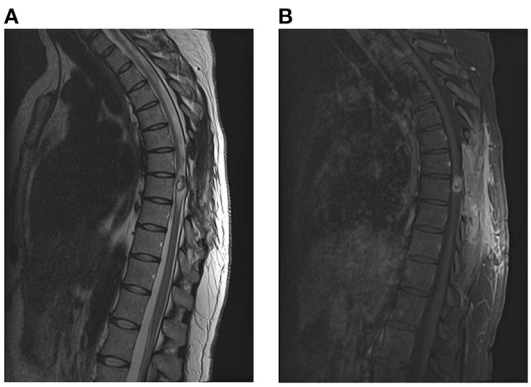

FIGURE 4
Post-operative MRI with and without contrast of the spine [**(A)**: T2, **(B)**: T1 w contrast], demonstrating interval decrease in size of the lesion as well as decrease in the edema surrounding the lesion.

There are thus four recognized radiographic stages of a neurocysticercosis infection: (1) a vesicular stage with a parasite visible on imaging with little or no inflammation; (2) a colloidal vesicular stage where the parasite dies and there is increased surrounding edema and inflammation; (3) a granular nodular stage where the scolex is mineralized and the surrounding edema and inflammation decreases; and (4) a nodular calcified stage where the cyst completely mineralizes without surrounding inflammation (23).

Isolated intramedullary spinal neurocysticercosis is an extremely rare entity, and may diagnostically be difficult and unexpected, especially in areas of the world where *Taenia solium* is not endemic. *Taenia solium* is most prevalent in Latin America, Asia, and Africa; given global migration of persons, its incidence has been increasing in countries outside of its endemic region (24). Intracranial neurocysticercosis is the most common form, and spinal cases are rare. These cases account for 0.7–5.85% of all cases reported. Even rarer are isolated intramedullary lesions (11). Our case is illustrative of the diagnostic difficulty of intramedullary spinal neurocysticercosis. The patient had a precursory diagnosis of a demyelinating plaque. Only after re-review of MR imaging when the patient failed to improve did we reach the tentative diagnosis of neurocysticercosis that was subsequently confirmed on surgical pathology.

For diagnosis of spinal neurocysticercosis, a good clinical history is paramount (5). In our review of literature (Table 1), 17 cases (68%) exhibited symptoms of motor weakness, 16 (64%) were with sensory symptoms (either radiculopathy or numbness/tingling with sensory level), seven (28%) had low back pain, and three (12%) had bowel/bladder difficulties. Affected areas tend to be isolated towards the mid or distal spinal cord, as 4 patients (16%) had lesions in the cervical spine, 16 patients (64%) had lesions in the thoracic spine, and two patients (8%) had lesions in the upper lumbar spine. This is consistent with prior reports suggesting a predominance of lower thoracic lesions for intramedullary spinal neurocysticercosis (23). A history of pork consumption and/or travel to endemic areas (particularly areas without access to clean water) should also increase clinical suspicion for spinal neurocysticercosis; the cases we sampled did not mention these salient points with enough frequency for us to draw specific conclusions.

Given the non-specific symptoms, further clinical studies are needed to increase the diagnostic suspicion for neurocysticercosis. Laboratory studies can be used to test for antibodies to *Taenia solium*, but these have variable sensitivity and specificity and may be falsely negative in "light" infections (25). Imaging studies provide more diagnostic confidence (23). Characteristic neurocysticercosis lesions appear nodular or cystic on MRI. The scolex, if present, appears as a mural nodule isointense to the surrounding tissue on T1WI, iso- to hyperintense on T2WI, and hyperintense on DWI; there is additionally peripheral ring-like enhancement but no enhancement in the scolex (4). Neurocysticercosis lesions can have variable diffusion restriction depending on its stage, but typically will display minimal to no diffusion restriction. A small comma-shaped area of diffusion restriction, present in our patient, has also been described in literature as characteristic of a neurocysticercosis cyst. This contrasts with many other spinal lesions, including active demyelinating plaque, tumor, and bacterial abscesses, which typically will show restricted diffusion on DWI.

Due to the low incidence of isolated intramedullary spinal neurocysticercosis, treatment has not been standardized. In our literature review, 18 patients (82%) underwent surgical intervention to remove the spinal lesion. Piecemeal removal of cysticerci has not been shown to increase risk of disseminated disease. The treatment paradigm was not described for 3 patients. Ten patients (45%) received albendazole and dexamethasone; two patients (9%) received only dexamethasone. Fourteen patients (64%) experienced complete recovery; six (27%) experienced partial recovery; and no patients had worsening deficits. Two patients did not have their recovery described. Review of the data suggests that recovery was not related to modality of treatment, and more related to length of symptomatology. We therefore propose a treatment protocol for managing intramedullary spinal neurocysticercosis (shown in Figure 5).

This case illustrates the diagnostic difficulty of isolated intramedullary spinal neurocysticercosis. A thorough clinical history, exam, and associated clinical and radiographic studies can help to narrow the differential diagnosis. The interventions and treatments performed on this patient mirror those in the few documented cases in literature. Our treatment

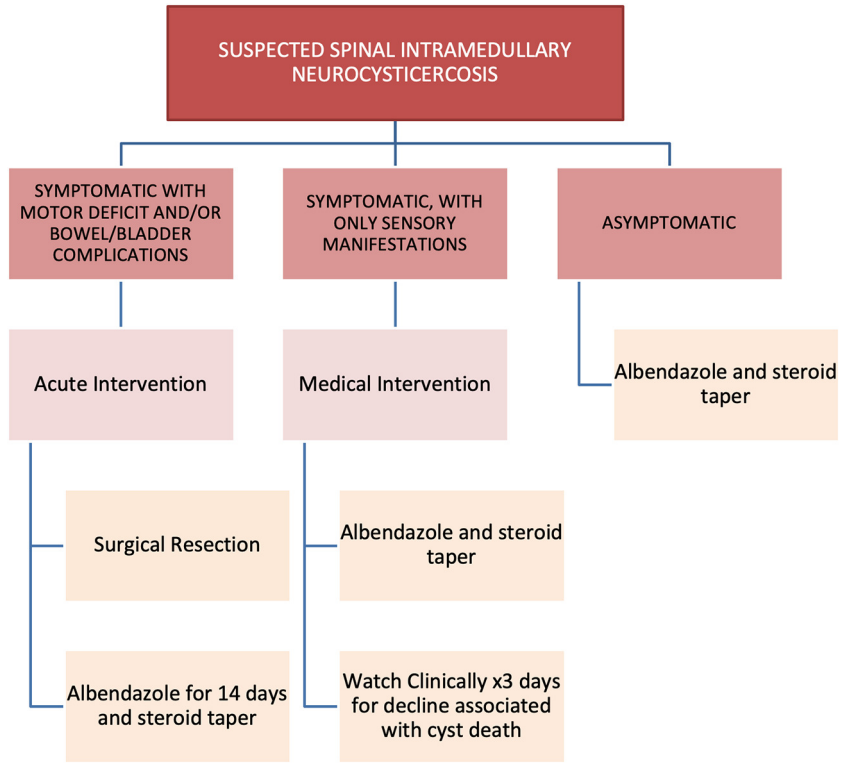

FIGURE 5
Proposed treatment protocol.

protocol therefore provides standardization and guidance in the treatment of this rare disease process.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Conception and design: DA. Acquisition of data and drafting the article: DA and JT. Analysis and interpretation of data: DA, EB, DP, NP, and JT. Critically revising the article: DA, JT, NP, RJ, JI, JZ, EB, DP, RN, and MS. Reviewed final version of the manuscript and approved it for submission: EB, DP, RN, and MS.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1030468/full#supplementary-material

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Leptospira infection complicated by demyelinating disease: A case report

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Leptospirosis is a zoonotic disease, found worldwide, that is caused by bacteria of the genus *Leptospira*. People can be infected with *Leptospira* if they come in direct contact with the urine of an infected animal. Leptospirosis may be associated with demyelinating lesions of the central nervous system. This case report describes a 66-year-old female patient who presented with fever and generalized aches and progressed to unconsciousness within a few hours of admission. Laboratory tests showed *Leptospira* infection, and brain magnetic resonance imaging revealed acute demyelinating lesions. The patient responded well to penicillin and intravenous methylprednisolone therapy. Leptospirosis presenting with acute disseminated encephalomyelitis is rare. In this patient, an interdisciplinary collaboration involving the neurologist, radiologist, and pathologist was crucial for diagnosis and management. Further studies are warranted to investigate whether there is a correlation between demyelinating lesions and leptospiral infection.

KEYWORDS

leptospirosis, leptospira burgdorferi, multiple organ dysfunction, emergency, infection

Introduction

In the past few decades, leptospirosis has become a significant infectious disease with high mortality (1). Yearly, an estimated one million people are infected with leptospirosis, and 5,000–6,000 people die (2). In both industrialized and developing countries, leptospirosis is a zoonotic disease affecting humans in rural and urban areas. Rats are the most common carriers of leptospirosis; those exposed to the urine of infected rats (e.g., through wounds) risk contracting it. Clinicians should therefore pay particular attention to any history of sewage exposure when taking a medical history. *Leptospira* bacteria directly damage tissues and immune-mediated mechanisms, leading to microcirculatory disorders as well as endothelial and organ dysfunction.

Leptospirosis often leads to severe complications such as acute kidney injury, liver dysfunction, myocardial involvement, and pulmonary hemorrhage (3). However, some atypical or unusual manifestations of leptospirosis, including ocular manifestations and neurological, hematologic, and gastrointestinal tract involvement, are often overlooked and rarely reported (4).

Case report

The patient was a 66-year-old female farmer with a history of exposure to field sewage. In the absence of precipitating factors, she experienced general pain with fatigue and anorexia 3 days before coming to the emergency department. On the following day, she presented to a local doctor with shortness of breath and was treated with traditional Chinese medicine (no details available), but her symptoms did not significantly improve. She was then referred to the emergency department at the end of September 2021 with fever and dyspnea, and was admitted to the general ward.

Upon admission, her temperature was 37.1°C, pulse rate was 86/min, respiratory rate was 30/min, blood pressure was 96/50 mm Hg, and peripheral oxygen saturation (SpO_2) was 90% in room air. Her physical examination was unremarkable. She had a previous medical history of hypertension and diabetes mellitus with poor blood glucose control. One hour after admission, her blood pressure dropped to 80/52 mm Hg, and her dyspnea increased. Eight hour after admission, her SpO_2 fell to 78%. She lost consciousness and was transferred to the intensive care unit.

Laboratory investigations showed a white blood cell count of 11.09 × 10^9/L with 87% neutrophils. Her interleukin-6 level was 208.6 pg/ml, and her procalcitonin was 3.8 ng/ml. Head CT on the 2nd day after admission revealed multiple lacunar cerebral infarctions in the bilateral corona radiata and right basal ganglia, mild brain atrophy, and intracranial arteriosclerosis; no other abnormalities were detected in the brain parenchyma. We performed a lumbar puncture on the 4th day after admission and sent the cerebrospinal fluid (CSF), along with her blood, for metagenomic next-generation sequencing (mNGS). Capillary blood glucose was 15.2 mmol/L at the time of lumbar puncture.

Information on the CSF workup is shown in Table 1. Organisms detected in the patient's CSF matched the *Leptospira* genomes in the reference database, identifying 7 sequencing reads of *Leptospira borgpetersenii* (Figure 1; Table 2). Table 2 also presents the details of the mNGS analysis. Likewise, high-throughput sequencing of her blood revealed the presence of *L. borgpetersenii*. In the meantime, the *Leptospira* IgG test was positive.

The blood collected for the mNGS was unfortunately misplaced by the third-party testing agency, so polymerase chain reaction validation could not be performed. No other pathogens were identified except *L. borgpetersenii*. The details of the confirmatory diagnostic testing for *L. borgpetersenii* are summarized in Table 3.

TABLE 1 Analysis of the cerebrospinal fluid workup.

Item	Results	Reference range (units)
Color	Light red	Colorless
Appearance	Slightly turbid	Clear
Clot	Nil	Nil
Cell count	2,000 ↑	0–8 (10ˆ 6/L)
WBC* count	20 ↑	0–8 (10ˆ 6/L)
Glu	6.98 mmol/L	
Cl	141 mmol/L	120–132 mmol/L
Pandy's test	(±)	(–)
Upperlayer appearance	Colorless and clear	Colorless and clear
Underlayer appearance	Redness deposition**	
Multinucleate cell	Few leukocytes are not classified	%
Mononuclear cell	Few leukocytes are not classified	%

*WBC, white blood cell. **Red blood cells (RBCs) are the result of puncture damage since MRI of the head did not indicate SAH. ↑ - Elevated.

The score on the Mini-Mental State Examination (education level: illiteracy) was 12. A magnetic resonance imaging (MRI) test of the brain revealed multiple symmetrical abnormal oval-shaped lesions with blurred boundaries in both cerebral hemispheres and the corpus callosum. A T2-weighted image (WI) showed hyperintense signals (see Figures 2, 3), and a T1 WI showed a hypointense signal. Accordingly, acute demyelinating lesions were considered. The patient's clinical presentation and results of the mNGS were consistent with a diagnosis of *Leptospira* infection and the MRI with acute- disseminated encephalomyelitis (ADEM).

Intravenous methylprednisolone pulse therapy (500 mg four times a day for 5 days) was started after the confirmatory diagnosis. The patient responded to treatment and was well oriented but still had some memory loss. The patient declined a repeat plain MRI for economic reasons. She was discharged after 3 months in the hospital, with her mental state restored to her preadmission level.

Discussion

Leptospira are widespread and transmitted through skin abrasions (5). The nervous system is involved in about 10–15% of cases, and central nervous system (CNS) involvement is manifested chiefly as meningitis, encephalitis, and cerebral arteritis. The most common type of CNS involvement is aseptic meningitis. Most of the clinical features of neuroleptospirosis are due to capillary endothelial injury and vasculitis (6, 7). This

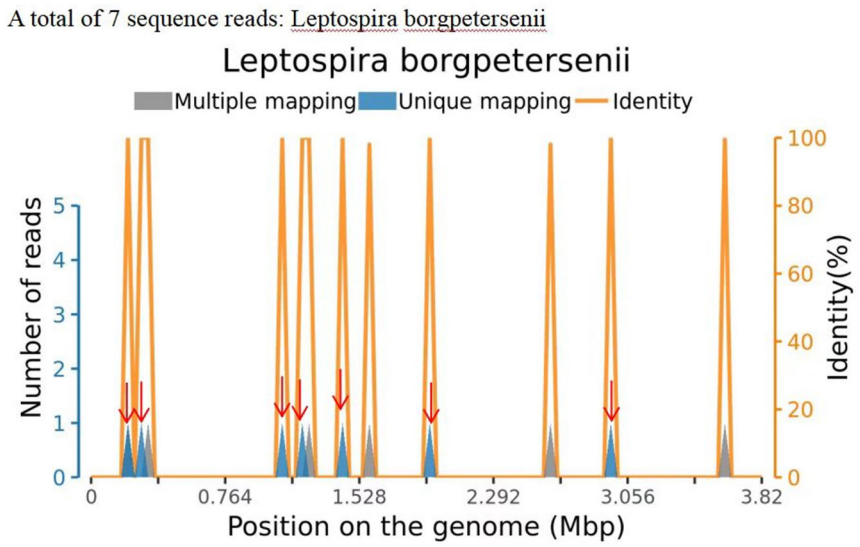

FIGURE 1
Sequence reads of *Leptospira borgpetersenii*, derived from the patient's cerebrospinal fluid (CSF) specimen and the *Leptospira* genome in the reference database. The coverage map shown above is a mapping for a specific microorganism, reflecting the distribution of the sequence of the microorganism on its genome; the abscissa represents the size of the microbe's gene group; and the ordinate represents the number of sequences detected in different genomic segments.

TABLE 2 Results of the mNGS analysis.

Type	Genus	Genus relative abundance (%)	Genus read number	Species	Identification confidence levels	Species read number
pla	*Leptospira*	0.24	13	*Leptospira borgpetersenii*	0.99	7
G+	*Cutibacterium*	14.61	806	*Cutibacterium acnes*	0.99	626
G+	*Staphylococcus*	5.49	303	*Staphylococcus saprophyticus*	0.99	96
G+	*Staphylococcus*	5.49	303	*Staphylococcus epidermidis*	0.99	72
G+	*Staphylococcus*	5.49	303	*Staphylococcus hominis*	0.99	35
G+	*Corynebacterium*	3.70	204	*Corynebacterium accolens*	0.99	21
G+	*Micrococcus*	1.83	101	*Micrococcus luteus*	0.99	93
fun	*Candida parapsilos*	2.96	10	*Candida parapsilosis*	0.99	10

patient's mental status rapidly worsened to coma within a few hours of admission. No lesions were found on plain spinal MRI, and an enhanced MRI scan was not performed.

In this case, a serological diagnosis by LEP-IgG followed by mNGS resources played a critical role in detecting *Leptospira* infection. The ELISA test is highly specific for detecting *Leptospira* antibodies, which peak in the blood after 2 to 3 weeks (8, 9). The mNGS, also known as high-throughput gene testing, is an attractive approach for pathogen detection that has facilitated the diagnosis, investigation, and tracking of infectious diseases (10). As early as 2014, Wilson et al. (11) reported a case of leptospirosis where the patient was finally diagnosed through high-throughput sequencing of CSF. High-throughput sequencing gave rapid results compared with other tests for leptospirosis (11). In this case, no other pathogens besides *L. borgpetersenii* were identified in the mNGS test or other tests. Given the patient's history of sewage exposure, a leptospirosis diagnosis was considered and subsequently confirmed.

Leptospirosis causes several types of nerve lesions, including mononeuritis, polyneuritis, polyradiculitis, myelitis, and cerebral arteritis. It is recommended that patients with leptospirosis presenting with neurological symptoms should undergo an MRI of the spine and brain, enhanced MRI scan, cerebral artery MRI, and digital subtraction angiography of the cerebral vessels (12). Brain magnetic resonance angiography (MRA) is helpful for the identification of leptospirosis-induced cerebral arteritis. However, a brain MRA was not performed on this patient.

Whether there is an overlap between demyelinating lesions and *Leptospira* infection needs further research. The spine

TABLE 3 Details of the confirmatory diagnostic testing for *L. borgpetersenii*.

Collection date	Result date	Sample type	Testing method	Results
2021-10-4	2021-10-7	Blood	mNGS	*L.borgpetersenii*
2021-10-4	2021-10-4	-	Head MR	acute demyelinating lesions
2021-10-5	2021-10-5	CSF	Biochemical analysis	Normal
2021-10-5	2021-10-8	CSF	mNGS	*L.borgpetersenii*
2021-10-8	2021-10-13	Serum	LEP-IgG antibody (ELISA method)	Positive
2021-10-13	2021-10-13	CSF	Biochemical analysis; AQP4 + MOG + MBP	Normal; negative

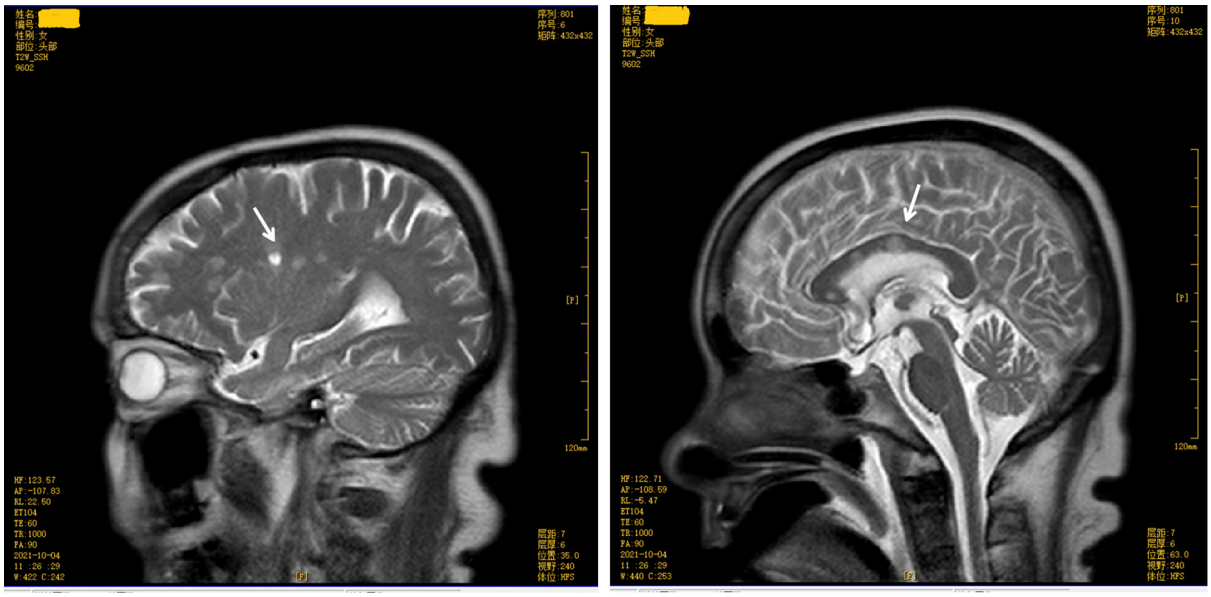

FIGURE 2
Brain magnetic resonance imaging (sagittal view) T2 weighted image shows multiple abnormal oval-shaped hyperintense signal lesions in the cerebral hemisphere and mesolobus.

MRI and neurological examination on admission showed no abnormality. The brain MRI showed acute demyelinating lesions. Demyelinating diseases are acquired and have different etiologies, but share some characteristics. The characteristic pathological changes are demyelinated nerve fibers seen in conjunction with relatively intact nerve cells.

ADEM is an immune-mediated demyelinating CNS disease. Its clinical features are multifocal neurological symptoms accompanied by neuroimaging evidence of multifocal demyelination (13). The disease mainly involves the brain and spinal cord, and is often secondary to infection or immunization. It was earlier believed that ADEM was caused by a viral infection (14).

The patient, in this case, had a sudden onset, confirmed infection, and neurological manifestations in the form of mental changes and cognitive impairment. A plain brain MRI revealed acute demyelinating lesions. The brain MRI scan showed multiple symmetrical abnormal oval-shaped lesions with blurred borders in both cerebral hemispheres and the corpus callosum, a high signal on T2 WI (see Figures 2, 3), and a low signal on T1 WI, suggesting acute-phase demyelination. The symptoms improved after high-dose active anti-infective steroid treatment. Thus, the diagnosis of ADEM (encephalitis type) was confirmed.

The incidence of neuroleptospirosis is ∼0.86%. The pathogenesis of ADEM may be mediated by the activation of autoreactive lymphocytes (*via* a non-specific inflammatory process) that enter the CNS through a temporary breach in the blood–brain barrier (15). The activation of autologous T-cells leads to a transient autoimmune response to myelin sheaths and other autoantigens (16).

Leptospirosis mainly damages the microvascular endothelial cells, causing hemorrhagic vasculitis and microcirculatory dysfunction. The detailed pathogenesis of leptospirosis has not been fully explained to date. The adhesion and invasion of *Leptospira* into endothelial cells and metabolites, such as lipopolysaccharides and hemolysin, are believed to be

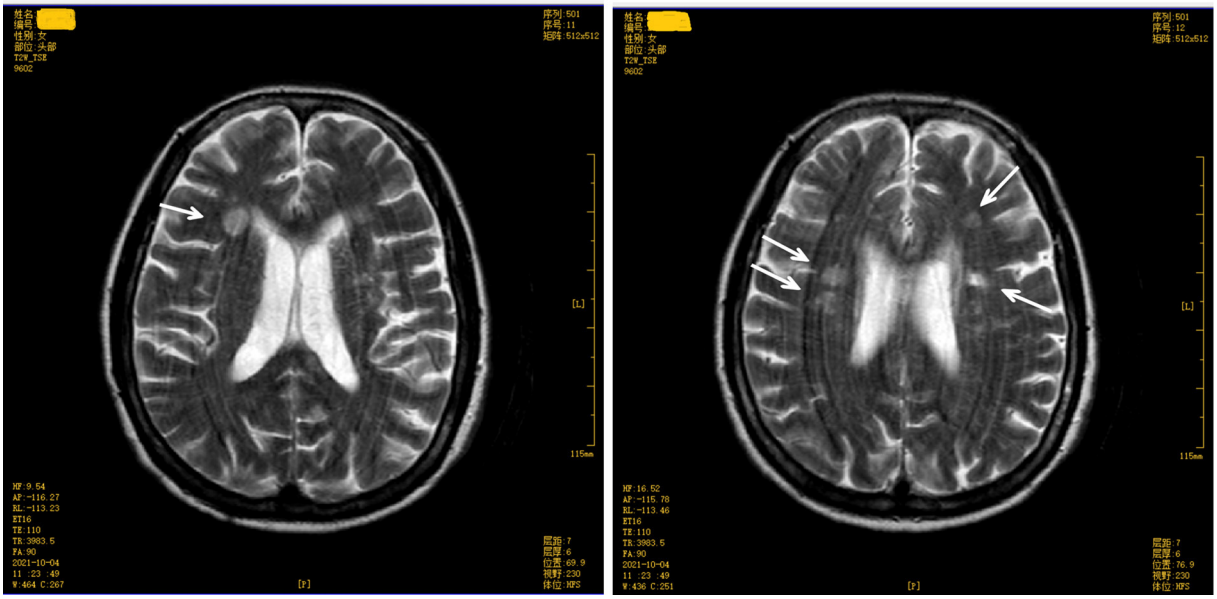

FIGURE 3
Brain magnetic resonance imaging (upper level of lateral ventricle) T2 weighted image shows multiple abnormal oval-shaped hyperintense signal lesions in the cerebral hemisphere and mesolobus.

responsible for the pathogenesis (17). In this patient, the possibility of infection through hidden wounds was considered, since there was a history of exposure to sewage in the field.

The intersections of CNS damage caused by ADEM and *Leptospira* infection require further study. The correlations between acute demyelinating disease and differences in *Leptospira* type, virulence, quantity, and individual reaction remain unknown. Patients with *Leptospira* infection complicated by CNS damage should alert the physician to the possibility of secondary demyelinating lesions. A brain MRI is essential for its diagnosis (18). Once an acute demyelinating syndrome is diagnosed, treatment should be aimed at reducing inflammation and immune activation as soon as possible to reduce the duration and severity of the disease. Treatment methods include high-dose intravenous corticosteroids, therapeutic plasma exchange, and intravenous immunoglobulins (19). This patient was treated with high-dose intravenous methylprednisolone.

For a precise diagnosis of demyelinating diseases, other relevant examinations are necessary (i.e., ADEM and multiple sclerosis are both inflammatory demyelinating diseases that should be differentiated). The electrophoretic test for oligoclonal bands in the CSF has diagnostic value for inflammatory diseases of the CNS, in particular, Guillain–Barre syndrome and multiple sclerosis (20). Unfortunately, this test was not performed on this patient.

This case report describes a patient with ADEM due to leptospirosis. This case report focuses on the diagnosis and treatment in a non-specialty hospital of an atypical presentation of secondary CNS damage attributable to leptospirosis. ADEM secondary to *Leptospira* infection requires differentiation from leptospiral cerebral arteritis. This case report focuses on the atypical presentation of secondary nervous system damage following leptospirosis. In this patient, mNGS provided a reliable method for diagnosing this complex case of leptospirosis and ensuring timely and effective treatment.

Limitation

Over all, this case has several limitations. First, the quality of clinical management can be improved. When the patient was admitted for fever, the risk associated with the patient being a farmer was ignored, and only empirical antibiotics were given. An mNGS is not easy to obtain. Second, the necessary medical tests for the differential diagnosis, such as OB and MRA, were not done. In addition, due to economic considerations, patients may not complete necessary examinations from physician recommendations during treatment and follow-up, which may present challenges for clinicians.

Conclusion

In patients with *Leptospira* infection exhibiting CNS symptoms, acute demyelinating disease and cerebral arteritis should be considered in the differential diagnosis. For patients

with demyelinating disease, as indicated by imaging results, CSF should be examined for anti-aquaporin-4 antibody, anti-myelin oligodendrocyte glycoprotein antibody, anti-myelin basic protein antibody, and oligoclonal bands to further clarify the diagnosis. At present, the pathogenesis of *Leptospira* infection remains unclear. Conducting multidisciplinary consultations for such patients with the assistance of the infectious disease, neurology, radiology, and pathology departments will significantly benefit patients in this regard.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Zhongshan People's Hospital Ethics Committee (Approval number 2022-026). The patients/participants provided their written informed consent to participate in this study.

Author contributions

S-XC and D-KH conceived the idea and conceptualized the study. YL and Z-HY collected the data and analyzed the data. KL and BX drafted the manuscript. H-qM reviewed the manuscript. All authors have read and approved the final draft.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Acute bacterial encephalitis complicated with recurrent nasopharyngeal carcinoma associated with *Elizabethkingia miricola* infection: A case report

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Elizabethkingia miricola (*E. miricola*) is an extremely rare pathogenic bacterium, which causes serious infections in patients with primary immunodeficiency or tumors, and it is often misdiagnosed. *E. miricola* has rarely been known to cause a neurologic infection. We describe the first case of acute bacterial encephalitis associated with *E. miricola* infection in a man with recurrent nasopharyngeal carcinoma, which was successfully cured by antibiotics. The patient initially presented with recurrent episodes of fever and later showed impaired consciousness but these symptoms were alleviated with antibiotic therapy including cefoperazone/sulbactam. This study highlights that rapid and accurate pathogen detection *via* metagenomic next-generation sequencing and early use of appropriate antibiotics can improve the prognosis of patients with suspected neurologic *E. miricola* infection. Early treatment for underlying primary diseases can also significantly improve the outcomes of patients.

KEYWORDS

***Elizabethkingia miricola*, encephalitis, metagenomic next-generation sequencing, diagnosis, treatment**

Introduction

Elizabethkingia miricola (*E. miricola*) is a non-fermenting Gram-negative bacterium that was first discovered in 2003 when it was isolated from condensation water in the Russian Space Laboratory Mir (1). Generally, *E. miricola* does not cause infections in healthy populations, but it is a serious conditional pathogen affecting individuals with compromised immunity. For instance, *E. miricola* was found to cause infection in an allogeneic stem cell transplant recipient with mantle cell lymphoma (2). It has also been reported to cause urinary tract infection in a female with abdominal pain (3), knee septic arthritis in a male patient with recurrent erysipelas (4), and oral superinfection in a woman with common variable immunodeficiency (5). However, *E. miricola* is rarely known to cause a neurologic infection. To date, only one case of meningoencephalitis caused by *E. miricola* has been reported, and the patient eventually died due to symptoms of aggravation (6). In addition, medically important species of *Elizabethkingia* include *Elizabethkingia meningosepticum*, *Elizabethkingia anophelis*, and *E. miricola*. The currently used routine morphological, biochemical, and molecular tests cannot accurately distinguish *E. miricola* from other *Elizabethkingia* species. Previous studies have also demonstrated that *E. miricola* was frequently misidentified as *E. meningosepticum* initially (2, 6). Given the limited reports on the diagnosis and treatment of this infection, the neurologic

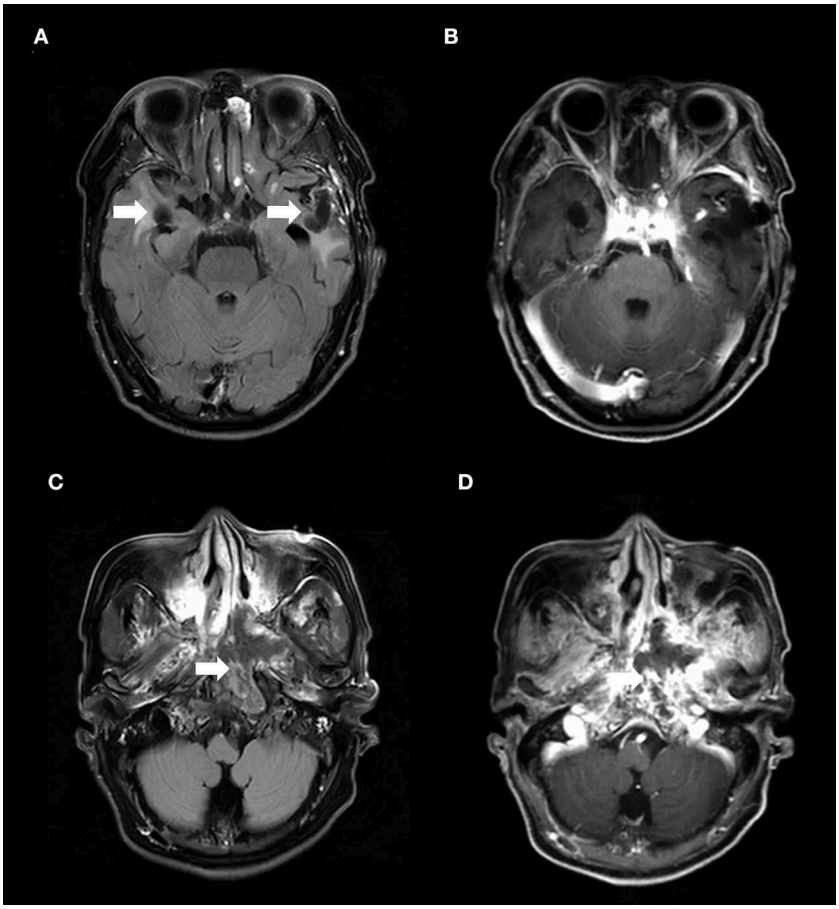

FIGURE 1
(A) The axial T2-weighted FLAIR imaging demonstrated irregular hypointense signal changes with patchy edema around them in the bilateral temporal lobes (arrows) and **(B)** without contrast enhancement in the similar brain structures. The MRI abnormalities on bilateral temporal lobes had been present for approximately 5 months before the patient's disturbance of consciousness. These abnormalities were presentation of radiation-induced brain necrosis and were not associated with *E. miricola* encephalitis. **(C)** Nasopharynx T2-weighted FLAIR imaging showed a heterogeneous signal mass in the left nasopharyngeal lateral wall (arrow). **(D)** T1-weighted nasopharynx MRI with contrast enhancement showed enhancing lesions in the mass (arrow). FLAIR, fluid-attenuated inversion-recovery.

infections caused by *E. miricola* are poorly understood. The aim of our study was to describe another case of bacterial encephalitis caused by *E. miricola* that was diagnosed early and accurately and treated successfully.

Case report

A 56-year-old man presented with recurrent episodes of fever with no trigger for 3 weeks and disturbance of consciousness for 2 weeks. The patient had undergone chemo-radiation treatment for nasopharyngeal carcinoma (NPC) 18 years ago. He denied a history of traumatic brain injury. The travel history of the patient was unremarkable. Neurologic examination revealed somnolence, confusion, enlargement of the left pupil with absent reaction to light, hearing decline in the left ear, normal muscle strength and tension in limbs, bilateral positive Chaddock signs, negative meningeal irritation signs, and Babinski signs.

Magnetic resonance imaging (MRI) of the brain revealed irregular hypointense signal changes with patchy edema around them in the bilateral temporal lobes (Figure 1A), without enhancing lesions in the same brain structures (Figure 1B). Nasopharynx MRI showed a heterogeneous signal mass in the left nasopharyngeal lateral wall (Figure 1C) and enhancement in the mass (Figure 1D). ^{18}F-Fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) scan demonstrated decreased fluorodeoxyglucose uptake lesions in the bilateral temporal lobes (Figures 2A–C) and increased fluorodeoxyglucose uptake lesions in the left nasopharyngeal lateral wall (Figures 2D–F).

A lumbar puncture was performed, and empirical antimicrobial treatment with cefmetazole was started. The cerebrospinal fluid (CSF) was cloudy and had a leukocyte count of 18×10^6 cells/L, a protein level of 3.60 g/L (normal: 0.15–0.45 g/L), a glucose level of 2.41 mmol/L (normal: 2.5–4.4 mmol/L), and a chloride level of 116 mmol/L (normal: 120–130 mmol/L). A culture of the CSF from the patient showed no growth for 5 days. Metagenomic next-generation sequencing (mNGS) of the CSF indicated *E. miricola* (sequence reads 115; MGISEQ-2000 platform, MGI Tech, China). The test results for immunity antibodies, parasites, other bacteria, and viruses were all negative. These results suggested a diagnosis of encephalitis caused by *E. miricola*.

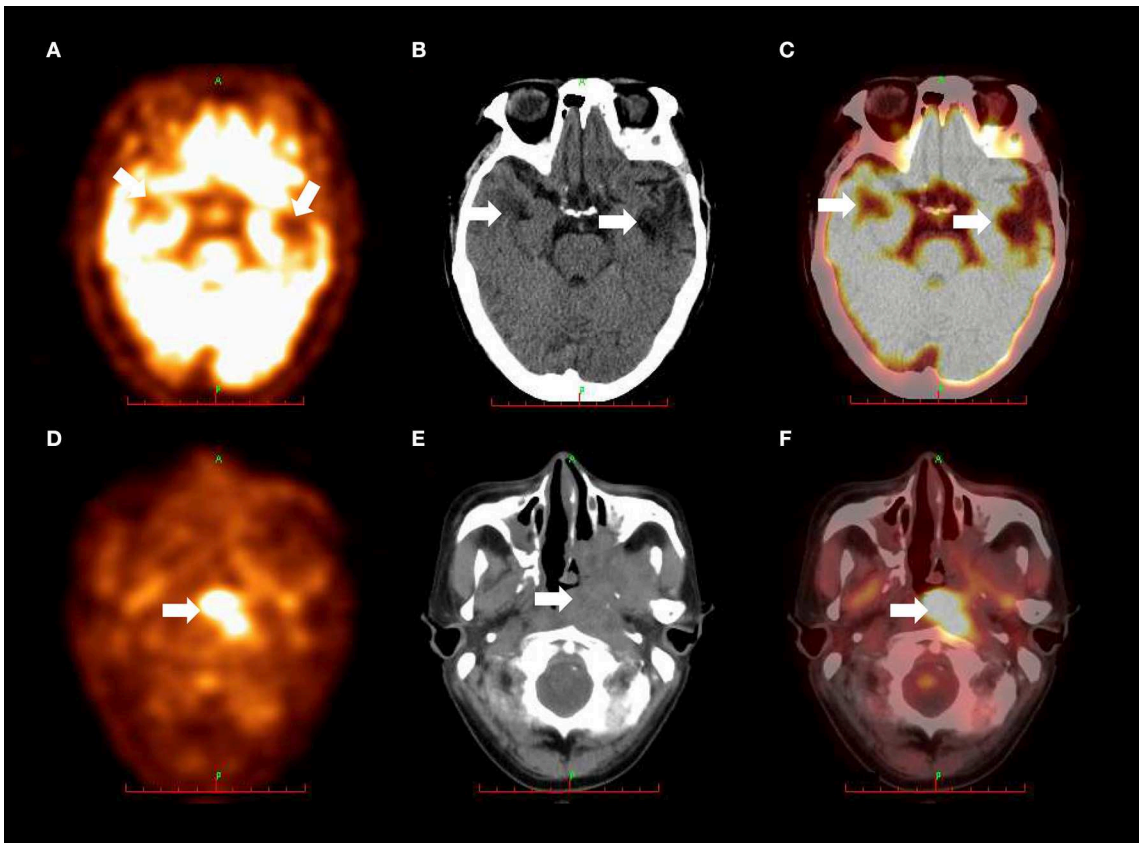

FIGURE 2
(A) PET scan revealed decreased *fluorodeoxyglucose* uptake in the bilateral temporal lobes (arrows). **(B)** CT scan showed patchy low-density areas in the bilateral temporal lobes (arrows). **(C)** ^{18}F-FDG PET/CT fusion imaging demonstrated decreased *fluorodeoxyglucose* uptake in the bilateral temporal lobes (arrows). These metabolic abnormalities on bilateral temporal lobes were appearance of radiation-induced brain necrosis and were not correlated with *E. miricola* encephalitis. **(D)** PET scan revealed increased *fluorodeoxyglucose* uptake in the left nasopharyngeal lateral wall (arrow). **(E)** CT scan showed soft tissue mass with unclear boundary in the left nasopharyngeal lateral wall (arrow). **(F)** ^{18}F-FDG PET/CT fusion imaging demonstrated increased *fluorodeoxyglucose* uptake in the left nasopharyngeal lateral wall (arrow). ^{18}F-FDG PET/CT, and ^{18}F-Fluoro-2-deoxyglucose positron emission tomography/computed tomography.

The patient's treatment was then changed to intravenous cefoperazone/sulbactam (3 g, two times per day) after the diagnosis. Two weeks later, the patient's symptoms were remarkably alleviated. Reexamination of the CSF mNGS revealed that *E. miricola* was completely cleared and the follow-up CSF culture was sterile. A biopsy of the mass in the nasopharynx showed well-differentiated squamous cell carcinoma, which indicated recurrent NPC. Serological Epstein–Barr Virus DNA result was negative. The patient was transferred to the Department of Radiation Oncology and received chemo-radiation treatment for NPC, and he is presently in stable condition. The timeline of disease manifestations and corresponding treatment regimens are presented in Tables 1, 2, respectively.

Discussion

In this report, we describe the first case of bacterial encephalitis associated with *E. miricola* infection that was successfully treated with antibiotics. *E. miricola* has been isolated from the blood, sputum, urine, and synovial fluid and has been found to cause sepsis, pneumonia, urinary tract infection, and knee septic arthritis (2–4, 7). However, *E. miricola* is rarely known to cause a neurologic infection in humans. Globally, only one case of meningoencephalitis caused by *E. miricola* has been reported, and the patient did not receive a timely diagnosis and treatment. Consequently, the patient died a few days after being discharged from the hospital (6). Due to the rarity and unknown etiology of the disease in the central nervous system, its diagnosis and treatment remain poorly understood.

The etiology of acute encephalitis cases is not identified in approximately 50% of patients (8). Failure to obtain a timely diagnosis in patients with central nervous system infections contributes to severe outcomes (9). *E. miricola* is an extremely rare pathogenic bacterium that is usually misidentified or considered to be other *Elizabethkingia* species or contaminants. This potentially masks the exact clinical significance of the bacterium. The first case of intracranial *E. miricola* infection was initially misdiagnosed as *E. meningosepticum*, which led to a delay in diagnosis and treatment (6). Therefore, it is challenging to determine the pathogenic role of infrequent isolates in patients with low immunity. Currently, the common detection methods for identifying *Elizabethkingia* include matrix-assisted laser desorption ionization-time of flight mass spectrometry, 16S rRNA gene, and mNGS (4, 10, 11). The former two methods are relatively inefficient and time-consuming since both of them require culturing of samples taken from sterile sites such as blood and CSF, which may not be applicable to patients with rapidly

TABLE 1 Timeline of disease manifestations.

Disease manifestations	18 years prior	3 weeks prior	2 weeks prior	Day 0	Day 6	Day 15	Day 16-19	Day 20	8 months later
Nasopharyngeal carcinoma									
Fever									
Disturbance of consciousness									
Somnolence									
Hearing decline									
Steady improvement									

TABLE 2 Timeline of treatment regimens.

Treatment regimens	18 years prior	Day 0	Day 6	Day 11	Day 12	Day 19	Day 26	1 months later	2 months later	3 months later
Chemo-radiation										
Cefmetazole (1.0 g q12 h)										
Aciclovir injection (0.5g q8 h)										
Cefoperazone/sulbactam (3.0 g q12h)										

progressing infections. In comparison, mNGS is a one-step, culture-independent approach used for the detection of all pathogens from a single specimen. With the technological advancements of mNGS, the identification of *E. miricola* has been improved, and this has led to a better understanding of this uncommonly isolated microorganism (10). In this case, *E. miricola* was accurately identified as the causative pathogen by mNGS, and we considered this bacterium to be the main cause of encephalitis.

In addition, *E. miricola* is known to be multidrug-resistant, and there is no best-known therapy for neurologic *E. miricola* infection (6, 11). A previous study has revealed that *E. miricola* in neurologic infection was resistant to ceftriaxone and imipenem but susceptible to tigecycline, cefoperazone/sulbactam, levofloxacin, among other drugs (6). Similar to the previously reported case of *E. miricola* infection, our patient received cefoperazone/sulbactam therapy for 2 weeks during hospitalization, and his symptoms were significantly relieved. The reexamination by mNGS showed 0 *E. miricola* reads in the CSF. This suggested that cefoperazone/sulbactam effectively treated the neurologic *E. miricola* infection. Therefore, it can be used to treat similar patients with suspected neurologic *E. miricola* infection.

Most patients with bacteremia, sepsis, knee septic arthritis, and oral superinfection caused by *E. miricola* had underlying comorbidities, such as cancer and immunodeficiency (2, 4, 5). Furthermore, *Elizabethkingia* infections in patients with underlying diseases were usually associated with poor prognosis. Thus, therapeutic interventions for underlying primary diseases can remarkably prevent severe outcomes of *E. miricola* infection. A previous study has demonstrated that high-dose immunoglobulin and targeted levofloxacin treatment could result in immune system reconstitution, oral healing, and eradication of *Elizabethkingia* infection in a female diagnosed with common variable immunodeficiency (5). We also detected NPC recurrence in our patients who received timely chemo-radiation treatment. The 8-month follow-up indicated that the patient had a good prognosis. Therefore, in addition to the need for early identification of pathogens in patients with encephalitis, timely and extensive screening is necessary to determine whether patients have potential tumors or primary immunodeficiency.

Overall, this case study has two strengths. First, *E. miricola* infection was rapidly diagnosed using the unbiased mNGS, which proved to be more sensitive than conventional methods such as CSF smear and culture. Furthermore, the follow-up information of the patient was available, and this could help to evaluate the long-term prognosis of neurologic *E. miricola* infection. Nevertheless, a limitation is also present in this study, the association between cancers and neurologic *E. miricola* infection could not be identified, and further research is necessary to determine this relationship.

In conclusion, we report the first case of bacterial encephalitis after *E. miricola* infection that was cured by antibiotics. Our case may provide novel insights into the treatment of patients with *E. miricola* encephalitis. Rapid and accurate pathogen detection *via* mNGS and early use of appropriate antibiotics can improve the prognosis of patients with suspected neurologic *E. miricola* infection. Moreover, our case also extends the spectrum of pathogens known to cause encephalitis. Finally, early treatment of the underlying primary diseases can also significantly improve the outcomes of patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee on Human Research of West China

Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XZ wrote the draft of the manuscript, collected the clinical data, and designed the ideas of the article. YZ collected the clinical data. LL designed the ideas of the article and edited the whole manuscript. All authors contributed to the article and approved the submitted version.

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Case report: Autoimmune glial fibrillary acidic protein astrocytopathy misdiagnosed as tuberculous meningitis

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Introduction: Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is a new form of autoimmunity-mediated central nervous system disease. It is especially easy to misdiagnose when clinical symptoms and cerebrospinal fluid (CSF) indicators are similar to those observed in patients with tuberculous meningitis (TBM).

Methods: We retrospectively analyzed five cases of autoimmune GFAP astrocytopathy that were initially misdiagnosed as TBM.

Results: In the five reported cases, all but one patient had meningoencephalitis in the clinic, and all patients exhibited increased pressure, lymphocytosis, increased protein levels, and decreased glucose levels in their CSF results and did not have typical imaging findings of autoimmune GFAP astrocytopathy. TBM was the initial diagnosis in all five patients. However, we found no direct evidence of tuberculosis infection, and anti-tuberculosis treatment had inconclusive effects. Following a GFAP antibody test, the diagnosis of autoimmune GFAP astrocytopathy was made.

Conclusion: When there is a suspected diagnosis of TBM but TB-related tests are negative, the possibility of autoimmune GFAP astrocytopathy should be considered.

KEYWORDS

autoimmune GFAP astrocytopathy, tuberculous meningitis, meningoencephalitis, anti-GFAP antibody, case report

1. Introduction

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy is a new type of autoimmune-mediated central nervous system disease that primarily affects the meninges, brain, spinal cord, and optic nerve. It is also associated with GFAP antibodies. It was first reported by Fang et al. in 2016 (1). The prevalence of autoimmune GFAP astrocytopathy is ~0.6 out of 100,000 individuals (2). In recorded cases, the patient age ranged from 8 to 103 years, with a median onset age between 44 and 54 years. The proportion of affected female individuals is nominally higher than that of male individuals (~55%), and children account for approximately 10% of patients (1, 3–5). Furthermore, no obvious racial differences exist (6). Although the etiology is unclear, autoimmune GFAP astrocytopathy can be associated with tumors or an infection, which is similar to other types of autoimmune encephalitis. Prodrome infection symptoms and signs, such as fever, runny nose, and sore throat, are present in ~ 40% of patients, and tumors may be present in 25% of patients (5, 6). In addition, the location and severity of the lesions are connected to the specific presentation

of autoimmune GFAP astrocytopathy symptoms. Subacute onset meningitis, encephalitis, myelitis, or a combination of these syndromes are common clinical features of these patients (7). When patients with autoimmune GFAP astrocytopathy exhibit meningoencephalitis, the presentation is easily confused with that of infectious meningoencephalitis (8). When cerebrospinal fluid (CSF) results are similar to those in a patient with tuberculous meningitis (TBM), the diagnosis is easily confused with that of TBM. As a result, the disorder must be precisely identified in clinical settings (8). In this retrospective study, five cases of autoimmune GFAP astrocytopathy that were initially diagnosed as TBM were reviewed. This case series is a reminder to clinicians, particularly those in TBM-endemic regions, to be aware of the possibility of autoimmune GFAP astrocytopathy when a patient presents clinically with TBM but the test results do not support TBM.

2. Methods

Five adult patients with autoimmune GFAP astrocytopathy from the Department of Neurology at the First Affiliated Hospital of Chongqing Medical University from January 2020 to January 2022 were retrospectively analyzed. The study population satisfied the following criteria (1): the clinical manifestations were consistent with meningitis, encephalitis, myelitis, or a combination of the abovementioned syndromes, and tests for anti-GFAP antibodies were positive in the CSF and serum. The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, and either the patients themselves or their families signed informed consent forms.

The demographic characteristics, clinical manifestations, laboratory examinations, imaging examinations, treatment processes, prognoses, and other clinical data throughout the course of the disease were collected and analyzed as part of the study. Prognostic conditions were evaluated through telephone or outpatient follow-ups, and the modified Rankin Scale (mRS) was used to assess the outcome.

The presence of anti-GFAP antibodies, as well as the antibodies associated with autoimmune encephalitis, and antibodies against aquaporin 4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG), was tested in the patient serum and CSF using an indirect immunofluorescence cell-based assay (CBA). Human embryonic kidney cells (HEK293) expressing antigens were used in a positive CBA. All antibody tests were carried out in our hospital's neurology laboratory.

Cerebrospinal fluid cytology was performed by staining with May Grunwald–Giemsa (MGG) and using the method of slide centrifugation; this modified Ziehl–Neelsen stain for CSF has been previously described as the Xijing Hospital method (9).

3. Results

3.1. Clinical features

The age of the five patients in this study ranged from 38 to 66 years, and there were four male patients (80%) and one female patient (20%). The five patients had fever before developing neurological symptoms, with the majority of the patients experiencing an acute or subacute onset. In addition, three patients complained of headaches. The patient in Case 2 experienced night sweats. The patient in Case 3 experienced exhaustion, and the patient in Case 4 experienced coughing and expectoration. The patients in both Cases 1 and 4 had reports of seizures and status epilepticus. Three patients suffered from mental symptoms that manifested as hallucinations and gibberish language. Each of the five patients had varying degrees of cognitive impairment and decreased consciousness. One patient (Case 1) required tracheal intubation ventilation to help with ventilation after developing respiratory failure. Another patient (Case 4) developed myelopathy during the course of the disease, which manifested as paraplegia and dysuria and was accompanied by paralytic intestinal obstruction. In all five patients, a stiff neck was present (Table 1).

3.2. Laboratory examinations

Routine blood examination: Only the patient in Case 4 exhibited elevated white blood cell counts during the early stages of the disease.

3.2.1. CSF analysis

All five patients experienced an increase in CSF pressure (range: 200–380 mmH_2O, reference range 80–180 mmH_2O), an increase in the number of nucleated cells (range: 29–238 × 106/L, reference range: 0–10 × 10^6/L), an increase in protein levels (range: 1.54–2.61 g/L, reference range: 0.12–0.6 g/L), a decrease in chloride levels (range: 106–120 mmol/L, reference range: 120–130 mmol/L), and a decrease in glucose levels (range: 34%—48% of blood glucose, reference range: >50%). Both CSF culture and routine bacterial smear results were negative. Furthermore, CSF cytology revealed an inflammatory response with lymphocytosis. The modified acid-fast staining results for CSF were negative. Furthermore, two of the five patients had positive results for the T-SPOT (Case 1 and Case 2). Three patients (Cases 1, 3, and 4) developed moderate hyponatremia, with the patient in Case 3 having a diagnosis of syndrome of inappropriate antidiuretic hormone (SIADH) and requiring admission to the endocrinology department.

3.2.2. Antibody test

All five patients tested positive for GFAP antibodies but negative for other antibodies associated with autoimmune encephalitis (both in the CSF and serum). The patient in Case 4 underwent MOG and AQP4 antibody tests using serum and CSF due to myelitis symptoms, but the results were negative. Furthermore, all of the patients tested negative for serum tumor markers as well as the antinuclear antibody spectrum (Table 1).

3.3. Imaging

Except for the patient involved in Case 1 (who had a history of brain trauma surgery and was suggested to have a focus on encephalomalacia), the other four patients exhibited various

TABLE 1 Clinical data of five patients.

Clinical data	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Male	Female	Male	Male	Male
Age (years)	51	66	65	38	51
Course of disease (days)	5	40	7	19	4
Clinical symptoms					
Fever	Yes	Yes	Yes	Yes	Yes
Headache	No	Yes	No	Yes	Yes
Seizures	Yes	No	No	Yes	No
Mental symptoms	No	Hallucinations and gibberish language	Hallucinations and gibberish language	No	Hallucinations and gibberish language
Cognitive impairment	Yes	Yes	Yes	Yes	Yes
Decreased consciousness	Yes	Yes	Yes	Yes	Yes
Weakness of limbs	No	Yes	No	Yes	No
Other symptoms	Hiccups, respiratory failure	Night sweats, dysphagia, urinary incontinence	Fatigue, dysuria	Fatigue, cough and expectoration, intestinal infarction, dysuria	Dysuria, constipation
Stiff neck	Yes	Yes	Yes	Yes	Yes
Routine blood examinations					
WBC (4–10 × 10^9/L)	8.72	4.62	7.83	13.4	7.86
N% (40%—75%)	75.9	73	76↑	86.1↑	67.4
RBC (4.3–5.8 × 10^{12}/L)	5.47	4.12	3.87	4.05	4.27
PLT (100–300 × 10^9/L)	205	333	198	376	255
Serum sodium (135–145 mmol/L)	127	145	121	124	139
CSF					
Pressure (80–180 mmH_2O)	340	198	380	330	250
Number of cells (0–10 × 10^6/L)	29	178	90	238	122
Protein levels (0.12–0.6 g/L)	2.1	2.61	1.78	1.54	2.16
Glucose/blood glucose (mmol/L, >50%)	3.1/8.3	2.6/5.9	2.6/7.7	2.41/6.4	5.1/10.7
Chlorine (120–130 mmol/L)	109	120	106	113	117
Cytology	Lymphocytosis	Lymphocytosis	Lymphocytosis	Lymphocytosis, eosinophilia	Lymphocytosis

(Continued)

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TABLE 1 (Continued)

Clinical data	Case 1	Case 2	Case 3	Case 4	Case 5
Modified Ziehl-Neelsen stain	Negative	Negative	Negative	Negative	Negative
GFAP antibody					
CSF	Positive	Positive	Positive	Positive	Positive
Serum	Positive	Positive	Positive	Positive	Positive
Other AE antibodies	Negative	Negative	Negative	Negative	Negative
Antinuclear antibody spectrum	Negative	Negative	Negative	Negative	Negative
X-Pert	Negative	ND	ND	ND	ND
T-SPOT	Positive	Positive	Negative	Negative	Negative
Cranial MRI	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal
Tumor	No	No	No	No	No
Anti-tuberculosis time (days)	21	3	34	3	7
Anti-tuberculosis medicine	INH, RFP, PZA	INH, RFP, PZA	INH, RFP, PZA	INH, RFP, PZA	INH, RFP, PZA
Diagnosis time	23	7	34	3	7
Treatment					
Methylprednisolone	Yes	Yes	Yes	Yes	Yes
IVIg	Yes	No	No	Yes	Yes
Hospital stay (days)	25	25	36	53	41
Prognosis					
mRS score	Death	1	0	4	0

WBC, white blood cell; N%, neutrophil percentage; RBC, red blood cell; PLT, platelet; AE, autoimmune encephalitis; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; mRS, modified Rankin Scale; ND, not detected; INH, isoniazid; PZA, pyrazinamide; RFP, rifampicin; IVIg, intravenous immunoglobulin.
Other AE antibodies included anti-NMDAR antibodies, anti-GABAB antibodies, anti-AMPAR antibodies, anti-LGI1 antibodies, and anti-CASPR2 antibodies.

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abnormal signals, mostly involving the subcortex, periventricular white matter, basal ganglia, and brainstem, among other areas on cranial MRI (Figure 1). Furthermore, four patients' MRI results showed a high signal or equal signal on T1-weighted images and a high signal on T2-weighted and T2 FLAIR images. The patient in Case 2 exhibited a bright signal on diffusion-weighted imaging (DWI) and a black signal on ADC in the basal ganglia and lateral ventricle, indicating cytotoxic edema in these lesions. Moreover, in the patients in Cases 2, 4, and 5, high T2 FLAIR signals were observed in the sulcus and pia mater. The cervical spinal cord MRI of the patient in Case 4 exhibited a high signal on T2-weighted images. Gadolinium-enhanced brain MRI was performed on all five patients, and the patient in Case 5 exhibited parieto-occipital sulci meningeal enhancement. There was no linear perivascular radial enhancement pattern in any of the patients. Chest and abdomen CT scans, as well as urinary color Doppler ultrasound, were used to screen each patient for tumors, but no space-occupying lesions were found.

3.4. Misdiagnosis process, treatment, and outcome

The five patients were initially diagnosed with TBM and were given anti-tuberculosis medication. The duration of anti-tuberculosis treatment ranged from 3 to 34 days. Specifically, the anti-tuberculosis therapy regimen included isoniazid (INH) at 1,000 mg intravenous drip, rifampicin (RIF) at 450 mg oral, pyrazinamide (PZA) at 1,500 mg oral, and dexamethasone (DXM) at 10 mg intravenous drip for anti-inflammatory treatment. Except for the patient in Case 1, who demonstrated a lung infection that worsened after anti-tuberculosis medication and who had symptoms that did not significantly improve, the symptoms of the other four patients did not worsen; instead, they slightly improved. After the anti-GFAP antibodies in the serum and CSF were detected, all patients were diagnosed with autoimmune GFAP astrocytopathy between 3 and 24 days after their initial diagnosis. The patients were given methylprednisolone at 1,000 mg daily for 3 days and intravenous immunoglobulin (IVIg) at 0.4 g/(kg·d) for 5 days. The length of stay in the hospital ranged from 25 to 53 days. Unfortunately, the patient in Case 1 died due to respiratory failure. The patient in Case 5 received additional therapy at a rehabilitation hospital after being discharged with grade 2 muscle strength in the lower limbs. The other three patients were discharged with mRS scores of 0 or 1 (Table 1).

4. Discussion

Prodrome symptoms of autoimmune GFAP astrocytopathy, such as fever and headache, are present in 40% of patients, and meningoencephalitis is the predominant clinical condition

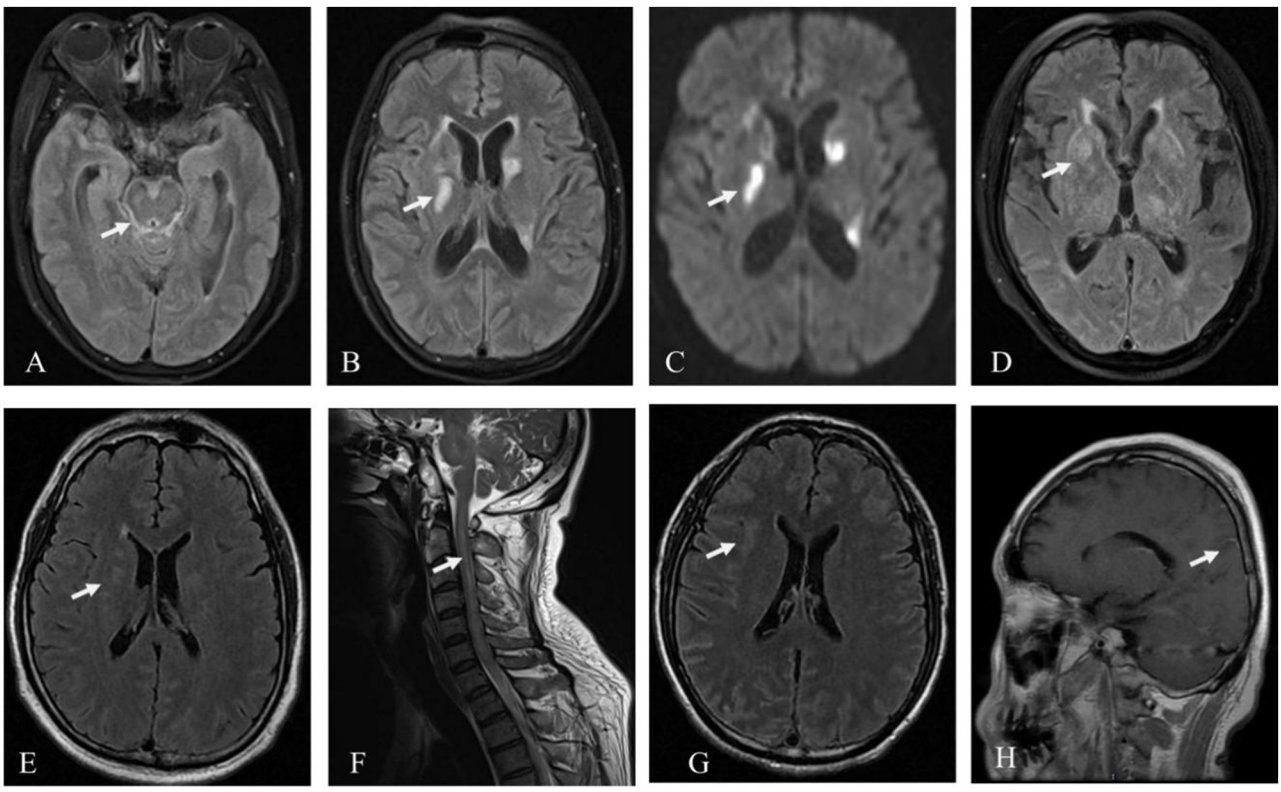

FIGURE 1
Patient MRI images. Hyperintensity signal inthe brainstem, pia mater, and basal ganglia on T2 FLAIR **(A, B)** and the basal ganglia on DWI in the patient in Case 2 **(C)**; hyperintensity signal in the basal ganglia on T2 FLAIR in Case 3 **(D)**; hyperintensity signal in the periventricular white matter on T2 FLAIR **(E)**, and the cervical spinal cord on T2 in the patient in Case 4 **(F)**; hyperintensity signal in the subcortex on T2 FLAIR and parieto-occipital sulci meningeal enhancement on T1 in the patient in Case 5 **(G, H)**.

in 55% of cases (5, 10). The diagnostic criteria for autoimmune GFAP astrocytopathy include meningitis, encephalitis, or myelitis (or a combination thereof) and anti-GFAP antibody positivity in CSF (7). The five cases of patients presented in this report had meningoencephalitis and tested positive for anti-GFAP antibodies in both their serum and CSF. As a result, they were ultimately diagnosed with autoimmune GFAP astrocytopathy.

If patients have clinical symptoms of meningitis or meningoencephalitis, autoimmune GFAP astrocytopathy must be distinguished from infectious meningitis or meningoencephalitis. CSF findings of leukocytosis ($>50 \times 10^6$/L), increased protein (>1 g/L), and hypoglycemia (<50% blood glucose during the testing period) are frequently indicative of tuberculous meningoencephalitis. In addition to the five cases reported here, other researchers have reported cases of autoimmune GFAP astrocytopathy that were initially misdiagnosed as infectious meningitis or tuberculous meningoencephalitis (11–13). Because autoimmune GFAP astrocytopathy and TBM have extremely similar clinical manifestations and features, it is critical to focus on identifying antibodies in the CSF and direct signs of tuberculosis infection to differentiate these conditions. Although detecting anti-GFAP antibodies in the CSF or serum is the primary method for diagnosing autoimmune GFAP astrocytopathy, antibody detection has not been widely adopted in clinical settings due to its high cost and the restrictions imposed by medical insurance. In addition, diagnosis of TBM requires an etiological diagnosis, but it is less likely to find *Mycobacterium tuberculosis* in the CSF or to identify *M. tuberculosis* DNA *via* PCR.

The five patients in our study were given a likely diagnosis of TBM based on the Vietnam TBM diagnostic scoring system from 2010 (14). Notably, when patients with autoimmune GFAP astrocytopathy have low CSF glucose levels, they are frequently suspected of having infectious encephalitis. A decreased glucose level was reported in the CSF of nine of the 59 patients with autoimmune GFAP astrocytopathy (15.25%) (8, 15–19). The precise mechanism and clinical importance of hypoglycorrhachia in autoimmune GFAP astrocytopathy remain unknown. Furthermore, lymphocytosis and an absence of lymphoma cells were found in the CSF of these five patients. Except for an increase in neutrophil levels during the very early stages of TBM, cytology primarily shows lymphocyte reactions throughout the course of the disease. Although some researchers have shown that autoimmune GFAP astrocytopathy involves a specific proportion of eosinophils in the CSF (8), eosinophils are nonspecific as a differential indicator because many factors, such as allergies, parasites, or tumors, can cause increased levels of these cells. In addition, T-SPOT is an ELISA test that uses tubercle bacillus (TB)-specific antigen to identify T lymphocytes in the peripheral blood that are specific to the TB antigen. Although T-SPOT has high sensitivity, it cannot be used to differentiate between ongoing infections, prior infections, or latent infections and therefore cannot yield a precise or unique diagnosis of tuberculosis (20). The T-SPOT-positive results in Cases 1 and 2 did not indicate an active TB infection. Patients with TBM are more likely to have hyponatremia, especially SIADH (21). Three of the five patients had moderate hyponatremia, with the patient in Case 3 being diagnosed with SIADH and the plasma sodium levels returning to normal after water restriction. In autoimmune encephalitis, anti-LGI1 antibody encephalitis is frequently associated with SIADH (22). Previous studies have reported hyponatremia in patients with autoimmune GFAP astrocytopathy (3, 5). More cases need to be analyzed to determine whether hyponatremia is a common symptom of autoimmune GFAP astrocytopathy.

The majority of patients with autoimmune GFAP astrocytopathy have abnormalities that can be identified using cranial MRIs, and the lesions can affect several brain regions, including the cerebellum, basal ganglia, hypothalamus, periventricular white matter, and meninges (23). The most specific imaging manifestation of autoimmune GFAP astrocytopathy is linear radial perivascular enhancement surrounding the lateral ventricle found in approximately half of the patients during enhanced MRI of the head (5). TBM imaging manifestations include hydrocephalus, meningeal enhancement, tuberculoma, infarcts, and basal ganglia calcification (24). In the five cases reported in this study, the longitudinal radial perivascular enhancement that typically characterizes autoimmune GFAP astrocytopathy surrounding the lateral ventricle was not present. In Case 2, DWI demonstrated restricted diffusion in the basal ganglia and lateral ventricle, which is uncommon for autoimmune GFAP astrocytopathy and more suggestive of TBM. Therefore, in the absence of measurable imaging changes, it is difficult to distinguish autoimmune GFAP astrocytopathy from TBM.

5. Conclusion

Five adult patients with autoimmune GFAP astrocytopathy misdiagnosed as TBM are summarized herein. Based on these cases as well as previous research, a certain percentage of autoimmune GFAP astrocytopathy and TBM manifestations are likely to be confused, especially when there is no direct evidence of relevant antibodies or TB infection. In regions where TBM is endemic, it is necessary to consider the possibility of autoimmune GFAP astrocytopathy when a patient's clinical symptoms and routine biochemical examinations in the CSF are similar to those of TBM but other examinations related to tuberculosis are negative and there are nonspecific changes in imaging.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NXQ: paper writing and data collection. XGW: paper writing and statistics. JW and YLM: data collection. WW: statistics. XFW: project design. LW: project design and paper writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cryptococcal infection causing longitudinal extensive transverse myelitis in an immunocompetent individual: Case report and literature review

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Cryptococcal CNS infections in immunocompetent individuals are occasionally reported in literature. The spinal manifestations of cryptococcal CNS infections are epidural abscess, chronic arachnoiditis, intramedullary granuloma, myelitis and vasculitis. We report a rare case of CNS cryptococcal infection presenting as a longitudinal extensive transverse myelitis (LETM) in an immunocompetent male. This report highlights cryptococcus as an important etiology among infectious causes in acute LETM patients in-spite of the immunocompetent status of the patient and the utility of CRAG (cryptococcal antigen) for diagnosis in such patients. We also present a literature review of all reported cases of cryptococcal myelitis.

KEYWORDS

cryptococcus, LETM, longitudinally extensive transverse myelitis, immunocompetent adult, cryptococcal antigen

Introduction

Cryptococcus neoformans, is a well-known fungal infection in immunocompromised patients. The most common CNS presentations are meningitis, meningoencephalitis, cerebral parenchymal abscess [cryptococcomas], gelatinous pseudocyst and hydrocephalus. The spinal cord manifestations include epidural abscess, chronic arachnoiditis, intramedullary granuloma, myelitis, and vasculitis. These manifestations have been reported in immunocompetent patients (1, 2). Transverse myelitis as a presenting feature of CNS cryptococcal infection has also been reported in literature (3) but longitudinal extensive transverse myelitis has been rarely reported (4). Herein, we report a 48-year-old immunocompetent male presenting with LETM due to cryptococcal infection, who regained normal functional status following treatment. We present this case to highlight (1) Cryptococcus neoformans as an important differential of infectious causes of acute LETM even in immunocompetent individuals, (2) Utility of Cryptococcal Antigen (CRAG) for diagnosis of cryptococcal CNS infections in immunocompetent individuals. We also present a review of all reported cases of cryptococcal myelitis in literature.

Case report

A 48-year-old male presented with a four-day history of acute onset progressive weakness of the lower limbs. The weakness started in the right lower limb and then progressed to involve the left lower limb leading to an inability to get out of the bed without support within 4 days of onset of symptoms. He also complained of sensory loss below the level of the upper abdomen with tingling and paresthesia in bilateral lower limbs. This was associated with a constant, deep-seated, ill-defined pain with dysthesias without any positional variation in the lower back and both lower limbs suggestive of a funicular pain. He also complained of urinary and stool retention. He had a history of fever with mild headache from 3 days prior to the onset of the weakness which persisted till admission (7 days). There were no significant past interventions, medical or family history. He belonged to the lower socio-economic strata and was a rickshaw puller by occupation. On examination, he was febrile and had a catheter *in situ*. He had hypotonia and motor weakness of lower limbs. The power was 2/5 in the right and 3/5 in the left lower limb, with absent deep tendon/superficial reflexes (anal/bulbo-cavernous) and mute plantar. He had brisk tendon reflexes in both the upper limbs. There was also complete loss of pain and temperature sensation below the T6 level. The sensorium, cognition, optic disc, cranial nerves, cerebellar system, and power in upper limbs were normal on examination. With this history and examination, the possibility of an acute transverse myelitis was considered.

The routine investigations including blood and urine cultures were negative. The contrast enhanced magnetic resonance imaging (CEMRI) of cervical-dorso-lumbar spine showed a T2W/STIR hyperintensity in the spinal cord extending from C7 to D11 vertebral level with partial enhancement, suggestive of a longitudinal extensive transverse myelitis (LETM). The CEMRI brain showed multiple T2W/FLAIR hyperintense lesions in the left frontal, right parietal and left temporal, periventricular white matter, pons, medulla and bilateral cerebellar lobes without any diffusion restriction or post contrast enhancement (Figure 1). Contrast enhanced MRI orbit did not reveal any significant abnormality. With these imaging findings, the diagnosis was revised to an encephalomyelitis. Infective, inflammatory, and demyelinating causes for LETM were investigated. Serum Antinuclear Antibody [ANA], Anti-Neutrophil Cytoplasmic Antibodies [ANCA] and Serum Neuromyelitis optica [NMO], Myelin oligodendrocyte glycoprotein [MOG] antibodies were negative. ELISA for serum viral markers of Hepatitis B, Hepatitis C and HIV were also negative. Serum Acetylcholinesterase (ACE) was normal [40 U/L]. Pathergy test was negative. Contrast enhanced computer tomography of chest and abdomen (CECT) did not reveal any abnormality. Visual evoked potential (VEP) showed bilateral normal P100 latency. The CSF examination showed decreased glucose, i.e., 67 mg/dl against the corresponding random blood sugar of 152 mg/dl and increased protein of 133 mg/dl with a cell count of 70 cells/mm3 (i.e., lymphocytes-56 cells/mm3, neutrophils-14 cells/mm3). No atypical cells were found. CSF gram stain, Ziehl-Neelsen [ZN] stain, India ink and CSF cultures were non-contributory. CSF neuroviral panel (Measles, Mumps, Epstein Barr, Parvo B19, Enterovirus, Varicella zoster, West Nile, Herpes simplex viruses) was also negative. CSF Cartridge based Nucleic Acid Amplification Test [CBNAAT] for Tuberculosis and Venereal Disease Research Laboratory [VDRL] was negative. However, CSF antigen was positive for Cryptococcus neoformans (CRAG) by lateral flow assay. Hence, a diagnosis of cryptococcal encephalomyelitis presenting as a LETM was made based on the clinical presentation and investigations. As the patient was immunocompetent and did not have any occupational exposure, detailed evaluation for any presence of cryptococcus in lungs/sinuses and CD4 counts for immunodeficiency were done but were found to be normal.

The clinical team started the patient on 4 weeks of induction therapy with intravenous liposomal amphotericin B at 5 mg/kg [250 mg] every 24 h and oral fluconazole 200 mg every 8 hourly. After 3 weeks of antifungal therapy his motor power improved to 4/5 and 5/5 in the right and left lower limbs, respectively. His bladder and bowel symptoms resolved completely. His sensory loss resolved, although he had occasional paresthesia. He was discharged in a stable condition with an advice to continue oral fluconazole 400 mg/day for 12 months. The patient is in follow up, he had no side effects, tolerated the medicines and on subsequent examination has now regained full functional capacity. The follow up imaging done after 6 months showed near complete resolution of lesions (Figures 2, 3).

Discussion

Our case presented a diagnostic challenge due to many unique features which we highlight in this report. (1) Cryptococcus presenting as an *acute LETM* in an *immunocompetent* patient, (2) Negative, Indian Ink for cryptococcus in the CSF, and (3) No source of cryptococcal infection found on investigations.

Cryptococcus presenting as an acute LETM

LETM has been described in demyelinating, autoimmune, systemic vasculitis and infective conditions. Among infections, Herpesvirus (herpes simplex, varicella zoster virus, cytomegalovirus, Epstein–Barr virus), HIV, HTLV-1 are the commonly described viral causes. Bacteria such as treponema pallidum, mycobacterium tuberculosis, mycobacterium bovis, borrrelia burgdorferi and parasites like schistosomiasis have also been described as causative microorganism of LETM (5). Although other spinal cord manifestations of cryptococcus infections like epidural abscess, chronic arachnoiditis, both intra and extramedullary granuloma, myelitis and vasculitis have been described (6, 7). A cryptococcal infection causing an acute LETM has been rarely described in literature (8, 9).

We did a literature search (English language articles only) on Pubmed using the MeSH terms "myelitis" OR "transverse myelitis" OR "longitudinal extensive transverse myelitis" AND "cryptococcus" OR "cryptococcal infection" which yielded 13 cases (10 case reports) of paraparesis associated with cryptococcal infection. Of these, 5 cases had intramedullary cryptococcomas on imaging. Eight cases had myelitis, with 2 of them harboring intramedullary granulomas in addition to the myelitis. LETM was reported in only three cases (Table 1). Our patient is the fourth case of cryptococcal LETM in literature to the best of our knowledge. Our patient also had T2/ FlAIR hyperintensities on brain imaging in addition to the LETM without any alteration in sensorium. This was similar to a 44 year-old male

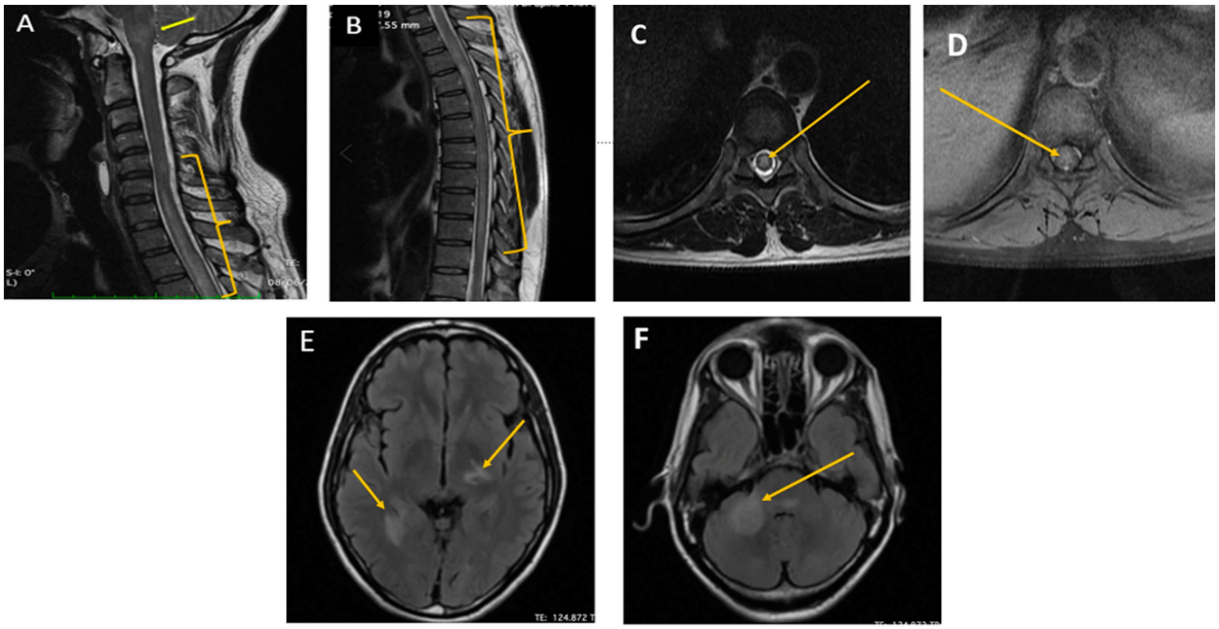

FIGURE 1
Pretreatment MRI cervicodorsal spine and brain image of the patient. **(A,B)** Sagittal T2/STIR images of the cervicodorsal MRI showed longitudinal extensive T2 hyperintensity in C5-D11 spinal cord segment (yellow bracket) along with brainstem involvement (yellow arrow). **(C,D)** Axial T2/STIR and T1 Contrast image of dorsal spine showing T2hyperintensity and partial enhancement, respectively, (Yellow arrow). **(E,F)** Axial FLAIR images how multiple hypointense lesions with surrounding hyperintensity in the left thalamus and the right mesial temporal and middle cerebellar peduncle suggestive of cryptococcal encephalitis (Yellow arrow).

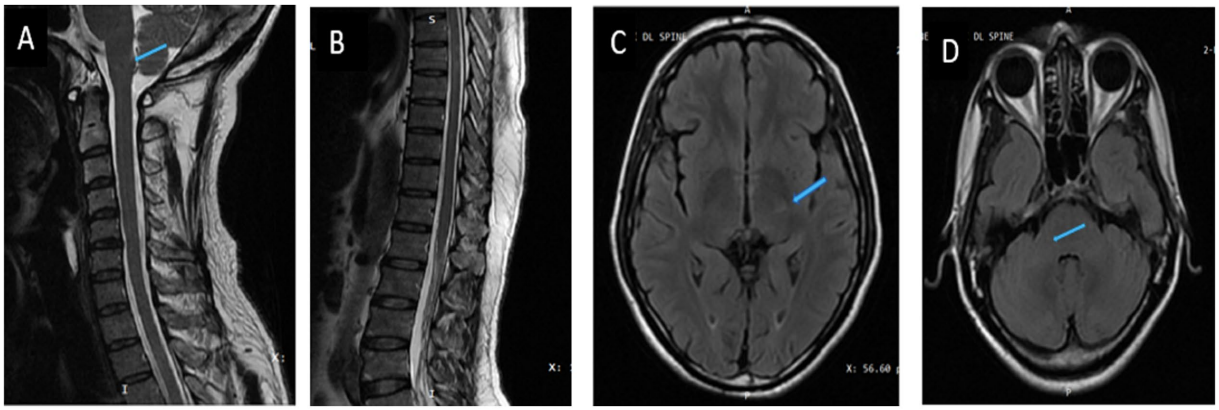

FIGURE 2
Post-treatment images (6months after treatment). **(A,B)** Sagittal T2/STIR image of the cervicodoral MRI. **(C,D)** Axial T2FLAIR image of brain showing resolution of lesions (blue arrow).

reported by Villafuerte et al. who had presented with quadriparesis but had an abnormal MRI brain imaging (9).

Overall, in cases of cryptococcal myelitis the median duration of onset of symptoms prior to admission was 38 days (IQR 9.5, 90). In the three cases of LETM reported in literature the duration of symptoms was 5, 10, and 150 days, respectively, (4, 8, 9). In our case, the patient had a four-day history of weakness prior to admission. This highlights that fungal diseases can also have acute CNS manifestations like a LETM.

Immunocompetent status of the patient

Usually, cryptococcus infections are seen in immunocompromised individuals who either have HIV or have undergone solid organ transplant and are on immunosuppressive therapy. Other than these, patients with organ failure syndromes, innate immunologic problems, common variable immunodeficiency, and hematologic disorders are also reported with cryptococcal infections (10). Cryptococcus infections have been reported in immunocompetent individuals.

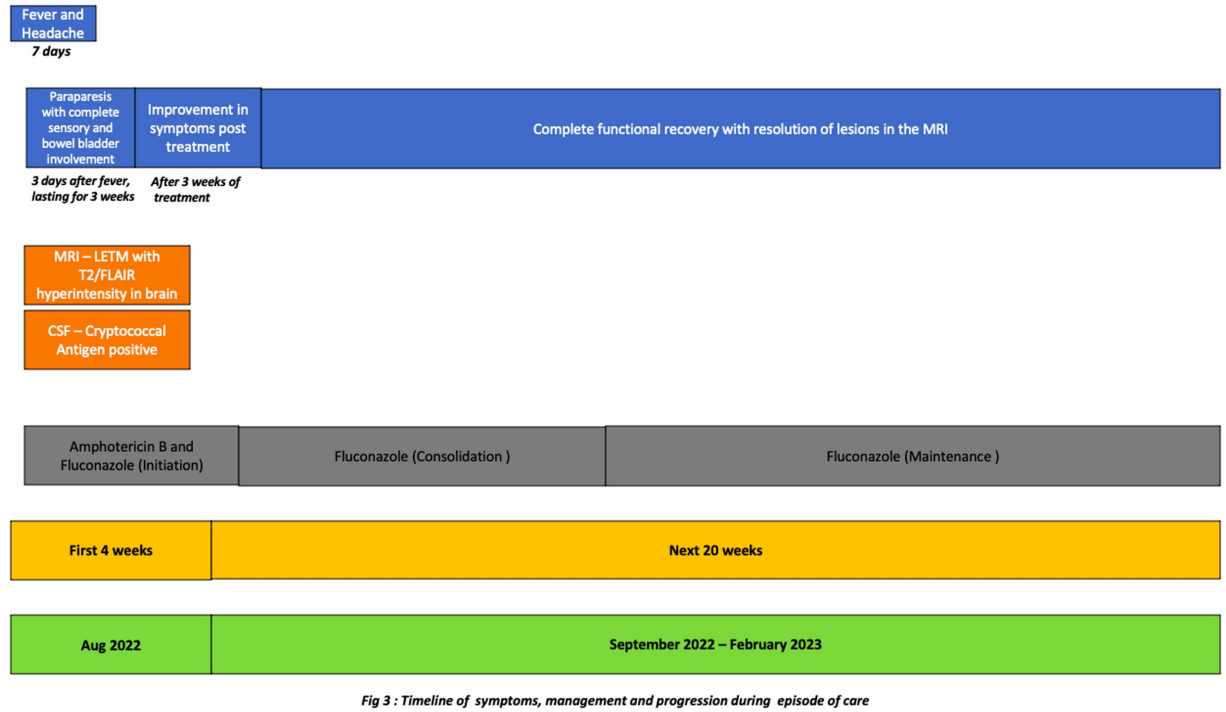

FIGURE 3
Timeline of symptoms, management and progression during episode of care.

Study in Australia, reported that 30% of total CNS cryptococcal infections occurred in immunocompetent individuals (11). It was also worth noting that, 75% (i.e., $n = 6/8$) of the cryptococcal myelitis cases reported in literature were immunocompetent individuals. In immunocompetent patients, robust CD4 T cells and Th1 inflammatory response causes inflammation, leading to clearing of the fungi and tissue damage. This is in contrast to a pauci-inflammatory and high infective burden state in the immunocompromised individual (12). Further, formation of granulomas is postulated to be influenced by an effective immune system through a trojan horse mechanism, i.e., passage across the cortical vasculature "within" phagocytes and neutrophils (13). Also, Liu J et al. mention a probable interaction of HLA class II alleles with cryptococcal meningitis, they report increased susceptibility and severe focal neurological deficits in patients with DQB1*05:02 loci (14). These mechanisms may explain the clinical presentation of our patient and the preponderance of immunocompetent individuals with myelitis in the literature.

Diagnosis of cryptococcal infection

In our patient, cryptococcus infection was diagnosed by a positive CRAG (in CSF) by lateral flow assay. As a CNS infection was suspected (owing to the CSF picture), the antigen was sent despite a negative report of Indian Ink and culture for cryptococcus. Indian Ink is a rapid and easy method of diagnosing cryptococcosis but has a limitation in individuals with low fungal burden, i.e., non-HIV or immunocompetent individuals. Boulware et al. in their seminal paper mention that Indian Ink testing has a low sensitivity when compared to CRAG, this further decreases in patients with a CFU of <1,000/mL in CSF cultures. They also report that Indian Ink has a negative predictive value of only 80%. The sensitivity of Indian Ink in non-HIV patients varies from 30 to 72% whereas the sensitivity and specificity of CRAG is >99% (15). Our case emphasizes that when suspecting cryptococcus, CRAG is a better diagnostic modality in an immunocompetent individual than an Indian Ink test despite the latter's cost effectiveness and wide availability.

No source of cryptococcal infection

Our patient had a CNS cryptococcal infection without any evidence of a systemic source. In the literature review of similar cases of myelitis (Table 1), only 2 cases of myelitis had a source of infection in the lung. Further, in 62% of the cases of myelitis reported in literature ($n = 5/8$), cryptococcus neoformans was isolated (Table 1). But we could not identify the genotype or speciate the cryptococcal infection found in this case. LETM has only been reported in cryptococcus neoformans and no cases of C. Gatti have been reported yet although C. Gatti is more common in immunocompetent individuals. As, we did not do a typing, C. Gatti can still be a possibility in our case. It is postulated that various factors like the species/strains/genotype of cryptococcus, host immunity and exposure determine the pathogenicity and further manifestations, i.e., only CNS manifestation or disseminated infection with lung/sinus involvement (16). Hence, we may not find a source of dissemination in all patients of cryptococcal CNS infection. The patient in our case did not have any occupational exposure in terms of dealing with pigeons/birds or soil or trees/forests, all of which have been reported as possible routes of de-novo infection. This makes a compelling argument toward a long

TABLE 1 Clinical symptoms, imaging and management details of cryptococcal myelitis patients reported in literature.

Author/ Year/ Country	Age/ Sex	Clinical features	Duration of symptoms	Primary infection site	Imaging findings	Lab features	Diagnosis	Immune status	Treatment	Outcome
Gumbo et al/1999-2000/ Zimbabwe[3]	31/M	Left lower limb weakness, sensory loss and urinary incontinence; occipital headache	9 days	NA	MRI - Normal	CSF India ink-**positive** Cryptococcal antigen-**not done** C/S -**negative**	Encephalomyelitis	HIV+	Amphotericin B Oral fluconazole	Died
	31/F	Chest pain; Paraparesis	63 days	NA	CT D-L spine-Normal	CSF India ink and culture-**positive** Cryptococcal antigen-**NA**	Myelitis	Competent	Itraconazole	Normal 7months
	39/F	Paraparesis	13 days	NA	MRI D-L spine -Normal	CSF India ink and culture **Positive** Cryptococcal antigen-**NA**	Myelitis	HIV+	Amphotericin B Fluconazole	Normal 30days
Grosse et al/2001/ Germany[7]	24/F	Paraparesis	90 days	Right lung	T2 hyperintense cranial and caudal to a ring like enhancement at L1 6 Ring enhancing lesions in the brain	Serum Cryptococcal antigen-**positive** CSF India ink-**negative** HPE c/s-**positive**	Encephalomyelitis	Competent	Amphotericin B + 5-flurocytosin + fluconazole+ operation	Normal 1year
Rai et al./2014/ India[8]	18/M	Paraparesis	150 days	NA	MRI spine-long segment dorsal cord (D4-D13) patchy hyper intensity in T2	CSF antigen and India ink**positive**	LETM	Competent	Fluconazole	Normal 6months
	39/M	Paraparesis	90 days	NA	MRI spine-Normal	CSF antigen**positive**	Myelitis	Competent	Fluconazole	Normal 8months
Qu et al./2020/ China[4]	55/M	Paraparesis	10 days	Lung	Longitudinal Extensive T2 hyperintensity (8 segments) and swollen thoracic cord with a Ring enhancing nodule at T9	Lung biopsy-**PAS staining positive** CSF Ag, India ink and culture-**negative**	Disseminated cryptococcosis	competent	Liposomal amphotericin B +Fluconazole+ Intrathecal dexamethasone	Normal 3months
Villafuerte/ \2022/USA[9]	44/M	Headache Quadriparesis	5 days	NA	MRI Brain-Multifocal supratentorial ovoid and nonspecific T2 hyperintensities. LETM with cord expansion from cervico-medullary junction till C7	CSF antigen and culture**positive.** Confirmed by**PCR.**	Encephalomyeltis	competent	Liposomal amphotericin B +Flucytosine +Fluconazole	Normal Lost to follow up

CSF, Cerebrospinal fluid; C/S, Culture and sensitivity; CT, computer tomography; D/L, Dorso-lumbar spine; NA, Not available; MRI, Magnetic resonance imaging; PCR, polymerase chain reaction; PAS-Periodic acid schiff.

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term latent infection in an individual later causing cryptococcal infections (17).

Treatment and outcome

The patient in our case recovered from the LETM clinically within 4 weeks of the induction therapy. He was put on consolidation therapy and is currently on maintenance therapy and has completely recovered on follow up. Others' studies (4, 8, 9) also showed that correct diagnosis and prompt treatment results in 90% of patients showing complete recovery. This highlights the notion that if there are clinical pointers toward an infective etiology in case of a LETM, one should rule out cryptococcus CNS infection as it is a treatable condition (18).

Strengths and limitations

In this case we could not speciate the cryptococcus, so we were unable to link the species and genotype of cryptococcus with the clinical symptoms and course of the illness. Although, the literature review revealed cryptococcal neoformans as an agent in majority of cryptococcal LETM. This case follows the patient from the onset of symptoms to a complete recovery from them, iterating the importance of investigating for treatable/infectious conditions implicated in LETM, as gaining neurological functionality in such individuals is possible. This case also emphasizes the need to use CSF CRAG as a diagnostic modality in immunocompetent individuals as low fungal burden in such individuals leads to negative Indian Ink and culture reports.

Conclusion

1. LETM is a rare but important manifestation of cryptococcus infection, and it should be considered as an important cause of acute LETM.
2. Cryptococcal Myelitis and LETM have been mostly reported in immunocompetent individuals.
3. In most cases of cryptococcal LETM, cryptococcus neoformans was isolated as the causative species.
4. Diagnosis by CRAG should be considered even if Indian Ink and culture is negative, especially in immunocompetent individuals.
5. No source of dissemination may be found in individuals with CNS cryptococcal infection.
6. Correct diagnosis and prompt management prevents the progression of symptoms and permanent disability.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AP and SK: conceptualizing drafting and editing the manuscript. SH and AA: diagnosis, management of the case, and first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Progressive multifocal leukoencephalopathy in a patient with multiple myeloma: a case report and analysis of the FDA adverse event reporting system

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This paper demonstrates a case of progressive multifocal leukoencephalopathy (PML) in a patient with multiple myeloma (MM) treated with nine different MM therapies. This case report contributes to the already published 16 cases of PML in patients with MM. Additionally, this paper presents an analysis of cases from the United States Food and Drug Administration Adverse Event Report System database (n = 117) with a description of demographics and MM-specific therapies. Patients with MM, that developed PML, were treated with immunomodulatory drugs (97%), alkylating agents (52%), and/or proteasome inhibitors (49%). Prior to PML diagnosis, 72% of patients received two or more MM therapies. These results indicate that PML in MM is underreported and could be related to treatment with multiple immunosuppressive therapies rather than MM as a disease itself. Physicians should be aware of potential PML in the late stage of heavily treated MM patients.

KEYWORDS

progressive multifocal leukoencephalopathy, multiple myeloma, PML, case report, immunosuppression, FAERS

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy, primarily occurring in elderly and middle-aged people with ∼85% diagnosed after the age of 55 years. Over the past three decades, MM treatment has improved leading to increased survival, first with high-dose chemotherapy (HDT) complemented by autologous stem cell transplantation (ASCT) and later with improved treatment regimens with immunomodulatory drugs (IMiD) including thalidomide, lenalidomide, and pomalidomide; proteasome inhibitors (PI) including bortezomib and carfilzomib; and monoclonal antibodies including daratumumab and elotuzumab (1–3).

Multiple myeloma is an incurable disease but sensitive to many different types of treatment. Early in the disease course, patients can experience longer periods of remission, but later on, the time between relapses will be shorter and patients will often need continuous treatment in order to control the malignant plasma cell clone. In recent years, most new treatment regimens have included continuous treatment and maintenance treatment with novel antimyeloma drugs compared to fixed-duration approaches (3–5). Maintenance with lenalidomide after ASCT leads to prolonged progression-free survival and, in some studies, prolonged overall survival (6–9). In addition, studies have demonstrated that daratumumab used in combination with lenalidomide or bortezomib given until progression is associated with a lower risk of disease progression and death (10, 11). This variety of new drugs and continuous treatment regimens lead to longer survival among MM patients but also to a prolonged state of severe immunosuppression.

Progressive multifocal leukoencephalopathy (PML) is an opportunistic central nervous system (CNS) infection caused by John Cunningham (JC) virus. Primary infection with the JC virus is common in the general population and likely occurs in the stromal or immune cells of the upper respiratory system. The virus is later trafficked by lymphocytes into the bone marrow or kidneys where it persists in a latent stage. Seroconversion increases with age and reaches ~60–80% at the age of 70 years. The pathogenesis of PML is the reactivation of the JC virus in glial cells in the CNS causing multifocal destructive brain lesions in patients with severe immunosuppression (12, 13). PML in patients with MM is rare but still a severe disease leading to disability and death. Currently, only 16 published cases, written in English, are available (13). This manuscript presents an additional case and a unique analysis of reported cases from the United States Food and Drug Administration (FDA) adverse events reporting system (FAERS) database.

Case presentation

A 39-year-old woman was diagnosed with IgG-kappa MM in 2005. The patient received HDT with ASCT four times over a period of 11 years. First ASCT was at the time of diagnosis and the second ASCT was 5 years later in 2010 due to MM relapse. Prior to the first and second ASCT, the patient was treated with cyclophosphamide and dexamethasone followed by high-dose melphalan. The third ASCT was 4 years later in 2014, and prior to this, the patient was treated with cyclophosphamide, bortezomib, and dexamethasone followed by high-dose melphalan. Treatment before the fourth ASCT, in 2016, was bortezomib, thalidomide, and dexamethasone followed by high-dose melphalan (Figure 1).

After the fourth ASCT, the patient was treated with 20 series of lenalidomide and dexamethasone to maintain remission. Due to disease progression in early 2018, treatment was switched to daratumumab, bortezomib, and dexamethasone, but after only one treatment, there was disease progression. Treatment was then changed to carfilzomib, lenalidomide, and dexamethasone, and eight series were given. The patient developed carfilzomib toxicity, and the treatment was halted at the end of 2018. Treatment was changed to pomalidomide, cyclophosphamide, and dexamethasone, and 21 series were given from 2019 to 2021. Eight of the 21 series were without cyclophosphamide due to severe neutropenia.

In 2019, 2 years prior to PML diagnosis, the patient had intracranial myeloma which regressed on treatment. In 2021, due to urinary retention, a history of intracranial disease and cognitive worsening a magnetic resonance imaging (MRI) examination of the brain and lumbar puncture were performed. Cerebrospinal fluid (CSF) was with normal levels of leukocytes ($\leq 5^{*}10^{6}$/L), and CSF flow cytometry revealed no plasma cells. CSF was not analyzed for the JC virus. Brain MRI showed no intracranial myeloma-related findings, but a non-specific lesion involving the splenium of the corpus callosum that could possibly represent a subacute ischemic change, a cytotoxic lesion of the corpus callosum, or a low-grade glioma was described (Figures 2A–C). The patient was afterwards treated with daratumumab, bendamustine, bortezomib, and dexamethasone for two series but stopped due to worsened general condition during the summer of 2021. The patient deteriorated cognitively and was bedbound most of the day. The symptoms debuted 1 month prior to the first MRI and progressed until death 5 months later. On neurological examination, the patient had left-sided hemianopsia.

This led to a new brain MRI, performed 12 weeks after the first brain MRI, showing progression of the corpus callosum lesion along with new brain lesions (Figures 2D–I). The appearance of new brain lesions, along with the enlargement of the corpus

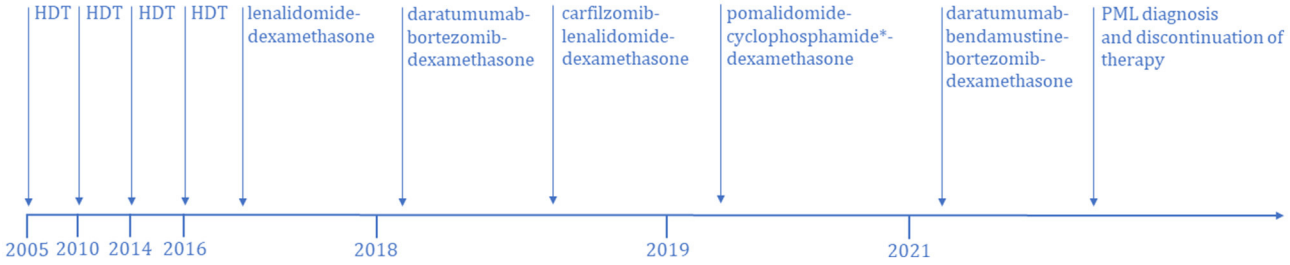

FIGURE 1
Treatment timeline of multiple myeloma-specific therapies from disease onset until the diagnosis of PML. HDT, high dose therapy. *Nine series without cyclophosphamide.

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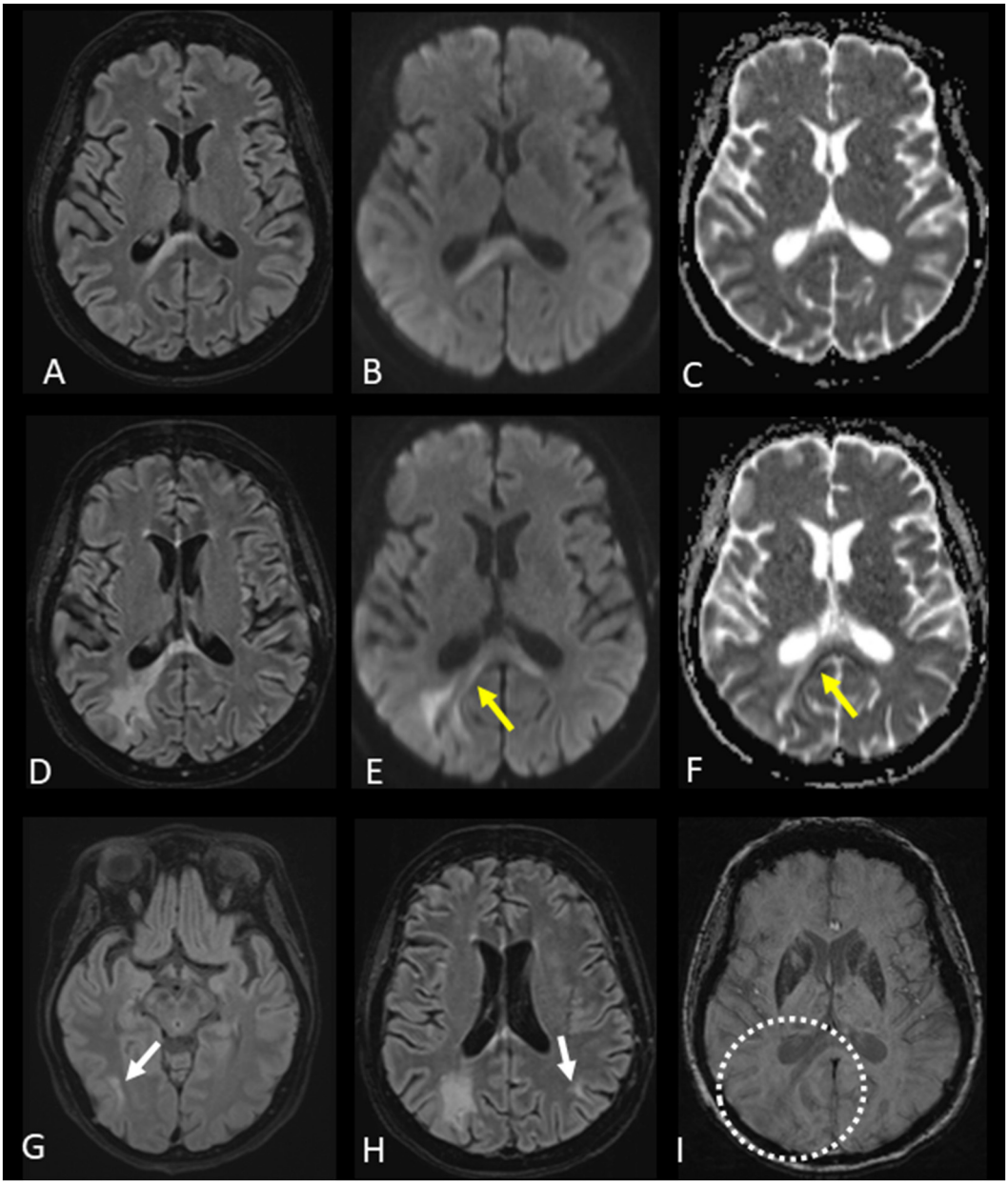

FIGURE 2
Evolution of progressive multifocal leukoencephalopathy (PML) and magnetic resonance imaging (MRI) changes. **(A–C)** First brain MRI with fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) b 1,000 images, and the apparent diffusion coefficient (ADC) map presented from left to right columns showing a lesion of the splenium of the corpus callosum, predominantly on the right side of the increased signal on FLAIR and DWI b 1,000 images, without restricted diffusion on the ADC map. **(D–F)** Second brain MRI with FLAIR and DWI b 1,000 images, as well as the ADC map, presented from left to right columns indicating an increase in the size of the corpus callosum lesion along with partial peripheral restricted diffusion visible on the DWI b 1,000 images and ADC map (yellow arrows). The newly appearing peripheral changes on diffusion images were indicative of PML. **(G, H)** FLAIR images of the second brain MRI demonstrating new lesions in the right temporal lobe and left parietal lobe (white arrows). **(I)** Susceptibility-weighted image of the second brain MRI without cortical-subcortical junction band of low signal intensity related to the expanding lesion from the corpus callosum (dotted circle). These susceptibility brain changes, which most likely represent iron accumulation, were described only in a part of PML patients.

callosum lesion and related changes on diffusion-weighted images, were highly suggestive of PML. A lumbar puncture was performed, and 51,900 copies/ml of JC virus were found in the CSF, confirming the diagnosis of PML.

Due to the PML diagnosis and the rapidly deteriorating general condition of the patient, no further MM treatment was given. Progressive cognitive impairment followed, and the patient died four weeks after the PML diagnosis.

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TABLE 1 Demographics and therapy characteristics of patients in the United States Food and Drug Administration adverse event reporting system database.

Population, *n*	117
Female	32,4%
Age (years), mean, SD	65.4, 7.5
Number of drugs pr. patient	
1	*N* = 33, 28.2%
2	*N* = 32, 27.4%
3	*N* = 24, 20.5%
9-Apr	*N* = 20, 17.1%
>10	*N* = 8, 6.8%
Proportion of patients treated with following drug classes	
Immunomodulatory drugs	96.60%
Alkylating agents	52.10%
Proteasome inhibitors	48.70%
Monoclonal antibodies	29.90%
Topoisomerase inhibitors	13.70%
Other cytostatic agents	12.80%
Other immunosuppressive agents	0.90%

FAERS database

The public available FEARS database is used to monitor serious adverse events for drugs. A search in the FAERS database was performed by matching cases of MM-associated PML reported from 2002 until 18 May 2022. The search term "progressive multifocal leukoencephalopathy" was used when searching for "reaction type" and yielded 6,165 cases with PML. All cases were listed with suspected product names, active ingredients, and reasons for use of the drug. To identify only MM cases, "myeloma" was used as an additional search term in "reasons for use of drug," and this search yielded 198 cases with both variables: "Plasma Cell Myeloma" and "PML." To reduce duplicates, cases were matched based on characteristics. Cases with the same age, gender, and country where the event occurred were matched, if the event date, FDA, or manufacturer report date were within the same 30 days. A detailed listing of matching criteria is found in Supplementary Table. After adjusting for duplicates, the number of cases was reduced to 117, corresponding to a reduction of 40.9%. Relevant-reported MM-specific therapies were included in the analysis. Demographics and therapy characteristics are reported in Table 1. Reported MM-specific therapies in patients with PML from the FAERS database are depicted in Figure 3. The most frequently given therapies were IMiD, alkylating agents (AA), PI, monoclonal antibodies (MAB), topoisomerase inhibitors (TI), other cytostatic agents (OCA), and other immunosuppressive agents, listed based on the frequency of use (shown in Table 1).

Discussion

This paper describes a case of PML in a patient having MM for more than 16 years. PML is a rare condition in MM, and so far, only 16 cases are described worldwide from 1,965 until now (13). To our knowledge, no studies have described the incidence of PML in patients with MM. This is the first analysis of reported cases of PML in MM from the FAERS database. Through an analysis of the FAERS database, this paper suggets that PML incidence in MM is higher than the 16 described cases, since 117 cases were identified from 2002 until May 2022.

In this case report, PML occurred after a treatment history with nine combined MM therapies. Only one case of PML in a patient with untreated MM is described in the literature, where PML was diagnosed prior to MM diagnosis (14). The FAERS database demonstrated that 72% of patients were treated with two or more different MM specific therapies, before a diagnosis of PML, especially IMiD were given more frequent than any other treatment. This paper suggets that PML in patients with MM is related to treatment with immunosuppressive therapies rather than the MM diagnosis itself and physicians should be aware of this, especially in the late stage of heavily treated MM patients. The analysis of the FEARS database demonstrates that 97% of patients with MM, that developed PML, were treated with IMiD and that AA (52%) and PI (49%) were the second and third most frequent treatments, respectively (Table 1). IMiD is among the most widely used treatments in MM, both in case of maintenance therapy after ASCT and in patients not eligible for ASCT. This could explain that almost all patients that developed PML received IMiD during the disease course. The FAERS analysis showed that PML after treatment with MAB and TI was relatively infrequent compared to IMiD, AA, and PI. This might be explained by the novelty of MAB in MM treatment and that TI is currently less frequently used since other therapies have been prioritized by treatment guidelines (15).

There are limitations when using FAERS as a database for drug-associated PML and for PML incidence in MM. First, healthcare professionals, consumers, and manufacturers submit reports voluntarily to the FDA. This means that there are duplicate reports, and some adverse events are not reported, which is why FAERS cannot be used solely to estimate incidence. Moreover, a report of an adverse event does not establish causation with the reported drug. The event might have been related to the underlying disease or caused by other drugs. The information from the FAERS database solely depends on the reporter. There are incomplete reports in the database that do not contain all the necessary information, and submission of a report does not require medical confirmation. Due to this, FAERS cannot be used as an absolute indicator of drug safety.

There were also limitations in the analysis of the FEARS database. Cases with similar dates that were not matched due to missing information regarding age and gender, could lead to an overestimation of the incidence. Vice versa, cases could have been matched as duplicates wrongly, causing an underestimation of the incidence.

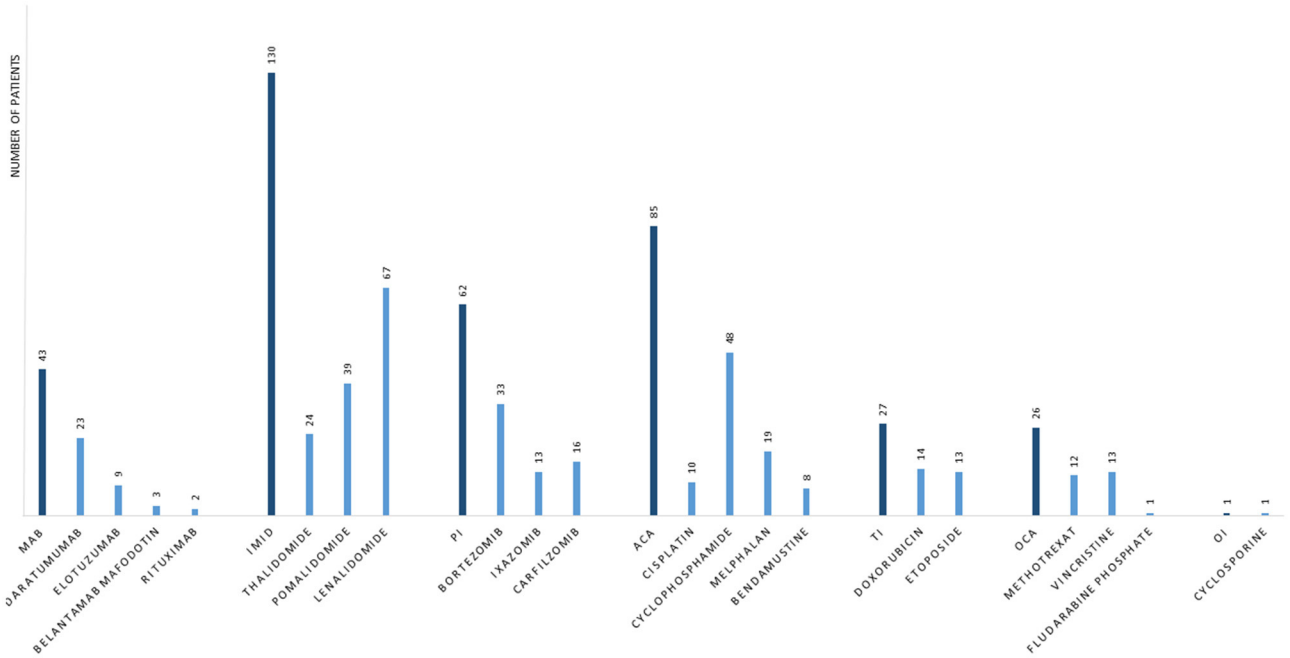

FIGURE 3
Frequency of specific multiple myeloma therapies in cases that developed progressive multifocal leukoencephalopathy. Data are from the United States Food and Drug Administration adverse events reporting system database. MAB, monoclonal antibodies; IMID, immunomodulatory drugs; PI, proteasome inhibitors; ACA, alkylating agents; TI, topoisomerase inhibitors; OCA, other cytostatic agents; OI, other immunosuppressive agents.

This paper demonstrates that PML in patients with MM is associated with treatment with immunosuppressive therapies, rather than the MM disease itself, and physicians should be aware of this, especially in the late stage of heavily treated MM patients.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the spouse of the patient for the publication of any potentially identifiable images or data included in this article.

Author contributions

EJ and TS conceptualized the manuscript. EJ, RA, PT, and TS contributed to data analysis, interpretation, drafting, and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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We thank the patient's spouse for consenting to this case report.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1098930/full#supplementary-material

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Neurosyphilis with positive anti-N-methyl-D-aspartate receptor antibody: a case report

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A case of neurosyphilis with a positive anti-N-methyl-D-aspartate receptor (NMDAR) antibody was reported. A 54-year-old man who presented with acute memory deficits was admitted to our hospital. Acute ischemic stroke (AIS) was initially considered, and he was prescribed intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA). However, the intermittent onset of episodic memory and orientation disorder still occurred. No diffusion restriction was indicated by magnetic resonance imaging (MRI), and subclinical seizures were frequently found by electroencephalogram (EEG). Rapid plasma reagin (RPR) test of serum showed positive results for syphilis. Analysis of cerebrospinal fluid (CSF) revealed elevated leukocyte count and protein level. RPR test, *Treponema pallidum* particle agglutination (TPPA) assay, and *Treponema pallidum* antibody (TP-Ab) in CSF showed positive results, and the anti-NMDAR antibodies were positive in CSF and serum. Finally, the patient was diagnosed with neurosyphilis with a positive anti-NMDAR antibody. The clinical symptoms were improved, and the leukocyte count in CSF was reduced after treatment with intravenous penicillin G and levetiracetam. This case suggests that in cases with positive results for neurosyphilis and NMDAR antibodies, the proper treatment has to be decided based on all of the available clinical and diagnostic testing data.

KEYWORDS

neurosyphilis, encephalitis, anti-N-methyl-D-aspartate receptor (anti-NMDAR), epilepsy, case report

Introduction

Treponema pallidum is one of the most common causes of sexually transmitted infections. Infection with *Treponema pallidum* is most commonly referred to as syphilis with modifiers to denote the phase of the disease or infection manifestations. Neurosyphilis is an infection of the central nervous system (CNS) caused by *Treponema pallidum*, which may occur at any stage of the infection (1). The incidence of syphilis declined after the introduction of penicillin. The incidence rate has shown an upward trend since the 2000's, and especially with the increase in the prevalence of acquired immunodeficiency syndrome (AIDS) and immunodeficiency, the number of patients with neurosyphilis has gradually risen (2, 3). In China, the incidence of syphilis ranks third after viral hepatitis and tuberculosis among infectious diseases. The upward trend was aligned with that of neurosyphilis (4).

Autoimmune encephalitis (AE) generally refers to a type of encephalitis mediated by autoimmunity. At present, the prevalence of AE accounts for about 10∼20% of encephalitis, and its clinical manifestations include acute or subacute cognitive impairment, epileptic seizures, mental disorders, and a variety of motor disorders (5). Anti-NMDAR encephalitis

is a relatively common form of AE and one of the most completely described forms of AE; however, we do not have accurate estimates for the incidence of NMDAR encephalitis or all other forms of AE. Initially, anti-NMDAR encephalitis was thought to be associated with malignancies, and it was later found to be common after viral infections (6).

Neurosyphilis may be latent and asymptomatic or accompanied by a variety of signs and non-specific clinical symptoms, mimicking several types of neurological and psychiatric diseases. To date, neurosyphilis with a positive anti-NMDAR antibody has been rarely reported. The present study aimed to report such a case.

Case presentation

A 54-year-old man was referred to the emergency department by his son, who complained of his father's memory impairment for 1 h, presenting that he could not find the way home and answer questions correctly, without movement and sensory disorders. Before the attack, he took a walk near his home as usual. His medical history included hypertension and diabetes. He suffered from a stroke 8 years ago, leaving over mild weakness of the right lower limb and mild memory decline, and was competent for agricultural work. Five years ago, he suffered a stroke again, presenting with increased weakness in his right lower limb, which gradually returned to baseline levels. However, his memory and executive function gradually decreased, and he was still able to pursue simple farm work, take care of himself, accompanied by personality change, and became irritable. He was taking aspirin regularly after the stroke. The patient had a history of smoking. Physical examination revealed disorientation, slow reaction, and lack of cooperation. The patient had an acute onset, and the cranial computed tomography (CT) showed multiple areas of signal abnormality consistent with encephalomalacia as a consequence of remote cerebral infarction. Acute ischemic stroke (AIS) was considered and he was prescribed intravenous thrombolysis with recombinant tissue-type plasminogen activator (rt-PA). After thrombolytic therapy, the patient regained his directional ability about half an hour later. and neurological examination indicated slow response, calculation decline, right-left agnosia, memory decline, 5-/5 strength of the right lower limb, and right Babinski's sign-positive. The other parameters of the neurological examination were normal. Mini-Mental State Exam (MMSE) score was 15/30 (middle school education level).

The patient was subsequently admitted to the neurology ward for further treatment. In addition, CT angiography (CTA) of the head and neck showed no obvious stenosis. Non-enhanced magnetic resonance imaging (MRI) of the brain revealed signal abnormality consistent with his history of ischemic stroke, including encephalomalacia and chronic lacunes (Figure 1). However, there was no evidence of restricted diffusion as it would be expected that his acute symptoms were caused by an AIS. After admission to the ward, the patient had recurrent episodic disorientation. It lasted for more than 10–30 min for each attack, and he could not recall it afterward. Therefore, non-convulsive status epilepticus (NCSE) was suspected. During Electroencephalogram (EEG) monitoring, the patient did not experience an acute disorientation attack. An EEG showed that more than 40 subclinical seizures were recorded within 16 h.

The routine blood parameters, liver function, kidney function, electrolyte, coagulation profile, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factors, thyroid function, anti-thyroglobulin antibodies, anti-thyroid peroxidase antibodies, serum tumor markers, and serological testing for hepatitis B and human immunodeficiency virus (HIV) were normal. Fasting blood glucose was 16.5 mmol/L. Triglyceride level was 3.31 mmol/L, and low-density lipoprotein cholesterol was 3.1 mmol/L. Rapid plasma reagin (RPR) testing indicated positive results for syphilis (serum RPR titer of 1:32). The patient's son supplemented his medical history. Syphilis had been identified when his father suffered from a stroke 8 years ago. He received standardized treatment for syphilis. He showed progressive cognitive impairment, personality change, and seizures on admission; therefore, neurosyphilis was considered. A lumbar puncture was performed, and normal opening pressure was indicated. The count of leukocytes in cerebrospinal fluid (CSF) increased to 117/μl, of which 97% were monocytes, and red blood cells (RBCs) were 2/μl. The glucose level in CSF was 5.9 mmol/L, and the protein level in CSF was elevated (829.19 mg/L). RPR test, *Treponema pallidum* particle agglutination (TPPA) assay, and *Treponema pallidum* antibody (TP-Ab) in CSF showed positive results. The oligoclonal immunoglobulin G (IgG) bands (OCB, type II) were positive in CSF, while they were negative in serum. In addition, the patient was tested for AE antibodies by cell-based assay (CBA), in which the anti-NMDAR antibodies were positive in CSF and serum, and the titers in CSF and serum were 1:20 and 1:10, respectively. Hu, Yo, and Ri antibodies were not detected in both serum and CSF.

Therefore, the patient was finally diagnosed with neurosyphilis with anti–NMDAR antibodies. Intravenous penicillin G (24 million units/d for 3 weeks) and levetiracetam (up to 500 mg twice daily) were given. Simultaneously, antiplatelet drugs and statins were prescribed for secondary prevention and treatment of cerebrovascular diseases. In addition, the blood glucose and blood pressure of the patient were well controlled. After the above-mentioned treatment, the patient's paroxysmal disorientation and cognitive impairment were alleviated. After 3 weeks of treatment with penicillin, we reviewed the patient's EEG, MMSE, and CSF tests. Reexamination of the EEG showed no clinical or subclinical seizures within 16 h. MMSE increased to 19/30 points. The protein level in CSF is 831.37 mg/L. The count of leukocytes in CSF was reduced to 15/μl, with 5 RBCs /μl. In addition, OCB in CSF remained positive and the anti-NMDAR antibody titer remained unchanged. After 5 weeks, the patient was positive for RPR with a serum titer of 1:8.

Discussion

A case of neurosyphilis with an anti-NMDAR antibody was reported in the present study. The patient presented with acute and non-specific changes in mental status manifested as memory loss and disorientation. AIS was initially considered, and rt-PA was prescribed, while recurrent disorientation was continued after admission to the ward. The brain MRI did

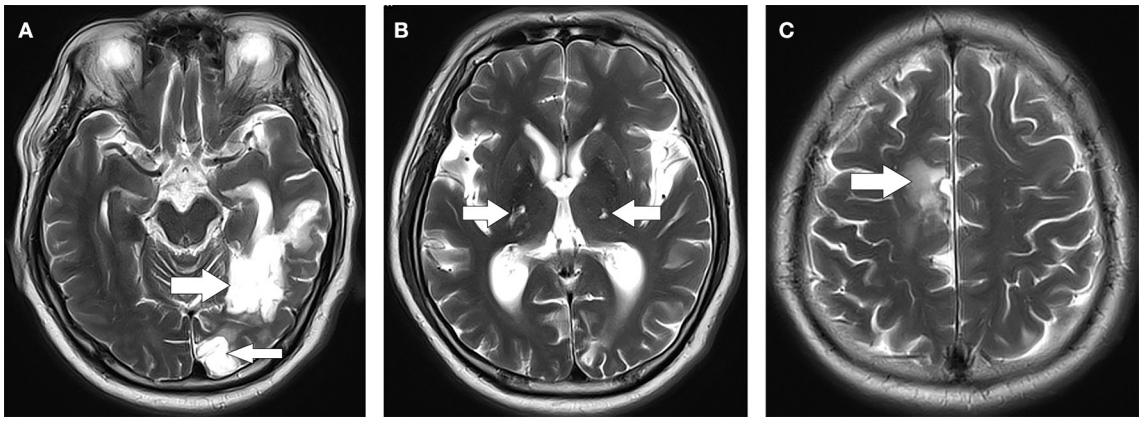

FIGURE 1
Axial section of T2 brain MRI. **(A)** Cerebral softening lesions in the left temporal-occipital lobe (indicated by arrows). **(B)** Multiple lacunar infarctions in the bilateral basal ganglia (indicated by arrows). **(C)** Cerebral softening lesions in the right corona radiata (indicated by arrow). MRI, magnetic resonance imaging.

TABLE 1 Cases of neurosyphilis with positive anti-NMDAR antibody.

	Age	Gender	Symptoms	Brain MRI	EEG	CSF	Treatment and outcome
Case 1 (24)	37	Male	Progressively reduced vision of both eyes for 6 months	A focal slightly high FLAIR signal on the right frontal lobe and low T2 signal adjacent to the right cornu posterious ventriculi lateralis	Nil	Leukocyte:6/mm3 Protein:1.237 g/L OB: positive	Penicillin G: improved
Case 2 (24)	39	Male	Progressive attention and memory impairments	Enlargement of lateral ventricles and the third ventricle, and focal high T2/FLAIR signal abnormality involving bilateral temporal lobe, and corona radiate	Nil	Leukocyte: normal Protein: normal OB: positive	Penicillin G + pulsed methylprednisolone + IVIG: improved
Case 3 (23)	35	Male	Abnormal mental and behavior changes for 3 months. Tonic-clonic seizures on admission	Normal	Intermittent frontal slowness	Leukocyte:52/Ul, 96% were monocytes Protein: 143 mg/dL OB: No description	IVIG: inefficiency Penicillin G: improved
Case 4 (25)	32	Male	Cognitive decline, diplopia and walking instability for 6 months	Symmetrical abnormal signals in the pons, midbrain, and bilateral basal ganglia	Normal	Leukocyte: normal Protein: normal OB: positive	Ceftriaxone: worsen Pulsed methylprednisolone + IVIG: improved

MRI, magnetic resonance imaging; FLAIR, Flow attenuated inversion recovery; EEG, electroencephalogram; CSF, cerebrospinal fluid; IVIG, intravenous immunoglobulin.

not show restricted diffusion, and multiple non-convulsive and subclinical seizures were recorded by EEG. Thus, the diagnosis of NCSE was considered to be more likely than a diagnosis of AIS evolving to NCSE. The patient had a history of syphilis, with clinical manifestations of epilepsy, dementia, and RPR, TPPA, and TP-Ab in CSF were positive. Therefore, he was diagnosed with neurosyphilis. After 3 weeks of intravenous penicillin G and antiepileptic therapy, the symptoms were relieved, and the leukocyte count in CSF was lowered down.

Neurosyphilis is a slow-progressing, destructive infection of the brain and spinal cord. The incidence of neurosyphilis was estimated to be 0.47–2.1 per 100,000 people (7, 8). The clinical stages of syphilis include early syphilis, late syphilis, and neurosyphilis. Early neurosyphilis occurs several months to several years after infection, and it is typically manifested as meningitis or

meningeal vascular disease, while late neurosyphilis occurs several years to several decades after infection, which is characterized by general paresis, including progressive dementia, psychiatric syndromes, personality change, manic delusions, tremor, and dysarthria (9). A study on 286 neurosyphilis patients found that general paralysis of the insane was the most common type of neurosyphilis (49%), followed by syphilitic meningitis (22%), meningovascular, and tabetic types (12%) (10). Multiple brain softening and infarct focus may be related to meningovascular neurosyphilis, however, they may also be related to atherosclerosis because of hypertension and diabetes. Therefore, the etiological diagnosis of cerebral infarction is still a clinical challenge. The patient had cognitive impairment after cerebral infarction. Moreover, the brain MRI showed temporal lobe infarction and vascular dementia was also indicated. However, the patient's cognitive impairment gradually worsened, and neurosyphilitic dementia was also considered. Thus, the patient was diagnosed with late neurosyphilis. A study on 120 neurosyphilis patients found that 25% of patients had seizures, among which half had generalized seizures, most had focal seizures, and few patients had status epilepticus (11). To the best of our knowledge, neurosyphilis has rarely been reported as NCSE. The changes of the patient in an acute mental state, manifested as memory loss and disorientation, can also be explained by NCSE, which further confirms the diversity of clinical manifestations of neurosyphilis.

Anti-NMDAR encephalitis was first described in 2005 as a clinical syndrome of acute episode psychosis, and a progressive while treatable encephalopathy. The disease mainly covers five distinct stages: prodromal phase, psychotic phase, unresponsive phase, hyperkinetic phase, and recovery phase (12–14). It may present with psychosis, memory deficits, seizures, dyskinesia, involuntary movements, decreased level of consciousness, and autonomic instability. Seizures are a common manifestation of this disease, and they were found in 76–82% of patients (15, 16). Extreme delta brush is a specific EEG pattern identified in 30% of patients with anti-NMDAR encephalitis (17). The mechanisms that may trigger AE include tumors, infections, or cryptogenic factors (18). Virus-mediated cerebral tissue damage may lead to antigen exposure that triggers the development of anti-neuronal antibodies (19). Therefore, it is reasonable to speculate that *T. pallidum* infects the CNS, resulting in the exposure of antigens that may produce anti-NMDAR antibodies.

To date, it has been reported that neurosyphilis is characterized by marginal lobe encephalitis, and studies have found the coexistence of AE antibodies with neurosyphilis (20–23). Furthermore, cases of neurosyphilis with anti-NMDAR antibodies were searched in PubMed with the target words "neurosyphilis" or "syphilis" and "anti-N-methyl-D-aspartate Receptor antibody" or "NMDA" or "anti-NMDAR encephalitis." A total of four cases (three reports) were matched (23–25), and all the cases were men aged over 30. Table 1 summarizes the characteristics of these four cases. Case 1 showed progressively reduced vision in both eyes, and the symptom was alleviated by penicillin. Case 2 presented progressive attention and memory impairment and symptoms were relieved after the use of penicillin combined with steroid hormone and intravenous immunoglobulin (IVIG). Case 3 presented with progressive psychobehavioral abnormalities and tonic-clonic seizures, which are ineffective after receiving IVIG. Symptoms are relieved after switching to penicillin. The condition of case 4 was worsened after the application of ceftriaxone, and symptoms were relieved after switching to steroid hormone and IVIG. The patient in our study started with NCSE and the anti-NMDAR antibody in CSF was positive, but AE was not considered. Because clinical presentation, course, imaging findings, CSF, and laboratory testing results of this patient could be explained by syphilis and seizure, and his symptoms were improved after treatment of penicillin and levetiracetam without immunomodulatory therapies, although neurosyphilis might induce immune abnormalities and lead to the generation of anti-NMDAR antibodies, we believe that it might not cause disease to this patient, and might be existed as a bystander. Case 1 and Case 3 also confirmed this viewpoint. Case 2 was treated with both penicillin and immunomodulatory therapy, and it is unclear which medication improved the symptoms. The symptoms of Case 4 were worsened after the application of ceftriaxone, but symptoms were improved after switching to hormones and IVIG, which seems contradictory. The roles of anti-NMDAR antibodies in neurosyphilis may be bystanders or pathogenic factors, which requires further theoretical and clinical research to clarify. In a word, in cases with positive results for syphilis/neurosyphilis and NMDAR, the proper treatment has to be decided based on the available clinical and diagnostic testing data. When IgG specific for the GluN1 subunit of the NMDAR is found in both serum and CSF, this antibody should not be considered as the cause of a person's neurologic illness unless a compatible clinical syndrome is available and alternative causes of encephalitis have been ruled out. In cases for which a treatable infection is also found, the risks and benefits of concomitant anti-microbial therapy and immunotherapy need to be evaluated.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZS collected data and drafted the manuscript. SJ consulted the relevant literature. GF and HH contributed to the guidance of the report. LX contributed to the guidance of the research and review of the manuscript.

All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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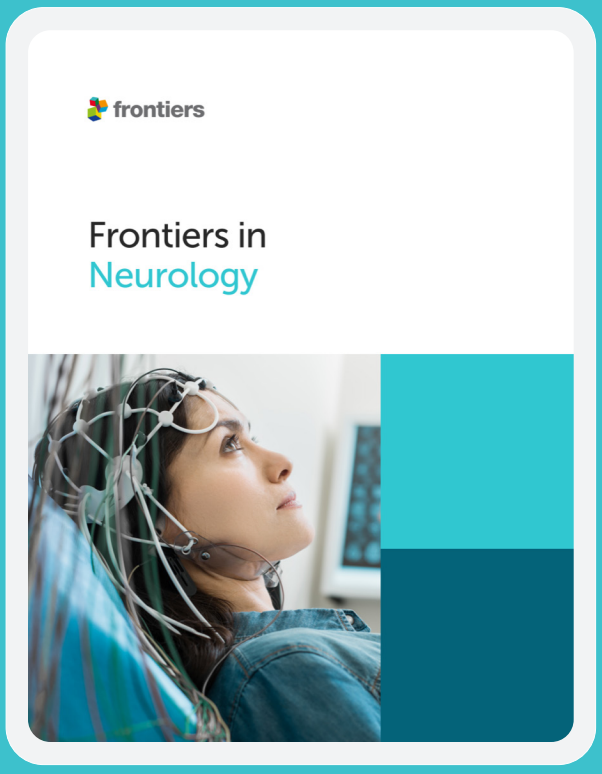

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