

# Brucellar meningitis complicated by epstein-barr virus meningitis: a case report and literature review

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## Abstract

**Objective** To analyze the clinical characteristics of a patient with brucellosis meningitis complicated by Epstein-Barr virus (EBV) meningitis in order to enhance awareness of this rare condition.

**Methods** A retrospective analysis was conducted using the clinical data of a patient admitted to Cangzhou Central Hospital on October 31, 2024, with brucellosis meningitis complicated by EBV meningitis. The patient's clinical features, treatment course, and prognosis were evaluated.

**Results** The patient presented with headache, nausea, and vomiting. Cerebrospinal fluid (CSF) examination revealed markedly elevated intracranial pressure. Metagenomic next-generation sequencing (mNGS) of the CSF detected both *Brucella* and EBV. Cranial magnetic resonance imaging (MRI) showed no significant abnormalities, and other etiological tests were negative. The diagnosis of brucellosis meningitis complicated by EBV meningitis was established. Initial therapy failed to adequately control the symptoms, but timely adjustment of medications led to improvement in clinical manifestations and laboratory findings, resulting in successful discharge.

**Conclusions** Concurrent meningitis caused by bacterial and viral pathogens is rare in clinical practice and is easily misdiagnosed or subject to delayed treatment. In patients with refractory symptoms, active CSF examination should be performed to achieve early diagnosis and timely intervention.

**Keywords:** brucellosis, Epstein-Barr Virus infections, meningitis, coinfection, case reports

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## Introduction

Brucellosis meningitis is a rare but severe complication of brucellosis, occurring in only 4%–7% of patients and

associated with a relatively high rate of disability. The condition often has an insidious onset and nonspecific clinical features, making early diagnosis challenging. Metagenomic next-generation sequencing (mNGS) is

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currently the most valuable detection method. Although cases of isolated brucellosis meningitis have been reported, concurrent Epstein-Barr virus (EBV) meningitis has not been previously documented. Here, we report a patient diagnosed and treated for brucellosis meningitis complicated by EBV meningitis, aiming to provide a clinical reference for such co-infections.

## Case Report

A 47-year-old female farmer was admitted to our department on October 30, 2024, with a chief complaint of headache accompanied by nausea and vomiting for over 20 days. In early October, she developed non-projectile vomiting without apparent cause. After receiving oral and intramuscular therapy at a local clinic, she subsequently developed a headache, while her temperature remained normal and no other significant symptoms were noted. She presented to the Infectious Diseases Department of the local hospital, where initial testing revealed: Brucella Rose Bengal Test (RBT): positive, and Brucella Standard Agglutination Test (SAT): 1:400. The next day, a lumbar puncture was performed, and mNGS of the cerebrospinal fluid (CSF) detected *Brucella* (sequence count: 5482, relative abundance: 90.65%) and Epstein-Barr virus (sequence count: 603, relative abundance: 95.96%). Despite 16 days of treatment, her symptoms persisted, prompting transfer to our hospital on October 30 for further management.

Since onset, the patient had been in good spirits but reported poor appetite and sleep, normal urination, and no significant weight change. She had a history of hypertension for three years (irregular medication) and brucellosis for over two months (intermittent oral medication). She had long-term exposure to sheep and cattle, frequently assisting in lambing.

On admission, vital signs were stable. Physical examina-

tion was unremarkable except for neurological assessment, which demonstrated neck stiffness. Initial diagnoses included brucellosis meningitis, EBV meningitis, and grade 3 hypertension (very high risk). On the day of admission, combination therapy was started: doxycycline (0.1 g bid, oral), rifampin (0.6 g qd, i.v.gtt), ceftriaxone (2 g q12 h), and ganciclovir (5 mg/kg q12 h). Due to elevated intracranial pressure identified in the previous lumbar puncture, mannitol (250 mL q8h) was administered. For hypertension, the patient received amlodipine besylate (5 mg qd) and irbesartan (75 mg qd).

On day 4, as the patient's headache persisted and a fever developed, additional therapies were started: methylprednisolone (40 mg qd, i.v.gtt) for inflammatory control, and glycerol fructose (250 mL q6h) to further reduce intracranial pressure.

On day 6, there was still no improvement, fever recurred, and dizziness developed alongside further elevated blood pressure. The oral doxycycline was replaced with etimicin (0.3 g q12 h, intravenous). Bilateral renal vessel ultrasound was normal. By day 8, she continued to experience intermittent fever, headache and dizziness, and persistent neck stiffness. Blood pressure ranged from 170–200/100–120 mmHg. Medications were adjusted to mannitol (250 mL q6 h), methylprednisolone (30 mg bid), and antihypertensive dosages were doubled.

Lumbar puncture on day 9 showed a pressure of 350 mmH<sub>2</sub>O, clear and colorless CSF, monocyte predominance, negative Pan's test, glucose 1.15 mmol/L, chloride 113.80 mmol/L, protein 0.80 g/L, and negative ink staining. mNGS of CSF detected *Brucella melitensis* (sequence count: 2191, relative abundance: 92.37%) and EBV (sequence count: 49, relative abundance: 95.00%).

During subsequent treatment, blood pressure remained poorly controlled and dizziness was intermittent. Cra-

nial MRI showed degeneration in the bilateral semioval center, corona radiata, basal ganglia, and periventricular regions. Antihypertensives were switched to amlodipine besylate (10 mg qd) plus sacubitril/valsartan (100 mg bid). By day 16, temperature and blood pressure normalized, and dizziness was significantly relieved. Repeat lumbar puncture revealed a pressure of 300 mmH<sub>2</sub>O; dehydration therapy was adjusted to mannitol (250 mL q8 h) and glycerol fructose (250 mL q12 h). Her condition gradually stabilized, headaches and dizziness resolved, and methylprednisolone was reduced to 20 mg bid. SAT titer decreased from 1:400 to 1:100.

Etimicin was changed to doxycycline (0.1 g bid) on day 23, and mannitol was adjusted to 250 mL q12h. On day 27, lumbar puncture again (details in Table 1): pressure 220 mmH<sub>2</sub>O, all measured indices—glucose, chloride, protein—back within normal range, and CSF PCR for EBV DNA was negative; ganciclovir and methylprednisolone (reduced to 32 mg qd, oral) were discontinued.

Symptomatically, the patient improved further and

reexamination indices were normal. Glycerol fructose and mannitol were gradually discontinued. Ceftriaxone was stopped on day 34, and methylprednisolone was reduced to 16 mg qd. The patient was discharged in stable condition.

At discharge, continued treatment included rifampin plus doxycycline for infection control, methylprednisolone (16 mg qd) for inflammatory control, and antihypertensives (amlodipine besylate 10 mg qd, sacubitril/valsartan 100 mg bid). At follow-up on December 10, lab results for blood count and liver and kidney function were normal, SAT titer remained at 1:100. The methylprednisolone dose was reduced to 8 mg qd. The patient was advised to return for evaluation after two weeks.

Discussion

Because the clinical manifestations of brucellosis are highly variable and nonspecific, and because some patients lack clear epidemiological exposure, misdiagnosis and delayed treatment are common, often allowing progression to subacute or chronic stages and resulting

Table 1. All data of CSF examination.

| Project                       | October 15 | October 25 | November 7<br>(Day9) | November 14<br>(Day16) | November 25<br>(Day27) | Normal    |
|-------------------------------|------------|------------|----------------------|------------------------|------------------------|-----------|
| Pressure (mmH <sub>2</sub> O) | -          | -          | 350                  | 300                    | 220                    | 80-180    |
| ADA(U/L)                      | -          | -          | 6.1                  | -                      | -                      | Under 10  |
| LDH(U/L)                      | -          | -          | 47                   | -                      | -                      | 8-32      |
| Protein(g/L)                  | 1.1        | 0.9        | 0.8                  | -                      | 0.39                   | 0.15-0.45 |
| Sugar(mmol/L)                 | 1.75       | 1.5        | 1.15                 | -                      | 2.54                   | 2.5-4.4   |
| Chlorine(mmol/L)              | 115.1      | 115.5      | 113.8                | -                      | 122.9                  | 120-132   |
| Clot                          | Normal     | Normal     | Normal               | Normal                 | Normal                 | Normal    |
| Color                         | Normal     | Normal     | Normal               | Normal                 | Normal                 | Normal    |
| Turbidity                     | Normal     | Normal     | Normal               | Normal                 | Normal                 | Normal    |
| Pandy test                    | Positive   | Positive   | Positive             | Positive               | mild positive          | Negative  |
| Cell count( 10~6/L )          | 60         | 210        | 441                  | 362                    | 260                    | Under 8   |
| Nucleated cell                | -          | -          | 341                  | 135                    | 245                    | -         |
| Mononuclear cells( % )        | 85%        | 85%        | 48.7%                | 85%                    | 99.2%                  | -         |
| polymorphonuclear cells( % )  | 15%        | 15%        | 51.3%                | 15%                    | 0.8%                   | -         |
| Cryptococcus test             | Negative   | -          | Negative             | -                      | -                      | Negative  |
| Gram staining test            | Negative   | -          | Negative             | -                      | -                      | Negative  |

Notes: LDH, lactate dehydrogenase; ADA, adenosine deaminase.

in a spectrum of complications and suboptimal outcomes <sup>[1]</sup>. These complications may involve joints, eyes, skin, heart, urinary tract, and nervous system. Neurobrucellosis may affect the central and/or peripheral nervous systems at any stage of the disease <sup>[2]</sup>, with meningitis and meningoencephalitis being most common. Symptoms may include headache, fever, nausea, vomiting, cerebrovascular events, brain or spinal abscesses, myelitis, peripheral neuropathy, psychiatric symptoms, or demyelinating lesions <sup>[3-5]</sup>. When these develop, neurological infection should be strongly suspected. Prompt cranial CT is recommended, with further MRI and CSF mNGS if possible to assist diagnosis and guide management <sup>[6]</sup>.

Several studies have reported on brucellosis meningitis, with treatment regimens varying. Evidence suggests that triple antibiotic therapy provides greater efficacy for neurobrucellosis than mono- or dual-drug regimens <sup>[7-9]</sup>. According to the 2023 Brucellosis Treatment Guidelines, the first-line regimen comprises doxycycline (0.1 g bid for 4–6 months), rifampin (0.6–0.9 g qd for 4–6 months), and ceftriaxone (2 g q12 h for 1 month). For patients unable to tolerate first-line agents, alternatives include streptomycin, trimethoprim-sulfamethoxazole, levofloxacin, or etimicin <sup>[10]</sup>, with adjustments based on individual tolerability.

Epstein-Barr virus (EBV), also known as Human Herpesvirus 4, is ubiquitous and associated with malignancy and infectious mononucleosis. It can also invade the central nervous system and cause meningitis <sup>[11]</sup>. The mechanisms of EBV-induced neurological damage remain unclear, but may include direct viral invasion, reactivation of latent infection, and immune-mediated secondary injury <sup>[12]</sup>. Treatment of EBV meningitis requires a multifaceted approach combining antiviral, anti-inflammatory, and immunomodulatory therapies for best results.

This study retrospectively analyzes a case of brucellosis meningitis complicated by EBV meningitis, exploring clinical features, diagnosis, and management, and providing insights for clinicians. Coinfection with *Brucella* and EBV complicates diagnosis and treatment, as both pathogens can produce meningeal irritation but require distinct approaches. Beyond history and physical examination, CSF analysis is critical. mNGS enables rapid, accurate pathogen detection. In this case, both *Brucella* and EBV were detected in CSF by mNGS, raising questions about infection sequence. The literature suggests that PCR detection of EBV DNA in CSF does not necessarily indicate active EBV infection, since EBV is often found with other pathogens <sup>[13]</sup>. Approximately 25–28% of EBV DNA-positive CSF samples harbor a second pathogen, often the true causative agent <sup>[14, 15]</sup>. Thus, EBV DNA detection in CSF is not highly specific, and coinfecting pathogens are variable with no predictable pattern. Kimiya et al. also noted that EBV DNA positivity often reflects reactivation rather than acute infection <sup>[16]</sup>. Brucellosis meningitis requires antibiotic therapy, while EBV meningitis mainly calls for symptomatic and immunomodulatory treatments. In this case, antiviral therapy was considered appropriate. Previous reports, such as coinfection with *Mycobacterium tuberculosis* and EBV, have indicated benefit from combined anti-tuberculous and antiviral therapy <sup>[17]</sup>. Advances in EBV-related neurological infections suggest antivirals may suppress viral replication, shorten treatment, and improve prognosis <sup>[18]</sup>. Therefore, such coinfections warrant careful assessment of pathogens, clinical findings, laboratory data, and immune function to guide therapy.

In the present case, EBV infection was more consistent with latent reactivation, supported by the following: after antiviral therapy, clinical symptoms including fever and headache improved; follow-up CSF testing showed marked reduction in EBV load. Notably, CSF

profile showed elevated protein and reduced glucose and chloride, characteristic of bacterial (rather than viral) infection, supporting a primary bacterial etiology. However, the possibility of coinfection or other confounders cannot be excluded. The mechanism of EBV reactivation remains unclear; although clinical improvement supports EBV involvement, the contribution of antiviral therapy to outcome requires further study.

Initial intensive therapy did not alleviate headache or control hypertension; given the history of irregular brucellosis management, decreased drug sensitivity was suspected. Based on literature and clinical experience, doxycycline was replaced with intravenous etimicin, resulting in significant improvement. Etimicin, an aminoglycoside with moderate blood-brain barrier permeability, was one of several options. Adjunctive corticosteroids and osmotic agents provided further symptom relief. Although corticosteroid use in meningitis is controversial, anti-inflammatory effects may benefit selected cases <sup>[19]</sup>. Response to therapy varies based on disease course, timing, severity, and regimen, necessitating close follow-up to monitor for relapse.

In summary, concurrent bacterial and viral meningitis is rarely reported, especially for the pathogens described here. In patients with unexplained, persistent headache, nausea, or vomiting, early CSF analysis is essential. mNGS is pivotal and warrants clinical attention, as early diagnosis and appropriate treatment can substantially improve prognosis.

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## Author Contributions

Cao Hanshuai: Case compilation, manuscript writing.  
Wang Qian: Writing guidance. Yang Liu: Writing guid-

ance, manuscript revision.

## Conflicts of Interest

All authors declare no conflicts of interest.

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