

Coexisting cryptococcal and tuberculous meningitis with glial fibrillary acidic protein antibody positivity in chronic lymphocytic leukemia: expanding the spectrum of infection–immunity interplay

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Abstract

Background Immunocompromised individuals are susceptible to *Cryptococcus* and *Mycobacterium tuberculosis* infections. Coinfection can complicate diagnosis, and both may cause cerebral infarction. No previous reports describe cases of cryptococcal meningitis (CM) or tuberculous meningitis (TBM) with cerebrospinal fluid (CSF) testing positive for glial fibrillary acidic protein (GFAP) antibodies.

Methods We present the case of a 60-year-old man with chronic lymphocytic leukemia, initially diagnosed with TBM, who developed cerebral infarction and was found to test positive for CSF GFAP antibodies, later confirmed as CM. A focused literature review was performed for cases involving CM/TBM coinfection, cerebral infarction, and GFAP antibody positivity.

Results This case highlights overlapping clinical and imaging features of CM and TBM, including basal ganglia and thalamic infarctions. CSF GFAP antibody positivity became negative following antifungal therapy, indicating transient astrocytic injury. A literature search identified no prior reports describing CSF GFAP antibody positivity in leukemia patients with dual central nervous system (CNS) infections.

Conclusion CM and TBM present with overlapping features and may coexist with autoimmune encephalitis in immunocompromised patients. Incorporating autoimmune antibody testing, including anti-GFAP, into routine

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CNS infection evaluation can facilitate early recognition of immune-mediated pathology and guide timely antimicrobial–immunomodulatory therapy.

Keywords: cryptococcal meningitis, cerebral infarction, GFAP antibodies, chronic lymphocytic leukemia, tuberculous meningitis

Introduction

Cryptococcus neoformans is an opportunistic pathogen transmitted primarily via the respiratory tract. Immunocompromised individuals, including those with hematologic malignancies, diabetes, or those receiving immunosuppressive therapy, are at increased risk^[1]. Cryptococcal meningitis (CM) can directly invade the central nervous system (CNS) and is often misdiagnosed as tuberculous meningitis (TBM) because of overlapping clinical and cerebrospinal fluid (CSF) features.

Glial fibrillary acidic protein (GFAP) antibodies have recently been identified as potential markers of astrocytic injury. Their presence in CSF may reflect infection-triggered autoimmune responses, but clinical reports in the context of CM or TBM are lacking. Here, we report a rare case of CM with cerebral infarction and a positive test result for CSF GFAP antibodies in a patient with chronic lymphocytic leukemia (CLL), initially misdiagnosed as TBM.

Clinical Data

Prehospital Course

A 60-year-old man presented on May 13, 2024, with a 6-month history of progressive fever and headache. His illness began in November 2023 with a fever ($T_{\max}$ 39.5 °C), a cough with white sputum, and a worsening headache. Despite empiric use of oseltamivir and

moxifloxacin, symptoms persisted.

At a local hospital, a lumbar puncture revealed an elevated CSF leukocyte count (predominantly lymphocytes), low glucose, and elevated protein. Acid-fast bacilli were detected in the CSF smear, whereas india ink staining was negative. Next-generation sequencing (NGS) of CSF did not detect *Cryptococcus* or *Mycobacterium tuberculosis*; the reported organisms (*Enterococcus faecium* and *Staphylococcus aureus*) were interpreted as contaminants with no clinical relevance. Chest imaging suggested pulmonary involvement, and a diagnosis of tuberculous meningitis with pulmonary infection was made. Standard antituberculosis therapy (isoniazid, rifampicin, pyrazinamide, and moxifloxacin) provided partial symptom relief.

By May 2024, his headaches worsened, accompanied by projectile vomiting. Repeat CSF analysis showed lymphocytic pleocytosis and elevated protein, while metagenomic NGS (mNGS) detected *Cryptococcus* (13 reads) and Epstein–Barr virus (1 read). The patient was subsequently referred to our hospital. His medical history was notable for type 2 diabetes mellitus (15 years duration). The patient had been diagnosed with CLL 2 years earlier and had remained untreated until recently. Zanubrutinib, initiated approximately 45 days before admission, was discontinued at the time of hospitalization due to intolerance and was not resumed thereafter.

Hospital Course

On admission, the patient was alert, but exhibited meningeal signs, right-sided pyramidal signs, and generalized weakness. Laboratory evaluation revealed marked lymphocytosis consistent with chronic lymphocytic leukemia and poorly controlled diabetes.

Lumbar puncture showed an opening pressure of 220 mmH₂O, lymphocytic pleocytosis, elevated protein, and normal glucose. Importantly, CSF india ink staining was positive, and mNGS identified 421 reads of *Cryptococcus neoformans*. GFAP antibody testing was positive in CSF but negative in serum (Figure 1A). Oligoclonal bands and elevated intrathecal IgG synthesis suggested concomitant immune activation.

Brain magnetic resonance imaging (MRI) demonstrated multiple patchy hyperintense lesions on T2-/FLAIR

and diffusion-weighted imaging sequences in the corpus callosum, basal ganglia, thalami, cerebellar hemispheres, and periventricular white matter (Figure 2), with ventricular enlargement and mild leptomeningeal enhancement (Figure 3). These findings were consistent with cryptococcal meningoencephalitis complicated by cerebral infarction. Chest computed tomography revealed subpleural reticular changes in both lower lobes (Figure 1B).

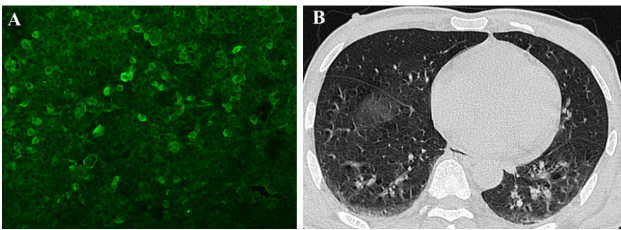


Figure 1. (A) Cerebrospinal fluid (CSF) GFAP antibody detection by a cell-based assay. Positive GFAP antibodies are indicated by green fluorescence in CSF cells. (B) Chest computed tomography showing subpleural reticular densities in the lower lobes of both lungs.

Table 1. Key clinical and laboratory findings in the patient.

Parameter	Prehospital	On Admission	Follow-up
CSF Opening Pressure (mmH ₂ O)	290	220	150
CSF Appearance	Colorless, slightly turbid	Colorless, transparent	Colorless, transparent
CSF WBC ($\times 10^6/L$)	85 (99% mononuclear)	468	495
CSF Protein (g/L)	2.61	2.12	>1.5
CSF Glucose (mmol/L)	4.24	4.8	2.6
CSF Chloride (mmol/L)	112	96	116
India Ink Stain	Negative	Positive	Not performed
mNGS Findings	13 <i>Cryptococcus</i> sequences, 1 EBV	421 <i>Cryptococcus</i> sequences, 11 EBV	Not performed
CSF GFAP Antibodies	Not tested	Positive (1:1)	Negative
Oligoclonal Bands	Not tested	Type III	Not performed
Brain MRI	Patchy lesions in bilateral thalami, right centrum semiovale	Multiple patchy T2/FLAIR & DWI hyperintense lesions in corpus callosum, basal ganglia, thalami, cerebellum, periventricular white matter; mild leptomeningeal enhancement	Not performed
Chest CT	Pulmonary lesions	Subpleural reticular changes in lower lobes	Not performed
Key Labs	WBC $131 \times 10^9/L$, Na 119 mmol/L, Glucose 11.9 mmol/L	WBC $166 \times 10^9/L$, Na 124 mmol/L, Glucose 12.7 mmol/L	WBC $110 \times 10^9/L$, Glucose 15.7 mmol/L

Note: Follow-up neuroimaging was not obtained because the patient sought further care at multiple local hospitals. CSF: cerebrospinal fluid; CT: computed tomography; EBV: Epstein–Barr virus; GFAP: glial fibrillary acidic protein; mNGS: metagenomic next-generation sequencing; WBC: white blood cell.

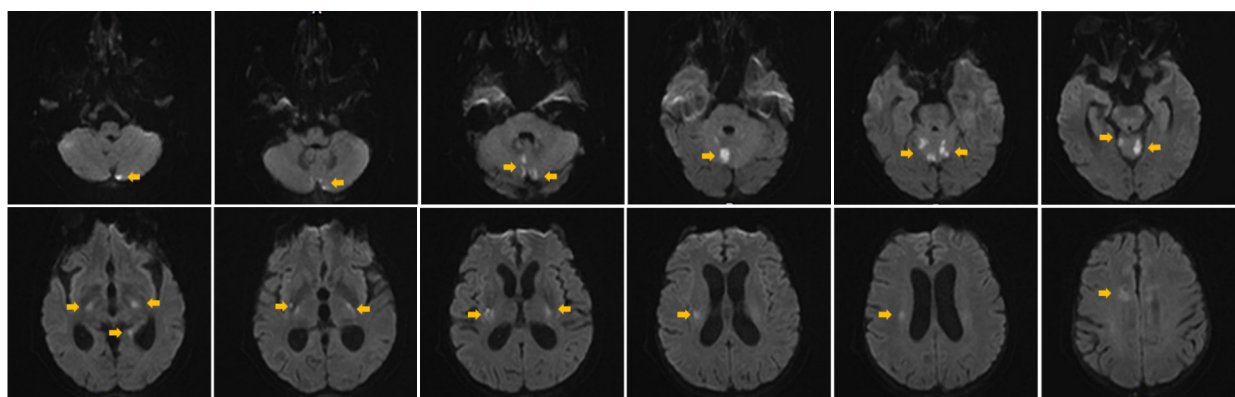


Figure 2. Brain MRI diffusion-weighted imaging sequence demonstrating multiple patchy hyperintense lesions in the corpus callosum, bilateral cerebellar hemispheres, basal ganglia, posterior horn of the left lateral ventricle, and right frontal lobe. Enlargement of the lateral and third ventricles is noted.

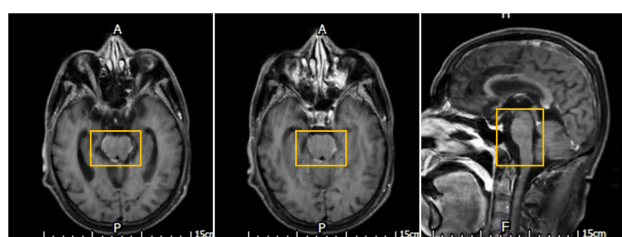


Figure 3. Enhanced T1-weighted brain MRI shows widening of cerebral sulci and expansion of supratentorial ventricles. Mild linear leptomeningeal enhancement is observed in the pia mater of the ambient, quadrigeminal, prepontine, and medullary cisterns (highlighted within yellow boxes).

The patient was treated with amphotericin B plus flucytosine, along with supportive therapies including anticoagulation, lipid-lowering agents, osmotic dehydration, and electrolyte/protein supplementation. Follow-up CSF showed reduced intracranial pressure and persistent pleocytosis, along with clearance of GFAP antibodies that paralleled clinical improvement. After discharge, the patient sought care at several local hospitals, during which time his clinical symptoms improved significantly, and he regained the ability to walk independently. However, he ultimately died 6 months later because of a pulmonary infection with *Burkholderia cepacia* complex.

Discussion

CM is the most common fungal infection of the CNS,

particularly in immunocompromised populations such as patients with HIV, malignancies, or diabetes [2]. The present patient, with CLL and diabetes, represented a high-risk profile. CM and TBM share overlapping clinical features, CSF findings, and imaging results, which often complicate diagnosis. Comparative studies suggest that CM is more frequently associated with cerebral ischemia or infarction and tends to have worse outcomes than TBM [3]. Increasingly, coinfection with *M. tuberculosis* and *Cryptococcus* has been recognized, especially in immunocompromised hosts [4]. In our case, the patient had been treated for TBM before subsequently developing proven CM, raising the possibility of secondary cryptococcal infection with a background of TB.

Although the patient was initially diagnosed with tuberculous meningitis (TBM) based on a single CSF acid-fast bacillus (AFB) smear from a local hospital, the diagnostic certainty of TBM is limited. AFB smears have poor specificity and may produce false-positive results, especially when based on a single specimen [5,6]. At our institution, all repeated CSF evaluations, including mNGS, TB-DNA, TB antibodies, and T-SPOT, were negative for *M. tuberculosis*. The patient had also received more than 5 months of antituberculosis treatment, which may suppress the

bacillary burden and reduce the sensitivity of subsequent tests [7,8]. The absence of confirmatory studies, such as the CSF Xpert MTB/RIF assay or mycobacterial culture, further contributes to diagnostic uncertainty [9]. Moreover, TBM and CM share overlapping CSF and imaging features, making misclassification possible in immunocompromised hosts [10–12]. Given the definitive microbiological evidence of CM and the lack of confirmatory evidence for active TBM, CM is considered the primary diagnosis, whereas TBM remains an unproven but not completely excludable coinfection.

Cerebral infarction is a recognized complication of both TBM and CM. Infarcts in TBM typically occur early or soon after initiation of antituberculous therapy, whereas in this patient, infarction developed after 6 months of treatment, suggesting a stronger link to cryptococcal infection. The mechanisms may include direct vascular inflammation, diabetes-related atherosclerosis, and malignancy-associated thrombosis. CM-related vasculitis and small-vessel occlusions are well described, frequently involving the basal ganglia and thalamus [13–15]. Diabetes accelerates atherosclerosis and independently increases the risk of stroke [16,17]. In addition, CLL has been associated with thrombotic events consistent with Trousseau's syndrome [18,19]. Thus, in this case, CM likely acted in concert with diabetes and leukemia to precipitate infarction.

Beyond vascular complications, infection-triggered autoimmunity is increasingly recognized. Several reports describe the coexistence of CM with autoimmune encephalitis, in which pathogen-driven tissue damage exposes neural antigens and induces autoantibody production [20–26]. Our patient tested positive for GFAP antibodies, which became undetectable after antifungal therapy. This result suggests a tran-

sient, nonpathogenic response reflecting astrocytic injury rather than a primary autoimmune process. GFAP antibodies are regarded as markers of astrocytic damage and neuroinflammation [27–30], and their presence in this context likely reflects bystander activation. Nevertheless, persistent cryptococcal infection could perpetuate astrocytic injury and antigen exposure, thereby facilitating secondary immune responses [31].

This case underscores the need for comprehensive diagnostic strategies in suspected CNS infections, especially when neuroimaging suggests vasculitis or infarction, when underlying immunodeficiency is present, or when CSF inflammatory markers and pathogen load appear discordant. Incorporating autoimmune antibody testing, including anti-GFAP, into the diagnostic panel may facilitate earlier recognition of immune-mediated pathology, enabling timely antimicrobial–immunomodulatory interventions and ultimately improving patient outcomes.

Ethical approval and consent to participate

This report was approved by the Ethics Committee of the Eighth Medical Center of the PLA General Hospital. Written informed consent for publication was obtained from the patient's family.

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Author contributions

Jinli Feng contributed to the research design and

writing/editing; Ming Fang contributed to the drafting of the original manuscript; Shuang Wang and Jun Zhao conducted the literature search; contributed to research design and writing/editing; Xu-Ling Wang and Zhuangzhuang Ren were responsible for figure preparation and data analysis; Feng Qiu and Jinming Han were involved in design and project administration, and they contributed equally as corresponding authors.

Conflicts of interest

The authors declare that they have no conflicts of interest regarding the publication of this case report.

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