American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2026; 27: e952923
DOI: 10.12659/AJCR.952923

Received: 2026.01.24
Accepted: 2026.04.30
Available online: 2026.05.25
Published: 2026.XX.XX

Case Report: Primary Central Nervous System Lymphoma With "Wine Glass" Sign Presenting as Somnolence and Fatigue

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Financial support: This work was supported by Joint Funds for the innovation of science and Technology, Fujian province (2023Y9286); Fujian Provincial Natural Science Foundation (2024J011004); Fujian Research and Training Grants for Young and Middle-aged Leaders in Healthcare (2022)

Conflict of interest: None declared

Patient: Male, 55-year-old
Final Diagnosis: Primary central nervous system lymphoma
Symptoms: Fatigue • somnolence
Clinical Procedure: —
Specialty: Neurology

Objective: Challenging differential diagnosis

Background: Primary central nervous system lymphoma (PCNSL) is a rare and aggressive extranodal non-Hodgkin lymphoma with highly heterogeneous clinical and imaging manifestations. Its atypical manifestations often lead to critical differential diagnosis challenges, resulting in high rates of misdiagnosis and delayed diagnosis.

Case Report: We report a case of PCNSL in a 55-year-old male patient. The patient was a chronic hepatitis B virus carrier, with a history of consumption of medicinal wine with unknown ingredients 1 month prior to onset. He presented with progressive somnolence and generalized fatigue as the core initial symptoms, accompanied by other non-focal neurological deficits, including fever, altered mental status and cognitive impairment. Brain magnetic resonance imaging (MRI) revealed abnormal signals around the third ventricle and midbrain aqueduct, with a rare "wine glass" sign. In contrast, multiple contrast-enhanced MRI scans showed no typical homogeneous enhancement signals. Tumor cells were found in the third cerebrospinal fluid analysis, and he was definitively diagnosed with PCNSL after stereotactic biopsy. The patient's symptoms improved following a single fraction of radiotherapy treatment.

Conclusions: The insidious onset and atypical features of PCNSL increase the risk of delaying diagnosis, which may negatively impact patient outcomes. Here, we present a case of PCNSL exhibiting atypical clinical manifestations and imaging findings, while differentiating it from other neurological disorders with overlapping features. It also highlights the critical value of serial cerebrospinal fluid cytology and early biopsy for timely diagnosis, providing a clinical reference for managing similar cases.

Keywords: Lymphoma, Primary Central Nervous System • Neurology • Somnolence • Asthenia • Magnetic Resonance Imaging • Case Reports

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare type of extranodal non-Hodgkin lymphoma (NHL) [1], predominantly occurring in immunocompromised people [2]. However, in recent years, the incidence of PCNSL among immunocompetent people has gradually increased [3]. PCNSL lesions are likely to occur in the periventricular and supratentorial regions, affecting the deep brain structures [4,5]. Due to its ambiguous clinical presentations and imaging features, PCNSL can easily be misdiagnosed as other neurological diseases [6]. Notably, PCNSL demonstrates the poorest prognosis among all non-Hodgkin lymphomas [2], so early diagnosis and treatment are the key to influencing its prognosis.

Case Report

A 55-year-old man was admitted to our hospital with a 1-month history of somnolence and fatigue, accompanied by nausea, memory loss, delayed reactions, and occasional incoherent speech lasting for 1 week. The patient had maintained chronic hepatitis B virus carrier status for 3 decades, and had a history of consumption of medicinal wine with unknown ingredients 1 month prior to onset. Both his personal and family medical histories were unremarkable.

On physical examination, the patient's temperature was 37.6°C. Neurological assessment demonstrated hypersomnia, impaired computing power and short-term memory loss. The initial brain magnetic resonance imaging (MRI) performed in October of 2024 showed abnormal signals around the third ventricle and cerebral aqueduct (**Figure 1**), with unremarkable findings on concurrent magnetic resonance angiogram. Laboratory findings were normal except for alanine aminotransferase (ALT) 69 U/L, creatinine 107 μmol/L, gastrin-releasing peptide precursor (ProGRP) 74.30 pg/mL. Cerebrospinal fluid (CSF) analysis showed a leukocyte count of 30×10^6/L, 83.0% lymphocytes, total protein 68.6 mg/dL, albumin 413.0 mg/L, and immunoglobulin G 76.30 mg/L, with remaining parameters within normal limits. Re-examination by MRI and contrast-enhanced MRI performed 3 days later showed abnormal signals in the third periventricular thalamus, tectum, infundibulum, and the bilateral medial parts of the cerebral peduncles, exhibiting mild enlargement compared with the initial result (**Figure 1**). During the initial week of hospitalization, the patient was diagnosed with viral encephalitis and treated with acyclovir (500 mg/8 h), ceftriaxone (2 g/d), human normal immunoglobulin (30 g/d), methylprednisolone injection (80 mg/d), human albumin (10 g/12 h) and other treatments. Despite therapeutic interventions, the patient's symptoms continued to progress. Serological study findings showed negative results for antibodies associated with inflammatory demyelinating disease and autoimmune encephalopathy, and polymerase chain reaction (PCR) analysis was negative for Japanese encephalitis virus nucleic acid. Re-examination by biochemical monitoring demonstrated persistent hyponatremia and routine blood analysis showed progressive decrease of trilineage hematopoiesis (**Figure 2**). Subsequent bone marrow puncture revealed a myelodysplastic image of trilineage hematopoiesis. Epstein-Barr virus was detected in CSF by next-generation sequencing (NGS), while atypical lymphocytes were found in CSF by flow cytometry. Interestingly, the patient's symptoms improved during the second week of hospitalization. Dynamic electroencephalogram revealed mild abnormalities, and electromyography revealed damage to the left median nerve and the left common peroneal nerve. Re-examination by MRI and contrast-enhanced MRI performed 15 days after the initial imaging showed that the lesion had become slightly smaller than the lesion in the secondary results (**Figure 1**). By the third week of hospitalization, the patient experienced high fever again accompanied by progressive consciousness disorder, limited ocular movements, and slight nuchal rigidity. Repeated CSF cytology examination identified tumor cells, suggesting cancerous meningitis (lymphomatous etiology suspected). Subsequent high-throughput cytokine detection in CSF demonstrated elevated interleukin 10 (IL-10), interferon-induced protein 10 (IP-10), and monocyte chemoattractant protein 1 (MCP-1).

In November of 2024, a repeated brain MRI, including T2-fluid-attenuated inversion recovery (FLAIR), showed abnormal signals in the third periventricular thalamus and the bilateral superior part of the midbrain. The lesion represented by these abnormal signals was slightly larger than the lesion seen in the secondary results. Notably, coronal T2-FLAIR imaging showed a distinctive "wine glass" sign that was consistently observed in prior MRI examinations (**Figure 1**). Moreover, positron emission tomography (PET)-CT showed space-occupying lesions in the third periventricular thalamus and the bilateral medial parts of the cerebral peduncle. In addition, the bilateral superior part of the midbrain had increased metabolism (**Figure 3**). Despite the absence of clinical improvement, the patient's family requested to have him discharged and transferred to another hospital for further treatment.

The patient was transferred to another hospital for a stereotactic biopsy, and diffuse large B-cell lymphoma was diagnosed (**Figure 4**). The immunohistochemistry assays revealed the following profile: GFAP (-), CD3 (positive in scattered T cells), CD5 (positive in scattered T cells), CD19 (diffuse +), CD20 (diffuse +), CD79α (diffuse +), Bcl-2 (diffuse +), CD10 (+), Bcl-6 (approximately 70%+), C-myc (approximately 20%+), MUM-1 (+), CyclinD1 (scattered +), CD30 (positive in individual cells), ALK (-), CD21 (-), CD23 (-), Ki-67 (approximately 95%+). In situ hybridization yielded a result of EBER (-). After the patient was diagnosed, he received radiation rather than chemotherapy due to

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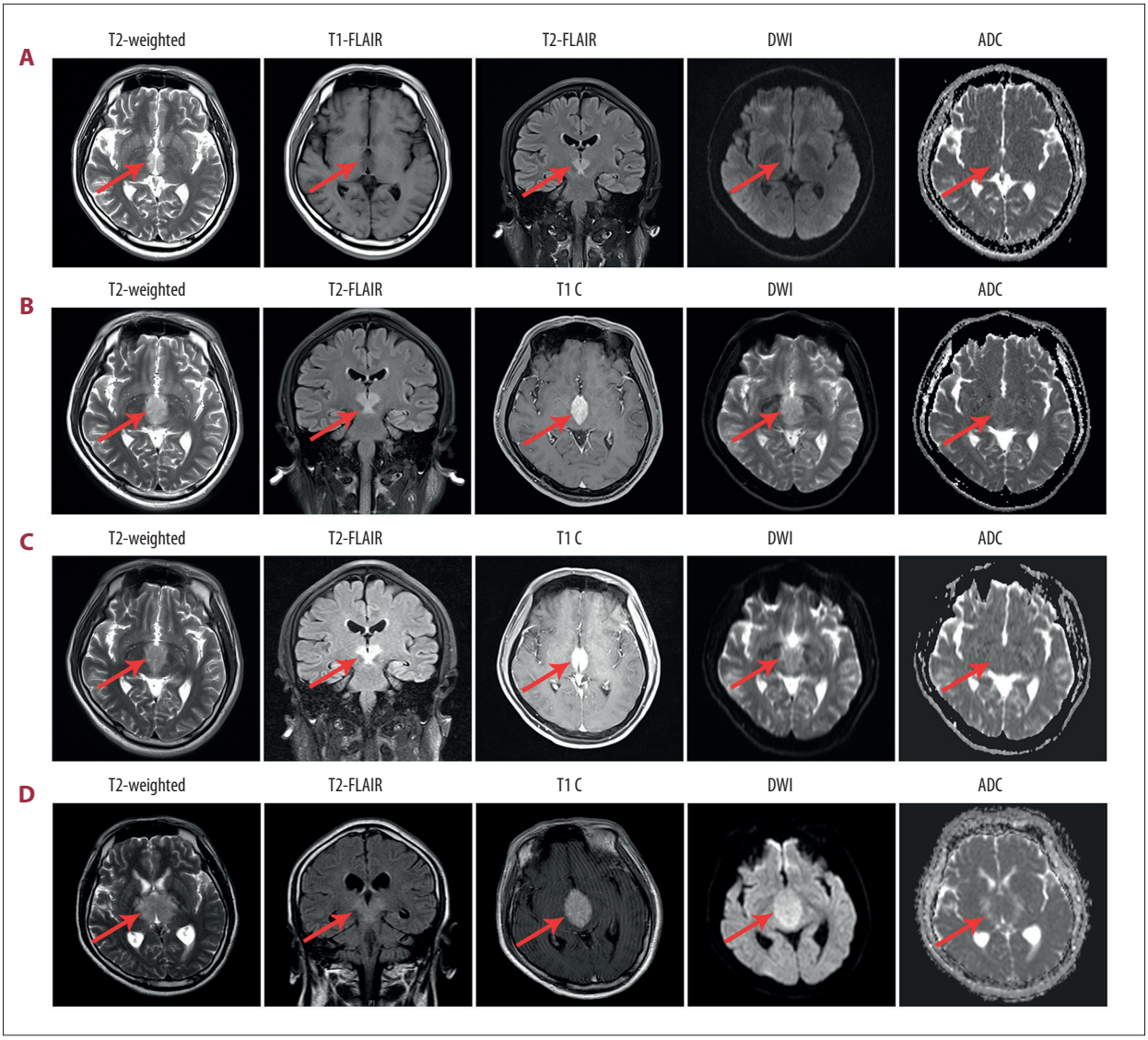

Figure 1. (**A-D**) The abnormal signals in the third periventricular thalamus, tectum, infundibulum, and bilateral medial parts of the cerebral peduncle showed hypointensity on T1-weighted imaging, slight hyperintensity on T2-weighted imaging and T2-FLAIR, hyperintensity on DWI, and hypointensity on ADC. Contrast-enhanced MRI (T1 C) revealed atypical enhancement, with slight compression of the adjacent optic chiasm and the third ventricle. FLAIR, Fluid-Attenuated Inversion Recovery; T1 C, T1 with contrast; DWI; diffusion-weighted imaging; ADC, apparent diffusion coefficient.

his abnormal liver and renal function. Fortunately, his symptoms demonstrated improvement following a single fraction of radiotherapy treatment.

Discussion

PCNSL is often confused with other neurological diseases. PCNSL lesions are often unifocal in immunocompetent patients, while in immunocompromised patients, they are multifocal [4]. Due to this difference, the clinical manifestations of PCNSL are diverse, including focal neurological deficits, headache, cognitive behavioral disorder, visual disorder, and other neurological manifestations [7]. This heterogeneity enables PCNSL to mimic other neurological disorders, resulting in delayed or incorrect diagnoses. In our case, the patient was an immunocompetent individual and initially presented with somnolence and fatigue as the main clinical manifestations. These symptoms typically suggest involvement of the diencephalon or periventricular structures, consistent with the patient's imaging findings. However, such nonspecific manifestations are inconsistent with the focal neurological deficits commonly observed in PCNSL, and the definitive etiology requires further clarification in combination with clinical context. Furthermore,

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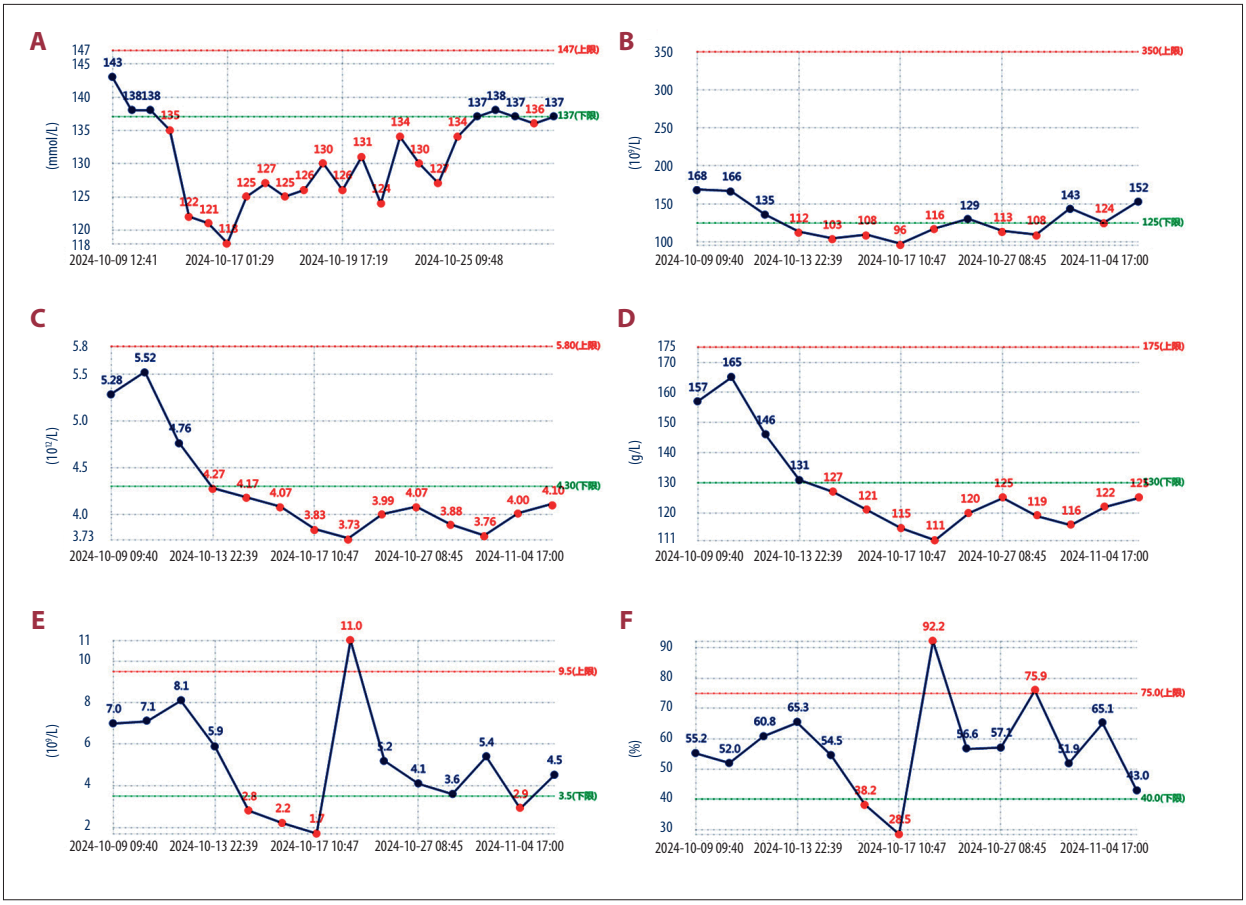

Figure 2. Trend charts of the patient's routine blood results and biochemical analyses. (**A**) Serum sodium; (**B**) Platelets; (**C**) Red blood cells; (**D**) Hemoglobin; (**E**) White blood cells; (**F**) Neutrophilic granulocyte percentage.

the patient also exhibited persistent unexplained fever, a common clinical manifestation of systemic hematologic malignancy which is uncommon in PCNSL [5]. Consequently, PCNSL was not initially suspected.

On admission, the patient presented with recurrent fever. Given this clinical presentation, an infectious etiology could not be excluded, thus leading to an initial working diagnosis of viral encephalitis. Multiple types of viral encephalitis may involve the thalamus, among which Japanese encephalitis is frequently common. Japanese encephalitis is characterized by an acute clinical course, with cardinal manifestations including fever, headache, generalized weakness, altered consciousness, mental and behavioral disorders, and movement disorders [8,9]. Notably, these clinical manifestations show partial overlap with the presenting features of this patient. However, viral encephalitis is typically characterized by a self-limiting clinical course, whereas this patient's clinical course presented with fluctuating symptoms and progressive deterioration. We performed targeted pathogen testing, yet only low-abundance Epstein-Barr virus sequences were detected via NGS of the CSF. Combined with the above results, the available clinical evidence does not support a diagnosis of viral encephalitis. Upon case review, it was observed that the patient experienced a progressive decrease of trilineage hematopoiesis during antiviral therapy, and abnormal lymphocytes were detected by CSF cytology at the same time, so the diagnosis of lymphoma could not be clinically excluded. Due to our inability to establish a causal relationship between the bone marrow suppression and acyclovir administration, the agent was discontinued. Notably, the patient's symptoms showed a transient improvement after acyclovir was discontinued; this may be attributable to the effects of methylprednisolone. High-dose corticosteroid therapy is a commonly used method for diseases manifesting as unclear intracranial mass lesions [10]. For PCNSL, corticosteroids can also induce lymphocyte apoptosis or lysis, resulting in an additional tumor-destructive effect [1,10], which leads to short-term improvement of neurological symptoms.

Furthermore, the patient had a history of consumption of medicinal wine with unknown ingredients, which posed a potential risk of thiamine deficiency. Therefore, we also included Wernicke encephalopathy (WE) in the differential diagnosis. WE has a high prevalence in the alcohol-dependent population.

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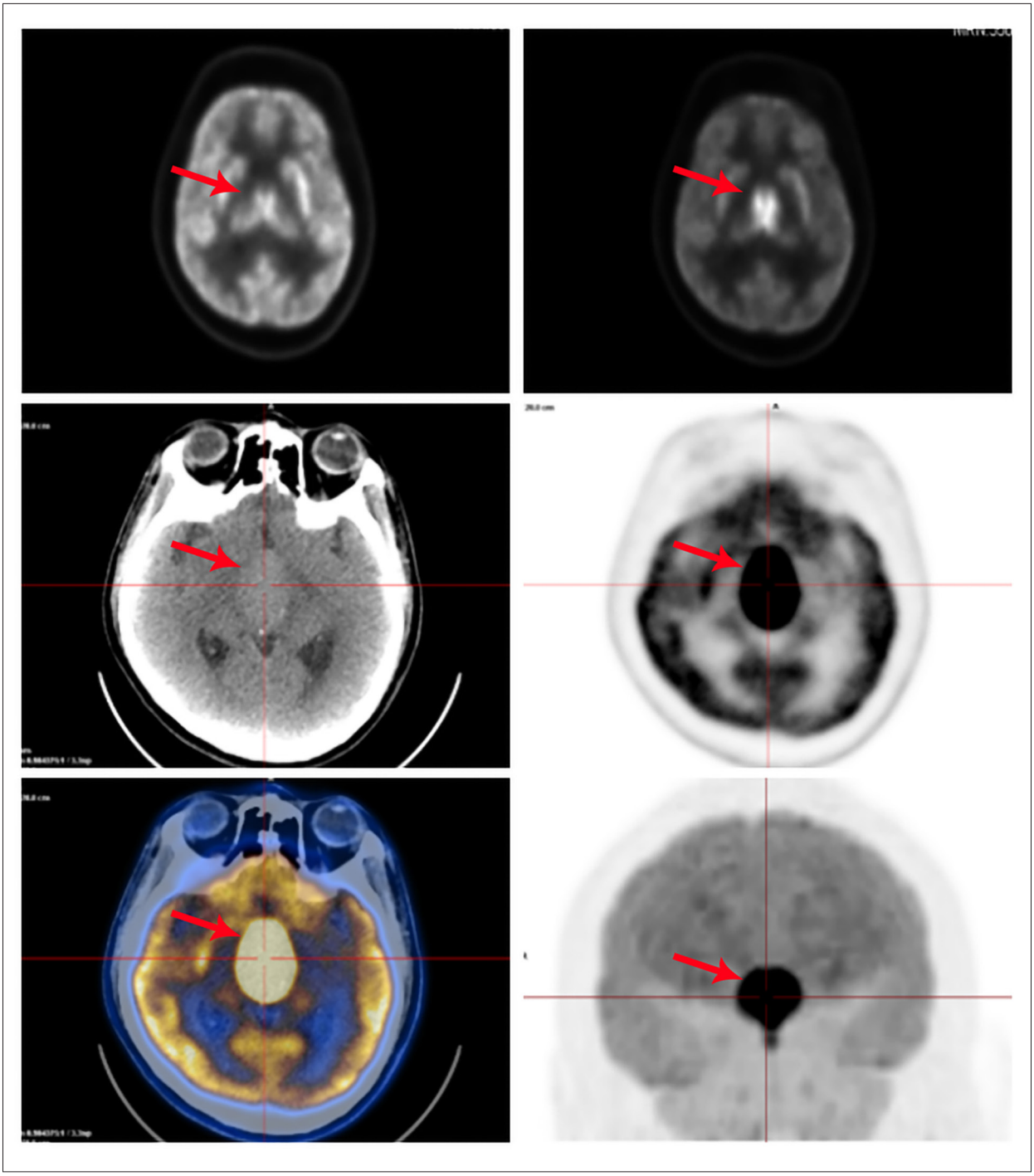

Figure 3. PET-CT, November 2024. The space-occupying lesions in the third periventricular thalamus, the bilateral medial parts of the cerebral peduncle and the bilateral superior part of the midbrain had increased metabolism. The largest one was about 2.7×4.0 cm. PET-CT, positron emission tomography-computed tomography.

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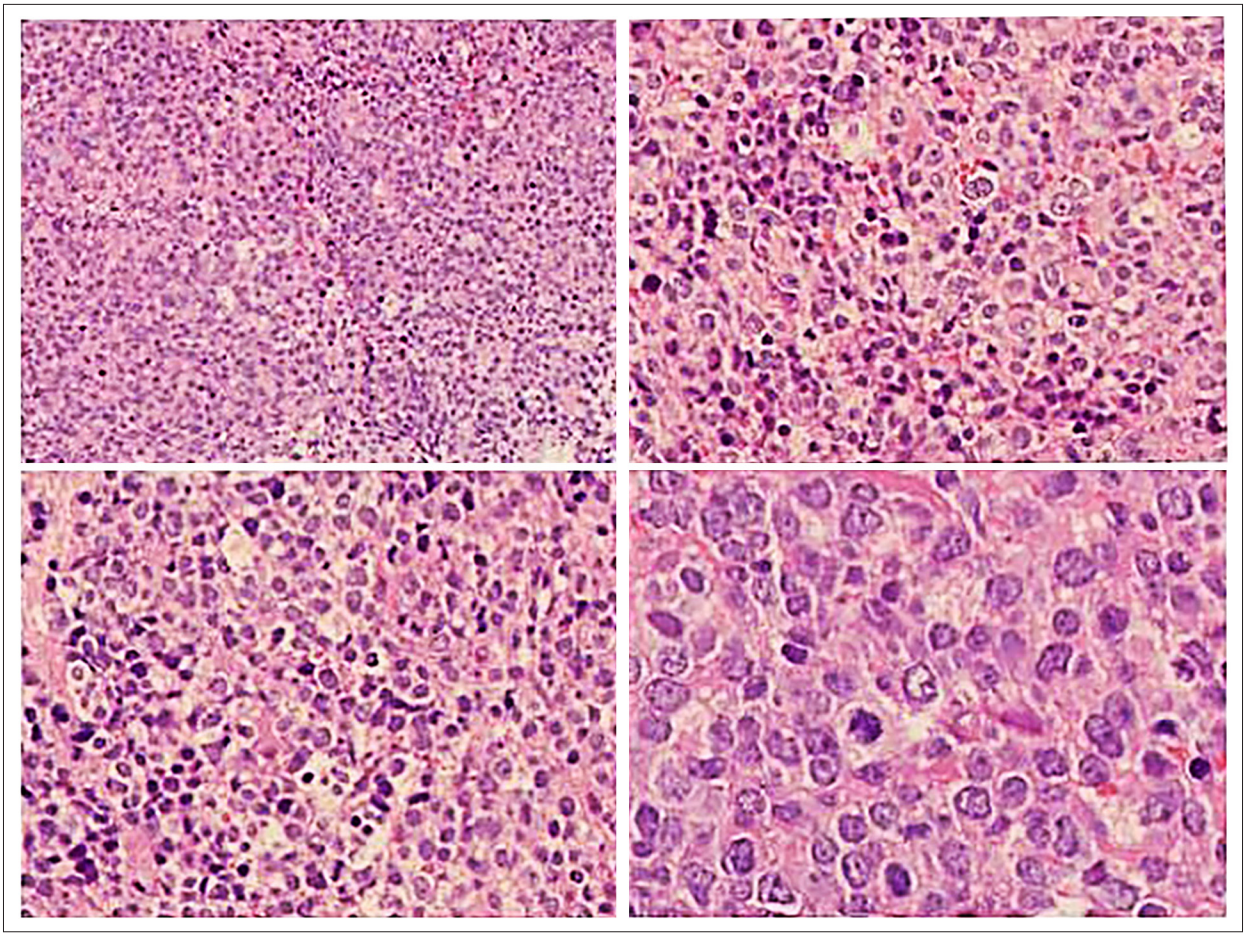

Figure 4. Histopathologic examination. Microscopic examination revealed infiltration of brain tissue by tumor cells. The tumor cells are large in size, with eosinophilic cytoplasm. The nuclei of tumor cells are round or oval, with a thick nuclear membrane, prominent nucleolus, and coarse nuclear chromatin. The presence of mitotic figures was also frequently observed (>5 tumor cells per high power field of view).

Its most common clinical manifestation is altered mental status, accompanied by a constellation of other symptoms including somnolence, memory impairment, dizziness, apathy, spatial disorientation, and impaired attention. The classic neuropathological lesions of WE typically involve the bilateral medial thalami, periaqueductal gray matter, hypothalamus, and mammillary bodies. Characteristic cranial MRI findings include bilateral symmetrical hyper-intensity on T2-weighted images and T2 FLAIR images [11,12].When lesions involve the hypothalamus, fever may occur secondary to dysfunction of the thermoregulatory center, which is further consistent with the clinical manifestations of this patient. Notably, WE presents with diverse clinical manifestations, and the 3 classic symptoms of WE are observed only in a minority of patients. Our patient's symptoms also failed to meet the widely accepted clinical diagnostic criteria for WE proposed by Caine and colleagues. However, given the high risk of missed diagnosis and misdiagnosis when relying solely on clinical symptoms, we further completed testing of the patient's serum thiamine levels. Even though the results did not indicate thiamine deficiency, we still initiated empirical thiamine supplementation therapy for the patient [11], but the patient's symptoms showed no significant improvement. Consequently, we provisionally excluded the diagnosis of WE based on the above findings.

The patient presented with somnolence and fatigue as the initial onset symptoms, which may indicate involvement of the periventricular structures in the early stage of the disease. Based on the patient's MRI findings, although no significant mass effect was observed, atypical lymphocytes were detected in the first CSF cytology examination. These findings indicated that the possibility of neoplastic lesions of the central nervous system could not be excluded clinically. Therefore, we performed repeated lumbar punctures to obtain CSF samples for further diagnostic workup. CSF cytology examination is the gold standard for diagnosing meningeal dissemination of PCNSL, but its sensitivity may be less than 16%, and the sensitivity of CSF flow cytometry to detect PCNSL is also only

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between 3% and 23%. Therefore, multiple tests are often required to improve diagnostic efficacy [13]. According to the International PCNSL Collaborative Group (IPCG) guidelines, CNS lymphoma can be confirmed if the CSF cytology results are positive and have typical brain imaging lesions at the same time [14]. Although the patient lacked characteristic imaging features of PCNSL, tumor cells were eventually found in the third CSF cytology examination following multiple lumbar punctures. High-throughput cytokine testing of the CSF showed an increase in IL-10, which was consistent with the manifestation of lymphoma [14]. Further improvement on PET-CT also suggested the possibility of lymphoma. The patient was ultimately diagnosed with diffuse large B-cell lymphoma (the type of lymphoma category of most PCNSLs) by stereotactic biopsy, which remains the gold standard for diagnosing PCNSL. Additionally, the presence of B cell markers such as CD20, CD79α, and PAX5 plays a crucial role in confirming the diagnosis of PCNSL [2].

PCNSL often occurs in periventricular structures, affecting the thalamus, deep white matter, basal ganglia, corpus callosum, and other deep brain structures. Less commonly, the disease can also involve the spinal cord, cerebellum, intraocular structures, and so on [5]. Its most common clinical manifestation is focal neurological deficits, frequently accompanied by altered mental status, cognitive impairment, and other associated neurological symptoms [2]. However, in the present case, PCNSL presented with somnolence and fatigue as the onset symptoms, accompanied by fever, hyponatremia, and other manifestations consistent with acute diencephalic syndrome. Notably, no focal neurological deficits were observed during the clinical course. Based on the lesion identified on cranial MRI, we considered that the altered consciousness state of somnolence may be associated with involvement of the the brainstem ascending reticular activating system, while fatigue was likely derived from the tumor itself [15], rather than hemiplegia caused by the lesion. These non-specific symptoms led directly to misdiagnosis and diagnostic delay in this patient.

In this case, although MRI had a limited contribution to the final diagnosis of PCNSL, conventional and contrast-enhanced MRI is consistently regarded as the first-line imaging test for diagnosing PCNSL [16]. The MRI of PCNSL in immunocompetent patients shows iso-hypointensity on T1-weighted imaging, and iso-hyperintensity or slight hyperintensity on T2-weighted and T2-FLAIR imaging [4], while contrast-enhanced MRI shows uniform enhancement, accompanied by "fist", "incision", or "angular" signs [1]. Although the patient's MRI findings aligned with the features mentioned above and showed a "wine glass" sign on coronal T2-FLAIR imaging, the contrast-enhanced MRI did not show any typical enhancement. The "wine glass" sign is commonly seen in amyotrophic lateral sclerosis and osmotic myelinolysis, but it is less frequently observed in PCNSL cases [17].

Collectively, this case fully demonstrates the high heterogeneity in clinical symptoms and imaging features of PCNSL. Clinically, the patient presented with somnolence and fatigue as the core initial symptoms, with no focal neurological deficits observed. However, these types of non-specific symptoms in the early disease course can indicate lesion involvement of the brainstem, diencephalon, and deep periventricular structures, thereby providing key clinical clues for the early identification of deep intraparenchymal PCNSL. Regarding imaging, the "wine glass" sign in this case represents an extremely rare atypical imaging feature of PCNSL, with only a small number of case reports documenting this sign [17]. In light of the above, clinicians should maintain a high index of suspicion when confronted with intracranial lesions showing the "wine glass" sign. PCNSL should be included in the differential diagnosis to avoid misdiagnosis and delayed diagnosis. Notably, diagnostic clues were first detected by CSF cytology in this case, and the definitive diagnosis was ultimately confirmed by pathological biopsy. This indicates that, for intracranial lesions highly suspicious for PCNSL but with atypical clinical and imaging features, early CSF examination and biopsy are the key to achieving early diagnosis and prompt treatment.

The treatment of PCNSL includes induction therapy and consolidation therapy. A combined high-dose methotrexate (HD-MTX)-based regimen can initially be used for induction therapy, followed by autologous stem cell transplant, non-myeloablative regimens, radiotherapy, and other consolidation therapy. This regimen can maximize the survival time of patients and improve their quality of life [1,2]. However, if patients cannot tolerate chemotherapy due to the toxicity of HD-MTX, radiotherapy can be considered as an alternative treatment [2]. Similar to this case, due to impaired hepatic and renal function, our patient did not receive an HD-MTX-based regimen but instead underwent radiotherapy. Fortunately, the patient's somnolence and fatigue were improved after a single session of radiotherapy.

Conclusions

In summary, this case highlights the diagnostic complexities of PCNSL. By demonstrating its atypical imaging features, it adds to the diagnostic significance of the rare "wine glass" sign for PCNSL. Meanwhile, it suggests that clinicians should maintain a high index of suspicion for atypical phenotypes of PCNSL in order to improve early disease recognition, ultimately leading to improved patient survival rates.

Department and Institution Where Work Was Done

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Patient Consent

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

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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