Diagnostic Pathology

CASE REPORT

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Overcoming missed diagnoses of primary central nervous system Lymphoma—The key role of cerebrospinal fluid cytology: a case report

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Abstract

Background Central nervous system (CNS) involvement in diffuse large B-cell lymphoma (DLBCL) is relatively rare, occurring at a rate of approximately 5%. Primary CNS lymphoma (CNS-DLBCL), a subtype of DLBCL, is rare clinically but highly malignant and invasive. Its atypical clinical symptoms and imaging features contribute to a high rate of misdiagnosis and a poor prognosis. Thus, early and accurate diagnosis is imperative for improving the patient's prognosis. Cerebrospinal fluid (CSF) cytology, a rapid and convenient diagnostic method, plays a crucial role in diagnosing intracranial tumors.

Case presentation In this instance, the patient presented with nonspecific early symptoms and exhibited atypical imaging findings. A lumbar puncture performed at another hospital yielded a low cell count in the CSF, leading to an incorrect diagnosis. Upon admission to our hospital, CSF cytology identified abnormal cells. A definitive diagnosis of CNS-DLBCL was established utilizing additional diagnostic methods, facilitating targeted treatment.

Conclusions This case underscores the pivotal role of CSF cytology in rapidly guiding the differential diagnosis of intracranial tumors and underscores the necessity of training laboratory personnel in morphological examination.

Keywords CNS DLBCL, PCNSL, Cerebrospinal fluid morphology (CSF) cytology, Intracranial tumor

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Background

Primary Central Nervous System Lymphoma (PCNSL) is an aggressive neoplasm, occurring solely within the central nervous system, affecting the brain, eyes, cranial nerves, leptomeninges, or spinal cord, with no evidence of extra-CNS disease [1–3]. Primary CNS DLBCL accounts for approximately 80–85% of all central nervous system lymphomas and currently accounting for 6.6% of all primary brain tumors [4].

A subset of patients with primary central nervous system lymphoma (PCNSL), ranging from 50 to 70%, may present with focal neurological deficits. Additionally, approximately 40–50% of PCNSL patients may exhibit nonspecific cognitive or behavioral changes, and around one-third of patients may also display signs indicative of elevated intracranial pressure, such as headache, vomiting, or nausea. However, it is important to note that these presentations are not always readily identifiable as neurological disorders [2].

The diagnosis of PCNSL relies on histopathological and immunohistochemical analyses, while imaging studies are primarily used to assess the extent and distribution of the disease [3]. CSF analysis often reveals significantly elevated protein and lymphocyte counts in patients with PCNSL [3] , and flow cytometry analysis and gene rearrangement testing also provide objective evidence [5]. Here, we report a case of a patient diagnosed with CNS-DLBCL based on morphological analysis of cerebrospinal fluid, following an initial misdiagnosis.

Case presentation

A 43-year-old female patient was admitted to our hospital (Hangzhou First People's Hospital) on day 1 of hospitalization, presenting with head and neck pain for 1 month, accompanied by vomiting and gait instability for 7 days. One month prior, the patient reported head and neck pain, nausea, and vomiting. Subsequently, within three days, she presented with blurred vision, facial asymmetry, and an inability to close her left eye. She underwent steroid acupuncture treatment. A week before hospitalization, the patient's gait became unsteady. Despite treatments aimed at dehydration, intracranial pressure reduction, cerebral stimulation, and neuro-nutritional support at a local hospital, her condition did not improve, prompting transfer to our hospital. Physical examination revealed a shallow left nasolabial fold, equal and round pupils bilaterally, muscle strength of grade 4 in the right upper and lower limbs, and grade 5 on the left. Muscle tone was normal. Bilateral Babinski signs were negative, and the biceps tendon reflex was 3 + on the right.

Table 1 CSF routine and CSF biochemistry

CSF routine	
cell count	39/μl
neutrophils	1%
lymphocytes	71%
monocytes	4%
abnormal cells	24%
CSF biochemical	
protein	87.4 mg/dL
glucose	2.22 mmol/L
chloride	124 mmol/L

Auxiliary examinations

CSF routine, CSF biochemistry, CSF culture, CSF flow cytometry

Three and a half weeks prior to admission, cranial MRI performed at the original hospital revealed multiple abnormal signal foci within the brain. On the day before admission, lumbar puncture at the original hospital demonstrated a CSF pressure of 370 mmH_2O and a cell count of 14/μL. At our hospital, lumbar puncture was repeated on the second day of admission. The routine CSF analysis revealed a nucleated cell count of 39/μL. The cell classification was as follows: neutrophils 1%, lymphocytes 71%, monocytes 4%, and abnormal cells 24% (Table 1).

The morphological analysis of the CSF (Fig. 1) indicated no significant increase in nucleated cells, with mature lymphocytes being the predominant cell type. Abnormally shaped cells with medium-sized, round, elliptical, or irregular cell bodies, pseudopodia-like protrusions, and abundant, pale blue cytoplasm lacking granules were observed. Their nuclei were round, elliptical, or irregularly shaped, with coarse chromatin and multiple distinct nucleoli. Based on these morphological features, a preliminary diagnosis of lymphoma cells was considered.

Cytomorphologic analysis of CSF served as a critical diagnostic starting point for this patient. And we proceeded with additional diagnostic evaluations aimed at corroborating our initial diagnostic hypothesis.

The CSF biochemical analysis revealed a protein level of 87.4 mg/dL, glucose level of 2.22 mmol/L, and chloride level of 124 mmol/L (Table 1). Tuberculosis (TB) Mycobacterium and Rifampicin Resistance Gene Detection showed that TB Mycobacterium DNA (Xpert) was not detected. The CSF Adenosine Deaminase (ADA) level was 9.90 U/L, and the CSF Immunoglobulin G (IgG) level was 75.50 mg/L. Additionally, the CSF bacterial and fungal culture and identification showed no growth of bacteria or fungi.

Fluid Hematologic Tumor Immunophenotyping (flow cytometry) (Fig. 2; Table 2) showed a predominance of mature lymphocytes, constituting 98.86% of nucleated cells. A subset of large abnormal B lymphocytes was identified, comprising 21.08% of nucleated cells. These cells display a phenotype characterized by elevated forward scatter (FSC) and side scatter (SSC). They express CD19, are CD3-, CD5-, partially CD10+, strongly

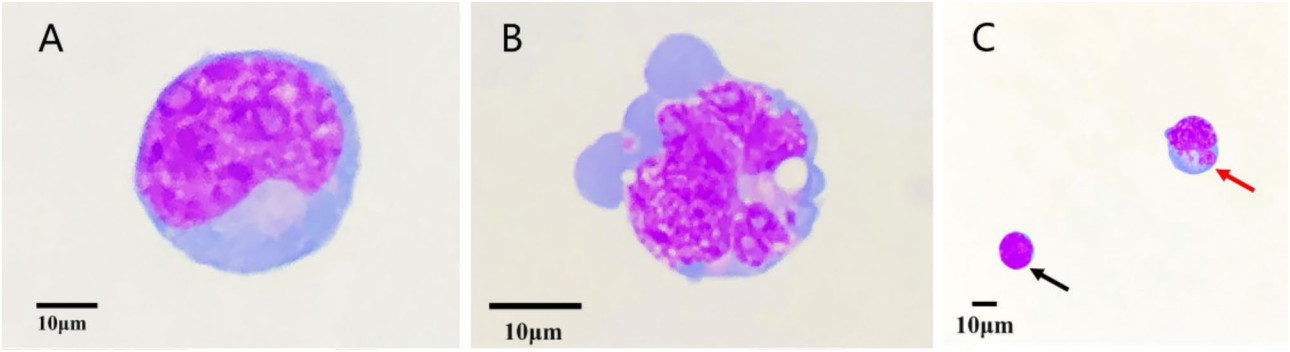

Fig. 1 Cerebrospinal Fluid Morphological Analysis. Wright-Giemsa staining, 1000x× magnification. In Fig. **1A**, the cell bodies are round, the cytoplasm is clear and stained pale blue, the nuclei are concave, with coarse chromatin, and multiple distinct nucleoli are visible. In Fig. **1B**, the cell bodies show prominent pseudopodia, the nuclei are malformed, and the nucleoli are clearly visible. In Fig. **1C**, the black arrow indicates normal mature lymphocytes, while the red arrow indicates abnormal cells with evident nuclear abnormalities and multiple prominent nucleoli.

CD20+, CD38-, and HLA-DR-, with faint kappa/lambda light chain expression. T cells exhibit expression of CD2, CD3, CD5, and CD7, with a CD4:CD8 ratio within the normal limits. NK cells express CD2, CD7, and CD56, with partial expression of CD8 and CD57. The potential for large B-cell lymphoma is considered. In the bone marrow hematologic tumor immunophenotyping, no distinct cluster of lymphoma cells was observed based on immunophenotypic analysis.

Cranial mri、chest CT, PET-CT

Cranial MRI revealed multiple abnormal signal foci in the intracranial region (Fig. 3A-G). The chest CT scan and high-resolution targeted scan revealed findings that are consistent with bronchitis and a minor infection in the right lower lobe, as shown in Fig. 3H-I.

The PET-CT scan revealed multiple slightly hypodense lesions within the brain parenchyma, which exhibited symmetrically increased FDG metabolism (Fig. 4A). Additionally, the right C6/7, C7/T1, T1/2, and left C4/5 nerve roots showed obvious thickening and elevated FDG metabolism. Similar findings were observed in the right L3/4 and left T12/L1 nerve roots, with increased FDG metabolism compared to their contralateral counterparts. These findings raise suspicion for central nervous system lymphoma. Furthermore, multiple enlarged lymph nodes were noted adjacent to the right iliac vessels, exhibiting increased FDG metabolism (Fig. 4B). While reactive hyperplasia is a possible etiology, lymphomatous involvement cannot be excluded. Multiple enlarged lymph nodes with significant FDG uptake are evident near the right iliac vessels. Reactive hyperplasia is currently considered the most likely etiology. However, given the invasive nature of lymph node biopsy and the associated risks (such as infection and bleeding), immediate histological examination of the lymph nodes was deemed imprudent. Additionally, the patient's clinical presentation is predominantly characterized by central nervous system symptoms, with no evidence of systemic lymphoma involvement. MRI findings are consistent with PCNSL. CSF analysis demonstrates elevated protein levels and the presence of malignant cells. In light of these findings, the diagnosis has been focused on PCNSL.

Diagnosis and treatment process

On Day 1, the patient was admitted to the Neurology Department. On Day 2, a cerebrospinal fluid cytology examination was performed. On Day 3, the patient was transferred to the Hematology Department. On Day 4, the patient exhibited delayed reactions compared to before, experienced water aspiration, lower extremity weakness, and unsteady walking. The diagnosis was diffuse large B-cell lymphoma involving the central nervous system. The R2 + BTK regimen was initiated for treatment, with the specific regimen consisting of 600 mg of Rituximab injection, 25 mg of Lenalidomide once daily, and 150 mg of Ibrutinib once daily. On Day 6, the patient was significantly drowsy, experienced headache and vomiting, had unequal pupil sizes, and exhibited delayed light reflex in the right eye. The original treatment regimen showed poor efficacy, so high-dose Methotrexate chemotherapy was added, specifically 4 g of Methotrexate injection. On Day 8, the patient regained consciousness, responded appropriately, experienced relief from headache, had equal and round pupils with sensitive light reflex, and the cardiac monitoring indicated stable vital signs. The treatment showed good efficacy. On Day 12, the patient was discharged.The patient were regularly reviewed following discharge. Currently, the patient's condition is well-controlled, with no recurrence observed.

The timeline of patient diagnosis and treatment process is shown in Fig. 5.

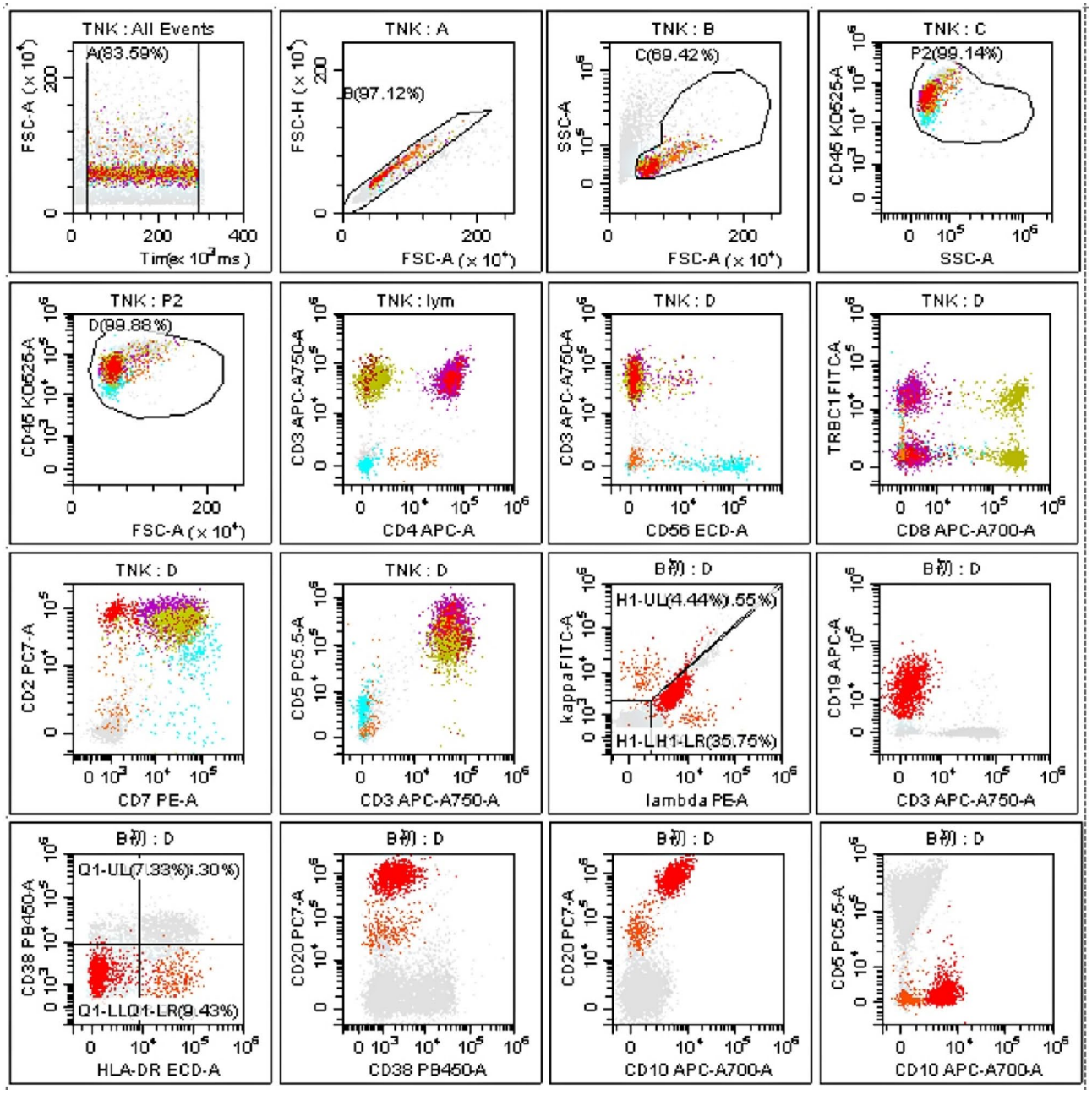

Fig. 2 Cerebrospinal Fluid Hematologic Tumor Immunophenotyping (flow cytometry). Mature lymphocytes: Account for 98.86% of the total nucleared cells. Abnormal B lymphocytes: Account for 21.08% of the total nuclear cells; Increased forward scatter (FSC), Increased side scatter (SSC), CD19 + , CD3-, CD5-, CD10part + ,CD20 + + , CD38-, HLA-, DR-,unobvious expression of kappa/lambda light chains. Phenotypic features of other cell types: T cells: Express CD2, CD3, CD5, CD7;CD4:CD8 ratio within normal range. NK cells: Express CD2, CD7, CD56; Partial expression of CD8, CD57.

Table 2 Cerebrospinal fluid hematologic tumor Immunophenotyping (flow cytometry)

Cerebrospinal Fluid Hematologic Tumor Immunophenotyping (flow cytometry)	
B lymphocytes	CD19+、CD3-、CD5-、CD10part+、CD20++、CD38-、HLA-、DR-;unobvious expression of kappa/lambda light chains.
T lymphocytes	CD2+、CD3+、CD5+、CD7+;CD4:CD8 ratio within normal range.
NK cells	CD2+、CD7+、CD56+; Partial expression of CD8、CD57.

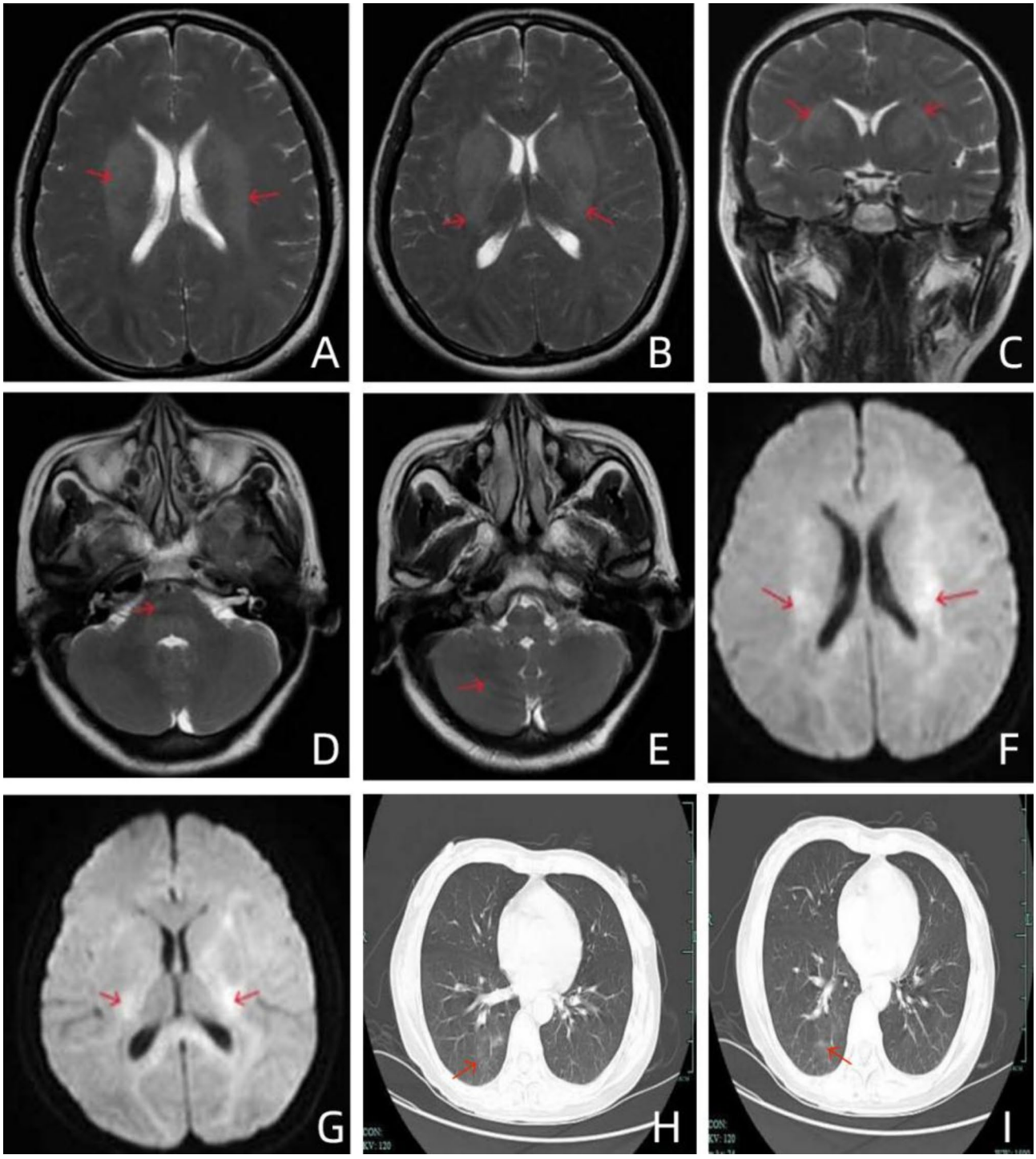

Fig. 3 Imaging Findings. Fig. **3A** and **3B** are transverse T2-weighted images, with red arrowheads indicating patchy slightly high signal areas adjacent to the bilateral ventricles and basal ganglia on T2WI. Fig. **3C** is a coronal T2-weighted image, with red arrowheads indicating patchy slightly high signal areas adjacent to the bilateral ventricles and basal ganglia on T2WI. Figure **3D** is a transverse T2-weighted image, with a red arrowhead indicating a patchy slightly high signal area in the brainstem on T2WI. Fig. **3E** is a transverse T2-weighted image, with a red arrowhead indicating a patchy slightly high signal area in the right cerebellum on T2WI. Fig. **3F** and **3G** are diffusion-weighted images (DWI), with red arrowheads indicating patchy slightly high signal areas adjacent to the bilateral ventricles and basal ganglia on DWI, showing mild restricted diffusion. Fig. **3H** and **3I** are chest CT scan images. Red arrowheads indicate scattered fluffy slightly high-density opacities with blurred borders in the right lower lobe of the lung, suggestive of infectious lesions.

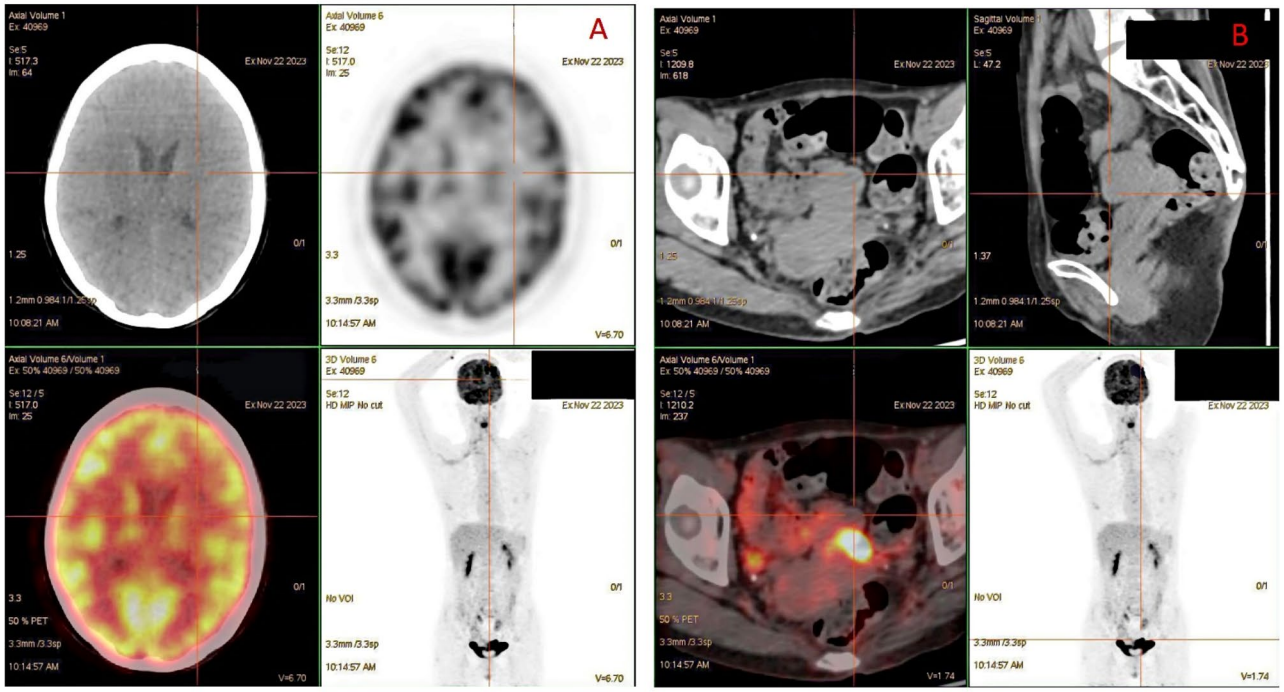

Fig. 4 PET-CT Findings. Fig. **4A** shows multiple slightly hypodense lesions within the brain parenchyma, which exhibit symmetrically increased FDG metabolism. Fig. **4B** shows multiple enlarged lymph nodes adjacent to the right iliac vessels, exhibiting increased FDG metabolism.

Discussion

PCNSL is now defined as primary diffuse large B-cell lymphoma (DLBCL) of the CNS and/or eyes, limited to immunocompetent patients. Other subtypes of lymphoma, including those that are primary or exclusive to the CNS, such as primary dural lymphoma and immunodeficiency-related lymphoma, are excluded from this definition. More than 90% of PCNSL cases are DLBCL [6]. In immunocompetent patients with invasive lymphomas, 2–10% may show involvement of the central nervous system during the course of the disease, and these invasive lymphomas are histopathologically classified as diffuse large B-cell lymphomas [7]. In this case, the patient initially presented with symptoms of headache, neck pain, nausea, and vomiting, followed rapidly by blurred vision, facial asymmetry, and inability to close the left eye. The patient initially underwent traditional Chinese medicine treatment involving steroid acupuncture, which led to a delay in diagnosis. However, from a medical perspective, the patient exhibited typical symptoms of increased intracranial pressure.

PCNSL accounts for 5% of malignant primary brain tumors [8] and shares some clinical manifestations with non-malignant brain tumors, and early differential diagnosis is necessary due to the need for prompt treatment of acute symptoms such as brain edema. According to WHO standards, the definitive diagnosis of PCNSL requires histopathological examination and immunohistochemical (IHC) analysis of brain biopsy specimens [9]. However, brain biopsies are invasive procedures associated with significant risks of complications, including intracranial hemorrhage. In certain cases, brain biopsies may be unfeasible due to difficulties in accessing the lesion or temporary tumor shrinkage or disappearance caused by the use of steroids, making it impossible to perform the biopsy [10]. Although neuroimaging studies have some characteristic findings for PCNSL, they are limited, and atypical cases can be particularly challenging to identify as intracranial tumors or other diseases. While biopsy remains the gold standard for diagnosing PCNSL, it is not applicable to all patients with suspected PCNSL. While neuroimaging studies such as MRI or other techniques are quite sensitive, their specificity is limited.

The cytological examination of CSF may have a high specificity for diagnosing PCNSL. Under normal conditions, CSF is a transparent fluid with a cell count of less than 5 cells/μL, predominantly composed of T cells (90%), B cells (5%), and mononuclear cells/macrophages (5%). In patients with PCNSL, CSF analysis typically reveals leukocytosis, normal glucose levels, and elevated protein concentrations, the latter of which is indicative of blood-brain barrier disruption [11]. However, low cell counts and/or malignant cells (including leukemia blast cells) in CSF samples pose a continuous challenge for laboratory analysis techniques [12]. Cytological methods are insufficiently sensitive for detecting low-abundance tumor cells, thereby increasing the risk of false-negative results. Additionally, the finite volume of obtainable CSF

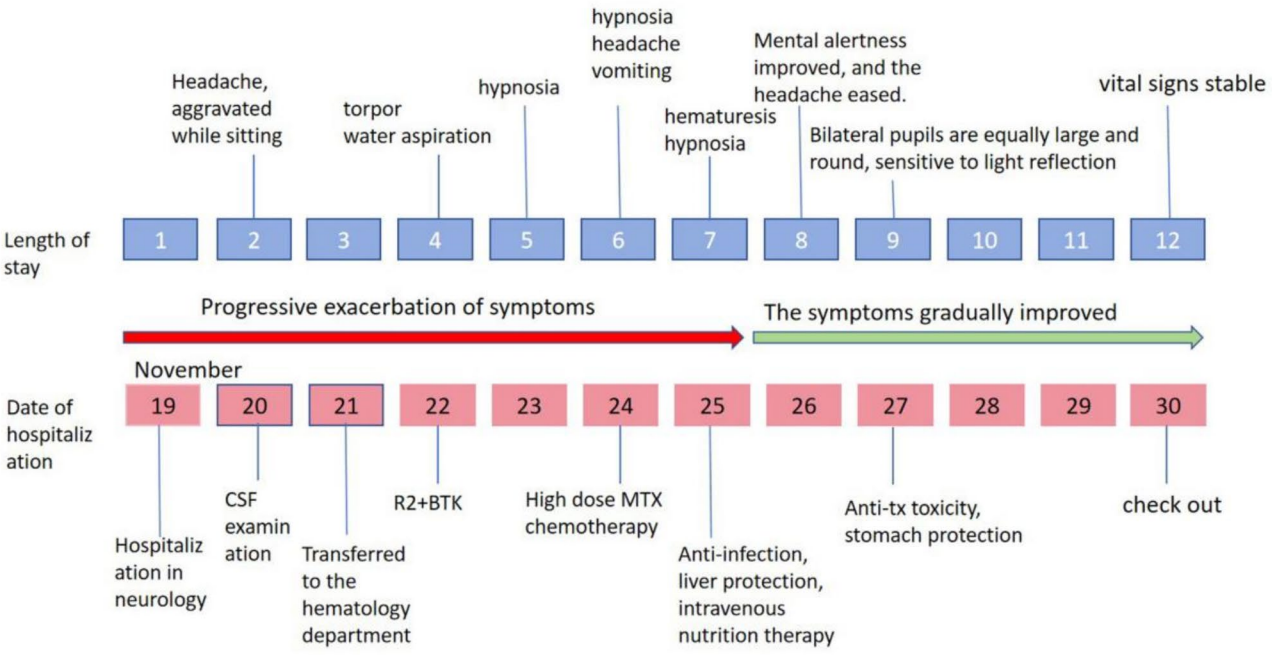

Fig. 5 The timeline of patient diagnosis and treatment process

samples, coupled with the rapid post-collection lysis or degradation of cells, significantly diminishes the pool of viable analyzable cells. Furthermore, the detection of malignant cells in CSF is further complicated by their heterogeneous presentation, which may include cellular debris and nonspecific staining artifacts.

Cytological examination of CSF is considered the "gold standard" for detecting central nervous system involvement by hematological malignancies due to its high specificity, but its sensitivity is limited, and its status as a gold standard is controversial [13]. In 2019, the Temple of Heaven Hospital in China also reported a case of central nervous system lymphoma diagnosed through cytological examination of CSF [5]. In the evidence-based guidelines from the College of American Pathologists (CAP) and the American Society of Hematology (ASH) in 2017 regarding initial diagnostic tests for acute leukemia, it was recommended that all patients with acute lymphoblastic leukemia (ALL) undergo cytological evaluation of CSF at the time of diagnosis, at the end of treatment, and when CNS relapse is suspected. It was also recommended to perform cytological examination of CSF in AML patients receiving intrathecal chemotherapy [14].

Flow cytometry, a commonly used laboratory technique, is employed to analyze and identify different types of cells within a cell population. It enables the detection of cell surface antigens, intracellular markers, and cell functionality. Flow cytometry is an objective process involving qualitative and quantitative measurements, and its results are not influenced by the same degree of subjectivity as morphological evaluations. In a review article from 2011, the authors emphasized that flow cytometry immunophenotyping serves as a cornerstone for many mature lymphoid tumor diagnostic strategies, as it facilitates the establishment of disease-specific phenotypes and the development of highly specific and sensitive methods for detecting tumor cells [15]. Recent reviews have demonstrated that flow cytometry immunophenotyping is highly effective for identifying lymphocyte subtypes in body cavity fluids, both in cases of recurrent hematological malignancies and in undiagnosed lymphomas [16].

PCNSL predominantly involves the cerebral parenchyma (92%) [11], and is frequently associated with multifocal lesions that commonly infiltrate deep brain structures. Resection of these lesions may result in postoperative neurological deficits, and surgical complexity is significantly heightened when the lesion exhibits cystic changes or an ill-defined tumor margin [3]. In this instance, the patient's initial presentation was with central nervous system symptoms, which made brain biopsy impractical. Moreover, considering the patient's overall clinical condition and other diagnostic findings, the medical team opted for alternative diagnostic and management approaches that were deemed safer and more suitable for this specific scenario. Given the low cerebrospinal fluid cell count and the complexities of pathological analysis, laboratory staff relied on morphological examination to detect abnormal lymphocytes. Consequently, the patient was referred to the Hematology Department for flow cytometry. The integration of imaging and additional diagnostic studies facilitated

a definitive diagnosis of CNS-DLBCL, after which the patient received targeted treatment.

In retrospect, the patient had previously undergone CSF cytology at an outside hospital. However, the report from that institution did not document the presence of any abnormal cells, and morphological analysis of the CSF was not performed. The absence of such analysis may have been attributable to the low cell count of the CSF sample, which could have precluded a reliable morphological evaluation. A low cell count in CSF does not rule out the possibility of the presence of abnormal cells. However, it is generally considered that morphological analysis is not necessary when the CSF cell count is less than 5cells/μL. Additionally, it is plausible that the laboratory staff at the referring hospital lacked specialized training in cytological morphology, which may have limited their diagnostic proficiency and contributed to the failure to detect significant cellular abnormalities.

Upon admission, the patient immediately underwent CSF testing, which facilitated the swift identification of abnormal cells by laboratory personnel during morphological analysis. Drawing on their expertise in morphological diagnostics, the laboratory staff promptly alerted the clinicians to the possibility of intracranial lymphoma. In response, the attending physician swiftly requested a hematology consultation and initiated immunophenotyping of the CSF tumor cells, which provided timely and supportive diagnostic evidence. Imaging studies revealed multiple abnormal brain signal lesions; together with chest CT and PET-CT results, these findings provided further support for a diagnosis of primary CNS DLBCL. Despite the patient's critical condition, the clinical team promptly delivered appropriate supportive care and adjusted the treatment plan based on the patient's evolving condition. Ultimately, the patient's condition improved, symptoms were alleviated, and the patient was discharged successfully.

The training of laboratory personnel in the morphological diagnosis of CSF is extremely important. Firstly, it enhances diagnostic accuracy. Through systematic training and practical experience, lab personnel can more precisely distinguish between normal and abnormal cells in CSF, reducing the incidence of misdiagnosis and missed diagnosis. This is crucial for identifying pathological conditions in the central nervous system. Secondly, it facilitates technological advancement and innovation. As medical technology evolves, new techniques like immunocytochemical staining and flow cytometry are increasingly integrated into CSF morphological diagnosis. These methods improve the precision and sensitivity of diagnostic procedures, allowing for more detailed and reliable analysis of cellular and subcellular components in CSF. Thirdly, it promotes interdisciplinary collaboration and integration. CSF morphological diagnosis involves multiple disciplines such as cytology, pathology, and microbiology. Effective collaboration with clinicians, radiologists, and other team members is essential for comprehensive patient care. By fostering communication and coordination among these disciplines, a more holistic and integrated diagnostic approach can be achieved, ultimately benefiting patient outcomes. In conclusion, training in CSF morphological diagnosis should be emphasized to enhance lab personnel's professional competence, improve diagnostic service quality, and better support clinical decision-making and therapeutic interventions.

The strengths of this case report lie in its comprehensive elucidation of the pivotal role played by CSF cytology in rapidly facilitating the differential diagnosis of PCNSL, as well as its emphasis on the importance of training laboratory personnel in morphological examination through a specific case study. Nevertheless, it is essential to recognize that although CSF cytology is indispensable for diagnosis, it is not without limitations, particularly regarding its sensitivity and specificity. Therefore, the diagnostic process still necessitates integration with other auxiliary diagnostic techniques.

Conclusion

PCNSL is an uncommon subtype of non-Hodgkin lymphoma, affecting the brain parenchyma, spinal cord, leptomeninges, and eyes. It lacks evidence of systemic lymphoma involvement. Due to its aggressive nature, rapid progression, and unfavorable prognosis, PCNSL poses a diagnostic challenge characterized by swift neurological deterioration and decline in performance status. Additionally, nonspecific clinical symptoms further complicate timely diagnosis and treatment initiation. In cases where brain biopsy is not feasible for confirming the diagnosis of PCNSL, comprehensive examination of CSF becomes crucial using techniques such as immunocytochemistry, flow cytometry, and IgH gene rearrangement assays.

CSF cytology is of paramount importance in the diagnosis of intracranial lymphoma. This diagnostic modality is distinguished by its rapidity, ease of performance, and accessibility. Through detailed examination of the quantitative, morphological, and proportional changes of cellular components within the CSF, in conjunction with a comprehensive integration of clinical presentations, neuroimaging findings, and laboratory data, a precise cytological diagnosis can be established. This approach serves as a robust foundation for the diagnosis and differential diagnosis of central nervous system disorders, while also providing valuable insights into therapeutic efficacy and prognostic evaluation. Therefore, we emphasize the promotion of cytological examination of CSF and the strengthening of training for related personnel, as it holds

significant value in the management of various lymphomas and other intracranial tumors. This approach will help improve the early detection rate and reduce misdiagnosis, leading to better patient outcomes and providing support for the development of individualized treatment plans.

Abbreviations

CNS	Central nervous system
DLBCL	Diffuse large B-cell lymphoma
PCNSL	Primary central nervous system lymphoma
FSC	Forward scatter
SSC	Side scatter
CD	Cluster of differentiation
CSF	Cerebrospinal fluid
IgG	Immunoglobulin G
MRI	Magnetic Resonance Imaging
PET-CT	Positron emission tomography computed tomography
TB	Tuberculosis
ADA	Adenosine Deaminase

Acknowledgements
We thank all the physicians from the Hangzhou First People's Hospital and the First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Traditional Chinese Medicine) who contributed to the patient care.

Author contributions
Yuli Zhou and Juan jin are responsible for collecting case data, collecting relevant literature, and preparing experimental reagents. Siqi Zhu is responsible for paper writing, literature retrieval, and submission. Hong Xu is mainly responsible for flow cytometry analysis. Yuyi Lai and Xinxin Wang are responsible for cellular morphology analysis of cerebrospinal fluid. Fuxian Zhou and Daojun Yu are responsible for language editing and technical guidance of the manuscript. All authors read and approved the final manuscript.

Funding
the Ministry of Education's Industry-University Cooperative Education Project in 2022 (Project No. 220906053235359); Hangzhou Biomedicine and Health Industry Development Support Science and Technology Project (the third phase of 2021) (2021WJCY090); Hangzhou Biomedicine and Health Industry Development Support Science and Technology Project (the fifth phase of 2021) (2021WJCY272);

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Hangzhou First People's Hospital and informed consent has been obtained from the patient prior to analysis.

Consent for publication
Informed consent has been obtained from the patient prior to analysis, for the case presentation.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

Received: 16 December 2024 / Accepted: 5 March 2025
Published online: 15 March 2025

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