Invasive and Multiple Lesions of Primary Central Nervous System Lymphoma: A Case Report

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Case report

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Abstract

Background: Primary central nervous system lymphoma (PCNSL) is rare, malignant, non-Hodgkin lymphoma in the central nervous system. Solitary lesions occurred in the majority of cases. Invasive and multiple lesions were rarely reported. As clinical presentations and neuroimage are variable, early diagnosis is challenging.

Case presentation: The patient was a 61-year-old male with normal immunity who firstly experienced drowsiness and dizziness. Cranial magnetic resonance imaging(MRI) revealed invasive and multiple lesions of cerebellar hemisphere, right pons, bilateral thalamus and right frontal lobe with slightly long T1 and T2 signal. Contrast-enhanced MRI demonstrated enhanced signal shadows in the cerebellar hemisphere rather than other areas. Magnetic resonance spectroscopy (MRS) showed lactate (Lac) peak increases and N-acetyl-aspartate (NAA) peak decreases moderately. Histopathological examination revealed infiltrative growth of abnormal lymphoid cells. The immunohistochemical analysis detected the result of CD10(-), Bcl-6(+), MUM-1(+), accessing the diagnosis of diffuse large B-cell lymphoma (Non-GCB).

Conclusions: PCNSL with invasive lesions distributed in supratentorial and infratentorial sites were rarely reported, resulting in the delayed diagnosis in this case. This case not only expands the clinical spectrum but also extends the distribution of PCNSL.

Background

Primary central nervous system lymphoma (PCNSL) is extra-nodal, malignant nonHodgkin lymphoma of the diffuse large B-cell type, involving brain, spinal cord, leptomeninges, or eyes[1]. It is confined to the central nervous system, in the absence of systemic lymphoma. PCNSL is rare, accounting for approximately 2% of all primary tumors of the central nervous system (CNS)[2]. Presenting symptoms vary according to the CNS site involved. Neurocognitive symptoms, behavioral changes and focal neurological deficits are common clinical features[3]. CSF cytology, flow cytometry and biopsy were helped to get a definitive diagnosis. Solitary, uniformly enhancing masses were commonly showed in contrast-enhanced magnetic resonance imaging (MRI) of the brain in immunocompetent patients[4]. Multiple lesions are rarely reported.

Here, we describe the clinical, histological, and MRI data of a Chinese patient with PCNSL characterized by invasive and multiple lesions distributed in supratentorial and infratentorial sites.

Case Presentation

In June 2019, a 61-year-old male presented to our hospital with drowsiness and dizziness. In April, the patient started to develop symptoms of excessive daytime sleepiness and instability while walking. He didn't have fever, headache, nausea and vomit, and he was admitted to a local hospital. The cranial magnetic resonance imaging(MRI) on May 20th showed a right cerebellar hemisphere, a right frontal lobe

and a bilateral thalamus subacute cerebral infarction. The therapy was uncertain for the patient at the beginning. His symptoms were improved when he was discharged from the hospital. One week later, due to the aggravation of drowsiness and dizziness, the patient went to the superior hospital to seek assistance. Results of cerebrospinal fluid (CSF) examination were insignificant. The diagnosis of images of MRI was encephalitis. Even though the patient's symptoms were improved again after he was treated with antiviral and glucocorticoid pulse therapy, the symptom of the drowsiness reoccurred. He was eventually admitted to the department of neurology at Peking University Shenzhen Hospital. He was diagnosed with hypertension and diabetes but had no history of heart disease, hepatitis, tuberculosis, or drug allergy. From the admission assessments, we found that the patient was somnolent and the Romberg's sign of the patient was positive. Other obvious symptoms were not observed.

A routine CSF examination showed that the CSF was a yellow and clear fluid. The total number of CSF cells was 14×10^6 /L, and the number of leukocytes was 4×10^6 /L. His CSF protein was 0.3g/L (0-0.5g/L). CSF culture, ink stain, the IgG oligoclonal band and autoimmune antibody tests were all negative. Liquid-based cytology showed mickle small lymphocyte. MRI, contrast-enhanced MRI and magnetic resonance spectrum (MRS) were conducted on June 10th. The result of MRI suggested that there were invasive and multiple lesions of cerebellar hemisphere, right pons, bilateral thalamus and right frontal lobe with slightly long T1 and T2 signal. Contrast-enhanced MRI demonstrated enhanced signal shadows in the cerebellar hemisphere rather than other areas, and the increased lactate (Lac) peak and decreased N-acetyl-aspartate (NAA) peak were also observed (Fig. 1). On June 12th, patient's symptoms were progressed, accompanied with vomiting several times. Nystagmus was observed during the physical examination. We called for consultation from the neurosurgery department, and they suggested to perform a brain biopsy. The patient was unconscious before performing the biopsy. The patient eventually received resection of the cerebellum lesion. Intraoperative frozen-section examination showed heteromorphic lymphoid cells with large cell size growing invasively. Immunohistochemistry obtained the following results: CD3(-), CD20(+), CD21(-), CD10(-), Ki-67(> 90%+), Bcl-2(80–90%+), CyclinD1(-), Bcl-6(+), MUM-1(+), PAX5(5%+), C-MYC(30–35%+), ALK(-), GFAP(-)(Fig. 2). Moreover, EBV-encoded RNA (EBER) showed negative staining in situ hybridization. The final histopathologic diagnosis was diffuse large B-cell lymphoma (Non-GCB). Then he was treated with rituximab and methotrexate. After being treated for a month, the repeat MRI and contrast-enhanced MRI showed that the lesions were smaller and improved. However, the patient was still unconscious. He died two months later due to a pulmonary infection.

Discussion

PCNSL is defined as extra-nodal non-Hodgkin lymphoma, which accounts for 2% of all primary CNS tumors. PCNSLs are rare diseases, which commonly occur in the elderly. It is identified that immune evasion and suppressed tumor immune microenvironment were key mechanisms in the pathogenesis of PCNSL. The main pathway was associated with B-cell receptor (BCR) and Toll-like receptor (TLR). BCR signaling pathway was activated by CD79B mutations while TLR signaling axis was activated by MYD88 mutations. They both targeted the Bruton Tyrosine Kinase, leading to CARD11 mutations. In normal B

cells, antigen receptor–induced NF- κ B activation requires CARD11, a cytoplasmic scaffolding protein. Due to the mutations of CARD11, NF κ B activity was amplifying, promoting the growth of PCNSL[5]. Symptoms of patients are diverse according to the CNS lesions area. The most common symptoms are cognitive decline, personality changes and increased intracranial pressure with subacute onset. Focal neurologic signs/symptoms are relatively unusual. Typically, lesions are solitary in 65–80% of cases[6]. It was reported that the 5- and 10-year survival rates for PCNSL are 29.9% and 22.2%. However, in recent years, the survival rate is increasing in the United States population who were immunocompetent[1, 7]. In this study, the patient was 61-year-old with normal immune functions. The primary symptoms involved drowsiness and dizziness, which were atypical and led to delayed diagnosis. A diffusely infiltrating process with involvements of the brainstem, thalamus and hemisphere without discrete were showed in this case. And the patient had poor prognosis.

As clinical prognoses are different, neuroimaging may help to support the diagnosis. In immunocompetent patients, the tumor lesion was isolated and mostly confined to the supratentorial and periventricular location. The most common sites were the cerebral hemisphere (38%), the basal ganglia and thalamus (16%), and the corpus callosum (14%)[8]. Gadolinium-enhanced brain MRI was recommended. It characteristically demonstrated a homogeneously enhancing mass, with surrounding vasogenic edema and no central necrosis. In the MRS, the manifestations of PCNSL include increased choline (cho) peak, moderately decreased NAA peak, slightly decreased creatine (Cr) peak, as well as a significant increase in Lipid and Lac peaks, which indicated neuron damage and increased tumor cell proliferation[9–12]. In this case, MRI showed invasive lesions distributed in not only supratentorial but also infratentorial sites, which was different from previous reports. MRS showed Lac peak increases and NAA peak decreases moderately, which provided us a clue of the malignant tumor.

Although enhanced brain MRI revealed lesions with an enhanced signal, it is a challenge to identify PCNSL and demyelinating diseases. Clinical manifestations and imaging examinations were lack of specificity. Therefore, histopathologic diagnosis is the gold standard for diagnosis of PCNSL, and stereotactic biopsy is currently used. The majority of PCNSL are DLBCL (90%). It separately recognized GCB and non-GCB immunohistochemical subgroups based on the Hans algorithm, which used antibodies to CD10, BCL6, and IRF4/MUM1[13]. It is worth noting that glucocorticoid should generally be avoided preoperatively due to the risk of a nondiagnostic biopsy. As the patient was treated with glucocorticoid pulse therapy before the biopsy, we choose the resection of the cerebellum lesion to improve the diagnostic accuracy. The morphological changes and the result of immunohistochemistry were typical, drawing a conclusion for DLBCL (non-GCB group).

Conclusions

We report an elderly Chinese male with invasive lesions distributed in supratentorial and infratentorial sites, diagnosing as PCNSL. His clinical presentation was atypical, and the condition deteriorated more rapidly compared with other reported cases. Our study not only expands the clinical spectrum but also extends the distribution of PCNSL. Nevertheless, the efficacy of chemotherapy needs further study.

Abbreviations

PCNSL: Primary central nervous system lymphoma; MRI: magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; Lac: lactate; Non-GCB: diffuse large B-cell lymphoma; CNS: central nervous system; CSF: cerebrospinal fluid; NAA: N-acetyl-aspartate; cho: choline; DLBCL: Primary diffuse large B-cell lymphoma; BCR: B-cell receptor; TLR: Toll-like receptor; H&E staining: Hematoxylin and eosin staining; Bcl-6: B-cell lymphoma 6 protein; MUM-1: lysozyme, multiple myeloma oncogene 1.

Declarations

Consent

Written informed consent for publication of this manuscript and the accompanying images was obtained from daughter of the patient. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

The data used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JZ: acquisition and analysis of data, drafting the manuscript; XZ: analysis and interpretation of histological samples; MZ: acquisition and analysis of data; analysis and interpretation of MRI imaging; JZ, HQ, JW: revising the manuscript. All authors have read and approved the final manuscript.

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Figures

Figure 1

Imaging performance. (A-E) Midline lesions of cerebellar hemisphere, right pons and bilateral thalamus on T1-weighted, T2-weighted MRI and FLAIR. (F) Enhanced signal shadows in the cerebellar hemisphere on contrast-enhanced MRI. (G) Lac peak increased, while NAA peak decreased on MRS.

Figure 2

Histopathology of cerebellum lesion. (A) Diffuse sheets of lymphoid tumor cells, H&E stain, 40x magnification. (B) Medium-sized tumor cells with big nuclei and nucleoli, H&E stain, 400x magnification. (C) CD20 immunostain, 400x magnification. (D) Bcl-2 immunostain (80-90% proliferation index), 400x magnification. (E) Bcl-6 immunostain, 400x magnification. (F) MuM-1 immunostain, 400x magnification.