Clinical Case Report

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Multiple primary central nervous system lymphoma in the elderly

A case report

Guangyong Chen, MS[a], Meiling Xu, MS[b], Xuemei Wang, MS[c], Yufei Gao, MD[a], Chengyan He, MD[d,*], Meiji Chang, MS[e], Jinnan Zhang, MD[a,*]

Abstract

Rationale: Multiple primary central nervous system lymphoma (MPCNSL) is a rare disease with differential diagnosis and treatment. As the underlying pathogenesis is not yet clarified, the early-stage clinical manifestations are occult and atypical. Also, the imaging manifestations are not specific, which is challenging for the clinical diagnosis and treatment. Therefore, additional clinical research is essential to understand the etiology of the disease.

Patient concerns: A 63-year-old male patient suffered from MPCNSLs but without typical clinical manifestations. The findings of the imaging examination were as follows. Magnetic resonance imaging (MRI) showed long T1 and T2 signal shadows in the right frontal lobe, right hippocampus, right cerebellar hemisphere, and the left occipital lobe. In addition, patchy T1-enhanced signal shadows were observed in the right frontal lobe and around the midline. Frontal lesions were detected in the magnetic resonance spectroscopy (MRS), Cho peak increased, and N-acetylaspartate (NAA) peak decreased. On the other hand, in the diffusion weighted imaging (DWI), apparent dispersion coefficient (ADC) showed low-value changes and high signal changes. The positron emission tomography-computed tomography (PET-CT) displayed radioactive accumulation in the right frontal lobe.

Diagnosis: Multiple primary central nervous system lymphoma.

Interventions: The patient received some conservative medical treatment, but his condition continued to worsen. Finally, he received a pathological biopsy, and refused further treatment after the result was reported.

Outcomes: The patient died 1 week after biopsy, and the course of disease was about 100 days.

Lessons: PCNSL is a primary intracranial malignancy with low incidence and a high degree of malignancy and specificity in clinical manifestations. To facilitate early clinical treatment and improve the long-term survival of patients, it is necessary to master the imaging diagnostic methods and its features. The comprehensive application of multiple imaging examinations, such as CT, MRI, PET/CT, and PET/MRI, as well as, cerebrospinal fluid cytology can greatly improve the diagnosis of PCNSL.

Abbreviations: CHO = chlorine compounds, Cho = choline, DWI = diffusion-weighted MRI, MPCNSLs = multiple primary central nervous system lymphomas, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, NAA = N-acetylaspartate, PCNSLs = primary central nervous system lymphomas, ROIs = regions of interests.

Keywords: diffusion-weighted MRI, multiple primary central nervous system lymphomas, magnetic resonance imaging, magnetic resonance spectroscopy, primary central nervous system lymphomas, PET-CT diagnosis

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Informed written consent was obtained from the patient for publication of this case report and accompanying images.

The authors declare that they have no competing interests.

[a] Department of Neurosurgery, [b] Department of Rheumatology, [c] Department of Pathology, [d] Department of Clinical Testing, China-Japan Union Hospital of Jilin University, [e] Department of Neurology, Changchun Central Hospital, Chang Chun, Ji Lin, China.

[*] Correspondence: Chengyan He, Department of Clinical Testing, China-Japan Union Hospital of Jilin University, 126 Sendai Street, Chang Chun, Ji Lin 130033, China (e-mail: chengyanhe469@vip.sina.com); Jinnan Zhang, Department of Neurosurgery, China-Japan Union Hospital of Jilin University, 126 Sendai Street, Chang Chun, Ji Lin 130033, China (e-mail: jnzhang@jlu.edu.cn).

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1. Introduction

Primary central nervous system lymphomas (PCNSLs) are rare that originate in the central nervous system (including the brain, spinal cord, eyes, and meninges) but does not affect other sites. Most of the PCNSLs are deep in location, multi-centered, and diffusely infiltrate the surrounding brain tissues. PCNSL accounts for about 3% of all the primary central nervous system tumors, of which, multiple primary central nervous system lymphomas (MPCNSLs) account for approximately 33% to 45% of PCNSLs[1,2] that are primarily diffuse large B-cell lymphoma. As the underlying pathogenesis is not clear, the early-stage clinical manifestations are occult and atypical, and the imaging manifestations are not specific, which result in great challenge for clinical diagnosis and treatment, meanwhile the MPCNSLs had a worse prognosis. In the present study, a patient admitted to the Neurology Department was reported and the imaging characteristics of the patient were summarized in combination with literature.

2. Case presentation

This case was a 63-year-old man, admitted to our hospital on September 24, 2016 due to emotional indifference, weakness in

both lower extremities for 50 days, and aggravated symptoms for 2 weeks. The patient developed emotional indifference without obvious triggers 50 days before the admission (July 25, 2016), manifested as no interest in communicating with other individuals and reduction of interests, followed by weakness in both lower extremities but still be able to walk by himself. The patient was considered to suffer from "cerebral infarction." However, the symptomatic treatment did not show any improvement. In the recent 2 weeks, mental abnormalities of the patient worsened that was manifested as no response to questions and increased sleep, especially at night. Furthermore, the patient was considered to be in "depression" by the mental health department, and thus, citalopram, bupropion, and olanzapine were orally administrated; however, the symptoms were not relieved. Moreover, the patient could not walk by himself; so, he was admitted to the Neurology Department. During disease, the patient suffered from incontinence, and both lower extremities trembled involuntarily. Physical examination showed that the conscious level of the patient was clear, the content of consciousness was blurred, orientation/memory/computational ability was normal, speech was normal, physiological reflexes were present, no pathological reflex was induced, muscle strength of both upper extremities was grade 5, and muscle strength of both lower extremities was grade 3; it seemed that the patient could not cooperate for the physical examination, and there was no stiff neck. Magnetic resonance imaging (MRI) (Fig. 1A and B) showed long T1 and T2 signal shadows in the right frontal lobe, the right hippocampus, the right cerebellar hemisphere, and the left occipital lobe. Furthermore, lacunar infarctions were observed in the corpus callosum, the right thalamus, bilateral basal ganglia, the corona radiata, and semioval center, as well as, demyelination of cerebral white matter was detected. Enhanced nuclear magnetic resonance (Fig. 1C) demonstrated multiple abnormal patchy enhancements in bilateral cerebellum and bilateral brains and the boundary was not distinct. Diffusion-weighted MRI (DWI) (Fig. 1E and F) indicated that DWI sequence showed multiple high signal changes in the bilateral frontal-parietal lobe, the left temporal-occipital lobe, and bilateral cerebellum, which showed low-value changes on ADC. The cerebrospinal fluid test showed that Immunoglobulin G was 69.3 mg/L (normal reference range: 0–34 mg/L). No cancer cells were observed by exfoliative cytology. Microscopic examination showed that the level of leukocytes was 12×10^6/L ($0–8 \times 10^6$/L): 92% lymphocytes, 8% monocytes, 75% mononuclear, and 25% polynuclear. The level of protein was 0.66 g/L (0.15–0.45 g/L), glucose 2.76 mmol/L (2.3–4.1 mmol/L), chlorine 115.3 mmol/L (119–129 mmol/L), and positive Pam's reaction. The level of serum hormones was as follows: FT3 was 3.07 pmol/L (3.1–6.8 pmol/L), FT4 was 10.41 pmol/L (12–22 pmol/L), Thyroid Stimulating Hormone was 1.330 μIU/mL (0.27–4.2 μIU/mL), A-TG was 10.0 IU/mL (<115.0 IU/mL), and thyroid peroxidase was 11.95 IU/mL (<35.0 IU/mL). The disease condition was aggravated progressively after phlegm elimination, protection of the liver, reduced blood pressure, free radical scavenging, improvement in circulation, nutritional support, and symptomatic treatment. One week after admission, the patient was in a light coma and resisted to open the eye passively. The pupils were of the same size and round with 1.5 mm diameter. Moreover, there were light reflexes, muscle tension increased in both the upper and lower extremities, and bilateral pathological signs were positive. Magnetic resonance

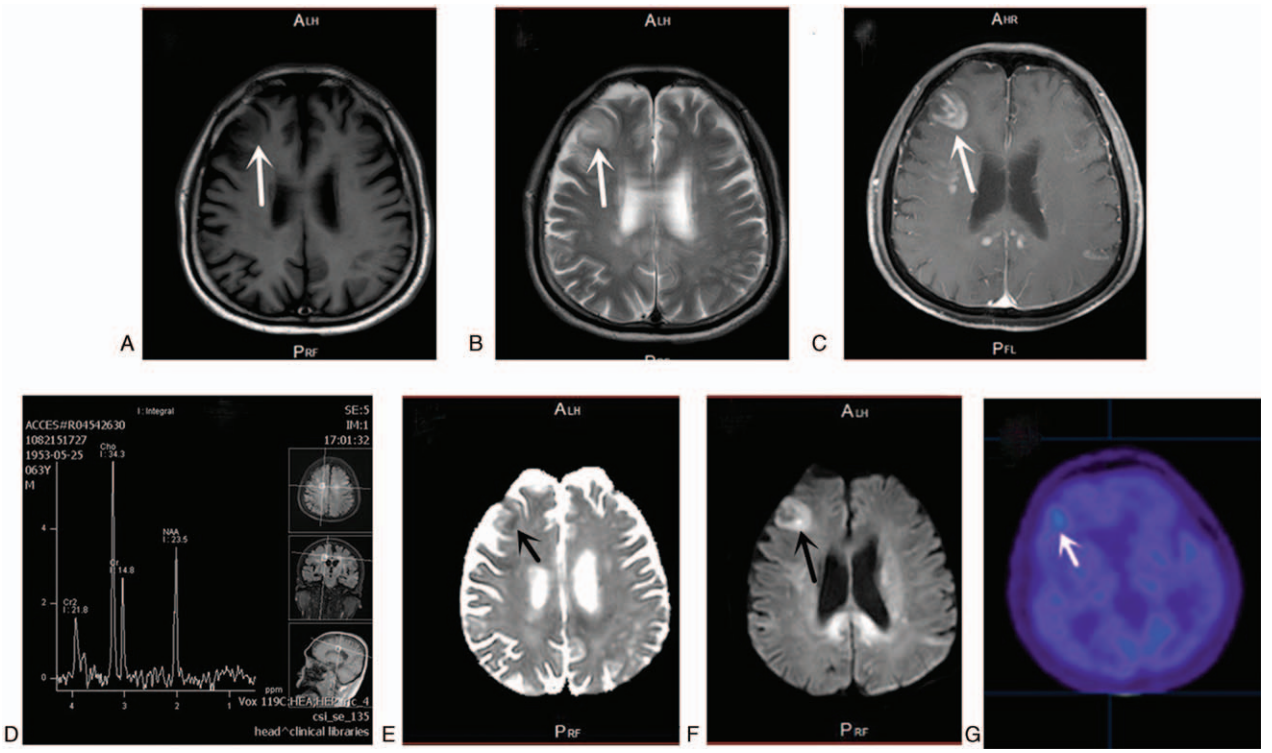

Figure 1. Imaging performance. A and B: The right frontal lobe pointed by the arrow show long T1 and T2 signal shadows. C: As pointed by the arrow, there were patchy T1 enhanced signal shadows in the right frontal lobe and around the midline. D: Cho peak increased, while NAA peak decreased. E and F: As pointed by the arrow, ADC showed low-value changes and DWI high signal changes. G: Radioactive accumulation in the right frontal lobe as pointed by the arrow. DWI = diffusion-weighted imaging, NAA = N-acetylaspartate.

spectroscopy (MRS) (Fig. 1D) showed that bilateral centrum semiovale, the right basal ganglia, and the corpus callosum were the regions of interests (ROIs). N-acetylaspartate (NAA) peak was reduced, chlorine compounds (CHO) peak was elevated slightly, choline (Cho) was positive, and the creatine (Cr)/NAA ratio ranged between 2.10 and 3.45. Positron emission tomography-computed tomography (PET-CT) (Fig. 1G) showed patchy radioactive uptake shadows in the right frontal lobe at the size of $2.4 \times 2.1\,cm^2$. The maximum value of standard uptake value (SUV) was 8.3, and the computed tomography (CT) value was 21.9 Hu. No abnormal dense shadow was observed in the residual parenchyma, and no widening and expansion were observed in the sulcus, gyrus, and cistern. Moreover, the density was normal. Cerebrospinal fluid antibody showed that CV2/CRMP5 (–), Ri (–), Yo (–), Hu (–), Amphiphysin (–), and PNMA2 (Ma2/Ta) (–). The level of blood/cerebrospinal fluid antibodies (10–18) was NMDA-R-Ab (–), GASPR2-Ab (–), AMPA1-R-Ab (–), LGI1-Ab (–), and GABAB-R-Ab (–). The disease of the patient cannot be diagnosed by the above examination results. Finally, the MRI-guided biopsy of the right frontal lobe was performed. The pathology demonstrated a round-cell tumor. Immunolabeling results demonstrated diffused large B-cell lymphoma that originated from non-germinal center cells. Immunohistochemistry obtained the following results: LCA (sporadic +), CD3 (–), CD20 (+) Bcl-2 (+), Bcl-6 (sporadic +), CD10 (–), Mum-1 (+), CD79a (+), CD34 (vessel +), GFAP (–), MGMT (–), Olig-2 (weak +), EMA (–), Ki67 (70% +), PAX-5 (+), and CyclinD1 (–). The disease condition of the patient aggravated progressively. The patient was clinically dead 1 week after the surgery, and the course of disease was about 100 days.

This study was approved by the Ethics Committee of the China-Japan Union Hospital of Jilin University. Informed written consent was obtained from the patient for publication of this case report and accompanying images.

3. Discussion

PCNSL is dominated by brain parenchyma, accounting for about 90%. The primarily involved sites are cerebral hemispheres, basal ganglia/thalamus, corpus callosum, ventricles, and cerebellum successively. Among these, single focal lesions account for about 65%, and multifocal lesions account for about 35%. Multiple primary central nervous system lymphomas (MPCNSLs) can occur at any age and are common in elderly patients.[3] Moreover, most patients have normal immune functions with non-specific clinical manifestations that are mainly associated with the involved sites. The most common symptoms are cognitive disorders, changes in consciousness, and intracranial hypertension.[4,5] In addition, manifestations of Parkinson syndrome such as trembling, tetanus, and bradykinesia are also observed.[6] In this study, the patient was 63-year-old with normal immune functions. The primary symptom was emotional indifference. Nuclear magnetic resonance observed the right frontoparietal lobe, the left parietal lobe, bilateral coronal radiata, the basal ganglia, the brain stem, and the cerebellum, which were consistent with those reported in the literature.

Increased protein content was detected by CSF examination, and immune-electrophoresis revealed monoclonal immunoglobulin. Lactate dehydrogenase or PZ macroglobulin increases, but glucose content is normal. Cytological examination of CSF showed that the number of lymphocytes often increased; however, immunohistochemistry confirmed the presence of reactive T lymphocytosis as reported.[7] Molecular biology techniques could detect the small number of tumor cells in cerebrospinal fluid. Most of the cerebrospinal fluid immunocytochemical examinations showed that B-cell markers are positive, such as CD19, CD20, CD79a, and CD79k, which are in agreement with the phenomenon that most of the tumors are non-Hodgkin large B-cell lymphoma. Recently, some studies[8–11] of the biomarkers in cerebrospinal fluid provide a new idea for diagnosing CNS lymphoma and monitoring the course of the disease. In this case, monitoring of the cerebrospinal fluid showed that the protein content was elevated, the number of lymphocytes increased, and glucose content normal, which were in line with the literature reports. However, there were no tumor cells in exfoliated cells, which might be related to the small number of specimens tested and the absence of continuous testing. In the present study, the patient underwent cerebrospinal fluid antibody-related examination, and paraneoplastic syndromes affecting the nervous system can be excluded. Limited by the testing level of our laboratory, CSF immunohistochemistry and biomarker tests were not performed.

The diverse imaging manifestations of MPCNSLs in <39% of the patients are definitely diagnosed by imaging manifestations alone. According to literature reports, MRI characteristics are as follows:

MRI scan showed that MPCNSLs lesions were mostly confined to the supratentorial site, and also involved the supratentorial and the subconjunctival sites. Moreover, the lesions usually occur in the midline region,[1,12–14] and most cases exhibit a mild space-occupying effect. MRI showed that intracranial lymphomas usually manifest as low signals on T1W1 and high signals on T2W1, while lesion boundaries are clear. A majority of the lesions on FLAIR sequence show high signals. Reports on cystic degeneration, necrosis, and bleeding in the lesions are only rarely available. Enhanced-MRI indicated that PCNSL belongs to tumors that lack blood supply. However, due to the infiltrating growth to the surroundings and destroying the adjacent blood–brain barrier, enhanced scan displays significant "nodule-like" enhancements. Moreover, some are in "bulk-like" and "fist clenching" shapes, which involve the corpus callosum and "butterfly wing-like" enhancement.[13] In this case, the MRI scan showed long T1 and T2 signal shadows in the right frontal lobe, the right hippocampus, the right cerebellar hemisphere, and the left occipital lobe. Enhanced MRI showed multiple enhancements in bilateral cerebellums and brains. Some of the enhancements were "nodule-like," "bulk-like," and "fist clenching-like" shadows. However, only the right corporis callosi splenium was involved, and no significant "butterfly wing-like" enhancement was observed.

In the MRS, it usually manifests as a significant decrease in the NAA peak in tumor parenchyma, decrease in Cr peak, increase in Cho peak, as well as, a significant increase in Lip (moving fat) and Lac (lactic acid) peaks. Moreover, the Lip peak of PCNSL was much higher than that of various types of gliomas that might be attributed to the thriving metabolism of atypical lymphocytes in PCNSL cells and accumulation of a large number of macrophages. However, the increase in the Lip peak of gliomas was due to the cystic degeneration or necrosis of tumors. PCNSL and gliomas can be differentially diagnosed using Lip peak. In this case, MRS showed that NAA peak decreases and Cho peak increases slightly, which was similar to that in literature. However, there is no significant Lip/Lac peak, it cannot be excluded, which might be caused by the coma state of the patient and reduced metabolic activity of the brain tissue.

In the diffusion-weighted imaging (DWI), there are low values in ADC and high signals in DWI sequence.[15] Gliomas and metastatic brain tumors also manifest as diffusive limitation. However, the limitation of PCNSL to water molecule diffusion is remarkable. Thus, ADC values can be used to differentiate PCNSL from gliomas and metastatic brain tumors. Recently, some studies showed that ADC value of the tumor parenchyma before treatment can predict the clinical prognosis of PCNSL. Low ADC values indicate that progression-free survival is short and overall survival rate is low.[16] The DWI results of this case were consistent with the above reports.

In perfusion weighted imaging (PWI), since the lesions did not have a significant blood supply, the low-perfusion tumor was significantly different from high-perfusion of high-grade gliomas. The cerebral blood flow was decreased, the relative cerebral blood volume decreased, and apex, as well as mean transit times, prolonged.

In susceptibility weighted imaging (SWI), since PCNSL is a vascular tumor, lesion bleeding, and infarction are rare. Moreover, relative blood volume is low and significantly lower than gliomas and metastatic brain tumors. Microvessel density is a pathological feature associated with relative blood volume that is also much lower than that of malignant gliomas in PCNSL. Therefore, SWI can be used to differentiate PCNSL from gliomas and metastatic brain tumors.

According to the PET-CT, PCNSL is one of the malignant tumors with strong glucose metabolism. 18F-FDG PET-CT imaging showed high-dense radioactive shadow that can be used in the evaluation of diffuse large B cell lymphoma diagnosis/staging/efficacy and prognosis.[17] Compared with other brain malignancies, PCNSL uptakes 18F-FDG uniformly and highly. Therefore, PCNSL can be differentiated from other brain malignancies, such as gliomas and metastatic brain tumors. Makino et al[18] suggested that the judgment accuracy of 18F-FDG PET/CT on the property of lesion was 86%, the sensitivity was 100%, and the specificity was 71.4% when the critical value of SUVmax was 12. In this case, the patchy radioactive uptake shadows can be observed in the right frontal lobe with the size about $2.4 \times 2.1\,cm^2$ and SUVmax of 8.3.

Because clinical manifestations and imaging examinations of PCNSL patients lack specificity, the vast majority of patients can be ultimately diagnosed after surgical biopsy. Since the growth of PCNSL is infiltrative, surgery cannot resect the lesions completely, and permanent functional impairment can be detected. Therefore, stereotactic biopsy is a currently preferred method to diagnose the disease, especially in patients with characteristic changes of lymphomas in imaging examination (such as distribution around the brain ventricle, multifocal lesions, necrosis without hemorrhage, and mild space-occupying effect). In addition, since some patients might also present meningeal involvement, diagnostic lumbar puncture should be performed in those suspected with PCNSL. Moreover, cerebrospinal fluid cytology and flow cytometry should be improved, which would be helpful in the early diagnosis of patients.

Studies have shown that the factors affecting the prognosis of PCNSL can be summarized as follows: age over 60 years; serum lactate dehydrogenase increased; cerebrospinal fluid protein content; the electrocorticogram of physical condition is level 2–4; the deep tissue in the brain is damaged.[19,20] Almost all of the indicators in this patient pointed to poor prognosis, and the poor directivity of the examination results eventually led to a long time for accurate diagnosis, and ultimately failed to receive timely symptomatic treatment and clinical death.

4. Conclusions

In summary, PCNSL is a primary intracranial malignancy with low incidence, a high degree of malignancy, and specificity in clinical manifestations. To facilitate early clinical treatment and improve long-term survival of patients, it is necessary to master the imaging diagnostic methods and imaging features. The comprehensive application of multiple imaging examinations, such as CT, MRI, PET/CT, and PET/MRI, as well as, cerebrospinal fluid cytology can greatly improve the diagnosis of PCNSL.

Author contributions

Conceptualization: Guangyong Chen, Jinnan Zhang.
Data curation: Meiling Xu, Xuemei Wang, Yufei Gao.
Formal analysis: Guangyong Chen, Xuemei Wang, Yufei Gao, Meiji Chang.
Methodology: Guangyong Chen, Meiling Xu, Jinnan Zhang.
Project administration: Meiling Xu, Yufei Gao, Chengyan He.
Resources: Guangyong Chen, Meiling Xu, Meiji Chang.
Software: Chengyan He, Meiji Chang.
Visualization: Meiji Chang.
Writing – original draft: Guangyong Chen.
Writing – review & editing: Guangyong Chen, Xuemei Wang, Chengyan He, Meiji Chang, Jinnan Zhang.

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