

# Primary Central Nervous System Lymphoma

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Primary central nervous system lymphoma (PCNSL) is an aggressive non-Hodgkin Lymphoma, most frequently diffuse large B-cell lymphoma in immunocompetent patients, which is confined to the central nervous system.<sup>[1]</sup> In the past two decades, its incidence has been steadily increasing. However, differential diagnosis, such as demyelinating disease, could be a challenge particularly in patients with atypical clinical symptoms and neurological imaging. Here, we described clinical presentation, imaging and pathological results of two cases of PCNSL and highlighted the importance of considering the possibility of PCNSL initially when cases were similar.

A 52-year-old immunocompetent man (case 1) presented with a 20-day history of fever and headache. Condition of the patient had no obvious improvement after anti-infection treatment. Physical examination revealed no evidence of neurological deficit other than mild rigidity of the neck. Routine blood tests and cerebrospinal fluid (CSF) examinations were normal. Serum tumor markers indicated an elevated ferritin level (0.826 mg/L). Tests for human immunodeficiency virus and treponema pallidum were negative. Electroencephalogram and serological tests for autoimmune autoantibodies were unremarkable. However, the patient developed glossolalia, gait disturbance, and transient unconsciousness at the night when admitted to our hospital. Magnetic resonance imaging (MRI) of the cerebrum revealed the hyperintensity in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images of the frontal lobe, parietal lobe, right temporal lobe, corpus callosum, and the periventricular cerebral white matter [Figure 1a]. Some areas, particularly the right splenium corporis callosi were enhanced in contrast enhancement in a T1-weighted image [Figure 1b]. Hydrogen-1 magnetic resonance spectroscopy (<sup>1</sup>H-MRS) of

lesion demonstrated an increased choline peak [Figure 1c]. Based on the patient's clinical course and brain MRI findings, "inflammatory demyelinating encephalopathy" was first considered. After treatment with intravenous dexamethasone sodium phosphate (10 mg/d for 7 days), the patient was discharged with a better health condition.

However, his condition deteriorated rapidly after the withdrawal of steroid therapy. A week after discharge, the patient developed left limb weakness progressively and could not be able to walk unaided at last. Repeated MRI examinations showed more extensive signal changes in the frontal lobes, parietal lobes, right temporal lobes, corpus callosums, basal ganglias, and brainstem, resulting in multiple patchy and strip hypointense on T1-weighted imaging, isointense T2-weighted imaging, and hyperintense FLAIR imaging [Figure 1d] with a relatively small edema. There were more extensive contrast-enhanced lesions in the right cerebellar hemisphere than the first MRI examination [Figure 1e]. Given the rapid clinicoradiological progression, the lymphoma was suspected. A stereotactic brain biopsy was performed. Pathological image [Figure 1f] and immunohistochemical staining results showed strongly positive signals for CD20 and leukocyte common antigen, weakly positive signals for CD3 and vimentin and negative signals for glial fibrillary acidic protein, isocitrate dehydrogenase-1, CD34 and cytokeratin pan, and high

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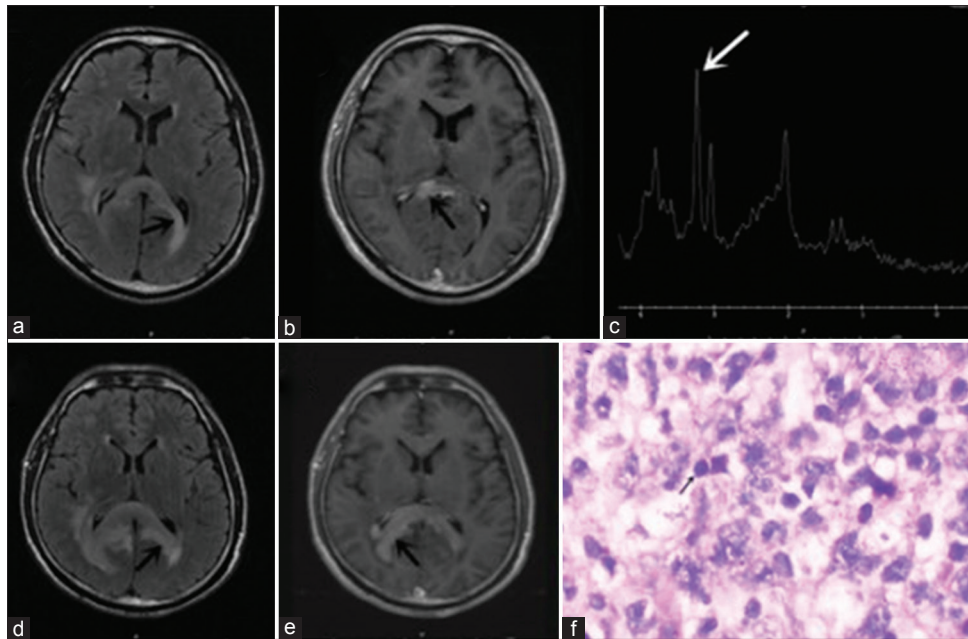
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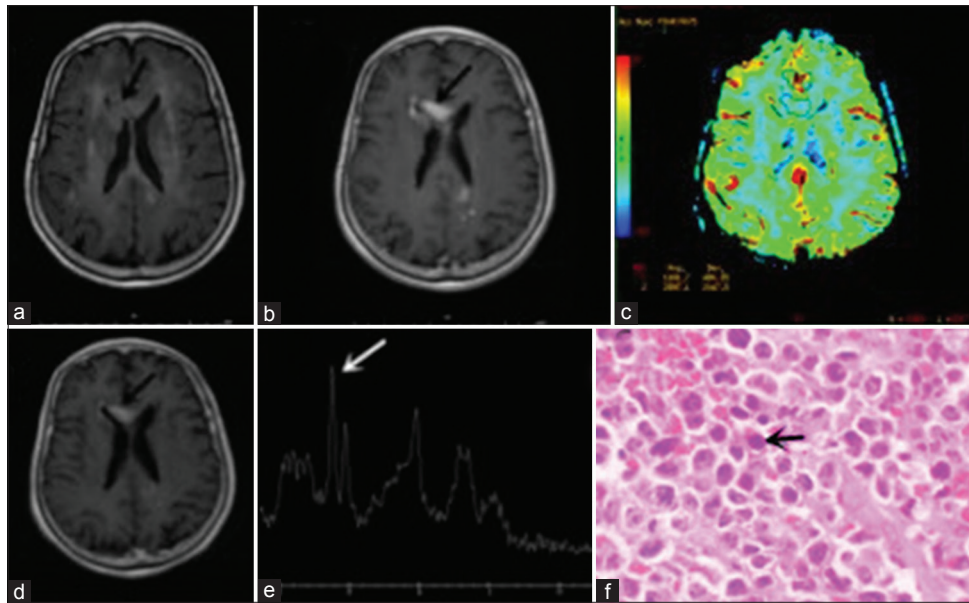
**Figure 1:** Magnetic resonance imaging examinations and pathological image of case 1. The first magnetic resonance imaging examination was carried out on March 13, 2015, fluid-attenuated inversion recovery images (a) showed hyperintensity of corpus callosum and the periventricular cerebral white matter (arrow); axial (b) contrast-enhanced image showed the signal of the right splenium corporis callosi which was enhanced; hydrogen-1 magnetic resonance spectroscopy (c) demonstrated an increased choline peak (arrow). Repeated magnetic resonance imaging examination was carried out on April 3, 2015, fluid-attenuated inversion recovery images (d) showed larger hyperintensity of corpus callosum (arrow); axial (e) contrast-enhanced image showed more extensive contrast-enhanced lesions in the right cerebellar hemisphere (arrow). Pathological image (f) (April 17, 2015) showed diffusely infiltrative tumor cells (arrow; hematoxylin-eosin staining; original magnification,  $\times 400$ ).

Ki-67 (>80%) revealed a diffuse large B-cell non-Hodgkin lymphoma. Following a bone marrow biopsy and positron emission tomography-computed tomography (PET-CT) scan, no evidence of lymphoma outside the central nervous system was found. The diagnosis of PCNSL was confirmed. Subsequently, the patient was treated with four courses of high-dose methotrexate-based chemotherapy. His condition improved gradually.

A 68-year-old immunocompetent woman (case 2) presented with dizziness, blurred vision, nausea, vomiting, and gait disturbance over 1 month, and then developed dysphagia after 2-week treatment in county hospital. A repeated diffusion weighted imaging at the local hospital revealed the larger hyperintensity of corpus callosum. Three days ago, the patient developed lower limbs weakness progressively and could not be able to walk unaided. She was admitted to the Department of Neurology of our hospital. The patient developed urinary incontinence and deteriorated progressively after admission. She had a history of touching methamidophos every summer. Neurological examination showed cognitive dysfunction and increased tendon reflex of right lower limb. The CT results of the chest and abdomen were unremarkable. CSF examination showed a protein level of 987 mg/L and elevated white blood cell ( $59 \times 10^6/L$ ). The analysis of CSF cytology revealed a moderately cellular fluid with increased lymphocytes and monocytes. Polymerase chain reaction for viruses in CSF found cytomegalovirus. MRI scan of the brain revealed slightly hyperintensity in T2-weighted or FLAIR images of corpus callosum, the

head of right caudate nucleus, cingulate gyrus, and centrum semiovale [Figure 2a]. A significantly gad-enhancing lesion was found in the corpus callosum [Figure 2b]. The lesions showed hypoperfusion in perfusion-weighted images (PWI) [Figure 2c]. Repeated MRIs performed after treating with intravenous methylprednisolone (80 mg/d for 8 days) revealed smaller enhanced lesions [Figure 2d] and an increased choline peak in  $^1H$ -MRS image of lesion [Figure 2e]. Based on those findings, demyelinating disease and lymphoma were considered. Then, a stereotactic brain biopsy was performed. Pathological image [Figure 2f] and immunohistochemical staining results were similar to case 1. Following a bone marrow biopsy and PET-CT scan, no evidence of lymphoma outside the central nervous system was found. The diagnosis of PCNSL was confirmed. Subsequently, the patient was treated with high-dose methotrexate-based chemotherapy, and then the patient's condition improved gradually.

The two cases suggest that it is significantly important to pay attention to differential diagnosis between PCNSL and demyelinating disease.<sup>[2,3]</sup> Symptoms of patients with PCNSL can be highly variable and range from generalized symptoms of increased intracranial pressure to various neurological symptoms, including cognitive dysfunction, headache, seizures, cranial nerve palsies, and other focal signs.<sup>[1,2]</sup> PCNSL is easy to be misdiagnosed as demyelinating disease during clinical assessment in the early stage, especially when it shows diffuse infiltrative lesions with atypical clinical symptoms and neurological imaging results.



**Figure 2:** Magnetic resonance imaging examinations and pathological image of case 2. The first magnetic resonance imaging examination was carried out on April 14, 2015, fluid-attenuated inversion recovery image (a) showed hyperintensity of corpus callosum, the head of right caudate nucleus and cingulate gyrus (arrows); axial contrast-enhanced image (b) on admission showed that the signal of corpus callosum was significantly enhanced; the lesion of perfusion-weighted image (c) showed hypoperfusion of the lesion. Repeated magnetic resonance imaging examination was carried out after treated with methylprednisolone for 8 days on April 23, 2015, axial (d) contrast-enhanced image revealed smaller enhanced lesions; hydrogen-1 magnetic resonance spectroscopy (e) demonstrated an increased choline peak (arrow); pathological image (f) (May 5, 2015) showed diffusely infiltrative tumor cells (arrow; hematoxylin-eosin staining; original magnification  $\times 400$ ).

For example, all findings of the patient in case 1 in the early stage, such as first complaint with fever and headache, the negative results of CSF, diffuse infiltrative leukoencephalopathy on MRIs, and the history of infection supported the diagnosis of inflammatory demyelinating encephalopathy rather than lymphoma.  $^1\text{H}$ -MRS may be helpful for discriminating PCNSL with atypical MR imaging features from tumefactive demyelinating lesions (TDLs). One study<sup>[4]</sup> found that higher choline/creation ratio ( $>2.58$ ), higher choline/N-acetyl aspartic acid ratio ( $>1.73$ ), and higher lipid-lactate peak grade suggested PCNSL rather than TDLs. An increase in lipid resonances has been reported as the specific finding for PCNSL.<sup>[4,5]</sup> However, only an increased choline peak can be seen in both cases, which is not helpful in the differential diagnosis.

PCNSL was not considered initially until rapid progression of symptoms and MRIs appeared, which delayed the time of earlier diagnosis and treatment. At the same time, the two cases could give us some enlightenments. PCNSL could be shrunk in size after treatment with methylprednisolone, so methylprednisolone may be one of the choices in the treatment of PCNSL. In addition, hypoperfusion of lesions on PWI may have some characteristics for us to distinguish the PCNSL from other tumors.

MRIs have some characteristics for PCNSL; however, it is sometimes difficult to distinguish the PCNSL from demyelinating disease, especially when lesions distribute diffusely in the early stage. The two cases emphasize the importance of considering the possibility of PCNSL

when the clinical symptoms and brain MRI findings are atypical to avoid misdiagnosis. When PCNSL is suspected, a stereotactic brain biopsy from a lesion should be performed in time. Early diagnosis and intervention for these patients may enable a more rational therapeutic approach and improve the outcomes.

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### Conflicts of interest

There are no conflicts of interest.

### REFERENCES

1. Korfel A, Schlegel U. Diagnosis and treatment of primary CNS lymphoma. *Nat Rev Neurol* 2013;9:317-27. doi: 10.1038/nrneurol.2013.83.
2. Deckert M, Brunn A, Montesinos-Rongen M, Terreni MR, Ponzoni M. Primary lymphoma of the central nervous system – A diagnostic challenge. *Hematol Oncol* 2014;32:57-67. doi: 10.1002/hon.2087.
3. Ohe Y, Hayashi T, Mishima K, Nishikawa R, Sasaki A, Matsuda H, *et al.* Central nervous system lymphoma initially diagnosed as tumefactive multiple sclerosis after brain biopsy. *Intern Med* 2013;52:483-8. doi: 10.2169/internalmedicine.52.8531.
4. Lu SS, Kim SJ, Kim HS, Choi CG, Lim YM, Kim EJ, *et al.* Utility of proton MR spectroscopy for differentiating typical and atypical primary central nervous system lymphomas from tumefactive demyelinating lesions. *AJNR Am J Neuroradiol* 2014;35:270-7. doi: 10.3174/ajnr.A3677.
5. Mora P, Majós C, Castañer S, Sánchez JJ, Gabarrós A, Muntané A, *et al.* (1) H-MRS is useful to reinforce the suspicion of primary central nervous system lymphoma prior to surgery. *Eur Radiol* 2014;24:2895-905. doi: 10.1007/s00330-014-3308-5.