



Diagnosis of Primary CNS Lymphoma

Chia-Chen Liu*, and Chun-Chieh Lin

*Department of Neurology, Tri-Service General Hospital, National Defense Medical Center,
Taipei, Taiwan, Republic of China*

In difficult-to-diagnose cerebral disease, brain biopsy is often necessary for optimal treatment. Primary central nervous system lymphoma (PCNSL) can mimic diverse neurological diseases and can remit through administration of corticosteroid alone. Corticosteroid use should be discontinued in the pre-biopsy period to improve diagnostic accuracy in suspected cases of PCNSL. We report on a 52 year-old female who presented with a recent history of introverted social behavior despite a history of normal social interactions. After a series of diagnostic evaluations, we determined that she suffered from primary CNS lymphoma.

Key words: primary CNS lymphoma, brain biopsy, corticosteroids, Methotrexate

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is an uncommon neoplasm that accounts for 1-3% of all intracranial tumors¹. It often presents as multiple lesions commonly found around the ventricles, basal nuclei, corpus callosum and leptomeninges. PCNSL has increased in incidence in the last three decades and occurs in both immunocompromised and immunocompetent patients. Unfortunately, clinical and radiological features may be misleading and delay diagnosis, especially with initial corticosteroid use. The first biopsy may therefore not be diagnostic. Here we report a case that describes the clinical characteristics of PCNSL.

CASE REPORT

A 52 year-old female presented with a recent history of introverted social behavior despite a history of normal social interactions. She recently began displaying signs of depressive mood and insomnia, as well as disorganized speech patterns and withdrawn social behavior in recent months. Medical evaluation resulted in a diagnosis of bipolar affective disorder. Symptom progression necessitated further clinical evaluation one week later. A few days

later, she was admitted to the hospital for additional evaluation.

A brain magnetic resonance image (MRI) was performed three days after admission following changes in consciousness level. The MRI (Figure 1A-D) suggested primary malignant brain tumors in the bilateral frontal lobe and left anterior temporal lobe. In addition, an acute ischemic infarction involving the bilateral occipital and medial temporal lobe was found (Figure 1E-F). Corticosteroid treatment with rinderon (4mg iv q6h) was initiated. A stereostatic brain tumor biopsy was performed seven days after admission, and the pathological report suggested a reactive or inflammatory lesion rather than a neoplastic change (Figure 2A). The clinical presentation transiently improved with steroid therapy. An additional MRI was performed to provide diagnostic certainty. The MRI suggested that the two lesions regressed in size. It also revealed new, growing lesions in the bilateral optic pathways. Possible differential diagnoses included multiple sclerosis, neoplasms, infections, and acute disseminated encephalomyelitis (ADEM).

Four weeks after admission, disturbances in consciousness developed. An ensuing brain computed axial tomography (CT) scan showed increased cerebral edema, and disease progression was considered. Progressive psychological disturbances developed despite several mini-pulse steroid therapies, and an additional brain CT scan indicated additional peri-focal edema. Eleven weeks after admission, a brain MRI showed interval deterioration with increased size in the corpus callosum lesions, and two other small enhancing tumors in the right temporal region and right thalamus. At this point, a primary malignant brain tumor was suspected. Twelve weeks after admission, craniotomy

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*Corresponding Author Chia-Chen Liu, Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, No. 325, Sec.2, Cheng-Gong Rd, Taipei 114, Taiwan, Republic of China. Tel: +886-968268289; Fax: +886-8792-7174; Email: bethy670@yahoo.com.tw

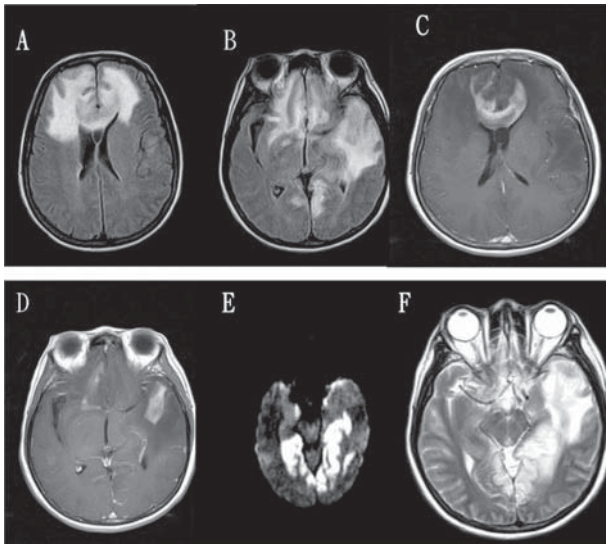


Fig. 1 Magnetic resonance imaging (MRI) of brain of patient. T2-FLAIR axial (A-B) and contrast-enhanced T1-weighted images (C-D) showed severe, diffuse white matter lesions over the bilateral frontal lobes crossing the genu of the corpus callosum and left anterior temporal lobe. Acute ischemic infarction involving the bilateral occipital and medial temporal lobes on Diffusion-weighted MRI (E) and T2-weighted (F) images.

with removal of brain tumor was performed. The pathological report showed diffuse large B cell lymphoma (Figure 2B).

Intra-thecal combination chemotherapy with Methotrexate (MTX), Antrex, and corticosteroids were prescribed for primary CNS lymphoma. The clinical condition progressively worsened, and the patient subsequently died one month after surgery.

DISCUSSION

Immunocompetent patients with PCNSL present with a median age of 53 to 57 years, with female-to-male ratio of 1.2-1.7:1². High — grade non-Hodgkin's lymphomas account for <1% of all brain tumors³. In immunocompetent patients, they are almost exclusively of the B-cell type. Mortality is high, and recurrence is common even after high-dose chemoradiotherapy.

PCNSL produces a broad range of symptoms. It can cause general symptoms and signs such as focal neurological deficits or increased intracranial pressure. Symptoms involving increased intracranial pressure and personality changes are most common. The most frequent single symptom at the time of admission is behavior change,

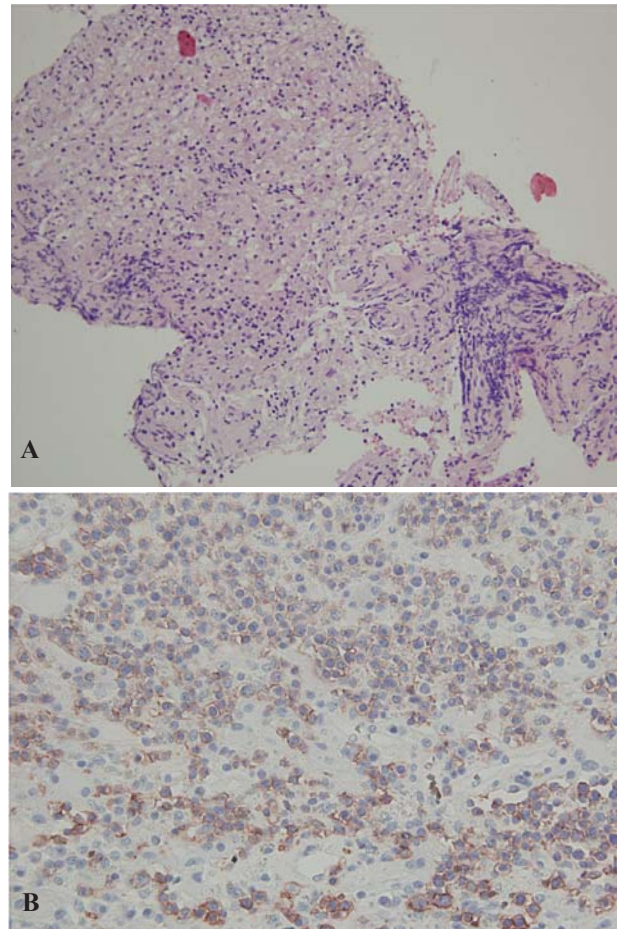


Fig. 2 Cell stain of brain tumor biopsy. (A) Inflammation cells were noted. (B) Positive CD20 stain for B cells.

which occurs in about 24-37% of patients⁴. Sometimes, behavioral changes can be the only symptoms, and these can persist for several months until the diagnosis is made. Patients with PCNSL often present with neurological symptoms rather than with a systemic syndrome, such as body weight loss or fever. Because PCNSL may involve the brain, cerebrospinal fluid (CSF) and eyes, diagnostic evaluation should include assessment of all of these regions as well as screening for possible occult systemic disease. Hemiparesis and ataxia are the most frequent focal neurological signs, with seizures, cranial palsies and ocular disease less common. Due to its frequent periventricular location, personality change may be the only symptom of PCNSL for a time. Since paraneoplastic syndromes may clinically present as acute psychoses, such as late-onset schizophreniform disorders with atypical presentation, brain imaging for possible tumor presentation should be performed.

A combination of neurological signs and symptoms, neuroimaging findings and steroid sensitivity are not sufficient to make a conclusive diagnosis of PCNSL. In immunodeficient patients, the time to onset of symptoms is short, a median of two months, but can be considerably longer in patients with slowly developing personality changes or fluctuating symptoms due to spontaneous or steroid-induced remission of sentinel lesions. In PCNSL, administration of corticosteroids may cause prolonged remission of clinical and radiographic signs and symptoms⁵, but remission may occur spontaneously^{6,7}. Relapsing, remitting lesions may disappear for as long as several months to a year or more. Then again, symptoms may recur despite multiple courses of high dose corticosteroids, as in our case.

Several case reports have reported that PCNSL can be preceded by demyelinating pseudotumoral brain lesions⁸⁻¹⁰. The “sentinel” demyelinating lesions recede spontaneously or with corticosteroids and are typically followed by development of PCNSL within 6-12 months. While most represent another episode of steroid responsive demyelination, a small number, as in this case, are malignant. As with multiple sclerosis (MS), PCNSL and glioma, the lesions were hypo-intense on T1-weighted MRI sequence, and hyper-intense on T2-weighted MRI sequence and contrast enhancement¹¹. One study found that dynamic susceptibility contrast-enhanced perfusion magnetic resonance imaging (DSC, perfusion MRI) may help differentiate PCNSL from high-grade gliomas based on differences in vascularity and contrast agent leakage¹². The vasogenic edema associated with MS is reported to be less extensive compared with high-grade tumors. Edema surrounding PCNSL lesions is also usually less marked than in other malignant CNS tumors. If multiple lesions are distributed throughout the periventricular white matter, MS may be the more likely condition. MRI may be used to monitor disease progression and serial MRIs performed over time without obvious progression will more likely suggest MS. No specific imaging method can differentiate aggressive MS from PCNSL, and biopsy may be required.

Resection does not increase survival and may cause functional deficits. If the first biopsy is inconclusive, repeat biopsy is often needed. If images suggest CNS lymphoma and corticosteroids have induced complete or partial remission (residual lesion <1cm), then a definitive diagnosis can be made using stereotactic biopsy¹³.

About 98% of PCNSLs are B-cell non-Hodgkin's lymphomas. The tumor cells invariably express B-cell antigens, such as CD20, whereas T-cell antigens are usually restricted to small reactive lymphomas. CD20 is an

unglycosylated transmembrane protein involved in cell activation and growth regulation of B-lymphocytes. Expressed specifically on B-cells, it is expressed by most human B-cell lymphomas and leukemias. CD3 is closely associated with the T-cell receptor and is reported to be expressed only on the surface of mature T-cells and thymocytes. The staining pattern of CD3 in PCNSL was granular and cytoplasmic rather than membranous, as would be expected in T-cells. At first, a stereotactic brain biopsy showed no evidence of gross, primary brain tumor. CD3 stain indicated T-cell involvement in brain parenchyma. Therefore, inflammatory disease could not be ruled out. The craniotomy brain biopsy in this case showed diffuse B-cells around the blood vessels with infiltration to brain parenchyma. Silver staining for reticulin demonstrated an intricate reticulin network surrounding the tumor cells. Immunohistochemical staining using monoclonal antibodies against the B-cell-associated antigen CD20 showed a large proportion of large lymphoid cells (Figure 2B). An autopsy study of 10 patients who died from PCNSL found evidence for the B-cell CD20-positive phenotype in all ten cases¹⁴. We diagnosed this tumor as diffuse large B-cell lymphoma.

Our patient also presented with evidence of an acute ischemic infarction over the bilateral occipital and medial temporal lobes. In our case, neoplasms compressing the bilateral posterior cerebral arteries may have caused the infarction. A 2008 report showed that stroke risk factors in patients with brain neoplasms are comparable to those in the general stroke population¹⁵. The most common brain tumors were gliomas (60%), meningiomas (25%) and primary CNS lymphoma (6%). Stroke was the initial clinical diagnosis in only 43% of cases.

Chemotherapy with or without radiotherapy is the main treatment for PCNSL. For immunocompetent patients with newly diagnosed PCNSL, treatment includes corticosteroids, radiation therapy and chemotherapy. Up to 40% of patients with PCNSL will have a significant initial response to corticosteroids alone. Because of their lymphotoxic properties and the subsequent difficulties in establishing a definitive histopathologic diagnosis, corticosteroids should not be administered before tumor biopsy, if possible¹⁶.

In summary, the clinical manifestations of PCNSL are variable, and early diagnosis and treatment are difficult. Corticosteroids often obscure the diagnosis. PCNSL should be considered a possibility when space-occupying lesions exist in previously-confirmed demyelination disease. The most frequent single symptom at the time of admission in patients with PCNS is behavior change. Careful analysis of

the patient is necessary in these cases to make a diagnosis. Patients with primary brain tumors are also at increased risk for ischemic infarction.

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