Central Nervous System Lymphoma Initially Diagnosed as Tumefactive Multiple Sclerosis after Brain Biopsy

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Abstract

A 72-year-old man was admitted with left homonymous hemianopsia and hemiparesis. Magnetic resonance imaging revealed a heterogeneously enhanced lesion in the right parietal lobe. A brain biopsy showed acute demyelination without malignancy, which led to a diagnosis of tumefactive multiple sclerosis (MS). The patient received corticosteroid therapy and experienced clinical and radiological improvement. Six months later, new lesions appeared, and a second biopsy revealed proliferation of dysplastic lymphocytes. This led to a revised diagnosis of primary central nervous system lymphoma (PCNSL). Because PCNSL mimics MS both clinically and radiologically, PCNSL is difficult to diagnose. Performing repeated brain biopsies may therefore be required when PCNSL is strongly suspected.

Key words: brain biopsy, primary central nervous system lymphoma, tumefactive multiple sclerosis


Introduction

Primary central nervous system lymphomas (PCNSLs) are known as ghost tumors (1) or sentinel lesions (2) because brain biopsies may fail to detect tumor cells and show only demyelination. Both PCNSL and demyelinating diseases respond to corticosteroid therapy or improve spontaneously, which makes it difficult to differentiate these disorders (1-5). However, making a definitive diagnosis is necessary because the treatments and long-term outcomes of these disorders are very different. The present patient was first diagnosed with tumefactive multiple sclerosis (MS) on the basis of the initial brain biopsy findings, which showed only acute demyelination. A second brain biopsy and positron emission tomography (PET) performed six months later led to the revised diagnosis of diffuse large B-cell lymphoma. We herein review the similar pathological findings of these two disorders and suggest that brain biopsies should not be considered the absolute method to diagnose brain tumors.

Case Report

A 72-year-old man had noticed loss of his left visual hemifield 20 days previously and was subsequently admitted to our hospital. He had a history of testicular lymphoma that had gone into remission 15 years earlier. A neurological examination revealed left hemianopsia and slight weakness in the left upper and lower extremities. The initial laboratory data revealed slightly elevated level of soluble interleukin-2 receptor (sIL-2R) of 202 U/mL, while the levels of other tumor markers were within the normal ranges. Cerebrospinal fluid (CSF) testing revealed a cell count of 69/μL (lymphocytes 57/μL, polymorphonuclear cells 12/μL), a protein concentration of 71 mg/dL and myelin basic protein (MBP) of 40 pg/mL. The glucose was normal, and no oligoclonal...
Fluid-attenuated inversion recovery (FLAIR) sequence magnetic resonance imaging (MRI) revealed a 3×2-cm high-intensity lesion in the patient's right parieto-occipital area (Fig. 1a, 1b). Postcontrast T1-weighted MRI showed a heterogeneously enhanced lesion in the right parietal lobe with marked edema (Fig. 1c).

18F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) revealed glucose hypometabolism in the right parieto-occipital lobes (Fig. 2a), and 11C-methionine-PET (MET-PET) (Fig. 2b) showed a focal area of increased uptake in the parietal lesion that corresponded to the lesion revealed on postcontrast MRI. PET showed no abnormalities in any organs other than the brain. Neoplasms such as PCNSLs were suspected, and a brain tissue biopsy was performed. The histological examination showed that the primary lesion was located in the subcortical white matter. Klüver-Barrera staining revealed severe myelin loss (Fig. 3a). Foamy macrophages and lymphocytes had infiltrated the subcortical white matter (Fig. 3b). The lymphocytes were especially numerous around blood vessels (Fig. 3c). Reactive astrocytes, including multinucleated cells (Creutzfeldt cells), were sparsely distributed (arrow, Fig. 3d). An immunohistochemical analysis revealed that the lymphocytes were positive for CD3 (Fig. 3e) and CD20 (Fig. 3f), which are markers of T- and B-cells, respectively. The CD3-positive cells were more numerous. There was no evidence of neoplasia or infection. The histopathological findings suggested the presence of acute demyelination, which led to a diagnosis of tumefactive MS. The patient received intravenous methylprednisolone at a dose of 1 g/day for three days. His symptoms disappeared, and the MRI findings had improved dramatically when the scans were re-
Repeated one month later (Fig. 1d, 1e, 1f).

Six months later, the patient was re-admitted to our hospital for attention disturbance and mental deterioration. His mini mental state examination score was 18/30, and new symptoms of preservation and disactivity indicated the presence of a frontal lobe lesion. The laboratory data revealed an elevated level of sIL-2R of 628 U/mL. CSF testing revealed a cell count of 54/μL (lymphocyte 54/μL, polymorphonuclear cells 0/μL), a protein concentration of 63 mg/dL and MBP of 102 pg/mL. No OB was detected. The result of cytology was class I. Brain MRI showed a new lesion in the left frontal lobe and enlarged lesions in the right parieto-occipital area (Fig. 1g, 1h, 1i), both of which lacked contrast enhancement. FDG-PET revealed increased glucose metabolism in the right parietal lobe, right insula, and left frontal lobe (Fig. 2c, 2e). MET-PET (Fig. 2d, 2f) showed focal areas of increased uptake in the right parietal lobe, right insula, and left frontal lobe. The findings of FDG- and MET-PET were different from the initial results, which strongly suggested the presence of a malignant tumor. Al-

Figure 2. a: ¹⁸F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) image obtained four days after admission shows evident glucose hypometabolism in the right parieto-occipital area. b: ¹¹C-methionine PET (MET-PET) image obtained one day after admission shows focally increased uptake (SUV \textsubscript{max}, 2.8) in the right parietal lobe. c, e: FDG-PET images reveal hypermetabolism in the right parietal lobe, right insula, and left frontal lobe seven days after admission. d, f: MET-PET images reveal a focal area of increased uptake in the right parietal lobe, right insula, and the left frontal lobe eight days after admission.
though methylprednisolone was again administered, it was ineffective, and a second biopsy of the left frontal lobe was performed. Hematoxylin and eosin (HE) staining revealed marked proliferation of dysplastic lymphocytes (Fig. 4a). An immunohistochemical study showed numerous CD20-positive cells, but no CD3-positive cells, which thus suggested lymphoma of B-cell origin (Fig. 4b, 4c). Most of the dysplastic cells were immunoreactive for MUM1, which indicated a poor prognosis (Fig. 4d). The histopathological findings of the second biopsy led to a diagnosis of PCNSL of the diffuse large B-cell type.

**Discussion**

In the present case, only the brain was affected, and we diagnosed the patient with PCNSL, despite his medical history of testicular lymphoma 15 years previously. PCNSL is an uncommon malignancy that accounts for just 0.85% to 2.0% of all primary brain tumors (6, 7). PCNSL is difficult to distinguish from MS because histological examinations sometimes show similar results. Krumholz et al. (8) reported that the central nervous system produces B-cell activating factor, which belongs to the tumor necrosis factor family and supports B-cell survival, both in PCNSL and in inflammatory diseases such as MS. This means that PCNSL and MS also share similarities at the molecular level.

PCNSL with pathological findings limited to inflammatory demyelination (3, 4) has been previously reported. Seven cases required a second brain biopsy to make an ultimate diagnosis of PCNSL (2-5, 9-11), and two cases were diagnosed as PCNSL only after autopsy (1, 12). All cases showed inflammatory demyelination only on the first brain biopsy. Kuroda et al. (4) reported a case of PCNSL with infiltrated lymphoid cells composed both of B- and T-cells. In that report, a histological study did not suggest clonal expansion of dysplastic cells. An analysis of the J lesion genes of Ig heavy and light chains of PCNS-infiltrating lymphoid cells revealed clonally rearranged bands, thus providing the first definite evidence of PCNSL. Similarly, our patient presented with lymphocytes that were immunohistochemically positive for both CD3 and CD20. This finding indicated that the infiltrative cells included both B- and T-cells. The first brain biopsy suggested a diagnosis of MS rather than PCNSL.

Previous studies of PCNSL using FDG-PET show remarkably increased glucose uptake (5, 13-15). In the present patient, glucose hypometabolism on the first brain PET showed a diagnosis of tumefactive MS rather than PCNSL. No or decreased FDG uptake has been reported in low-grade tumors; however, such results in patients with PCNSL are unusual (15-17). In our case, ambiguous findings on the first FDG-PET contributed to the misdiagnosis of MS. The second FDG-PET showed increased uptake. Why the glucose metabolism changed is not clear; however such changes have been previously reported in patients with PCNSL (5).

MET-PET shows increased uptake in tumors, including lymphomas. This is due to increased membrane transport of amino acids, disruption of the blood-brain barrier (BBB),
and accelerated protein synthesis (18). The acute phase of MS is accompanied by BBB disruption (19, 20), and MET-PET showed increased uptake in the present case. Similar to the histological study, MET-PET failed to precisely distinguish PCNSL from MS, which complicated the diagnosis in the present case.

PCNSL is sometimes indistinguishable from MS due to clinical, radiological and histological similarities. Even after making a pathological diagnosis of demyelinating disease, the possibility of PCNSL should be considered and careful follow-up should be provided. In some cases, PET should be repeated, and performing a second brain biopsy may therefore be necessary.

The authors state that they have no Conflict of Interest (COI).

References

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