□ CASE REPORT □

A Case of Primary Central Nervous System Lymphoma Presenting Diffuse Infiltrative Leukoencephalopathy

Tatsuya Yamamoto¹, Kazuho Kojima¹, Katsura Koibuchi¹, Shoichi Ito¹, Yoshinori Higuchi², Yasuo Iwadate², Takashi Oide³ and Satoshi Kuwabara¹

Abstract

A 58-year-old immunocompetent man gradually developed loss of appetite, cognitive decline, gait disturbances, and personality changes over 4 months. Brain magnetic resonance imaging (MRI) revealed bilateral diffuse leukoencephalopathy without mass formation on admission. His condition progressively deteriorated, and we treated him with intravenous high-dose steroids. His symptoms improved rapidly, but exacerbated when therapy was withdrawn. A brain biopsy was performed, and the diagnosis of primary central nervous system lymphoma (PCNSL) was confirmed. He was successfully treated with high-dose methotrexate therapy. Although it is difficult to diagnose PCNSL without mass formation in the early stages, steroid responsiveness is important and brain biopsy is essential for the correct diagnosis of PCNSL.

Key words: leukoencephalopathy, primary central nervous system lymphoma (PCNSL)

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Introduction

The etiology of the leukoencephalopathy on brain computed tomography or magnetic resonance imaging (MRI) includes various neurological disorders such as cerebrovascular diseases, demyelinating diseases, metabolic diseases, intoxication, and infectious diseases. Although tumors rarely manifest as part of the clinical course of leukoencephalopathy, it is usually difficult to diagnose correctly when they do not form solitary lesions (1). Primary central nervous system lymphoma (PCNSL) is a rare central nervous system tumor, accounting for approximately 4% of all primary central nervous system tumors (2). In immunocompetent patients, PCNSL forms solitary or multiple mass lesions with homogeneous contrast enhancement on brain MRI. However, cases of PCNSL without mass or contrast-enhanced lesions are rarely reported (3).

Here, we report the case of pathologically proven PCNSL without mass formation on admission.

Case Report

A 58-year-old immunocompetent man gradually developed loss of appetite, cognitive decline, gait disturbances, and personality changes over 4 months. He eventually became apathetic and consulted a psychiatrist. He was initially diagnosed with depression and was treated with antidepressant drugs. However, his neurological symptoms gradually worsened, and because a brain MRI revealed bilateral diffuse leukoencephalopathy, he was referred to our neurology clinic 6 months after the onset of symptoms. On examination, he was moderately drowsy and could obey only simple commands. Mini-Mental State Examination indicated severe dementia (score, 11/30). Neurological examination showed a weak voice, mild to moderate rigidity in the neck and extremities, and moderate bradykinesia, which appeared to be parkinsonian in nature. Plain brain MRI on admission showed diffuse, bilateral high signal intensities in the brain stem, basal ganglia, and white matter without mass formation (Fig. 1a). Based on the patient's clinical course and brain MRI findings, his differential diagnosis included hy-

¹Department of Neurology, Graduate School of Medicine, Chiba University, Japan, ²Department of Neurosurgery, Graduate School of Medicine, Chiba University, Japan and ³Department of Diagnostic Pathology, Graduate School of Medicine, Chiba University, Japan

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Correspondence to Dr. Tatsuya Yamamoto, tatsuya-yamamoto@mbc.nifty.com

Figure 1. Temporal changes observed on brain MRI scans. (a) T2-weighted image on admission. Diffuse high signal intensity areas were observed in the bilateral basal ganglia and white matter. (b) Contrast-enhanced image taken 2 months after admission. The right middle cerebellar peduncle was slightly enhanced. (c) Contrast-enhanced image taken 4 months after admission. The enhanced lesion in the right middle cerebellar peduncle was markedly extended to the right pons and right cerebellar hemisphere. The fourth ventricle was significantly compressed. (d) Contrast-enhanced image taken 2 months after the initiation of high-dose methotrexate therapy. The enhanced lesion in the right middle cerebellar peduncle was dramatically reduced.

pertensive encephalopathy, infection, demyelinating disease and autoimmune encephalitis (CNS lupus or Hashimoto encephalopathy). However, hypertensive encephalopathies appeared to be unlikely because of his medical history. Routine blood tests were normal, and his serum and cerebrospinal fluid (CSF) were negative for anti-virus antibodies. Serum lactate dehydrogenase (LDH) was 147 IU/L. Moreover, testing for HIV was negative, and serological tests for autoimmune autoantibodies including antinuclear antibody (ANA), anti-ds-DNA antibody, anti-thyroid peroxidase (TPO) and anti-cryoglobulin antibody were unremarkable. CSF examination indicated mild pleocytosis (25 monocytes/ 3 mm^3) and an elevated protein level (76 mg/dl); CSF cytology was negative. CSF was not cultured because the patient did not show any signs of bacterial or fungal infections of the central nervous system (CNS).

His condition deteriorated progressively after admission. Although the diagnosis was not confirmed, mild pleocytosis in CSF suggested mild inflammatory responses in CNS. Since infectious diseases seemed unlikely, autoimmune me-

diated inflammations were considered for the etiology of pleocytosis in CSF. The brain tumor including lymphoma was not considered for the differential diagnosis due to the lack of mass formation. The patient was treated with intravenous methyl prednisolone (1 g/day for 5 days) a month after admission aimed at suppressing inflammation and to confirm the efficacy of steroid therapy. His cognitive and motor functions improved dramatically soon after the initiation of therapy. However, his condition deteriorated rapidly immediately after the withdrawal of high-dose steroid therapy. Repeated MRIs performed after the two courses of intravenous high-dose steroid therapy (i.e., 2 months after admission) revealed slight contrast-enhanced lesions in the right middle cerebellar peduncle, in addition to diffuse high signal intensities in the bilateral white matter (Fig. 1b). Although he was treated with intravenous high-dose steroids three times, clinical improvement was transient and deteriorated progressively. The transient steroid effectiveness was considered to be atypical as inflammatory diseases. The diffuse encephalopathy with contrast-enhanced lesions sug-

Figure 2. Microscopic findings. (a) Hematoxylin and Eosin staining revealing diffusely infiltrative tumor cells in the white matter. (b) The large atypical cells (arrow) were proliferated in the perivascular lesions. (c) Some of the tumor cells were immunopositive for the B cell marker CD 20.

gested the brain tumor such as glioma or malignant lymphoma in addition to the inflammatory diseases as the differential diagnosis of this case. The serum interleukine-2 receptor (sIL2-R) measured after the two courses of intravenous high-dose steroid therapy was 194 U/mL (145-519 U/mL). sIL2-R was not measured before the steroid therapy.

A stereotactic brain biopsy was performed after the three courses of intravenous high-dose steroid therapy to confirm the diagnosis. The biopsy was performed in the deep white matter in the vicinity of the anterior horn of lateral ventricle, where diffuse high intensity lesions were detected on a T2-weighted image without contrast enhancement. Pathological results indicated atypical lymphocytes positive for the leukocyte common antigen (LCA), CD20, and negative for CD3 and the glial fibrillary acid protein (GFAP). Although these pathological findings were not sufficient to diagnose as diffuse infiltrative B cell lymphoma due to the extremely sparse parenchymal and perivascular infiltration of B cell, the negative findings of inflammation, demyelinating diseases, vasculitis, brain tumor or other immunological central nervous system disease with predominant T cell infiltration, and clinical aspect of transient steroid effectiveness strongly suggest diffuse infiltrating diffuse infiltrative B cell lymphoma (Fig. 2a-c). Diagnostic difficulty includes the timing and the site of biopsy. Since the infiltrating cells are very sparse, Ki-67 index was very low. He went into a coma 20 days after brain biopsy was performed. Brain MRI eventu-

ally showed extensive contrast-enhanced mass lesions with edema in the right cerebellar hemisphere and middle peduncle (Fig. 1c). Subsequently, the patient was treated with three courses of intravenous high-dose methotrexate (4,300 mg/body) therapy. His cognitive and motor functions improved gradually, and the contrast-enhanced lesions were dramatically reduced (Fig. 1d). The patient was transferred to another hospital 9 months after admission.

Discussion

Because the differential diagnosis of leukoencephalopathy includes various neurological etiologies, it is usually difficult to diagnose PCNSL in the early stage especially when PCNSL shows diffuse infiltrative leukoencephalopathy without mass lesion formation (1). In the present case, the correct diagnosis was confirmed a year after the onset of symptoms. One of the reasons for the delay in the correct diagnosis of PCNSL may be that the clinical symptoms and brain MRI findings are nonspecific and indistinguishable from other leukoencephalopathies in the early stage (4). Since the present case showed progressive dementia, mild pleocytosis in CSF and infectious diseases seemed unlikely according to the laboratory data, we initially considered autoimmune-mediated encephalitis, such as CNS lupus or Hashimoto encephalopathy as the diagnosis of this case. Although it is known that lymphoma and glioma rarely show infiltrative

leukoencephalopathy and therefore should be considered in the differential diagnosis, we did not have sufficient evidence to perform brain biopsy before steroid therapy. We performed high dose steroid therapy initially aimed at suppressing inflammation, which might be the cause of progressive dementia and leukoencephalopathy. However, the steroid effectiveness was transient, which was atypical as inflammatory diseases, and contrast-enhancement lesions were detected even after steroid therapy, we consequently considered brain tumor as the differential diagnosis and performed brain biopsy. Although the timing of brain biopsy in this case was delayed and ideally, brain biopsy should be performed before steroid therapy, brain biopsy is invasive examination and the indication should also be evaluated carefully.

It has been reported that some patients with PCNSL have presented as diffuse symmetrical leukoencephalopathy with mild or no contrast enhancement on brain MRI known as lymphomatosis cerebri (LC) (1). In some cases with LC, the tumor is usually not considered as the initial differential diagnosis and cannot be treated appropriately, at least in the early stages. Although some patients with LC show contrast-enhanced mass lesions typical of PCNSL in the later stages, many patients with LC are not treated successfully (5, 6). The present case is similar to the cases with LC in that the confirmation of the diagnosis and the therapy was delayed. It is very difficult to determine when to perform the brain

biopsy in patients with PCNSL lacking obvious mass formation. Although the timing of brain biopsy might vary case by case, what is important is to add PCNSL in the differential diagnosis of progressive dementia with leukoencephalopathy.

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

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