Interleukin 10 Level in the Cerebrospinal Fluid as a Possible Biomarker for Lymphomatosis Cerebri

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Abstract

A 71-year-old immunocompetent man developed cognitive decline and gait disturbance. Brain magnetic resonance imaging (MRI) revealed bilateral diffuse leukoencephalopathy without a mass lesion. An analysis of the cerebrospinal fluid (CSF) showed elevated levels of interleukin (IL)-10. The condition of the patient progressively deteriorated, and intravenous high-dose steroids proved ineffective. Detection of non-destructive, diffusely infiltrating, large B-cell lymphoma in biopsy and autopsy specimens led to a diagnosis of lymphomatosis cerebri (LC). On serial MRI, the basal ganglia and white matter lesions increased in parallel with the levels of IL-10. These findings suggest that the IL-10 level in the CSF may represent a potentially useful biomarker for the early diagnosis and monitoring of the disease progression in LC.

Key words: lymphomatosis cerebri, primary central nervous system lymphoma, interleukin 10, leukoencephalopathy, autopsy

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Introduction

Primary central nervous system lymphoma (PCNSL) accounts for 3-5% of primary brain tumors, and most often presents as a space-occupying mass lesion in the brain (1). Lymphomatosis cerebri (LC), an atypical rare form of PCNSL, presents as a diffuse infiltration without the formation of a mass lesion (2). Its appearance on brain MRI is characterized by diffuse leukoencephalopathy, making LC difficult to distinguish from white matter disorders such as infection, inflammation and vascular and toxic diseases (3-7).

The interleukin (IL)-10 levels in cerebrospinal fluid (CSF) are used to distinguish typical PCNSLs from other brain tumors that show similar neuroradiological findings (8). In patients with intracranial tumors, the levels of IL-10 in the CSF have been found to be significantly higher in those with PCNSLs than in those with other brain tumors (9). However, the utility of the IL-10 levels in CSF for identifying LC has not been clarified.

In this report, a longitudinal analysis revealed that the levels of IL-10 in the CSF increased in parallel with the progression of LC, and we therefore propose that the levels of IL-10 in the CSF may provide a useful biomarker for the early diagnosis and for determining the disease severity of LC.

Case Report

A 71-year-old immunocompetent man developed increasing cognitive decline and gait disturbance over the course of two days before admission to the previous hospital. He was initially diagnosed with cerebral infarction due to the presence of high-intensity lesions in the basal ganglia and corpus callosum on diffusion-weighted imaging (DWI). How-
However, his neurological symptoms gradually deteriorated, and he was transferred to our hospital one month later.

On admission, the patient was bedridden, moderately drowsy and only responsive to simple commands. A neurological examination showed a weak voice, moderate bradykinesia and cerebellar ataxia in the left upper limb and trunk. The first MRI study after admission showed asymmetrical diffuse white matter hyperintensities in bilateral cerebral hemispheres, including the corpus callosum and basal ganglia (Fig. 1A-C). Subtle gadolinium enhancement was detected in the left basal ganglia and corpus callosum (Fig. 1D, E). Routine blood testing showed slight leukocytosis and slight elevation of the C-reactive protein level (0.33 mg/dL). Further serum examinations, including tumor markers, collagen vascular profiles and human immunodeficiency virus, JC virus and anti-aquaporin-4 antibody were all negative. The plasma soluble IL-2 receptor (sIL-2R) level was 221.5 U/mL (normal, 145-518 U/mL). A CSF analysis showed a normal cell count (2/μL) and a protein level of 45 mg/dL (normal, 30-45 mg/dL). The level of sIL-2R in the CSF was normal at 5.4 U/mL (normal, <85 U/mL). However, the IL-10 level in the CSF was markedly high, at 168 pg/mL (normal, <5 pg/mL). Moreover, the levels of β2-microglobulin in the CSF were high, at 2,383 ng/mL (normal, <1,240 ng/mL).

The CSF cytology yielded negative results for malignant cells. Neither viral antibodies nor bacteria were found in the CSF. Whole-body enhanced computed tomography showed no malignancy. On whole-body fluorodeoxyglucose (FDG)-positron emission tomography (PET), no abnormal FDG uptake was observed in the trunk or extremities. Brain FDG-PET showed abnormal FDG uptake in the deep white matter, including the corpus callosum (Fig. 1F).

The patient developed akinetic mutism over the course of one month after admission to our hospital. Repeated MRI studies showed progressively enlarging lesions in the bilateral basal ganglia and white matter (Fig. 2A-C). High-dose steroids were tried from day 22 (intravenous methylprednisolone, 1 g/day for three days), but this treatment was ineffective. To achieve a definite diagnosis, a stereotactic biopsy of the left parietal lobe was performed on day 38.

The pathological examination revealed atypical lymphocytes with irregularly-shaped nuclei diffusely scattered within the white matter. These atypical cells did not form a mass or exhibit perivascular concentric accumulation. Immunohistochemically, the atypical cells were positive for CD20,
CD5 and CD79a, a B-cell marker. In contrast, the cells were negative for CD3, CD10, cyclin D1 and glial fibrillary acid protein (GFAP). Negative findings were observed for inflammation, demyelination and vasculitis. As tumor cells were scattered throughout the white matter without mass formation, a pathological diagnosis of LC was made.

Brain MRI eventually revealed extensive contrast-enhancing lesions with edema in the bilateral hemispheres and brainstem. The IL-10 level in the CSF increased in parallel with the enlargement of the contrast-enhanced lesions (Fig. 2D). The patient finally progressed to a vegetative state and died on hospital day 78 due to cerebral herniation.

A postmortem examination showed diffuse infiltration of atypical large cells into the cerebral cortex, white matter and basal ganglia. Immunohistochemically, these cells were positive for CD20, CD79a and CD5, and negative for CD3, CD10, GFAP, cyclin D1, bcl-6 and MUM-1 (Fig. 3). Moreover, these cells were positive for IL-10 (Fig. 3). No lymphoma cells were observed in any other organs. Based on these findings, we diagnosed the patient with CD5-positive diffuse large B-cell lymphoma. These findings were consistent with PCNSL, specifically LC.

**Discussion**

LC is a rare variant of PCNSL, characterized by the diffuse infiltration of lymphoma cells into the cerebral white matter and basal ganglia without the formation of a cohesive...
tumor mass (2). The prognosis is worse for LC than for typical PCNSL, and most patients die within six months after onset due to the poor response to steroids (7, 10). Conventional PCNSL most often presents with isolated focal or multifocal mass lesions associated with contrast enhancement on MRI. In contrast, MRI shows diffuse leukoencephalopathy without contrast enhancement in the early stage of LC, indicating that significant blood-brain barrier disruption by lymphoma cells has not yet occurred (1). Diagnosing LC presenting with leukoencephalopathy is difficult, because the differential diagnoses include diseases such as Binswanger’s disease, demyelinating disorders like MS and neuromyelitis optica, infectious encephalomyelitides (including progressive multifocal leukoencephalopathy), metabolic encephalitis, neurosarcoidosis, prion disease and brain tumors such as glioma. In fact, our case had initially been misdiagnosed to have a cerebral infarction or MS prior to admission to our hospital.

Although we also initially had difficulty reaching a diagnosis, the rapidly deteriorating clinical course and MRI lesions, abnormal findings on FDG-PET and elevated IL-10 levels in the CSF prompted us to consider malignant lymphoma, including LC, as the clinical diagnosis and to perform a brain biopsy. The final diagnosis was made following immunostaining for GFAP and other leukocyte markers. CD20 immunostaining allowed us to visualize the extent of infiltration of the lymphoma cells throughout the white matter (11, 12). Hans et al. subclassified diffuse large B-cell lymphoma into germinal center B-cell-like (GCB) and non-GCB profiles with immunostaining for CD10, bcl-6 and MUM1. Bcl-6 and CD10 are markers of germinal center B cells, and are associated with the GCB phenotype and a better overall survival, whereas MUM1 is a marker of the non-GCB phenotype, which has a poor prognosis (13). Our case was negative for MUM1, but since both bcl-6 and CD10 were also negative, the LC was considered to represent the non-GCB phenotype. This phenotype was consistent with the poor prognosis, with survival of less than three months in our case. Although these immunohistochemical analyses are necessary to obtain a definitive diagnosis and prediction of the prognosis for LC, we demonstrated that the IL-10 level in the CSF might also prove useful in diagnosing and assessing the status of LC (Fig. 2).

IL-10 is a pleiotropic cytokine produced by type-2 helper cells, monocytes, macrophages and normal and neoplastic B lymphocytes. IL-10 was first described as a growth and differentiation factor for B lymphocytes that induces activated B cells to secrete large amounts of immunoglobulin (14). IL-10 may promote the development and progression of lymphoma due to broad anti-inflammatory properties against
both macrophages and dendritic cell function, as well as inhibition of apoptosis. Several investigators have demonstrated the usefulness of IL-10 for distinguishing PCNSL from other brain tumors (8, 15, 16). Sasayama et al. recently reported that the levels of IL-10 in the CSF were significantly higher in patients with PCNSL than in those with other brain tumors (cut-off level, 9.5 pg/mL; 71.0% sensitivity, 100% specificity). They also proposed that elevated levels of IL-10 in the CSF were significantly associated with a shorter progression-free survival (9). Since conventional PCNSL is tumor-forming, the differential diagnosis is mainly restricted to brain tumors. On the other hand, LC demonstrates diffuse leukoencephalopathy without tumor formation on MRI, requiring consideration of a much larger number of differential diagnoses. In this regard, measuring the levels of IL-10 in the CSF might help to substantially narrow the differential diagnosis. In fact, in the present case, even on hospital day 8 when a suspicion of malignant lymphoma based on the brain MRI findings would have been difficult, the IL-10 level in the CSF was substantially elevated.

The specificity of CSF IL-10 for the diagnosis of LC remains unclear, because the levels are not usually measured in patients with other diseases that should be differentiated from LC. However, the CSF levels of IL-10 in patients with neuro-Behçet disease, MS (17), tuberculous meningitis (18), Alzheimer’s disease (19) and migraine headache (20) are known to show no elevation. To clarify the direct correlation between elevated CSF levels of IL-10 and the progression of LC, we examined whether the tumor cells actually express IL-10. Our case showed considerable expression of IL-10 in lymphoma cells (Fig. 3F). We therefore suppose that the expansion of IL-10-producing lymphoma cells is directly reflected by elevated levels of IL-10 in the CSF, consistent with the results shown in Fig. 2.

Other than IL-10, the β2-microglobulin level in the CSF has also been reported to be a useful marker of central nervous system lymphoma (21). In our case, the levels of β2-microglobulin correlated with the clinical course in a manner similar to IL-10 (Fig. 2). However, the specificity of CSF β2-microglobulin was reported to be inferior to that of CSF IL-10 in a study of PCNSL (9).

In conclusion, our data from this case strongly suggest that the levels of IL-10 in the CSF may be useful as a potential biomarker for the early diagnosis and monitoring of disease progression, not only in typical PCNSL, but also in LC.

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

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