Primary Central Nervous System Cytotoxic T-cell Lymphoma Mimicking Demyelinating Disease

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Abstract

A 40-year-old man visited to our hospital due to progressive right hemiparesis. Magnetic resonance imaging demonstrated a heterogeneous contrast-enhanced lesion in the left basal ganglia with compression of the ventricles. A brain biopsy did not demonstrate central nervous system (CNS) lymphoma, although acute demyelination was observed. Despite the administration of steroids, the lesion increased in size, and the patient died three months after admission. An autopsy disclosed perivascular and parenchymal infiltration of lymphoma cells. An immunohistochemical analysis showed that the lesion was a cytotoxic T-cell lymphoma. This case indicates that the development of primary CNS lymphoma of this immunophenotype may be preceded by demyelination with subsequent rapid progression, thus requiring a careful evaluation and meticulous diagnosis.

Key words: primary central nervous system lymphoma, brain biopsy, tumefactive multiple sclerosis, cytotoxic T-cell

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Introduction

Most primary central nervous system (CNS) lymphomas belong to the group of diffuse large B-cell lymphomas. Only approximately 2% of primary CNS lymphomas are of the T-cell lineage (1). Making an accurate diagnosis is critical in order to provide appropriate treatment and acquire a favorable prognosis in patients with brain lymphomas. Obtaining an accurate diagnosis is particularly important for T-cell lineage lymphomas, which are especially difficult to distinguish from demyelinating disease because small lymphoid cells mimic the actions of reactive T-cell processes (2). We herein describe the case of a 40-year-old man who was first diagnosed with tumefactive multiple sclerosis following a brain biopsy. As seen at autopsy, the patient actually had a primary CNS T-cell lymphoma with a cytotoxic immunophenotype.

Case Report

A 40-year-old man with a history of untreated diabetes developed progressive right-sided hemiparesis over one week. On admission, he was drowsy and obese and exhibited motor aphasia with right-sided hemiparesis. Laboratory studies revealed normal levels of soluble interleukin-2 receptor (159 U/mL) and LDH (208 U/L). Because we did not suspect neuromyelitis optica or adult T-cell leukemia, we did not measure the levels of anti-aquaporin 4 antibodies in the serum or anti-human T-cell leukemia virus type I antibodies in the serum and cerebrospinal fluid (CSF). A CSF analysis disclosed an elevated cell count of 13/μL (lymphocytes: 12/μL and polymorphonuclear cells: 1/μL), an increased protein level of 71 mg/dL, a slightly decreased glucose level of 83 mg/dL (blood glucose: 220 mg/dL), an increased myelin basic protein level of 686 pg/mL and positive oligoclonal bands. The results of cytology of the CSF indicated a class...
II status. T2-weighted magnetic resonance imaging (MRI) showed high-intensity lesions in the left thalamus, basal ganglia and deep white matter (Fig. 1A). Postcontrast T1-weighted MRI demonstrated heterogeneous enhancement (Fig. 1B). Perfusion-weighted MRI showed a decreased relative cerebral blood flow in the left thalamus and basal ganglia (Fig. 1C), while $^{11}$C-methionine positron emission tomography (PET) revealed a decreased uptake in the left basal ganglia. In spite of the results of perfusion-weighted MRI and PET, a diagnosis of neoplasms was not excluded; thus, a stereotactic-guided biopsy of the deep brain lesions was performed (Fig. 1B, red square). The histopathological examination showed tissue necrosis with infiltration of lymphocytes and foamy macrophages (Fig. 2A). The lymphocytes were numerous around the blood vessels (Fig. 2B). Klüver-Barrera staining demonstrated myelin loss in the deep white matter (Fig. 2C). Immunostaining for neurofilament proteins revealed relative axonal preservation within the lesion (Fig. 2D). An immunohistochemical analysis revealed that the lymphocytes were positive for CD3, CD4, CD8 and CD20 (Fig. 2E-H). CD3-positive cells were numerous, indicating that most of the infiltrating cells were T-cells. The possibility of T-cell monoclonality was not investigated. These findings suggested that the lesion contained acute demyelination, and we made a diagnosis of tumefactive multiple sclerosis. The patient received intravenous methylprednisolone at a dose of 1 g/day for three days. However, his symptoms did not improve. Repeated brain MRI performed 35 days after admission showed further enlargement of the mass, extending to the ipsilateral midbrain (Fig. 1D-F). Due to the failure of steroid therapy, immuneadsorption plasmapheresis was performed five times; however, it also did not ameliorate the disease. Three months after admission, the patient lapsed into a coma and died of respiratory failure.

An autopsy was performed, and the brain was pathologically examined. Macroscopically, necrotic lesions were observed in the left hemisphere with a central focus in the thalamus. The lesions had spread to the right hemisphere, cerebellum and brainstem (Fig. 3A). A histological examination of the area indicated by the red square in Fig. 3A showed perivascular infiltration of small- to medium-sized lymphoid cells with nuclear atypia (Fig. 3B, C). An immunohistochemical analysis revealed that the lymphocytes were positive for CD3, CD8, granzyme B and perforin and negative for CD4 and CD20 (Fig. 3D-I). An in situ hybridization...
study for Epstein-Barr virus-encoded RNA was negative. We detected T-cell receptor γ-chain gene rearrangement with a clonal appearance using a polymerase chain reaction analysis (data not shown). A thorough systemic workup of the patient revealed no lesions outside of the brain. The final diagnosis was primary CNS T-cell lymphoma with a cytotoxic immunophenotype.

Discussion

We herein reported a case in which a brain biopsy revealed demyelination, although an autopsy performed three months later suggested a final diagnosis of primary CNS T-cell lymphoma. Corticosteroid treatment, which can induce the remission of CNS lymphoma and the disappearance of dysplastic cells, was not administered before the initial biopsy. Therefore, the false-negative findings of the initial biopsy were not the result of the preceding therapy. Demyelination occurs before the appearance of tumor cells in some CNS lymphoma cases. Demyelinating lesions are called “sentinel lesions” and are associated with contrast enhancement on MRI (3). Similar cases of the development of “sentinel lesions” preceding primary CNS lymphoma have been reported (4, 5).

The immunohistochemical analysis in this case revealed that the tumor cells were positive for CD3 and CD8 but negative for CD4, which suggested that the lymphoma was of the T-cell lineage. The detection of cytoplasmic granule-associated proteins, such as granzyme B and perforin, indicated that this T-cell lymphoma had a cytotoxic phenotype. To our knowledge, only a few previous cases of primary CNS cytotoxic T-cell lymphoma have been reported (6, 7). This is a rare phenotype that may be associated with more pronounced necrosis and infiltration of macrophages than lymphoma cells. The present case indicates that the development of primary CNS lymphoma of this immunophenotype may be preceded by demyelination with a subsequent rapidly progressive course. Providing a careful evaluation and meticulous diagnosis is thus required.

Lymphoma cells are detected in the CSF in only 25% of primary CNS lymphoma cases (8). As lymphocytic pleocytosis in the CSF and the presence of CSF oligoclonal bands are detected in approximately 50% and 27% of primary CNS lymphoma patients, respectively (9), these examinations may not yield a definitive diagnosis. Although primary CD8 T-cell CNS lymphoma is rare, it should be considered...
in the differential diagnosis even though the lesions are difficult to distinguish, as underdiagnosis may result in unfavorable consequences.

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

References