Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids with a Significant Elevation of β-2 Microglobulin Levels

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Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a relapsing-remitting disorder for which steroid administration is a key to control the progression. CLIPPERS can exhibit radiological features similar to malignant lymphoma, whose diagnosis is confounded by prior steroid administration. We report a case of CLIPPERS accompanied by abnormal elevation of β-2 microglobulin in the cerebrospinal fluid (CSF). A 62-year-old man started to experience numbness in all fingers of his left hand one year ago, which gradually extended to his body trunk and legs on both sides. Magnetic resonance imaging demonstrated numerous small enhancing spots scattered in his brain and spinal cord. CSF levels of β-2 microglobulin were elevated; although this often indicates central nervous system involvement in leukemia and lymphoma, the lesions were diagnosed as CLIPPERS based on the pathological findings from a biopsy specimen. We emphasize the importance of biopsy to differentiate between CLIPPERS and malignant lymphoma because the temporary radiological response to steroid might be the same in both diseases but the treatment strategies regarding the use of steroid are quite different.

Key Words: Biopsy · β-2 microglobulin · Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids · Diagnosis · malignant lymphoma.

INTRODUCTION

Since chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) was first reported in 20107, approximately 50 cases have been described in the literature. Despite several recent case reports,3,7,10,12 the clinical presentation, methods of diagnosis, and pathogenesis of CLIPPERS have not been fully elucidated. Clinical symptoms frequently include a variety of focal neurological deficits10,11, which complicates early diagnosis. There are no specific methods, such as serum chemistry or cerebrospinal fluid (CSF) examination, for diagnosis of CLIPPERS. Imaging studies are not definitive, particularly when initial magnetic resonance (MR) images show minimal abnormal findings.12 These concerns render the diagnosis of CLIPPERS difficult. Here we report a case of CLIPPERS in which we experienced some diagnostic difficulties. We initially suspected malignant lymphoma because the level of β-2 microglobulin in the CSF were significantly elevated. A biopsy played a critical role in diagnosing CLIPPERS.

CASE REPORT

A 62-year-old man with no past medical history started to experience numbness in all fingers of his left hand one year ago. His numbness gradually extended to his fingers and lips on his right side, and ultimately to his body trunk and legs on both sides. He visited a neurologist at our institution. A detailed neurological examination showed bilateral facial numbness, mild dysarthria, abnormal feeling of tightness in the Th4 level, and mild bilateral cerebellar ataxia. No other cranial nerve deficits were noted. He had no motor paresis, and deep tendon reflexes were normal and symmetrical. Pathological reflexes, including Babinski and Chaddock reflexes were absent. A physical examination revealed no systemic abnormalities such as lymph node swelling. A blood test revealed a normal complete blood count, no abnormal biochemistry, and no autoimmune antibodies, includ-
ing antinuclear antibody, antineutrophilic cytoplasmic antibody, antithyroid peroxidase antibody, and anti-phospholipid antibody. Epstein-Barr virus was negative, and serum lactate dehydrogenase (LDH) levels were within normal limits. Analysis of the CSF demonstrated a slight increase in cell counts 22/3 and normal concentrations of protein (63 mg/dL) and glucose (69 mg/dL). However, it also showed a remarkable increase in the β-2 microglobulin level (up to 4144 μg/L). The oligoclonal band was not identified and CSF cytology was class I. CSF levels of LDH were slightly elevated (34 IU/L, normal ≤25). Amounts of immunoglobulins were also elevated: IgG, 11.7 mg/dL (0.2–4.0); IgA, 1.6 mg/dL (0.1–0.6); IgM, 0.8 mg/dL (0.03–0.06). MR images demonstrated diffuse abnormal small spotty lesions in the pons and cerebellum that had low intensity on T1-weighted images (Fig. 1A) and high intensity on T2-weighted images (Fig. 1B). T1-weighted images with gadolinium showed that these lesions were enhanced (Fig. 1C). A few solitary enhanced spots were also identified in the deep white matter of the temporal and frontal lobes (Fig. 1D, E). Similar enhanced lesions were present in the spinal cord, as well (Fig. 1F). The size of the lesions in the pons and cerebellum, and spinal cord ranged from 1 mm to 5 mm while that of the spinal lesions were slightly larger. They were sparsely distributed in some areas and formed clusters in other areas. At this point, possible diagnoses included malignant lymphoma, intravascular malignant lymphoma, glioma, metastatic tumor, cerebrovascular angitis, multiple sclerosis, sarcoidosis, central nervous system Behcet’s disease, viral encephalitis, and rare pathologies such as CLIPPERs. Because multiple enhancements along the surface and the inside of the brain stem appeared to indicate perimedullary venous dilation, we performed a cerebral and spinal angiogram to eliminate cerebrovascular diseases such as a dural arteriovenous fistula. The angiogram did not detect any apparent abnormalities.

During the course of these examinations, the patient’s symptoms rapidly progressed within a week, and bilateral lower cranial nerve dysfunction occurred. This dysfunction caused severe dysarthria, dysphagia, and respiratory distress that required emergency intubation followed by tracheostomy. Because some immunological disease was suspected, we had a careful discussion with neurologists and hematologists regarding the efficacy of steroid as a diagnostic therapy. However, use of steroid was considered inappropriate because malignant lymphoma had not been excluded. Therefore, we biopsied the enhanced cerebellar mass to obtain the correct diagnosis (Fig. 1G). With the aid of an intraoperative navigation system, a 1.5-cm square block was prepared. Pathological examination of the block showed that small lymphocytes had invaded all layers of the blood vessels in the white matter, whereas the structures of the cerebellar cortex and white matter were preserved (Fig. 2A). Closely aggregated cell invasions containing scattered histiocyte-like cells and plasma cells were observed in the vessel walls and the adjacent brain parenchyma. Immunohistochemistry showed a mixture
of T cells and B cells (Fig. 2B, C), with dominancy of T cells in the brain parenchyma and of B cells in the perivascular areas. CD4-positive T cells were more prominent than CD8-positive T cells (Fig. 2D, E). These findings are consistent with the characteristics of CLIPPERS. The absence of monoclonal proliferation of lymphocytes and of small RNAs derived from Epstein-Barr virus support this diagnosis.

Postoperatively, based on the diagnosis, the patient received steroid therapy (two courses of 500 mg intravenous methylprednisolone for five consecutive days). Oral prednisone was initiated at 50 mg/day and tapered to 5 mg/day. Apparent improvement was noted on MR images obtained two months after steroid administration. The patient's neurological deficits showed gradual improvement over the course of three months. After six months of rehabilitation, he was discharged with a slight gait disturbance. He was neurologically intact on prednisone 5 mg/day on a 1.5-year follow-up with no sign of recurrence (Fig. 3).

**DISCUSSION**

CLIPPERS is a recognized clinical entity first reported in 2010 by Pittock et al.\(^7\). Because of the paucity of data, its diagnostic criteria have not been fully established\(^3\). CLIPPERS is often indirectly diagnosed by excluding central nervous system lymphoma, cerebrovascular disease, and other immunological disorders such as angiitis\(^10\). Radiological features are important in the diagnosis of CLIPPERS. Pittock et al.\(^7\) summarized eight cases of CLIPPERS, in which they observed punctate and curvi-
lymphoma. Pathological confirmation to differentiate CLIPPERS from CNS can be performed safely. CLIPPERS is a relapsing-remitting disorder whose progression may be useful in distinguishing lymphoma from CLIPPERS, Pittock SJ, Debruyne J, Krecke KN, Giannini C, van den Ameele J, De Stock et al.: Expanding the clinical, radiological and neuropathological phenotype of chronic lymphocytic inflammation with pontocerebellar perivascular enhancement responsive to steroids (CLIPPERS). J Neurol Neurosurg Psychiatry 83: 15-22, 2012

CONCLUSION

Abnormal elevation of β-2 microglobulin in the CSF can be observed in CLIPPERS as well. Biopsy to differentiate between CLIPPERS and malignant lymphoma is essential because the temporary radiological response to steroid might be the same in both diseases but the treatment strategies regarding the use of steroid are quite different.

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References