—Report on Clinics and Experiments—

Human T-cell lymphotropic virus type-I associated myelopathy complicated by optic neuritis

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Summary

A 48-year-old Japanese woman from Kyushu was admitted to the Nippon Medical School First Hospital with complaints of numbness in both legs, gait disturbance, and urinary problems. On examination, her lower extremities were spastic with increased reflexes and positive Babinski sign. Sensation was absent below the T₄ spinal level. The cerebrospinal fluid contained HTLV-I antibodies and she was diagnosed with HTLV-I associated myelopathy. Her symptoms were resolved with prednisolone, but six months later a visual disturbance of the left eye edema developed. Orbital CT scans showed that left optic nerve was edematous. T₂ enhanced MRI revealed a high intensity lesion of the left optic nerve. ERG was normal and no VEP was detected in response to flashing stimulation to the left eye. The HTLV-I antigen titer of CBF was very high. Her optic neuritis improved following oral administration of prednisolone and retrobulbar injections of dexamethasone. This is the first case report of HTLV-I associated myelopathy complicated by optic neuritis.

Key words: HTLV-I associated myelopathy, tropical spastic paraparesis, optic neuritis

Introduction

Human T-cell lymphotropic virus type I (HTLV-I) is the etiologic organism in adult T-cell leukemia (ATL)¹⁾, and also involved in the pathogenesis of HTLV-I associated myelopathy (HAM)²⁾. HAM is a chronic progressive myelopathy characterized by prominent pyramidal tract signs with mild sensory and urinary bladder involvement. HAM mainly affects the spinal cord, particularly the thoracic cord, but rarely affects the optic nerve. We report a case of HAM complicated by optic neuritis.

Case

A 48-year-old Japanese woman had numbness in her hips and legs which worsened by walking long distances on January 17th, 1992. A gait disturbance developed subsequently.

HTLV-I antibodies (titer 128: 1), but oligoclonal bands were not detected. Light microscopic examination of peripheral blood lymphocytes demonstrated ATL-like cells characterized by lobulated nuclei.

Sagittal T₂ weighted MR scans showed a high signal intensity lesion in the thoracic spinal cord (**Fig. 1**).

Her neurological symptoms, the presence of HTLV-I antibodies in the cerebrospinal fluid and the findings on the MR scanning led to the diagnosis of HAM. She was treated with 30 mg of prednisolone daily with nearly complete resolution of her symptoms. She was discharged on 70th hospital day. Seven months after the onset of her initial symptoms, she experienced a disturbance in visual acuity. We initiated prednisolone therapy (per os), 50 mg daily, and admitted her to the hospital nine days later. Visual acuity in the left eye was impaired but no other cranial nerve and motor system impairment was found. Although she felt numbness in her left leg, we found no objective sensory disturbance.

Orbital CT scans showed edema of the left optic nerve (**Fig. 2**). Axial T₂ weighted MR scanning revealed a high signal intensity lesion of the left optic nerve (**Fig. 3**).

ERG examination were normal and VEPs were not detected from her left eye in response to flashing stimulation. The titer of HTLV-I antigen in the cerebrospinal fluid was 1024 × at admission.

She was diagnosed as optic neuritis and treated with prednisolone (per os, 100 mg/day) and retrobulbar injections of dexamethasone. Corticosteroid treatment improved her visual acuity and lowered the level of HTLV-I antibodies.

Discussion

Our patient was a native of the Island of Kyushu, Japan, a region with one of the highest endemic levels of ATL in the world³). Corticosteroid treatment⁴), plasmapheresis⁵) and azathioprine³) have been all used to treat patients with HMA with some success, as was illustrated by the response of our patient to corticosteroids. The histopathological feature of HAM is characterized by a chronic progressive inflammatory process with marked parenchymal exudation of lymphocytes and monocytes into the spinal cord resulting in severe degeneration of the white matter⁶). In our patient, sagittal T₂ weighted MRIs showed a high signal intensity lesion in the thoracic spinal cord. We believed that this finding represented the neuroradiologic manifestation of histopathological features of HAM. Several hypotheses regarding the pathogenesis of HAM have been proposed: (1) viral infection of the nervous system, (2) a cell-mediated immune reaction to infected nervous system, (3) a humoral immune reaction to the infected nervous system, (4) an autoimmune reaction to neuronal self-antigens as a result of HTLV-I infection. High antibody titers to HTLV-I are found in sera and cerebrospinal fluids from infected patients. Tsukada et al have reported that serum levels of both soluble CD4 and soluble CD8 are significantly elevated in patients with HAM⁷). Ijichi et al (1989) have shown that patients with both CD4⁺ and CD8⁺ CBF lymphocytes of HAM/tropical spastic paraparesis (TSP) contain higher percentages of HLA-DR-positive cells than those other neurological diseases⁸). Jacobson et al have reported the presence of

high levels of circulating HTLV-I-specific cytotoxic T lymphocytes (CTL) in patients with HAM/TSP but the absence in HTLV-I seropositive individuals without neurological involvement. These CTLs were CD8⁺ and predominantly recognized the HTLV-I gene product encoded in the regulatory region pX⁹). Umehara et al have reported that CD4⁺ cells, CD8⁺ cells and macrophages were evenly distributed in active-chronic inflammatory lesions in patients with a shorter duration of illness. In striking contrast, they noted the predominance of CD8⁺ cells over CD4⁺ cells in the inactive-chronic inflammatory lesions of patients with a longer duration of illness¹⁰). Kubota et al have reported that the decline in the amount of lymphocyte HTLV-I proviral DNA in thoracic cord lesions parallels the decrease in the proportion of CD4⁺ T lymphocytes in patients with HAM/TSP¹¹). They have suggested that a preferential virus reservoir may infiltrate the CD4⁺ T lymphocytes of the spinal cord lesions of patients with HAM/TSP. Using two-step PCR in situ hybridization, Hare et al recently found that HTLV-I proviral DNA was detected only in the nuclei of lymphocytes infiltrating the spinal cord and not in other neuronal cells¹⁵). Usuku et al discovered a CD8⁺ T cell line with cytotoxic activities against autologous CD4⁺ T cell lines infected with HTLV-I¹²). Umehara et al have also indicated that TIA-1⁺ and CD8⁺ cells are distributed in the active inflammatory lesions of spinal cords from autopsied patients with HAM/TSP and found apoptosis of helper-inducer CD45RO lymphocytes in the active inflammatory lesions¹³). TIA-1 which is a marker for CTL and TIA-1 protein has been associated with the induction of apoptosis in target cells. Hara et al have reported that the TCR (T-cell antigen receptor) V β gene sequence lymphocytes in spinal cord lesions taken from the same HAM/TSP autopsy cases revealed unique and restricted CDR3 (complementarity determining region 3) motifs: CASSLXG (G) (X is some amino acid), CASSPT (G), and CASSGRL. Three hypervariable regions in the TCR are referred to as CDRs. CDR1 and CDR2 are the combining sites for MHC peptides. CDR3 is the combining site for the foreign antigen with which the MHC has combined. Each TCR consists of an α chain and a β chain, or of a γ chain and a δ chain. The CDR3 is encoded by the V, D and J genes in TCR β . They stated that these CDR3 motifs were similar to those found in the brain lesions of MS patients and in the T cell clones derived from experimental allergic encephalomyelitis. There has been only one previous case report of a TSP/HAM patient with a lesion of the optic nerve¹⁴). Moore et al reported a patient who died at the age of 59 after treatment as a probable case of MS, was considered possible TSP. Neurological examination revealed spastic paraparesis and sensory loss in the lower extremities. They recognized a loss of visual acuity in the right eye and slowing of the VEP. HTLV-I antibodies were not determined when she was alive, because she died prior to the recognition of an association between HTLV-I and TSP. In autopsy, HTLV-I p19 core protein was demonstrated immunohistochemically in the spinal cord lesion and a diagnosis of TSP was made.

This is the first case report of HAM complicated by optic neuritis in a living patient. When the optical neuritis developed, the titer of HTLV-I antibodies in the cerebrospinal fluid was high, suggesting an etiologic association. We could diagnose optic neuritis associated with HTLV-I, and as a result, could treat our patient successfully. Corticosteroid treatment

improved her visual acuity and lowered the HTLV-I antibody level. There may be common mechanisms involved in the development of lesions of the spinal cord and the optic nerve in patients with HAM.

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(Received for publication, May 21, 1996)