Human T Cell Leukemia Virus Type I-associated Myelopathy in a Patient with Systemic Lupus Erythematosus

Takanori Miura, Hirotoshi Tanaka, Yuichi Makino, Kensaku Okamoto, Takahisa Ida, Keiji Komura, Etsushi Fukawa, Fuminori Hirano and Isao Makino

A case of human T cell leukemia virus type I (HTLV-1) associated myelopathy (HAM)/tropical spastic paraparesis (TSP) with 14-year history of systemic lupus erythematosus (SLE) is reported. For 9 years, the numbness of the feet and sacral region progressed with occasional urinary incontinence and constipation. She was admitted to hospital due to gait disturbance and aggravation of SLE and the diagnosis of HAM/TSP was confirmed, indicating that HTLV-1 infection is associated with the development of not only HAM/TSP but also SLE.

Key words: retrovirus, infection, autoimmune disease

Introduction

A correlation of the type C retrovirus with human autoimmune disease has been investigated (1, 2), since some animal retroviruses have been indicated to be the etiological agents in animal autoimmune diseases (3, 4). Human T cell leukemia virus type I (HTLV-1) is the first detected exogenous human type C retrovirus, which was isolated from patients with adult T cell leukemia/lymphoma (ATL) (5, 6), and has a close association with a variety of diseases including slowly progressive myelopathy known as HTLV-1-associated myelopathy (HAM)/tropical spastic paraparesis (TSP) (7, 8). Moreover, HTLV-1 infection has been considered to play a role in various autoimmune diseases, such as Sjögren’s syndrome (9, 10), arthritis or chronic inflammatory arthropathy (11, 12), thyroiditis (13), and polymyositis (14). However, the pathogenetic role of HTLV-1 in systemic lupus erythematosus (SLE) is still controversial. We report here a case of SLE-associated HAM, and a possible etiological role of HTLV-1 in SLE is discussed.

For editorial comment, see also p 459.

Case Report

A 61-year-old Japanese woman with a 14-year history of SLE was admitted to our hospital in September 1995. She was born in Manchuria, and then came to Hokkaido, Japan, where she still resides. She denied transfusion history and extramarital relationships. She was diagnosed as having SLE in 1981 after presenting with polyarthritis, malar rash, oral aphtha, and pericarditis. Laboratory examination revealed a positive test for antinuclear antibodies (ANA) and anti double-strand DNA antibody (ds-DNA), and decreased serum complement values. Anti-cardiolipin antibodies were negative. After daily administration of prednisolone, she became asymptomatic and prednisolone was tapered to 15 mg. Since 1986, the numbness of the feet and sacral region gradually progressed over years, which has been associated with occasional urinary incontinence and constipation. In 1995, her gait disturbance gradually progressed for months and she developed arthralgia, low grade fever, fatigue and body weight loss with the increase in serum titers of antibodies to ds-DNA and the decline in serum complement levels, and was admitted to our hospital again. Physical examination on admission revealed malar erythema, but neither hepatosplenomegaly nor lymphadenopathy was noticed. Neurological examination revealed spastic gait. The lower limb deep tendon reflex was hyperactive, and slight decrease of light touch and pain sensation in the lower limbs was found. A sphincter disturbance characterized by urgency and occasional urinary incontinence was also present. White blood cell count was 4,180/mm³, red blood cell count 389×10⁶/mm³, hemoglobin 12.1 g/dl, and platelet 14×10⁴/mm³. Serum creatinine was 0.5 mg/dl. ANA was positive at a titer of 1:1,280, and antibodies to ds-DNA also elevated (114 IU/ml, normal <12). Anti-Sm antibodies were positive. C3, C4, and CH50 were 49 mg/dl, 7.9 mg/dl, and 29 U/ml, respectively. Peripheral blood smear and bone marrow examination showed no abnormalities. Lumbar
SLE and HTLV-1 Infection

Figure 1. Western immunoblot for antibodies against purified HTLV-1 antigens. Lane 1: negative control, lane 2: positive control, lane 3: patient’s sera, lane 4: patient’s CSF.

Figure 2. HTLV-1 proviral DNA was detected in the patient’s peripheral blood mononuclear cells by PCR. Closed arrowhead: HTLV-1 proviral DNA (pol). Lanes 1–3: positive control, lane 4: negative control, lane 5: patient’s peripheral blood mononuclear cell.

puncture showed normal cerebrospinal fluid (CSF) pressure. Analysis of CSF showed protein 119 mg/dl, sugar 73 mg/dl, mononuclear cells 7/μl, Cl 123 mEq/l, lactate dehydrogenase (LDH) 68 IU/l. Oligoclonal bands in CSF and culture of CSF were negative. Particle agglutination methods suggested the presence of anti-HTLV-1 antibodies in her sera and CSF at a titer of 1:256 and 1:16, respectively. Using Western immunoblot analysis of her serum and CSF confirmed the presence of antibodies against env (gp46) and gag (p19, p24, p53) (Fig. 1). Moreover, polymerase chain reaction demonstrated the HTLV-1 provirus integration (Fig. 2). Magnetic resonance imaging (MRI) showed slight atrophy of the thoracic cord (Fig. 3), with central artifact on T2-weighted image. In the brain, small high-intensity lesions were scattered in the deep white matter on T2-weighted image (Fig. 4). Thus, she fulfilled the diagnostic criteria for HAM developed by Osame et al (15), and prednisolone was increased to 30 mg, which was partially effective for gait disturbance. Her husband and children were negative for anti-HTLV-1 antibodies.

Discussion

Although the cause of SLE remains still elusive, the most popular candidate agents for the etiopathogenesis of SLE have been viruses, especially type C retroviruses (1^-). The studies of New Zealand black (NZB) mice, which are the murine model of SLE, have revealed the endogenous type C retrovirus to be implicated in the pathogenesis of the SLE-like symptoms. High levels of immune complexes containing viral envelope glycoprotein, gp70, were also found in sera of NZB mice (3), and the pathogenesis of glomerulonephritis in NZB mice of SLE is considered to be related to the deposition of gp70 in the glomeruli (4). Thus, endogenous type C retroviruses and their gene products have been suggested to be implicated in the pathogenesis of murine SLE. Thus much effort has been directed toward elucidation of the participation of the type C retrovirus in the pathogenesis of human SLE. Mellors and Mellors reported the deposition of an antigen related to mammalian type C retroviral p30 proteins in renal glomeruli of humans with SLE (1), and Panem et al found a putative human type C retrovirus in the glomeruli from 11 SLE patients (2).

HTLV-1 is the first detected exogenous human type C retrovirus that was isolated from patients with ATL (5, 6), and has been found to have a close relation to outbreaks not only of leukemia or lymphoma but also of HAM/TSP. Some investigators have studied the etiological role of HTLV-1 for SLE, but they have found no evidence for the participation of HTLV-1 infection in the pathogenesis of human SLE. Mellors and Mellors reported the deposition of an antigen related to mammalian type C retroviral p30 proteins in renal glomeruli of humans with SLE (1), and Panem et al found a putative human type C retrovirus in the glomeruli from 11 SLE patients (2).

The association of SLE and HAM/TSP is extremely rare and it may be a mere coincidence. Takayanagui et al (20) recently reported two HAM/TSP patients complicated with SLE and raised the possibility that the development of SLE or SLE-like manifestations might be due to HTLV-1 infection. These
patients showed neurological abnormalities before the onset of SLE. In the present case, however, SLE was diagnosed before the manifestation of myelopathy. We, therefore, cannot exclude the possibility that myelopathy developed as a complication of SLE. SLE-associated myelopathy is generally considered to be extremely acute on onset (21–23), whereas HAM/TSP an insidious onset (20). Moreover, SLE patients complicated with myelopathy are frequently positive for anti-phospholipid antibodies in their sera (24, 25). HTLV-1 was thought to be transmitted to the patient by her mother, most possibly due to breast feeding, and our patient showed insidious progression of myelopathy and a negative test for anti-phospholipid antibodies. Together, we suggest an etiological link between HTLV-1 infection and SLE in the present patient. Fur-
other studies, however, are needed to clarify the correlation between HTLV-I infection and human SLE.

Reference