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CASE REPORT

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The occurrence of systemic lupus erythematosus in an asymptomatic carrier of human T-cell lymphotropic virus type I

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Abstract A 63-year-old asymptomatic carrier of human T-cell lymphotropic virus type I (HTLV-1) infection was admitted because of chest oppression, a high-grade fever, polyarthralgia, and erythematous rashes. Laboratory examination revealed lymphocytopenia, proteinuria, and high titers of antinuclear antibodies and antidouble-stranded DNA antibody; thus, she was diagnosed as having systemic lupus erythematosus (SLE). This case indicates that HTLV-1 infection might be related with the pathogenesis of SLE.

Keywords Human T-cell lymphotropic virus type I · Systemic lupus erythematosus

Introduction

An association between systemic lupus erythematosus (SLE) and retroviruses has long been suspected [1, 2]. Human T-cell lymphotropic virus type I (HTLV-1) is a member of a group of mammalian C-type retroviruses, which is well known to cause adult T-cell leukemia/lymphoma (ATL) and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [3]. Recently, HTLV-1 infection has been considered to play an important role in the pathogenesis of various autoimmune diseases, such as T-lymphocyte alveolitis, Sjögren's syndrome, arthropathy, and uveitis [3–6]. HTLV-1 infection has been reported to be accompanied also by mixed connective tissue disease [7]. In this study, we report a patient with persistent carrier state HTLV-1 infection, who developed typical SLE.

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Case report

A 63-year-old Japanese woman was referred to our hospital and admitted in March 2004 because of chest oppression. One month before admission, she developed a high-grade fever, 7-kg body weight loss, and polyarthralgia. She also had erythematous rash on face, hands, and feet. She had a 15-year history of Hashimoto's thyroiditis and had supplementation of thyroid hormone. When her daughter became pregnant 5 years before, she and her daughter were diagnosed as HTLV-1 carriers. The patient had experienced angina pectoris in 2002 and she was taking medication for angina.

On physical examination, she was alert but in moderate distress. Her temperature was 38.0°C, pulse rate was 72 beats min^{-1}, and her blood pressure was 148/70 mmHg. The chest was clear on auscultation, heart sounds were regular, and no murmur was heard. Abdominal examination revealed no abnormalities. Bilateral ankle joints were swollen with tenderness. Erythematous skin lesions were noted on her face and bilateral hands including palms. No neurological abnormalities were identified.

The laboratory examination at admission showed slight anemia and lymphocytopenia (790/μl) and mild thrombocytopenia. No hematological abnormalities were found in peripheral blood smear examination. The erythrocyte sedimentation rate was increased to 82 mm h^{-1}, and C-reactive protein was slightly increased to 1.3 mg/dl. No liver dysfunction was found. Renal impairment was manifested by the elevated levels of blood urea nitrogen 35 mg/dl and creatinine 1.78 mg/dl. Urinalysis showed 3+ proteinuria and 2+ occult bloods, and the daily urinary protein excretion was 1.2 g day^{-1}. Chest X-ray and abdominal echogram showed no significant abnormalities. Although there were no significant differences in electrocardiogram compared with the last one, her clinical

manifestations suggested she had unstable angina; thus, continuous infusion of nitroglycerine and heparin was started.

Because of persistent fever, skin rash, arthritis, proteinuria, and renal dysfunction, we suspected she had systemic connective tissue diseases, and we performed further immunological examination. The serum levels of complement 3 (42 mg/dl, normal value 75–165) and complement 4 (12 mg/dl, normal value 12–42) were decreased, and high titers of antinuclear antibodies (1:1280) and antidouble-stranded DNA antibody (33.5 IU/ml, normal <20) were identified, but anti-U1-ribonucleoprotein (RNP) antibody, anti-Lo/Ra antibodies, or myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA) and protease 3-ANCA were not identified. Skin biopsy specimen obtained from the skin rash on her foot showed vaculopathic interface dermatitis with mild perivascular lymphocyte infiltration in the dermis. These clinical and laboratory findings were compatible with the diagnostic criteria of SLE; thus, she was diagnosed as at the onset of SLE.

Treatment with prednisolone at 20 mg day^{-1} was started on day 7. The high fever and arthritis promptly improved after the prednisolone treatment. On day 10, coronary angiography showed no newly identified coronary artery lesions. However, her chest oppression had not resolved and the high fever reappeared. Thus, the dose of prednisolone was increased to 40 mg day^{-1}, after which her symptoms, such as fever, chest oppression, and skin rash, disappeared.

While HTLV-1 proviral DNA was identified with polymerase chain reaction in her peripheral blood mononuclear cells, bone marrow aspiration examination and neurological examination showed no pathological findings, indicating that she was a nonsymptomatic carrier of HTLV-1 infection. As her symptoms improved and the proteinuria also decreased to less than 0.1 g/day, she was discharged in May 2004. The dose of prednisolone was gradually tapered at outpatient clinic and she was symptom-free at prednisolone dose of 10 mg day^{-1} in September 2005.

Discussion

Several cases of the association of SLE and HAM/ATL have been reported [8–12]. Takayanagui et al. [10] and Miura et al. [11] reported cases of SLE associated with HAM, and Ito et al. [12] reported a case of lupus nephritis with ATL, indicating that HTLV-1 infection might be linked to the pathogenesis of SLE. The association of SLE and HTLV-1 infection is extremely rare compared with the incidence of other rheumatologic conditions in HTLV-1-infected patients, such as Sjögren's syndrome or arthropathy [3, 5, 6]; thus, this raises the possibility of a mere coincidence, or SLE-like systemic manifestations of HTLV-1 infection [4]. As in our case, the histological findings of erythematous skin lesion are compatible with SLE. Although we could not obtain renal tissue because the patient was being treated wit anticoagulants, she had significant proteinuria, high titers of antinuclear antibodies and double-stranded DNA antibody, and hypocomplementemia, indicating that she had lupus nephritis. Moreover, her skin and urinary abnormalities improved with a moderate amount of treatment of prednisolone, which is compatible with a typical case of SLE, not with ATL. We could not find any hematological, neurological, or laboratory findings which were specifically associated with HTLV-1 infection, such as ATL or HAM, indicating that she was an asymptomatic carrier. To our knowledge, this is the first report of the occurrence of SLE in the asymptomatic carrier state of HTLV-1 infection.

The cause and pathogenesis of SLE remain unknown. Several environmental factors, such as bacteria, viruses, or ultraviolet light, have been speculated as candidate agents for the pathogenesis of SLE [1]. For example, several viruses such as Epstein–Barr virus, cytomegalovirus, human parvovirus B19, and human endogenous retroviruses have been thought to play an important role in the development of SLE [1]. A human 68-kd U1-RNP protein contains a region of amino acid sequence that is homologous with a p30 gag sequence of several mammalian retroviruses, and immunization with the p30 gag protein has induced anti-RNP antibodies in experimental animals [13]. These data suggest that exposure to certain retroviruses leads to immune responses that may result in the production of autoantibodies that can react to a variety of human nuclear proteins through molecular mimicry. Although anti-U1-RNP antibody was not found in our patient, we speculate that the insidious infection of HTLV-1 might stimulate her immune system and cause autoimmune reactions, which induce the onset of SLE. No epidemiological evidence for the participation of HTLV-1 infection in human SLE has yet been found [14, 15]. However, the occurrence of SLE associated with HTLV-1 infection might be overlooked because 95% of HTLV-1-infected individuals are asymptomatic [3]. Further studies at the molecular level and a larger set of clinical data are needed to confirm the relationship with SLE and HTLV-1 infection.

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