Successful Treatment of HTLV-1-Related Overlap Syndrome Using Tacrolimus

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Abstract

A 56-year-old HTLV-I-positive woman, initially diagnosed as having Sjögren’s syndrome, presented with muscle weakness, myalgia, face erythema and leg edema. Based on the presence of various autoantibodies, the diagnosis of overlap syndrome (dermatomyositis/Sjögren’s syndrome) was made. Treatment with high-dose corticosteroid plus cyclosporine improved her symptoms. However, three months after the start of these treatments, exacerbation of myositis occurred. A muscle biopsy revealed prominent perivascular accumulation of mononuclear cells with perifascicular atrophy, which were consistent with dermatomyositis. Tacrolimus, which was substituted for cyclosporine led to marked improvement of the myositis symptoms.

Key words: dermatomyositis, HTLV-I, overlap syndrome, Sjögren’s syndrome, tacrolimus


Introduction

Retroviruses have been discussed as important etiologic factors in autoimmune rheumatic diseases (1). Human T-lymphotropic virus type 1 (HTLV-I) is the causative agent of adult T cell lymphoma/leukemia and HTLV-I-myelopathy/tropical spastic paraparesis (HAM/TSP) (2, 3). Several inflammatory rheumatic conditions, such as RA and Sjögren’s syndrome, have been reported in HTLV-I infected patients (4, 5). The pathogenesis of these associations is unclear, but some evidence suggests that activated lymphocytes and increased cytokine production in HTLV-I infected patients may cause rheumatic symptoms (6). Herein, we report a HTLV-I infected patient who was clinically diagnosed as having overlap syndrome with typical dermatomyositis and Sjögren’s syndrome. Immunohistochemical findings suggested a possible link between HTLV-I infection and proinflammatory changes, such as perivascular inflammatory cells infiltration in the affected muscle lesions.

Case Report

A 56-year-old woman was admitted our hospital in May 2009, due to Raynaud’s phenomena, face erythema, myalgia and leg edema. She had suffered from the symptoms of Sjögren’s syndrome and had been treated with low-dose steroids (prednisolone 5 mg/day) for 3 years prior to the onset of the present symptoms. Physical examination of the patient revealed heliotrope rash on the face, swollen hands, symmetric tenderness and weakness of the proximal muscle and leg edema. The tendon reflex was preserved and no signs of cranial-nerve or central nervous system involvement were noted. Laboratory findings (Table 1) revealed elevated levels of creatine kinase (CK, 1,209 IU/L). Using specific ELISA tests, high titers of anti-RNP, SSA, SSB and low titers of anti-ds-DNA, Sm, Jo-1 antibodies were detected. A positive reaction for HTLV-1 virus was proven by the parti-
However, typical “flower cell” (ATL cell)-like lymphocytes were not detected in peripheral blood. Chest CT examination revealed ground glass opacities in the lower lobes of both lungs, consistent with interstitial pneumonia (data not shown).

The diagnosis of overlap syndrome (dermatomyositis/Sjögren’s syndrome) was made. The patient was treated with high doses of steroid (prednisolone 40 mg/day) plus cyclosporine A (150 mg/day), and her symptoms, including face erythema, muscle weakness and myalgia, improved. However, three months after the start of these treatments, exacerbation of the inflammatory myopathy occurred with severe pain in both legs. MRI (STIR) showed symmetrical inflammation in the affected muscle and perifascicular lesions (Fig. 1A). Therefore, we performed muscle biopsy. Biopsy specimens from the left quadriceps muscle revealed perivascular infiltration of mononuclear cells and perifascicular atrophy, which were consistent with dermatomyositis. In immunohistochemical analysis, the inflammatory infiltrates were found to be predominantly CD4+ T cells, some of which expressed Foxp3 (Fig. 2A).

We also investigated the presence of Foxp3-positive T lymphocytes using the biopsied muscle specimen from a HTLV-I-negative dermatomyositis patient (67-year-old male). We observed the infiltrates of CD4+ T lymphocytes around the muscle fiber, however, we could not detect Foxp3-expressing T lymphocytes in these infiltrates (Fig. 2B). These findings suggest that HTLV-1-infected T cells existed

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**Table 1. Laboratory Findings on Admission**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Serological tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid</td>
<td>normal</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>Hemoglobin (Hb)</td>
<td>11.3 g/dL</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>36.3%</td>
<td>IgG</td>
</tr>
<tr>
<td>Ht</td>
<td>36.3%</td>
<td>IgA</td>
</tr>
<tr>
<td>Plt</td>
<td>17.6 × 10^4 μL</td>
<td>IgM</td>
</tr>
<tr>
<td>White blood cells</td>
<td>3000 µL</td>
<td>C3</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>62.2%</td>
<td>C4</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>1.0%</td>
<td>7.0g/dL</td>
</tr>
<tr>
<td>Monocyte</td>
<td>7.6%</td>
<td>ANA</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>28.2%</td>
<td>Anti-Jo-1 Ab</td>
</tr>
<tr>
<td>Baso</td>
<td>1.0%</td>
<td>ds-DNA Ab</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td></td>
<td>ss-DNA Ab</td>
</tr>
<tr>
<td>Total protein</td>
<td>10.2 g/dL</td>
<td>Anti-Sm Ab</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.4 mg/dL</td>
<td>Anti-RNP Ab</td>
</tr>
<tr>
<td>Alb</td>
<td>3.0 g/dL</td>
<td>Anti-SSA Ab</td>
</tr>
<tr>
<td>Glutamic-oxaloacetic transaminase</td>
<td>75 IU/L (7-33)</td>
<td>PR3-ANCA</td>
</tr>
<tr>
<td>Glutamic-pyruvic transaminase</td>
<td>29 IU/L (5-30)</td>
<td>MPO-ANCA</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>443 IU/L (260-480)</td>
<td>KL-6</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>158 IU/L (80-250)</td>
<td>SF-D</td>
</tr>
<tr>
<td>CK</td>
<td>1209 IU/L (45-163)</td>
<td>HBs Ag</td>
</tr>
<tr>
<td>Aldolase</td>
<td>23.4 IU/L (1.1-6.1)</td>
<td>HCV Ab</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>12.6 mg/dL</td>
<td>HTLV-I Ab (PA method)</td>
</tr>
<tr>
<td>Cr</td>
<td>0.4 mg/dL</td>
<td>HTLV-I Ab (western blot)</td>
</tr>
<tr>
<td>Na</td>
<td>137 mEq/L</td>
<td>gp46(+), p53(+)</td>
</tr>
<tr>
<td>K</td>
<td>3.7 mEq/L</td>
<td>p24(+), p19(+)</td>
</tr>
<tr>
<td>Cl</td>
<td>106 mEq/L</td>
<td></td>
</tr>
</tbody>
</table>

in the muscle tissues of the present HTLV-1 positive dermatomyositis patient.

The trough concentrations of cyclosporine A (87 ng/mL) had reached the therapeutic range. Therefore, tacrolimus (3 mg/day), which was substituted for cyclosporine A (150 mg/day), was combined with maintenance doses of corticosteroid (prednisolone 20 mg/day). These treatments resulted in a marked improvement of the muscle symptoms, and follow-up MRI showed that the symmetrical inflammation of the affected muscle had disappeared (Fig. 1B).

Discussion

In this case report, we presented a woman who was seropositive for HTLV-I virus and had clinical and pathological features of overlap syndrome, which consisted of Sjögren’s syndrome and dermatomyositis. Another feature of the present case was the high IgG levels and the presence of various autoantibodies. Furthermore, immunohistochemical analysis demonstrated massive perivascular infiltrates and these infiltrating mononuclear cells were predominantly CD4+ T lymphocytes, some of which expressed Foxp3. Recent studies have demonstrated that Foxp3, a Treg-specific transcription factor, is expressed in leukemic cells from patients with ATL (7). Taken together with our immunohistochemical findings from the muscle biopsy specimen, we speculate that HTLV-I-infected T cells accumulate in the affected muscle and contribute to the perivascular infiltration of mononuclear cells. To support this hypothesis, the development of necrotizing arteritis was demonstrated in transgenic rats carrying the *env-PX* gene of HTLV-I (8). In another animal study, HTLV-I transgenic mice developed inflammatory infiltrates in the salivary glands with histopathology resembling Sjögren’s syndrome (9). In a clinical study, myositis-linked HTLV-1 infection was reported in an HTLV-1 endemic area (10). The relevance of these studies to the clinic-pathological features seen in the present case suggests that HTLV-I infection-related altered immune regulation, such as T cell activation and various auto-antibodies, may contribute to the development of overlap syndrome. HTLV-I infected T cells are thought to proliferate and infiltrate into the affected organs (11), and T cells transformed by HTLV-I have been reported to induce and secrete a variety of cytokines, including IL-1, IL-2, IL-3, IL-6, TNF-α and IFN-γ (12). IL-6 is a cytokine that can induce autoantibody production and TNF-α appears to be responsible for

Figure 2A. Histological findings and characterization of mononuclear cells in the biopsied muscle tissues in the present case. Sections of the muscle tissue were prepared and stained as follows. a) Hematoxylin and Eosin staining section shows the perivascular mononuclear cell infiltrates (necrotizing vasculitis) and perifascicular muscle atrophy (original magnification ×100). b) Staining with anti-CD4 shows that the majority of perivascular mononuclear cells are CD4 positive T cells (original magnification ×200). c) Staining with anti-CD8 shows the few CD8 positive cells in the inflammatory cell infiltrates (original magnification ×200). d) Staining with anti-Foxp3 shows the presence of Foxp3-positive T cells in the inflammatory cell infiltrates (original magnification ×400).
Sjögren’s syndrome in an HTLV-1 endemic area.

...that HTLV-I infection could be involved in a subset of pro-
...importance in certain overlap syndromes in which HTLV-I-
...refractory polymyositis/dermatomyositis (PM/DM) and PM/
...have been highlighted by several recent findings, such as
...the immunosuppressive effects of cyclosporine and tacrolimus
...the overlap syndrome in the present case.

In the present case, the effects of high-dose corticosteroid
plus cyclosporine were transient, however, tacrolimus was
effective in controlling the myositis. A major component of
the immunosuppressive effects of cyclosporine A and
tacrolimus could be accounted for by the antagonism of cal-
cineurin activity (15). However, the differences between the
immunosuppressive effects of cyclosporine and tacrolimus
have been highlighted by several recent findings, such as
tacrolimus-mediated induction of apoptosis (16). It was also
reported that tacrolimus was effective in cyclosporine-refractory
polymyositis/dermatomyositis (PM/DM) and PM/
DM-associated interstitial lung disease (17, 18).

In summary, HTLV-I infection may be of pathogenic im-
portance in certain overlap syndromes in which HTLV-I-
infected activated T cells are considered to be responsible
for the inflammatory processes. This case report suggests
that HTLV-I infection could be involved in a subset of pro-
totypical rheumatic diseases, including dermatomyositis and
Sjögren’s syndrome in an HTLV-1 endemic area.

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

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