Interstitial lung disease associated with juvenile dermatomyositis: clinical features and efficacy of cyclosporin A

I. Kobayashi, M. Yamada, Y. Takahashi, N. Kawamura, M. Okano, Y. Sakiyama and K. Kobayashi

**Objectives.** Interstitial lung disease (ILD) is a rare complication of juvenile dermatomyositis (JDM). The aim of this study was to clarify the clinical features of JDM-associated ILD and to evaluate the efficacy of cyclosporin A (CSA).

**Methods.** We reviewed clinical records of 10 cases of JDM that were admitted to Hokkaido University Hospital between April 1990 and March 2001.

**Results.** Five cases were complicated with ILD, three with interstitial pneumonia and two with bronchiolitis obliterans organizing pneumonia. ILD was associated with active JDM and progressed despite corticosteroid therapy. Testing for anti-Jo-1 antibody was negative in all cases. Respiratory symptoms were initially noticed in only one case. In the other cases, ILD was first detected by routine examination of chest X-ray. All the cases received CSA (3–5 mg kg\(^{-1}\) day\(^{-1}\)) in combination with prednisolone. One patient died of respiratory failure, but the others responded well to treatment with CSA.

**Conclusion.** ILD should be evaluated carefully in all cases of JDM regardless of respiratory symptoms. CSA is a choice for steroid-resistant cases of JDM-associated ILD.

**KEY WORDS:** Juvenile dermatomyositis, Interstitial lung disease, Interstitial pneumonia, Bronchiolitis obliterans organizing pneumonia, KL-6, Cyclosporin A.

Dermatomyositis (DM) is an inflammatory disease characterized by muscle weakness and erythematous skin lesions [1, 2]. Interstitial lung disease (ILD) is an established complication of adult DM which occurs in up to 50% of cases [3, 4]. Abnormal pulmonary function is demonstrated in more than half of juvenile dermatomyositis (JDM) cases [2, 5]. Nevertheless, reported cases of JDM-associated ILD confirmed by radiological imaging have been limited [6–10]. JDM-associated ILD, once it occurs, is often rapidly progressive and fatal despite intensive corticosteroid therapy [6, 7]. Recent studies have demonstrated that an immunosuppressant, cyclosporin A (CSA), is beneficial in steroid-resistant cases of JDM as well as adult cases [11–13]. CSA is also effective against adult DM-associated ILD [12, 13]. However, clinical features of JDM-associated ILD and the efficacy of CSA have not been well established. Here, we present clinical features of five cases of JDM-associated ILD and evaluate the efficacy of CSA.

**Patients and methods**

**Patients**

Ten cases of JDM, six boys and four girls, who were admitted to Hokkaido University Hospital between April 1990 and March 2001, were reviewed. All of the cases were classified as probable or definite JDM according to the diagnostic criteria proposed by Bohan and Peters [1]. None of the cases fulfilled diagnostic criteria of other collagen vascular diseases, such as...
systemic lupus erythematosus, mixed connective tissue disease and juvenile rheumatoid arthritis. Five cases, two boys and three girls aged 4–14 yr, were complicated with ILD and were included in this study (Table 1). At the initial examination, all the cases had typical skin rash, whereas myositis was not evident in cases 1 and 3. In addition to ILD, two cases were complicated with severe thrombocytopenia during the course of the disease.

**Table 1. Clinical and laboratory features**

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Age at onset of JDM (yr)</td>
<td>8</td>
<td>14</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Diagnosis of ILD*</td>
<td>2 months</td>
<td>4 months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 months&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 months&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diagnosis on CT</td>
<td>IP</td>
<td>IP</td>
<td>BOOP</td>
<td>IP</td>
</tr>
<tr>
<td>Complications</td>
<td>Thrombocytopenia</td>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose of PSL (mg/kg)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.3</td>
<td>1.5</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Other treatment</td>
<td>AZA mPSL</td>
<td>IVIG mPSL</td>
<td>mPSL</td>
<td>mPSL</td>
</tr>
<tr>
<td>Dose of CSA (mg/kg)</td>
<td>5</td>
<td>3–4</td>
<td>3–5</td>
<td>3–5–4.5</td>
</tr>
<tr>
<td>CK (IU/l)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>65</td>
<td>26</td>
<td>15</td>
<td>231</td>
</tr>
<tr>
<td>AST (IU/l)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>77</td>
<td>213</td>
<td>32</td>
<td>103</td>
</tr>
<tr>
<td>LDH (IU/l)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>539</td>
<td>567</td>
<td>507</td>
<td>795</td>
</tr>
<tr>
<td>Aldolase (IU/l)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>8.5</td>
<td>24.9</td>
<td>7.3</td>
<td>ND</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Negative</td>
<td>1:20</td>
<td>1:80</td>
<td>1:320</td>
</tr>
<tr>
<td>Neopterin (pmol/ml)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>36</td>
<td>30</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>KL-6 (U/ml)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2460</td>
<td>1096</td>
<td>1029</td>
<td>1065</td>
</tr>
</tbody>
</table>

ASA, aspartate aminotransferase; LDH, lactate dehydrogenase.
<sup>*</sup>Interval after onset of JDM.
<sup>b</sup>Mild abnormal findings on chest X-ray were observed 3 and 4 months before the diagnosis of ILD in cases 2 and 3 respectively.
<sup>c</sup>ILD developed simultaneously with relapse of the skin lesion.
<sup>d</sup>Dose of prednisolone when CSA was started.
<sup>f</sup>Laboratory data at the time of diagnosis of ILD. Normal reference values: CK, 30–165 IU/l; AST, 5–40 IU/l; LDH, 200–460 IU/l; aldolase, 2.0–4.8 IU/l; KL-6, < 500 U/ml; Neopterin, 2–8 pmol/ml.

Assessment of ILD

Severity of ILD was assessed by chest CT scan, pulmonary function test (for patients over 7 yr of age) and serum levels of KL-6; a recently developed marker for ILD [10, 14]. KL-6 was tested with an enzyme immunoassay system according to the manufacturer’s protocol (Eitest KL-6; Eizai, Tokyo, Japan) [10, 14].

Results

Clinical and laboratory features and treatment are summarized in Table 1. Non-productive cough and resting dyspnoea were noticed only in case 1 as initial symptoms. Cases 2, 4 and 5 showed mild dyspnoea on exercise without hypoxaemia as ILD progressed. Case 3 had neither cough nor dyspnoea during the disease course. In these four cases, ILD was suspected by routine examination of the chest X-ray and was confirmed by chest CT scan 1–7 months after the onset of JDM.ILD developed simultaneously with the relapse of skin lesions in case 3. Although the diagnosis of ILD was confirmed 4 and 2 months after the onset of JDM in cases 2 and 4 respectively, very mild abnormalities were observed retrospectively on the chest X-rays that were taken at the initial examination. Accordingly, the onset of ILD was estimated to be during the first 2 months after the onset or relapse of JDM in all cases. Radiological diagnoses were interstitial pneumonia (IP) in three cases and bronchiolitis obliterans organizing pneumonia (BOOP) in two cases. Serum levels of transaminases, lactate dehydrogenase, aldolase and/or neopterin were mildly or moderately elevated at the diagnosis of ILD in all cases. The serum creatine phosphokinase level was initially elevated but returned to the normal range at the diagnosis of ILD in cases 1 and 4. Serum levels of creatine phosphokinase, neopterin and KL-6 became elevated later in association with deterioration of the CT findings in case 5. Antinuclear antibody was weakly to moderately positive in four cases (Table 1). Tests for anti-Sm, anti-double-stranded DNA, anti-RNP and anti-Jo-1 antibodies were negative in all cases. Although methylprednisolone pulse therapy was carried out, improvement of CT findings or pulmonary function was absent or partial in all cases.

Case 1 showed a rapidly progressive course despite repetitive methylprednisolone pulse therapy in combination with azathioprine for a month. He died of respiratory failure following pneumothorax after 4 days of treatment with CSA. Chest CT findings of cases 2, 3 and 4 improved gradually following the commencement of CSA. Abnormal CT findings, such as consolidation and
Interstial lung disease in JDM

Fig. 1. (A) Changes in percentage vital capacity during CSA treatment with CSA in patients 2, 4 and 5. (B) Changes in serum KL-6 concentration during treatment in all five patients.

ground grass findings in cases 2 and 3, disappeared completely within 1 yr of follow-up. Case 5 showed deterioration of CT findings despite the first course of methylprednisolone pulse therapy followed by 10 days of oral administration of CSA (3.5 mg/kg/day). Following an increase in the dose of CSA (4.8 mg/kg/day) combined with the second course of methylprednisolone pulse therapy, her CT findings gradually improved, except for an episode of mild pneumomediastinum, which resolved spontaneously. Additionally, she showed cytomegalovirus (CMV) antigen in her peripheral blood mononuclear cells and CMV DNA in bronchoalveolar lavage fluid, which disappeared after 2 weeks of treatment with ganciclovir.

Percentage vital capacity (%VC) before and after treatment with CSA is demonstrated in Fig. 1A for cases 2, 4 and 5. Values increased within 2 months after treatment.

The serum KL-6 level was transiently elevated and remained high following treatment with CSA in two cases (cases 4 and 5), and then gradually decreased. The level returned to the normal range after 1 yr of treatment with CSA in cases 2 and 3 (Fig. 1B).

The dose of prednisolone was 0.7–1.5 mg/kg/day when CSA was started. Following the administration of CSA, the dose of oral prednisolone was slowly reduced to 0.1–0.3 mg/kg/day.

Hirsutism was observed in all the surviving cases. There was no other adverse effect of CSA, such as renal dysfunction.

Discussion

We report five cases of JDM-associated ILD. ILD developed and progressed during the first 2 months after the onset or relapse of JDM in all cases. Three cases showed elevated levels of creatine phosphokinase during this period. Furthermore, all cases showed elevated serum levels of transaminases, aldolase and/or neopterin, all of which are known to be markers of activity of JDM [2]. These findings suggest that ILD developed in the active phase of JDM, even though the skin rash or muscle weakness had subsided with corticosteroid therapy. In adult DM-associated ILD, respiratory symptoms, such as cough and dyspnoea, occur simultaneously or precede the skin or muscle manifestation in about half of all cases [3, 4]. In contrast, the respiratory symptoms were initially mild or absent in most of the JDM cases, whereas abnormalities were observed on chest X-ray or CT scanning. Thus, careful evaluation for pulmonary complication is necessary in cases of JDM regardless of pulmonary symptoms, particularly at the onset and on relapse of JDM. The incidence of apparent ILD was 50% in our series. This seems to be much higher than the true incidence, because only severe cases are referred to our hospital. Given that abnormal respiratory functions are observed in about half of all JDM patients [2, 5], it is possible that asymptomatic pulmonary diseases occur frequently in JDM and, in most cases, are cured by conventional corticosteroid therapy for skin and muscle lesions. Only steroid-resistant pulmonary diseases may progress during the course of disease. Although lung biopsy was not performed in our cases, CT findings suggested IP and BOOP in three and two cases respectively. Recent studies have demonstrated that CT findings correlate with histopathological findings and can be used for the differentiation of ILD [15]. Air leak was observed in two cases, supporting previous reports that JDM-associated ILD could cause pneumothorax or pneumomediastinum [6, 7, 9]. One case (case 5) was complicated with CMV infection. CMV was possibly reactivated by immunosuppressive therapy but was not pathogenic, because ganciclovir showed no effect on ILD; otherwise, CMV infection might have triggered the exacerbation of ILD, as suggested by a previous report [9].

ILD progressed even during treatment with prednisolone and was refractory to methylprednisolone pulse therapy in all cases. In addition, adverse effects of corticosteroid were apparent in three cases. In the four surviving cases, CSA clearly had a steroid-sparing effect on both skin and muscle lesions, supporting previous reports that CSA is effective in JDM [9, 11, 12]. Furthermore, our results demonstrated that CSA was also effective in JDM-associated ILD in these cases. Only one patient (case 1) died, of respiratory failure, after 4 days of treatment with CSA. Maeda et al. [13] have suggested that CSA is effective in adult DM/PM-associated ILD when used early in the disease course. Thus, it is possible that earlier commencement of CSA could have been effective in case 1. In contrast to CT findings and %VC, serum level of KL-6 was transiently elevated and remained at a high level for several months. This may reflect the process of repair of the lung tissue, including fibrotic changes, because KL-6 is produced by type II pneumocytes and acts as a chemotactic factor for fibroblasts [10, 14].

Recent studies have demonstrated that CSA inhibits the activation of alveolar macrophages and peripheral blood monocytes as well as T cells, and that its effects on
macrophages are greater than those of corticosteroids *in vitro* [16]. On the other hand, the involvement of activated T cells and macrophages are suggested in both JDM and ILD [2]. Thus, the therapeutic effect of CSA in JDM and ILD may be mediated by suppression of both T-cell and macrophage functions. Prospective studies are necessary to compare its efficacy and adverse effects with those of other immunosuppressive agents, such as methotrexate and cyclophosphamide, and to establish an optimal treatment for ILD associated with JDM.

In conclusion, ILD develops in association with active JDM and requires careful evaluation by imaging, pulmonary function testing and determination of serum levels of KL-6, regardless of clinical respiratory symptoms. Although the present study was uncontrolled, the results indicate that CSA is a choice for cases of steroid-resistant JDM-associated ILD. Early commencement of CSA is recommended for rapidly progressive ILD.

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**References**