Clinical and laboratory features of fatal rapidly progressive interstitial lung disease associated with juvenile dermatomyositis

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Abstract

Objective. Rapidly progressive interstitial lung disease (RP-ILD) is a rare but potentially fatal complication of JDM. The aim of this study was to establish markers for the prediction and early diagnosis of RP-ILD associated with JDM.

Methods. The clinical records of 54 patients with JDM were retrospectively reviewed: 10 had RP-ILD (7 died, 3 survived), 19 had chronic ILD and 24 were without ILD. Routine tests included a high-resolution CT (HRCT) scan of the chest and measurement of serum levels of creatine phosphokinase, ferritin and Krebs von den Lungen-6 (KL-6). Anti-melanoma differentiation-associated gene 5 (MDA5) antibodies and IL-18 levels were measured by ELISA.

Results. No differences were found in the ratio of juvenile clinically amyopathic DM between the three groups. Initial chest HRCT scan findings were variable and could not distinguish between RP-ILD and chronic ILD. Anti-MDA5 antibodies were positive in all 8 patients with RP-ILD and 10 of 14 with chronic ILD, but none of the patients without ILD. Serum levels of anti-MDA5 antibody, ferritin, KL-6 and IL-18 were significantly higher in the RP-ILD group than in the chronic ILD and non-ILD groups. Serum levels of IL-18 positively correlated with serum KL-6 ($R = 0.66, P < 0.001$).

Conclusion. High serum levels of IL-18, KL-6, ferritin and anti-MDA5 antibodies (e.g. >200 units by ELISA) are associated with RP-ILD. These can be used as an indication for early intensive treatment. Both alveolar macrophages and autoimmunity to MDA5 are possibly involved in the development of RP-ILD associated with JDM.

Key words: juvenile dermatomyositis, interstitial lung disease, interleukin-18, anti-melanoma differentiation-associated gene 5, KL-6, ferritin.
Introduction

JDM is a rare inflammatory disease characterized by typical skin rashes and muscle weakness. It affects 2–3/ million children/yr, however, the frequency differs between ethnic groups [1–3]. Prior to the 1960s, more than one-third of patients died of the disease [4]. Advances in treatment with corticosteroids and immunosuppressants have reduced the mortality rate of JDM to 1–5% [5, 6].Interstitial lung disease (ILD) is observed in up to 50% of adult DM cases and is a major cause of death when rapidly progressive ILD (RP-ILD) develops in association with clinically amyopathic DM (CADM) [7]. Nevertheless, radiologically confirmed ILD complicates only 2–14% of JDM cases [8, 9]. In a recent Japanese nationwide physician questionnaire-based survey of severe paediatric rheumatic diseases from 2005 to 2009, 13 deaths in patients with JDM were reported; there were > 3 deaths in patients with SLE during the same period [10]. Complete clinical records and sera were available in 6 of the 13 JDM patients who died. Surprisingly, all six deaths were attributed to ILD. The Japanese survey demonstrates that RP-ILD is a major cause of death related to JDM in Japan. This prompted this study to establish markers for the prediction and early diagnosis of RP-ILD associated with JDM.

We have reported that the serum Krebs von den Lungen-6 (KL-6) level is a useful marker of ILD associated with JDM [11]. Furthermore, similar to adult cases, anti-CADM-140/melanoma differentiation-associated gene 5 (MDA5) autoantibodies are possible diagnostic markers of JDM-associated ILD [12–14]. Recent studies on adult DM-associated ILD have demonstrated elevated serum levels of both ferritin and IL-18, which is produced by macrophages and dendritic cells (DCs) and activates Th1 response [15–18]. However, cytokine profiles have not been reported in JDM-associated ILD, possibly because of the rarity of the complication. In the present Japanese nationwide collaborative study, we focused on the clinical, radiological and laboratory features of patients with JDM-associated RP-ILD and compared them with those of JDM patients without RP-ILD.

Patients and methods

Definition

Classic JDM was diagnosed according to Bohan and Peter [1]. As this was a retrospective study, muscle weakness was determined by the assessing physician and was not based on validated muscle assessment such as manual muscle test. Juvenile CADM (JCADM) was diagnosed according to modified Gerami et al. [19] criteria: hypomyopathic DM was defined as patients with classical cutaneous manifestations of DM and no proximal muscle weakness but with evidence of myositis on laboratory, electrophysiological and/or radiological testing; amyopathic DM patients had no clinical or laboratory evidence of myositis. Gerami et al. [19] originally defined JCADM as patients fulfilling the above conditions for > 6 months after onset without systemic treatment. However, in the present study we classified all patients without weakness at the commencement of treatment as having CADM, because most of the patients with ILD require early treatment with systemic corticosteroids and immunosuppressants, usually within 6 months after the onset of JDM. The diagnosis of ILD was made by using high-resolution CT (HRCT) scan of the chest and was confirmed by both a radiologist and a paediatric rheumatologist at each institute. RP-ILD was defined as the progression of dyspnoea or HRCT findings within 3 months after the onset of respiratory symptoms or at the time of diagnosis of JDM.

Patients

In the nationwide survey of severe paediatric rheumatic diseases, paediatricians in inpatient health care facilities in Japan were asked about the number of patients with rheumatic disease who had visited the clinic in 2009 and the number of deaths between 2005 and 2009. All the patients were Japanese. Nine institutes reported 13 deaths of children with classic JDM or JCADM. Furthermore, respondents were asked to answer questions about data based on the patients’ medical charts. Among the 13 deaths in children with JDM, complete clinical records and sera were available in six patients and were retrospectively analysed. One patient died of Pneumocystis jirovecii pneumonia and was excluded. The other five patients died from RP-ILD [10, 21–24]. The number of cases of RP-ILD was increased by including two patients who died of JDM-associated RP-ILD before 2004 and by including three surviving cases with RP-ILD available from the authors’ institutes [14, 25]. As a result, 10 patients (7 deceased and 3 survivors) were included in this category. Twenty patients with ILD associated with JDM (followed up by the authors) did not show a rapidly progressive course. One patient was excluded, leaving 19 patients in this chronic ILD group. The excluded patient had chronic ILD and severe myositis complicated by macrophage activation syndrome (MAS); the associated macrophage activation was presumed to be the cause of markedly elevated levels of IL-18 [20]. The clinical features of seven patients with ILD have been previously reported [14, 20–25]. Twenty-four patients with JDM without ILD on chest CT scan from Shinshu University Hospital, Aichi Children’s Health and Medical Center and Hokkaido University Hospital were included in the non-ILD group.

Biochemical and serological analyses

Sera were collected from the patients at diagnosis of ILD or, in the case of patients without ILD, at diagnosis of JDM and stored at −20°C until use. Routine laboratory tests included measurement of serum levels of creatine phosphokinase (CK), ferritin and a marker for ILD, KL-6. Anti-MDA5 antibody levels were measured by both ELISA and immunoprecipitation as previously described [13]. Serum IL-18 levels were measured by ELISA according to the manufacturer’s protocol (MBL, Nagoya, Japan).
Statistical analyses

The data were analysed by Tukey-Kramer’s multiple comparison tests, Fisher's exact tests with Bonferroni adjustment and Pearson’s product-moment correlation coefficient using JMP 10.0 for Windows (SAS Institute, Cary, NC, USA).

Ethics

The ethics committee of Shinshu University approved the present study. Written consent was obtained from the parents of the patients according to the Declaration of Helsinki.

Results

Clinical and radiological features of JDM-associated RP-ILD

The clinical and laboratory findings of 10 children with RP-ILD are shown in Table 1. Eight patients showed apparent muscle weakness, although the other two patients were classified as having JCADM. Nine of the 10 patients had characteristic skin findings and high fever (temperature >38°C). Gottron’s papules were the most common skin lesion, followed by malar erythema and erythema of the knees and elbows. In contrast, heliotrope rash and ulcerative lesions were rarely observed. Respiratory symptoms such as dry cough, dyspnoea and fine crackles were observed in five, four and six patients, respectively, at diagnosis of ILD. The remaining patients had no respiratory symptoms or signs of ILD at diagnosis. Seven of the 10 patients with RP-ILD died of respiratory failure 1–4 months after the diagnosis of ILD.

HRCT findings of RP-ILD

Lung HRCT scan findings at the time of diagnosis of ILD are summarized in Table 1. Subpleural curvilinear shadow was the most predominant finding. Although localized ground glass opacity (GGO) was observed in six patients, GGOs developed during the disease course in all patients who died of ILD. Three patients (patients 3, 4 and 6) had consolidation around bronchovascular bundles (CABBs) accompanying extensive GGOs. Four patients (patients 1, 4, 6 and 7) developed an air leak such as pneumomediastinum and pneumothorax during the course of the disease. Although patient 1 had only bilateral pleural effusion on the initial HRCT, both elevated serum KL-6 levels and increased galium-67 uptake on scintigraphy of the lungs were noted. One month later, chest HRCT demonstrated marked consolidation at the base of both lungs [22]. In all cases of death, the final diagnosis leading to death was acute interstitial pneumonia with acute and progressive respiratory failure accompanied by GGOs on HRCT. The clinical diagnosis was consistent with diffuse alveolar damage (DAD) patterns on autopsy or biopsy.

Comparison of the clinical features of the chronic ILD and non-ILD groups

The clinical features of the three groups are summarized in Table 2. The age of onset was significantly higher in the chronic ILD group than in the non-ILD group. No differences were found in the ratio of JCADM among the three groups. Seven of the 10 patients with RP-ILD died despite intensive treatment with methylprednisolone pulse therapy in combination with CSA and/or i.v. CYC, whereas none of the patients in the chronic ILD and non-ILD groups died.

Comparison of the laboratory features of the chronic ILD and non-ILD groups

The laboratory findings of the three groups are summarized in Table 2. Although serum CK levels were significantly higher in the non-ILD group than in the chronic ILD group, there was no significant difference between the RP-ILD and non-ILD groups. Serum KL-6 levels were significantly higher in the RP-ILD group than in either the chronic ILD or the non-ILD group. Serum ferritin levels in both the RP-ILD and chronic ILD groups were higher than those in the non-ILD group.

All 8 patients with RP-ILD and 10 of 14 patients with chronic ILD were positive for anti-MDA5 antibodies, but none of the 22 patients without ILD were positive for the antibodies. Titres of anti-MDA5 antibodies were significantly higher in the RP-ILD group than in either the chronic ILD or the non-ILD group (Table 2 and Fig. 1). Serum IL-18 levels were significantly higher in the RP-ILD group than in the chronic ILD or non-ILD group (Table 2 and Fig. 2). Serum IL-18 levels correlated well with serum KL-6 levels (R=0.66) but not with ferritin levels (Fig. 3 and data not shown). A patient with severe myositis, MAS and chronic ILD, who was excluded from statistical analyses, showed high serum levels of IL-18 (3265 pg/ml), ferritin (2235 ng/ml) and KL-6 (2096 U/ml), but only mild elevation of anti-MDA5 antibody levels (9.5 units) [20].

Sera were serially tested in two patients with RP-ILD who survived and two patients with chronic ILD who were positive for anti-MDA5 antibody. Serum levels of anti-MDA5 antibodies and IL-18 returned to below the cut-off values or to undetectable levels at remission of ILD (data not shown).

Discussion

Although previous studies have reported multiple organ involvement such as muscle weakness, aspiration pneumonia, myocarditis, peptic ulcer and sepsis as causes of death in JDM, the prognosis has improved through recent advances in the management of the disease [5, 26]. The Japanese nationwide survey demonstrated RP-ILD as a remaining major cause of death in JDM. The UK and Ireland national registry from 2000 to 2005 indicated only one death in patients with JDM [27]. A recent study in the USA that enrolled 329 patients with JDM recorded only eight deaths from 1999 to 2011, three of which were due to ILD [28]. Given the higher prevalence of adult CADM-associated RP-ILD in Asian countries, Japanese children with JDM may also be predisposed to RP-ILD compared with other ethnicities [7, 29]. In our previous nationwide survey we analysed the number of patients...
### Table 1: Clinical course of 10 children with JDM or JCADM-associated rapidly progressive ILD

<table>
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<th>Sex</th>
<th>Male</th>
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<tr>
<td>Interval between onset of JDM and diagnosis of ILD, months</td>
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<td>3</td>
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<td>6</td>
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**Outcome**

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<th>CABB, GGO, SCS</th>
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**Autopsy**

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<th>DAD</th>
<th>DAD</th>
<th>ND</th>
<th>ND</th>
<th>DAD</th>
</tr>
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</table>

**Interval between diagnosis of ILD and death, months**

| 4 | 4 | 1 | 3 | 2 | 1 | 2 |

**Interval between onset of respiratory symptoms and death, months**

| 4 | 2 | 1 | 7 weeks | 6.5 | 5 | 2 |

**Reference**

[22] [23] [20] [20]

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Surgical lung biopsy. CABB: consolidation around bronchovascular bundles; DAD: diffuse alveolar damage; GGO: ground-glass opacity; JCADM: juvenile clinically amyopathic dermatomyositis; ND: not done; PE: pleural effusion; RP-ILD: rapidly progressive interstitial lung disease; SCS: subpleural curvilinear shadow; TB: traction bronchiectasis.

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### Table 2: Comparison of clinical and laboratory features

<table>
<thead>
<tr>
<th></th>
<th>RP-ILD (n = 10)</th>
<th>Chronic-ILD (n = 19)</th>
<th>Non-ILD (n = 24)</th>
<th>P-value</th>
</tr>
</thead>
</table>
| Age, mean (s.d.), years | 6.3 (3.5) | 9.0 (3.6) | 6.0 (3.3) | 0.119  
| Sex, male/female | 4/6 | 7/12 | 11/13 | 0.486  
| JCADM, n | 2 | 2 | 3 | 0.337  
| Mortality, % (n dead/ n alive) | 70.0 (7/3) | 0.0 (0/19) | 0.0 (0/24) | <0.001  
| CK, mean (s.d.), IU/l | 403.1 (604.2) | 473.7 (1304.8) | 1790.3 (3202.1) | 0.019  
| KL-6, mean (s.d.), units | 2045.6 (881.5) | 718.3 (899.0) | 283.1 (113.3) | 0.001  
| Anti-MDA5, mean (s.d.), units | 387.9 (288.9) | 33.3 (30.1) | 2.4 (1.7) | <0.001  
| Anti-MDA5 positive cases (cut-off value 8.0 units), % | 100 (n = 8) | 71.4 (n = 14) | 0.0 (n = 22) | <0.001  
| IL-18, mean (s.d.), pg/ml | 1447.0 (941.4) | 470.0 (341.6) | 570.1 (474.0) | <0.001  
| Ferritin, mean (s.d.), ng/ml | 355.4 (136.8) | 222.8 (129.3) | 131.2 (160.4) | <0.001  

**P-value**

<table>
<thead>
<tr>
<th>a</th>
<th>b</th>
<th>c</th>
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<tr>
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<td>Tukey-Kramer test&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Fisher’s exact test&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>0.613</td>
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<td>Fisher’s exact test&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Fisher’s exact test&lt;sup&gt;b&lt;/sup&gt;</td>
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<sup>a</sup>To identify the difference among three groups, Fisher’s exact test with Bonferroni adjustment was performed. <sup>b</sup>P < 0.016 was considered significant. <sup>c</sup>Tukey-Kramer test after log transformation. a: RP-ILD vs chronic-ILD; b: chronic-ILD vs non-ILD; c: RP-ILD vs non-ILD; CK: creatine phosphokinase; ILD: interstitial lung disease; JCADM: juvenile clinically amyopathic DM; KL-6: Krebs von Lungen-6; MDA5: differentiation-associated gene 5; ns: not significant; RP-ILD: rapidly progressive ILD.
with rheumatic diseases who visited hospitals in 2009 and the number and causes of deaths between 2005 and 2009. Furthermore, we included five additional patients with RP-ILD who had presented to our hospital before the study period. A cohort study that captured all JDM cases nationwide is needed to determine the actual prevalence of ILD and the mortality rate of Japanese patients with JDM.

In the present study we could not identify any characteristic clinical features specific to JDM associated with RP-ILD. HRCT showed diffuse GGOs in all the deceased patients, which was consistent with a DAD pattern on autopsy. However, initial HRCT findings were variable and indistinguishable from those of survivors with RP-ILD or chronic ILD. Final radiological and pathological findings may represent merely the end stage of the disease, regardless of the original clinicopathological entities of ILD. Two of the four patients with pneumomediastinum and pneumothorax (patients 6 and 7, respectively) showed ulcerative lesions of their skin. Vasculopathy associated with JDM could have caused ulceration of both skin and airway walls, as suggested in adult cases [30].

We have reported that anti-MDA5 antibody is a useful disease marker of JDM-associated ILD [14]. The present study also demonstrated that higher levels of the antibody (e.g., >200 units by ELISA) were found in all but one of the RP-ILD group (patient 1), whereas the chronic ILD group had lower titres (<100 units). In addition, the titre of anti-MDA5 antibody declined to below the cut-off value (data not shown). Thus the antibody may help to differentiate RP-ILD from chronic ILD and may help in monitoring the response to treatment in JDM-associated RP-ILD. A similar correlation of the antibody titre with the activity of ILD has recently been reported in adult DM [31]. The antibody was originally reported as a disease marker of CADM-associated RP-ILD but is also detected in some adult cases of DM with chronic ILD on the basis of sensitive immunoblot analyses [12, 13, 32]. Given that anti-MDA5 antibodies were detected regardless of the severity of muscular lesions in our series, the antibodies are possibly related to ILD itself rather than JCADM. On the other hand, anti-MDA5 antibodies are associated with symmetrical arthritis, myositis and ILD, but not with CADM-associated RP-ILD in the USA [33]. Thus the clinical significance of the antibodies may differ between ethnic groups.

In addition to anti-MDA5 antibody, serum levels of ferritin, KL-6 and IL-18 were associated with RP-ILD, although the highest serum level of IL-18 was detected in a patient with severe myositis complicated by MAS and
chronic ILD. IL-18 is produced by both macrophages and DCs in the muscle tissues of patients with DM; IL-18 attracts plasmacytoid DCs that produce type 1 IFNs and correlates with disease activity in adult DM/PM patients without ILD [16, 17]. Extremely high levels of ferritin and IL-18 are reported in systemic JIA-associated MAS [34]. In addition, the association of elevated serum IL-18 levels with RP-ILD, as demonstrated in the present study, has also been reported in adult DM-associated ILD [35–37]. Activated alveolar macrophages are consistently found in bronchoalveolar lavage fluid from patients with DM-associated ILD [15]. Together, macrophages or DCs in the muscle, bone marrow and lungs are likely to play critical roles in myositis, MAS and JDM-associated ILD, respectively. Thus high levels of IL-18 for fibroblasts may not necessarily reflect the presence of RP-ILD in patients with severe myositis or MAS.

Studies of bronchoalveolar lavage fluid have also demonstrated restricted V$\beta$ gene usage of T cell receptors and the presence of CD8$^+$HLA-DR$^+$ T cells in DM-associated ILD [38, 39]. Because IL-18 stimulates Th1 cells [18], T cells activated by alveolar macrophage-derived IL-18 could contribute to tissue destruction of the lung in an antigen-specific manner. Furthermore, since autoantigens identified by reactivity with autoantibodies also stimulate self-reactive T cells [40], MDAS could be a target antigen of the T cells in DM/JDM-associated RP-ILD. Of note, there was strong correlation between serum levels of IL-18 and KL-6. KL-6 is produced by type II pneumocytes and bronchiolar epithelial cells, particularly during their regeneration. Furthermore, KL-6 functions as a chemoattractant for fibroblasts and is generally considered a biomarker of ILD that reflects the severity of the disease [41–43]. Given that the correlation between KL-6 and IL-18 is not initially observed in adult DM-associated ILD [44], remodelling of the lung may occur at an earlier phase of RP-ILD in JDM rather than in adulthood.

All three survivors with RP-ILD were found to have ILD on the basis of elevated KL-6 levels and HRCT findings and were treated with methylprednisolone pulse therapy in combination with CSA and/or monthly i.v. CYC before the development of respiratory symptoms. Thus screening for ILD using chest HRCT scan and routine monitoring of KL-6 levels is recommended for all patients with JDM regardless of respiratory symptoms. We have reported the efficacy of CSA in combination with methylprednisolone pulse therapy for JDM-associated ILD [21]. Early combination therapy with corticosteroid, CSA and i.v. CYC may further reduce the mortality of RP-ILD as reported in adult cases [45].

In conclusion, our results suggest the involvement of both autoimmune and alveolar macrophages in the development of RP-ILD. Initial CT findings are often indistinguishable between RP-ILD and chronic ILD associated with JDM, however, early development of diffuse GGOs may predict poor outcome. Elevated serum levels of IL-18, KL-6, ferritin and anti-MDA5 antibody (>200 units by ELISA) are associated with RP-ILD in JDM and are indications for early intensive treatment.

### Rheumatology key messages
- Rapidly progressive interstitial lung disease is a major cause of death in Japanese patients with JDM and needs early attention.
- Elevated serum IL-18, KL-6, ferritin and MDA5 antibodies are associated with RP-ILD.
- Both autoimmune processes and alveolar macrophages could be involved in the development of JDM-associated RP-ILD.

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### Disclosure statement
The authors have declared no conflicts of interest.

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