High-Resolution Computed Tomography Characterization of Interstitial Lung Diseases in Polymyositis/Dermatomyositis

SHINICHIRO HAYASHI, MASAHIDE TANAKA, HIROMI KOBAYASHI, TAKAHIKO NAKAZONO, TOSHIMI SATOH, YUJI FUKUNO, NAOKO ARAGANE, YOSHIFUMI TADA, SHUICHI KOARADA, AKIHIDE OHTA, and KOHEI NAGASAWA

ABSTRACT. ***Objective.*** Interstitial lung disease (ILD) associated with polymyositis (PM) and dermatomyositis (DM) sometimes progresses rapidly and is resistant to therapy. Clinical features that forecast the prognosis of the disease remain to be elucidated. Our aim was to assess if selected clinical features and high-resolution computed tomography (HRCT) findings can assist in predicting the clinical course of ILD in PM/DM.

Methods. We examined HRCT findings retrospectively for ILD identified in 17 patients with PM and 16 with DM. Radiological patterns and clinical features are analyzed in comparison with clinical course.

Results. Mortality rates were 12% and 44% for ILD associated with PM and DM, respectively. Most patients with DM died of rapidly progressive lung deterioration. No patient in the PM group died of respiratory failure. In the DM group, all patients with fatal ILD had ground-glass attenuation and reticular opacity as the principal radiological findings. Consolidation was recognized frequently as the principal pattern in nonfatal cases. Radiological patterns were categorized into 3 groups; A: consolidation dominant, B: ground-glass attenuation/reticular opacity dominant without chronic fibrosing process, and C: ground-glass attenuation/reticular opacity dominant with chronic fibrosing process. Occurrences of fatal disease were 0%, 83%, and 20%, in groups A, B, and C.

Conclusion. The prognosis of ILD associated with DM differs from that with PM. The former can be classified into 3 subgroups on the basis of radiological findings, which are closely associated with clinical course. (First Release Dec 15 2007; J Rheumatol 2008;35:260–9)

Key Indexing Terms:
POLYMYOSITIS DERMATOMYOSITIS INTERSTITIAL LUNG DISEASE

Polymyositis (PM) and dermatomyositis (DM) are systemic inflammatory disorders characterized by skeletal muscle involvement, and typical cutaneous lesions in DM. Interstitial lung disease (ILD) is one of the frequent complications of PM/DM[1-7]. The clinical course of ILD in patients with PM/DM varies widely. Some patients die of rapidly progressive ILD despite treatment with corticosteroids and immunosuppressants, while others respond well to corticosteroids[1,3]. Therefore, clarifying the clinical manifestations that predict the responsiveness of ILD to therapy is clinically highly relevant. Recent progress in high-resolution computed tomography (HRCT) has made it possible to characterize pulmonary involvement precisely. We analyzed the HRCT findings of ILD in patients with PM/DM to clarify the relationship between radiological phenotype and response to therapy.

From the Department of Pulmonary Medicine, Department of Radiology, Department of Pathology, and Department of Collagen Vascular Disease and Rheumatology, Saga University School of Medicine, Saga, Japan.

S. Hayashi, MD, PhD, Associate Professor, Pulmonary Medicine; M. Tanaka, MD, Instructor, Pulmonary Medicine; H. Kobayashi, MD, Instructor, Pulmonary Medicine; T. Nakazono, MD, Instructor, Radiology; T. Satoh, MD, PhD, Associate Professor, Pathology; Y. Fukuno, MD, PhD, Instructor, Pulmonary Medicine; N. Aragane, MD, PhD, Assistant Professor, Pulmonary Medicine; Y. Tada, MD, PhD, Assistant Professor, Collagen Vascular Disease and Rheumatology; S. Koarada, MD, PhD, Instructor, Collagen Vascular Disease and Rheumatology; A. Ohta, MD, PhD, Professor, Collagen Vascular Disease and Rheumatology; K. Nagasawa, MD, PhD, Professor, Collagen Vascular Disease and Rheumatology.

Address reprint requests to Dr. S. Hayashi, Department of Internal Medicine, Saga University School of Medicine, 5-1-1 Nabeshma, Saga 849-8501, Japan. E-mail: hayashs@cc.saga-u.ac.jp

Accepted for publication September 20, 2007.

MATERIALS AND METHODS

Thirty one patients with PM and 24 with DM, diagnosed at Saga University Medical School Hospital from January 1995 to April 2005, were studied retrospectively. Informed consent was not required by the committee of ethics at Saga University Medical School Hospital to conduct this study. Diagnosis of PM/DM was based on the criteria of Bohan and Peter[8]. The PM group included 23 patients with definite disease and 7 with possible disease. DM was distinguished from PM by the presence of heliotrope rash or Gottron's lesions (Gottron's papules and/or Gottron's sign). The DM group included 17 definite disease and 7 possible disease. Muscle biopsy was done on 28 patients with PM and 18 with DM. Specific findings were noted in 86% and 22% of the patients, respectively. Diagnoses of ILD were made on clinical, radiological, and physiological grounds. The criteria used included history of exertional dyspnea and cough, fine crackles on physical examination, compatible findings on chest radiograph, physiological abnormalities of restrictive lung defects including decreased diffusing capacity, and abnormal PaO_2 at rest

and/or with exertion. Aspiration pneumonia was differentiated from ILD based on clinical, radiological, and bacteriological findings; symptoms associated with aspiration, coarse crackle on physical examination, segmental consolidation on chest radiograph and CT scan, and bacteria of normal oral flora phagocytosed by neutrophils on sputum gram-staining. ILD was found in 17 patients with PM and 16 with DM. Among them, 15 with PM and 16 with DM who had HRCT on a view slice ≤ 3 mm performed before treatment were investigated retrospectively in this study. Patients concurrently having other collagen vascular diseases were excluded. The clinical courses of patients were observed from 0.4 to 120 months (median 18 mo, average 41 mo). Serum creatine kinase (CK) and antinuclear antibody were measured in the Clinical Laboratory of Saga University Medical School Hospital. Normal values for CK ranged from 40 to 160 IU/l.

Analysis of HRCT pattern. HRCT before treatment was reviewed by 2 of the authors (TN and HK) who were blinded to diagnosis and clinical course. The reviewers evaluated the presence of major patterns of ILD, reticular opacity, ground-glass attenuation (GGA), and consolidation. The presence of each pattern was graded (–), (+), or (2+), according to the area of the pattern on HRCT; (–): 0%, (+): trace to 10%, and (2+): more than 10%. When a pattern was graded (2+), it was recognized as the principal pattern. The presence of accessory findings of ILD, such as honeycombing, subpleural band, and traction bronchiectasis, was also evaluated. Representative presentations of each finding are shown in Figure 1. After the 2 reviewers assessed HRCT independently, the consistency of their evaluations was found to be 88% for major patterns and 85% for accessory findings. Thereafter, the reviewers had discussions to reach a consensus on inconsistent findings.

Data analysis. Numerical data are shown as median (range). Chi-square test was used to compare categoric variables. Analysis of variance (ANOVA) was used for multiple comparisons of continuous variables. When there was a significant difference, the difference between each group was tested using Scheffé's test. Because relatively small samples were subjected to statistical comparison, power (1 – ß) was calculated using a post-hoc analysis with the G*Power 3 computer program[9]. The length of survival was defined as the interval between the day of the first visit to Saga University Medical School Hospital until the date of death or last followup date. Survival was estimated by the Kaplan-Meier method, and differences in survival were evaluated with the log-rank test. All tests were 2-sided with a 5% level of significance. The power of the survival test was examined using the PS Power and Sample Size Calculations computer program[10]. To analyze relationships among HRCT findings, a joining cluster analysis was performed using SPSS 10.0J (SPSS Co. Ltd., Tokyo, Japan).

RESULTS

Clinical features of patients with PM and DM are summarized in Table 1. The occurrences of ILD were 54.8% in PM and 66.7% in DM. When comparing 4 groups, PM with ILD (PM-ILD), PM without ILD (PM-no ILD), DM with ILD (DM-ILD), and DM without ILD (DM-no ILD), age and sex data were similar. Duration from the onset of systemic symptoms, such as muscle and/or skin lesions, to the first visit to Saga

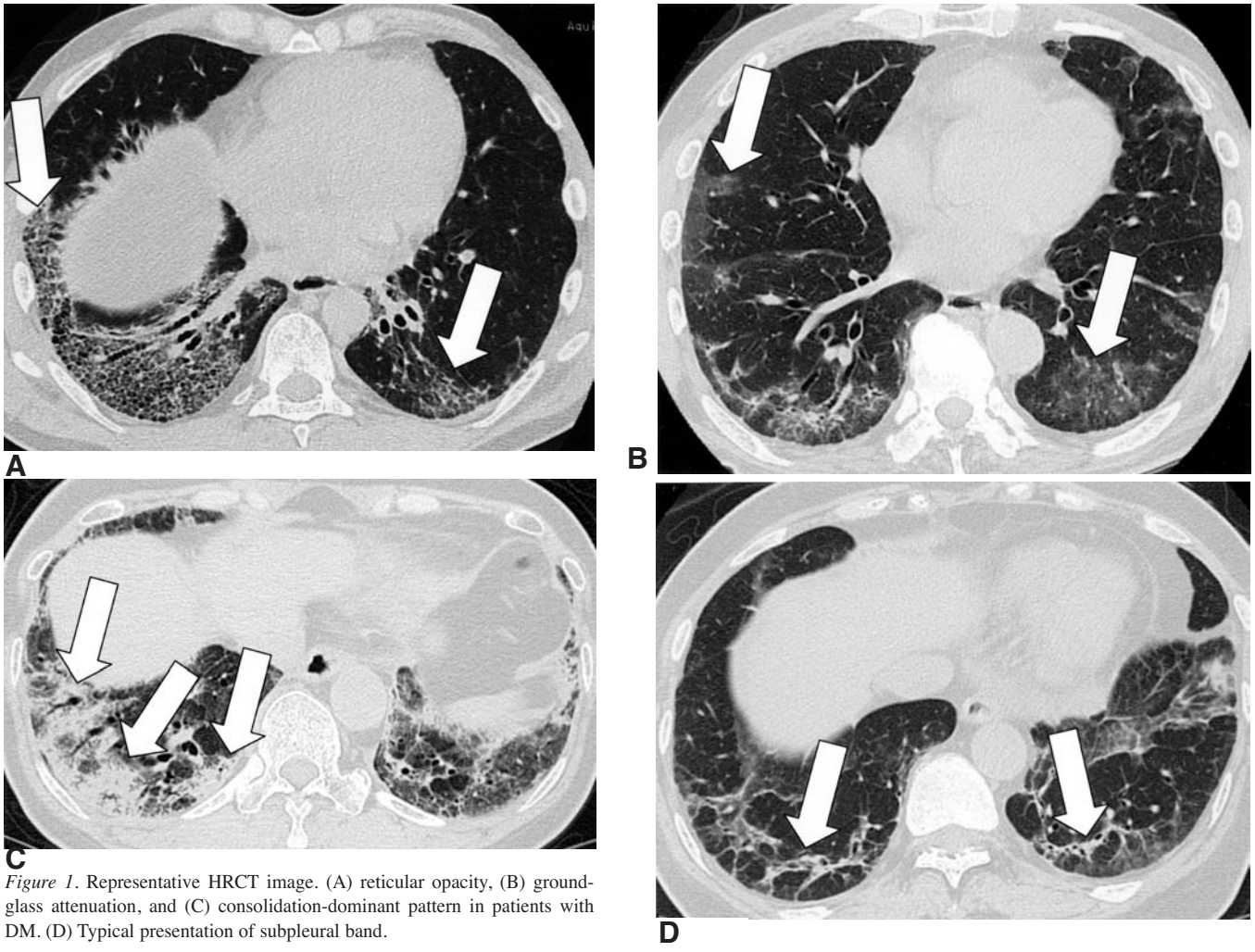

Figure 1. Representative HRCT image. (A) reticular opacity, (B) ground-glass attenuation, and (C) consolidation-dominant pattern in patients with DM. (D) Typical presentation of subpleural band.

Table 1. Clinical features and course of patients with polymyositis (PM) and dermatomyositis (DM).

	PM		DM		
	No ILD, n = 14	ILD, n = 17	No ILD, n = 8	ILD, n = 16	p*
Age, yrs median (range)	52 (20–73)	54 (21–81)	60 (26–75)	47 (27–70)	NS
Sex, M:F	3:11	7:10	2:6	5:11	NS
Duration, mo, median (range)					
From PM/DM symptom onset					
To first visit	3 (0–14)	4 (1–15)	2 (1–6)	1 (0–7)	NS
To therapy start	5 (0–18)	5 (1–15)	3 (2–6)	2 (1–9)	NS
To recognition of ILD		3 (–60–15)		1 (–36–7)	NS
From recognition of ILD					
To first visit		0 (–1–66)		0 (–1–36)	NS
To therapy start		0 (0–66)		0 (0–37)	NS
Creatinine kinase < 500 IU/l, n (%)	0 (0)	4 (24)	2 (25)	11 (69)	< 0.001
Antinuclear antibody-negative, n (%)	7 (50)	7 (41)	2 (25)	12 (75)	NS
Therapy, effective/tried					
Oral CS	10/14	14/15	4/7	4/8	
CS pulse	0/0	1/1	2/2	0/1	
Simultaneous CS + CyA	0/0	1/1	0/0	4/7	
Addition of immunosuppressant to CS	4/4	1/1	2/2	2/5	
Clinical course, alive/dead	14/0	15/2	6/2	9/7	< 0.01
Cause of death					
ILD	0	0	0	6	
Infection	0	0	0	1	
Malignancy	0	0	2	0	
Other	0	2	0	0	

* Calculated using ANOVA for age and chi-square test for other variables. ILD: interstitial lung disease; CS: corticosteroids; CyA: cyclosporin A; NS: statistically not significant.

University Medical School Hospital was longer for PM than DM, while the difference did not reach a significant level. ILD was first recognized at the first evaluation at Saga University Medical School Hospital in 83% of PM-ILD and 63% of PM-ILD. Duration from the first recognition of ILD by radiological methods to the first visit was –1 to +66 months (median 0 mo) in PM-ILD and –1 to +36 months (median 0 mo) in DM-ILD. ILD preceded systemic symptoms in 3 patients: 1 with PM (60 mo) and 2 with DM (36 and 6 mo). When these 3 patients were excluded, durations from recognition of ILD to start of therapy ranged from 0 to 2 months (median 0 mo) in both PM-ILD and DM-ILD. Duration from systemic symptom onset to therapy start tended to be longer in PM than DM.

Serum CK findings at the first visit were PM-no ILD 2076 IU/l (range 548–33,800); PM-ILD 2532 IU/l (95–10,859); DM-no ILD 1618 IU/l (13–13,619); and DM-ILD 266 IU/l (36–4197) (Figure 2A). Eleven of 16 patients (69%) had a serum CK level < 500 IU/l in the DM-ILD group, while 25% of patients or less had serum CK level < 500 IU/l in the other groups (Table 1). The difference among groups was statistically significant ($p < 0.001$, chi-square test). The frequency of patients who were negative for antinuclear antibody seemed to be higher in the DM-ILD group (Figure 2B, Table 1), although the difference did not reach a significant level.

The therapies that were tried and the responses to them are summarized in Table 1. Most of the PM-no ILD patients responded to oral corticosteroid (0.5 to 1 mg/kg). Oral corticosteroid was not enough for some patients in the PM-ILD and DM-no ILD groups. These patients were successfully treated by adding pulse corticosteroid or immunosuppressants such as cyclosporin A (CyA), azathioprine, and methotrexate. Around half of the DM-ILD group was resistant not only to oral corticosteroid but also to other intensive therapies such as corticosteroid pulse, simultaneous initiation of corticosteroid (including pulse therapy) and CyA, and addition of CyA to corticosteroid. Clinical course was significantly different among the PM-no ILD, PM-ILD, DM-no ILD, and DM-ILD groups ($p < 0.01$, chi-square test), with the highest mortality rate (43.8%) in the DM-ILD group (Table 1). The relevant Kaplan-Meier survival curve is shown in Figure 3. Survival rates at 2 years were 91.8% in PM, 100% in PM-no ILD, 83.3% in PM-ILD, 61.5% in DM, 71.4% in DM-no ILD, and 58.9% in DM-ILD. Survival in DM was significantly worse than that in PM ($p < 0.01$, log-rank test). When survival was compared between PM-no ILD and DM-no ILD and between PM-ILD and DM-ILD, DM patients tended to have poorer prognoses. The differences did not reach a significant level ($p = 0.055$ and $p = 0.052$ in log-rank tests, respectively). In both PM and DM, survival was not significantly different in the presence or the absence of ILD ($p = 0.150$ and $p = 0.379$ in log-rank tests). However, the powers of these 4 statistical comparisons remained at rather a low level (0.2 to 0.39). It is

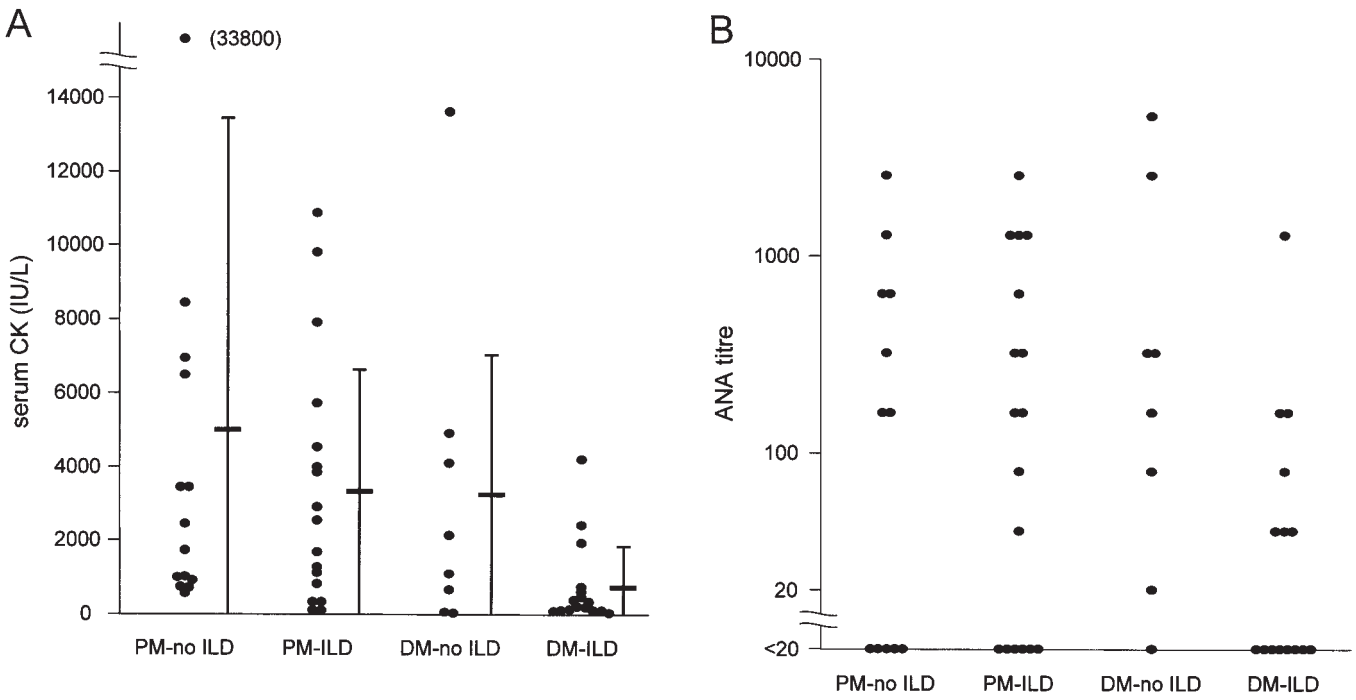

Figure 2. (A) Serum creatinine kinase level in patients with PM and DM. Bars indicate mean ± standard deviation of each group. (B) Antinuclear antibody titer in patients with PM and DM.

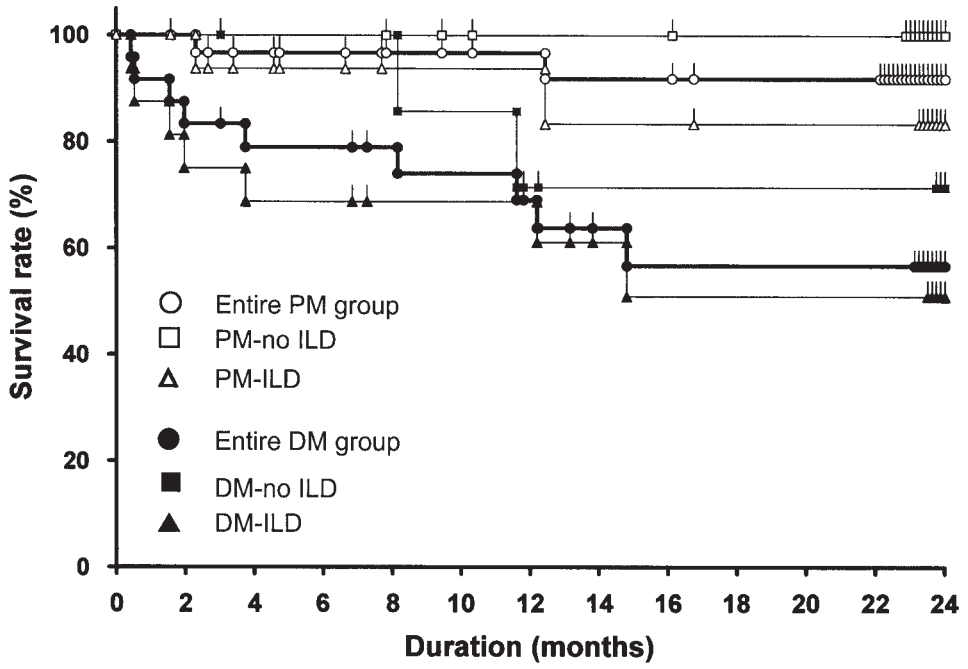

Figure 3. Kaplan-Meier survival curve of entire PM group, PM-no ILD, PM-ILD, entire DM group, DM-no ILD, and DM-ILD. Survival in entire DM group was significantly worse than that in entire PM group ($p < 0.01$, log-rank test). Differences between PM-no ILD and DM-no ILD and between PM-ILD and DM-ILD did not reach a significant level ($p = 0.055$, $p = 0.052$, respectively). In PM and DM groups, survival was not significantly different in the presence or the absence of ILD ($p = 0.150$, $p = 0.379$).

noteworthy that the survival curve declined steeply in the first 3 months in the DM-ILD group compared to the other groups. In this group, 6 patients died of respiratory failure due to ILD. The remaining patient died of mucor sepsis during immunosuppressive therapy. By contrast, no patient died of respiratory failure in the PM-ILD group, whereas 2 patients died of

acute heart failure or acute pancreatitis. In the DM-no ILD group, 2 patients died of malignant tumors.

We analyzed HRCT patterns for 15 patients with PM-ILD and 16 patients with DM-ILD (Table 2). GGA was the principal pattern in patients with PM-ILD (73%) and DM-ILD (63%). Reticular opacity was the principal pattern in around half of the patients in both groups, and often overlapped with GGA. Three patients (20%) with PM-ILD and 5 patients (31%) with DM-ILD had multifocal consolidation as the principal pattern on HRCT. Statistical analysis indicated that the frequencies of these 3 major patterns did not differ between the PM-ILD and DM-ILD groups. Traction bronchiectasis, suggesting the presence of a chronic fibrosing process, was significantly more frequent in PM-ILD than DM-ILD ($p < 0.05$, chi-square test). The frequencies of honeycombing and subpleural bands were similar in the 2 groups. It is possible that the character of the CT findings could be related to the duration of pulmonary disease. Because a large part of ILD was first recognized at the first evaluation at Saga University Medical School Hospital, we compared such patients to patients whose ILD was recognized prior to the first evaluation. The frequencies of GGA, reticular shadow, consolidation, and traction bronchiectasis were similar. Frequencies of subpleural bands and honeycombing tended to be higher in the prior-ILD group (data not shown).

Because the prognosis of the DM-ILD group seemed to be strongly dependent on ILD, we further analyzed factors that affected the clinical course of ILD in this group (Table 3). Age and sex did not differ between patients who died of ILD (fatal ILD group) and the others (non-fatal ILD group). Durations from onset of systemic symptoms and from when ILD was first recognized to start of therapy did not differ between groups. Frequency of acute respiratory symptoms on admission seemed to be higher in fatal ILD than in non-fatal ILD. Antinuclear antibody titer did not differ between the 2 groups. Serum CK levels were 421 IU/l (range 120–4197) in fatal ILD and 152 IU/l (36–2409) in non-fatal ILD, but the difference between the 2 groups was not statistically significant. The frequency of patients with a serum CK level < 500 IU/l was also similar in both groups. The difference in major patterns between the 2 groups was statistically significant. All patients with fatal ILD had GGA with or without reticular opacity as the principal HRCT finding. By contrast, non-fatal ILD patients had lower extents of GGA and reticular opacity. Consolidation was recognized as the principal pattern in 50% of patients with non-fatal ILD. Frequencies of honeycombing, subpleural bands, and traction bronchiectasis were not statistically different between the 2 groups. When HRCT findings were subjected to multivariate analysis, interaction among the findings was suggested. Thus, a joining cluster analysis was performed using distances between HRCT findings based on the prognosis of a patient. The analysis indicated a close relationship among honeycombing, subpleural bands, and traction bronchiectasis, and between GGA and reticular opacity. Therefore, we categorized DM-ILD patients into 3 groups according to HRCT findings: Group A: consolidation (2+); Group B: GGA and/or reticular opacity (2+) without honeycombing, subpleural bands, and traction bronchiectasis; and Group C: GGA and/or reticular opacity (2+) with honeycombing, subpleural bands, or traction bronchiectasis. Clinical features and clinical course of each group are summarized in Table 4. Acute respiratory symptoms occurred

Table 2. Frequency of HRCT findings in patients with interstitial lung disease (ILD) associated with polymiositis (PM) and dermatomyositis (DM).

		PM-ILD, n = 15*		DM-ILD, n = 16		p†
Major pattern						
Reticular opacity	(2+)	9	60%	7	44%	NS
	(1+)	3	20%	4	25%	
	(–)	3	20%	5	31%	
GGA	(2+)	11	73%	10	63%	NS
	(1+)	4	27%	5	32%	
	(–)	0	0%	1	6%	
Consolidation	(2+)	3	20%	5	31%	NS
	(1+)	6	40%	5	31%	
	(–)	6	40%	6	38%	
Accessory findings						
Honeycombing	(+)	3	20%	1	6%	NS
	(–)	12	80%	15	94%	
Subpleural band	(+)	6	40%	3	19%	NS
	(–)	9	60%	13	81%	
Traction bronchiectasis	(+)	6	40%	1	6%	< 0.05
	(–)	9	60%	14	94%	

* HRCT was not available in 2 patients with PM-ILD. † Calculated using chi-square test. NS: statistically not significant; GGA: ground-glass attenuation.

Table 3. Analysis of prognostic factors in DM-ILD.

		DM-ILD		
		Fatal, n = 6	Non-fatal, n = 10	p†
Age, yrs, median (range)		52 (42–70)	46 (27–64)	NS
Duration, mo, median (range)				
From systemic symptom onset to start of therapy		2 (1–7)	2 (1–4)	NS
From ILD recognition to start of therapy		0 (0–2)	0.5 (0–37)	NS
Acute respiratory symptoms, n (%)		5 (83)	5 (50)	NS
Creatinine kinase < 500 IU/l		4 (67)	7 (70)	NS
Antinuclear antibody-negative		4 (67)	8 (80)	NS
HRCT, n (%)				
Major pattern				
Reticular opacity	(2+)	5 (83)	2 (20)	< 0.05
	(1+)	0 (0)	4 (40)	
	(–)	1 (17)	4 (40)	
GGA	(2+)	6 (100)	4 (40)	< 0.05
	(1+)	0 (0)	5 (50)	
	(–)	0 (0)	1 (10)	
Consolidation	(2+)	0 (0)	5 (50)	< 0.05
	(1+)	3 (50)	2 (20)	
	(–)	3 (50)	3 (30)	
Accessory findings				
Honeycombing	(+)	0 (0)	1 (10)	NS
	(–)	6 (100)	9 (90)	
Subpleural band	(+)	0 (0)	3 (30)	NS
	(–)	6 (100)	7 (70)	
Traction bronchiectasis	(+)	1 (17)	1 (10)	NS
	(–)	5 (83)	9 (90)	

† Calculated using ANOVA for age and chi-square test for other variables. NS: statistically not significant; GGA: ground-glass attenuation.

Table 4. HRCT typing and clinical features.

HRCT Typing	n	Patients with Acute Symptoms	Serum CK, IU/l, median (range)	Total	Treatment, Patients Who Died of ILD/All Patients		
					CS Alone	CS, Then Added CyA	Simultaneous CS + CyA
Group A. consolidation-dominant	5	4	105 (78–611)	0/5*	0/1	0/1	0/3 (nonsignificant)
Group B. GGA/reticular opacity-dominant without HC, SB, and BE	6	5	333 (36–4197)	5/6	0/0	2/2	3/4
Group C. GGA/reticular opacity-dominant with HC, SB, or BE	5	1	421 (120–1939)	1/5	0/4	1/1	0/0
p		< 0.01	NS	< 0.05			

* 1 patient died of mucor sepsis. CS: corticosteroids; CyA: cyclosporin A; GGA: ground-glass attenuation; HC: honeycombing; SB: subpleural band; BE: traction bronchiectasis; NS: nonsignificant.

more significantly in Group A (consolidation-dominant) and Group B (GGA/reticular opacity-dominant without accessory findings) than in Group C (GGA/reticular opacity-dominant with accessory findings). Serum CK level was lowest in Group A (consolidation-dominant). The difference in survival rate among groups was statistically significant when evaluated by chi-square test ($p < 0.05$). Although it did not reach a significant level ($p = 0.053$ in log-rank test), the survival curve of Group B showed a faster decline than the other groups (Figure 4). The survival curve of Group B (GGA/reticular opacity-dominant without accessory findings) showed a faster decline than the other groups (Figure 4). Statistical comparison between Group B and Group A, and Group B and Group C did not reach a significant level ($p = 0.053$ in log-rank tests for both comparisons). Powers of statistical analyses were 0.65 and 0.91, respectively. All patients in Group A (consolidation-dominant) responded to antiinflammatory therapy. One patient responded well to corticosteroid therapy, and another patient required CyA due to insufficient response to corticosteroid therapy. The other patients responded to corticosteroid and CyA therapy started simultaneously. One patient died of mucor sepsis 4 months after initiation of the treatment. The

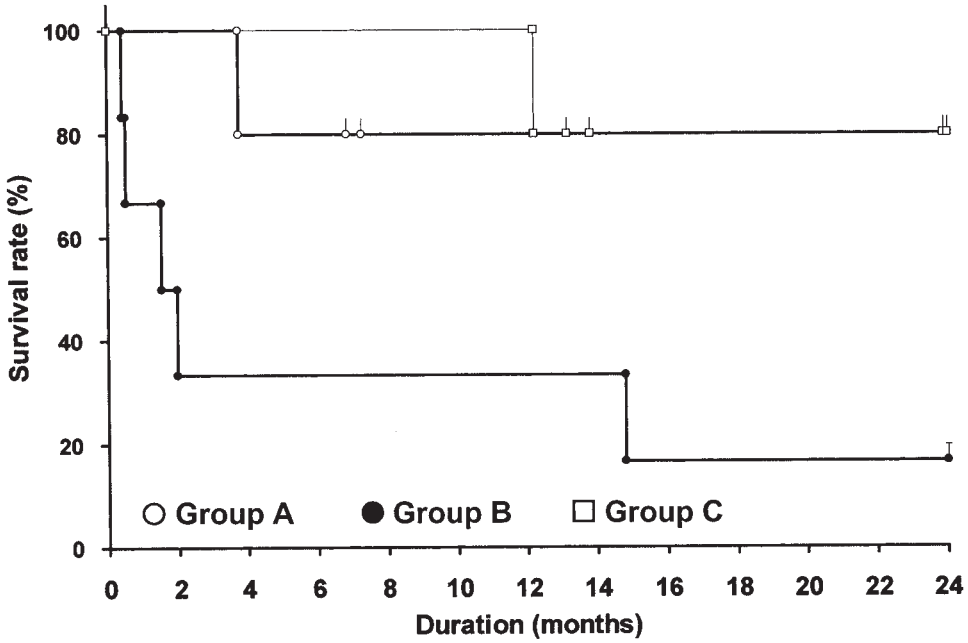

Figure 4. Kaplan-Meier survival curve for patients with DM-ILD. Patients were classified into 3 groups according to HRCT findings. Group A: consolidation-dominant; Group B: GGA/reticular opacity-dominant without honeycombing, subpleural band, and traction bronchiectasis; and Group C: GGA/reticular opacity dominant with honeycombing, subpleural band, or traction bronchiectasis. Survival curve of Group B showed a faster decline than the other groups, while the difference did not reach a significant level ($p = 0.053$).

others had no signs of reactivation of ILD thereafter. Some patients remain with various degrees of respiratory symptoms due to pulmonary fibrosis following the inflammatory process. Among 6 patients in Group B (GGA/reticular opacity-dominant without accessory findings), only one patient who was treated with simultaneous corticosteroid and CyA survived. The other patients did not respond to intensive therapy including corticosteroid and CyA. In Group C (GGA/reticular opacity-dominant with accessory findings), 4 patients responded to corticosteroid therapy with minimal pulmonary symptoms. The other patient, whose ILD became rapidly progressive during corticosteroid treatment, did not survive despite additional CyA treatment.

No surgical lung biopsy was performed on any patient in Group A (consolidation-dominant) or Group B (GGA/reticular opacity-dominant without accessory findings). Transbronchial lung biopsy specimens collected from Group A patients revealed histopathological changes compatible with organizing pneumonia (Figure 5A). Postmortem histological examinations performed in 2 patients in Group B indicated diffuse alveolar damage (Figure 5B). A patient in Group C (GGA/reticular opacity-dominant with accessory findings) received surgical biopsy. Homogeneous fibrosing interstitial pneumonia compatible with fibrosing nonspecific interstitial pneumonia (NSIP) was noted on histological examination.

DISCUSSION

ILD is a common complication in patients with PM and DM. In our study, ILD was found in 60% of the patients, which is comparable to the incidences of ILD, 23% to 65%, reported in recent studies[1,3-7]. ILD is known to be one of the major prognostic determinants in patients with PM and DM, and the presence of ILD results in increased morbidity and mortality rates[4]. Many factors, such as Hamman-Rich-like lung symptoms[4], mild muscle symptoms[11,12], low serum CK level[1,3,13,14], low autoantibody titer[12,15], low diffusing capacity of carbon monoxide[4], and increase of neutrophils or CD25+CD8+ positive T cells in bronchoalveolar lavage fluids[4,5,16], have been implicated as predictors of corticosteroid resistance and/or poor prognosis in patients with PM/DM-ILD. It has been reported that there is a subgroup of DM patients with rapidly progressive ILD who have mild muscle symptoms[11], slightly increased level of muscle enzymes[13], and the absence of anti-Jo-1 antibody[1]. Most of these results were obtained by studies involving patients with PM and also with DM[3-5,11,14,16].

Despite their clinical similarities, recent studies suggest that PM and DM have different immunopathological mechanisms[17-21]. PM is primarily caused by cell-mediated immune processes, while DM is mediated by the humoral immune response. In our study, the survival rate of patients with DM was significantly lower than that of PM. Although the difference in survival rate between PM-ILD and DM-ILD did not reach a significant level, the mortality rate of DM-ILD was higher than that of PM-ILD. More than one-third of DM-ILD patients died of respiratory failure due to ILD, while ILD was not fatal in PM. These data reconfirmed the findings of Fujisawa and colleagues, in which patients with DM-ILD had

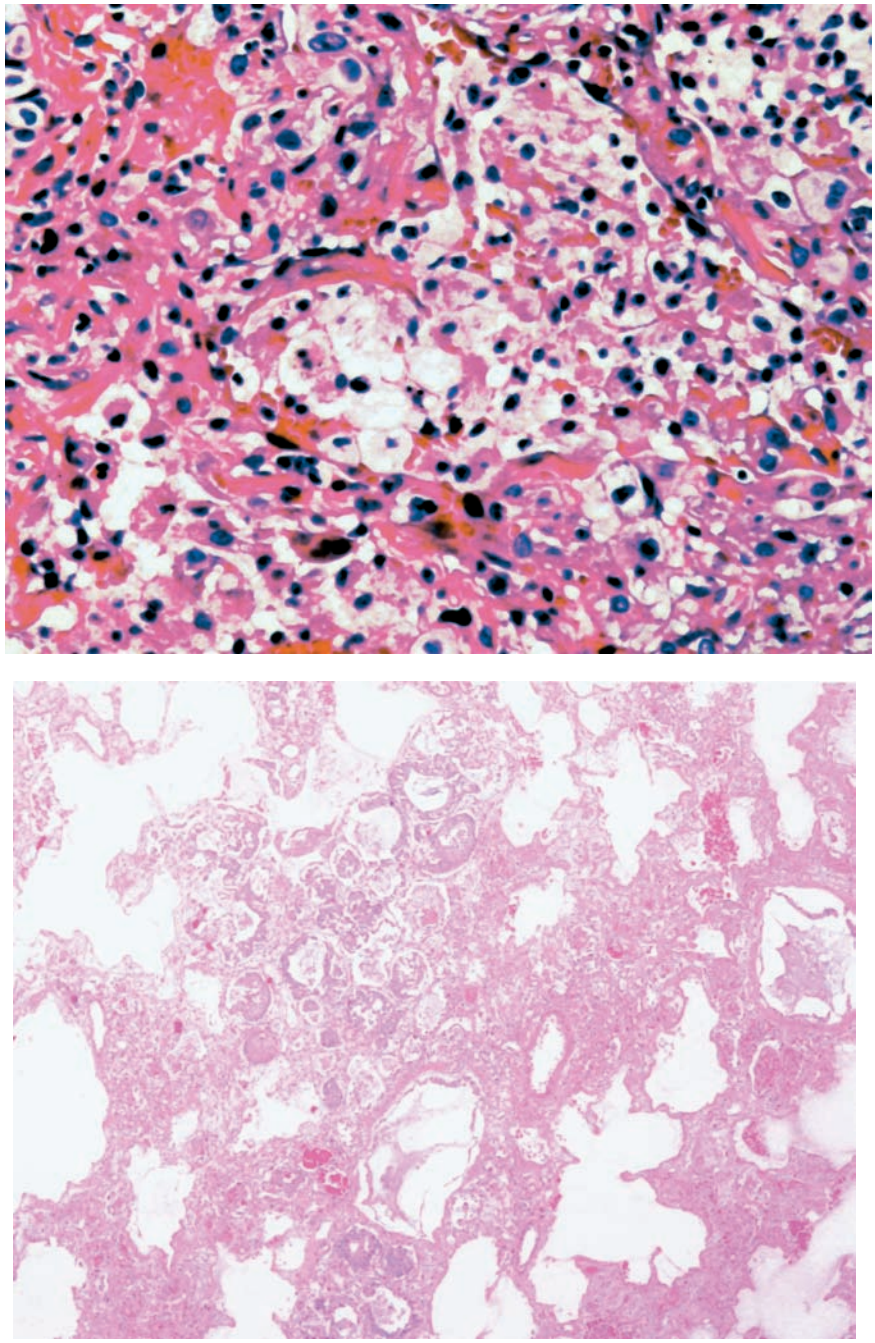

Figure 5. (A) Representative histopathologic findings of transbronchial lung biopsy specimen from a Group A patient (H&E, stain; ×400) shows foamy macrophages in alveolar airspaces and mild infiltration of lymphocytes. The findings were compatible with organizing pneumonia. (B) Autopsy lung specimen from a Group B patient (H&E stain; ×200) shows hyaline membrane formation in air spaces and fibrous thickening of alveolar septa that suggest diffuse alveolar damage.

a significantly lower survival rate than those with PM-ILD[22], and further suggest that ILD associated with DM differs in nature from that associated with PM. Therefore, the clinical course and response to therapy of DM-ILD should be discussed separately from those of PM-ILD.

This is the first report on a clear association of HRCT findings with the clinical course of DM-ILD. When PM and DM were analyzed together, we could find no difference in HRCT findings between patients who died of ILD and the others (data not shown). Our findings were comparable with those of Marie, *et al* that HRCT findings in PM/DM-ILD did not differ between deteriorating and nondeteriorating groups[4]. After

removing the effects of PM-ILD, which have HRCT findings similar to those of DM-ILD but with a good prognosis, we showed that HRCT findings between fatal ILD and non-fatal ILD were different. The frequencies of GGA and reticular opacity were significantly higher in fatal ILD than in non-fatal ILD. By contrast, consolidation was recognized as the principal pattern more frequently in non-fatal ILD. According to the results of a joining cluster analysis, we categorized HRCT patterns of DM-ILD into 3 groups. Of these, Group B (dominant GGA and/or reticular opacity without honeycombing, subpleural bands, and traction bronchiectasis) was closely related to fatal ILD. It should be emphasized that our fatal ILD does not correspond to the status of rapidly progressive ILD or deteriorating ILD described in previous studies. In addition to fatal ILD, the latter includes ILD that progresses acutely but responds to intensive immunosuppressive therapy. In our series, most Group A (consolidation-dominant) patients belong to this type. In our study, acute respiratory symptoms were more frequent in fatal ILD than in the other groups. This is consistent with the finding that a Hamman-Rich-like pattern in symptoms is one of the indicators for a poor outcome in patients with PM/DM-ILD[4]. Even so, there remains difficulty in differentiating fatal ILD, which requires the development of newer effective therapies, from ILD that responds to traditional intensive immunosuppressive therapy. We propose that adding the HRCT classification makes clinical decisions more accurate.

Classification based on histopathological findings should be the gold standard for ILD. However, recent progress in HRCT makes it possible to precisely evaluate morphological changes occurring in the entire lung. Tansey, *et al* reported that lung specimens from 2 lobes showed different histopathological findings in some patients[23]. Another advantage of HRCT evaluation is that the procedure is noninvasive and can be performed even when a lung biopsy under video-assisted thoracic surgery is not possible due to the patient's condition. Therefore, classifying ILD based on HRCT findings seems to be of clinical relevance if it can be associated with response to therapy and histopathologic classification. Our study indicates a possible association of Group A (consolidation-dominant), Group B (GGA/reticular opacity-dominant without accessory findings), and Group C (GGA/reticular opacity-dominant with accessory findings) with organizing pneumonia, diffuse alveolar damage, and nonspecific interstitial pneumonia, respectively. However, this should be reevaluated in a further study for the following reasons. First, lung biopsy, especially surgical biopsy, was performed on only a small number of patients in our series. Second, although our findings are consistent with CT features of idiopathic interstitial pneumonia[24], they are not consistent with previous studies on DM-ILD[21]. In a small group of histopathologically-proven NSIP, DAD, and UIP patients associated with PM/DM, consolidation and GGA were seen in 86%–100% of patients with NSIP and DAD. In contrast, these findings were seen in 33% of patients with UIP. Third, assuming that Group A (consolidation-dominant) corresponds to organizing pneumonia, the frequency of organizing pneumonia is much higher than that reported in recent studies[4,25-27].

Low CK level has been implicated in the poor prognosis of ILD in PM and DM[1,3,13,14]. However, our data indicate that serum CK level was similar in DM-ILD patients who died of ILD and those who did not. Based on HRCT classification, Group A (consolidation-dominant), which had acute respiratory symptoms but responded to immunosuppressive therapy, had the lowest CK level. These results suggest that low CK is a hallmark of acutely progressive ILD, but is not a suitable predictor for ILD that is resistant to intensive treatment. Nawata, *et al* reported that corticosteroid-resistant rapidly progressive ILD occurred in some patients whose serum CK level was elevated initially and then fell to the normal range[3]. Such a case was not seen in our series. A possible explanation for the discrepancy is that early initiation of CyA in patients with acute respiratory symptoms might protect them from late-onset rapidly progressive ILD. Because an objective assessment is difficult to make in a retrospective study, we did not evaluate muscle weakness.

The major limitations and possible confounders of this study are retrospective design, small sample sizes, and the small number of lung biopsies. Its retrospective structure leads to a diversity of treatments, and made it difficult to examine prognostic variables such as clinical manifestations and pulmonary function test results. Some negative associations in the statistical analyses might be due to inadequate power derived from the small sample sizes. Our results suggest the possibility that HRCT Group B (GGA/reticular opacity-dominant without accessory findings) is a good predictor of fatal ILD. On the basis of our findings, a prospective study focusing on DM-ILD using pathological and HRCT typing as phenotyping variables should be done to investigate prognostic factors in greater detail. A recent study reported that DM patients with positive autoantibodies to aminoacyl-tRNA synthetase (ARS) had significantly higher incidences of ILD than antibody-negative patients[28]. Some immunosuppressive agents, in addition to oral corticosteroids, were required more frequently in antibody-positive patients with DM than antibody-negative patients. These findings indicate that anti-ARS antibodies are important phenotyping variables for patients with DM. An analysis of these autoantibodies should also be included in future prospective studies.

REFERENCES

1. Takizawa H, Shiga J, Moroi Y, Miyachi S, Nishiwaki M, Miyamoto T. Interstitial lung disease in dermatomyositis: clinicopathological study. J Rheumatol 1987;14:102-7.
2. Tazelaar HD, Viggiano RW, Pickersgill J, Colby TV. Interstitial lung disease in polymyositis and dermatomyositis; clinical features and prognosis as correlated with histologic findings. Am Rev Respir Dis 1990;141:727-33.
3. Nawata Y, Kurasawa K, Takabayashi K, et al. Corticosteroid-resistant interstitial pneumonitis in dermatomyositis/polymyositis:

prediction and treatment with cyclosporine. J Rheumatol 1999;26:1527-33.
4. Marie I, Hachulla E, Cherin P, et al. Interstitial lung disease in polymyositis and dermatomyositis. Arthritis Rheum 2002;47:614-22.
5. Schnabel A, Reuter M, Biederer J, Richter C, Gross WL. Interstitial lung disease in polymyositis and dermatomyositis: clinical course and response to treatment. Semin Arthritis Rheum 2003;32:273-84.
6. Fathi M, Dastmalchi M, Rasmussen E, Lundberg IE, Tornling G. Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis. Ann Rheum Dis 2004;63:297-301.
7. Selva-O'Callaghan A, Labrador-Horrillo M, Munos-Gall X, et al. Polymyositis/dermatomyositis-associated lung disease: analysis of a series of 81 patients. Lupus 2005;14:534-42.
8. Bohan A, Peter JB. Polymyositis and dermatomyositis (first and second of 2 parts). N Engl J Med 1975;292:344-7.
9. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175-91.
10. Dupont WD, Plummer WD. PS power and sample size program available for free on the Internet. Controlled Clin Trials 1997;18:274.
11. Saag KG, Kline JN, Hunnighake GW. Idiopathic inflammatory myopathy. Interstitial lung diseases. In: Baum GL, Crapo JD, Celli BR, Karlinsky JB, editors. Textbook of pulmonary diseases. 6th ed. New York: Lippincott-Raven; 1988:360-3.
12. Ito M, Kaise S, Suzuki S, et al. Clinical-laboratory characteristics of patients with dermatomyositis accompanied by rapidly progressive interstitial lung disease. Clin Rheumatol 1999;18:462-7.
13. Fudman EJ, Schnitzer TJ. Dermatomyositis without creatinine kinase elevation. A poor prognostic sign. Am J Med 1986;80:329-32.
14. Takada T, Suzuki E, Nakano M, et al. Clinical features of polymyositis/dermatomyositis with steroid-resistant interstitial lung disease. Intern Med 1998;37:669-73.
15. Benbassat J, Gefel D, Larholt K, Sukenik S, Morgenstern V, Zlotnick A. Prognostic factors in polymyositis/dermatomyositis. Arthritis Rheum 1985;28:249-55.
16. Kurasawa K, Nawata Y, Takabayashi K, et al. Activation of pulmonary T cells in corticosteroid-resistant and -sensitive interstitial pneumonitis in dermatomyositis/polymyositis. Clin Exp Immunol 2002;129:541-8.
17. Kissel JT, Mendell JR, Rammohan KW. Microvascular deposition of complement membrane attack complex in dermatomyositis. N Engl J Med 1986;314:329-34.
18. Dalakas MC. Immunopathogenesis of inflammatory myopathies. Ann Neurol 1995;37 Suppl 1:S74-S86.
19. Amato AA, Barohn RJ. Idiopathic inflammatory myopathies. Neurol Clin 1997;15:615-48.
20. Hilton-Jones D. Inflammatory muscle diseases. Curr Opin Neurol 2001;14:591-6.
21. Kikuchi Y, Koarada S, Tada Y, et al. Difference in B cell activation between dermatomyositis and polymyositis; analysis of the expression of RP105 on peripheral blood B cells. Ann Rheum Dis 2001;60:1137-40.
22. Fujisawa T, Nakamura Y, Enomoto N, et al. Differences in clinical features and prognosis of interstitial lung diseases between polymyositis and dermatomyositis. J Rheumatol 2005;32:58-64.
23. Tansey D, Wells AU, Colby TV, et al. Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. Histopathology 2004;44:585-96.
24. Wittram C, Mark EJ, McLoud TC. CT-histologic correlation of the ATS/ERS 2002 classification of idiopathic interstitial pneumonia. RadioGraphics 2003;23:1057-71.
25. Akira M, Hara H, Sakatani M. Interstitial lung disease in association with polymyositis-dermatomyositis: long-term follow-up CT evaluation in seven patients. Radiology 1999;210:333-8.
26. Douglas WM, Tazelaar HD, Hartman TE, et al. Polymyositis-dermatomyositis-associated interstitial lung disease. Am J Respir Crit Care Med 2001;164:1182-5.
27. Cottin V, Thivolet-Bejui F, Reynaud-Gaubert M, et al. Interstitial lung disease in amyopathic dermatomyositis, dermatomyositis and polymyositis. Eur Respir J 2003;22:245-50.
28. Matsushita T, Hasegawa M, Fujimoto M, et al. Clinical evaluation of anti-aminoacyl tRNA synthetase antibodies in Japanese patients with dermatomyositis. J Rheumatol 2007;34:1012–8.