Interstitial lung disease in patients with polymyositis, dermatomyositis and amyopathic dermatomyositis

E. H. Kang¹, E. B. Lee^{1,3}, K. C. Shin¹, C. H. Im¹, D. H. Chung^{2,3}, S. K. Han^{1,3} and Y. W. Song^{1,3}

Objective. To assess the prevalence, characteristics and prognostic factors of interstitial lung disease (ILD) in Korean patients with polymyositis (PM), dermatomyositis (DM) and amyopathic dermatomyositis (ADM).

Methods. We reviewed the medical records of 72 consecutive PM and DM patients, including six patients with ADM, who were seen at the Rheumatology Clinic of Seoul National University Hospital between 1984 and 2003.

Results. Twenty-nine PM/DM patients (40.3%) developed ILD. Anti-Jo-1 antibody and arthralgia were associated with the presence of ILD (P = 0.022 and P = 0.041, respectively), whereas dysphagia was more frequently found in patients without ILD (P = 0.041). Lung biopsies revealed diffuse alveolar damage (DAD) (n = 2), usual interstitial pneumonia (UIP) with DAD (n = 2), UIP (n = 1), and non-specific interstitial pneumonia (n = 2). Of the 29 patients, 11 (37.9%) died. The mean survival time in ILD patients was significantly shorter than in those without ILD (13.8±1.8 vs 19.2±0.9 yr, P = 0.017). Poor survival in ILD patients was associated with a Hamman–Rich-like presentation (P = 0.0000), ADM features (P = 0.0001) and an initial forced vital capacity (FVC) $\leq 60\%$ (P = 0.024).

Conclusions. ILD was observed in 40.3% of Korean PM/DM patients and was associated with poor survival. A Hamman–Rich-like presentation, ADM features and an initial FVC $\leq 60\%$ were associated with poor survival in ILD.

KEY WORDS: Polymyositis, Dermatomyositis, Amyopathic dermatomyositis, Interstitial lung disease.

Polymyositis (PM) and dermatomyositis (DM) are systemic inflammatory diseases of unknown aetiology that affect skeletal muscles and other internal organs. Patients who show a characteristic DM rash with little or no muscle involvement are regarded as PM/DM patients with the diagnosis of amyopathic dermatomyositis (ADM) [1–3].

Pulmonary involvement in PM/DM includes respiratory muscle weakness, aspiration pneumonia, interstitial lung disease, infection and drug-induced pneumonia [4]. Interstitial lung disease (ILD), which develops in 23.1-65.0% of PM/DM patients [5-8], is a major cause of death in this disease [5, 7, 9-11]. Poor prognostic factors of ILD in PM/DM have been reported to include a Hamman-Rich-like pattern, low creatine kinase (CK) levels, low diffusing capacity of the lung for carbon monoxide (DLCO), neutrophilic bronchoalveolar lavage (BAL) fluid or poor lung histology, such as diffuse alveolar damage (DAD) or usual interstitial pneumonia (UIP) [7, 11-14]. Recently, several reports have been issued on rapidly progressive, steroid-resistant ILD in ADM patients and in DM patients with low CK levels [15-21]. Therefore, we investigated the clinical characteristics and prognostic factors of ILD in PM/DM, including ADM patients.

Patients and methods

Study population

Seventy-two patients with a diagnosis of PM (n=22) or DM (n = 50) were included in this study. All were seen as in-patients or out-patients at the Rheumatology Clinic of Seoul National University Hospital between the years 1984 and 2003. Patients with overlap syndromes were excluded. Of the 72 patients, 66 fulfilled Bohan and Peter's criteria (definite, n = 63; probable, n=3) [22], and the remaining six were diagnosed as having ADM on the basis of a typical DM rash (Gottron's papules or Gottron's sign), no muscle weakness and a normal CK level. All patients underwent detailed clinical examination to determine whether they had gastrointestinal or cardiac complications. Oesophageal manometry, electrocardiography and echocardiography were performed in symptomatic cases. Cardiac involvement was defined as abnormalities of electrocardiography or echocardiography results. All patients underwent cancer screening, including detailed clinical examinations, chest radiography, CT of the abdomen and pelvis, and gastrofibrescopy. Women also underwent a gynaecological examination.

¹Department of Internal Medicine and ²Department of Pathology, Seoul National University College of Medicine and ³Clinical Research Institute, Seoul National University Hospital, Seoul, Korea.

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Correspondence to: E. B. Lee, Department of Internal Medicine, Seoul National University Hospital, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea. E-mail: leb7616@snu.ac.kr

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ILD status

All patients underwent detailed clinical examination and chest radiography for ILD. If any abnormalities were detected, they underwent pulmonary function tests (PFT) and high-resolution computed tomography (HRCT). Patients were considered to have ILD when they showed HRCT findings compatible with ILD (nodular, reticulonodular, linear or ground-glass opacities; consolidations; irregular interface; honeycombing; or traction bronchiectasis). Patients without ILD at the first visit were examined for newly developed ILD whenever pulmonary symptoms (dyspnoea or dry cough) or signs (basal rales) were subsequently noted.

Pulmonary function tests

Forced vital capacity (FVC) and DLCO divided by volume of alveoli (DLCO/VA) were measured by spirometry using a watersealed spirometer (Vmax 20 system; SensorMedics, Yorba Linda, CA, USA) and the single-breath method (Vmax 229 system; SensorMedics), respectively. Data were expressed as percentages of the predicted values, which were obtained on the basis of a patient's sex, age, height and weight.

Initial presentations of ILD

Initial presentation of each patient was classified into 3 categories. (i) The Hamman–Rich-like pattern was defined as rapidly progressive dyspnoea that led to respiratory failure requiring mechanical ventilation within 3 months from ILD symptom onset. (ii) The slowly progressive pattern was defined as progressive pulmonary symptoms not as rapid as the Hamman–Rich like pattern. (iii) The asymptomatic pattern was defined as no pulmonary symptoms.

ILD courses

The clinical course of each patient was determined based on the last follow-up results compared with the basal results. It was defined as (i) 'improvement' if there was more than a 15% improvement in PFT results or any improvement in radiographic images; (ii) 'deterioration' if there was more than a 15% drop in PFT results or any worsening in radiographic images; and (iii) 'stationary' if the change did not satisfy either criteria of improvement or deterioration.

Lung biopsy

Seven patients had a lung biopsy. Three of these were open-lung biopsy, three were video-assisted thoracoscopic surgery and one was transbronchial lung biopsy. All the tissue samples were reviewed by a single pathologist.

Statistical analysis

For group comparisons between binary data, we used either the χ^2 test or Fisher's exact test. The Mann–Whitney U-test was used to compare continuous data. Cumulative survival rates were analysed using the Kaplan–Meier method and the log-rank (Mantel-Cox) test. All statistical calculations were done using SPSS software (SPSS, Chicago, IL, USA).

Results

The 72 consecutive patients with PM/DM consisted of 14 men and 58 women with a mean (\pm sD) age of 43.7 \pm 14.3 yr at the time of diagnosis. The mean duration of follow-up was 5.9 \pm 5.6 yr.

Clinical features

ILD developed in 29 patients (40.3%), including five ADM patients. The mean age at PM/DM diagnosis was 45.1 ± 13.6 yr, and the female to male ratio was 4.8 to 1. ILD was diagnosed concurrently with PM/DM in all cases except one in which non-specific interstitial pneumonia (NSIP) had been diagnosed 18 months earlier. Initial pulmonary symptoms included dyspnoea in 13 patients (44.8%), dry cough in 12 patients (41.4%) and cough with sputum in six patients (20.7%). Crackles in both lower lung fields were heard in 21 patients (72.4%).

HRCT findings

Of 29 ILD patients, 11 had initial HRCT findings of the UIP pattern with basal or subpleural honeycombing and traction bronchiectasis. Thirteen had the cryptogenic organizing pneumonia (COP) pattern, which was formerly referred to as bronchiolitis obliterans organizing pneumonia, showing patchy consolidation predominantly in a peripheral and lower lung distribution with or without geographic ground-glass opacities. Four had the NSIP pattern showing bilateral patch areas of ground-glass opacities with preference for the lower lung zones, often with bronchiectasis. The remaining patient had a combined pattern of UIP, COP and pneumomediastinum.

Lung biopsy results

Lung biopsy specimens of seven patients demonstrated DAD (n=1), DAD with alveolar neutrophil infiltration (n=1), UIP combined with DAD (n=2), UIP (n=1) or NSIP (n=2). Initial HRCT findings of five patients whose biopsy results showed UIP or DAD were COP in three patients, UIP in one and a combined pattern of COP, UIP and pneumomediastinum in one. In contrast, initial HRCT findings of two NSIP patients were COP in both cases.

Clinical course of ILD

Of the 29 ILD patients, clinical presentation patterns were Hamman–Rich-like in six (20.7%), slowly progressive in 14 (48.3%) and asymptomatic in nine (31.0%). Among the 25 patients for whom interval PFT and radiographic data were available, ILD deteriorated in 11 (44.0%), improved in six (24.0%) and remained stationary in eight (32.0%). Of the 11 who deteriorated, six had presented with the Hamman–Rich-like pattern and five with a slowly progressive pattern. Of the six patients who improved, four had presented with a slowly progressive pattern. Of the eight who remained stationary, four had presented with a slowly progressive pattern.

High-dose corticosteroid treatment ($\geq 1 \text{ mg/kg}$) was given to all patients except one who concomitantly had hepatitis B. Immunosuppressive/modulative agents, including cyclosporin, cyclophosphamide, azathioprine, methotrexate and λ immunoglobulin, were given to seven of the patients who deteriorated, one of the patients who improved and four of the patients who remained stationary.

Mortality and survival

Eleven patients (37.9%) died during a mean follow-up of 5.9 ± 5.6 yr. Of these, eight died from the progression of ILD, one from respiratory muscle failure and two from stomach or colon cancer.

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All six patients who presented with a Hamman–Rich-like pattern died due to rapidly progressive respiratory failure. Five of the six patients died within 3 weeks to 4 months of ILD detection. All five lacked anti-Jo-1 antibody, and three of the patients showed ADM features. Corticosteroids, immunosuppressive and immunomodulative treatments (cyclosporin in four, cyclophosphamide in two, azathioprine in one, methotrexate in one) were not effective in these patients, except for one ADM patient who survived the first attack of slowly progressive, corticosteroid-resistant ILD with cyclosporin.

The presence of ILD was significantly detrimental to patient survival rates (survival time, $13.8 \pm 1.8 vs 19.2 \pm 0.9 yr$, P = 0.017). This tendency was more prominent when paraneoplastic cases were excluded ($13.3 \pm 1.9 vs 20.1 \pm 0.7 yr$, P = 0.0015) (Supplementary Fig. 1; available as supplementary data at *Rheumatology* Online). ILD shortened survival in both DM and PM patients (Supplementary Fig. 2; available as supplementary data at *Rheumatology* Online).

Factors associated with poor prognosis

Factors that significantly shortened the mean survival time of ILD patients were as follows: an initial Hamman–Richlike presentation (P = 0.0000); an initial FVC $\leq 60\%$ (P = 0.024); and features of ADM (P = 0.00010), regardless of whether paraneoplastic cases were included (Fig. 1). Gender distribution, age at diagnosis, the presence of ANA or anti Jo-1 antibody, the initial DLCO/VA value and CK or LD levels did not significantly affect ILD patients' survival.

As shown in Table 1, anti-Jo-1 antibody and arthralgia were associated with the presence of ILD (P=0.022 and P=0.041 respectively), whereas dysphagia was more frequently found in patients without ILD (P=0.041). No significant difference between patients with and without ILD was found in terms of gender distribution, age at diagnosis, symptom duration of PM/DM prior to diagnosis, the presence of cancer, CK or LD levels, or ANA status.

Discussion

In this study, we found that the prevalence of ILD in Korean patients with PM/DM was 40.3% (29/72). Anti-Jo-1 antibody and arthralgia were more frequently seen in the ILD group, as reported previously [7, 9, 23, 24]. The survival of ILD patients was impaired compared with that of non-ILD patients. The identified poor prognostic factors in ILD patients were a Hamman–Rich-like presentation, features of ADM and an initial FVC $\leq 60\%$.

In this study, four patients with a Hamman–Rich-like pattern demonstrated a COP-like appearance at initial HRCT. However, the actual pathology results were not COP, but DAD. The time gap between HRCT and biopsy may explain this discrepancy. The early proliferative phase of DAD can mimic COP on HRCT [25], or COP may progress to UIP or UIP with DAD [26, 27].

With respect to treatment, our series shows that usual immunosuppressive treatments, including corticosteroid, cyclo-phosphamide, azathioprine and methotrexate, seem to be insufficient in ILD patients who present with a rapidly progressive pattern. Cyclosporin was effective in one of five patients tried. There have been several reports that early use of cyclosporin is effective in DM patients with steroid-resistant ILD [28–31].

Our study shows that an initial presentation with a Hamman–Rich-like pattern is strongly correlated with a poor outcome in ILD patients. DAD, UIP and a combination of the two were identified as the predominant patterns of lung

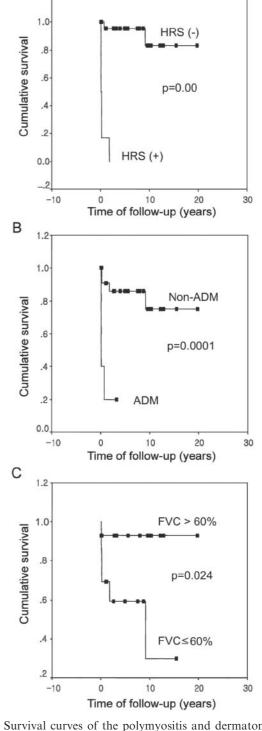


FIG. 1. Survival curves of the polymyositis and dermatomyositis patients with interstitial lung disease. The data shown compare survival rates according to (A) the presence of Hamman-Rich-like presentation (HRS, n=6; non-HRS, n=23), (B) the presence of amyopathic dermatomyositis features (ADM, n=5; non-ADM, n=24) and (C) the low FVC (FVC $\leq 60\%$, n=13; FVC $\geq 60\%$, n=14).

histology in rapidly progressive ILD. This finding is consistent with previous reports in which DAD, UIP and COP were identified as the features of histology responsible for rapidly progressive ILD in PM/DM patients [14, 16, 21].

TABLE 1. Clinical and laboratory findings of polymyositis/dermatomyositis patients according to their ILD status
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	Total $(n=72)$	With ILD $(n=29)$	Without ILD $(n=43)$	<i>P</i> -value (ILD vs non-ILD)
Female	80.6 (58)	82.8 (24)	79.1 (34)	0.70
Age at diagnosis (yr, mean \pm sD)	43.7 ± 14.3	45.1 ± 13.6	42.7 ± 14.8	0.45
Time until diagnosis (yr, mean \pm sD)	0.9 ± 1.4	0.4 ± 0.3	1.1 ± 1.7	0.10
Polymyositis	30.6 (22)	20.7 (6)	37.2 (16)	0.14
Dermatomyositis	69.4 (50)	79.3 (23)	62.8 (27)	0.14
Arthralgia	37.5 (27)	51.7 (15)	27.9 (12)	0.041
Dysphagia	15.3 (11)	3.4 (1)	23.3 (10)	0.041
Cardiac involvement ^a	8.3 (6)	10.3 (3)	7.0 (3)	0.68
Malignancy	8.3 (6)	6.9 (2)	9.3 (4)	1.000
Initial PFT (%, mean \pm sD)				
FVC $(n=49)$	70.0 ± 19.5	63.0 ± 19.1	79.6 ± 16.5	0.0070
DLCO/VA (n=42)	82.6 ± 25.9	70.3 ± 23.3	100.7 ± 17.9	0.00
Creatine kinase (IU/l, mean \pm sD)	3778.8 ± 11898.5	5266.4 ± 17719.9	2787.1 ± 5381.9	0.16
Lactate dehydrogenase (IU/l, mean \pm sD)	612.1 ± 400.7	622.4 ± 417.8	605.4 ± 380.1	0.76
ANA $(n = 69)$	63.8 (44/69)	58.6 (17/29)	67.5 (27/40)	0.45
Anti-Jo-1 $(n=42)$	14.3 (6/42)	27.3 (6/22)	0.0 (0/20)	0.022
Mean survival (yr, mean \pm sp)	17.2 ± 1.0	13.8 ± 1.8	19.2 ± 0.9	0.017

Data are % (n) unless otherwise stated.

Reference ranges: creatine kinase, 20-270 IU/l; lactate dehydrogenase, 100-225 IU/l.

^aPresence of electrocardiographic or echocardiographic abnormalities.

Rapidly progressive ILD in ADM has been reported predominantly in Asia, including Japan, Hong Kong, and Taiwan [18–21]. In contrast, Cottin *et al.* [32] reported a benign course of ILD in European ADM patients with a histological finding of NSIP. The poor outcome of ILD in Korean ADM patients, as evidenced by our series, may suggest racial differences in the manifestation of ILD in ADM patients.

This study has the following potential limitations. First, the frequency of ILD might have been underestimated since the study was performed retrospectively. Secondly, the actual prevalence of ILD in ADM patients could be lower than our result (83.3%), since a portion of ADM patients might be seen at a dermatology clinic. Thirdly, the clinical severity of ILD could have been overestimated since mild cases of ILD might not have been referred to our hospital. Fourthly, the number of death events was too small for multivariate regression analysis to be applied.

In conclusion, our series shows a high frequency of ILD in PM/DM patients, which is found to be responsible for shortened survival. This study also indicates that a Hamman–Rich-like presentation, ADM features and an initial FVC $\leq 60\%$ are poor prognostic factors in ILD. Further prospective studies are warranted to establish optimal treatment for these patients.

	Key messages		
Rheumatology	 Interstitial lung disease significantly shortens the survival of inflammatory myositis patients. Hamman–Rich-like presentation, amyopathic dermatomyositis features and initial low forced vital capacity are poor prognostic factors. 		

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

The authors have declared no conflicts of interest.

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