# Differences in Clinical Features and Prognosis of Interstitial Lung Diseases Between Polymyositis and Dermatomyositis

TOMOYUKI FUJISAWA, TAKAFUMI SUDA, YUTARO NAKAMURA, NORIYUKI ENOMOTO, KYOTARO IDE, MIKIO TOYOSHIMA, HIROSHI UCHIYAMA, RYOJI TAMURA, MASAAKI IDA, TAKESHI YAGI, KAZUMASA YASUDA, HITOSHI GENMA, HIROSHI HAYAKAWA, KINGO CHIDA, and HIROTOSHI NAKAMURA

*ABSTRACT.* ***Objective.*** To assess the difference in clinical features and prognosis of patients with interstitial lung disease (ILD) comparing polymyositis (PM) and dermatomyositis (DM).

***Methods.*** Medical records of 28 ILD patients with PM/DM (16 PM-ILD, 12 DM-ILD) were reviewed retrospectively.

***Results.*** Serum CPK concentrations were significantly higher in PM-ILD than in DM-ILD. Bronchoalveolar lavage analysis showed that the percentages of lymphocytes and eosinophils were significantly higher in DM-ILD than in PM-ILD. Ten patients (5 PM-ILD, 5 DM-ILD) underwent surgical lung biopsy, and 3 (3 DM-ILD) had an autopsy. Nonspecific interstitial pneumonia (NSIP) was found in 7 (4 PM-ILD, 3 DM-ILD) and usual interstitial pneumonia (UIP) in 3 (1 PM-ILD, 2 DM-ILD). Interestingly, diffuse alveolar damage (DAD) was found in 3 patients with DM-ILD, who all died of deterioration of ILD; but no one with PM-ILD had DAD. Corticosteroid treatment alone achieved a favorable response in 6 patients (37.5%) with PM-ILD, but in only one (8.3%) with DM-ILD. Administration of cyclosporine in the early phase of onset benefited 4 corticosteroid-resistant patients with DM-ILD. Conclusively, survival in DM-ILD was significantly worse than that in PM-ILD.

***Conclusion.*** DM-ILD is more refractory to corticosteroid therapy, resulting in poorer prognosis compared with PM-ILD. These data indicate that intensive therapy, including cyclosporine, should be considered for DM-ILD. (J Rheumatol 2005;32:58–64)

*Key Indexing Terms:*
INTERSTITIAL LUNG DISEASE POLYMYOSITIS DERMATOMYOSITIS

Polymyositis (PM) and dermatomyositis (DM) are systemic inflammatory disorders affecting muscles and other organs including the lungs. Although DM is characterized by a classic rash, patients with both PM and DM have idiopathic inflammatory myositis, which primarily involves skeletal muscle[1]. Despite their clinical similarities, a great deal of evidence has accumulated to suggest that PM and DM have different immunopathological mechanisms[2-5]. PM is primarily caused by cell-mediated immune processes, in which autoreactive cytotoxic T cells may mediate MHC-I-restricted cytotoxicity against self-antigens expressed on muscle[2–4]. These inflammatory cells infiltrate muscle fascicles. Conversely, DM is largely mediated by the humoral immune response, in which the complement system is activated, resulting in the deposition of the membrane attack complex within capillaries[2-5]. Ischemia caused by destruction of capillaries leads to fiber necrosis, microinfarcts, and perifascicular atrophy in muscles. The inflammatory cells infiltrating muscle are of a perivascular distribution. These immunological variations possibly cause, in part, a difference of clinical features between PM and DM.

Interstitial lung disease (ILD) is common in patients with PM and DM, and the reported incidence of ILD in the PM-DM complex varies between 20% and 65% in cross-sectional studies, depending on whether clinical, radiological, functional, or pathological criteria have been used[6-11]. In PM/DM, ILD is one of the major prognostic determinants, and the presence of ILD results in increased morbidity and mortality rates[8]. Many reports have depicted the clinical features and prognosis of ILD associated with PM/DM, but most of them have investigated patients with PM-associated ILD (PM-ILD) and those with DM-associated ILD (DM-ILD) together. Considering a possible disparity in the immunological pathogenesis between PM and DM, the clinical characteristics of ILD are likely to differ between the 2 diseases. To clarify this, we compared patients with PM-ILD and DM-ILD in terms of their clinical features and prognosis.

*From the Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan.*

*T. Fujisawa, MD; T. Suda, MD, PhD; Y. Nakamura, MD, PhD; N. Enomoto, MD; K. Ide, MD, PhD; M. Toyoshima, MD, PhD; H. Uchiyama, MD; R. Tamura, MD, PhD; M. Ida, MD; T. Yagi, MD, PhD; K. Yasuda, MD, PhD; H. Genma, MD, PhD; H. Hayakawa, MD, PhD; K. Chida, MD, PhD; H. Nakamura, MD, PhD.*

*Address reprint requests to Dr. T. Suda, Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu, Shizuoka, 431-3192, Japan.*
*E-mail: suda@hama-med.ac.jp*

*Submitted January 22, 2004; revision accepted August 16, 2004.*

## MATERIALS AND METHODS

*Patient selection.* The study subjects consisted of 28 patients diagnosed as having PM (n = 16) and DM (n = 12) with ILD between 1985 and 2001. The diagnosis of PM or DM was confirmed on the basis of Bohan and Peter criteria[1]: (1) systemic muscle weakness, (2) increased serum muscle enzymes, (3) myopathic changes on electromyography (EMG), (4) typical histologic findings on muscle biopsy, and/or (5) characteristic dermatologic manifestations of DM. The diagnosis was considered definite, probable, or possible, according to the number of criteria fulfilled (at least 4, 3, or 2, respectively, including the dermatologic manifestations for diagnosis of DM). Our study subjects included 6 cases of definite PM, 10 of probable PM, 3 of definite DM, and 9 of probable DM. Muscle biopsy was performed in 14 of 16 patients with PM and in 8 of 12 patients with DM, and no evidence of inclusion body myositis was found in these patients. ILD was diagnosed based on the presence of radiologic abnormalities with respiratory symptoms.

*Data collection.* Clinical data, including history, treatment, and laboratory findings, were obtained from patients' medical records at the first encounter, which eventually led to a diagnosis of ILD and PM/DM. Signs and symptoms were also recorded. The following pulmonary function test variables were assessed: vital capacity (VC) and forced expiratory volume in 1 second (FEV1.0).

*High resolution computed tomography (HRCT).* HRCT examinations of the lung were performed on sections 1.0 or 1.5 mm thick to evaluate radiographic abnormalities. The HRCT images were reviewed for presence of each of the following signs: consolidation, ground glass opacities, traction bronchiectasis, irregular linear opacities, honeycombing, and pleural effusion.

*Bronchoalveolar lavage (BAL).* BAL was performed as described[12]. Briefly, a fiberoptic bronchoscope was passed transorally and wedged in a segmental or subsegmental bronchus of the middle lobe. Three 50-ml aliquots of sterile 0.9% saline were instilled and the returns gently aspirated through the side channel of the bronchoscope. BAL fluid was centrifuged at 800 g for 10 min to obtain the cellular components. The total cell count was determined using a hemocytometer and a differential cell count was taken on Giemsa-stained cytocentrifuged preparations. To characterize the phenotype of the lymphocytes in the BAL fluid, flow cytometric analysis was performed (Epics Profile, Coulter Electronics, Nancy, France) using mAb OKT3 (anti-CD3; Coulter), OKT4 (anti-CD4; Coulter), and OKT8 (anti-CD8, Coulter).

*Lung biopsy.* Thirteen patients (5 PM, 8 DM) had lung biopsy, including 10 surgical biopsies (5 PM, 5 DM) and 3 autopsies (3 DM). The specimens were categorized using the following abnormalities consistent with ILD: usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), bronchiolitis obliterans organizing pneumonia (BOOP), and diffuse alveolar damage (DAD) according to the current classification of interstitial pneumonias[13,14]. UIP is characterized by heterogeneous appearance at low magnification with alternating zones of normal lung, collagen fibrosis, and honeycomb change. Scattered foci of fibroblast proliferation are also usually present. The fibrotic changes preferentially affect subpleural and paraseptal parenchyma. Patchy chronic inflammation accompanies the interstitial fibrosis, and consists mainly of lymphocytes, plasma cells, and histiocytes with a minor component of neutrophils and eosinophils. NSIP is defined by mild to moderate interstitial chronic inflammation and dense or loose interstitial fibrosis lacking the temporal heterogeneity pattern. The NSIP are divided into 3 groups with varying degrees of alveolar wall inflammation or fibrosis[14]. Group I consists primarily of mild to moderate interstitial chronic inflammation, usually with lymphocytes and a few plasma cells. Dense fibrosis is inconspicuous or absent. Group II exhibits a lymphoplasmacytic infiltrate similar to that in Group I, but in addition there is a significant amount of admixed fibrosis. Group III consists mainly of dense or loose interstitial fibrosis in varying degree and connective tissue is temporal homogeneous. DAD is a form of acute lung injury that progresses through an exudative phase, characterized by pneumocyte and endothelial cell necrosis, edema, and formation of hyaline membranes, to an organizing phase with alveolar septal organizing interstitial fibrosis and prominent type 2 pneumocyte proliferation.

*Treatment and outcome.* During the course of treatment, we assessed respiratory symptoms, chest radiograph/CT findings, pulmonary function (vital capacity, VC), and $PaO_2$. According to the International Consensus Statement of idiopathic pulmonary fibrosis of the American Thoracic Society[15] with slight modification, "improvement" or "favorable (or good) response" is defined by 2 or more of the following: (1) A decrease in symptoms (dyspnea on exertion); (2) reduction of parenchymal abnormality on chest radiograph or HRCT scan; and (3) physiological improvement defined by one of the following: > 10% increase in vital capacity or total lung capacity; or > 10 Torr increase in $PaO_2$.

*Statistical analysis.* For 2 group comparisons involving binary data, we used either the chi-square test or Fisher's exact test, depending on the sample size. Comparisons involving continuous data were by Mann-Whitney U test. The cumulative survival rate was calculated using the Kaplan-Meier test; the log-rank test was also used to compare survival of patients with PM-ILD and DM-ILD. The p value < 0.05 was considered significant. All data are expressed as mean ± SD.

## RESULTS

*Clinical features and laboratory findings.* Clinical characteristics of the PM/DM patients with ILD are shown in Table 1. Sixteen patients (8 men, 8 women, age 51.6 ± 8.0 yrs) and 12 patients (3 men, 9 women, age 55.3 ± 17.0 yrs) were diagnosed as having PM-ILD and DM-ILD, respectively. No patient had been given any drug that might have caused ILD. Age and sex did not differ between the 2 groups. Followup months were significantly longer for PM-ILD patients than DM-ILD patients. Most patients presented with dyspnea and arthralgia in both the PM and DM groups, and no significant differences were seen in the incidence of each symptom between them. Chest auscultation revealed fine crackles in 81% of PM patients and 92% of DM patients. ILD onset preceded initial diagnosis of PM/DM in 3 patients (19%) with PM (range 4–10 mo) and 4 (33%) with DM (range 4–48 mo). ILD were concomitant with

*Table 1.* Patient characteristics.

| | PM-ILD, n = 16 | DM-ILD, n = 12 | p |
|---|---|---|---|
| Age, yrs | 51.6 ± 8.0 | 55.3 ± 17.0 | NS |
| M/F | 8/8 | 3/9 | NS |
| Followup, mo | 71.4 ± 48.5 | 35.5 ± 38.2 | < 0.05 |
| Malignancy | 1 | 0 | NS |
| Dyspnea on effort, % | 63 | 75 | NS |
| Cough, % | 56 | 50 | NS |
| Fever, % | 50 | 75 | NS |
| Arthralgia, % | 63 | 67 | NS |
| Raynaud's phenomenon, % | 19 | 8 | NS |
| Fine crackles, % | 81 | 92 | NS |
| Time of ILD diagnosis | | | |
| Before PM/DM diagnosis, % | 19 | 33 | |
| Concomitant with PM/DM diagnosis, % | 81 | 59 | |
| After PM/DM diagnosis, % | 0 | 8 | |

NS: nonsignificant.

diagnosis of PM/DM in 13 PM patients (81%) and 7 DM patients (59%). A DM patient was diagnosed as having ILD after 20 months of DM diagnosis.

Laboratory findings are presented in Table 2. The serum creatine phosphokinase (CPK) concentrations were significantly higher in PM-ILD than in DM-ILD ($p < 0.01$). No other laboratory test data differed significantly between PM-ILD and DM-ILD groups. Antinuclear antibody was positive in 13% of PM-ILD and 8% of DM-ILD. The frequencies of anti-Jo-1 antibody were 19% and 8% in PM-ILD and DM-ILD, respectively, and did not differ between the 2 diseases. Mild hypoxia and restrictive impairment were seen in both groups.

*HRCT findings*. HRCT scans of the lung were available in 12 patients with PM-ILD and 9 with DM-ILD. Predominant findings are summarized in Table 3. Consolidation, ground glass opacities, traction bronchiectasis, and irregular linear opacities were common in both PM-ILD and DM-ILD. No significant difference was found in frequency of each HRCT finding between PM-ILD and DM-ILD.

*BAL analysis*. BAL was performed in 18 patients (9 PM, 9 DM). In both PM-ILD and DM-ILD, the total number of BAL cells increased ($4.2 \pm 3.9 \times 10^5$/ml BAL fluid and $4.2 \pm 1.7 \times 10^5$/ml, respectively; Figure 1). Significantly higher percentages of lymphocytes and eosinophils were observed in DM-ILD than in PM-ILD [lymphocytes 29.5 ± 21.5% vs 18.5 ± 25.0%, respectively ($p < 0.05$); eosinophils 1.3 ± 1.7% vs 0.5 ± 0.7%, respectively ($p < 0.05$)]. DM-ILD patients had a significantly lower percentage of alveolar macrophage than PM-ILD patients [57.7 ± 26.2% vs 77.4 ± 28.0%, respectively ($p < 0.05$)]. The ratio of CD4+/CD8+ lymphocytes was almost equal in both groups.

*Table 2*. Laboratory findings.

| | PM-ILD, n = 16 | DM-ILD, n = 12 | p |
|---|---|---|---|
| WBC, $mm^3$ | 8277 ± 2959 | 7058 ± 3872 | NS |
| ESR, mm/h | 48.1 ± 29.0 | 54.7 ± 29.4 | NS |
| CPK, IU/l | 3823 ± 4696 | 399 ± 423 | < 0.01 |
| LDH, IU/l | 890 ± 732 | 558 ± 214 | NS |
| IgG, mg/dl | 1879 ± 657 | 1862 ± 624 | NS |
| Positive ANA, % | 13 | 8 | NS |
| Positive RF, % | 19 | 25 | NS |
| Positive Jo-1, % | 19 | 8 | NS |
| $PaO_2$, Torr | 78.4 ± 11.3 | 74.3 ± 7.1 | NS |
| VC, % | 77.0 ± 23.8 | 78.4 ± 17.0 | NS |
| FEV1.0, % | 84.9 ± 9.9 | 84.3 ± 8..8 | NS |

WBC: white blood cells (reference values 3600–9200); ESR: erythrocyte sedimentation rate (2–10); CPK: creatine phosphokinase (55–204); LDH: lactic dehydrogenase (115–208); ANA: antinuclear antibody; RF: rheumatoid factor; VC: vital capacity; FEV: forced expiratory volume; NS: nonsignificant.

*Table 3*. High resolution computed tomography findings.

| | PM-ILD, n = 12, n (%) | DM-ILD, n = 9, n (%) | p |
|---|---|---|---|
| Consolidation | 9 (75) | 6 (67) | NS |
| Ground glass opacities | 12 (100) | 8 (89) | NS |
| Traction bronchiectasis | 8 (67) | 6 (67) | NS |
| Irregular linear opacities | 10 (83) | 6 (67) | NS |
| Honeycombing | 2 (17) | 2 (22) | NS |
| Pleural effusion | 0 (0) | 1 (11) | NS |

*Pulmonary pathology*. Specimens obtained from surgical lung biopsy (5 PM-ILD, 5 DM-ILD) and autopsy (3 DM-ILD) were reviewed. The most common pattern was NSIP, occurring exclusively in group II (Table 4). In PM-ILD, most patients (80.0%) showed NSIP and none showed DAD. Conversely, in DM-ILD, DAD was equally as common (37.5%) as NSIP.

Most patients with NSIP and DAD showed ground glass opacities and consolidation on HRCT (Table 5). Honeycombing was seen only in patients with UIP (Table 5). In BAL analysis, patients with NSIP and DAD showed a tendency to have higher percentages of lymphocytes than those with UIP (Table 5). Those with DAD had higher percentages of neutrophils than those with NSIP and UIP (Table 5).

*Treatment*. All the patients received corticosteroids, usually in the form of oral prednisolone (40–60 mg/day), but occasionally by intravenous (IV) methylprednisolone pulse therapy (1 g/day for 3 days). Immunosuppressive agents such as cyclosporine (150–500 mg/day), cyclophosphamide (daily oral treatment, 50–100 mg/day, or monthly IV treatment 500–700 mg/mo), and azathioprine (50–100 mg/day) were added to corticosteroid therapy in cases in which there was not a favorable response to corticosteroids (Table 6).

Corticosteroids alone resulted in a favorable response in 6 patients (37.5%) with PM-ILD, but in only one (8.3%) with DM-ILD. Thus, more than 90% of DM-ILD patients received further immunosuppressive agents, while 63% of PM-ILD patients did so. In PM-ILD, 5 patients given azathioprine showed a favorable response. Among 4 PM-ILD patients receiving cyclophosphamide, 2 (daily oral treatment) achieved a favorable response and one (monthly IV treatment) showed improvement by replacement with cyclosporine, but one (monthly IV treatment) died in spite of replacement therapy with cyclosporine. Two of 3 PM-ILD patients treated with cyclosporine showed a favorable response, but one died, as described. In DM-ILD, azathioprine achieved a favorable response in 2 patients, but not in one patient, who eventually died. Cyclophosphamide had no therapeutic effect in all 4 DM-ILD patients (1 daily oral treatment, 3 monthly IV treatment), and it was replaced with cyclosporine in 3 of them, but they died of respiratory failure. In 4 DM-ILD patients, cyclosporine was administered early in the course of the disease, and all achieved a favorable response.

The intervals between the first medical examination and

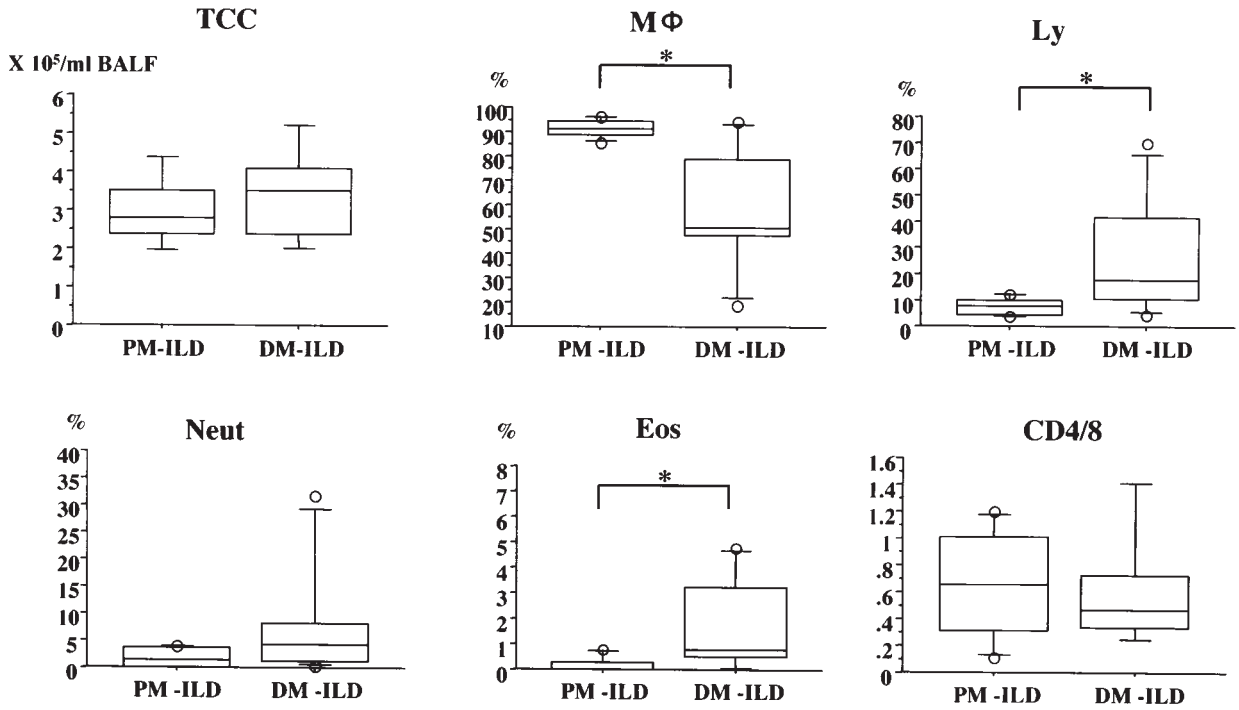


*Figure 1*. Total cell counts (TCC) and percentage values of neutrophils (Neut), lymphocytes (Ly), eosinophils (Eos), and alveolar macrophages (Mϕ) and CD4/8 ratio of BAL fluids. Significantly higher percentages of lymphocytes and eosinophils were observed in cases of DM-ILD than in PM-ILD. Percentage of alveolar macrophages was significantly lower in DM-ILD than in PM-ILD. *$p < 0.05$, statistically different between PM-ILD and DM-ILD.

*Table 4*. Pulmonary pathological findings.

| | PM-ILD, n = 5 | DM-ILD, n = 8 | Total | Cases of Death |
|---|---|---|---|---|
| NSIP | 4 | 3 | 7 | 1 |
| Group I | 0 | 0 | | |
| Group II | 4 | 3 | | |
| Group III | 0 | 0 | | |
| UIP | 1 | 2 | 3 | 0 |
| DAD | 0 | 3* | 3* | 3 |

* At autopsy. NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; DAD: diffuse alveolar damage.

the start of therapy were widely varied among the patients, and no difference was observed between the PM-ILD and DM-ILD groups. The interval between initial corticosteroid therapy and addition of immunosuppressive agents was significantly shorter in patients with DM-ILD than in those with PM-ILD.

*Survival*. During the observation period, 3 (19%) of the PM-ILD patients and 5 (42%) of the DM-ILD patients died. In PM-ILD, causes of death included cancer, pulmonary infection, and respiratory failure. In contrast, all the DM-ILD patients died of respiratory failure due to deterioration of ILD. A comparison of survival in the 2 groups is shown in Figure 2. Those with DM-ILD had a significantly worse survival rate than those with PM-ILD (5-year survival, 55.6% vs 87.1%, respectively; $p < 0.05$). Interestingly, 4 of 5 DM-ILD patient deaths happened within 3 months, suggesting that a failure of initial treatment was associated with early death in DM-ILD.

## DISCUSSION

Recent understanding of the pathogenesis of PM and DM has highlighted the distinct immunological processes involved in each disease; cases of PM are primarily characterized by cell-mediated immune response, while DM is caused predominantly by abnormal humoral immunity[2-5]. Thus, it is hypothesized that there is a difference in clinical features associated with ILD between cases of PM and DM. To clarify this, we retrospectively compared our patients

*Table 5*. Difference in HRCT findings and BAL analysis between pulmonary pathologic patterns.

| HRCT Findings | NSIP, n = 7, n (%) | UIP, n = 3, n (%) | DAD, n = 2, n (%) |
|---|---|---|---|
| Consolidation | 6 (86) | 1 (33) | 2 (100) |
| Ground glass opacities | 6 (86) | 1 (33) | 2 (100) |
| Bronchiectasis | 5 (71) | 2 (67) | 2 (100) |
| Irregular linear opacities | 3 (43) | 1 (33) | 1 (50) |
| Honeycombing | 0 (0) | 2 (67) | 0 (0) |
| Pleural effusion | 1 (14) | 0 (0) | 1 (50) |
| **BAL Analysis** | **NSIP, n = 7** | **UIP, n = 2** | **DAD, n = 2** |
| Total cells (× $10^5$/ml) | 3.6 ± 2.1 | 2.3 | 4.5 |
| Macrophages, % | 68.6 ± 29.4 | 86.8 | 42.5 |
| Lymphocytes, % | 27.6 ± 26.6 | 7.3 | 24.9 |
| Neutrophils, % | 2.4 ± 2.1 | 4.2 | 31.6 |
| Eosinophils, % | 1.4 ± 1.9 | 0.8 | 0.5 |

For definitions see Table 4.

with PM-ILD to those with DM-ILD. We observed the following: (1) The serum CPK concentration was significantly lower in DM-ILD than in PM-ILD, and the proportions of BAL lymphocytes and eosinophils were significantly higher in DM-ILD than in PM-ILD. (2) In assessing pulmonary pathology, DAD, which was closely related to poor outcomes, was more frequent in DM-ILD than PM-ILD. (3) Corticosteroids alone did not achieve a favorable effect in most patients with DM-ILD, and administration of cyclosporine during the early phase of onset may benefit these patients. (4) Conclusively, patients with DM-ILD had a significantly poorer prognosis than those with PM-ILD.

Comparing PM-ILD with DM-ILD, we basically found no significant differences in their clinical characteristics, except during followup periods. In addition, the results of blood gas analysis and pulmonary function tests did not differ between PM- and DM-ILD, and neither did their HRCT findings. However, BAL analysis exhibited a significant difference in the profiles between the 2 ILD groups. Patients with DM-ILD showed a significant increase in the percent-

*Table 6*. Treatment and outcome.

| | PM-ILD, n = 16, n (%) | DM-ILD, n = 12, n (%) | p |
|---|---|---|---|
| Corticosteroids only | 6 (37.5) | 1 (8.3) | NS |
| Corticosteroids + immunosuppressive agents | 10 (62.5) | 11 (91.7) | NS |
| Azathioprine | 5 | 3 | |
| Cyclophosphamide | 4 | 4 | |
| Cyclosporine | 3 | 7 | |
| Interval between first medical examination and start of therapy, weeks | 10.1 ± 9.7 | 2.3 ± 1.9 | NS |
| Interval between start of corticosteroid therapy and start of immunosuppressive agents, weeks | 95.1 ± 96.9 | 27.8 ± 32.1 | < 0.05 |
| Duration of therapy, months | 62.7 ± 42.1 | 31.0 ± 33.3 | < 0.05 |
| Death due to pulmonary dysfunction | 1 | 5 | NS |

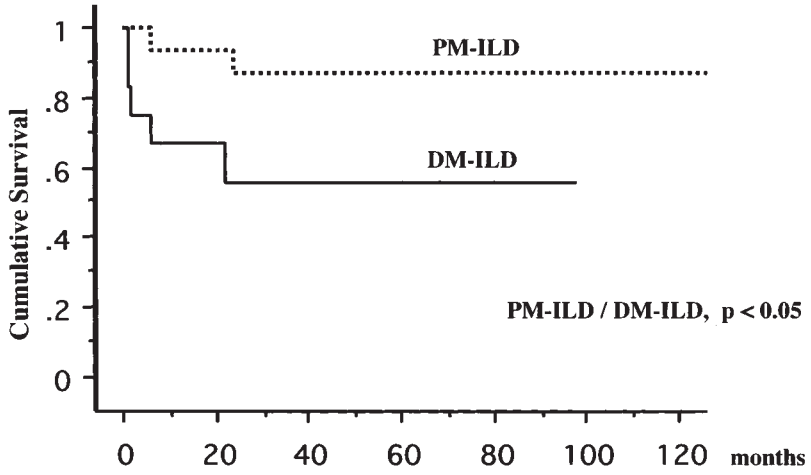


*Figure 2*. Survival curves of cases of PM-ILD (n = 16) and DM-ILD (n = 12). DM-ILD had a significantly worse survival rate than PM-ILD ($p < 0.05$).

ages of BAL lymphocytes and eosinophils compared to those with PM-ILD. To date, there has been no study comparing the BAL findings of PM-ILD with those of DM-ILD. Recent reports in which PM-ILD and DM-ILD were examined together[7,8,16-19] showed that patients had a poor outcome when the initial BAL fluid analysis revealed neutrophil alveolitis[7,8]. In this study, the percentage of BAL neutrophils tended to be higher in DM-ILD than PM-ILD, but the difference was not statistically significant. The implication of the higher percentage of lymphocytes and eosinophils in BAL fluid of DM-ILD is unclear. In patients with idiopathic pulmonary fibrosis, however, it is generally accepted that an increase in the percentage of eosinophils is associated with poor prognosis[15], although the exact mechanism by which eosinophils influence prognosis is unknown. Possibly the same condition may occur in PM/DM-ILD, but further studies are needed to clarify this. Collectively, these data suggest that the differences in the BAL profiles between PM- and DM-ILD may indicate distinct immunological pathogenesis of the 2 diseases.

The serum CPK concentration has been used most widely as a marker of PM/DM. Several studies have reported poor prognosis of PM/DM-ILD patients with no increase of CPK concentration[20], and others have described that corticosteroid resistance was associated with a low CPK level in patients with PM/DM-ILD[10,16]. In our study, CPK level was significantly lower in DM-ILD patients than in PM-ILD patients. Nawata, *et al*[10] reported that the proportion of DM-ILD patients with a normal CPK level was 28.5%, while all patients with PM-ILD revealed an increase in CPK level. Takizawa, *et al*[11] and Miyake, *et al*[21] also independently reported that 75% and 60% of patients, respectively, with DM-ILD had a normal CPK level. Taken together, these observations suggest that patients with DM-ILD have lower CPK levels than those with PM-ILD, but further studies in larger series of patients will be needed to clarify this.

Studies on the histopathology of PM/DM-ILD have recognized various histologic patterns such as UIP, NSIP, BOOP, and DAD and emphasized their prognostic significance[8,22-25]. Douglas, *et al*[22] reported that the majority of PM/DM-ILD patients (81.8%) had NSIP, and this may be associated with the better survival of patients with PM/DM-ILD than those with idiopathic interstitial pneumonia having UIP. Recently, Marie, *et al*[8] described that of 11 PM/DM-ILD patients who underwent lung biopsy, 4 had NSIP, 5 had UIP, and 2 had BOOP. Patients with UIP had a poorer outcome than those with NSIP or BOOP. Consistent with results of other studies[22,25], we found that NSIP was the most common histologic pattern in cases of PM/DM-ILD. Interestingly, all our patients with DAD died of respiratory failure, indicating that DAD is a prognostic indicator of poor outcome. In contrast with the previous studies, however, no prognostic difference was found between NSIP and UIP. Comparing cases of PM-ILD and DM-ILD, most patients (80%) with PM-ILD had NSIP and none had DAD, while DAD was most frequently seen (37.5%) in patients with DM-ILD. Thus, the high occurrence of DAD in DM-ILD may be related to its poorer prognosis compared to PM-ILD.

An optimal treatment for patients with PM/DM-ILD has not been established because of a lack of placebo controlled randomized trials. Corticosteroid therapy is still considered the first-line treatment for PM/DM[26-29], but PM/DM-ILD can often be resistant to this drug. Thus, immunosuppressive agents, including cyclophosphamide and azathioprine, have been used in these cases[7-10,17,18,22-24,26,27,30,31]. In our study, corticosteroids alone achieved a favorable effect in 6 patients (37.5%) with PM-ILD, but in only one (8.3%) with DM-ILD, suggesting that DM-ILD is more refractory to corticosteroids than PM-ILD. Seven patients (5 PM-ILD, 2 DM-ILD) treated with azathioprine showed an improvement. Because azathioprine has been recommended as the preferred immunosuppressant for PM/DM[28,29], it was suggested that it would also benefit some patients with PM/DM-ILD. Interestingly, recent studies[9,10,17,21,30,32] have highlighted the effectiveness of cyclosporine in corticosteroid-resistant PM/DM-ILD. Miyake and colleague[21] showed that combined administration of cyclosporine and corticosteroids was beneficial in 4 of 10 corticosteroid-resistant cases of DM-ILD. In addition, Maeda, *et al*[30] reported that cyclosporine was effective, particularly when administered in the early phase of rapidly progressive DM-ILD. In our series, a total of 7 patients with DM-ILD were treated with cyclosporine. Among them, 4 patients initially receiving cyclosporine as the first immunosuppressive agent had an excellent response, but the other 3, given cyclosporine as replacement therapy for other ineffective immunosuppressive drugs in the late course of the disease, died of ILD deterioration. Based on the results of previous studies and our own, early administration of cyclosporine should be considered in the treatment of corticosteroid-resistant DM-ILD. More recently, intravenous immunoglobulin (IVIG) has been reported to be the most efficacious treatment in PM/DM[29,32,33]. Although no patient was treated with IVIG in our series, this treatment may be a potential option for corticosteroid-resistant PM/DM-ILD.

Most notably, our study demonstrated that patients with DM-ILD had a poorer outcome than those with PM-ILD. In interpretation of the outcome, the variation in treatment for each ILD should be taken into account. In our series, the proportion of patients given immunosuppressive agents was higher in DM-ILD than for those with PM-ILD (91.7% vs 62.5%), and the interval between the start of corticosteroid therapy and the addition of immunosuppressive agents was significantly shorter in those with DM-ILD than in PM-ILD (27.8 vs 95.1 weeks). Thus, our patients with DM-ILD were treated more intensively than those with PM-ILD, but their outcomes were reversed; the survival in DM-ILD was worse than that of PM-ILD. Duration of therapy was significantly

longer in cases of PM-ILD than in DM-ILD. This may be due to a difference in followup periods, because DM-ILD patients had shorter followup periods than PM-ILD patients because of its poor prognosis. In most of our patients, the first medical examination was done by general practitioners, and these patients were subsequently referred to our institution after several visits. Thus, the intervals between the first medical examination and the start of therapy were relatively long, with wide variations. Together, these results indicate the poor prognosis of DM-ILD even though more rigorous therapy was given to patients with DM-ILD than those with PM-ILD. The reason for this is unclear, but the distinction of immunological processes involved in each disease may be associated with this prognostic difference. In terms of histology, DAD was more common in cases of DM-ILD than in PM-ILD, which may be partially responsible for the poor prognosis of DM-ILD.

Our study illustrates the difference in clinical features between PM-ILD and DM-ILD. DM-ILD was more refractory to corticosteroid therapy, resulting in a poorer prognosis compared with PM-ILD. These data emphasize that intensive therapy should be considered for DM-ILD.

## REFERENCES


1. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of 2 parts). N Engl J Med 1975;292:344-7.
2. Dalakas MC. Immunopathogenesis of inflammatory myopathies. Ann Neurol 1995;37 Suppl 1:S74-86.
3. Amato AA, Barohn RJ. Idiopathic inflammatory myopathies. Neurol Clin 1997;15:615-48.
4. Hilton-Jones D. Inflammatory muscle diseases. Curr Opin Neurol 2001;14:591-6.
5. Kissel JT, Mendell JR, Rammohan KW. Microvascular deposition of complement membrane attack complex in dermatomyositis. N Engl J Med 1986;314:329-34.
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. 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.
8. Marie I, Hachulla E, Cherin P, et al. Interstitial lung disease in polymyositis and dermatomyositis. Arthritis Rheum 2002;47:614-22.
9. Hirakata M, Nagai S. Interstitial lung disease in polymyositis and dermatomyositis. Curr Opin Rheumatol 2000;12:501-8.
10. 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.
11. 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.
12. Suda T, Sato A, Ida M, Gemma H, Hayakawa H, Chida K. Hypersensitivity pneumonitis associated with home ultrasonic humidifiers. Chest 1995;107:711-7.
13. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002;165:277-304. [Erratum in Am J Respir Crit Care Med 2002;166:426]
14. Katzenstein AL, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis. Histologic features and clinical significance. Am J Surg Pathol 1994;18:136-47.
15. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000;161:646-64.
16. 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.
17. Grau JM, Miro O, Pedrol E, et al. Interstitial lung disease related to dermatomyositis. Comparative study with patients without lung involvement. J Rheumatol 1996;23:1921-6.
18. Marie I, Hatron PY, Hachulla E, Wallaert B, Michon-Pasturel U, Devulder B. Pulmonary involvement in polymyositis and in dermatomyositis. J Rheumatol 1998;25:1336-43.
19. Enomoto K, Takada T, Suzuki E, et al. Bronchoalveolar lavage fluid cells in mixed connective tissue disease. Respirology 2003;8:149-56.
20. Fudman EJ, Schnitzer TJ. Dermatomyositis without creatine kinase elevation. A poor prognostic sign. Am J Med 1986;80:329-32.
21. Miyake S, Ohtani Y, Sawada M, et al. Usefulness of cyclosporine A on rapidly progressive interstitial pneumonia in dermatomyositis. Sarcoidosis Vasc Diffuse Lung Dis 2002;19:128-33.
22. Douglas WW, Tazelaar HD, Hartman TE, et al. Polymyositis-dermatomyositis-associated interstitial lung disease. Am J Respir Crit Care Med 2001;164:1182-5.
23. Nobutoh T, Kohda M, Doi Y, Ueki H. An autopsy case of dermatomyositis with rapidly progressive diffuse alveolar damage. J Dermatol 1998;25:32-6.
24. 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.
25. 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.
26. Villalba L, Adams EM. Update on therapy for refractory dermatomyositis and polymyositis. Curr Opin Rheumatol 1996;8:544-51.
27. Choy EH, Isenberg DA. Treatment of dermatomyositis and polymyositis. Rheumatology Oxford 2002;41:7-13.
28. Amato AA, Griggs RC. Treatment of idiopathic inflammatory myopathies. Curr Opin Neurol 2003;16:569-75.
29. Grogan PM, Katz JS. Inflammatory myopathies. Curr Treat Options Neurol 2004;6:155-61.
30. Maeda K, Kimura R, Komuta K, Igarashi T. Cyclosporine treatment for polymyositis/dermatomyositis: is it possible to rescue the deteriorating cases with interstitial pneumonitis? Scand J Rheumatol 1997;26:24-9.
31. al-Janadi M, Smith CD, Karsh J. Cyclophosphamide treatment of interstitial pulmonary fibrosis in polymyositis/dermatomyositis. J Rheumatol 1989;16:1592-6.
32. Danieli MG, Malcangi G, Palmieri C, et al. Cyclosporin A and intravenous immunoglobulin treatment in polymyositis/dermatomyositis. Ann Rheum Dis 2002;61:37-41.
33. Dalakas MC. High-dose intravenous immunoglobulin in inflammatory myopathies: experience based on controlled clinical trials. Neurol Sci 2003;24 Suppl 4:S256-9.