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Original Research Article

Predicting Factors of Interstitial Lung Disease in Dermatomyositis and Polymyositis

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Abstract

The aim of this study was to define the predicting factors and evaluate the prognosis of interstitial lung disease in dermatomyositis/polymyositis. For the period 2018–2022, we retrospectively reviewed the clinical information and laboratory data of 56 patients who were diagnosed as definite and probable dermatomyositis and polymyositis. Interstitial lung disease is common (41.9%) in these patients. Dyspnoea and cough were the two most common initial presentations. Anti-Jo1 antibody was more common in those with interstitial lung disease. Univariate and multivariate analyses identified primary idiopathic dermatomyositis subtype, cough and dyspnoea at onset to be the three independent clinical predicting factors of interstitial lung disease. High serum lactate dehydrogenase level (>400 U/l) was inversely associated with development of interstitial lung disease (OR 0.088, p=0.031). Serum lactate dehydrogenase level and presence of anti- Jo1 antibody can serve as laboratory indicators of lung complications. Patients with malignancy and older age at onset (more than 60 years) had poorer prognosis for dermatomyositis/polymyositis (p=0.047 and p=0.035, respectively). Interstitial lung disease did not affect the survival of dermatomyositis/polymyositis patients.

Keywords: Dermatomyositis; Polymyositis; Interstitial Lung Disease; Predicting Factor; Lactate Dehydrogenase Level.

Introduction

Dermatomyositis (DM)/polymyositis (PM) comprises a rare spectrum of inflammatory myopathies with systemic manifestations, including cutaneous, skeletal muscle and other internal organ involvement [1]. Pulmonary involvement in DM/PM includes respiratory muscle weakness, aspiration pneumonia, interstitial lung disease (ILD), infection and drug-induced pneumonia [2]. ILD is now recognized as a direct manifestation of DM/PM and occurs in 23.1–65% of all patients with DM/PM [3–5]. ILD has been reported to be a major cause of death in patients with DM/PM and contributes substantially to morbidity and mortality [6–8]. The clinical manifestations of ILD in patients with DM/PM may vary from asymptomatic to severe, rapidly progressive dyspnoea with eventual fatal outcome. Clinical respiratory symptoms alone may not lead to early detection of ILD. Therefore, routine investigation of lung involvement by chest radiography, pulmonary function tests (PFT) or high-resolution computerized tomography (HRCT), regardless of clinical lung

symptoms, is common in clinical practice. In this study, we attempted to define clinical signs or laboratory indicators for early diagnosis of ILD in patients with DM/PM and evaluated the impact of ILD on survival of patients with DM/PM.

Materials and Methods

Subjects

For the period 2018–2022, 120 patients were newly diagnosed with probable or definite DM/PM in the Departments of Internal Medicine and Dermatology at Taichung Veterans General Hospital, Taiwan. Excluding 41 patients associated with other connective tissue diseases, 22 patients documented as having ILD but without HRCT or pulmonary function examinations and one patient who had ILD before diagnosis of DM/PM, a total of 56 patients were enrolled in this study. All patients were admitted via inpatient or outpatient departments, and classified into 4 groups: primary idiopathic DM, primary idiopathic PM, juvenile DM/PM and amyopathic DM(ADM), according to the criteria for DM/PM proposed by Bohan &Peter in 1975 (9). Juvenile DM/PM was defined as occurring in patients with age at onset of less than 17 years (10). Patients with ADM were presented with typical cutaneous manifestations of DM, but without clinical or laboratory findings of muscle involvement for at least 6 months after the onset of skin rash.

All patients received complete evaluation, including detailed medical history, physical examinations, muscle scan by nuclear medicine or magnetic resonance imaging, electromyography, skin or muscle biopsy and a series of laboratory examinations and chest radiography. Detailed clinical examinations were performed to determine the association of complications. Suspected lung involvement, detected by physical examination, such as abnormal crackles or rales, and clinical presentations, such as dyspnoea or cough, was initially screened by chest radiography, and confirmed by PFT and HRCT. Only with changes in HRCT or PFT were patients diagnosed with ILD. Nuclear medicine oesophageal transit scan, electrocardiography and echocardiography were performed in symptomatic patients. All patients underwent cancer screening, including detailed physical examinations, chest radiography, upper gastrofibroscopy, CT of the abdomen and pelvis and ear-nose-throat evaluations. Female subjects also received gynaecological examination.

Forty-one patients who presented with other connective tissue diseases, such as systemic lupus erythematosus and Sjogren syndrome, progressive systemic sclerosis (PSS), rheumatoid arthritis or mixed connective tissue diseases(MCTD), and one patient with ILD before diagnosis of DM/PM were excluded. The remaining 56 patients with DM/PM were enrolled in the study. We retrospectively reviewed their clinical data, including age at onset, gender, clinical features at presentation, fully developed manifestations, systemic complications, associated malignancies, and laboratory data at the time of presentation. The survival interval and the onset time intervals of complications and malignancies were also recorded.

Laboratory analysis

Serum muscular enzymes, such as glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase (LDH) and creatinine kinase (CK), and antinuclear antibodies, anti-Ro, anti-La and anti-Jo1 antibody were measured and routine blood cell tests were conducted upon diagnosis of myositis. These parameters were regularly checked during follow-up visits. We used the laboratory data at onset in our analyses.

Statistical analysis

univariate and multivariate analyses for potential prognostic factors of patients with DM/PM were performed by the cox proportional hazards model. Poor prognosis was defined as death of patients. A *p*-value of less than 0.05 was considered statistically significant. The survival study was performed using Kaplan–Meier method and Cox regression method. The survival of patients was calculated from the date of diagnosis to the date of last follow-up or death. Odds ratios(OR)are presented with a 95% confidence interval(CI). All analyses were performed using the program SPSS 11.0 (SPSS, Chicago, IL, uSA).

Results

Epidemiological Data

Among the 56 patients, DM was the most common presentation (50%), followed by ADM (21.4%), PM (19.6%) and juvenile DM/PM (8.9%) (Table I). The overall mean age at onset was 40.8 years, with older onset in patients with DM (46 years) and ADM (45.2 years) than with PM (38.2 years). There were more female patients than male patients (M/F 21/35, about 1.67/1).

Initial Presentation

Among the varied clinical manifestations at onset, cutaneous signs (82.1%) and proximal muscle weakness (73.2%) were the most common. Other manifestations included arthritis/arthralgia (37.5%), dysphagia (32.1%), dyspnoea (30.4%), fever (19.6%), muscle pain (14.3%) and Raynaud's phenomenon (14.3%).

Cutaneous Manifestations

Typical cutaneous manifestations of DM included heliotropesign, Gottron's sign, skin erythema (V-sign erythema, Shawl sign), poikiloderma, photosensitivity, and periungual telangiectasia/erythema. Several cutaneous signs could be present in one individual patient. Gottron's sign represented the most common cutaneous manifestation (37 in 45 cases excluding polymyositis, 82.2%), followed by periungual erythema/ telangiectasia (58.9%), heliotrope sign (48.2%), and skin erythema (Shawl's sign and V-sign) (46.2%). Other cutaneous manifestations including mechanic's hand, photosensitivity and poikiloderma were also found in some individuals.

Associated Malignancies

Malignant diseases were seen in 10 patients (17.9%). (Table I) Most were associated with DM (7 cases). None of them were diagnosed in patients with juvenile DM/PM. Among the 10 cases of malignancy, nasopharyngeal carcinoma (NPC) was the most common (4 in 10, 40%). There were also single cases of other cancers, including breast cancer, hepatoma, colon cancer, ovarian cancer with peritoneal and lung metastasis, pleomorphic liposarcoma and cervical carcinoma. Three malignant diseases were documented before diagnosis of DM/PM (68 months, 4 months and 1 month before diagnosis, respectively). Two were diagnosed at the onset of DM/PM. The other 5 malignant diseases developed after diagnosis (1 month, 3 month and 48 months after diagnosis, respectively).

Causes of death

We observed 8 deaths during follow-up. There were 6 deaths in patients without ILD: 4 deaths due to malignancies and 2 due to aspiration pneumonia caused by respiratory muscle weakness. Only 2 of the patients with ILD died. One death was due to aspiration pneumonia (laryngeal muscle weakness) and the other due to sepsis from lobar pneumonia and liver cirrhosis.

Associated ILD complications

Forty-two patients with DM/PM had systemic complications (75%) with ILD being the most common (23 cases, 41.1%). ILD cases were mostly associated with DM(TableI).

Half of the patients with ILD were diag-

nosed at onset (13 cases among 23 ILDs, 56.5%). Six of them were a symptomatic at onset (26.1%). The most common initial symptoms of lung involvement were dyspnoea (11 in 23 cases, 47.8%) and cough (9 cases, 39.1%). Among the patients with ILD, 6 were diagnosed with acute fibrosing alveolitis based on findings of HRCT and PFT. None of these 6 patients died during follow-up. Dyspnoea and cough seldom occurred in patients without signs of ILD on radiography/HRCT or PFT (6 of 33 cases and 3 of 33 cases, respectively).

Other systemic complications included dysphagia/ oesophageal involvement (33.9%), cor pulmonale (19.6%) and calcinosis (12.5%).

Table 1: Epidemiological data of patients with dermatomyositis/ polymyositis (DM/PM)

	DM	PM	JDM	ADM	Total
Number	28	11	5	12	56
Sex (M/F)	13/15	3/8	2/3	3/9	21/35
Age at onset (mean)	46	38.2	6.8	45.2	40.8
(years)					
Malignancy, n (%)	7 (25)	2 (18.2)	0	1 (8.3)	10 (17.9)
Complicated with ILD, n (%)	16 (57.1)	3 (27.3)	0	4 (33.3)	23 (41.1)
Mortality, n	7	1	0	0	8

JDM, juvenile dermatomyositis; ADM, amyopathic dermatomyositis; ILD: interstitial lung disease.

Univariate analyses of predicting factors of ILD in DM/PM

To define the possible predicting factors of ILD in the studied patients, we analysed several clinical and biochemical parameters, such as gender, age at onset, specific myositis subtypes, initial clinical presentations, cutaneous manifestations, systemic complications and laboratory data, using Cox proportional hazards model. Several potential predicting factors of ILD were identified on univariate analysis (Table II): DM subtype (OR 4, $p = 0.017$), initial presentation with dyspnoea (OR 4.13, $p = 0.02$), cough (OR 7.69, $p = 0.006$) and arthritis (OR 5.28, $p = 0.004$) were associated with development of ILD.

Eight of 56 patients did not receive anti-Jo1antibody test during follow-up. Of the 6 patients with positive anti-Jo1 antibody, 5 presented with ILD (83.3%). Presence of anti-Jo1 antibody was found to be a strong indicator of ILD in patients with DM/PM ($p = 0.027$ by Pearson's chi-square method). However, anti-Jo1 antibody was not found to be a predicting factor of ILD in univariate analysis (OR8.99, $p=0.054$). Abnormally high serum LDH level (more than 400Iu/L) was observed more commonly in patients who had no ILD (OR 0.22, $p=0.04$).

We chose the significant factors identified on univariate analyses to carry out multivariate analyses. (Table III) Cough (OR 26.6, $p = 0.004$), dyspnoea at onset (OR 9.60, $p = 0.029$) and arthritis at onset (OR 10.34, $p=0.021$) represented the 3 independent clinical predicting factors of ILD. Abnormally high serum LDH level above 400 u/l was inversely associated with the development of ILD (OR 0.088, $p=0.031$).

Table 2: Univariate analysis of predicting factors of interstitial lung disease in dermatomyositis/polymyositis (DM/PM) using Cox regression proportional hazards model.

	Odds ratio (95% CI)	p value
Sex (M/F)	0.82 (0.27–2.48)	NS
Older onset of age (> 60 years)	1.14 (0.27–4.8)	NS
Specific subtypes		
DM*	4 (1.28–12.45)	**0.017**
Juvenile DM/PM	0	–
Amyopathic DM	0.66 (0.17–2.51)	NS
Initial presentation		
Muscle weakness	3.81 (0.93–15.53)	0.062
Dyspnoea*	4.13 (1.24–13.8)	**0.02**
Cough*	7.69 (1.813–32.631)	**0.006**
Dysphagia	0.62 (0.19–1.99)	NS
Fever	0.78 (0.2–3.1)	NS
Arthritis/arthralgia*	5.28 (1.87–18.9)	**0.004**
Muscular pain	0.84 (0.18–3.93)	NS
Skin manifestations		
Gottron's sign	0.68 (0.22–2.07)	NS
Heliotrope sign	0.72 (0.25–2.11)	NS
Periungual erythema	1.15 (0.39–3.39)	NS
Skin erythema	1.1 (0.38–3.20)	NS
Mechanic's hand	7.43 (0.76–73.03)	NS
Presence of malignancy	0.30 (0.06–1.56)	NS
Laboratory data		
Anti-Jo1 antibody	8.99 (0.96–84.34)	0.054
Raised LDH (> 400u/l)*	0.22 (0.05–0.93)	**0.04**
Raised GOT	1.31 (0.42–4.07)	NS
Raised GPT	1.09 (0.35–3.40)	NS
Positive ANA antibody	1.04 (0.33–3.20)	NS
Positive SSA antibody	1.21 (0.16–9.42)	NS

Statistically significant, $p < 0.05$.

LDH, lactate dehydrogenase; GOT, glutamate oxaloacetate; GPT, glutamate pyruvate transaminase; ANA, antinuclear antibodies; SSA, anti- Ro; NS, not significant.

Table 3: Multivariate analysis of predicting factors of interstitial lung disease using Cox proportional hazards model.

	Odds ratio (95% CI)	**p-value**
DM subtype	4.03 (0.66–24.60)	0.131
Dyspnoea*	9.60 (1.25–73.51)	0.029
Cough*	26.57 (2.77–255.29)	0.004
Arthritis*	10.34 (1.42–75.49)	0.021
Raised LDH level*	0.088 (0.01–0.80)	0.031

*Statistically significant, $p < 0.05$.DM, dermatomyositis; LDH, lactate dehydrogenase.

Survival analyses and prognostic factors of DM/PM

The mean follow-up time among patients with DM/ PM was 42.87± 36.34 months (range 1–122 months). There was no significant difference in survival time between patients with and without ILD, with mean survival times of 50.43 ± 41.57 and 37.61 ± 31.81 months, respectively. Seven of the 8 deaths occurred during the first year of follow-up, and the remaining death occurred in the second year. The 1-year, 2-year and 3-year survival rates were 86.14%, 83.78% and 83.78%, respectively.

We analysed several potential prognostic factors of DM/PM, such as myositis subtypes, older age at onset, complicated with ILD, heart or oesophageal complications, presence of malignancy, raised serum muscular enzymes, and other clinical manifestations, using Cox regression method on univariate and multivariate analyses. Presence of malignancy (OR4.10,95%CI1.01–16.50, p= 0.047) and older age at onset (more than 60 years) (OR4.68,95%CI1.11–19.66,p=0.035) were 2 Independent prognostic factors of patients with DM/PM. Specific subtypes of myopathies, initial presentations of cutaneous manifestations, dysphagia, dyspnoea and complications with ILD, cor pulmonale or calcinosis bore no prognostic impact on patients with DM/PM.

Discussion

In our study, ILD represented the most common complication (41.1%) in patients with DM/PM, whereas dyspnoea and cough were the most common symptoms at onset, as reported previously (3–5). One-quarter of our patients with ILD were asymptomatic at onset. Clinical manifestations, such as muscle weakness, arthritis/arthralgia and mechanic's hands were found to occur frequently in myositis patients with ILD compared with those without ILD, but the difference was not statistically significant. Cutaneous manifestations were irrelevant to the occurrence of ILD. In contrast with previous reports, which showed that clinical symptoms are unreliable in the detection of the development of ILD in DM/PM patients [4,11], our study revealed that presence of arthritis, dyspnoea and cough are good predictors of the development of ILD. In addition to these clinical signs, patients with DM subtype tended to have a greater chance of developing ILD than patients with other subtypes. However, the statistical power was lacking in multivariate analysis, probably due to limited case numbers.

Several laboratory markers can be used to predict the Development of ILD, for example, presence of positive anti-aminoacyl tRNA synthetase antibodies, of which the anti-histidyl tRNA synthetase antibody, anti-Jo1, is the strongest predictive factor for ILD in patients with myositis [11]. The reported frequency of ILD in patients with anti-Jo1 antibodies is more than 70% [4,5,12,13]. In our study, the frequency of ILD in our patients with anti-Jo1 was 83.3%. On the other hand, the presence of anti-Jo1 antibody was found in 25% of patients with ILD, compared with 3.6% of patients without ILD. The presence of anti-Jo1antibody was highly associated with ILD in DM/PM patients (p=0.027 using Pearson's chi-square method, OR 8.99, p= 0.054 in logistic regression analysis). The borderline statistical significance is probably due to the limited number of patients we enrolled; however, we could still see the strong association between anti-Jo1 antibody and ILD. We therefore suggest routine testing of anti-Jo1 anti-bodies in patients who present with arthritis, dyspnoea or cough, and their presence requires careful evaluation of lung involvement using HRCT and PFT.

In addition, high serum LDH level was found to be inversely associated with ILD complications in both univariate and multivariate analyses. Raised serum LDH

level has been reported to be correlated with the activity and poor prognosis of idiopathic interstitial pneumonia and ILD associated with connective tissue diseases [14, 15]. High serum LDH levels tended to decrease in patients who survived after therapy (15). Patients with a lower ratio of CK/LDH were reported to be resistant to various treatments for ILD [15]. Our results suggested patients with serum LDH level higher than 400 u/l have significantly less chance to develop ILD. It may provide physicians a rapid screening tool for evaluating the possibility of ILD development in myositis. However, there were no consistent findings in the literature. One possible explanation for the discrepancy may be differences between the patient groups in previous studies and this study. Previous studies mainly evaluated the activity and prognosis or response to treatments specifically on patients with ILD. Our study was designed to compare patients with and without ILD. Further larger series studies may help clarify the issue.

The mechanisms of ILD in patients with DM/PM could be numerous due to the various histological features of ILD in myositis [16]. On histopathological analysis, ILD-associated collagen vascular diseases have been shown to be diverse and include non-specific interstitial pneumonia, usual interstitial pneumonia, bronchiolitis obliterans organizing pneumonia, apical fibrosis, diffuse alveolar damage, and lymphocytic interstitial pneumonia [16]. Although proportions of interstitial pneumonias vary, non-specific interstitial pneumonia accounts for a large proportion, especially in PSS, DM/PM and MCTD. ILD-associated collagen vascular diseases have been reported to have a more favourable prognosis than idiopathic interstitial pneumonias, probably because of the larger proportion of non-specific interstitial pneumonia in ILD-associated collagen vascular diseases [16]. However, lung biopsies are seldom performed for the purpose of diagnosis, partly because of the potential morbidity during procedure, and partly because of the high incidence of patient refusal. More specifically, DM-associated ILD has recently been reported to have a poorer prognosis than PM-ILD because DM-ILD is more resistant to corticosteroid therapy [17].

Several studies have attempted to identify independent risk factors for predicting poor outcome in DM/PM. Poor prognostic factors include recalcitrant disease, delay of diagnosis and therapy, old age, malignancy, fever, asthenia-anorexia, pulmonary interstitial fibrosis, dysphagia and leukocytosis [18–21]. ILD has also been regarded as a main cause of death, in addition to malignancy, cardiac complications and iatrogenic complications [2,6–8]. In our study, the most common cause of death was concomitant malignancy (50%), followed by sepsis due to aspiration pneumonia (25%) and lobar pneumonia (25%). Presence of malignancy and older age at onset (more than 60 years) appeared to be the 2 independent prognostic factors in DM/PM. NPC remained the most common concurrent malignant disease in DM/PM patients. Two deaths due to infectious pneumonias were observed among patients with ILD, probably related to the decreased reserve of lung functions. Six patients were reported to have acute fibrosing alveolitis, but none of them progressed into severe fulminant fatal pneumonitis, and none of them died during follow-up. It is interesting to note that these 6 patients showed younger age at onset (none of them exceeded 48 years of age). In brief, ILD itself bears no adverse influence on the survival of these DM/PM patients. We postulated the reason to be the early detection and aggressive treatment of these ILD patients.

Current approaches to the treatment of these inflammatory myopathies are

problem oriented. For cutaneous involvement, photo protection and topical corticosteroid or non-steroid immunomodulators are the main drugs. Advanced treatments include oral antimalarials or other systemic immunomodulators, such as methotrexate, thalidomide, mycophenolate mofetil, dapsone, retinoids or other biologics [22–25]. For muscular involvement, combination of corticosteroids and other systemic im-immunomodulators, such as cyclophosphamide, methotrexate, azathioprine, cyclosporine and mycophenolate mofetil, or intravenous immunoglobulins show good results. As for other associated complications or malignancies, individual tailored treatment is required (22–25). Resistance to therapeutic agents including corticosteroid is one of the reasons why ILD accounts for a significant proportion of mortality and morbidity of patients with DM/PM. New therapeutic management for ILD includes combination of corticosteroid and T-cell specific immunosuppressant, such as cyclosporine or FK 506 (26). All of our 23 patients with ILD received combinational therapy including corticosteroid, methyl- prednisolone pulse therapy, methotrexate, Plaquenil and cytotoxic drugs including cyclophosphamide and aziothprine. Cyclosporine was seldom used. In general, they responded to treatment well and only 2 deaths occurred during follow-ups.

To study the specific association of ILD in patients with DM/PM, we excluded many patients with other connective diseases who may also have complications of ILDs. Finally, the case numbers enrolled in this study seemed insufficient to perform extensive univariate and multivariate analyses. Despite the limited results, we still have some suggestions: routine chest radiography evaluation of patients with DM/PM may prevent delay of diagnosis of ILD complication in dyspnoeic or even asymptomatic patients, especially in patients of primary idiopathic DM subtype. In addition, anti-Jo1 antibody and serum LDH testing is mandatory for ILD evaluation. With early diagnosis and adequate treatment, ILD does not necessarily represent a poor prognostic factor for myositis patients.

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