



Clinical and Radiological Predictor of Polymyositis and Dermatomyositis Associated Interstitial Lung Disease

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Abstract

Background: Polymyositis (PM) and dermatomyositis (DM) often have interstitial lung disease (ILD) and progression of ILD is important cause of death.

Objectives: This study is conducted to clarify the important clinical, radiological factors of PM/DM ILD patients.

Methods: We reviewed medical records, pulmonary function test (PFT), chest high-resolution computed tomography (HRCT) findings from January 1, 2001 to December 31, 2014 retrospectively at Okinawa Chubu Hospital.

Results: We identified 41 patients. Men were 14 and women were 27. Median age was 52 ± 16.3 (17-80). 19 was DM and 22 was PM. Compared to PM patients, DM patients more often had heliotrope rash, Gottron sign, and subungual erythema (47.4% vs. 4.5%, $p = 0.0009$, 68.4% vs. 9.1%, $p < 0.0001$, 52.6% vs. 9.1%, $p = 0.0016$). In terms of radiological findings, lung tip consolidation was more often detected in DM patients. In survival time, DM-ILD patients showed poor survival compared with that of PM patients (44.7 vs. 88.6 months: $p = 0.0242$). Cox proportional hazard ratio showed diagnosis of DM, Gottron sign, subungual erythema, Anti-MDA5 antibody, and lung tip consolidation were strong predictors of PM/DM-ILD patients [Hazard Ratio (HR): 6.343, $p = 0.021$, HR: 7.330, $p = 0.019$, HR: 8.784, $p = 0.004$, HR: 25.764, $p = 0.001$, HR: 2.494, $p = 0.042$].

Conclusions: In our cohort of PM/DM associated ILD patients, diagnosis of DM, Gottron sign, subungual erythema and lung tip consolidation were strong predictors.

Keywords

PM, DM, ILD, Gottron sign, Lung tip consolidation

Introduction

Dermatomyositis (DM) and polymyositis (PM) are two major idiopathic inflammatory myopathies (IIMs), which mainly affect skin, muscle, lung [1,2]. The estimated annual incidence of PM/DM ranges from 6 to 10 per 1 000 000 [3]. In general, PM associated interstitial lung disease (ILD) have rather chronic course [4,5]. And among the PM-ILD patients, autoantibodies against aminoacyl-tRNA synthetases (ARS) syndrome have good prognosis [6].

On the other hand, DM especially clinically amyopathic dermatomyositis (CADM) which have typical rash of DM with

little or no definite muscle symptoms or hypomyopathic DM which mild muscle weakness with no elevation of muscle enzyme for > 6 months associated ILD patients have more poor prognosis [7,8]. Approximately one-third of the patients with DM, CADM, PM develop ILD during their clinical course [4,9]. In addition, acute severe forms of ILD sometimes occur in DM or CADM patients. Therefore, ILD is important extra-muscular manifestation of IIMs [10-12]. Regarding DM, CADM, there was some reports about poor prognosis of especially CADM associated ILD patients.

In addition, ILD causes substantial morbidity and resulting in mortality of approximately 50% in some series [13]. There are substantial heterogeneity exists within the spectrum of IIMs, from mild chronic course to fulminant rapidly progressive course [14]. Some reports have shown clinical characteristics of PM. DM associated ILD. However, little is known about both clinical and radiological findings of each phenotype, the aim of this retrospective study were evaluating clinical and radiological predictors of PM/DM patients.

Methods

Patient inclusion: We identified 41 patients diagnosed with PM (n = 22), DM (n = 15), and CADM (n = 4) associated with ILD patients from 2000 April to 2014 December at Okinawa Chubu Hospital. The diagnosis of PM/DM was based on the criteria of Bohan and Peter [1]. 1) systemic muscle weakness, 2) increased serum muscle enzyme levels, 3) electromyographic (EMG) evidence of myopathic changes, 4) typical histologic findings in muscle biopsies, and/or 5) characteristic dermatologic manifestations of DM. CADM, or dermatomyositis sine myositis, is defined by the absence of clinically significant muscle symptoms and normal muscle enzymes such as creatine kinase (CK) level [7,12,15,16] for periods of > 6 months, and is associated with an acute severe form of interstitial lung disease (ILD) [9]. All clinical information including pulmonary function test, radiological findings were baseline at diagnosis.

Clinical information: We reviewed clinical symptoms such as fever, cough, dyspnea, myalgia, arthralgia, mechanic hand, rash, subungual erythema, erythema, heliotrope rash, Gottron sign, finger swelling and Raynaud phenomenon. In terms of laboratory findings, we evaluated WBC, CRP, CPK, GOT, GPT, ALP, γ -GTP, LDH, Sialylated carbohydrate antigen KL-6 (KL-6), surfactant

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Table 1: Clinical characteristics of combined PM/DM associated ILD patients.

Age	52 (17-80)
Gender (Men/Women)	14/27
Smoking (Ever/Never)	12/29
WBC	9106 (3600-18400)
CRP	1.9 (0-6.84)
CPK	3314 (30-29380)
GOT	157 (15-1034)
Ferritin	942 (46-2958)
LDH	624 (181-2790)
KL-6	1387 (272-9100)
SP-D	159 (18-525)
Survival time (months)	68.2 (0.3-181)

Data are expressed as median (range)

Definition of Abbreviations: PM = Polymyositis; DM = Dermatomyositis; ILD = Interstitial lung disease; WBC=White blood cell; CRP = C-reactive protein; CPK = Creatine Phosphokinase; GOT = glutamic oxaloacetic transaminase; LDH = Lactate dehydrogenase; KL-6 = Sialylated carbohydrate antigen KL-6; SP-D = Surfactant protein D

Table 2: Clinical characteristics between PM and DM associated ILD patients.

	PM-ILD (n = 22)	DM-ILD (n = 19)	p-value
Age	52.8 (18-77)	51.1 (17-80)	0.741
Gender (Men/Women)	8/14	6/13	0.755
Smoking (Ever/Never)	8/14	4/15	0.294
WBC	10245 (4700-18400)	7907 (3600-16900)	0.051
CRP	2.1 (0-6.6)	1.7 (0.05-6.8)	0.615
CPK	4544 (52-29830)	1956 (30-9710)	0.125
GOT	178 (24-1034)	135 (15-463)	0.493
Ferritin	703 (133-1324)	1156 (46- 2958)	0.259
LDH	726 (252-2790)	517 (181-895)	0.151
KL-6	1812 (272-9100)	748 (325-1342)	0.157
SP-D	151 (17.8-524.7)	172 (78.8-336.6)	0.891
Survival time (months)	88.6 (2.0-181.1)	44.7 (0.33-175.9)	0.024

Data are expressed as median (range).

Definition of Abbreviations: PM = Polymyositis; DM = Dermatomyositis; ILD = Interstitial lung disease; WBC=White blood cell; CRP = C-reactive protein; CPK = Creatine Phosphokinase; GOT = glutamic oxaloacetic transaminase; LDH = Lactate dehydrogenase; KL-6 = Sialylated carbohydrate antigen KL-6; SP-D = Surfactant protein D

Table 3: Clinical symptoms and signs of between PM and DM associated ILD patients.

	PM-ILD (n = 22)	DM-ILD (n = 19)	p-value
Fever	31.8%	36.8%	0.743
Cough	27.2%	42.1%	0.330
Dyspnea	50%	42.1%	0.624
Myalgia	72.7%	57.9%	0.330
Arthralgia	40.9%	42.1%	0.940
Heliotrope rash	4.5%	47.4%	< 0.001
Gottron sign	9.1%	68.4%	< 0.001
Subungual erythema	9.1%	52.6%	0.002
Mechanic hand	18.2%	10.5%	0.502
Generalized rash	42.9%	84.2%	0.006

Data are expressed as percentage.

Definition of Abbreviations: PM = Polymyositis; DM = Dermatomyositis; ILD = Interstitial lung disease

protein-D (SP-D), ferritin. Auto-antibodies including Jo-1 [17] and anti-melanoma differentiation-associated gene 5 (MDA-5) antibody [18,19]. If patient underwent broncho-alveolar lavage (BAL), we checked cell population such as neutrophils, lymphocytes, eosinophils and CD4/8 ratio in broncho-alveolar lavage fluid (BALF). In physiology findings, we reviewed forced vital capacity (FVC), percent predicted FVC, forced expiratory volume in 1 second (FEV₁), percent predicted FEV₁, total lung capacity (TLC), percent predicted TLC, diffusing capacity or transfer factor of the lung for carbon monoxide (DLco) and percent predicted DLco.

Radiological findings: Chest high resolution computed tomography (HRCT) findings without contrast material were

reviewed. These images comprised 1.5 mm collimation sections at 10 mm intervals. We evaluated the presence of consolidation, ground-glass opacity, reticular opacity, traction bronchiectasis and lung tip consolidation at below 1 cm of right diaphragm. Definition of ground-glass opacity was hazy increased attenuation of the lung that did not obscure the underlying vessels. Consolidation was defined as homogeneous increase in pulmonary parenchymal attenuation that obscured the underlying vessels. Definition of reticular opacity was regular interlacing linear shadows separated by a few millimeters. Traction bronchiectasis was defined as Irregular bronchial dilatation within or around areas with parenchymal abnormality. Definition of lung tip consolidation was thick consolidation > 3 mm with connection of both right diaphragm and pleura. Extent of consolidation, ground-glass opacity, reticular opacity, traction bronchiectasis was defined as follows; 0: none, 1: < 25%, 2: 25% < 50% >, 3: 50% < 75% >, 4: > 75% [20]. Extent of lung tip consolidation was defined as 0: none, 1: one thick consolidation, 2: more than two thick consolidations. Thick was defined over 3 mm. Lung tip consolidation looks like migratory bird. Therefore, we call it migratory bird sign. The score of each finding was defined as total sum divided into patient's number.

Our institutional board waived informed consent because of retrospective study.

Statistical Analysis

Continuous variables are presented as means ± standard deviations, and categorical variables are presented as percentages. The Chi-square and Fisher's exact tests were used to analyze categorical data, and the unpaired *t*-test and Mann-Whitney U test were used for continuous data. Cox regression analysis was used to identify significant variables predictive of mortality.

The Kaplan-Meier survival curves and the log-rank test were used to evaluate survival. The level of statistical significance was set at *P* < 0.05. All analyses were performed using Stata Data Analysis and Statistical Software STATA version 11.0; (Stata Corp., College Station, TX, USA).

Results

The clinical characteristics of PM/DM associated ILD patients (14 men, 27 women) are summarized in table 1. Mean age was 52 (17-80). Mean partial pressure of oxygen (PaO₂) was 76.2 mmHg and partial pressure of carbon dioxide (PaCO₂) was 31.3 mmHg. In BALF findings, mean neutrophils, lymphocytes, eosinophils and CD4/8 were 19.2% (0-81), 38.8% (4-93), 1.2% (0-4), and 1.2 (0.1-1.3) respectively. We compared clinical, physiological findings between PM-associated ILD and DM including CADM-associated ILD patients. PM-associated ILD patients tended to show more elevation of CPK, LDH and KL-6 (4544 vs 1956, 726 vs 517, 1812 vs 748) (Table 2). However, it did not show statistical significance. In autoantibody, four patients had positive for Anti-MDA-5 antibody and seven patients showed positive for Jo-1 antibody. When we evaluated survival time between PM-associated ILD patients and anti-MDA-5 negative DM-ILD patients, there was still statistically significance (88.6 months vs 52.9 months, *p*-value = 0.04). We also evaluated clinical symptoms and signs between PM and DM ILD patients. As shown in table 3, DM patients had more heliotrope rash (47.4% vs. 4.5%, *p* < 0.001), Gottron sign (68.4% vs. 9.1%, *p* < 0.001), subungual erythema (52.6% vs. 9.1%, *p* = 0.002), generalized rash (84.2% vs. 42.9%, *p* = 0.006).

In PFT, PM-ILD patients tended to show decreased %FVC, TLC and % DLco (71.4 vs. 78.3, 84.6 vs. 90.9, 65.6 vs. 94.8), however, it did not show statistically significance (Table 4). In terms of radiological findings, DM-associated ILD patients showed more lung tip consolidation than PM-ILD patients. (0.44 vs. 0.11, *p* = 0.025) (Table 5). Among five CADM-associated ILD patients, 80% of the patients had lung tip consolidation, on the other hand, 14% of the PM-ILD patients and 43% of the DM-associated ILD patients had lung tip consolidation. Representative image of lung tip consolidation is shown in figure 1. We call this finding migratory bird sign. Regarding treatment, 39 patients received high dose prednisolone initially.

Table 4: Pulmonary function test between PM and DM associated ILD patients.

	PM-ILD (n=22)	DM-ILD (n=19)	p-value
FVC	1.83 (1.19-2.68)	2.23 (1.55-3.48)	0.321
%FVC	71.4 (60.7-80.5)	78.3 (62.5-100.6)	0.428
FEV1	1.56 (1.06-2.25)	1.97 (1.31-3.2)	0.246
TLC	3.87 (3.24-4.73)	3.89 (3.15-5.69)	0.975
%TLC	84.6 (75-90.1)	90.9 (81-106.8)	0.392
DLco	12.9 (8.6-19.8)	18.6 (11.4-39.3)	0.543
%DLco	65.6 (41.8-95.6)	94.8(48.8-192.3)	0.511

Values are expressed ad range.

Definition of Abbreviations: PM = Polymyositis; DM = Dermatomyositis; ILD = interstitial lung disease; FVC = forced vital capacity; %FVC = percent predicted forced vital capacity; FEV1 = forced expiratory volume in 1 second; TLC = total lung capacity; %TLC = percent predicted total lung capacity; DLco = diffusing capacity or transfer factor of the lung for carbon monoxide; %DLco = percent predicted diffusing capacity or transfer factor of the lung for carbon monoxide

Table 5: Radiological findings between PM and DM associated ILD patients.

	PM-ILD (n = 22)	DM-ILD (n = 19)	p-value
Consolidation score	1.72	1.69	0.940
GGO score	1.72	1.81	0.773
Reticular opacity score	0.50	0.63	0.666
Traction bronchiectasis score	0.28	0.50	0.390
Lung Tip consolidation	0.11	0.44	0.025

Data are expressed as mean and these numbers are categorical.

Definition of Abbreviations: PM = Polymyositis; DM = Dermatomyositis; ILD = Interstitial lung disease; GGO = Ground-glass opacity

Table 6: Cox proportional Hazard Model for PM/DM associated ILD patients.

	Hazard ratio	95% CI	p-value
Gottron sign	7.330	1.381-38.9-6	0.019
Subungual erythema	8.783	2.001-38.420	0.004
Lung Tip consolidation	2.494	1.035-6.007	0.042
Diagnosis of DM	6.343	1.320-30.478	0.021
Anti-MDA-5 antibody	25.764	4.116-161.287	0.001

Definition of Abbreviations: PM = Polymyositis; DM = Dermatomyositis; ILD = Interstitial lung disease;

MDA = melanoma differentiation associated gene; CI = Confidence Interval

Especially, we did steroid pulse with immunosuppressants such as cyclosporine or tacrolimus for CADM associated ILD patients. In maintenance phase, PM-associated ILD patients more often took prednisolone alone (54.5% vs. 33.3%) and DM-ILD patients received more prednisolone plus tacrolimus (38.9% vs. 9.1%). Among the four anti-MDA-5 antibody positive patients, three patients (75%) died finally despite intensive therapy. Kaplan-Meier survival curve showed DM associated ILD group showed poor prognosis compared with that of PM related ILD group (88.6 months vs. 44.7 months, $p = 0.009$) (Figure 2). Overall, ten patients died during observation period. Cox proportional hazard model showed Gottron sign, subungual erythema, lung tip consolidation, diagnosis of DM and Anti-MDA-5 antibody [hazard ratio(HR); 7.33; $p = 0.020$, HR; 8.78; $p = 0.004$, HR; 2.494; $p = 0.042$, HR; 6.343; $p = 0.021$, HR; 25.76; $p = 0.001$, respectively] were strong predictors of PM/DM associated ILD patients at our cohort (Table 6).

Discussion

In this study, we clarified the clinical characteristics, physiological findings, radiological findings and prognosis of 41 PM/DM including CADM associated ILD patients at our cohort. Our result showed DM-specific signs such as Gottron sign and subungual erythema, anti-MDA-5 antibody were predictor of mortality. In addition, we also focused on radiological findings and lung tip consolidation or migratory bird sign was a useful predictor of mortality in DM associated ILD patients, which is a novel finding. There were a few studies which evaluated the prognostic factors for PM/DM ILD [5,8,16]. Therefore, our study contributes to meaningful information for evaluation of PM/DM associated ILD.

We described diagnosis of DM and DM-specific clinical signs such as Gottron sign and subungual erythema were strong predictors of

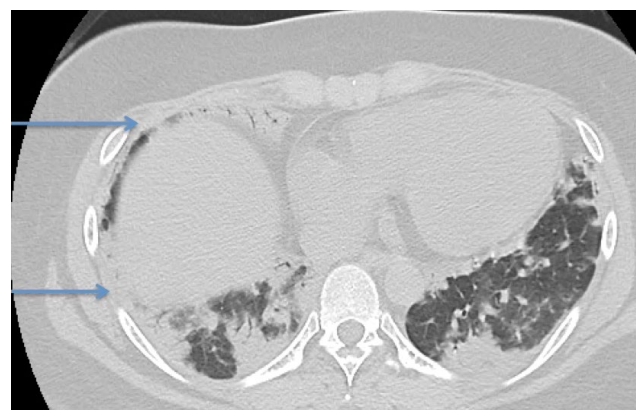


Figure 1: Representative image of Lung Tip consolidation. Arrow indicates two thick consolidation and migratory birds sign.

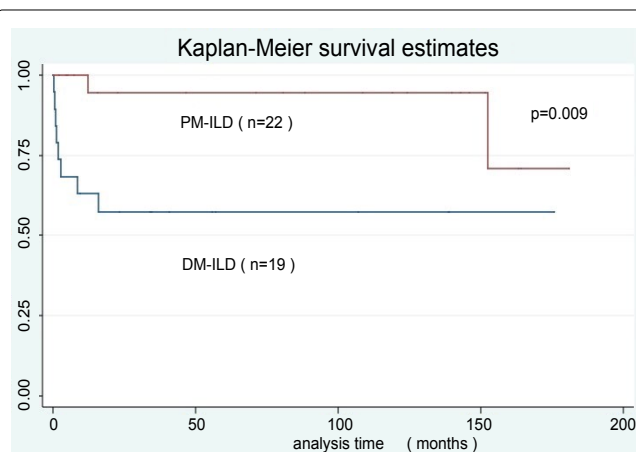


Figure 2: Survival curve of between PM and DM associated ILD patients. DM-ILD patients showed poor prognosis compared to PM-ILD patients.

mortality in DM-ILD at our cohort [21,22]. Physicians who diagnose ILD should have comprehensive overview of physical findings to distinguish from connective tissue disease (CTD) associated ILD especially in middle-aged patients. Among all CTDs, CADM have aggressive presentation of ILD [23,24]. Therefore, we should look for DM-specific physical findings such as Gottron sign, Heliotrope rash carefully. Subungual erythema is often detected systemic sclerosis (SSc) or PM-limited SSc overlap syndrome [25,26]. However, SSc or overlap syndrome is possible to be excluded by detailed clinical information or specific antibody such as anti-PM/Scl autoantibodies [22]. So, rapid clinical course with subungual erythema and DM-specific sign will be alarming signs for DM-associated ILD patients. Both Gottron sign and subungual erythema are associated extensive vasculitis. Therefore, poor prognosis of DM-associated ILD can be explained by these specific physical findings.

In autoantibodies, we showed anti-MDA 5 autoantibody-related ILD was poor prognosis and this antibody was strong predictor of mortality. This antibody is specific for dermatomyositis and may be found approximately 10% of adult PM/DM patients [27-29]. Both DM specific signs and anti-MDA 5 autoantibody are useful predictor of poor prognosis for DM associated ILD at our cohort. On the other hand, anti-tRNA-synthetase (Anti-ARS) autoantibodies was first described by Marguerie, et al. and this antibody associated ILD showed good prognosis compared with that of anti-MDA 5 autoantibody-related ILD in our study. Anti-ARS autoantibodies especially anti-Jo1 antibody is most frequently found in PM patients [14]. Recently ten anti-ARS autoantibodies including PL-7, PL-12 have reported in several studies [30,31]. Both PL-7 and PL-12 often have ILD. However, it requires more evidence. Connors et al. proposed revised Anti-ARS syndrome criteria with major items (arthritis, myositis, and ILD) and minor criteria (unexplained fever, Raynaud phenomenon and Mechanic's hand) [4].

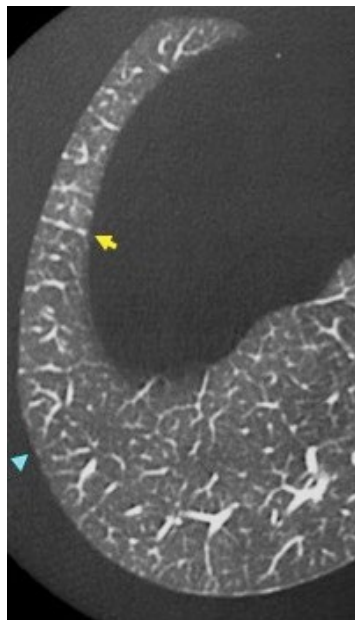


Figure 3: Normal image of right lung base.

This criteria is easy to use and practical for daily practice. These syndrome patients have good response with prednisolone. However, they often have relapse. Therefore, long-term careful follow-up will be required. Anti-MDA 5 autoantibody-related ILD and Anti-ARS syndrome have quite different clinical course. CADM and Anti-MDA 5 autoantibody positive patients are more prevalent in Japanese patients compared with non-Asian patients [32]. We should pay attention to detailed history and specific symptoms, signs such as Gottron sign, subungual erythema for PM/DM associated ILD patients.

In pulmonary function test (PFT), especially our DM ILD patient had preserved pulmonary function including %FVC, %TLC and %DLco at initial stage.

In PM/DM patients, restrictive disorder is affected by ILD or muscle involvement. Therefore, interpretation of PFT is rather difficult. Even if initial PFT is preserved, PM/DM associated ILD can develop acute deterioration during clinical course. Therefore, we should monitor both clinical, physiological and radiological changes carefully.

In terms of radiological findings, chest HRCT is crucial for evaluation of CTD-ILD. Among PM/DM patients, interstitial changes are frequently located in bilateral lower lobes [33,34]. GGO, consolidation, reticular opacity, traction bronchiectasis and linear opacities are frequent HRCT findings of PM-DM ILD. Linear opacity was found all our PM/DM ILD patients. Therefore, we thought this may not be possible prognostic discriminator and excluded our analysis. In Anti-ARS syndrome often have volume loss of lower lung field and peri-bronchovascular consolidation [31]. These HRCT findings correspond pathologically to organizing pneumonia (OP) or non-specific interstitial pneumonia (NSIP) or variant of organizing pneumonia with supervening fibrosis [35,36]. GGO and reticulation correspond to reversible fibrosis. We focused on lung tip consolidation. Because such findings were often seen in our CADM associated ILD. On the other hand, this consolidation was not detected in normal population (Figure 3). We think grade of lung tip consolidation was rather mild in PM-associated ILD patients. Therefore, more extensive lung tip consolidation of CADM patients caused strong limitation of movement of diaphragm and overall lower lung field. With these findings, we provide more intensive treatment immediately. We built up hypothesis that these lung tip consolidation or migratory bird sign may limit the movement of right diaphragm. In addition, there are more gravity dependent and more respiratory movement for removal of exudates in this extreme basal area. If

persistent inflammation or fibrosis continue in this area, this will lead to severe restrictive disorder or profound dyspnea. Our study showed lung tip consolidation predicted mortality of CADM associated ILD patients. Therefore, our proposed hypothesis might be correct.

In treatment, PM related ILD patients can be managed with prednisolone alone especially anti-ARS syndrome group or with prednisolone and immunosuppressants such as azathioprine [13]. Over half of our PM-ILD cohort was controlled with prednisolone alone. However, regarding PM-associated ILD patients, PSL + FK506 improved mortality recently. On the contrary, DM associated ILD especially CADM ILD patients have poor prognosis as shown by our study.

Based on our useful predictor, when we diagnose CADM-ILD, we should start intensive therapy such as steroid pulse with calcineurin inhibitor such as cyclosporine or tacrolimus and intravenous cyclophosphamide, azathioprine [33,37-39].

We have limitations. First, it was a single-center retrospective study. Therefore, it did not represent overall PM/DM ILD patients. However, clinical symptoms, signs were comparable with previous reports. Second, some data were missing such as Ferritin and anti-ARS autoantibody. However, most important issue is tracing clinical course and catch-up prognostic signs or marker for PM/DM ILD. Third, radiological point of view, detecting clinical meaning of lung tip consolidation is novel finding. All facilities cannot perform chest HRCT. However, it is important to create close cooperation between private clinic and special center.

In conclusion, Gottron sign, subungual erythema, lung tip consolidation, diagnosis of DM and Anti-MDA-5 antibody are useful predictor of mortality in PM/DM associated ILD patients. Further studies are needed to evaluate the multi-dimension of PM/DM ILD patients.

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