ORIGINAL

Clinical characteristics of dermatomyosits/polymyositis associated interstitial lung disease according to the autoantibody

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Abstract : Background : Dermatomyositis (DM) and polymyositis (PM) often have association with interstitial lung disease (ILD) which have disease specific autoantibody. Methodology : We reviewed medical records of DM/PM associated ILD from January 2000 to December 2017 according to the autoantibody. Result : We identified 52 patients, of whom 30 were antibody negative, 18 had anti aminoacyl-tRNA synthetases (ARS) antibodies and 4 had anti melanoma differentiation-associated gene (MDA)-5 antibody. In high resolution computed tomography (HRCT) of the chest, area of ground glass opacity (GGO), consolidation, and lung tip consolidation were more extensive in anti MDA-5 antibody positive patients (p=0.051, p=0.026, and p=0.027, respectively). Among laboratory findings, GOT had strong correlations with CPK (r=0.889, p<0.001), and LDH (r=0.910, p<0.001). Among roentgenographic findings, there were moderate correlations between GGO and consolidation (r=0.668, p< 0.001), and between reticular shadow and traction bronchiectasis (p=0.633, p<0.001). ILD patients with anti MDA-5 antibodies had decreased survival (1.00 vs 84.3, 22.9 months, p<0.001). Conclusion : ILD patients with anti ARS antibody had intense inflammation, but reversible fibrosis and good prognosis. On the other hand, anti MDA-5 antibody positive ILD patients had shorter survival. Extent of parenchymal shadow and serum GOT were useful indicator of disease activity of PM/DM associated ILD patients in our cohort. J. Med. Invest. 65 : 251-257, August, 2018

Keywords **:** *Polymyositis/Dermatomyositis (PM/DM), Interstitial lung disease (ILD), aminoacyl-tRNA synthetases (ARS), Anti melanoma differentiation-associated gene (MDA)-5, GOT*

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 million (3). Traditionally, PM associated interstitial lung disease (ILD) have been thought to have a chronic clinical course (4, 5). Recently, autoantibodies against aminoacyl- tRNA synthetases (ARS) have been shown to indicate a subacute course and good prognosis (6, 7). In contrast, some patients with ILD associated with DM, especially those with clinically amyopathic dermatomyositis (CADM), who have the 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 who have anti melanoma differentiation-associated gene (MDA)-5 antibody present with rapid progressive disease and have a poor prognosis (7-9). Approximately one-third of the patients with DM, CADM, PM develop ILD (4, 10) and acute severe forms of ILD sometimes occur in DM or CADM patients. Therefore, ILD is an important extra-muscular manifestation of IIMs (11, 12), which causes substantial morbidity and results in up to 50% of mortality (13). The spectrum of IIMs ranges from a mild chronic course to a fulminant rapidly progressive course (14, 15). Some reports have described clinical characteristics of ILD associated with PM or DM, but little is known about the clinical, laboratory and radiological findings of each phenotype, including myositis specific antibodies such as anti ARS autoantibody and anti MDA-5 antibody, which have been recently shown to have associations with these diseases (16). The aim of this retrospective study was to evaluate clinical and radiological characteristics of PM/DM patients according to autoantibody status.

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METHODOLOGY

Study population

We retrospectively identified ILD patients from 2000 April to 2017 December at Okinawa Chubu Hospital, and determined whether anti ARS antibody or anti MDA-5 antibody were present. 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 defined by the absence of clinically significant muscle symptoms and normal muscle enzymes such as creatine kinase (CK) for periods of > 6 months. CADM is associated with an acute severe forms of ILD (7, 9, 12, 15, 16). Baseline clinical parameters including pulmonary function testing (PFT), and radiological findings were collected from the time of diagnosis.

We included PM/DM patients who had parenchymal shadow and were screened autoantibodies, including anti-Jo-1 antibody at least. PM/DM patients without interstitial pneumonia were excluded.

Clinical information

We reviewed clinical symptoms such as fever, cough, dyspnea, myalgia, arthralgia, Raynaud phenomenon, and physical findings such as mechanic hand, rash, subungual erythema, erythema, heliotrope rash, Gottron's sign, and finger swelling. We collected laboratory results for WBC, CRP, CPK, GOT, GPT, ALP, LDH, Krebs von den Lungen-6 (KL-6),and ferritin. Auto-antibodies including anti-Jo-1 (17, 18) other anti ARS antibody and anti-melanoma differentiation-associated gene 5 (MDA-5) antibody were measured (19, 20). In physiological findings, we reviewed forced vital capacity (FVC), percent predicted FVC, total lung capacity (TLC), and percent predicted TLCs. The interval between PFT and chest high resolution computed tomography (HRCT) was within three months.

We evaluated disease activity on the basis of degree of muscle inflammation such as serum GOT and ILD activity with extent of parenchymal shadow.

Autoantibody measurement

Anti-ARS antibody was measured by [35S]methionine-labelled protein immunoprecipitation (IPP) using extracts of HeLa cells and by RNA-IPP using NET-2 buffer (50 mM Tris–HCl at pH 7.5, 150 mM NaCl, 0.05% NP-40) (21, 22).

Radiological findings

Non-contrast chest HRCT findings were reviewed. These images comprised 1.5 mm collimation sections at 10 mm intervals. We evaluated for consolidation, ground-glass opacity (GGO), reticular shadow, traction bronchiectasis and lung tip consolidation at below 1 cm of right diaphragm. Evaluation field were six which including carina, right inferior pulmonary vein, and below 1 cm of right diaphragm of both lungs. Ground-glass opacity was defined if there 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. Reticular shadow was defined as regular interlacing linear shadows separated by a few millimeters. Traction bronchiectasis was defined as Irregular bronchial dilatation within or around areas with parenchymal abnormalities such as consolidation or GGO. Definition of lung tip consolidation was thick consolidation > 2 mm with connection of both right diaphragm and pleura (23). Extent of consolidation, GGO, reticular shadow, traction bronchiectasis was categorized as follows ; 0 : none, 1 :< 25%, 2 : 25%< 50%>, 3 : 50%< 75%>, 4 :> 75% (24).The extent of lung tip consolidation was defined as 0 : none, 1 : one thick consolidation, 2 : more than two thick consolidations. A thick consolidation was defined as one that measured more than 2 mm. The score of each findings was defined as total sum divided into six.

Treatment protocol

We commenced systemic prednisolone 0.5~1.0 mg/kg/day or plus cyclosporine or tacrolimus with monitoring trough value. Once disease stabilized, we tapered prednisolone every 2 or 4 weeks. When we saw progressive disease, we started intravenous methyl-prednisolone 1 g/day consecutive 3 days plus cyclosporine or tacrolimus and intravenous cyclophosphamide.

This study was approved by the institutional Review Board Board at Okinawa Chubu Hospital with a waiver of informed consent to allow the retrospective study of de-identified data.

Statistical analysis

Continuous variables are presented as median (min, max) or means ± standard deviations, as appropriate. Categorical variables are presented as percentages. Chi-square and Fisher's exact tests were used to analyze categorical data, and Kruskal-Walls rank tests were used for continuous data. Pearson correlation coefficient were calculated for each laboratory value and radiological finding. Kaplan–Meier survival curves and the log-rank tests were used to evaluate survival. The level of statistical significance was set at $p < 0.05$. All analyses were performed using STATA version 11.0 ; (Stata Corp., College Station, TX, USA).

RESULTS

Baseline clinical differences among the PM/DM associated ILD patients based on the autoantibody status

We identified 52 ILD patients with PM or DM. The clinical characteristics are organized in Table 1 according to the autoantibody status. Among anti ARS antibody group, Jo-1 were 14, PL-7 were 2, KS was 1 and OJ was 1. Median age was around 50 and 69.2% were female. Cough was slightly more frequent in anti MDA-5 group, but this was not statistically significant (p=0.062). Rash, subungual erythema, splinter hemorrahge, erythema, Gottron's sign and heliotrope rash were seen more often in anti MDA-5 group (p=0.016, 0.003, 0.001, 0.013, and 0.004, respectively). Survival in the anti MDA-5 group was decreased compared with that of other two groups. (1.00 vs 84.3 and 22.9 months, $p < 0.001$) (Table 1).

Table 1. Clinical characteristics of three groups at diagnosis

	Antibody unknown (n=30)	Anti-ARS antibody (n=18 : Anti-Jo-1 14, Anti PL-7 2, Anti KS 1, Anti OJ 1)	Anti-MDA-5 antibody (n=4)	p-value
Age	55.5 (17, 80)	60.5 (26, 76)	45.5 (23, 55)	0.135
Gender (M/F)	9/21	6/12	1/3	0.940
Smoking (Pack-year)	0 (0, 1400)	13.8 (0, 45)	27 (0, 90)	0.245
Fever (%)	30	38.9	50	0.661
Cough (%)	26.7	55.6	75	0.051
Dyspnea (%)	40	55.6	75	0.316
Myalgia (%)	66.7	44.4	25	0.147
Arthralgia (%)	33.3	27.8	50	0.693
Raynaud (%)	6.7	5.6	0	0.867
Rash (%)	63.3	16.7	100	< 0.001
Subungual erythema (%)	26.7	11.1	100	0.002
Splinter Hemorrahge (%)	13.3	11.1	50	0.139
Mechanic Hand (%)	16.7	11.1	0	0.621
Erythema (%)	46.7	16.7	100	0.006
Gottron's Sign (%)	36.7	5.6	100	0.001
Heliotrope Rash (%)	26.7	0	75	0.003
Sausage Finger (%)	26.7	5.6	75	0.010
Initial PSL dose (mg/day)	40.1± 19.6	44.4± 15.9	52.5± 9.6	0.292
Combination therapy (%)	40	66.7	75	0.711
Survival time (months)	84.3	22.9	1.00	< 0.001

Definition of abbreviation : M=men ; F=female ; ARS=aminoacyl-tRNA synthetases ; MDA-5=melanoma differentiation-associated gene 5 ; PSL=prednisolone.

Laboratory findings : WBC was significantly elevated in the anti-ARS antibody group (p=0.001). Both CRP and KL-6 tended to be elevated in anti-ARS antibody and ferritin tended to show high value. However, there were no statistically significance (Table 2).

Table 2. Laboratory findings according to antibody status at diagnosis

	Antibody unknown (n=30)	Anti-ARS antibody (n=18)	Anti-MDA-5 antibody (n=4)	p-value
WBC (3300-8600/mm^3)	8700 (3700, 16900)	13100 (4900, 21500)	5025 (3600, 8100)	0.001
CRP (0.00-0.14 mg /dl)	0.8 (0, 6.8)	3.8 (0.01, 22.6)	1.4 (0.2, 5.6)	0.133
GOT(13-30 U/ L)	41 (15, 1034)	61 (17, 251)	95 (56, 116)	0.824
GPT(10-42 U/ L)	28 (8, 510)	50 (13, 300)	63 (12, 105)	0.525
CPK(59-248 U/ L)	1079 (30, 29830)	774 (37, 7810)	366 (44, 2107)	0.330
LDH (124-222 U/ L)	490 (169, 2790)	547 (177, 1093)	499 (366, 832)	0.903
KL-6 (105-435 U/ mL)	860 (272, 3650)	909 (169, 9100)	549 (455, 1342)	0.553
Ferritin (30-400 ng/ mL)	981 (46, 2958)	308 (34, 1096)	512 (172, 852)	0.222
SS-A (%)	13.3	33.3	0	0.146

Definition of abbreviation : ARS=aminoacyl-tRNA synthetases ; MDA-5= melanoma differentiation-associated gene 5 ; WBC=white blood cell ; CRP=C-reactive protein ; CPK=creatine phosphokinase ; LDH= lactate dehydrogenase ; KL-6=Krebs von den Lungen-6.
Findings are presents as median (interquartile range)

Pulmonary function test

Baseline median FVC and %FVC of anti-ARS antibody group tended to show more restrictive disorders[1.49 (0.95, 1.75) vs 1.89 (1,19, 3.48), p=0.051][60.8 (44.8, 79.5) vs 70.9 (60.7, 100.6), p= 0.078]compared to that of antibody negative group.

Imaging

The extent of GGO, consolidation, and lung tip consolidation were significantly increased in anti MDA-5 group (p=0.051, p= 0.026, and p=0.027, respectively) (Table 3).

Representative imaging of reticular shadow, traction bronchiectasis and lung tip consolidation are shown in Figure1, Figure 2 and Figure 3. Among four anti MDA-5 antibody associated ILD patients, all but one had lug tip consolidation.

Correlation Analyses

WBC and CRP (r=0.481, p=0.001), GOT and ferritin (r=0.496. p= 0.019), and anti MDA-5 antibody and lung tip consolidation (r= 0.435, p=0.009) were all weakly correlated. Reticular shadow and traction bronchiectasis (p=0.633, p< 0.001) consolidation and GGO (r=0.668, p< 0.001) were moderately correlated. GOT was strongly correlated with both CPK (r=0.889, p< 0.001) and LDH (r=0.910, p < 0.001) (Table 4). In addition, GOT value of 7 death patients out of 10 showed over 100 IU/L at diagnosis.

Treatment

18 (60%) of the antibody negative group received prednisolone alone. On the other hand, 12(67%) of the patients in the anti ARS associated ILD group received prednisolone with other immunosuppressants, such as cyclosporine A or tacrolimus. 3(75%) of the patients in the anti MDA-5 associated ILD group received intensive therapy consisting of pulse corticosteroids, tacrolimus and intravenous cyclophosphamide (IVCY). In maintenance therapy, anti ARS antibody positive ILD patients were more likely to be treated with prednisolone only (54.5% vs 33.3%) and antibody negative patients more likely to receive prednisolone plus tacrolimus (38.9% vs 9.1%). Among 48 patients except for anti-MDA-5 patients, 6 patients showed relapse. And 4 out of 6 relapse patients showed over 100 IU/L of serum GOT at diagnosis. Two anti-MDA-5 antibody positive patients died within a month despite intensive therapy. Kaplan-Meier survival curves show decreased survival in the anti MDA-5 associated ILD group, compared to other two groups (1.0 months vs 79.7 and 23.7 months, p< 0.001). (Figure 4) Among 48

Table 3. Radiological findings of three groups at diagnosis

	Antibody Unknown (n=30)	Anti-ARS antibody (n=18)	Anti-MDA-5 antibody (n=4)	p-value
GGO	2 (0, 3)	2 (0, 4)	2.5 (2, 4)	0.051
Consolidation	1 (0, 4)	1 (0, 4)	3.5 (2, 4)	0.026
Reticular shadow	0 (0, 3)	1 (0, 2)	0.5 (0, 2)	0.203
Traction bronchiectasis	0 (0, 2)	0 (0, 2)	0 (0, 2)	0.667
Lung tip consolidation	0 (0, 2)	0 (0, 2)	2 (0, 2)	0.027

Definition of abbreviation : ARS=aminoacyl-tRNA synthetases ; MDA5= melanoma differentiation-associated gene 5 ; GGO= ground glass opacity. Findings are presented as median (interquartile range)

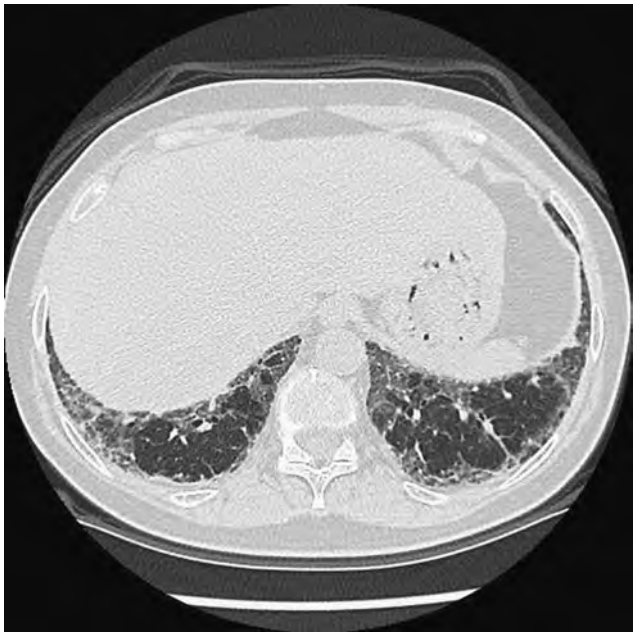

Figure 1. 60-year-old woman of anti PL-7 antibody with reticular shadow
Subpleural reticular shadow were demonstrated.

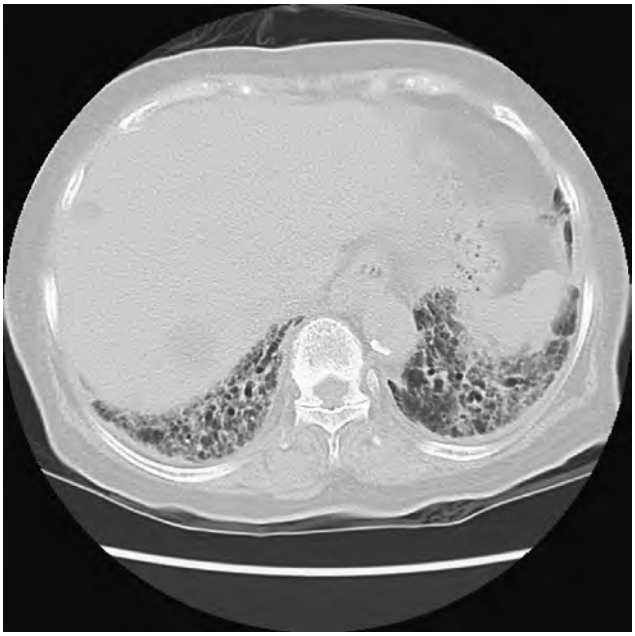

Figure 2. 70-year-old woman of Anti Jo-1 antibody with traction bronchiectasis
Traction bronchiectasis were evident in peribronchovascular bundle.

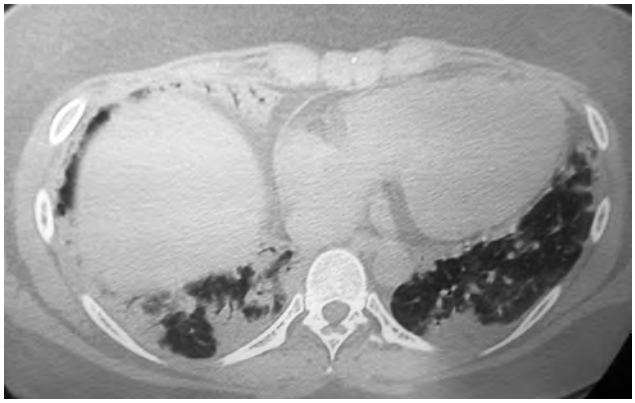

Figure 3. 22-year-old woman of anti MDA-5 antibody with lung tip consolidation
Lung tip consolidation was shown in edge of right diaphragm.

Table 4. Correlation coefficients among clinical parameters

WBC	r=0.481	CRP
GOT	r=0.889	CPK
LDH	r=0.910	GOT
Ferritin	r=0.496	GOT
anti MDA-5 antibody	r=0.435	Lung tip consolidation
Consolidation	r=0.668	GGO
Reticular shadow	r=0.633	Traction bronchiectasis

Definition of abbreviation : WBC=white blood cell ; CRP=C-reactive protein ; CPK=creatine phosphokinase ; LDH=lactate dehydrogenase ; KL-6=Krebs von den Lungen-6 ; GGO=ground glass opacity.

patients who survived acute phase, 6 patients relapsed. Overall, ten patients died during observation period. 4 anti MDA-5 positive patients died from progressive respiratory failure, and 5 patients died from infection and 1 patients died from cancer. And 2 MDA-5 patients were deceased within 1 month from commencing treatment. (Table 5)

DISCUSSION

We described the clinical characteristics, laboratory findings, radiological findings and correlations between laboratory and radiological findings in a series of 52 PM/DM patients, according to their autoantibody status. Cough, rash, subungual erythema, splinter hemorrahge, erythema, Gottron's sign, and heliotrope rash were more often seen in anti MDA-5 group, who also had more extensive shadow involving of central bronchi and experienced cough more frequently compared to other two groups. In addition, all four anti MDA-5 positive patients satisfied clinical criteria of

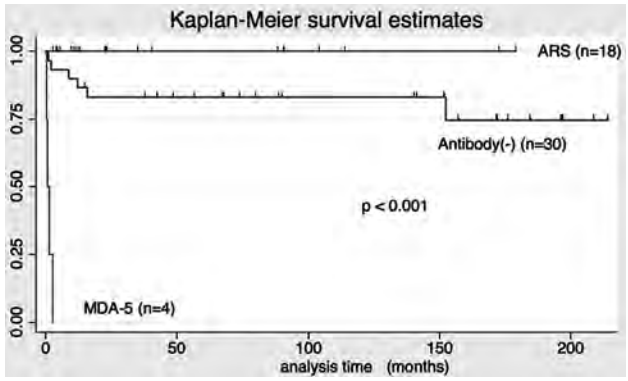

Figure 4. Kaplan-Meier survival curve
Anti MDA-5 antibody positive patients showed statistically significant poor survival compared to other two groups. (Log rank = p< 0.001)

Table 5. Cause of death and interval from initial treatment

	Antibody Type	Cause of Death	Interval from Initial treatment (months)
Case 1 89y F	Unknown	Pneumonia	152.4
Case 2 44y F	Unknown	Pneumonia	12.2
Case 3 80y F	Unknown	Pneumonia	1.9
Case 4 80y M	Unknown	Pneumonia	8.6
Case 5 50y M	MDA-5	Respiratory failure	0.3
Case 6 41y F	MDA-5	Respiratory failure	2.7
Case 7 57y F	Unknown	Cancer	15.8
Case 8 56y F	Unknown	Pneumonia	1.0
Case 9 56y F	MDA-5	Respiratory failure	1.3
Case 10 23y F	MDA-5	Respiratory failure	0.7

Definition of abbreviation : y=year-old ; M=male ; F=female ; MDA5=melanoma differentiation-associated gene 5.

dermatomyositis, with multiple skin manifestations. WBC and CRP were elevated patients with anti-ARS antibody, suggesting a higher degree of inflammation in these patients. KL-6 was also elevated in anti-ARS antibody group, which had reduced lung volume based on FVC and chest HRCT (25-27). Therefore, elevated KL-6 might reflect chronic volume loss with fibrosis. Alternatively, low KL-6 levels were associated with the more acute disease process in anti MDA-5 positive patients. KL-6 is a high molecular weight protein, so induction of KL-6 by epithelial injury and fibrosis may not be able to occur within the limited survival of MDA-5 positive patients. Among radiological findings, significant lung tip consolidation was seen exclusively in anti MDA-5 positive patients, and only minimally present among ILD patients that were anti MDA-5 antibody negative. The more extensive lung tip consolidation of anti MDA-5 antibody positive ILD patients limited diaphragmatic excursion and decreases overall lower lung field volume (23). Based on these findings, we now provide early, high-intensive treatment to patients with lung tip consolidation, hoping to avoid progressive limitation of the smooth movement of right diaphragm. In addition, the removal of exudates in the basal area is more dependent upon gravity and respiratory movement, so persistent inflammation or fibrosis can lead to severe restrictive disorders or profound dyspnea. Among laboratory values, GOT had strong positive correlation with CPK and LDH, but not ferritin, which suggests that muscle dysfunction, inflammation and cell lysis play an important role. We could not demonstrate an association between serum ferritin and mortality, which has been reported in prior studies, especially in anti MDA-5 associated ILD patients (27, 28). The mechanism of inflammation or disease history in our patients might differ. Our results suggest that common laboratory assays for GOT, CPK and LDH are useful for analyzing disease activity in both antibody negative and anti ARS positive antibody associated ILD patients. However, high-risk patients with anti MDA-5 antibody frequently do not have CPK elevation, which should encourage rapid and comprehensive evaluation of ILD progression (28-31).

In serum biomarker, Chen,*et al*. reported that serum KL-6 was useful predictor of disease progression and treatment response of PM/DM ILD patients (32). KL-6 is associated with type Ⅱ alveolar cell injury and extent of fibrosis. Therefore, decrease KL-6 might be associated with improvement of lung parenchymal shadow. We did not check serum KL-6 of PM/DM ILD patients in our cohort repeatedly. So, trace of serial KL-6 of PM/DM ILD patients warrants future study in Japan.

We noted that the. initial prednisolone dosage was somewhat higher in anti MDA-5 positive or anti ARS positive ILD patients compared to antibody negative ILD patients, but this was not statistically significant. In addition, both anti MDA-5 positive and anti ARS positive ILD patients were more likely to receive combination therapy compared to antibody negative patients, although this difference was also not significant. Patients with anti-ARS antibody often have relapse of ILD (32, 33). Therefore, meticulous clinical monitoring of symptoms, biomarkers, and radiological findings, is essential. Anti ARS antibody positive ILD patients often have relapse of parenchymal shadow in the same anatomical location as the original infiltrate. Among our anti ARS antibody positive ILD patients, prednisolone with tacrolimus was more likely to stabilize clinical condition (34). Our ILD patients with anti MDA-5 antibody had a poorer prognosis in our study, which is consistent with prior reports (35-40). Patients with anti-MDA-5 antibody should therefore start intensive therapy as soon as possible. ILD patients with anti MDA-5 antibody who survive the acute phase seldom have been reported to relapse. Therefore, control of disease activity of acute phase is crucial for these high-risk ILD patients with anti MDA-5 antibody. Among 48 patients who survived acute phase, 6 patients relapsed despite slow tapering of systemic prednisolone. These patients often relapsed under 20 mg of prednisolone. Therefore, meticulous monitoring of disease activity and sensible use of immunosuppressants are required.

The strength of this study is the detailed clinical information obtained on patients from a large ILD program. Certain limitations are worth noting. This was s single-center retrospective study, and may not therefore generalize to all PM/DM ILD patients. However, the clinical signs and symptoms of our patients were comparable with previous reports. Secondly, we lack results for ferritin and new anti-ARS autoantibody for some of our older cases. However, anti Jo-1 antibody was screened for every patient. It is therefore possible that the associations of these tests may have been different if those data were not missing. We also lack PFT in some of the anti MDA-5 associated ILD patients, because of rapid progression and limited survival. Finally, the HRCT performed in our program is not uniformly available in all hospitals, so coordination between referral clinic and special center is important.

In conclusion, ILD patients with anti MDA-5 antibody have a poor prognosis. Cough and leukocytosis are useful indicators, especially in patients with anti ARS antibodies. Muscle enzyme levels such as GOT, CPK and LDH have strong associations with the acute phase of both antibody negative and anti ARS antibody positive ILD patients. Multi center studies are needed to evaluate the clinical findings and define the course of PM/DM ILD patients based on autoantibody status.

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FOOTNOTE

Conflicts of Interest : The authors have no conflicts of interest to declare.

ETHICAL STATEMENT

Informed consent was waived by the local Ethics Committee of Okinawa Chubu Hospital. (No.17, 2017)

CONTRIBUTIONS

(Ⅰ)Conception and design : T.K, Y.N (Ⅱ) Administrative support : R.M,S.Y(Ⅲ)Provision of study materials or patients : M.M, K.N (Ⅳ) Collection and assembly of data : T.K,H.N,M.M,K.N(Ⅴ) data analysis and interpretation : T.K,R.M,Y.N,S.I(Ⅵ)Manuscript writing : T.K,R.M (Ⅶ)Final approval of manuscript : All authors.

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