Original Article

Predictors of relapse of polymyositis/dermatomyositis associated interstitial lung disease

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Background: Polymyositis/dermatomyositis (PM/DM) patients often develop interstitial lung disease (ILD), which can lead to relapse despite anti-inflammatory treatments. This study aims to elucidate the clinical characteristics of relapses in PM/DM-associated ILD patients.

Methods: We gathered clinical data, including laboratory results, pulmonary function tests, chest high-resolution computed tomography findings from patients treated at Okinawa Chubu Hospital between January 1, 2010 and December 31, 2018.

Results: We identified a total of 74 patients, comprising 21 men and 53 women. Among them, 38 patients remained relapse-free with maintenance therapy, while 36 experienced relapses despite immunosuppressive management. We followed these patients until June 30, 2023, and 13 patients died. The median survival period was 51.4 months (range, 0.3–214 months). When comparing clinical variables, relapsed patients tended to be younger (49.9 *vs.* 64.1 years), reported myalgia and rash more frequently (63.9% *vs.* 28.9% and 61.15% *vs.* 21.1%, respectively). In terms of laboratory findings, lactate dehydrogenase (LDH) levels were higher in relapsed patients (613±464 *vs.* 381±203 U/L). Radiological findings showed that ground glass opacity (GGO) was more prevalent in relapsed patients (58.3% *vs.* 16.7%). A Cox-proportional hazards model for relapse demonstrated that serum LDH [hazard ratio (HR) 1.005, 95% confidence interval (CI): 1.000–1.009, P=0.02] and GGO (HR 1.863, 95% CI: 1.103–3.147, P=0.02) were valuable predictors of relapse. Receiver operating characteristic curve analysis of serum LDH indicated that a threshold of 450 correctly classified relapse in PM/DM-associated ILD patients.

Conclusions: Serum LDH and GGO may serve as predictors of relapse in PM/DM-associated ILD patients.

Keywords: Dermatomyositis (DM); ground glass opacity (GGO); interstitial lung disease (ILD); lactate dehydrogenase (LDH); polymyositis (PM)

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Introduction

Inflammatory myopathies and dermatomyositis (DM) encompass several complications (1-5). Among these, interstitial lung disease (ILD) is paramount, with a reported prevalence of approximately 40% (6,7). The severity of polymyositis (PM)/DM-associated ILD ranges from mild to fulminant (8,9). Notably, ILD associated with anti-melanoma differentiation-associated gene 5 (MDA-5) antibodies carries the poorest survival rate among PM/DM-associated ILD cases (10,11). Consequently, the management strategy depends on the severity of ILD (12). On the other hand, aminoacyl tRNA synthetase (ARS) syndrome-associated ILD generally has a good prognosis, with a positive response to prednisolone (PSL) (13,14). However, ARS syndrome-associated ILD patients often experience relapses despite anti-inflammatory treatments (15,16). With the exception of anti-MDA-5-associated ILD, such as amyopathic DM, PM/DM-associated ILD patients typically have a more favorable prognosis (17,18). Furthermore, clinical research on predictive factors for relapse in PM/DM-associated ILD patients is scarce. Therefore, the purpose of this study is to elucidate the clinical parameters for predicting relapse in PM/DM-associated ILD patients. We present this article in accordance with the TRIPOD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1736/rc).

Highlight box

Key findings

- Serum lactate dehydrogenase (LDH) over 450 can be predictor of relapse polymyositis/dermatomyositis (PM/DM) associated interstitial lung disease (ILD) patients with area under the curve of 0.718.
- Chest high-resolution computed tomography (HRCT) ground glass opacity might predict relapse of PM/DM associated ILD patients.

What is known and what is new?

- PM/DM associated ILD patients often relapse during tapering immunosuppressants.
- Regarding predictor of relapse, continuation of immunosuppressant has been reported, However, serum biomarker and chest HRCT findings have been scarce as predictors of PM/DM associated ILD.

What is the implication, and what should change now?

- Serum LDH and chest HRCT is easy to apply in daily practice. Therefore, the results of our study will be useful for monitoring and management of PM/DM associated ILD patients.

Methods

Data source

This is a single center retrospective study. We identified 74 consecutive PM/DM-associated ILD patients between January 1, 2010, and December 31, 2018, at Okinawa Chubu Hospital. We collected clinical information, including laboratory data such as white blood cell (WBC), C-reactive protein (CRP), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and ferritin, pulmonary function test (PFT) results, chest high-resolution computed tomography (HRCT) findings, and the treatments administered at the time of PM/DM-associated ILD diagnosis.

Regarding autoantibodies, we assessed both ARS antibodies and anti-MDA-5 antibodies. If both of these autoantibodies were negative, we categorized the patient as belonging to the double-negative group.

For PFT, we collected forced vital capacity (FVC), percent predicted forced vital capacity (%FVC), total lung capacity (TLC), percent predicted total lung capacity (%TLC), and percent predicted diffusing capacity for carbon dioxide (%DLco). Missing data were handled as complete-case analysis.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Okinawa Chubu Hospital Institutional Review Board (IRB) (IRB No. 2021 chubu kenkyu rinri 19-2). The informed consent was waived because it is a retrospective study.

ILD diagnosis and HRCT

ILD was diagnosed based on the presence of inflammatory or fibrotic changes in chest HRCT scans with a 1 mm thickness. The chest HRCT findings were assessed for consolidation, ground glass opacity (GGO), reticular shadow, and traction bronchiectasis (BE). Drug, other connective tissue disease and occupational associated ILD were excluded clinically.

Consolidation was defined as increased opacity obscuring the parenchymal vessel. GGO was defined as increased opacity without complete obscuring of the parenchymal vessel. Reticular shadow was defined as interlacing lines within the secondary lobule, while traction BE was defined as abnormal bronchial dilatation with irregular bronchial walls. These definitions were based on the Fleischner Society (19). Additionally, when these abnormal shadows

were present in more than 5% of any lung zone, they were considered significant.

Diagnosis of PM/DM

The diagnosis of PM/DM was made clinically based on Bohan and Peter criteria (20,21). Regarding myositis antibody, we checked anti-ARS antibody consisted of anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ and anti-KS (SRL Inc., Tokyo, Japan). If ILD is diagnosed initially, we excluded secondary causes such as other connective tissue disease, drug and occupational exposures. The final diagnosis was established based on clinical symptoms, physical findings, the presence of autoantibodies, and chest HRCT results, as evaluated by a team of medical professionals, including a chest physician, rheumatologist, and radiologist. Therefore, we included definite or probable PM/DM associated ILD patients in our study.

Definition of relapse

Relapse was defined as an increase in PSL dosage or the addition of immunosuppressants such as tacrolimus, cyclosporin, azathioprine, and mycophenolate mofetil. Additionally, relapse patients typically exhibited increased opacity in chest HRCT scans or a recurrence of PM/DM symptoms or both. We compared relapse date imaging with previous chest HRCT at same location. When increase of opacities with worsening of clinical symptoms, we considered as relapse of PM/DM associated ILD. In addition, we excluded any infection, heart failure and pulmonary embolism using sputum culture, cardiac echo and chest CT with contrast material. Before relapse, we confirmed clinical stability such as decreased PSL dosage or improvement of cough and dyspnea. We defined relapse at time from treatment initiation.

Outcome measures

We checked serum LDH and other laboratory data at diagnosis of PM/DM associated ILD. Regarding chest HRCT findings including GGO, we compared relapse date imaging with previous chest HRCT at same location.

Statistical analysis

Data were presented as means with standard deviations, medians with interquartile ranges, or frequencies and percentages. The Mann-Whitney *U* test was used to compare means, and Fisher's exact test was used to compare proportions among groups. The observation period was calculated from the date of ILD diagnosis to the date of the last visit or death. We followed up until June 30, 2023. Patient survival was assessed using the Kaplan-Meier method. Cox proportional hazards analyses with time-dependent covariates were performed to identify predictive factors associated with relapse. For the optimal threshold of serum LDH value for classification of relapse, receiver operating characteristic (ROC) curve was used. In all analyses, a P value <0.05 was considered statistically significant. All data were analyzed using the commercially available software STATA version 16.1 (Stata Corp., College Station, TX, USA).

Results

Clinical characteristics

We identified 74 consecutive patients with PM/DM-associated ILD between January 1, 2010 and December 31, 2018 at Okinawa Chubu Hospital. We divided them into 36 in the relapse group and 38 in the non-relapse group during the observation period. The relapse group tended to be younger (49.9±15.5 *vs.* 64.1±13.1 years), and the gender ratio showed no significant difference (male/female: 13/23 *vs.* 8/30, P=0.08). In terms of clinical symptoms, myalgia was more often observed in the relapse group (63.9% *vs.* 28.9%, P=0.002). There were no significant statistically difference of MDA-5 positive patients between relapse group and non-relapse group, and double negative autoantibody patients were more prevalent in relapse group (*Table 1*).

Physical findings

Concerning physical findings, both rash and heliotrope rash were more frequently detected in the relapse group (61.15% *vs.* 21.1%, P<0.001 and 27.8% *vs.* 10.5%, P=0.06). Moreover, mechanic hand was less frequently observed in the relapse group (13.9% *vs.* 34.2%, P=0.04). Relapse patients usually exhibited increased opacity in chest HRCT scans or a recurrence of PM/DM symptoms.

Laboratory findings

In laboratory findings, both WBC and CRP were somewhat lower in the relapse group (8,742±3,701 *vs.* 10,486±

Table 1 Clinical characteristics of PM/DM associated ILD patients according to the relapse status

Item	Relapse group (n=36)	Non-relapse group (n=38)	P value
Age (years)	49.9±15.5	64.1±13.1	<0.001
Gender (male/female)	13/23	8/30	0.08
Fever	12	13	0.94
Cough	13	9	0.25
Dyspnea	18	22	0.50
Myalgia	23	11	0.002
Arthralgia	12	11	0.69
Rash	22	8	<0.001
Nail erythema	11	7	0.23
Mechanic hand	5	13	0.04
Gottron sign	11	8	0.36
Heliotrope rash	10	4	0.06
Anti ARS antibody	7	31	0.11
Anti-MDA-5 antibody	4	2	0.97
Antibody negative	25	5	0.05
PSL alone	18	10	0.02
Survival time (months)	89.4 (0.3–214.1)	28.2 (1.9–201.7)	<0.001

Data are presented as mean ± standard deviation, number, or median (minimum to maximum). PM, polymyositis; DM, dermatomyositis; ILD, interstitial lung disease; ARS, aminoacyl tRNA synthetase; MDA-5, melanoma differentiation-associated gene 5; PSL, prednisolone.

4,103 mm^3, P=0.65 and 1.8±2.2 *vs.* 3.5±5.3 mg/dL, P=0.11). CPK, LDH, and ferritin were higher in the relapse group (3,224±5,486 *vs.* 901±1,735 U/L, P=0.02; 613±464 *vs.* 381±203 U/L, P=0.008; 959±906 *vs.* 352±333 ng/mL, P=0.01) (*Table 2*). Additionally, we had 38 anti-ARS antibody-positive patients, 6 anti-MDA-5 antibody-positive patients, and 30 double-negative antibody patients.

Chest HRCT findings

In terms of chest HRCT findings, consolidation showed similar frequency (69.4% *vs.* 65.8%, P=0.63). GGO was more frequently observed in the relapse group (58.3% *vs.* 16.7%, P=0.02). Both reticular shadow and traction BE were less frequently detected in the relapse group (33.3% *vs.* 76.3%, P<0.001 and 19.4% *vs.* 52.6%, P=0.002) (*Table 2*).

PFT

On PFT, FVC, %FVC, TLC, %TLC, and %DLco were slightly better in relapse patients (2.01 *vs.* 1.73 L, P=0.17; 76.1% *vs.* 70.6%, P=0.41; 3.89 *vs.* 3.22 L, P=0.09; 90.9% *vs.* 82.2%, P=0.36; and 94.8% *vs.* 60.7%, P=0.11) (*Table 3*).

Treatment

Regarding management, PSL alone was more commonly administered in relapse patients (50% *vs.* 26.3%, P=0.02). Eight patients received intravenous cyclophosphamide. Nineteen patients took tacrolimus, 12 patients received cyclosporin, 10 patients took azathioprine, 4 patients received mycophenolate mofetil and 1patient took Janus kinase inhibitor. In terms of initial treatment, 19/36 (52.8%) patients took PSL alone and 4/36 (11.1%) patients received PSL and tacrolimus in relapse group. On the other hand, 6/16 (37.5%) patients took PSL alone and 8/16 (50%) patients received PSL and tacrolimus in non-relapse group.

Predictors of relapse

In the prediction of relapse in PM/DM-associated ILD patients, Cox-proportional hazards analysis showed that

Table 2 Laboratory and chest HRCT findings of PM/DM associated ILD patients according to the relapse status

Item	Relapse group (n=36)	Non-relapse group (n=38)	P value
WBC (mm^3)†	8,742±3,701	10,486±4,103	0.07
CRP (mg/dL)†	1.8±2.2	3.5±5.3	0.11
CPK (U/L)†	3,224±5,486	901±1,735	0.02
LDH (U/L)†	613±464	381±203	0.008
Ferritin (ng/mL)†	959±906	352±333	0.02
Consolidation (%)	69.4	65.8	0.63
Ground glass opacity (%)	58.3	16.7	0.02
Reticular shadow (%)	33.3	76.3	<0.001
Traction bronchiectasis (%)	19.4	52.6	0.002

†, data are presented as mean ± standard deviation. HRCT, high resolution computed tomography; PM, polymyositis; DM, dermatomyositis; ILD, interstitial lung disease; WBC, white blood cell; CRP, C-reactive protein; CPK, creatine phosphokinase; LDH, lactate dehydrogenase.

Table 3 PFT findings of PM/DM associated ILD patients according to the relapse status

Item	Relapse group (n=36)	Non-relapse group (n=38)	P value
FVC (L)	2.01 (1.19–3.48)	1.73 (0.95–2.78)	0.17
%FVC (%)	76.1 (60.7–100.6)	70.6 (44.8–113.2)	0.41
TLC (L)	3.89 (3.15–5.69)	3.22 (2.27–4.88)	0.10
%TLC (%)	90.9 (81–106.8)	82.2 (49.3–126.8)	0.36
%DLco (%)	94.8 (48.8–192.3)	60.7 (33.2–101.3)	0.11

Data are expressed as median (minimum to maximum). PM, polymyositis; DM, dermatomyositis; PFT, pulmonary function test; ILD, interstitial lung disease; FVC, forced vital capacity; %FVC, percent predicted forced vital capacity; TLC, total lung capacity; %TLC, percent predicted total lung capacity; %DLco, percent predicted diffusing capacity for carbon dioxide.

serum LDH and GGO in chest HRCT were useful predictors of relapse [hazard ratio (HR) 1.005; P=0.02, 95% confidence interval (CI): 1.000–1.009 and HR 1.863; P=0.02, 95% CI: 1.103–3.147] (*Table 4*). The threshold for serum LDH distinguishing relapse was 450 U/L according to the ROC curve (*Figure 1*). An LDH level of 450 showed a sensitivity of 62.5% and specificity of 75%.

Survival

In terms of survival, the median value was longer in relapse patients (89.4 *vs.* 28.2 months, P<0.001) (*Table 1*). MDA-5 antibody-positive patients showed poorer survival compared to double-negative and anti-ARS antibody-positive patients (14.3 *vs.* 61.3 and 99.5 months, P<0.001) (*Figure 2*).

Discussion

We have demonstrated that both serum LDH and GGO are predictors of relapse in PM/DM-associated ILD patients. Serum LDH is a classic biomarker for ILD and reflects early and intensive lung injury (22-24). Thus, LDH is useful for the early detection of ILD activity and provides earlier detection of acute exacerbation compared to krebs von den lungen-6 (KL-6) or surfactant protein D (SP-D) (25,26). KL-6 has a higher molecular weight than SP-D and LDH (27,28). These differences may be related to the detection of disease activity and its phase (29). Serum ferritin has been reported as a strong indicator in anti-MDA-5 antibody-associated ILD (30,31). Ferritin has a strong association with cytokine storms in amyopathic DM and severe pneumonia, such as coronavirus infectious

Table 4 Cox-proportional hazards for relapse of PM/DM associated ILD patients

Item	Hazard ratio (95% CI)	P value
Age	1.007 (0.982–1.034)	0.58
Myalgia	1.238 (0.556–2.756)	0.60
Rash	1.485 (0.643–3.432)	0.36
Mechanic hand	0.480 (0.174–1.319)	0.16
Heliotrope rash	2.444 (0.987–6.053)	0.05
WBC	0.999 (0.999–1.000)	0.12
CRP	1.135 (0.854–1.507)	0.38
CPK	0.999 (0.999–1.000)	0.94
LDH	1.005 (1.000–1.009)	0.02
Ferritin	0.999 (0.999–1.000)	0.37
Consolidation	1.215 (0.833–1.771)	0.31
GGO	1.863 (1.103–3.147)	0.02
Reticular shadow	0.713 (0.324–1.569)	0.40
Traction BE	0.783 (0.300–2.046)	0.62

PM, polymyositis; DM, dermatomyositis; ILD, interstitial lung disease; CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein; CPK, creatine phosphokinase; LDH, lactate dehydrogenase; GGO, grand glass opacity; BE, bronchiectasis.

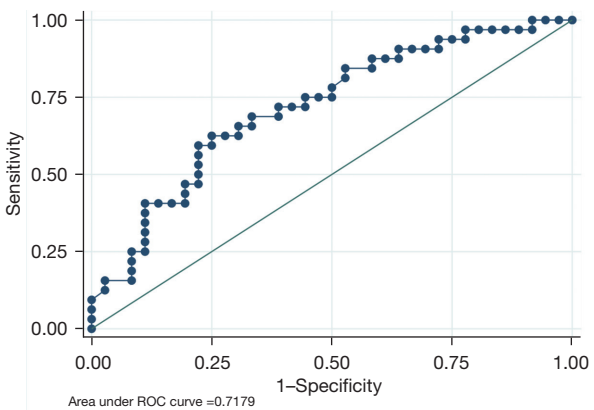

Figure 1 ROC curve of LDH for relapse. ROC, receiver operating characteristic; LDH, lactate dehydrogenase.

disease (32,33). Based on this evidence, serum ferritin may be a useful predictor of mortality in rapidly progressive ILD. Regarding double negative autoantibody patients were more prevalent in relapse group in our cohort. Anti-OJ, anti-Zo and anti-Ha might contribute to our relapse group. However, we could not measure these three autoantibodies,

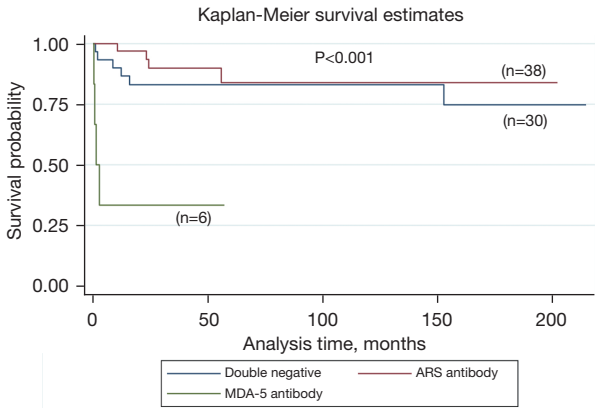

Figure 2 Kaplan-Meier survival curve showed significant difference between anti-MDA-5-antibody group and anti-ARS antibody, double negative antibody groups. ARS, aminoacyl tRNA synthetase; MDA-5, melanoma differentiation-associated gene 5.

which is limitation.

Concerning chest HRCT findings, GGO was found to be a helpful predictor of relapse in PM/DM-associated ILD patients in our cohort. In PM/DM-associated ILD, GGO is often detected in the lower lung field with consolidation of the broncho-vascular bundle or peripheral areas (34,35). Consolidation often disappears completely with PSL treatment. We defined GGO as positive when it was present in over 5% of any lung zone. Based on these findings, the GGO in our cohort may not simply indicate inflammation but instead suggest the presence of reversible fibrosis. Therefore, to some extent, GGO might be associated with resistance to anti-inflammatory management. Nevertheless, the overall prognosis of the relapse group was good compared to the non-relapse group. Consequently, the association between the volume or extent of GGO and progressive pulmonary fibrosis is a topic for future investigation (36). Both reticular shadow and traction BE were more frequently identified in the non-relapse group. These fibrotic shadows are associated with a rather irreversible process in ILD (37,38). Based on the results of our study, these fibrotic shadows might be predictive of long-term prognosis in PM/DM-associated ILD. Traction BE, especially, has been reported as a poor predictor of fibrotic ILD, such as idiopathic pulmonary fibrosis (IPF) (39). Our non-relapse group were more elderly and tended to be fibrotic with reduced DLco. Therefore, these patients might tend to show slowly progression of fibrotic change without dramatic response of anti-inflammation. Robust investigation of progressive pulmonary fibrosis

of PM/DM associated ILD patients will be a future research topic.

We selected various clinical parameters for predicting relapse in PM/DM-associated ILD patients using Cox-proportional hazard analysis. Both myalgia and rash were more frequently observed in the relapse group. However, there were no statistically significant differences regarding predictors of relapse. Myalgia and generalized rash suggest muscle inflammation and vasculitis (40,41). Therefore, when these symptoms and physical findings are noted, physicians should be vigilant about disease activity and potential future relapse. Several previous reports have shown that PSL alone is related to the recurrence of ILD in patients with anti-ARS antibodies (42,43). Different proportion of immunosuppressant usage of both relapse group and non-relapse group might affect on the relapse in our cohort. Especially, tacrolimus was often used in non-relapse group. As shown in previous reports, combination therapy might be useful for relapse candidate group.

However, the purpose of our study was to identify clinical parameters in PM/DM-associated ILD patients before initiating treatment. Consequently, we excluded PSL alone from the Cox-proportional hazard model in our cohort.

We acknowledge several limitations in our study. First, this is a retrospective study conducted at a single institution. Therefore, a multi-center study is needed to validate our results. Second, our cohort consisted solely of Japanese patients, and our findings may not be applicable to other ethnic backgrounds.

Third, our cohort was managed by pulmonologists and rheumatologists, and the same protocol was not uniformly applied to all patients. This could introduce treatment bias. Fourth, physical findings were evaluated by attending physicians, so not all patients were assessed by rheumatologists. False negative findings could exist. Fifth, the CT extent of abnormal findings was set arbitrarily at over 5%. A different threshold might yield different results. However, our threshold was based on interstitial lung abnormality (44) and previous IPF study (45), so we believe that 5% is a reasonable cutoff.

Conclusions

In conclusion, serum LDH and GGO in chest HRCT may serve as useful predictors of relapse in PM/DM-associated ILD patients. A multi-center prospective study will be warranted in the near future.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1736/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1736/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1736/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Okinawa Chubu Hospital Institutional Review Board (IRB) (IRB No. 2021 chubu kenkyu rinri 19-2). The informed consent was waived because it is a retrospective study.

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