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ORIGINAL RESEARCH

Prognosis of spontaneous pneumomediastinum occurring in dermatomyositis or polymyositis patients with interstitial lung disease according to antimelanoma differentiation-associated gene 5 antibody status: a retrospective cohort study

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ABSTRACT

Objectives Spontaneous pneumomediastinum (SPNM) historically has been considered a poor prognostic factor in dermatomyositis/polymyositis patients complicated with interstitial lung disease (ILD). However, there is a lack of actual data regarding the association between SPNM occurrence and mortality in dermatomyositis/polymyositis patients. This study aimed to assess the association between SPNM occurrence and mortality in myositis patients with ILD according to antimelanoma differentiation-associated gene 5 (MDA5) antibody status.

Methods Dermatomyositis/polymyositis patients with ILD who were hospitalised at five Japanese hospitals from 2016 to 2020 were included in this retrospective observational study. We collected data about baseline characteristics including myositis-specific autoantibodies, treatments, SPNM and death within 1 year from therapy initiation or strengthening. Baseline characteristics and outcomes were compared between patients with and without SPNM (the SPNM group and the non-SPNM group, respectively).

Results A total of 119 patients were analysed. SPNM occurred in 23 patients, and 15 patients died. Fifteen patients with SPNM were anti-MDA5 antibody positive. The mortality rate was significantly higher in the SPNM group (34.8%) than in the non-SPNM group (7.3%) (p=0.001). All deaths in the SPNM group occurred in anti-MDA5 antibody-positive patients (8/15), whereas none of the anti-MDA5 antibody-negative patients in the SPNM group died (0/8). In anti-MDA5 antibody-positive patients, the mortality rate was significantly higher in patients with SPNM occurrence (53.3%) than in those without SPNM occurrence (4.0%) (p=0.001).

Conclusion SPNM occurred more frequently in anti-MDA5 antibody-positive than in anti-MDA5 antibody-negative myositis patients. SPNM occurrence was associated with higher mortality risk, especially in anti-MDA5 antibody-positive patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Historically, spontaneous pneumomediastinum (SPNM) has been considered a risk factor for death in patients with polymyositis or dermatomyositis with interstitial lung disease (ILD). Recently, various myositis-specific autoantibodies with their own clinical symptoms were identified.

WHAT THIS STUDY ADDS

⇒ Our study revealed that SPNM occurred more frequently in antimelanoma differentiation-associated gene 5 (MDA5) antibody-positive myositis with ILD patients than in anti-MDA5 antibody-negative myositis with ILD patients. SPNM occurrence was associated with higher mortality risk in anti-MDA5 antibody-positive patients with ILD, while none of the anti-MDA5 antibody-negative patients with ILD who had SPNM died in this study.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In daily clinical practice, an individualised approach based on autoantibody status is needed when SPNM occurred in myositis patients with ILD.

INTRODUCTION

Dermatomyositis (DM) and polymyositis (PM) are autoimmune diseases that affect the musculoskeletal system.[1] DM/PM is often

complicated by interstitial lung disease (ILD),[2] which can lead to a life-threatening condition.[3] In patients with DM/PM with ILD, several prognostic factors, including spontaneous pneumomediastinum (SPNM), have been reported.[4] SPNM occurs in 8.3% of patients with DM-ILD.[5] Conventionally, SPNM has been considered a poor prognostic factor in patients with DM-ILD,[6 7] and it was reported that 25% of patients with DM-ILD complicated with SPNM died within 1 month.[8] On the other hand, in patients with mild ILD, the opposite result was reported that SPNM was not a fatal complication.[9] Thus, the prognosis of SPNM occurring in patients with DM/PM-ILD remains controversial.

A recent study identified rapidly progressive ILD (RP-ILD), antimelanoma differentiation-associated gene 5 (MDA5) antibody positivity, skin ulcer, low creatine kinase titres and clinically amyopathic DM (CADM) as factors related to SPNM occurrence in DM patients.[10] These factors can be aggregated into the characteristics of DM patients with anti-MDA5 antibody positivity. Anti-MDA5 antibody-positive patients are a new subgroup of DM patients that are often complicated with ILD, and their clinical features include frequent RP-ILD, high mortality rate, skin ulcers and lack of muscular symptoms.[11 12] Thus, we considered that SPNM itself might not be a mortality risk but just an intermediate variable between anti-MDA5 antibody positivity and mortality risk in patients with DM-ILD.

This study aimed to assess the association between SPNM occurrence and mortality in DM/PM-ILD patients according to anti-MDA5 antibody status.

METHODS

Patients

In this retrospective cohort study, patients with DM, PM and CADM complicated with ILD, aged over 20 years old and hospitalised from April 2016 to March 2020 were identified from medical records in five Japanese hospitals. We included the patients who were hospitalised for treatment of active DM/PM/CADM with over 15 mg/day of prednisolone. DM/PM/CADM patients who were hospitalised due to other reasons (eg, infections) were excluded.

DM and PM were diagnosed as probable or definite according to the criteria of Bohan and Peter.[13] CADM was diagnosed according to the criteria of Sontheimer.[14] ILD was confirmed by chest CT.

Assessment

The primary exposure in this study was the occurrence of SPNM detected by chest CT. Chest CT was repeatedly performed to evaluate treatment effects on ILD in the daily clinical practice setting, but it was not performed to evaluate the occurrence of SPNM at regular intervals. We did not stratify the time of SPNM occurrence. The primary outcome was death within 1 year from initiating/strengthening treatments for DM/PM-ILD.

Information regarding diagnosis (PM, DM or CADM), sex, age, smoking habits, myositis-specific autoantibodies status (anti-MDA5, ARS, Tif-1γ and Mi-2 antibodies), laboratory data (lactate dehydrogenase, creatine kinase, krebs von lungren 6 antigen (KL-6), CRP and ferritin), the maximum dose of glucocorticoids (daily prednisolone dose equivalent), use of methylprednisolone pulse therapy, use of immunosuppressants (cyclophosphamide, tacrolimus, ciclosporin, tofacitinib and others), intravenous immunoglobulin, plasma exchange, a complication of RP-ILD, use of a ventilator and time to discharge were collected from retrospective chart review. RP-ILD was defined as ILD with acute and progressive worsening of dyspnoea requiring hospitalisation, supplementary oxygen or respiratory failure requiring intubation within 3 months of the diagnosis of ILD.[15]

Statistics

Summary statistics were presented as median with IQR and as numbers with proportions. Continuous variables were compared by Mann-Whitney U test, and categorical variables were compared by χ^2 test between the patients with/without SPNM occurrence (the SPNM and non-SPNM groups). In addition, we separately compared deaths within 1 year between the SPNM and non-SPNM groups in anti-MDA5 antibody-positive and anti-MDA5 antibody-negative patients. The HR for death between the SPNM and non-SPNM groups was calculated by a Cox-regression analysis. We also performed multivariable analysis by Cox-regression analysis to assess the HR of death by SPNM with the covariates of age and anti-MDA5 antibody status. In addition, we performed another analysis to assess the HR of death by SPNM with the covariates of age and the presence of RP-ILD as sensitivity analysis. We also performed Cox-regression analysis with a stepwise method using covariates of SPNM, age, anti-MDA5 antibody status and presence of RP-ILD as sensitivity analysis. In addition, we calculated Cramer's coefficient of association between anti-MDA5 antibody status and RP-ILD.

Missing values were excluded from the analysis. Statistical significance was defined as a $p<0.05$. All statistical analyses were performed with R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study population

A total of 146 PM/DM/CADM-ILD patients who were hospitalised from April 2016 to March 2020 were identified from the chart review. Twenty-seven patients were excluded due to hospitalisation for reasons other than active PM/DM/CADM and/or not receiving more than 15 mg/day of prednisolone. Consequently, 119 patients were included in this study. All patients had active ILD, and 25 of 119 patients had RP-ILD. There were no missing data in any of the variables except ferritin and KL-6.

Table 1 Patient characteristics

	No SPNM (n=96)	SPNM occurred (n=23)	P value
Diagnosis			
Dermatomyositis, n (%)	40 (41.7)	5 (21.7)	0.126
Polymyositis, n (%)	15 (15.6)	1 (4.3)	0.279
CADM, n (%)	41 (42.7)	17 (73.9)	0.014
RP-ILD, n (%)	14 (14.6)	11 (47.8)	0.001
Age, years, median (IQR)	63 (52–71)	23 (56–68)	0.505
Female, n (%)	50 (47.9)	10 (57.5)	0.611
Smoking habits, n (%)	41 (42.7)	10 (43.5)	1
Autoantibodies status			
Anti-MDA5 antibody-positive, n (%)	25 (26.0)	15 (65.2)	0.001
Anti-ARS antibody-positive, n (%)	47 (49.0)	6 (26.1)	0.080
Anti-Tif1-γ antibody-positive, n (%)	0 (0)	0 (0)	None
Anti-Mi-2 antibody-positive, n (%)	4 (4.2)	0 (0)	0.725
Antibodies-negative,* n (%)	20 (20.8)	2 (8.7)	
Anti-SSA (Ro52) antibody-positive, n (%)	9 (10.1)	1 (4.5)	0.689
Treatments			
Maximum prednisolone dose, mg/day, median (IQR)†	50.0 (40–50)	50 (42.5–60)	0.006
Methylprednisolone pulse therapy, n (%)	16 (16.7)	14 (60.9)	<0.001
Intravenous cyclophosphamide	41 (42.7)	18 (78.3)	0.005
Tacrolimus, n (%)	68 (70.8)	16 (69.6)	1
Ciclosporin, n (%)	6 (6.2)	9 (39.1)	<0.001
Tofacitinib, n (%)	4 (4.2)	7 (30.4)	<0.001
IVIg, n (%)	7 (7.3)	1 (4.3)	0.966
Plasma exchange, n (%)	3 (3.1)	8 (34.8)	<0.001
Treatments, types			
GC monotherapy, n (%)	16 (16.7)	0 (0)	0.078
GC with one immunosuppressant, n (%)	43 (44.8)	4 (17.4)	0.029
GC with two immunosuppressants, n (%)	31 (32.3)	13 (56.5)	0.055
GC with three or more immunosuppressants, n (%)	6 (6.2)	6 (26.1)	0.014
Laboratory test result			
LDH, median (IQR)	343.5 (268.0–475.3)	347 (251.5–425.5))	0.714
CK, median (IQR)	166.5 (67.0–887.6)	134.0 (54.5–338.5)	0.183
KL-6, median (IQR)	841.0 (559.0–1348.0)	888.0 (628.5–1396.5)	0.648
CRP, median (IQR)	0.38 (0.11–1.33)	0.35 (0.20–0.70)	0.599
Ferritin, median (IQR)	300.4 (105.3–790.0))	526.3 (318.8–790.0)	0.078
Use of a ventilator, n (%)	3 (3.1)	6 (26.1)	< 0.001
Death within 1 year, n (%)	7 (7.3)	8 (34.8)	0.001

*'Antibodies-negative' means that anti-MDA5, ARS, TIF1-γ and Mi-2 antibodies were negative. This study did not collect data regarding other myositis-specific antibodies, because only anti-MDA5, ARS, TIF1-γ and Mi-2 antibodies were approved tests in a daily practice setting in Japan.
†Maximum prednisolone dose means the highest amount of prednisolone dose or equivalent except for methylprednisolone pulse therapy.
CADM, clinically amyopathic dermatomyositis; CK, creatine kinase; CRP, C reactive protein; GC, glucocorticoids; KL-6, Krebs von Lungren-6; LDH, lactate dehydrogenase; MDA5, melanoma differentiation-associated gene 5; RP-ILD, rapidly progressive interstitial lung disease; SPNM, spontaneous pneumomediastinum.

Baseline characteristics

SPNM occurred at 23 PM/DM/CADM-ILD patients (19.3%). The mean age was not significantly different between the SPNM and non-SPNM groups (61.5 years and 60.3 years, p=0.507) (table 1). Proportions of DM (41.7%) and CADM (42.7%) were higher than PM (15.6%) in the non-SPNM group, whereas CADM (73.9%) was dominant in the SPNM group. The proportion of RP-ILD was higher in the SPNM group than in the non-SPNM group (47.8% and 14.6%, p=0.001). Notably, 10 of 11 patients with RP-ILD in the SPNM group were anti-MDA5 antibody-positive. The proportion of

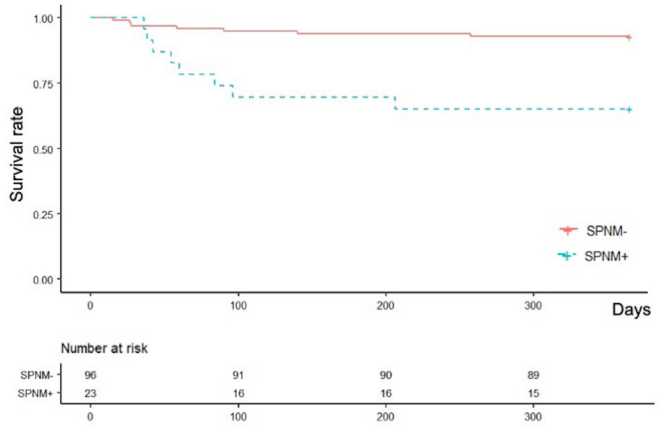

Figure 1 Survival curve comparison between SPNM occurrence group and no occurrence group. SPMN, spontaneous pneumomediastinum; SPMN–, the group without SPNM occurrence, SPNM+, the group with SPNM occurrence.

anti-MDA5 antibody-positive patients was also significantly higher in the SPNM group than in the non-SPNM group (65.2% and 26.0%, p=0.001), and SPNM occurred in 15 of 40 anti-MDA5 antibody-positive patients (37.5%). Six patients in the SPNM group required ventilation, and five required ventilation after the SPNM occurrence.

Incidence of death and mortality risk of SPNM

The number of deaths within 1 year from therapy initiation or strengthening was seven (7.3%) in the non-SPNM and eight (34.8%) in the SPNM groups (p=0.001). Significantly more frequent deaths were observed in the SPMM than in the non-SPNM groups. The median time from therapy initiation or strengthening to death was 57 days in the non-SPNM and 58 days in the SPNM groups. Survival curves are shown in figure 1. We also show the dead patients' characteristics and cause of death in online supplemental table 1. The HR of mortality in the SPNM group compared with the non-SPNM occurrence group was 5.49 (95% CI 1.99 to 15.18) in the univariate analysis and 4.10 (95% CI 1.37 to 12.24) in the multivariate analysis adjusting age and anti-MDA5 antibody status (table 2). We also performed the multivariate analysis adjusted by age and the presence of RP-ILD as a sensitivity analysis (online supplemental table 2). It showed a similar result as the model adjusted by age and anti-MDA5 antibody status; SPNM occurrence was a mortality risk. Cox-regression analysis with a stepwise method using covariates of SPNM, age, RP-ILD and anti-MDA5 antibody status that the model including SPNM, age and RP-ILD was the most mathematically appropriate model. As the result, the most appropriate model was the same as online supplemental table 2.

Analysis of patients according to anti-MDA5 antibody status

In anti-MDA5 antibody-positive patients, the mortality rate within 1 year was significantly higher in patients with SPNM occurrence (53.3%) than in ones without SPNM occurrence (4.0%) (p=0.001) (table 3). On the other hand, in anti-MDA5 antibody-negative patients, none of the eight patients with SPNM occurrence died. Survival curves according to anti-MDA5 antibody status are shown in figure 2. In addition, we compared the characteristics of anti-MDA5 antibody-positive patients to those of anti-ARS antibody-positive patients in online supplemental table 3. The presence of RP-ILD and the occurrence of SPNM were significantly more frequent in anti-MDA5 antibody-positive patients than in anti-ARS antibody-positive patients. In our cohort, Cramer's coefficient of association between anti-MDA5 antibody positivity and RP-ILD was 0.463.

DISCUSSION

Based on the previous reports,[6 7] historically SPNM occurrence has been considered a poor prognostic factor in DM/PM-ILD patients. However, such reports were before identification of new myositis-specific autoantibodies (eg, anti-MDA5, Mi-2 and Tif-1γ antibodies).[16] Currently, DM/PM patients are divided into subgroups based on the autoantibodies, and they have different frequencies of organ involvement, severity and treatment responses. Among those subgroups, characteristics of anti-MDA5 antibody-positive patients are the absence of muscle symptoms, skin vasculitis and poor prognosis due to RP-ILD.[15] This retrospective cohort study investigated the relationship between SPNM occurrence and short-term mortality risk in DM/PM-ILD patients according to anti-MDA5 antibody status. SPNM occurred more frequently in anti-MDA5 antibody-positive patients than in anti-MDA5 antibody-negative patients. Furthermore, our study showed that SPNM occurrence was associated with significantly higher mortality risk in DM/PM-ILD patients. However, all deaths in the SPNM group were

Table 2 HR of SPNM occurrence for death adjusted by age and anti-MDA5 antibody status

	HR for death (95% CI)			
	Unadjusted		Adjusted	
	HR	P value	HR	P value
SPNM occurrence	5.49 (1.99 to 15.18)	0.002	4.10 (1.37 to 12.24)	0.012
Anti-MDA5 status	3.22 (1.14 to 9.06)	0.02	2.81 (0.90 to 8.82)	0.076
Age	1.03 (0.98 to 1.08)	0.2	1.05 (1.00 to 1.10)	0.073

MDA5, melanoma differentiation-associated gene 5; SPNM, spontaneous pneumomediastinum.

Table 3 Characteristics of anti-MDA5 antibody-positive patients

	No SPNM (n=25)	SPNM occurred (n=15)	P value
Diagnosis			
Dermatomyositis, n (%)	5 (20)	2 (13.3)	0.914
Polymyositis, n (%)	0 (0)	0 (0)	None
CADM, n (%)	20 (80)	13 (86.7)	0.914
RP-ILD, n (%)	9 (36.0)	10 (66.7)	0.06
Age, years, median (IQR)	54 (46–63)	59 (56–65)	0.288
Female, n (%)	12 (48.0)	9 (60.0)	0.683
Smoking habits, n (%)	10 (40.0)	6 (40.0)	1
Treatments			
Maximum prednisolone dose*, mg/day, mean±SD	52.40±9.80	56.33±15.17	0.379
Methylprednisolone pulse therapy, n (%)	10 (40.0)	12 (80.0)	0.033
Intravenous cyclophosphamide, n (%)	24 (96.0)	13 (86.7)	0.642
Tacrolimus, n (%)	25 (100)	12 (80.0)	0.088
Ciclosporin, n (%)	1 (4.0)	6 (40.0)	0.013
Tofacitinib, n (%)	3 (12.0)	7 (46.7)	0.038
IVIg, n (%)	2 (8.0)	0 (0)	0.708
Plasma exchange, n (%)	2 (8.0)	8 (53.3)	0.005
Treatments, types			
GC monotherapy, n (%)	0 (0)	0 (0)	None
GC with one immunosuppressant, n (%)	1 (4.0)	1 (6.7)	1.000
GC with two immunosuppressants, n (%)	19 (76.0)	8 (53.3)	0.257
GC with three or more immunosuppressants, n (%)	5 (20.0)	6 (40.0)	0.315
Laboratory test result			
LDH, median (IQR)	333 (259–390)	349 (281–426)	0.548
CK, median (IQR)	99 (67–191)	82 (49–206)	0.418
KL-6, median (IQR)	841 (547–1195)	926 (835–1523)	0.150
CRP, median (IQR)	0.35 (0.10–0.56)	0.24 (0.15–0.42)	0.614
ferritin, median (IQR)	504.7 (273.9–848.0)	666.9 (382.3–1085.1)	0.235
Use of a ventilator, n (%)	1 (4.0)	6 (40.0)	0.013
Death within 1 year, n (%)	1 (4.0)	8 (53.3)	0.001

*Maximum prednisolone dose means the highest amount of prednisolone dose or equivalent except for methylprednisolone pulse therapy.
CADM, clinically amyopathic dermatomyositis; CK, creatine kinase; CRP, C reactive protein; GC, glucocorticoids; KL-6, Krebs von Lungren-6; LDH, lactate dehydrogenase; MDA5, melanoma differentiation-associated gene 5; RP-ILD, rapidly progressive interstitial lung disease; SPNM, spontaneous pneumomediastinum.

observed in anti-MDA5 antibody-positive patients, while all anti-MDA5 antibody-negative patients in the SPNM group survived. These results suggest that the prognostic significance of SPNM might be different between anti-MDA5 antibody-positive and negative patients.

The association between SPNM and the prognosis of DM/PM-ILD patients can be biologically plausible. In general, known causes of SPNM occurrence are soft tissue infections, disruption of cutaneous or mucosal barriers, or alveoli rupture induced by the pressure gradient between the alveoli and their surroundings.[17] A previous study reported that all CADM patients with recurrent SPNM presented with cutaneous vasculitis.[18] In addition, PM/DM patients complicated with skin vasculitis were reported to have a higher frequency of SPNM occurrence.[5] Those reports might suggest that alveoli rupture due to vasculitis (alveolitis) is the main pathology of anti-MDA5 antibody-positive/CADM patients. On the other hand, the vulnerability of the lungs induced by chronic ILD or lung fibrosis is another candidate for alveoli rupture. Therefore, SPNM could occur regardless of lung inflammation in patients with DM/PM-ILD without vasculitis, who are typically anti-MDA5 antibody-negative. Such differences in the pathogenesis of SPNM occurrence might be linked to different prognoses between anti-MDA5 antibody-positive and negative patients with SPNM.

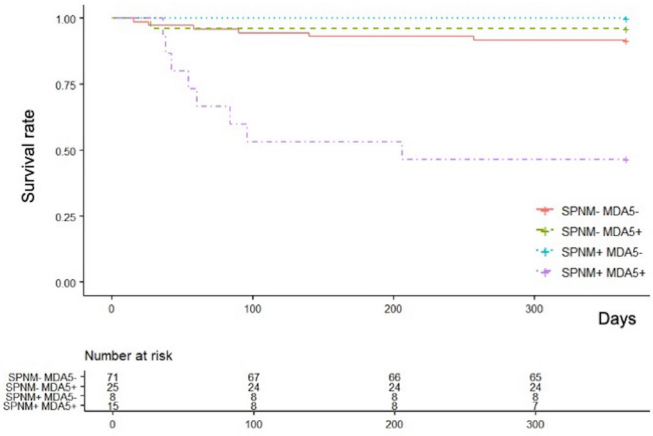

Figure 2 Survival curve comparison of SPNM occurrence/no occurrence groups with anti-MDA5 antibody status. SPMN, spontaneous pneumomediastinum; SPMN-MDA5-: group with no SPNM occurrence that was anti-MDA5 antibody negative; SPMN- MDA5+: group with no SPNM occurrence that was anti-MDA5 antibody positive; SPMN+MDA5-: group with SPNM occurrence that was anti-MDA5 antibody negative; SPMN+MDA5+: group with SPNM occurrence that was anti-MDA5 antibody positive.

In anti-MDA5 antibody-positive patients, the mortality rate was significantly higher in patients with SPNM than those without SPNM. It might suggest that the occurrence of SPNM reflected severe and/or uncontrolled vasculitis in the lungs of anti-MDA5 antibody-positive patients. So far, in a daily clinical practice setting, including the cohort of this study, immunosuppressive therapies were not usually strengthened after finding SPNM occurrence. However, our results might suggest that the treatment should be strengthened for DM/PM/CADM patients with SPNM, especially in anti-MDA5 antibody-positive patients. Such patients might require additional strong immunosuppressive therapies, such as Janus kinase inhibitors, immediately after finding SPNM occurrence.[19 20] The efficacy of additional treatment at SPNM occurrence should be assessed by a prospective study in the future.

Different from our results, Yoshida *et al* reviewed 21 DM cases with SPNM and stated their speculation that a major risk factor for death was not SPNM but the severity of ILD.[9] However, they speculated it without any analysis (eg, the SPNM group vs the non-SPNM group, anti-MDA5 antibody-positive vs -negative), which might be the reason for different conclusions from ours.

There are several limitations in our study. First, the event number of SPNM was not large enough to perform a multivariate analysis. Thus, we could not adjust for all confounding factors between mortality and SPNM occurrence (eg, age, smoking history and use of immunosuppressive treatments). Second, SPNM was identified based on an X-ray or CT, which was performed to evaluate treatment response for ILD. The follow-up interval varied among the patients, and there is a possibility that some asymptomatic or mild SPNM cases were missed. Third, there might be a selection bias due to the retrospective nature of this study. However, a multicentre design involving university hospitals and community hospitals could minimise the healthcare access bias. Fourth, subjects in this study were limited to Japanese, although the regional difference of anti-MDA5 positive patients has been known.[21] ILD is observed less frequently in non-Asian anti-MDA5 antibody-positive patients than in Asian anti-MDA5 antibody-positive patients. Our results may not apply to non-Asian patients. Fifth, anti-ARS antibody measurements used in daily clinical practice in Japan detect only five anti-ARS antibodies (anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ and anti-KS antibodies) but not anti-OJ, anti-Zo or anti-Ha antibodies. Since the detection is performed in batches, information on individual anti-ARS antibodies is not available. Therefore, we could not individually evaluate the characteristics of anti-ARS antibodies, although anti-PL-7 and anti-PL-12 antibody positivity has been reported to be associated with severe ILD.[22]

In summary, SPNM occurred more frequently in anti-MDA5 antibody-positive DM/PM patients than in anti-MDA5 antibody-negative DM/PM patients, and two-thirds of the SPNM group were anti-MDA5 antibody-positive. Overall, the SPNM group had a significantly higher mortality rate than the non-SPNM group. Focusing on anti-MDA5 antibody status, all deaths in the SPNM group occurred in anti-MDA5 antibody-positive patients. On the other hand, none of the anti-MDA5 antibody-negative patients with SPNM occurrence died. Daily clinical practice requires an individualised approach based on autoantibody status when SPNM occurs in PM/DM/CADM patients with ILD.

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Contributors SF is responsible for the overall content as guarantor. KA contributed to the conceptualisation of the study and analysis of the dataset. SF contributed to the conceptualisation of the study and supervision. HN contributed to the supervision. KA, YK, TS, S-IK and DN contributed to data collection. KA, SF, KI and HN wrote the first draft of the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content and gave final approval. SF had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was conducted following the Declaration of Helsinki. This study was approved by the ethics committee of School of Medicine, Chiba University (reference number: 3751). The ethics committee waived the requirement for patient's written informed consent according to the local regulations for a retrospective observational study. All data were fully anonymised before being analysed.

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Data availability statement Data are available upon reasonable request. Data requests should be sent to Dr Shunsuke Furuta at shfuruta@chiba-u.jp.

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