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ORIGINAL ARTICLE

Clinical features of patients with anti-melanoma differentiation-associated gene-5 antibody-positive dermatomyositis complicated by spontaneous pneumomediastinum

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Abstract

Background Dermatomyositis (DM) with autoantibody against melanoma differentiation-associated gene-5 (MDA5) is characterized by elevated risk of rapidly progressive interstitial lung disease (RP-ILD) with a potentially fatal course. Pneumomediastinum (PNM) is a common pulmonary manifestation which accompanies ILD. However, the clinical features of the patients with anti-MDA5 antibody-positive DM who develop PNM remain unclear.

Methods We retrospectively examined 31 patients with DM having anti-MDA5 antibody and compared the clinical features between patients with PNM (PMN(+)) ($n = 11$) and those without (PNM(−) ($n = 20$). In addition, we evaluated the treatment-related prognoses in PNM(+) group.

Results CT score (total ground-glass opacity (GGO) score, $P = 0.02$; total fibrosis score, $P = 0.02$) before treatment, and mortality ($P = 0.04$) were significantly higher in PNM(+) group. The cumulative survival rate as assessed by Kaplan–Meier method was significantly lower for the PNM(+) group ($P = 0.02$). Among 11 PMN(+) patients, 9 patients (9/11, 81.8%) underwent intensive immunosuppression therapy for RP-ILD, and 5 patients (5/11, 45.5%) did not respond to it and died from the respiratory failure. At the time of diagnosis of PNM, nonsurvivors had worse liver function (ALT, $P = 0.03$; LDH, $P = 0.01$), worse respiratory status (A-aDO2, $P = 0.01$), and worse CT score (total GGO score, $P < 0.01$).

Conclusions A subgroup of patients with DM having anti-MDA5 antibody complicated by PNM as well as RP-ILD did respond to intensive immunosuppression therapy. Initial aggressive immunosuppressive therapy should be considered for these patients.

Key Points

- *This study clearly demonstrate the presence of PNM was associated with elevated risk of death due to respiratory failure from RP-ILD among patients with DM having circulating anti-MDA5-antibody.*
- *This study demonstrate evaluation of CT image may be helpful to find patients with better response to the intense immunosuppression therapy for the patients with DM having circulating anti-MDA5-antibody and PNM.*

Keywords Anti-melanoma differentiation-associated gene 5 antibodies · Dermatomyositis · Pneumomediastinum · Rapidly progressive interstitial lung disease

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Introduction

Mediastinal emphysema or pneumomediastinum (PNM) is characterized by free air surrounding the interstitial mediastinal structures. Besides being occurred by trauma or as a complication of assisted ventilation, PNM is associated with various types of lung diseases including idiopathic interstitial pneumonia and interstitial lung disease (ILD) accompanying connective tissue disorder [1–3]. Among these, dermatomyositis (DM) is mostly predisposed to develop severe PNM [4]. In particular, amyopathic DM (CADM) and with DM that have circulating autoantibodies against melanoma differentiation-associated gene-5 (MDA5) are characterized by an increased risk for PNM. Furthermore, PNM complicating anti-MDA5 antibody-positive DM often is frequently associated with rapidly progressive interstitial lung disease (RP-ILD), a debilitating disorder with a poor prognosis [5]. There have been several reports demonstrating that the intense immunosuppression by combination therapy (CombT) using prednisolone (PSL), calcineurin inhibitor (CNI), and intravenous pulse cyclophosphamide (IVCY) could have reduced mortality from the RP-ILD [6, 7]. To date, the clinical features of patients with anti-MDA5 antibody-positive DM and PNM who have favorable outcome in response to immunosuppressive CombT remain unknown. Therefore, in this study, we retrospectively examined the clinical characteristics of 31 patients with anti-MDA5 antibody-positive DM with particular relevance to the prognostic significance of complicating PNM.

Methods

Patients

In this study, we retrospectively examined 31 patients with DM (classic DM: $n = 4$, CADM: $n = 27$) who were treated at the Gunma University Hospital between 2008 and 2018 and had anti-MDA5 antibody. DM was diagnosed according to the criteria of Bohan and Peter, and CADM was diagnosed using Sontheimer's criteria [8]. RP-ILD was defined as a respiratory failure that developed within 3 months from the initial respiratory symptoms or first medical examination [9]. Chronic-ILD was defined as the progression of ILD over 3 months [10]. All 31 patients were treated in Pulmonary Division in Gunma University Hospital. We examined their medical records for laboratory data before treatment and during follow-up. Patients with PNM were also examined to investigate the clinical features at the onset of PNM and the treatment regimens of each patient. Some of the laboratory data have been shown in earlier studies [11, 12]. This study was approved by the Institutional Review Board in Gunma University Hospital.

Measurement of autoimmune antibodies

We analyzed serum anti-MDA5 antibodies with ELISA using MESACUP anti-MDA5 test (MBL) [13] or a biotinylated recombinant protein [14].

High-resolution CT scoring

High-resolution CT (HRCT) imaging was performed using a multidetector CT scanner (Aquilion 64; Toshiba Medical Systems, Tochigi, Japan). CT slice thickness was 1.0–1.5 mm at 10 mm intervals in the entire lung. All patients were evaluated before the treatment. Patients with PNM were revaluated at the onset of the disease.

Ground-glass opacity (GGO) and fibrosis score of ILD were determined according to previous reports [15, 16]. In brief, the percentage of GGO in each of five lung lobes was expressed as scores of 0–5 (0, none; 1, ≦ 5%; 2, 5 to < 25%; 3, 25–49%; 4, 50–75%; 5, > 75% of the lobe), and according to the sum of those scores (0–25), GGO severity was classified into five grades (GGO 0–5). Likewise, the severity of fibrotic change in each of five lobe was classified into 5 grades (0, no fibrosis; 1, interlobular septal thickening without honeycombing; 2, honeycombing < 25%; 3, 25–49%; 4, 50–75%; 5, > 75% of the lobe) and according to the sum of these scores, fibrotic changes were graded as fibrotic score 0–5.

Statistical analysis

Statistical analyses were performed using the SPSS Version 25 software (IBM Corp., Armonk, NY, USA). Comparisons between groups were performed using Student's t test and the Mann–Whitney U test for mean and median values, respectively. Fisher's exact test was used to evaluate the frequencies. Overall survival rates were calculated by the Kaplan–Meier method and were compared by log-rank tests stratified by PNM status (with or without). $P < 0.05$ was considered to be statistically significant.

Results

Comparison of the clinical features between PNM(+) and PMN(−) groups in anti-MDA5-antibody-positive DM patients

We retrospectively evaluated the clinical features of 31 patients with anti-MDA5-antibody-positive DM or CADM, complicated with ILD at the time of diagnosis (Table 1). Of the 31 patients, 11 developed PNM during follow-up (range 1.4 months–4.8 years). Table 1 shows the comparison of clinical characteristics between

Table 1 Comparison of clinical features between PNM(+) and PNM(−) groups

	PNM(+) ($n = 11$)	PNM(−) ($n = 20$)	P
Age (years)	57 ± 12	51 ± 13	0.21
Male sex, no. (%)	3 (27.3)	9 (45)	0.28
CADM, no. (%)	10 (90.9)	17 (85)	0.55
Rapidly progressive ILD, no. (%)	9 (81.8)	12 (60)	0.2
Skin ulcer	6 (54.5)	7 (35)	0.25
Laboratory tests			
WBC (M3/μl)	4950 (3700–7500)	4500 (3300–11,400)	0.53
CRP (mg/dl)	0.73 (0.02–3.11)	0.35 (0.07–2.34)	0.21
AST (U/l)	51 (36–158)	61 (22–559)	0.86
ALT (U/l)	39 (15–97)	55 (11–270)	0.64
LDH (U/l)	368 (233–501)	374 (252–753)	1
CK (IU/l)	95 (22–297)	145 (55–657)	0.45
Max ferritin (ng/ml)	1184 (71–2647)	1240 (89–5667)	0.88
KL-6 (U/ml)	819 (253–3410)	756 (251–2043)	0.45
A-aDO2 (mmHg)	37 (17–46)	26 (8–60)	0.13
CT score before treatment			
Total GGO score	6 (2–12)	4 (1–10)	0.02
Total fibrosis score	4 (1–5)	2 (0–5)	0.02
Disease duration (days)[a]	449 (43–2024)	1133 (20–3354)	0.09
Combination immunosuppresive therapy, no. (%)[b]	9 (81.8)	13 (65)	0.29
Mortality, no. (%)	5 (45.5)	2 (10)	0.04

The values of age presented as mean (± SD) and those of the laboratory markers indicate the median (interquartile range). P value was established by using the Fisher's exact test, t test, or Mann–Whitney U test

PNM pneumomediastinum, *CADM* clinical amyopathic dermatomyositis, *ILD* interstitial lung disease, *WBC* white blood cell, *CRP* C-reactive protein, *AST* aspartate transaminase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *CK* creatine kinase, *KL-6* Krebs von den Lungen-6, *A-aDO2* alveolar-arterial oxygen difference, *GGO* ground-glass opacities

[a] Median days of follow-up after diagnosis (interquatile range)

[b] Triple therapy comprising corticosteroid, calcineurin inhibitor, and intravenous cyclophosphamide therapy

patients who developed PNM (PNM(+) group, $n = 11$) and those who did not develop it (PNM(−) group, $n = 20$). There was no significant between-group difference in age, sex, proportion of DM and CADM, comorbidity of RP-ILD, presence or absence of skin ulcer, serum white blood cell and C-reactive protein, liver function [aspartate transaminase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH)], creatine kinase, max ferritin level, Krebs von den lungen-6 (KL-6), or alveolar–arterial oxygen difference (A-aDO2). The PNM(+) group had higher CT score before treatment (total GGO score ($P = 0.02$) and total fibrosis score ($P = 0.02$)).

For the treatment for DM and CADM, we used IVCY every 2–4 weeks for 1–10 times, combined with PSL and CNI. The two groups did not significantly differ in the protocol of these treatments. However, the mortality rate was significantly higher in PNM(+) group ($P = 0.04$). Consistently, the cumulative survival rate as assessed by Kaplan–Meier method was significantly lower in the PNM(+) group ($P = 0.02$; Fig. 1).

Comparison of clinical features between the survivors and nonsurvivors within the PMN(+) group

Table 2 shows the comparison of the clinical characteristics between the survivors ($n = 6$) and nonsurvivors ($n = 5$) within the PMN(+) group at the time of the diagnosis of PMN. No significant differences were observed in the two groups in age, sex, DM or CADM diagnoses, the comorbidity of RP-ILD, presence of skin ulcer, white blood cell count, C-reactive protein levels, and ferritin levels. There were no significant differences in treatment strategies using steroid pulse therapy, PSL and CNI or their CombT between the two groups. Liver function test (AST, $P = 0.03$; LDH, $P = 0.01$), alveolar–arterial oxygen difference (A-aDO2, $P = 0.01$), and CT score was significantly worse in nonsurvivors than the survivors (total GGO score, $P < 0.01$) although no significant

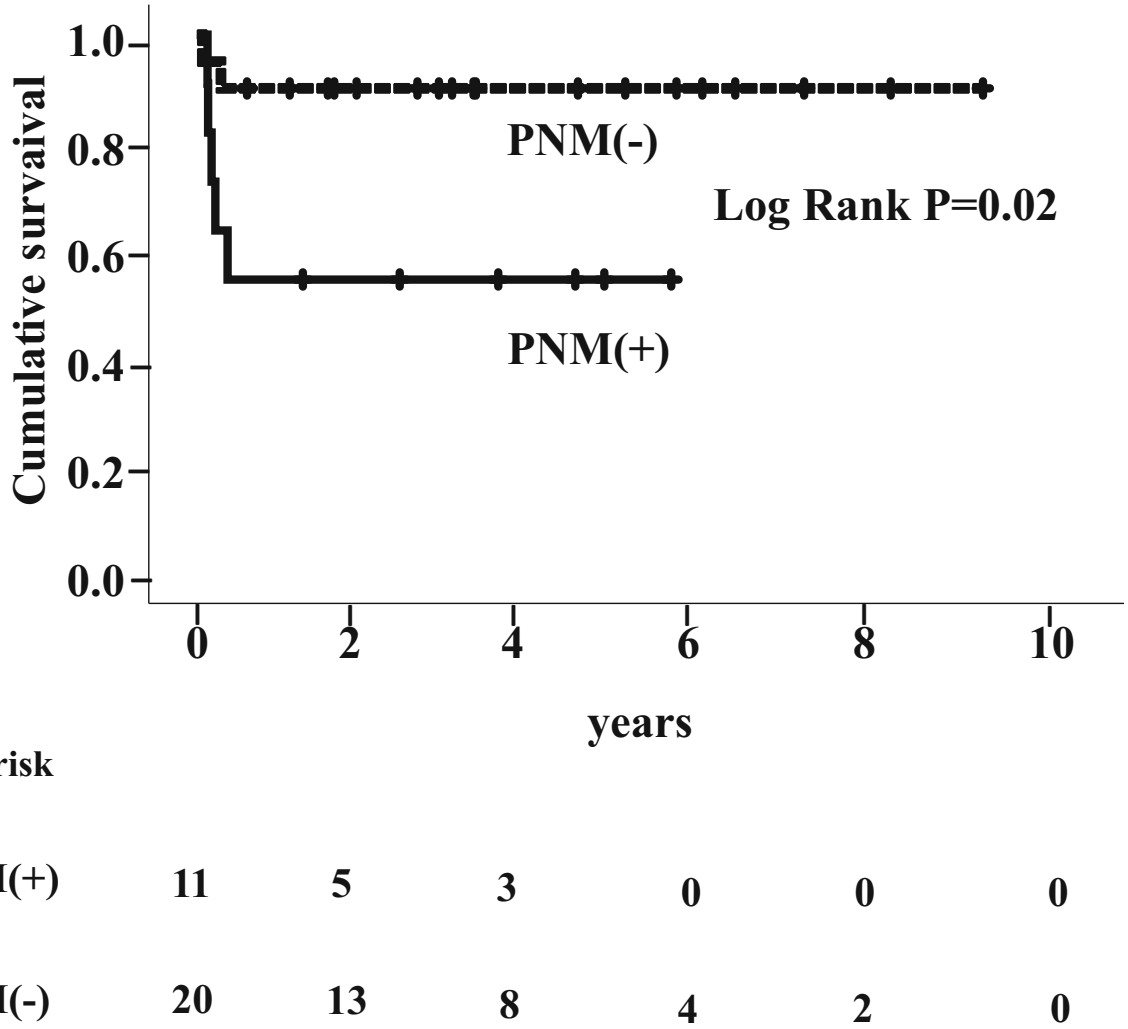

Fig. 1 Cumulative survival of patients with and without PNM

between-group difference was observed before the onset of PMN.

Table 3 shows clinical features and treatment in patients with PNM. Notably, 4 patients, comprising of 3 CADM and 1 DM, out of 6 patients who could have survived despite the complication of RP-ILD. All of these patients received CombT and reduced PSL doses for exacerbated PNM because corticosteroids may attenuate the integrity of the alveolar walls [17]. Three of these 4 patients additionally received steroid pulse therapy. All four PNM(+) patients presented the signs of exacerbation of RP-ILD during the CombT, and IVCY had been continued for 2–4 weeks; one patient who was refractory to the IVCY received rituximab and intravenous immunoglobulin (IVIG) for RP-ILD. One of the two survivors who did not have RP-ILD at the time of PNM diagnosis received IVCY for the chronic progression of ILD despite the administration of PSL and TAC.

With regard to 5 nonsurvived patients, all were CADM and died from respiratory failure from RP-ILD after short period (range 3–27 days) from the onset of PNM. Four patients received steroid pulse therapy and CombT, which included PSL, CNI, and IVCY and two of them added IVIG. One patient received steroid pulse, PSL, and CsA.

Discussion

This retrospective study showed that among patients with DM having circulating anti-MDA5-antibody, PNM may be associated with poor prognosis, and among patients complicated with PNM, there was a subgroup of patients who were successfully treated with intensive immunosuppression therapy using combination of PSL, CNI, and IVCY. Our data indicate that patients who survived by the intensive treatment are characterized by early stage of ILD as evaluated by the CT images. These results

Table 2 Comparison of clinical manifestations between survivors and nonsurvivors within the PNM(+) group

	Survivors ($n = 6$)	Nonsurvivors ($n = 5$)	P
Age (years)	54 ± 11	61 ± 13	0.36
Male, no. (%)	1 (17)	0 (0)	0.55
CADM, no. (%)	5 (83)	5 (100)	0.55
Rapidly progressive ILD, no. (%)	4 (66.7)	5 (100)	0.27
Skin ulcer	4 (67)	2 (40)	0.39
Laboratory tests (at onset of PNM)			
WBC (M3/μl)	5200 (3200–13,000)	5350 (2300–7800)	1
CRP (mg/dl)	0.21 (0.01–4.34)	3.49 (0.46–6.48)	0.13
AST (U/l)	26 (18–48)	78 (35–283)	0.03
ALT (U/l)	36 (21–111)	65 (12–612)	0.43
LDH (U/l)	309 (213–403)	585 (355–687)	0.01
Ferritin (ng/ml)	656 (224–1302)	1359 (730–2245)	0.12
A-aDO2 (mmHg)	33 (5–52)	183 (53–372)	0.01
CT score (at onset of PNM)			
Total GGO score	9 (4–12)	18 (15–25)	< 0.01
Total fibrosis score	5 (3–5)	4 (2–5)	0.8
Treatment			
Steroid pulse therapy, no. (%)	3 (50)	5 (100)	0.12
PSL + CNI[a]	1 (17)	1 (20)	0.73
PSL + CNI + IVCY	5 (83)	4 (80)	0.73
IVCY (times)	6 (0–10)	2 (1–3)	0.13
Time until PNM from diagnosis (days)	63 (27–127)	37 (16–126)	0.66
Disease duration (days)[b]	1299 (449–1737)	47 (43–128)	< 0.01

The values of age is presented as mean (SD) and those of laboratory markers indicate median (interquartile range). P value was established by using the Fisher's exact test, t test, or Mann–Whitney U test

PNM pneumomediastinum, *CADM* clinical amyopathic dermatomyositis, *ILD* interstitial lung disease, *WBC* white blood cell, *CRP* C-reactive protein, *AST* aspartate transaminase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *A-aDO2* alveolar-arterial oxygen difference, *GGO* ground-glass opacites, *PSL* predonisolone, *CNI* calcineurine inhibitor, *IVCY* intravenous pulse cyclophosphamide therapy

[a] CNI comprising CSA or TAC

[b] Median days of follow-up after diagnosis (interquatile range)

suggest that initial and early aggressive immunosuppressive treatments should be considered for the patients with DM having circulating anti-MDA5-antibody and PNM.

PNM is a common complication in the patients with DM, in particular with CADM. Muscle weakness and initial respiratory dysfunction may precede the onset of PNM, and this complication predicts poor prognosis [4]. Serological features of the patients with DM complicated by PNM include the presence of anti-MDA5-antibody [5]. In addition to PNM, CADM, and RP-ILD, patients with anti-MDA5-antibody often had cutaneous complications such as ulcers and palmar papules [18]. To date, it remains to be described whether presence or absence of PNM in the context of RP-ILD affects the prognosis in patients with anti-MDA5-antibody. In our study, PNM was associated with increased mortality rate with 6/11 patients dying within the first 6 months. Age, sex, cutaneous manifestation, treatment regimens, or follow-up periods were not associated with increased mortality rate.

The PNM associated with lung disease develops by rupture of the alveoli due to either raised intra-alveolar pressure in the presence of ILD [19] and pulmonary vasculitis [20], or weakened alveolar walls by corticosteroids [21, 22]. In our study, while no difference was observed in the vasculitis status including cutaneous lesions between PNM(+) and PNM(−) groups, significant difference in the CT score compiling GGO and fibrotic change was observed between the two groups before starting the immunosuppression therapy, suggesting that more severe interstitial pneumonitis had already been present in PNM(+) group.

Previous study showed that among 79 Japanese patients with DM, comprising 58 classic DM and 21 CADM, patients with CADM positive for anti-MDA5 antibody had significantly worse prognosis compared with patients without anti-MDA5 antibody. In that

Table 3 Clinical features and treatment in patients with PNM

No.	Sex	Age	Treatment	ILD	PSL dosage initial time (mg)	PSL dosage PNM onset (mg)[a]	PSL dosage PNM resolution (mg)[b]	IVCY times (among PNM)	IVCY times (total)	Prognosis	Diagnosis	Time to PNM onset (days)[c]	Time to PNM resolution (days)[d]	Follow-up (days)
1	F	71	Steroid pulse, CombT[e] rituximab, IVIG	RP-ILD	50	27.5	22.5	1	6	Alive	CADM	77	42	1724
2	F	55	Steroid pulse, CombT	RP-ILD	40	25	14	3	10	Alive	CADM	49	71	985
3	F	40	Steroid pulse, CombT	RP-ILD	50	40	10	4	6	Alive	CADM	27	108	564
4	F	52	CombT	RP-ILD	50	50	17.5	4	7	Alive	DM	29	77	449
5	F	61	CombT	Chronic	45	30	30	0	2	Alive	CADM	101	14	1613
6	M	45	PSL + TAC	Chronic	50	40	15	0	0	Alive	CADM	127	56	1737
7	M	78	Steroid pulse, CombT, IVIG	RP-ILD	50	35	–	1	2	Dead	CADM	54	–	76
8	F	55	Steroid pulse, CombT ,IVIG	RP-ILD	50	50	–	0	1	Dead	CADM	16	–	43
9	F	63	Steroid pulse, CombT	RP-ILD	60	50	–	0	1	Dead	CADM	31	–	47
10	F	66	Steroid pulse, CombT	RP-ILD	50	30	–	0	3	Dead	CADM	37	–	45
11	F	44	Steroid pulse, PSL + CsA	RP-ILD	50	50	–	0	0	Dead	CADM	126	–	128

ILD interstital lung disease, *PSL* predonisolone, *PNM* pneumomediastinum, *IVCY* intermittent pulse intravenous cyclophosphamide therapy, *RP-ILD* rapidly progressive interstitial lung disease, *CADM* clinically amyopathic dermatomyositis, *TAC* tacrolimus, *CombT* combination therapy, *CsA* cyclosporine, *IVIG* intravenous immunoglobulin

[a] PSL dose, 1st day of PNM

[b] PSL dose, last day of PNM

[c] Time until PNM from diagnosis

[d] Time in improved PNM from diagnosis

[e] CombT, combination therapy using corticosteroid, calcineurin inhibitor, and intravenous cyclophosphamide therapy

study, the cumulative survival rate at 6 months was 57.4 and 98.4% for DM with anti-MDA5 antibody and those without, respectively, and all the death in patients positive for anti-MDA5 antibody was attributable to respiratory failure due to RP-ILD [18]. In contrast, mortality rate was somewhat lower in our cohort in which all of 31 patients have anti-MDA5 antibody, 7 patients (7/31, 22.6%) died within the 6 months after diagnosis. Fujiki et al. described the clinical prognostic factors in anti-MDA5 antibody-positive DM complicated by interstitial pneumonia. In their study, 9 out of 18 patients died (50%). They showed that the respiratory status, serum ferritin levels, and the right middle lobe GGO score were related to prognosis. Total GGO scores tended to be higher in the death group, although there was no statistical difference [15]. Importantly, our study provides evidence that PNM(+) is likely to be associated with poor prognosis among anti-MDA5 antibody-positive DM patients. However, there was a report describing that PNM not accompanied by ILD may not be a poor prognostic factor [21]. Further study is required to validate the prognostic significance of PNM.

Our study showed that 4 patients out of 9 patients who had RP-ILD were successfully treated. Increasing numbers of literatures have described the efficacy of CombT using corticosteroids, CNI, and IVCY for the treatment of acute interstitial pneumonia associated with DM [6, 7]. CombT with PSL and CNI seem to be effective for DM and interstitial pneumonia to allow rapid tapering of PSL doses as the symptoms of PNM disappeared [23, 24]. Kameda et al. reported that PNM improved by the CombT consisting of PSL, CNI, and IVCY in 4 patients out of 10 patients with DM complicated by acute/subacute interstitial pneumonia [6].

Several case reports described the characteristic response to CombT for PNM and RP-ILD in DM patients with anti-MDA5 antibody. They include a paradoxical appearance of PNM after improvement of ILD [25], and PNM accompanied by deteriorated respiratory condition of RP-ILD [26, 27] during CombT. Consistent with these previous reports, PNM appeared after starting CombT for RP-ILD in 5 of our patients.

Our study has several limitations. This was a retrospective, single-institution study with a small study cohort, and should be verified with a larger cohort from several institutions.

In conclusion, among patients with DM having circulating anti-MDA5 antibody and RP-ILD, the presence of PNM was associated with elevated risk of death due to respiratory failure from RP-ILD. Evaluation of CT image, GGO and fibrotic change, may be helpful to find patients with better response to the intense immunosuppression therapy using combination of PSL, CNI, and IVCY.

Compliance with ethical standards

This study was approved by institutional review board of Gunma University. This study was conducted by the principles of the Declaration ofHelsinki.

Conflict of interest The authors declare that they have no conflict of interest.

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