



Differential clinical features of patients with clinically amyopathic dermatomyositis who have circulating anti-MDA5 autoantibodies with or without myositis-associated autoantibodies



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ABSTRACT

Background: Anti-melanoma differentiation-associated gene 5 (MDA5) autoantibodies have been identified as myositis-specific autoantibodies that are often associated with clinically amyopathic dermatomyositis (CADM) and a poor prognosis due to rapidly progressive interstitial lung disease (RP-ILD) in East Asian patients. Besides anti-MDA5 autoantibodies, patients with CADM may have myositis-associated autoantibodies (MAAs), which characterize other connective tissue diseases such as rheumatoid arthritis and Sjögren's syndrome. However, the clinical significance of the coexistence of anti-MDA5 autoantibodies and MAAs in patients with CADM remains unclear.

Methods: We retrospectively analyzed 24 patients with CADM who had anti-MDA5 autoantibodies. Their clinical phenotypes including laboratory test results, high-resolution lung computed tomography data, response to therapy, and prognosis were compared between those who were positive and negative for MAAs, such as antinuclear antibody (ANA), anti-cyclic citrullinated peptide (CCP), anti-SSA, and anti-SSB antibodies.

Results: Among 24 patients, 9 (37.5%) additionally had at least one of the MAAs examined in this study: 1 patient was positive for ANA, 5 for anti-CCP, 5 for either anti-SSA or anti-SSB, 1 for anti-cardiolipin, and 1 for anti-Scl-70. Although all anti-MDA5-positive patients with CADM had ILD, the MAA-positive patients showed a lower risk of developing RP-ILD ($p = 0.03$), a more favorable response to combination therapy of corticosteroids and immunosuppressive agents, and a lower mortality rate than patients with no MAAs ($p = 0.03$).

Conclusions: Our data suggest that anti-MDA5-positive patients with CADM who also have MAAs have a better prognosis than those without MAAs; thus, anti-MDA5 autoantibodies by themselves may not be strong predictors of worse clinical outcomes in patients with CADM. Coexistent MAAs could be biomarkers for a favorable prognosis in anti-MDA5-positive patients with CADM.

1. Introduction

Dermatomyositis (DM), defined by hallmark cutaneous manifestations and skeletal muscle weakness resulting from a characteristic pattern of autoimmune myositis, has a heterogeneous clinical presentation. Myositis-specific autoantibodies are found in approximately 60% of patients with myositis and are strongly associated with distinct

clinical phenotypes [1]. For example, autoantibodies to histidyl transfer RNA synthetase (Jo-1) or aminoacyl tRNA synthetase are associated with a clinical phenotype termed “antisynthetase syndrome,” which consists of myopathy, fever, interstitial lung disease (ILD), Raynaud's phenomenon, nonerosive arthritis, and mechanic's hands [2]. Anti-TIF1- γ -positive patients with DM have an increased risk for an associated internal malignancy. Further, anti-Mi-2 autoantibodies are

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associated with a more severe cutaneous form of DM that responds favorably to therapy [3] [4].

A subset of patients with DM has circulating myositis-associated autoantibodies (MAAs) that are often found in other connective tissue diseases (CTDs) and are thus less specific for myositis than are myositis-specific autoantibodies. Several MAAs can be correlated with the clinical features of DM [5]. For example, anti-PM/Scl autoantibodies that target the nucleolar exosome complex are found in various CTDs such as overlap of polymyositis and scleroderma and are associated with an increased risk of ILD, arthritis, mechanic's hands, and Raynaud's phenomenon. Anti-U1 ribonucleoprotein autoantibodies are generally found in patients with overlap of myositis and mixed CTD, and myositis reportedly responds favorably to steroid treatment. Patients with anti-Ku autoantibody appear to have myositis that responds well to treatment, while ILD in these patients is corticosteroid-resistant. However, little is known about whether the clinical features of anti-MDA5-positive patients with clinically amyopathic DM (CADM) differ depending on the coexistence of MAAs.

In this study, we retrospectively analyzed the clinical features, including the prognosis and response of ILD to immunosuppressive therapy, of patients with CADM who had anti-MDA5 autoantibodies with or without MAAs.

2. Methods

2.1. Patients

We retrospectively studied 24 patients diagnosed with CADM who were positive for serum anti-MDA5 autoantibodies at Gunma University Hospital from 2008 to 2017. CADM was diagnosed in patients with skin lesions but no muscle-related symptoms [6]. All patients had ILD, which was diagnosed by a clinical pulmonologist based on clinical symptoms, physical examination findings, and computed tomography (CT) imaging findings. ILD was classified as rapidly progressive ILD (RP-ILD) when respiratory failure developed within 3 months from the initial respiratory symptoms or the initial visits [7] and was classified as chronic ILD when it developed over 3 months [8].

2.2. Measurement of autoimmune antibodies

We performed laboratory screening including tests for the following autoantibodies: antinuclear antibody (ANA) using indirect immunofluorescence (MBL, Nagoya, Japan) (high autoantibody titers of $> 1:160$ [9]), antineutrophil cytoplasmic antibody using enzyme-linked immunosorbent assay (ELISA) or chemiluminescent enzyme immunoassay (CLEIA) (MBL, Ro60/SSA, La/SSB using ELISA (MBL), cyclic citrullinated peptide (CCP) using ELISA (MBL), Jo-1 using ELISA (Fuji Rebio, Tokyo, Japan) or CLEIA (MBL), and *t*-RNA synthetase using enzyme immunoassay (LSI Medience Corp., Tokyo, Japan). No patients in this study had Jo-1 antibodies or *t*RNA synthetase antibodies. Anti-MDA5 antibody was measured with ELISA using a biotinylated recombinant protein [10] or MESACUP anti-MDA5 test (MBL) [11].

2.3. Clinical evaluation

All patients were diagnosed by two rheumatologists at the time of hospitalization. CADM was diagnosed by Sontheimer's criteria [12]. With respect to overlapping syndromes, rheumatoid arthritis (RA) was diagnosed according to the 1987 revised criteria of the American Rheumatism Association [13]. Sjögren's syndrome was diagnosed according to the American-European Consensus Group criteria [14].

High-resolution CT (HRCT) imaging was performed by a multi-detector CT scanner (Aquilion 64; Toshiba Medical Systems, Tochigi, Japan). CT images were evaluated for the presence of ground-glass attenuation (GGA) consolidation, bronchiectasis, intralobular reticular opacity, interlobular septal thickening, non-septal linear or plate-like

opacity, and lobular volume loss; the distribution of shadows was distinguished as upper, lower, diffuse, or random according to a previous report [15].

2.4. Statistical analysis

Statistical analyses were performed using SPSS Version 22 software (IBM Corp., Armonk, NY, USA). Group comparisons were made using the *t*-test for mean values and Mann–Whitney's test for median values; Fisher's exact test was used to assess frequencies. The distribution of overall survival was estimated by the Kaplan–Meier method and compared by means of log-rank tests stratified according to the status of MAAs (with or without). A *p* value of < 0.05 indicated statistical significance.

3. Results

3.1. Baseline characteristics of the study patients

Nine of 24 (37.5%) anti-MDA5-positive patients with CADM were also positive for at least one MAA; these patients are hereafter referred to as MAA (+) patients. Fifteen of 24 (62.5%) anti-MDA5-positive patients with CADM were negative for any of the MAAs tested; these patients are hereafter referred to as MAA (–) patients. Table 1 shows the demographics, clinical characteristics, and laboratory test results of the MAA (+) and MAA (–) patients. Among the nine MAA (+) patients, one had ANA (ANA antibody titer of $\geq 1:160$), five had anti-CCP antibodies, five had either anti-SSA or anti-SSB antibodies, one had anti-cardiolipin antibodies (IgG, 23 U/ml), and one had anti-Scl-70 antibody. Three patients had concurrent RA and one had concurrent Sjögren's syndrome.

3.2. Coexistent lung disease

While all patients in this study had either RP-ILD or chronic ILD, the proportion of patients with RP-ILD among those with ILD was higher in MAA (–) than MAA (+) patients [12/15 (80.0%) vs. 3/9 (33.3%), respectively; *p* = 0.03]. Table 2 shows the details of the individual clinical features of MAA (+) and MAA (–) patients, including the type of ILD, type of treatment, duration of treatment, and prognosis along with the coexisting MAAs, if present.

3.3. HRCT evaluation

Table 3 compares the HRCT findings between MAA (+) and MAA (–) patients. MAA (–) patients were more likely to have interlobular septal thickening (*p* = 0.02) and non-septal linear or plate-like opacity (*p* = 0.02) than were MAA (+) patients. The HRCT distribution pattern such as lower consolidation/GGA, lower reticular opacity, and random GGA was similar between MAA (+) and MAA (–) patients.

3.4. Treatment and outcomes

All patients but one received treatment (Table 4). In this patient, the prognosis of ILD was indeterminable. Two patients (one MAA (+) and one MAA (–) patient) improved by prednisolone (PSL) only or PSL plus azathioprine therapy. MAA (+) patients tended to show greater improvement by PSL and calcineurin inhibitors (cyclosporine or tacrolimus) than MAA (–) patients (*p* = 0.05). The duration of hospitalization was comparable between the two groups.

While none of the 3 MAA (+) patients with RP-ILD died, 6 of the 12 MAA (–) patients with RP-ILD died of respiratory failure despite intensive treatment using a combination of high-dose PSL and biweekly intravenous cyclophosphamide (IVCY) with a calcineurin inhibitor (tacrolimus or cyclosporine) according to a previously described protocol [16,17] [18]. [19]. Sixteen patients required triple therapy

Table 1
Comparison of clinical manifestations between MAAs (+) and MAAs (–) patients.

	MAAs (+) (n = 9)	MAAs (–) (n = 15)	P
Age - years	49 ± 10	63 ± 14	0.07
Male sex - no. (%)	6 (66.7)	4 (26.7)	0.07
ILD			
Rapidly progressive ILD	3 (33.3)	12 (80)	0.03
Chronic ILD	6 (66.7)	3 (20)	0.03
Smoking ^a	6 (66.7)	2 (13.3)	0.02
Non-smoker	3 (33.3)	13 (86.7)	
Ex-smoker	4 (44.4)	2 (13.3)	
Current smoker	2 (22.2)	0 (0)	
Laboratory tests			
WBC (M3/μl)	4500 (4200–7500)	4700 (3300–10800)	0.73
CRP (mg/dl)	0.39 (0.07–3.11)	0.71 (0.19–2.34)	0.77
AST (U/L)	53 (22–168)	77 (48–507)	0.07
ALT (U/L)	49 (11–94)	17–135 (68)	0.3
LDH (U/L)	321 (233–615)	379 (294–712)	0.36
CK (IU/L)	92 (22–352)	159 (61–657)	0.33
Ferritin (ng/ml)	1065 (121–1842)	479 (239–1783)	0.92
Max Ferritin (ng/ml)	1248.9 (216.3–4136.6)	1231 (357.2–2958.6)	0.33
KL-6 (U/ml)	943 (340–1743)	666 (251–1157)	0.24
AaDO2 (mmHg)	25 (8–42)	35 (17–60)	0.12
Antibodies			
ANA (≥1:160)	1 (7.7)	0 (0)	
Anti-CCP antibody	5 (38.5)	0 (0)	
Anti-SSA antibody or anti-SSB antibody	5 (38.5)	0 (0)	
Other (Anti-cardiolipin, Anti-SCL70) ^b	2 (15.4)	0 (0)	
Overlap syndrome - no. (%)	3 (33)	1 (7)	0.13
Median months before admission (IQR)	2 (0.5–8)	1 (1–12)	0.38
Median months of follow-up after diagnosis (IQR)	36 (11–85)	21 (0.5–93)	0.42
Prognosis			
Survivors - no. (%)	9 (100)	9 (60)	0.04

The values of age presented as mean (S.D.) 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.

Abbreviation: 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; AaDO2, alveolar-arterial oxygen difference; ANA, anti-nuclear antibody; Anti-CCP, anti-cyclic citrullinated peptide, IQR interquartile range.

^a Smoking: ex-smoker and current smoker.

^b Anti-cardiolipin (n = 1), Anti-SCL70 (n = 1).

including PSL (1 mg/kg per day), tacrolimus (0.0375 mg/kg twice a day; trough concentration of 5–10 ng/ml), and IVCY (500–750 mg/m² every 2–4 weeks). Fourteen of 16 patients who underwent triple therapy developed RP-ILD. Two patients had chronic ILD and underwent treatment with IVCY later because their ILD did not improve by treatment with PSL and calcineurin inhibitors. MAA (–) patients showed a tendency to require triple therapy, although a significant difference was not observed (*p* = 0.09). The frequency of IVCY administration differed between MAA (+) and MAA (–) patients who required triple therapy. The number of IVCY treatment sessions ranged from 1 to 10, including those patients who stopped therapy because of death. The period of time from administration of PSL and calcineurin to administration of IVCY was significantly longer in MAA (+) than MAA

(–) patients (*p* = 0.02). Two MAA (–) patients also received rituximab because triple therapy, including three or six IVCY treatment sessions, was not effective. These patients improved after rituximab administration. As shown in Fig. 1, overall survival was significantly longer in the MAA (+) group than MAA (–) group (log-rank test, *p* = 0.036).

3.5. Complications during treatment

Mediastinal emphysema is a frequent complication of anti-MDA5-positive CADM and RP-ILD [20]. In the present study, all patients with RP-ILD had mediastinal emphysema. The incidence of mediastinal emphysema as well as bacterial, fungal, or cytomegalovirus (CMV) infection was comparable between MAA (+) and MAA (–) patients (Table 5).

The serum CMV antigen level was measured in each patient regardless of clinical symptoms or the need for treatment. We administered ganciclovir to patients with an increasing serum CMV antigen level during the course of therapy for DM. Fungal infections were diagnosed based on clinical symptoms, laboratory and imaging data, and sputum examination (culture and pathology). One patient was diagnosed with pulmonary aspergillosis, which improved with voriconazole treatment. Three patients were diagnosed with pneumocystis pneumonia and were treated with trimethoprim/sulfamethoxazole, but these patients died of progression of RP-ILD.

4. Discussion

In the present study, we demonstrated that patients with CADM who have both anti-MDA5 autoantibodies and MAAs appear to express favorable clinical features; the incidence of RP-ILD and the mortality rate were significantly lower than those of MAA (–) patients. Our data suggest that the RP-ILD in MAA (+) patients was more responsive to combination therapy using corticosteroids and immunosuppressive agents (calcineurin inhibitors) than that in MAA (–) patients.

Previous studies have identified several risk factors that are potentially associated with a poor prognosis in patients with CADM who develop ILD. Tanizawa et al. [21] reported that a high fever, anti-MDA5 autoantibodies, specific CT shadows (especially lower consolidation), and a ferritin level of ≥ 500 ng/ml are associated with a high 90-day mortality rate in patients with concurrent ILD and DM. Among anti-MDA5-positive patients with DM, the P/F ratio, alveolar-arterial oxygen gradient, and levels of aspartate transaminase and gamma glutamyl transpeptidase are reportedly associated with a poor outcome [22]. Some reports have also described a serum ferritin level of 500–2000 ng/ml as a prognostic marker [23] [24]. Notably, these values were not significantly different between MAA (+) and MMA (–) patients in the present study.

These findings raise the following question: What is a possible explanation for the difference in clinical outcomes, especially the risk of developing fatal RP-ILD, between MAA (+) and MMA (–) patients? Previous studies have shown that ILD accompanying DM with anti-MDA5-autoantibodies is characterized by distinct HRCT patterns (i.e., predominant lower consolidation, predominant random GGA, and absence of lower reticulation) suggesting a lower prevalence of a pathological nonspecific interstitial pneumonia pattern and a higher prevalence of an organizing pneumonia or localized diffuse alveolar damage pattern [21] [15] [25]. In the present study, the HRCT distribution patterns of the major lung abnormalities were comparable between MAA (+) and MMA (–) patients. However, we found that the frequency of interlobular septal thickening and non-septal linear or plate-like opacity was significantly higher in MAA (–) than MMA (+) patients (*p* = 0.02 for both). Although the clinical significance of these HRCT findings remains unclear, our results suggest that the presence or absence of MAAs is associated with the lung pathology shown by HRCT imaging in anti-MDA5-positive patients with CADM.

Table 2
Clinical features of MAAs(+) and MAAs(−) patients.

No	Sex	Age	Smoking	ILD	Treatment	IVCY (times)	Days from PSL + CNI to IVCY	Prognosis	Diagnosis	Antibodies	Follow up (months) ^a
1	M	46	Current	Chronic	PSL,TAC	0	0	Alive	CADM· RA	Anti-CCP, Anti-SCL70	38
2	F	38	Current	Chronic	PSL,TAC	0	0	Alive	CADM	Anti-SSA	36
3	M	62	Never	Chronic	PSL,TAC,IVCY	2	107	Alive	CADM· RA	Anti-CCP	36
4	M	53	Ex-smoker	Chronic	PSL,TAC,IVCY	3	122	Alive	CADM	ANA, Anti-SSA	22
5	F	65	Never	Chronic	PSL	0	0	Alive	CADM	Anti-SSA	58
6	M	58	Never	Chronic	PSL,CsA	0	0	Alive	CADM	Anti-SSA, Anti-cardiolipin	85
7	M	46	Ex-smoker	RP-ILD	PSL,TAC	0	0	Alive	CADM,RA	Anti-CCP	16
8	M	45	Ex-smoker	RP-ILD	Steroid pulse ^b , PSL,TAC,IVCY	2	12	Alive	CADM	Anti-SSA, Anti-CCP	13
9	F	40	Ex-smoker	RP-ILD	Steroid pulse, PSL,TAC,IVCY	6	158	Alive	CADM	Anti-CCP	11
10	M	37	Never	RP-ILD	Steroid pulse, PSL,CsA,IVCY	1	1	Alive	CADM	Negative	53
11	F	71	Never	Chronic	No treatment	0	0	Alive	CADM	Negative	53
12	F	45	Never	RP-ILD	Steroid pulse, PSL,TAC,IVCY	1	1	Alive	CADM	Negative	49
13	F	73	Never	RP-ILD	Steroid pulse, PSL,TAC,IVCY, retuximab	6	4	Alive	CADM	Negative	49
14	F	65	Never	RP-ILD	Steroid pulse, PSL,TAC,IVCY	1	4	Dead	CADM	Negative	0.5
15	F	40	Ex-smoker	RP-ILD	Steroid pulse, PSL,TAC,IVCY, retuximab	2	1	Alive	CADM	Negative	43
16	F	55	Never	RP-ILD	Steroid pulse, PSL,TAC,IVCY	10	3	Alive	CADM	Negative	25
17	F	57	Never	RP-ILD	PSL,TAC,IVCY	2	36	Alive	CADM	Negative	21
18	F	72	Never	Chronic	PSL,TAC,	0	0	Alive	CADM, SjS	Negative	18
19	M	78	Never	RP-ILD	Steroid pulse, PSL,TAC,IVCY	2	47	Dead	CADM	Negative	2
20	F	55	Never	RP-ILD	Steroid pulse, PSL,TAC,IVCY	1	30	Dead	CADM	Negative	1
21	F	63	Never	RP-ILD	Steroid pulse, PSL,TAC,IVCY	1	28	Dead	CADM	Negative	1.5
22	M	49	Never	Chronic	PSL	0	0	Alive	CADM	Negative	93
23	M	73	Ex-smoker	RP-ILD	Steroid pulse, PSL,CsA,IVCY	2	51	Dead	CADM	Negative	3
24	F	66	Never	RP-ILD	Steroid pulse, PSL,TAC,IVCY	3	1	Dead	CADM	Negative	1.5

Abbreviations: RP-ILD, rapidly progressive ILD; PSL, prednisolone; TAC, tacrolimus; CsA, cyclosporine; CNI, calcineurin inhibitor; IVCY, intermittent pulse intravenous cyclophosphamide therapy; CADM, clinically amyopathic dermatomyositis; RA, rheumatoid arthritis; SjS, Sjögren syndrome; ANA, antinuclear antibody; Anti-CCP, anti-cyclic citrullinated peptide.

^a Follow-up period from diagnosis.

^b Steroid pulse therapy: methylprednisolone 1 g daily for 3 days.

Table 3
HRCT pattern between patients with MAAs(+) and MAAs(−).

	MAAs(+) (n = 9)	MAAs(−) (n = 15)	P
GGO	4 (44.4)	11 (73.3)	0.16
Consolidation - no. (%)	4 (44.4)	9 (60.0)	0.38
Bronchoectasis - no. (%)	6 (66.7)	5 (33.3)	0.12
Intralobular reticular opacity - no. (%)	3 (33.3)	3 (20.0)	0.4
Interlobular septal thickening - no. (%)	0 (0.0)	7 (46.7)	0.02
Nonseptal linear or plate-like opacity - no. (%)	1 (11.1)	9 (60.0)	0.02
Lobular volume loss - no. (%)	8 (88.9)	10 (66.7)	0.24
HRCT distribution			
Lower consolidation/GGA - no. (%)	4 (44.4)	8 (53.3)	0.5
Lower reticular opacity - no. (%)	2 (22.2)	1 (6.7)	0.31
Random GGA - no. (%)	1 (11.1)	2 (13.3)	0.69
Others - no. (%)	2 (22.2)	4 (26.7)	0.6

^a Diffuse consolidation, n = 1; Lower consolidation and diffuse GGA, n = 4; Pleural effusion + Lower reticular opacity, n = 1.

Abbreviations: GGA, ground-glass opacity; HRCT, high-resolution computed tomography.

In this study, MAA (+) patients were more likely to have bronchiectasis and lobular volume loss in HRCT. In a previous report, bronchial lesions were prevalent in patients with pulmonary collagen vascular disease, particularly in those with RA and Sjögren's syndrome [26]. Consistent with that report, all MAA (+) patients in the present study had autoantibodies traditionally associated with either RA or Sjögren's syndrome; five patients had anti-CCP antibodies and five had

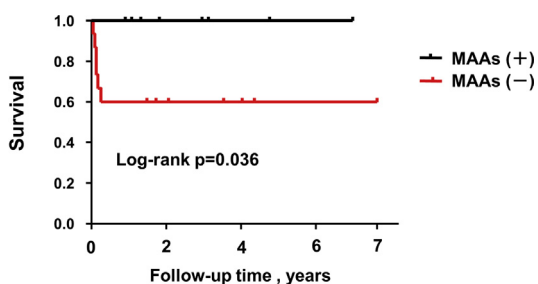
Table 4
Comparison of treatment between patients with MAAs(+) and MAAs(−).

	MAAs(+) (n = 9)	MAAs(−) (n = 15)
PSL alone or + AZA	1 (11.1)	1 (6.7)
PSL + CNI	4 (44.4)	1 (6.7)
PSL + CNI + IVCY	4 (44.4)	12 (80)
IVCY(times)	2.5 (2–6)	2 (1–10)
Time from PSL + CNI to initial IVCY administration - days (IQR)	114.5 (12–158)	4 (1–51)
Add on retuximab	0 (0)	2 (13.3)
No treatment	0 (0)	1 (6.7)

Abbreviations: PSL, prednisolone; AZA, azathioprine; CNI, calcineurin inhibitor; IVCY, intermittent pulse intravenous cyclophosphamide therapy; IQR, interquartile range.

anti-SSA or anti-SSB antibodies. While three MAA (+) patients fulfilled the criteria for RA, the remaining six patients were diagnosed with CADM alone. ILD may precede the overt clinical phenotypes of CTDs, and MMA (+) patients with CADM may eventually manifest clinical features of definitive CTDs during follow-up. Thus, ILD in MAA (+) patients may be, at least in part, attributed to overlapping/accompanying CTDs such as RA and Sjögren's syndrome rather than solely to CADM by itself.

Some selection bias may have been present in this study because it was a small single-center retrospective study. However, the single-center design may also be viewed as a strength of this study because a specific therapeutic strategy has not been well established for RP-ILD in patients with CADM and is therefore likely to differ among centers. In this study, patients with RP-ILD were treated based on a consistent protocol involving a combination of high-dose PSL and biweekly IVCY



Number at risk

MAAs (+)	9	5	2	1	1
MAAs (-)	15	7	5	1	1

Fig. 1. Overall Survival. Shown are Kaplan-Meier estimates of overall survival, according to the MAA status.

Table 5
Complications between patients with MAAs (+) and MAAs (-).

	MAAs (+) (n = 9)	MAAs (-) (n = 15)	P
Infection - no. (%)	5 (55.6)	11 (73.3)	0.33
Bacteria - no. (%)	1 (11.1)	9 (60.0)	0.02
Fungi - no. (%)	0 (0.0)	4 (26.7)	0.13
CMV - no. (%)	4 (44.4)	7 (46.7)	0.63
Mediastinal emphysema - no. (%)	3 (33.3)	6 (40.0)	0.55

Abbreviation: CMV, cytomegalovirus.

with a calcineurin inhibitor (tacrolimus or cyclosporine) as previously described [16,17] [18]. [19]. In addition, we treated patients with ILD who developed life-threatening CMV infection according to a consistent strategy proposed by Arai et al. [27].

In conclusion, this study has shown that patients with CADM who have both anti-MDA5 autoantibodies and MAAs have more favorable clinical features, including a lower incidence of RP-ILD and a lower mortality rate, than patients with CADM who have anti-MDA5 autoantibodies alone. MAAs could serve as valuable biomarkers that predict a better response of RP-ILD to combination therapy involving immunosuppressive agents in anti-MAD5-positive patients with CADM. Further studies are needed to confirm our findings.

Declarations of interest

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