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Original article

The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody testing for predicting the prognosis of Japanese patients with DM

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Abstract

Objective. Interstitial lung disease (ILD), especially rapidly progressive ILD (RPILD), is a major poor prognostic factor in patients with DM. We investigated the association of anti-melanoma differentiation-associated gene 5 (MDA5) antibody (Ab) with clinical characteristics and mortality in Japanese patients with DM.

Methods. Seventy-nine DM patients, comprising 58 classic DM and 21 clinically amyopathic DM (CADM) patients, were enrolled. Serum Abs were screened by immunoprecipitation assays, and an immunosorbent assay (ELISA) was used for MDA5. The relationships of clinical characteristics and mortality with each Ab were investigated.

Results. Anti-MDA5 Ab was detected in 17 patients. Anti-clinically amyopathic DM 140 kDa polypeptide Abs (anti-CADM-140 Abs) were found in 16 of the 17 anti-MDA5 Ab^+ patients. Skin ulcers, palmar papules, CADM, RPILD and mediastinal emphysema were widely distributed in anti-MDA5 Ab^+ patients. Mortality at 6 months as well as 5 years was also significantly higher in anti-MDA5 Ab^+ patients than in anti-MDA5 Ab^- patients. In a multivariable Cox regression analysis, mortality was independently associated with anti-MDA5 Ab (relative hazard 6.33; 95% CI 1.43, 28.0). All of the deaths in anti-MDA5 Ab^+ patients were attributed to respiratory failure of RPILD; however, RPILD did not worsen in any of the anti-MDA5 Ab^+ patients who survived the first 6 months.

Conclusion. The presence of anti-MDA5 Ab identifies the characteristic skin, musculoskeletal, pulmonary and prognostic features in patients with DM. In addition, anti-MDA5 Ab seems to predict a group of patients with CADM-complicated fatal RPILD.

Key words: anti-MDA5 Ab, CADM, RPILD.

CLINICAL SCIENCE

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Introduction

A number of autoantibodies can be detected in the sera of patients with DM, some of which are specific to DM and are known as myositis-specific autoantibodies (MSAs). Moreover, these autoantibodies are closely associated with clinical manifestations of DM, such as symptoms, complications, reactivity to therapy and prognosis [1].

In recent years, the autoantibodies found in patients with inflammatory myopathies have been mainly classified into several types by immunoprecipitation assays: anti-aminoacyl-tRNA synthetase antibodies (anti-ARS Abs), Abs to the signal recognition particle (anti-SRP Abs), anti-Mi2 Abs, PM/Scl-100 Abs and PM/Scl-75 polypeptides Abs (anti-PM-Scl Abs), anti-clinically amyopathic DM 140 kDa polypeptide Abs (anti-CADM-140 Abs), anti-155/140 kDa polypeptide Abs (anti-p155/140 Abs) and autoantibodies to a 142 kDa protein (anti-MJ Abs). These autoantibodies are strongly associated with the clinical presentation [2–6]. In this regard, we have reported a high frequency of rapidly progressive interstitial lung disease (RPILD) and clinically amyopathic DM (CADM) associated with anti-CADM-140 Abs [7, 8]. Recently RNA helicase encoded by melanoma differentiation-associated gene 5 (MDA5) was identified as a major autoantigen in patients with CADM, which is targeted by anti-CADM-140 Abs [9, 10].

Gono *et al*. [11] have also recently reported that anti-MDA5 Ab predicts a fatal outcome in patients with DM combined with RPILD; however, the long-term prognosis and other clinical characteristics of anti-MDA5 Ab$^+$ DM patients remain to be elucidated. In the present study we have tried to investigate the clinical value of anti-MDA5 Ab for DM patients in a single cohort.

Patients, materials and methods

Patients

Sera samples were obtained from 79 patients with DM who were undergoing medical treatment at the Graduate School of Biomedical Sciences, Nagasaki University, from September 1999 to August 2010, and were stored at −20°C until use. Most of the sera samples were obtained at the first visit so the interval from initiation of therapy was minimal. We collected the data from all of the DM patients examined in our department. Twenty-one patients did not fulfill Bohan and Peter's criteria [12, 13] but fulfilled Sontheimer's criteria (CADM) [14, 15] because of the absence of clinical skeletal muscle symptoms and the presence of persistent clinical DM skin features. Clinical manifestations, laboratory data, radiographic data and the presence of internal malignancies were extracted from medical records and verified by T.K., N.I. and K.F. The patients were diagnosed with ILD according to the results of chest X-ray and high-resolution chest CT, reported by Japanese board-certified radiologists. All of the subjects underwent routine examination of internal malignancies and chest radiography. A subset of patients with RPILD was defined as those presenting with progressive dyspnoea and progressive hypoxaemia, and a worsening of interstitial change on chest radiography within 1 month from the onset of respiratory symptoms, as described previously [2]. A signed consent form to participate in the study, which was approved by the Institutional Review Board of Nagasaki University, was obtained from each patient.

Immunoprecipitation and ELISA

MSAs, including anti-CADM-140 Abs, anti-ARS Abs and anti-155/140 Abs, were detected by immunoprecipitation assays using extracts of leukaemia cell line K562, as described previously [3]. Interpretation of the results of immunoprecipitation was undertaken without knowledge of patients' clinical status. An ELISA system using recombinant MDA5 as an antigen source was performed as described previously [10]. All samples were examined in duplicate, and the Ab units were calculated from the optical density at 450 nm, using a standard curve obtained from serial concentrations of a serum sample containing a high titre of anti-CADM-140 Abs. The cut-off level was set at 8.0 U, based on 10 S.D. above the mean value obtained from 32 healthy control sera. Interpretation of the results of ELISA was undertaken without knowledge of the clinical status of the patients and the results of immunoprecipitation assays.

Statistical analysis

Fisher's exact probability test and the Mann–Whitney U-test were used to compare the differences. We also examined the cumulative survival rates from the first visit to the hospital with DM-related symptoms up to 5 years by the multivariate Cox proportional hazard model adjusted for patient age at symptoms onset, gender, with or without CSs and with or without immunosuppressants. A $P < 0.05$ was considered significant.

Results

Clinical characteristics of anti-MDA5 Ab$^+$ patients

Table 1 summarizes the 17 DM patients with anti-MDA5 Ab and the 62 DM patients without anti-MDA5 Ab. There were 21 patients with CADM in the present study and we have found that anti-MDA5 Ab is detected in 14 of 21 patients. In this group, 11 of 14 (79%) patients had complicated RPILD and 7 (50%) patients died. Our present data confirm the recent publications regarding the characteristics of anti-MDA5 Ab$^+$ patients, including the CADM, RPILD, low CK, high ferritin and high mortality found in these patients [11]. Since anti-MDA5 Ab is mostly attributed to anti-CADM-140 Abs, a high prevalence of palmar papules and mediastinal emphysema, which has been reported as typical of anti-CADM-140 Abs$^+$ DM patients by our group [7], was also preferentially found in anti-MDA5 Ab$^+$ patients. The present finding that skin ulcers are highly prevalent in anti-MDA5 Ab$^+$ patients is new, however. Muscle biopsy or lung biopsy was not performed. Skin biopsies were taken from eight patients positive for anti-MDA5 Abs, and six patients were

Table 1 Comparison of clinical manifestations between patients with anti-MDA5 Ab and patients without anti-MDA5 Ab

Variable	Anti-MDA5 Ab		*P*-value
	Positive ($n = 17$)	Negative ($n = 62$)	
Age at onset, years	55.5 (13.0)	55.3 (15.0)	0.27
Female, *n* (%)	15 (88)	37 (60)	0.056
Skeletal muscle and skin features			
Muscle weakness, *n* (%)	4 (24)	38 (62)	**0.005**
Gottron's sign, *n* (%)	13 (76)	32 (52)	0.07
Ulcer region, *n* (%)	10 (59)	7 (12)	**0.00007**
Heliotrope rash, *n* (%)	8 (47)	23 (39)	0.56
Palmar papules, *n* (%)	11 (65)	13 (22)	**0.0014**
Periungual erythema, *n* (%)	10 (59)	24 (41)	0.2
Clinical diagnosis			
CADM, *n* (%)	14 (82)	7 (11)	$\mathbf{4.2 \times 10^{-9}}$
Pulmonary involvement and malignancy			
ILD, *n* (%)	16 (94)	37 (61)	**0.008**
RPILD, *n* (%)	12 (71)	4 (7)	$\mathbf{9.8 \times 10^{-9}}$
Mediastinal emphysema, *n* (%)	6 (35)	1 (2)	$\mathbf{2.1 \times 10^{-5}}$
Malignancies, *n* (%)	0 (0)	6 (10)	0.17
Laboratory data			
CPK, IU/l	173 (53–468)	905 (107–1607)	**0.00024**
KL-6, U/ml	1361 (825–1903)	1040 (345–1510)	0.36
Ferritin, ng/ml	1365 (894–1751)	180 (90–244)	**0.016**
Therapy			
Maximum PSL, mg/day	40 (35–50)	40 (22.5–50)	0.99
Immunosuppressant, *n* (%)	16 (94)	29 (47)	0.17
Outcome			
Death, *n* (%)	7 (41)	3 (5)	$\mathbf{6.6 \times 10^{-6}}$
MSA profile			
Anti-140 Ab positive, *n* (%)	16 (94)	0 (0)	$\mathbf{3.76 \times 10^{-15}}$
Anti-155/140 Ab positive, *n* (%)	0 (0)	7 (11)	0.35
Anti-ARS Ab positive, *n* (%)	0 (0)	30 (48)	**0.002**
Autoantibody negative	1 (6)	25 (40)	**0.005**
Anti-MDA5 Ab titre	230 (22–448)	1.3 (1.1–1.9)	$\mathbf{1.62 \times 10^{-10}}$

Ages are presented as mean (S.D.) values, while laboratory markers are medians (interquartile range). *P*-values were established using Fisher's exact test or the Mann–Whitney U-test. Bold indicates significant values. CPK: creatinine phosphokinase; PSL: prednisolone.

diagnosed pathologically with dermatitis consistent with DM. One patient revealed only mild mucin deposition, and another revealed only hyperpigmentation. A potential limitation of the present study is the fact that biopsies were taken from only a small number of patients. EMG was performed in one anti-MDA5 Ab$^+$ patient, revealing myogenic conversion consistent with myositis. Only one patient was found to have preceding ILDs among anti-MDA5 Ab$^+$ patients. Skin manifestations preceded ILDs in the other patients. We showed the typical images about mediastinal emphysema, palmar pustule and regional ulcers in anti-MDA5 Ab$^+$ patients with CADM (Fig. 1). In the frequency of cancer, anti-MDA5 Ab$^+$ patients have no malignancy (0/17), whereas 6 of 62 (10%) patients in anti-MDA5 Ab$^-$ group were complicated malignancies. Anti-155/140 Abs were found in all six patients with cancer. We confirmed the profile of autoantibodies regarding the presence or absence of anti-MDA 5 Ab: namely, all DM patients positive for anti-ARS Abs, anti-155/140 Abs and other types of autoantibodies were among the anti-MDA5 Ab$^-$ group. There was no overlap between anti-MDA5 Ab and any other types of autoantibodies. Immunoprecipitation of anti-CADM-140 Abs from patients with anti-MDA5 Ab is shown in Fig. 2.

Survival rate of anti-MDA5$^+$ patients

Ten (12%) patients died within 5 years from the first treatment. The cumulative 6-month survival rates were 57.4 and 98.4% for DM with anti-MDA5 Ab and those without anti-MDA5 Ab, respectively (Fig. 3). The survival rates from the first visit to our hospital after adjusting for age, gender, with or without CSs and with or without immunosuppresants were significantly different between each subset ($P = 0.0151$). The first visit to our hospital was almost identical to the diagnosis of each patient. The presence of anti-MDA5 Ab was independently associated with mortality (relative hazard 6.33; 95% CI 1.43, 28.0) in a multivariable Cox regression model that included patient age at onset, gender, with or without CSs and with or without immunosuppresants. We have tried to compare

FIG. 1 Typical clinical manifestations of patients with anti-MDA5 Ab. The palmar pustules (**A**) were mainly located near the MCP and PIP joints (arrows) and multiple ulcer regions (**B**) were also observed. Chest CT scan (**C**) shows mediastinal emphysema in the middle of the chest cavity (arrows).

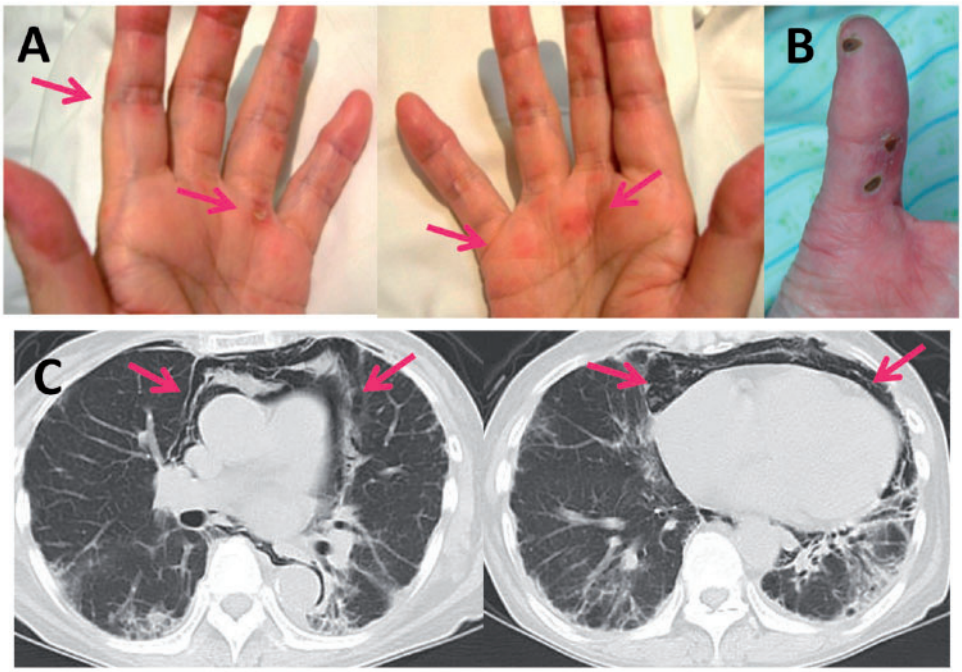
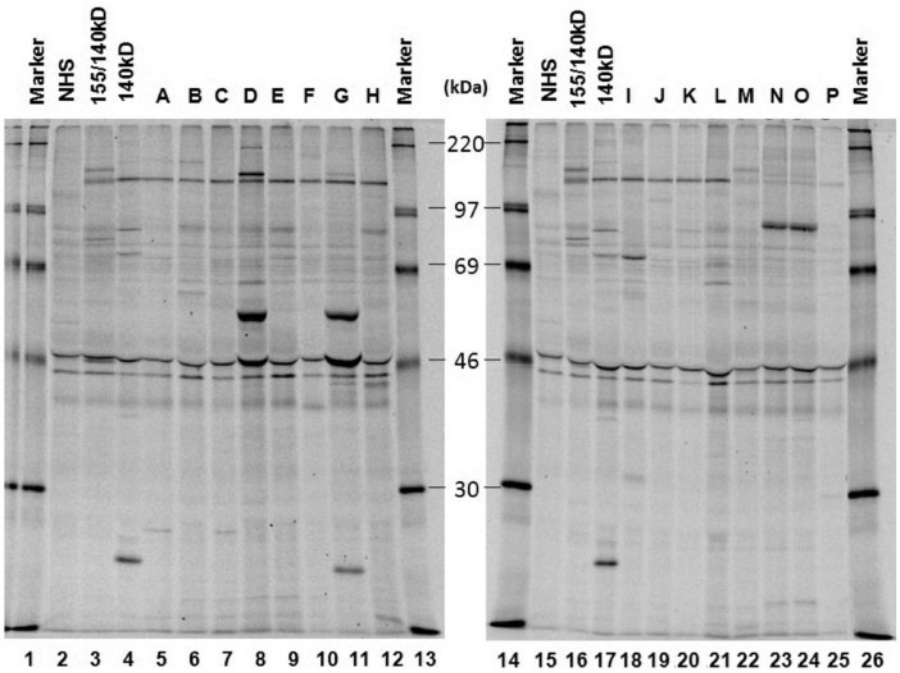
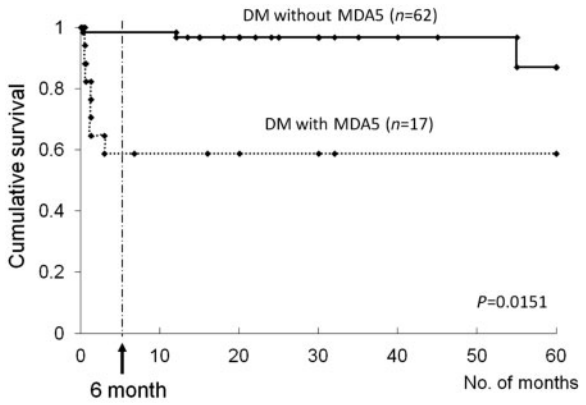


FIG. 2 Immunoprecipitation with anti-CADM-140 Ab from the 35S-labelled K562 cell extract. Lanes 5–12 and 18–25 show the results with anti-CADM-140-positive sera from DM patients with anti-MDA5 Ab$^+$ (A–P). The results of the prototype sera of anti-155/140 Abs and anti-CADM-140 Abs are also shown (lanes 3, 16 and 4, 17, respectively). One sera of an anti-MDA5 Ab$^+$ patient immunoprecipitated not anti-CADM-140 Abs, but anti-U1-RNP Ab, which was deleted from Fig. 2.



the variables within anti-MDA5 Ab$^+$ DM patients who were alive or dead and found that the regime of therapy was not different between two groups although the PaO_2/FiO_2 and serum CPK levels were higher in the former. The value of anti-MDA5 Ab is significantly lower in the former (Table 2). All the deaths in the anti-MDA5 Ab$^+$ patients were attributed to respiratory failure of RPILD. However, importantly, there was no acute exacerbation or progressive worsening of ILD by CT images after initial treatments in any of the anti-MDA5 Ab$^+$ patients. In fact, all of the deaths of anti-MDA5 Ab$^+$ patients occurred within the first 6 months (Fig. 3). In addition, no patient required home oxygen therapy after discharge among anti-MDA5 Ab$^+$ patients who were alive during the first 6 months. We showed a short case presentation describing a patient with CADM positive for anti-MDA5 Ab. A 60-year-old female developed erythemas on the upper eyelids, fingers and elbows in July 2005. Three months later she developed exertional dyspnoea. A CT scan revealed interstitial lung shadow (Fig. 4A). We measured anti-CADM-140 Ab levels and anti-MDA5 Ab levels, which were both positive (anti-140 kDa Abs were detected by immunoprecipitation assay, and the titre of anti-MDA5 Abs was 544.109 U). She has been treated at our outpatient department and is in a stable condition (Fig. 4B).

Fig. 3 The adjusted cumulative survival rates in the presence or absence of anti-MDA5 Ab. The cumulative survival rates from the first visit to the hospital with DM-related symptoms up to 5 years were examined as described in the text. Survival rate of anti-MDA5 Ab$^+$ patients was significantly low compared with that of anti-MDA5 Ab$^-$ patients. $P = 0.0151$, between the two groups.



Discussion

Other Japanese groups recently identified the characteristics of anti-MDA5 Ab$^+$ DM patients [11]. Our present data confirmed their findings. Additionally, we have shown some new characteristics of these patients, such as high frequencies of palmar papules, skin ulcers and mediastinal emphysema, as well as no overlapping of other types of autoantibodies. These data may help physicians to recognize features of anti-MDA5 Ab$^+$ patients among DM patients. Since physicians are urged to start intense immunosuppressive therapy early for anti-MDA5 Ab$^+$ DM patients, this information may be clinically indispensable.

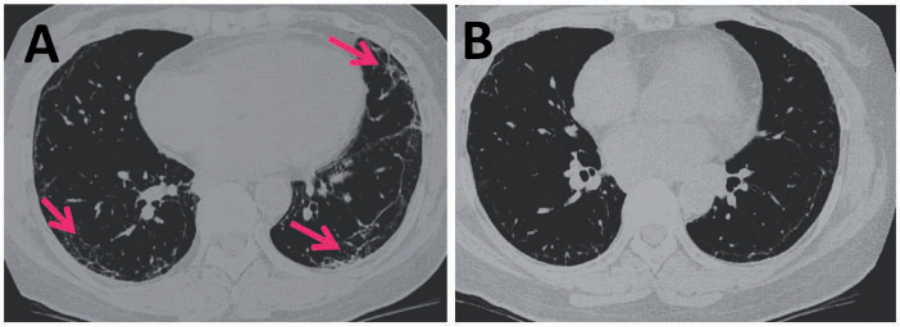
Although the prognosis of anti-MDA5 Ab$^+$ patients was worse than that of anti-MDA5 Ab$^-$ patients, none of the surviving anti-MDA5 Ab$^+$ patients experienced acute exacerbation or progressive worsening of ILD after the initial treatment. This is quite different from anti-MDA5 Ab$^-$ patients, since ILD recurred in several of these patients and death ensued during long-term follow-up (Fig. 3). One of the characteristics of anti-MDA5 Ab$^+$ patients is hyperferritinaemia [11, 16]. There are many

Table 2 Comparison of clinical parameters between alive and dead anti-MDA5 Ab$^+$ patients

Variable	Anti-MDA5 Ab positive ($n = 17$)		*P*-value
	Alive ($n = 10$)	Dead ($n = 7$)	
Age at onset, years	52 (42–58.5)	59 (53–70)	0.051
Female, *n* (%)	9 (90)	6 (86)	1.00
Ulcer region, *n* (%)	5 (50)	5 (71)	0.70
Palmar papules, *n* (%)	7 (70)	5 (71)	1.00
CPK, IU/l	208 (90.3–864)	169 (33.5–359)	**0.014**
Anti-MDA5 Ab titre	168 (16.3–436)	230 (76.0–478)	**0.032**
PaO_2/FiO_2 before treatment, mmHg	395 (370–462)	203 (114–240)	**0.027**
Therapy			
Steroid pulse therapy, *n* (%)	5 (50)	7 (100)	0.09
CYC, *n* (%)	4 (40)	4 (57)	0.84
Oral calcinurin inhibitor, *n* (%)	6 (60)	7 (100)	0.18
I.V. calcinurin inhibitor, *n* (%)	1 (10)	3 (43)	0.32

Ages are presented as mean (S.D.) values, while laboratory markers are medians (interquartile range). *P*-values were established using Fisher's exact test or the Mann–Whitney U-test. Bold indicates significant values. PaO_2: partial pressure of arterial oxygen; FiO_2: fractional inspired oxygen concentration.

FIG. 4 A chest CT scan before and after treatment. A reticular shadow was revealed in the lower lung field (**A**) and it improved 4 years after disease onset (**B**). Arrows indicate the region that improved with treatment.



reports evaluating hyperferritinaemia in patients with autoimmune diseases [17]. The highest ferritin levels in autoimmune disorders are typically seen in patients with macrophage activation syndrome (MAS), often associated with adult-onset Still's disease (AOSD) [18]. It is well known that many viruses produce double-stranded (ds) RNA that can be recognized by two major arms of the innate immune system: the toll-like receptors (TLRs) and the Rig-I-like receptors (RLRs). MDA5 is a member of the RLR family that recognizes dsRNA within the cytosolic compartment and induces the production of inflammatory cytokines and cell surface molecules involved in the anti-viral response [19]. Considering that MAS could be induced by various infectious agents [20], and given the critical role of MDA5 in innate immune defence against viruses, one hypothesis is that the production of anti-MDA5 Ab is an epiphenomenon during virus infection that is associated with the onset of CADM and RPILD; namely, infection of the skin and lung epithelium by certain viruses. In general, innate immune responses do not recur; therefore we have not found exacerbation of ILD during the follow-up periods of anti-MDA5 Ab^+ DM patients.

Most patients with ILD-complicated DM appear to be well controlled by CSs and immunosuppressants [21]. In contrast, patients with RPILD observed in DM were resistant to a variety of treatments [22, 23]. We have introduced CSs, cyclophosphamide and calcineurin inhibitor to anti-MDA5 Ab^+ patients with RPILD. We could not find any significant difference in therapy between alive and dead patients. PaO_2/FiO_2, serum CPK level and the value of anti-MDA5 Ab before treatment were prognostic factors. We showed the significance of the duration of preceding symptoms in patients positive for anti-MDA5 Abs. Although we do not have any definitive evidence, shorter duration of preceding symptoms to treatment could lead to better outcomes (supplementary Table 1, available as supplementary data at *Rheumatology* Online). Thus it is recommended that anti-MDA5 Ab^+ patients who have typical CADM with signs of ILD be treated promptly with the combination of CSs, cyclophosphamide and calcineurin inhibitor.

In conclusion, the measurement of anti-MDA5 Ab by ELISA enables us to predict the prognosis of patients with CADM-complicated fatal RPILD. The characteristics of anti-MDA5 Ab^+ DM patients could be explained by the nature of MDA5 in innate immune responses to viruses. A multicentre, prospective study is warranted to confirm our results.

Rheumatology key messages

- Anti-MDA5 Ab is associated with characteristic pulmonary and skin involvement in patients with DM.
- Anti-MDA5 Ab predicts patients with CADM complicated by RPILD.

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Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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