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Original article

Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis

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Abstract

Objective. The aim of this study was to investigate the precise clinical characteristics and to analyse the association between the anti-MDA5 antibody (anti-MDA5ab) titre and disease status in patients with anti-MDA5ab-positive DM.

Methods. Twenty-seven patients who presented with DM and were positive for the anti-MDA5ab were enrolled. The association between the clinical manifestations and the clinical parameters, including the anti-MDA5ab, was analysed.

Results. The complication of rapidly progressive interstitial lung disease (RP-ILD) occurred in 20 (74%) patients. The frequencies of fatal outcome, relapse and malignancy were 33, 4 and 4%, respectively. Remarkably, a fatal outcome occurred within the first 6 months. Compared with six non-RP-ILD patients, elderly age at onset, severely involved pulmonary function and high levels of serum ferritin were present in 20 RP-ILD patients with anti-MDA5ab. Alveolar–arterial oxygen difference ($AaDO_2$) $\geqslant$32 mmHg and ferritin $\geqslant$828 ng/ml at admission were poor prognostic factors in RP-ILD patients with anti-MDA5ab-positive DM. The median value of the anti-MDA5ab titre on admission was higher in patients who later died than in those who survived. The efficacy of treatment was indicated by the anti-MDA5ab, ferritin and IL-18 concentrations. The decline index of the anti-MDA5ab titre after treatment was lower in the subset of patients who died than in the subset of patients who lived. Sustained high levels of anti-MDA5ab, ferritin and IL-18 were present in the patients who died.

Conclusion. Anti-MDA5ab titre and ferritin and IL-18 concentrations are useful for the evaluation of the response to treatment and the status of ILD in patients with anti-MAD5ab-positive DM.

Key words: dermatomyositis, interstitial lung disease, anti-MDA5 antibody, ferritin, interleukin-18.

Introduction

DM is characterized by inflammation of the skin and muscles [1]. Rapidly progressive interstitial lung disease (RP-ILD) in particular is of prime importance in the clinical management of patients with DM because it is an intractable and life-threatening complication [2–5]. Clinically amyopathic DM (CADM) includes typical skin lesions with amyopathy or hypomyopathy [6]. CADM patients with the anti-MDA5 antibody (anti-MDA5ab) frequently develop the complication of RP-ILD, especially in Japan [7–10]. Sato *et al*. [7] identified melanoma differentiation-associated gene 5 (MDA5) as the CADM-140 antigen. The MDA5 protein plays a role in the innate immune response. MDA5 initially recognizes picornaviruses and evokes antiviral responses by eliciting the production of type I IFNs

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BASIC SCIENCE

and TNF-α [11]. We previously reported that high levels of ferritin are associated with the development and prognosis of RP-ILD with DM [9, 12]. In addition, IL-18 is a potential contributor to ILD with DM [13]. High levels of ferritin and IL-18 are also implicated in macrophage activation syndrome (MAS) [14, 15]. Although a cytokine storm may contribute to the pathogenesis of RP-ILD with anti-MDA5ab-positive DM, especially in the skin and lungs, the precise pathogenesis remains unknown. Moreover, long-term prognosis, frequency of recurrence, complication with malignancy and the association between the anti-MDA5ab titre and the clinical course remain unclear in anti-MDA5ab-positive DM.

Thus we investigated the clinical characteristics and the correlation between the anti-MDA5ab titre and clinical parameters, such as ferritin and IL-18 levels, in patients with anti-MDA5ab-positive DM. In addition, we analysed the association between the anti-MDA5ab titre and the clinical course in these patients.

Patients and methods

Patients

The present retrospective study included patients with idiopathic inflammatory myopathy who were admitted to the Tokyo Women's Medical University Aoyama Hospital or Keio University Hospital from August 1992 to December 2009. All of the enrolled patients suffered from skin rash, myopathy or respiratory symptoms (or a combination thereof) at admission. These patients were diagnosed with DM or CADM based on the criteria of Bohan and Peter [16] or Sontheimer [17], respectively. In general, CADM presents with typical skin lesions and either amyopathy or hypomyopathy for >6 months. A subset of the CADM group included patients who developed fatal ILD within the first 6 months of this study. Medical records were obtained from 142 and 53 patients who were diagnosed with DM and CADM, respectively. In the present study, 5 DM patients and 22 CADM patients who were positive for the anti-MDA5ab were enrolled. The frequencies of anti-MDA5ab positivity were 4 and 42% in the DM patients and in the CADM patients, respectively. Clinical data were obtained from medical records on admission. The study was approved by the ethical committee of the Institute of Rheumatology, Tokyo Women's Medical University, and the study complied with the Declaration of Helsinki guidelines. Disease duration was defined as the time between the appearance of symptoms, such as skin rash, myopathy or respiratory symptoms, and the initiation of treatment.

Evaluation of clinical laboratory parameters and the anti-MDA5ab

Blood tests evaluated creatine kinase (CK), lactate dehydrogenase (LD), KL-6, CRP, ferritin and ANA. Serum IL-18 was measured with an ELISA (R&D Systems, Minneapolis, MN, USA). The median level (range) of IL-18 was 50.5 (18–121) pg/ml in 30 healthy controls. Anti-MDA5ab was detected with an ELISA using recombinant MDA-5 as an antigen, as described previously [7]. The normal value for the anti-MDA5ab titre was ⩽8 U/ml.

Evaluation of pulmonary function and classification of ILD

The PaO_2/F_iO_2 (P/F ratio), pulse oximeter oxygen saturation/FiO_2 (S/F ratio), alveolar–arterial oxygen difference ($AaDO_2$), forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio, VC percentage (%VC) and diffusing capacity of the lung for carbon monoxide (DLco) were used to evaluate pulmonary function. The normal values are defined as >380 for the P/F ratio, >450 for the S/F ratio, <10 mmHg for $AaDO_2$, >70% for the FEV1/FVC ratio, >80% for %VC and >20 ml/min/mmHg for the DLco. The ILD was assessed with chest radiography and CT or high-resolution CT of the chest. RP-ILD is defined as a progressive ILD within 3 months of the onset of respiratory symptoms. Chronic ILD is defined as an asymptomatic, non-rapidly progressive ILD or slowly progressive ILD over 3 months by the International Consensus Statement of Idiopathic Pulmonary Fibrosis of the American Thoracic Society and the European Respiratory Society [18].

Statistical analysis

Statistical analyses were performed using the Student's *t*-test to compare mean values, the Mann–Whitney U-test to compare median values and Fisher's exact test to compare frequencies. Correlation coefficients were established by employing Spearman's correlation coefficients. The cumulative survival rate was calculated using the Kaplan–Meier test. The Wilcoxon signed-rank test was performed when comparing clinical parameters upon admission with those parameters after treatment in each patient. The data were analysed using JMP® software (SAS Institute, Cary, NC, USA). A value of $P < 0.05$ indicated statistical significance.

Results

Clinical characteristics in patients with anti-MDA5ab-positive DM

The clinical characteristics of 27 patients with anti-MDA5ab-positive DM are shown in Table 1. The laboratory data were obtained at the first examination upon admission. The frequency of CADM was 81%. The median value of CK was 92 IU/l (interquartile range: 67–271). The complication of RP-ILD was present in 20 (74%) patients. Six additional patients had the complication of chronic ILD, and one patient had neither complication. Although the values of FEV1/FVC ratio and %VC were normal in almost all patients, the DLco levels were decreased. The median values of KL-6, CRP, ferritin and IL-18 were high. ANA positivity was found in four patients (homogeneous and speckled pattern in two patients, homogeneous pattern in one patient and nucleolar pattern in one patient). In 9 of the other 23 patients without ANA positivity, a cytoplasmic pattern was revealed. The frequencies of the fatal

Table 1 Clinical characteristics of patients with anti-MDA5ab-positive DM ($n = 27$)

Characteristic	Value
Age, years	48 (13)
Female, *n* (%)	20 (74)
Disease duration, weeks	6 (3–8)
CADM, *n* (%)	22 (81)
RP-ILD, *n* (%)	20 (74)
P/F ratio	348 (324–438)
$AaDO_2$, mmHg	26.2 (10.2–41.5)
FEV1/FVC ratio ($n = 18$)	82 (78–89)
%VC ($n = 22$)	76 (71–84)
DLco, ml/min/mmHg ($n = 9$)	10 (9.1–13.6)
LD, IU/l	382 (253–512)
KL-6, U/ml (normal value $\leqslant$ 500) ($n = 23$)	735 (570–985)
CRP, mg/dl	0.63 (0.13–1.37)
Ferritin, ng/ml	642 (217–1120)
IL-18, pg/ml (normal range 18–121) ($n = 21$)	550 (328–746)
ANA $\geqslant 160\times$, *n* (%)	4 (15)
Fatal outcome, *n* (%)	9 (33)
Relapse, *n* (%)	1 (4)
Malignancy, *n* (%)	1 (4)

The values of age indicate the mean (S.D.), and the laboratory markers and pulmonary function tests are presented as the median (interquartile range).

outcome, relapse and malignancy were 33, 4 and 4%, respectively.

Comparison of clinical manifestations between patients with anti-MDA5ab-positive DM with and without RP-ILD

Clinical manifestations were compared between patients who had anti-MDA5ab-positive DM with and without RP-ILD (Table 2). The following information indicates the significant results for the patients with RP-ILD: elderly age at onset ($P = 0.0021$), decreased P/F ratio ($P = 0.0079$), increased $AaDO_2$ ($P = 0.0031$), increased ferritin ($P = 0.036$) and high frequency of fatal outcome ($P = 0.036$). The median values of %VC and DLco were lower in patients with RP-ILD than in those without RP-ILD, although the difference was not statistically significant. The ferritin level was significantly higher in the patients with RP-ILD. The frequency of fatal outcome was high: 45% in the patients with RP-ILD. The cut-off value as a predictor for RP-ILD was estimated by a receiver operating characteristic (ROC) curve of age at onset, P/F ratio, $AaDO_2$ and ferritin. The following parameters can be used as cut-off values (odds ratio, *P*-value): age $\geqslant 46$ years (14, 0.011), P/F ratio <438 torr (23, 0.0047), Aa $DO_2 \geqslant 22$ mmHg (34, 0.0017) and ferritin $\geqslant 217$ ng/ml (48, 0.0014).

No association between anti-MDA5ab titre and clinical parameters

Correlation coefficients between the anti-MDA5ab titre and clinical parameters were established in patients with anti-MDA5ab-positive DM. The clinical parameters included $AaDO_2$, %VC and laboratory markers (KL-6, CRP, ferritin and IL-18). All of these clinical parameters were obtained from 18 patients at the first examination upon admission. There was no significant correlation between anti-MDA5ab titre and other clinical parameters. Significant correlations were only found between $AaDO_2$ and ferritin ($r_s = 0.47$, $P = 0.014$) in patients with anti-MDA5ab-positive DM.

Comparison of clinical manifestations in living patients and patients who died with RP-ILD with anti-MDA5ab-positive DM

We analysed the clinical manifestations of the patients who had anti-MDA5ab-positive DM and died, and compared them with the manifestations of the surviving anti-MDA5ab-positive DM patients with RP-ILD (Table 3). The P/F ratio and $AaDO_2$ on admission were significantly worse and the ferritin levels were significantly higher ($P = 0.017$) in the patients who died. The median anti-MDA5ab titre was higher, although not significantly ($P = 0.099$), in patients who died than in those who survived. RP-ILD was refractory and progressive in the patients who died, although almost all of these patients received combination therapy, including prednisolone (PSL), i.v. CYC therapy (IVCY) and calcineurin inhibitor (CNI). The cut-off values as a predictor of fatal outcome in RP-ILD were estimated by the ROC curve of the P/F ratio, $AaDO_2$ and ferritin and are as follows (odds ratio, *P*-value): P/F ratio <324 torr (9.3, 0.035), Aa $DO_2 \geqslant 32$ mmHg (9.3, 0.035) and ferritin $\geqslant 828$ ng/ml (14, 0.025).

Survival rates of patients with anti-MDA5ab-positive DM

The cumulative 100-month survival rate was 66% for the entire anti-MDA5ab-positive DM patient group (Fig. 1A). Fatal outcome occurred remarkably often within the first 6 months. The median survival duration was 2 months in the nine patients who died. In contrast, the median survival duration was 29 months in the 18 surviving patients. Next, the patients with anti-MDA5ab-positive DM were divided into an RP-ILD subset and a non-RP-ILD subset. As shown in Fig. 1B, the cumulative 100-month survival rates were significantly lower in the RP-ILD subset than in the non-RP-ILD subset (log-rank test, $P = 0.039$).

Association between the anti-MDA5ab titre and the clinical course in patients with anti-MDA5ab-positive DM

We investigated the association between the clinical parameters and the clinical course. Clinical parameters included the anti-MDA5ab titre, the S/F ratio, KL-6, ferritin and IL-18 concentrations. Seventeen patients with anti-MDA5ab-positive DM, including 15 patients with RP-ILD and 2 patients with chronic ILD, were enrolled. Eleven patients were categorized as the living subset and the remaining six patients formed the dead subset. All six patients in the dead subset had the complication of

Table 2 Comparison of the clinical manifestations between patients with anti-MDA5ab-positive DM with and without RP-ILD

Variable	RP-ILD (−) ($n = 7$)	RP-ILD (+) ($n = 20$)	*P*
Age, years	35 (4)	52 (2)	0.0021
Female, *n* (%)	6 (86)	14 (70)	0.63
Disease duration, weeks	8 (6–16)	4 (2–8)	0.098
CADM, *n* (%)	6 (86)	16 (80)	1
CK, IU/l	165 (84–271)	85 (47–345)	0.36
LD, IU/l	472 (221–643)	373 (267–500)	0.51
P/F ratio	448 (348–522)	339 (308–388)	0.0079
$AaDO_2$, mmHg	4 (0–18)	30 (24–54)	0.0031
%VC	82 (74–98) ($n = 6$)	76 (67–82) ($n = 16$)	0.21
DLco, ml/min/mmHg	14.7 (12.5–16.9) ($n = 2$)	9.6 (8.9–12.7) ($n = 7$)	–
KL-6, U/ml (normal value $\leqslant 500$)	346 (278–1104) ($n = 5$)	801 (675–1009) ($n = 18$)	0.1
CRP, mg/dl	0.46 (0.02–0.80)	0.72 (0.15–1.85)	0.22
Ferritin, ng/ml	186 (120–626)	835 (285–1480)	0.036
IL-18, pg/ml (normal range 18–121)	550 (216–736) ($n = 5$)	552 (243–765) ($n = 16$)	0.65
Anti-MDA5ab, U/ml	258.8 (217.1–542.7)	152.3 (56.7–376.8)	0.21
Fatal outcome, *n* (%)	0 (0)	9 (45)	0.036

The values of age indicate the mean (S.D.), and laboratory markers and pulmonary function tests are presented as the median (interquartile range).

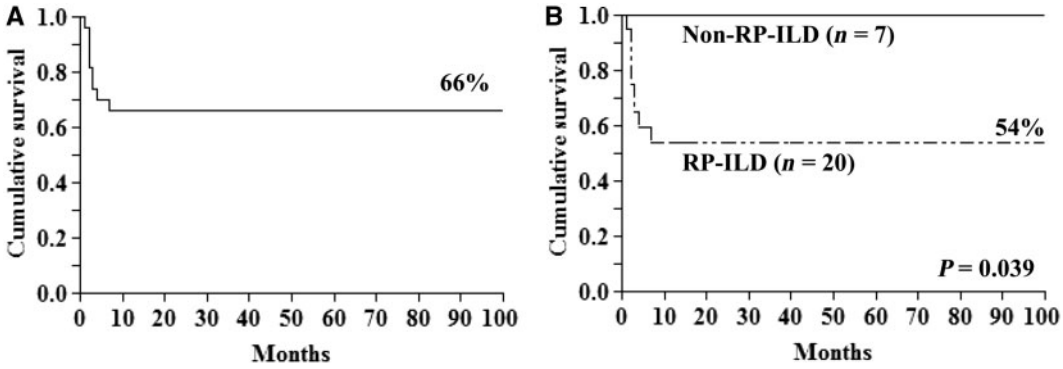
Table 3 Comparison of the clinical manifestations between living patients (alive) and patients who died (dead) with RP-ILD and anti-MDA5ab-positive DM upon admission

Variable	Alive ($n = 11$)	Dead ($n = 9$)	*P*
Age, years	50 (3)	54 (3)	0.29
Female, *n* (%)	9 (82)	5 (56)	0.34
Disease duration, weeks	8 (2–12)	4 (3–7)	0.76
CADM, *n* (%)	9 (82)	7 (78)	1
CK, IU/l	95 (38–383)	77 (62–324)	0.91
P/F ratio	369 (331–403)	319 (246–352)	0.03
$AaDO_2$, mmHg	26 (22–34)	41 (30–102)	0.044
%VC	76 (71–90) ($n = 10$)	71 (62–78) ($n = 6$)	0.25
DLco, ml/min/mmHg	9.5 (7.8–13.2) ($n = 4$)	10 (8.9–12.7) ($n = 3$)	–
LD, IU/l	364 (243–488)	460 (308–518)	0.3
KL-6, U/ml (normal value $\leqslant 500$)	842 (678–1009) ($n = 10$)	731 (602–1099) ($n = 8$)	0.59
CRP, mg/dl	0.63 (0.10–1.96)	1.06 (0.17–2.16)	0.7
Ferritin, ng/ml	409 (248–843)	1600 (835–1935)	0.017
IL-18, pg/ml (normal range 18–121)	503 (343–727) ($n = 10$)	540 (338–798) ($n = 7$)	0.70
Anti-MDA5ab, U/ml	129.3 (44.6–254.0)	332.1 (92.0–599.8)	0.099
Treatment			
PSL + IVCY + CNI	5 (46)	7 (78)	0.2
PSL ± IVCY or CNI	6 (54)	2 (22)	
Improvement of ILD	11 (100)	0 (0)	<0.0001

The age values are presented as the mean (S.D.), and laboratory markers and pulmonary function tests are presented as the median (interquartile range).

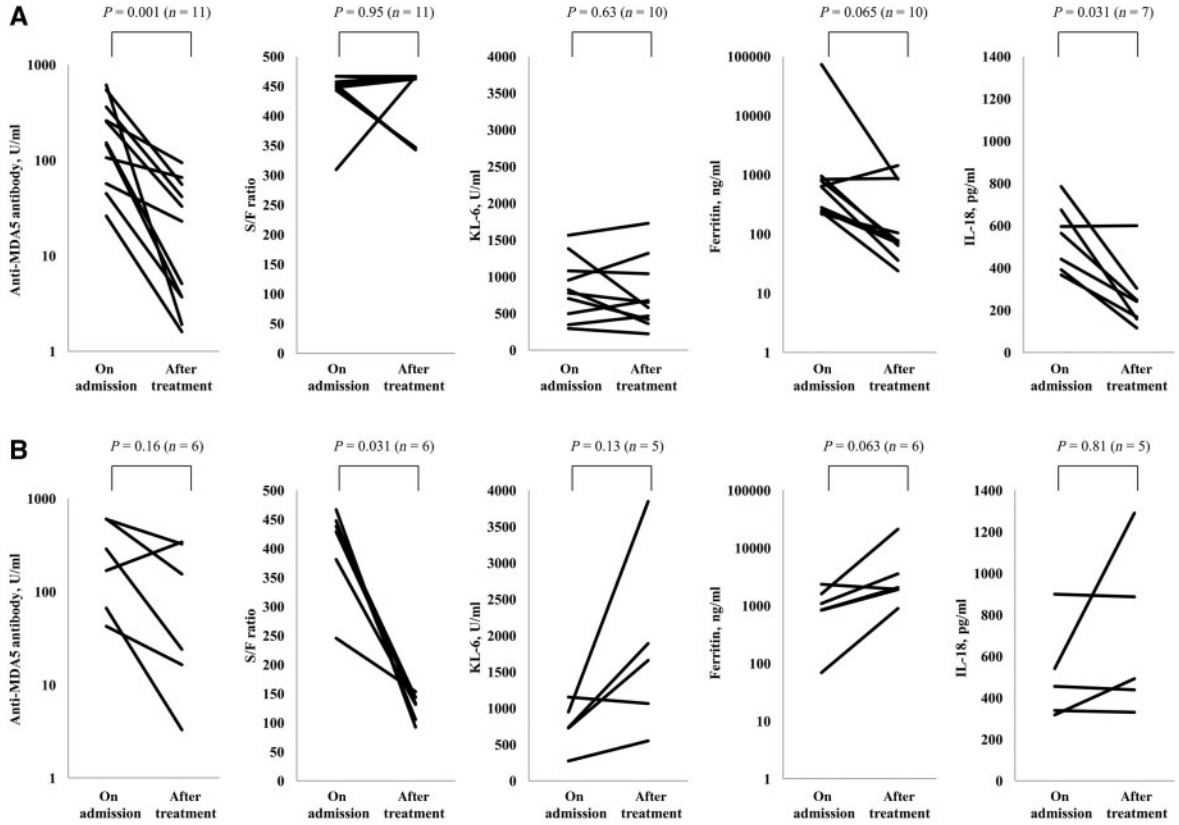
refractory RP-ILD and died within 6 months of treatment because of respiratory failure resulting from RP-ILD. We compared the clinical parameters upon admission with the parameters after treatment in each subset (Fig. 2). The median duration of evaluation after treatment was 3 months in the living subset and 2 months in the dead subset. There was no significant difference ($P = 0.21$) between the two subsets in terms of the duration of evaluation after treatment. The data for each clinical parameter could only be partially obtained in some patients. The number of patients for whom data were obtained is indicated in each figure panel.

FIG. 1 Cumulative 100-month survival rates for all patients with anti-MDA5ab-positive DM (**A**), and the RP-ILD and non-RP-ILD subsets of anti-MDA5ab-positive DM patients (**B**).



The cumulative 100-month survival rates were calculated using the Kaplan–Meier test. The log-rank test was also used to compare survival rates. Survival rates and *P*-values are indicated in each figure panel.

FIG. 2 Comparison between clinical parameters upon admission and after treatment in patients with anti-MDA5ab-positive DM.



Based on patient survival, we analysed clinical parameters in two subsets: the living subset and the dead subset (**A** and **B**). The number of patients for whom data were obtained is indicated in each figure panel. Statistical analyses were performed with the Wilcoxon signed-rank test for comparisons of median values.

Anti-MDA5ab titre was significantly lower ($P = 0.001$) after treatment than on admission in the living subset (Fig. 2A). Anti-MDA5ab disappeared after treatment in 5 (45%) of the 11 living patients. On the other hand, there was no statistically significant difference ($P = 0.16$) in the dead subset between the anti-MDA5ab titre upon admission compared with the antibody titre after treatment (Fig. 2B). Anti-MDA5ab was still present after treatment in all dead patients except one. Moreover, the decline index of the anti-MDA5ab titre after treatment was analysed and compared among each subset. The decline index of the anti-MDA5ab was calculated as follows: (the antibody titre after treatment—the antibody titre upon admission) $\times$ 100/(the antibody titre upon admission). The median decline indices of the anti-MDA5ab titre (interquartile range) were 90% (63–97%) and 68% (9–92%) in the living and dead subsets, respectively.

In the dead subset, the S/F ratio was significantly lower after treatment ($P = 0.031$). The levels of KL-6 tended to decrease in the living subset and increase in the dead subset. On the other hand, the levels of ferritin more sensitively reflected the response to treatment than the levels of KL-6. The median values of ferritin after treatment were 76 ng/ml and 1987 ng/ml in the living and dead subsets, respectively ($P = 0.0017$). Moreover, the levels of IL-18 were significantly lower ($P = 0.031$) after treatment in the living subset. In the dead subset, the levels of IL-18 were not significantly lower after treatment.

Discussion

We have measured the clinical characteristics of disease and have demonstrated an association between clinical parameters and clinical course in patients with anti-MDA5ab-positive DM. The clinical manifestations of anti-MDA5ab-positive DM have been reported, mainly in Japanese studies [7–10]. Two different subsets of ILD with CADM patients are those with RP-ILD or with chronic ILD [19]. Fathi *et al*. [20] have reported that patients with inflammatory myopathy with ILD require careful evaluation of their clinical features because the course of ILD cannot be predicted at the first examination. However, we determined that investigation of both the anti-MDA5ab and the serum ferritin concentration are useful for predicting the onset of RP-ILD in DM [7, 21]. On the other hand, the serum ferritin level was <500 ng/ml in some patients with DM-associated RP-ILD [12]. These patients with RP-ILD were occasionally positive for the anti-aminoacyl-tRNA synthetase antibody and appeared to be well controlled with CSs and immunosuppressant agents compared with patients with DM-associated RP-ILD having anti-MDA5ab and/or hyperferritinaemia. This distinction in response to treatments might be responsible for the cellular phenotypes affecting the pathogenesis of ILD. Taken together, if the serum ferritin level is high in patients with DM, it should be considered that these patients may have anti-MDA5ab, and their clinical course may be complicated by RP-ILD.

CADM with RP-ILD showed a rapidly progressive pattern with a 6-month survival rate of 40.8–45%, which corresponded to the results in our study [22, 23]. In our study, $AaDO_2$ levels $\geqslant 32$ mmHg and ferritin levels $\geqslant 828$ ng/ml on admission were poor prognosis factors for RP-ILD with anti-MDA5ab-positive DM. The median anti-MDA5ab titre on admission was higher in the patients who died than in the living patients, although the difference between the two subsets was not statistically significant. However, the median anti-MDA5ab titre on admission was higher in the patients without RP-ILD than in those with RP-ILD. The anti-MDA5ab titre before treatment was not predictive of the prognosis of RP-ILD in anti-MDA5ab-positive DM. Measuring levels of serum ferritin and $AaDO_2$ before treatment is useful for predicting the prognosis of RP-ILD in DM.

We analysed the association between the anti-MDA5ab titre and the clinical course. We confirmed that the anti-MDA5ab titre has disappeared in improving surviving patients in our longitudinal observation (data not shown). Relapse has not occurred in any of the improving surviving patients except one. In the future we will investigate whether the anti-MDA5ab titre is increased again in either a pulmonary flare or skin exacerbation. Moreover, we have analysed several patients, in whom the serum ferritin level and IL-18 level were high, and were correlated with the clinical course in patients with RP-ILD with DM [24]. Immunosuppressive therapy had some effect on clinical parameters such as cytokines and antibodies regardless of clinical course. In the present study, however, immunosuppressive therapy was received more intensively in the dead subset than in the living subset of patients with anti-MDA5ab-positive DM. The frequency of receiving PSL + CNI + IVCY was higher in the dead subset than in the living subset. Moreover, there was no significant difference between the two subsets in terms of the duration of evaluation after treatment. Taken together, the sustained high levels of anti-MDA5ab, ferritin and IL-18 could be attributed to the poor response to treatment in the dead subset. Investigations of the anti-MDA5ab titre, ferritin level and IL-18 level after treatment are useful for predicting the clinical course and evaluating the response to treatment in patients with ILD with anti-MDA5ab-positive DM.

The levels of serum ferritin and IL-18 were associated with the status of ILD with anti-MDA5ab in the present study, as shown in previous reports [9, 12, 24]. Serum ferritin is an important laboratory finding of MAS [14]. MAS is now an accepted term that is used to refer to a form of secondary haemophagocytic lymphohistiocytosis observed in the context of rheumatic disorders [14, 15]. The pathophysiology of MAS involves a lack of T lymphocyte regulation and the excessive production of cytokines, such as TNF-α, IL-1β, IL-6 and IL-18, resulting in the activation of macrophages [15, 25]. The mRNA for IL-18 and IL-12 is readily detected in Kupffer cells and activated macrophages, and dendritic cells produce IL-18 in active inflammatory myopathies [26, 27]. We also reported that IL-18 is a key mediator in ILD with DM [13]. Moreover,

alveolar macrophages activated by some antigens, microbes and autoimmune stimuli are induced to produce leukotriene B4 and IL-8. These factors stimulate neutrophils to induce fibrosis in the lungs [28]. The MDA5 protein initially recognizes picornaviruses, such as the Coxsackie virus, and evokes antiviral responses by producing type I IFNs and TNF-α [11]. Previously, Coxsackie virus infection was reported to be one of the contributing factors in the pathogenesis of JDM [29]. Anti-MDA5ab-positive DM may be a type of MAS mainly in the skin and lungs that contributes to infections such as those caused by the Coxsackie virus. In conclusion, anti-MDA5ab titre, serum ferritin and IL-18 are useful for the evaluation of the response to treatment of RP-ILD with anti-MDA5ab-positive DM.

Rheumatology key messages

- Anti-MDA5ab is a disease-specific marker in DM with RP-ILD.
- Anti-MDA5ab titre, ferritin and IL-18 are useful for evaluation of response to treatment in DM with RP-ILD.

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