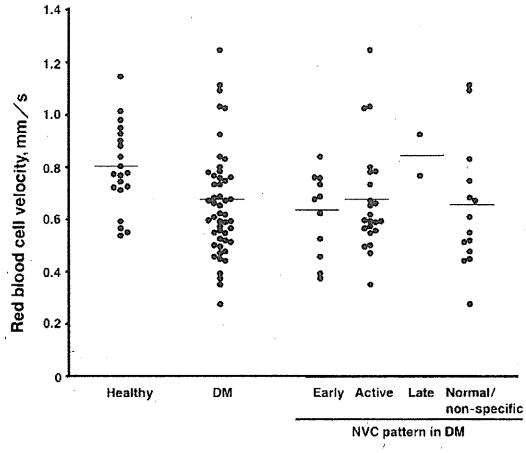
Fig. 1 Red blood cell velocity in patients with DM and in healthy controls. In patients with DM, the data were also shown dependent on the NVC pattern. Red blood cell velocity was evaluated using frame-to-frame determination of the position of a plasma gap in the capillary. The short bar indicates the mean value in each group.



velocity was not significantly changed by treatment [0.739 (0.149)→0.653 (0.161) mm/s]. Thus, the NCV abnormalities, especially irregularly enlarged capillaries, and haemorrhages and loss of capillaries likely reflect therapeutic effects in patients with DM.

Discussion

Using a video capillaroscopy system, we assessed morphological change and red blood cell velocity in the nail-fold capillaries of DM patients. The NVC scleroderma pattern was frequently detected in patients with DM, and was associated with disease activity, especially muscle disease activity. Among various NVC findings, loss of capillaries was significantly associated with muscle and global disease activities. In addition, haemorrhage was significantly associated with cutaneous disease activity. Findings of irregularly enlarged capillaries, haemorrhage and loss of capillaries were decreased after stabilization of disease activity by treatment. Red blood cell velocity was not significantly reduced in patients with DM compared with normal controls and was not changed by treatment.

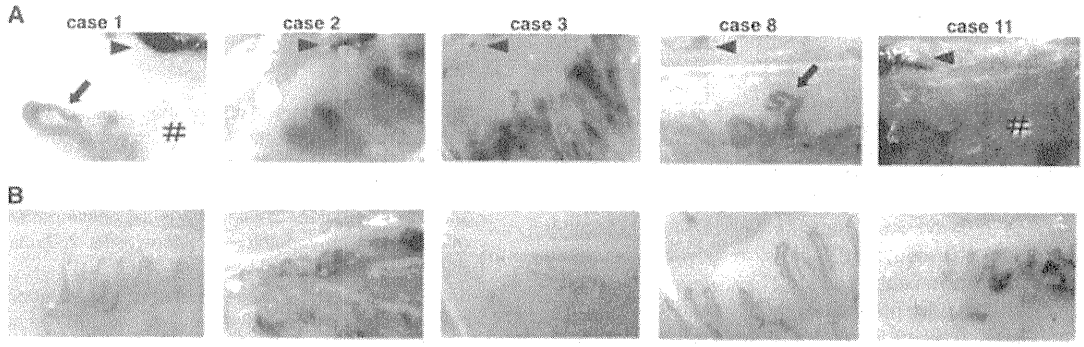
Although information regarding nail-fold capillary changes and red cell velocity had been previously available for SSc, such information was not fully established for adult DM. In our study, the NVC scleroderma pattern was found in 74% of DM patients, which was slightly lower than, but comparable to, what we previously reported in SSc patients (84%) [14]. Previous studies have reported significant positive correlation between cutaneous blood flow measured by laser Doppler imaging, and disease severity in adult patients with DM [36]. In contrast, reduced cutaneous blood flow detected by laser Doppler imaging has been reported in patients with

Table 4 The profile of patients followed until the stabilization of disease activity

Case	Age	Sex	Duration, months	Muscle weakness	ILD	Internal malignancy	RP	Serum CK level, IU/l	Autoantibodies	Initial therapy	Follow-up period, months	Therapy at the second point (inactive)
1	40	Female	2	++	−	−	−	6942	Mi-2	PSL 50 mg, mPSL pulse, CYC, IVIG	15	Rinderon 1 mg, tacrolimus 5 mg
2	42	Male	1	++	−	−	−	4795	Mi-2	PSL 50 mg, mPSL pulse, tacrolimus 3 mg	3	Rinderon 2.5 mg, tacrolimus 3 mg
3	44	Female	3	+	−	+	−	9388		Rinderon 100 mg × 3 days, PSL 30 mg	1	PSL 20 mg
4	51	Female	12	+	+	−	+	345	ARS (Jo-1)	PSL 30 mg	2	PSL 20 mg, tacrolimus 2 mg
5	53	Female	14	−	−	−	−	100	negative	PSL 20 mg	6	PSL 7.5 mg
6	57	Female	3	−	−	−	−	63	U1	PSL 20 mg	5	PSL 10 mg
7	59	Female	9	−	+	−	−	64	Wa	PSL 45 mg, mPSL pulse	3	PSL 25 mg
8	61	Female	30	+	+	+	−	49	ARS (Jo-1)	PSL 50 mg, CSA 750 mg	9	PSL 20 mg, tacrolimus 3 mg
9	61	Male	18	+	+	−	−	8261	ARS (Jo-1)	PSL 50 mg	1.5	PSL 35 mg
10	70	Male	8	+	−	+	−	1700	155/140	PSL 50 mg, mPSL pulse	6	PSL 18 mg
11	73	Female	4	+	+	−	−	126	CADM140	PSL 50 mg, CYC, tacrolimus 2 mg	4	PSL 30 mg, tacrolimus 3 mg
12	82	Female	3	+	−	+	−	169	155/140	PSL 20 mg	2	PSL 15 mg

mPSL: methylprednisolone.

FIG. 2 Representative NVC images at (**A**) base line and (**B**) after treatment, demonstrating how changes can be followed after stabilization of the disease activity in patients with DM. ◄: haemorrhages; ✎: irregularly enlarged capillaries; #: loss of capillaries.



PM/DM [19]. However, as far as we know, red blood cell velocity using video capillaroscopy has not been assessed by other groups. We previously reported that patients with SSc showed a 63% decrease in red blood cell velocity compared with healthy controls [34]. In that study, DM patients included as disease controls exhibited slightly but not significantly reduced red blood cell velocities compared with healthy controls. In this study, we confirmed that result in a larger DM population, and assessed the association with clinical features. Although the NVC findings in DM are indistinguishable from those in SSc [12], our findings indicate that the reduction in red blood cell velocity is more modest in DM patients than that in SSc patients. This may reflect somewhat different microcirculation injuries in DM *vs* SSc.

Our findings indicate that NVC changes are significantly associated with disease activity in patients with DM. Patients with the scleroderma pattern had elevated serum CK levels more frequently and had higher VAS scales of muscle disease activity than patients without the scleroderma pattern. Patients with scleroderma pattern also showed skin symptoms more frequently and elevated cutaneous disease VAS scales compared with patients without scleroderma pattern, although these differences were not significant. On the other hand, the frequency and disease activity of interstitial pneumonia was comparable between patients with the scleroderma pattern and patients without it. Since interstitial pneumonia is often retractable, our findings may at least partly reflect the difficulty of evaluating lung activity. Thus, the current study suggests that NVC change is associated with disease activity, especially muscle disease activity.

Our study identified several disparities between DM patients who displayed the scleroderma pattern and those who did not. For example, scleroderma pattern DM patients had shorter disease duration than DM patients without the scleroderma pattern, although the difference was not significant. Furthermore, patients without scleroderma pattern were receiving PSL and CSA more frequently than patients with scleroderma pattern, although these difference were not significant. These findings likely reflect the fact that patients with short disease duration tend to have active disease, whereas most patients with long disease duration are stable with treatment. In fact, the clinical features at their active phase (before treatment) were not significantly different between patients treated with PSL or CSA and patients not receiving treatment (data not shown). In addition, DM patients with the scleroderma pattern had internal malignancies more frequently than DM patients without the scleroderma pattern, although the difference was not significant. Consistent with this, anti-155/140 autoantibody, which is commonly detected in DM patients with internal malignancy, tended to be more frequently detected in DM patients with the scleroderma pattern than in patients without it. Since DM patients with either anti-155/140 antibody or internal malignancy typically exhibit cutaneous eruption and myositis without lung involvement [3, 4], such associations may be due to the cutaneous and muscle disease activity in these patients.

Importantly, NVC changes were improved by disease stabilization in DM patients during the follow-up period. Among NVC changes, irregularly enlarged capillaries, haemorrhages and loss of capillaries were significantly reduced after stabilization of disease activity (Fig. 2). Therefore, monitoring these changes will likely be useful in evaluating disease activity and therapeutic efficacy. On the other hand, it has been reported that capillary loss is associated with progression of SSc and generally of the microvascular damage in secondary Raynaud's syndrome, at least in SSc [37–39]. In SSc patients, giant capillaries and haemorrhages were not considered critically important in the evaluation of SSc microangiopathy, as these abnormalities are evident only in the early stages of the disease, and then disappear or become rare in the advanced stages [33, 40]. Thus, our study demonstrates that the significance of each NVC change is different in some degree between DM and SSc.

A previous study of adult-onset PM and DM patients found that RP, arthritis and pulmonary involvement were

associated with increased numbers of enlarged capillary loops and more severe avascular lesions [18]. In that study, the severity of the observed abnormalities did not correlate with the occurrence of malignancy or active myositis, but tended to decline with prolonged disease remission [18]. In a recent study including 53 adult patients with inflammatory myopathy, disease activity and severity were both significantly associated with alterations in capillary morphology [20]. Furthermore, marked abnormalities of capillaries were significantly associated with the involvement of internal malignancy or ILD. There are also some reports regarding NVC findings in JDM. One study found that NVC abnormalities are associated with skin involvement in patients with JDM [22]. Another study demonstrated that capillary loss was associated with skin involvement in JDM [21]. A prospective study involving 13 JDM patients demonstrated that capillary dropout was most frequently correlated with disease activity [23]. Longer duration of untreated disease and severe skin lesions were associated with capillary reduction in JDM [41]. Regarding associations with autoantibody, anti-Jo-1 antibody was associated with reduced capillary density [17]. Thus, our findings show some discrepancies with previous findings in patients with inflammatory myopathy. The main cause is likely due to the heterogeneity of inflammatory myopathy, and this makes the case for studying adult DM exclusively. Most previous papers have assessed inflammatory myopathy, both DM and PM, whereas our study is restricted to DM. For example, it has been reported that microhaemorrhages and capillary enlargement appear to represent the characteristic NVC pattern in patients with DM, but not in those with PM [20]. Ethnic differences also affect the results. Nonetheless, our results in DM, along with previous findings in inflammatory myopathy, are at least consistent in finding that general disease activity and severity are associated with prominent morphological changes.

Thus, our findings, together with previous reports, indicate that NVC findings are useful for diagnostic purposes, as well as for assessment of disease activity and response to treatment in patients with DM. Nonetheless, this study has some limitations. Although DM is rare, the number of patients analysed was not large and the study was restricted to Japanese individuals. Furthermore, most patients were already stable due to treatment at the time of evaluation. Therefore, further prospective multicentre studies using larger patient populations will be needed to confirm our results.

Rheumatology key message

- Morphological variation of nail-fold capillaries but not red blood cell velocity is associated with disease activity of DM.

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LETTER TO THE EDITOR

Dermatomyositis with anti-OJ antibody

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Dear Editor,

A subset of patients with polymyositis (PM)/dermatomyositis (DM) has autoantibodies to aminoacyl-tRNA synthetases (ARS). The most common anti-ARS antibody is anti-Jo-1 (histidyl-tRNA synthetase) antibody, which is positive in up to 20% of patients with PM/DM [1]. In addition to anti-Jo-1 antibody, seven autoantibodies to ARS have been identified, including anti-OJ (isoleucyl-tRNA synthetase) antibody [1].

A 49-year-old Japanese woman presented with a 2-month history of erythema involving her eyelids, shoulders, hands, upper chest and back, and lateral thighs with associated fatigue and fever. On examination, proximal muscle weakness in her neck and lower limbs was detected. Dermatological assessment was notable for heliotrope rash involving periorbital skin, Gottron's lesions over both extensor and flexor surfaces of metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints (Fig. 1), mechanic's hands, periungual erythema, nail fold bleeding, edematous erythema across shoulders, anterior chest and back, and thighs with some ulceration. Laboratory examinations showed increases in aldolase (11.4 U/ml, normal: <6.1) and KL-6 (622 U/ml, normal: <500). Creatine kinase (CK; 149 IU/l) and SP-D (33.5 ng/ml) were within normal ranges. Anti-nuclear antibodies (ANA) were negative by indirect immunofluorescence. Anti-Jo-1 antibody was not detected by enzyme-linked immunosorbent assay. Electromyographic examination demonstrated myogenic pattern on iliopsoas muscle, compatible with myositis. Pulmonary function tests were within normal limits. Chest computed tomography showed ground glass opacities in bilateral lower lung fields. Histological examination of skin biopsy specimens demonstrated epidermal atrophy, liquefaction degeneration, dermal edema, and a perivascular lymphocytic infiltrate in the superficial dermis (Fig. 2). An extensive search detected no underlying malignancy. Based on these findings, she was diagnosed with DM and interstitial lung disease (ILD). Oral prednisone 60 mg/day (1 mg/kg per day) was administered. Fever shortly resolved, and her skin lesions and muscle weakness were gradually improved.

Immunoprecipitation assay was conducted, and the antibody recognizing OJ antigens was identified in the serum of the present case (Fig. 3). Since DM patients with anti-ARS antibody often fail to fully respond to oral corticosteroid and manifest recurrent flares during the tapering of corticosteroid, the patient was administered with oral cyclosporine 150 mg/day. At 3 months after the initiation of cyclosporine, prednisone was successfully tapered to 20 mg/day and aldolase and KL-6 were decreased to normal ranges.

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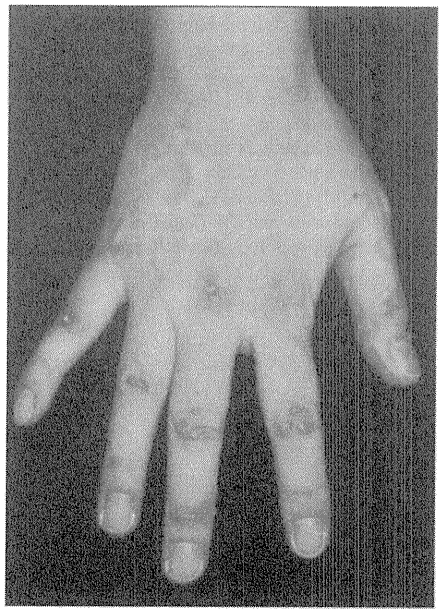

Fig. 1 Gottron's lesions over extensor surfaces of metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints

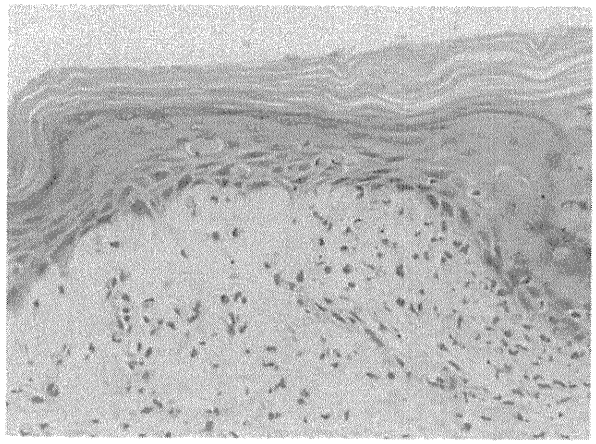

Fig. 2 An atrophic epidermis showing liquefaction degeneration associated with dermal edema and a perivascular lymphocytic infiltrate in the superficial dermis on histological examination. Hematoxylin and eosin staining; original magnification ×400

Close association of each anti-ARS antibody with a certain set of clinical features of PM/DM has been reported over the last decade. Clinical features of patients with anti-OJ antibody, which is positive in less than 5% of patients with PM/DM [2], have been well described both in North America [3] and in Japan [4]. According to these reports, the frequency of patients having DM rashes among those with anti-OJ antibody was 33% (3/9) in North America and 0% (0/7) in Japan, suggesting that anti-OJ antibody is

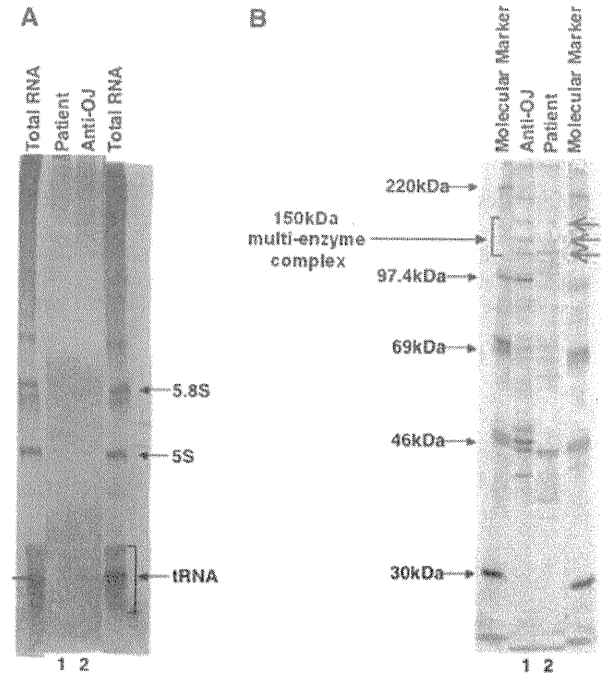

Fig. 3 **a** Immunoprecipitation for RNA with the patient and standard anti-OJ sera. 7 M urea-10% polyacrylamide gel (PAGE) of phenol-extracted immunoprecipitates from K562 cell extract, developed with silver stain. Total RNA lane indicates the 5.8S and 5.0S small ribosomal RNA and the tRNA region. *Lane 1* and *2* show the result of the patient serum and a standard anti-OJ serum, respectively. The identical tRNA pattern was found in these two sera (an *arrow*). **b** Immunoprecipitation for proteins with the patient and standard anti-OJ sera. Autoradiogram of 8.5% SDS–PAGE of immunoprecipitates from ^{35}S-methionine-labeled K562 cell extract. *Lane 1* and *2* show the result of a standard anti-OJ serum and the patient serum, respectively. The same pattern including three bands around 150 kDa (*arrows*), which were considered to represent glutamine, isoleucine, and leucine tRNA synthetases, was detected in the both sera

specific for PM rather than DM, especially in Japanese patients. This is the first report of a Japanese patient with anti-OJ antibody, presenting a set of typical DM rashes.

Anti-ARS antibody-positive patients generally share certain clinical symptoms such as myositis, ILD, polyarthritis, Raynaud's phenomenon, fever, and mechanic's hands. The present case had these characteristic features except for Raynaud's phenomenon. This finding is consistent with the previous observation that Raynaud's phenomenon is rare in patients with anti-OJ antibody [3, 4]. Especially in Japanese cases, none experienced Raynaud's phenomenon among 7 patients with anti-OJ antibody [4]. Although further studies in a large population are required to clarify the clinical features related to anti-OJ antibody, this antibody may be a serological marker for a subset of PM/DM patients characterized by milder vascular involvement. Further studies regarding the association of autoantibodies with clinical symptoms would provide us

useful serological markers for the diagnosis and the prediction of prognosis in PM/DM.

Conflict of interest None.

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Anti-p155/140 Antibody-positive Dermatomyositis with Metastases Originating from an Unknown Site

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Dermatomyositis (DM) is a systemic inflammatory myopathy with characteristic cutaneous manifestations (a heliotrope rash, Gottron's papules, paronychial erythema and nailfold bleeding) and is often associated with interstitial lung disease and internal malignancy. Thus far, some autoantibodies specific for myositis have been discovered, including antibodies to aminoacyl-tRNA synthetases (ARS), anti-Mi-2 antibodies, anti-CADM 140 antibody, anti-p155/140 antibody and others (1–3). The various autoantibody-positive subgroups of DM vary in their clinical features. Of these myositis-specific autoantibodies, the anti-p155/140 antibody is a 155-kDa reactive nuclear protein relevant to cancer-associated DM (1, 4–8). However, the frequency of malignancies in patients with anti-p155/140 antibody is undefined because no large epidemiological studies have been undertaken. We describe here a patient with anti-p155/140 antibody-positive DM who had a poorly differentiated metastatic adenocarcinoma; however, the primary tumour could not be identified despite comprehensive examination.

CASE REPORT

A 57-year-old man presented with refractory erythema on the hands and face, muscle weakness and dysphagia. Two months before consultation, he had had erythema on the face, which had spread to the precordium and limbs.

At the first presentation the patient had a typical heliotrope rash, Gottron's papules, paronychial erythema, nailfold bleeding and hyperkeratotic erythema over the elbow (Fig. 1). Blood examination revealed a high erythrocyte sedimentation rate (62 mm/h), high levels of lactate dehydrogenase (LDH) (295 IU/l), C-reactive protein (CRP) (8.13 mg/dl), creatine kinase (CK) (863 IU/l; reference values: 50–200 IU/l), myoglobin (240 ng/ml) and aldolase (8.6 U/l). The antinuclear antibody titre was positive at 1:40 with a homogeneous and speckled pattern. As for tumour markers, carcinoembryonic antigen (CEA) was high at 115 ng/ml (reference values: < 5.0 ng/ml). He was later found to be positive for anti-p155/140 antibody by an immunoprecipitation study performed using extracts of the leukaemia cell line, K562 (4, 9) (Fig. 2). Chest computerized tomography (CT) revealed aspiration pneumonia. However, there were no signs of interstitial pneumonia.

Biopsy specimens were obtained from the left deltoid muscle and the Gottron's papule on the fifth metacarpophalangeal joint of the left hand. Histology of the muscle showed inflammatory infiltration of mainly lymphocytes around the muscle fibres. The muscle fibres showed necrotic changes, including size irregularities and reduced staining. The skin biopsy showed hyperkeratosis, thickening of the granular layer, slight lymphocyte infiltration and pigment incontinence at the dermo-epidermal junction.

On the basis of the clinical and pathological findings, we diagnosed this case as DM. Taking into account the high CEA, upper gastrointestinal endoscopy and colonoscopy, hepatic and mammary ultrasonography, systemic contrast-enhanced CT, head magnetic resonance imaging (MRI) and tumour scintigraphy were performed; however, no malignancies were found.

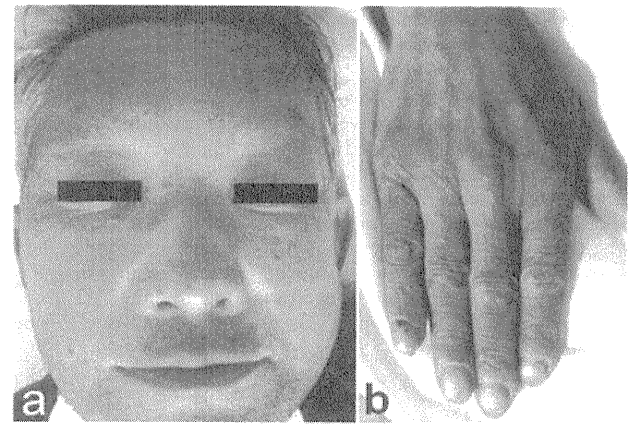

Fig. 1. (a) Heliotrope rash and (b) Gottron's papules, paronychial erythema, and nailfold bleeding were observed on examination.

From initial consultation we started the patient on 60 mg/day of prednisolone and antibiotics for aspiration pneumonia. Since the cutaneous manifestations and muscle weakness improved, we gradually tapered the dose of prednisolone. Although these symptoms did not recur, CEA continued to rise. The systemic PET-CT scan showed abnormal accumulation of fluorine 18 fluorodeoxyglucose (FDG) in the lymph node swelling in the supraclavicular fossa and mediastinum. Therefore, a mediastinal lymph node biopsy was carried out by fine needle aspiration through upper gastrointestinal endoscopy. On haematoxylin and eosin staining, the biopsy showed a poorly differentiated adenocarcinoma. Immunostaining for cytokeratin 7 and thyroid

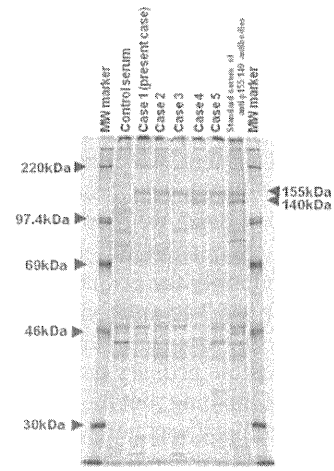

Fig. 2. Results of immunoprecipitation study: the sera of Cases 1–5 immunoprecipitated 155-kDa and 140-kDa bands. See Table I for description of cases.

Table I. *Characteristics of five cases of dermatomyositis with the anti-p155/140 antibody and no interstitial pnemonia*

Case no. Age/sex	Heliotrope rash	Gottron's sign	Serum creatine kinase[a]	Internal malignancy	Anti-nuclear antibody
1. 57/M[b]	+	+	863	Poorly differentiated adenocarcinoma (the primary unidentified)	40× (Hom, Spe)
2. 76/F	–	+	523	Unexamined	80× (Spe)
3. 65/F	–	+	894	Lung (large cell carcinoma)	160× (Hom, Spe)
4. 74/F	+	+	146	Lung (large cell carcinoma)	80× (Hom, Spe)
5. 58/M	+	+	300	Metastatic hepatocarcinoma (the primary unidentified)	80× (Hom, Spe)

[a]Reference values of creatine kinase: 50–200 IU/l. [b]Present case.
Hom: homogeneous type; Spe: speckled typ.

tissue factor-1 (TTF-1) was positive, but immunostaining for cytokeratin 20 was negative. Taking these histological findings into account, we suspected that the primary tumour in our patient was a lung or thyroid carcinoma. Therefore, cervical MRI and bronchoscopy were performed, but failed to show any signs of malignancy in these organs.

One month after the mediastinal lymph node biopsy, bone scintigraphy showed multiple metastases to the ribs. The patient died of a relapse of aspiration pneumonia 2 days after re-hospitalization. Autopsy was not carried out due to non-consent of his family.

DISCUSSION

Anti-p155/140 antibody is an antinuclear antibody that appears in a speckled pattern, and its target is proposed to be transcriptional intermediary factor 1-gamma (10). This autoantibody is strongly relevant to cancer-associated DM (1, 4) and has a high specificity (95.9%) (6). Cancer onset is mostly concomitant with DM or occurs within a year of diagnosis of DM (6). Currently, only the anti-Jo-1 antibody is examined in routine tests concerning DM. Thus, it is necessary to develop a simpler and more widely available test to help precise and early diagnosis of anti-p155/140 antibody-positive DM.

The clinical features of anti-p155/140 antibody-positive myositis are considered to be typical skin eruptions (such as V-sign rash, heliotrope rash and Gottron's papules) and the absence of interstitial pneumonia (1). Moreover, flagellate erythema is the most significant type of skin eruption, and most patients have muscle weakness or elevated serum CK levels (4).

Although flagellate erythema was absent in our patient, the other typical symptoms and absence of interstitial pneumonia were all evident, which along with the continuous increase in CEA levels strongly suggested an internal malignancy. Indeed, we discovered mediastinal lymph node metastases and diagnosed their histological type, but could not identify the primary tumour. The association with anti-p155/140 antibody is reported to be with carcinomas of the stomach, lung, breast and gall bladder (4). The possible primary cancer in our patient was thought to be of the lung, but the diagnosis remains unknown because autopsy was not performed.

In Table I, we have summarized five cases of dermatomyositis positive for the anti-p155/140 antibody (Fig. 2), including the present case, reported in our affiliated hospitals. Although the heliotrope rash was not present in two cases, none of the cases had interstitial pneumonia. All except the one patient who could not be examined had malignant tumours. Four patients with elevated CK levels showed muscle weakness, and the anti-nuclear antibody titres were not very high in any of the cases.

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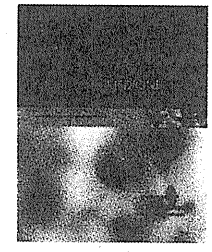

HRCT features of interstitial lung disease in dermatomyositis with anti-CADM-140 antibody

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Anti-CADM-140 antibody;
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High-resolution computed tomography

Summary
Background: Anti-CADM-140 antibody (anti-CADM-140), also referred to as anti-melanoma differentiation-associated gene 5 (MDA5) antibody, is a myositis-specific antibody identified in the sera of patients with clinically amyopathic dermatomyositis (C-ADM) and is associated with a worse prognosis in dermatomyositis-associated interstitial lung disease (DM-ILD). We sought to determine high-resolution computed tomography (HRCT) features of DM-ILD with anti-CADM-140.
Methods: Twenty-five patients newly diagnosed with DM-ILD at Kyoto University Hospital between 2005 and 2009 were retrospectively reviewed. Serum anti-CADM-140 was measured in all patients at their first visit. Chest HRCT images taken prior to treatment were classified based on the dominant findings and their distribution, and compared between patients with and without the antibody.
Results: Of 25 DM-ILD patients, 12 were positive and 13 were negative for anti-CADM-140.

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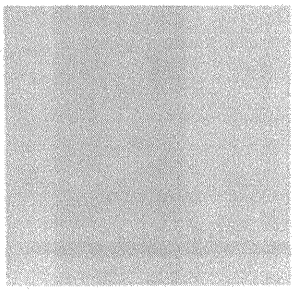

HRCT patterns differed significantly between anti-CADM-140-positive and negative patients ($P = 0.002$). Lower consolidation or ground-glass attenuation (GGA) pattern (50.0%) and random GGA pattern (33.3%) were the predominant patterns in anti-CADM-140-positive cases, while lower reticulation pattern (69.2%) was frequently seen in anti-CADM-140-negative cases. Anti-CADM-140-positive cases were also significantly characterized by the absence of intralobular reticular opacities (0% in anti-CADM-140 (+) vs. 84.6% in anti-CADM-140 (−), $P < 0.0001$). *Conclusions:* Anti-CADM-140-positive DM-ILD was characterized by lower consolidation or GGA pattern, random GGA pattern, and the absence of intralobular reticular opacities.

Introduction

Interstitial lung disease (ILD) is observed in 5–65% of polymyositis (PM) and dermatomyositis (DM) cases,[1,2] and is a significant prognostic factor.[1] PM/DM-associated ILD (PM/DM-ILD) can be divided into acute and chronic types.[3] The acute type of PM/DM-ILD is often rapidly progressive and refractory to treatment, resulting in fatal outcome.[3]

PM and DM are also characterized by several serum autoantibodies specific to PM/DM, designated as myositis-specific antibodies (MSAs).[4] Anti-CADM-140 antibody (anti-CADM-140) was the MSA identified in 2005 by Sato and coworkers in the sera of patients with clinically amyopathic dermatomyositis (C-ADM).[5] It recognizes interferon (IFN)-induced with helicase C domain protein 1/melanoma differentiation-associated gene 5 (IFIH1/MDA5)[6] and is thus also referred to as anti-MDA5 antibody.[7] It is specific to DM and is associated with the acute type of DM-ILD.[6,7] As expected from these findings, anti-CADM-140 was reported to be associated with a worse prognosis in patients with DM-ILD, compared to anti-aminoacyl-tRNA synthetase (ARS) antibodies (anti-ARS).[7] On the other hand, acute and chronic types of DM-ILD were shown to display different radiological features.[3] However, the radiological features of DM-ILD with anti-CADM-140 or the relationships between anti-CADM-140 and radiological findings have not been elucidated thus far.

In the present study, we aimed to define high-resolution computed tomography (HRCT) features of DM-ILD with anti-CADM-140. We compared HRCT findings between anti-CADM-140-positive and negative DM-ILD cases, and investigated whether the HRCT features could discriminate between the antibody-positive and negative cases.

Methods

Patients

The study population included all patients who were diagnosed with DM at Kyoto University Hospital between 2005 and 2009. DM was diagnosed using the Bohan and Peter criteria.[8] C-ADM was diagnosed if a patient had the characteristic skin rash of DM but little or no muscle symptoms and serum creatine kinase (CK) was <300 IU/L during the study period, as described previously.[5,6] We excluded patients who had active neoplasm or other connective tissue disease (CTD), or had been treated with systemic corticosteroid (CS) or immunosuppressive agents before referral to our hospital. Among the remaining 32 patients, ILD was confirmed in 25 (78.1%) based on HRCT. Acute and subacute DM-ILD subtypes were diagnosed when respiratory failure developed within 1 month and within 1–3 months, respectively, from the onset of symptoms or the initiation of treatment.

All patients provided written informed consent before blood sample collection. The Kyoto University Hospital Institutional Review Board approved this retrospective study.

Clinical evaluation

Clinical information was retrospectively collected from medical records. All patients were evaluated by at least two rheumatologists prior to treatment and had blood tests at their first visit. Most patients also underwent standardized pulmonary function tests,[9] and arterial blood gas analysis was done before treatment. Published equations for Japanese adults were used to determine predicted values of each parameter.[10]

Measurement of MSAs

Serum samples were obtained from all patients at the first visit prior to receiving immunosuppressive therapies. The presence of MSAs was determined by RNA-immunoprecipitation (RNA-IPP) for anti-ARS and protein-immunoprecipitation (P-IPP) for anti-CADM-140 as described previously.[6] Patients were divided into two groups based on the presence or absence of anti-CADM-140: anti-CADM-140 (+) or (−), respectively.

HRCT scanning protocol

Thin-section CT images were obtained with a multidetector CT scanner (Aquilion 64; Toshiba Medical Systems, Tochigi, Japan). Whole lung scans were performed at peak tube voltage of 120 kVp with variable mAs setting using an automatic exposure control system (SD value 8.5). Contiguous 7-mm-thick images and HRCT images (2 mm) were prepared for review.

HRCT evaluation

All patients underwent chest HRCT prior to treatment, and images were reviewed by three independent observers (T.K., T.H., and K.T. with 15, 12, and 10 years of

experience, respectively) blinded to clinical information. Inter-observer disagreements were resolved by consensus.

Images were assessed for the presence of ground-glass attenuation (GGA), consolidation, intralobular reticular opacities, interlobular septal thickening, non-septal linear or plate-like opacity, substantial micronodules, honeycombing, emphysema, traction bronchiectasis, and lobar volume loss. The presence of mediastinal lymph node enlargement or pleural effusion and the laterality of abnormalities were also assessed. HRCT findings were interpreted according to the recommendations of the Nomenclature Committee of the Fleischner Society.[11] Non-septal linear or plate-like opacity was defined as an elongated line of soft tissue attenuation that was distinct from interlobular septa and bronchovascular bundles, including subpleural curvilinear lines and subpleural bands.[12]

Through reviewing all HRCT images, we found that all 25 cases could be categorized into a few HRCT patterns, based on dominant CT findings, and the craniocaudal and axial distribution of these findings. The dominant findings were classified as GGA, consolidation, or reticulation (intralobular reticular opacities, interlobular septal thickening, or non-septal linear or plate-like opacity). The craniocaudal distribution was assessed as upper, lower, diffuse, or random. Upper distribution was defined as extensive findings predominantly above the level of inferior pulmonary veins, lower when there were more below this level, diffuse when generalized, and random for no zonal predominance. The axial distribution was classified as peribronchovascular when the dominant findings were along the bronchi and vessels, peripheral when in the outer one-third of the lung, diffuse when generalized, or random when no distribution pattern was apparent.

Statistical analysis

Statistical analysis was performed using JMP® version 6 (SAS Institute Inc. Cary, NC, USA). All statistical variations in quantitative data were expressed as a single determination standard deviation, and a P value less than 0.05 was considered to indicate statistical significance.

Group comparisons were made using Fisher's exact test, χ^2 test, and Mann–Whitney U test. Cumulative survival probabilities were estimated using the Kaplan–Meier method and the log-rank test.

Results

Initial clinical features

Demographics, clinical manifestations and laboratory test results of patients in the anti-CADM-140 (+) and (−) groups are summarized in **Table 1**. The prevalence of C-ADM showed no significant difference (50.0% vs. 30.8%, $P = 0.43$). Acute DM-ILD was diagnosed in 25% of patients in

Table 1 Patient demographic, clinical characteristics and laboratory test results at diagnosis.

	Anti-CADM-140 (+) (n = 12)	Anti-CADM-140 (−) (n = 13)	P
Clinical features			
Sex, male/female	4/8	4/9	>0.99
Smoking	0 (0.0%)	6 (46.2%)	0.01
Age (years)	53.5 ± 9.4	52.7 ± 7.7	>0.99
C-ADM at diagnosis	6 (50.0%)	4 (30.8%)	0.43
Acute ILD[a]	3 (25.0%)	0 (0.0%)	0.10
Acute or subacute ILD[b]	5 (41.7%)	1 (7.7%)	0.07
Laboratory tests			
WBC (/mm^3)	5140 ± 1390 (n = 12)	8860 ± 2940 (n = 13)	<0.01
Plt (×10^4/mm^3)	19.8 ± 7.09 (n = 12)	29.9 ± 9.38 (n = 13)	<0.01
CRP (mg/dL)	1.03 ± 0.84 (n = 12)	1.52 ± 1.76 (n = 13)	0.81
LDH (IU/L)	423.2 ± 199.4 (n = 12)	429.2 ± 161.7 (n = 13)	0.96
CK (IU/L)	261.3 ± 314.6 (n = 12)	1348.8 ± 1707.0 (n = 13)	<0.01
Aldolase (IU/L)	9.0 ± 4.4 (n = 12)	25.1 ± 26.5 (n = 13)	0.03
Ferritin (ng/mL)	1267.6 ± 2077.3 (n = 10)	196.7 ± 252.0 (n = 10)	0.01
Maximal ferritin[c] (ng/mL)	3035.7 ± 5253.2 (n = 10)	1575.2 ± 4117.5 (n = 10)	0.04
KL-6 (U/mL)	511.8 ± 162.3 (n = 12)	907.2 ± 750.4 (n = 12)	0.32
SP-D (ng/mL)	44.0 ± 20.0 (n = 8)	154.1 ± 119.4 (n = 8)	<0.01
Anti-ARS antibodies	0 (0.0%)	10 (76.9%)	<0.01

All values are number (percentage) or mean ± standard deviation (number).
Abbreviations: anti-CADM-140, anti-CADM-140 antibody; C-ADM, clinically amyopathic dermatomyositis; ILD, interstitial lung disease, WBC, white blood cell; Plt, platelet; CRP, C-reactive protein; LDH, lactate dehydrogenase; CK, creatine kinase; SP-D, surfactant protein-D; ARS, aminoacyl-tRNA synthetase.
[a] Acute ILD was diagnosed when respiratory failure developed within one month from the onset of symptoms or the initiation of treatment.
[b] Subacute ILD was diagnosed when respiratory failure developed within one to three months from the onset of symptoms or the initiation of treatment.
[c] Highest value through the whole course.

Table 2 HRCT findings in anti-CADM-140 (+) and (−) groups.

	Anti-CADM-140 (+) (n = 12)	Anti-CADM-140 (−) (n = 13)	P
Ground-glass attenuation	10 (83.3%)	13 (100.0%)	0.22
Consolidation	7 (58.3%)	6 (46.2%)	0.70
Intralobular reticular opacities	0 (0.0%)	11 (84.6%)	<0.01
Interlobular septal thickening	8 (66.7%)	6 (46.2%)	0.43
Non-septal linear or plate-like opacities	10 (83.3%)	7 (53.8%)	0.20
Honeycombing	0 (0.0%)	0 (0.0%)	N.A.
Traction bronchiectasis	0 (0.0%)	3 (23.1%)	0.22
Lobular volume loss	5 (41.7%)	7 (53.8%)	0.70
HRCT pattern			
Lower consolidation/GGA	6 (50.0%)	2 (15.4%)	
Lower reticulation	0 (0.0%)	9 (69.2%)	<0.01
Random GGA	4 (33.3%)	0 (0.0%)	
Others[a]	2 (16.7%)	2 (15.4%)	

All values are number (percentage).
Abbreviations: N.A., not available; GGA, ground-glass attenuation.
[a] In the anti-CADM-140 (+) group, upper GGA pattern in one and diffuse GGA in another. In the anti-CADM-140 (−) group, lower but axially diffuse GGA pattern in one and diffuse reticulation in another.

the anti-CADM-140 (+), and 0% of patients in the anti-CADM-140 (−) group (P = 0.10), while the sum of acute and subacute subtypes was 41.7% and 7.7%, respectively (P = 0.07). Before treatment, white blood cells, platelets, CK, and aldolase levels were lower in the anti-CADM-140 (+) group. Pretreatment ferritin and its maximal value were both higher in the anti-CADM-140 (+) group. In the anti-CADM-140 (−) group, 10 patients (76.9%) were positive for anti-ARS: three with EJ, three with PL-7, two with Jo-1, one with OJ, and one with PL-12. Arterial blood gas analyses and pulmonary functional tests revealed no significant differences (data not shown). No patients underwent surgical lung biopsy (SLB) in either group.

HRCT evaluation

HRCT findings are shown in Table 2. Common findings were GGA (83.3%), non-septal linear or plate-like opacity (83.3%), and interlobular septal thickening (66.7%) in the anti-CADM-140 (+) group; and GGA (100.0%), intralobular reticular opacities (84.6%), non-septal linear or plate-like opacity (53.8%), and lobular volume loss (53.8%) in the anti-CADM-140 (−) group. Among the HRCT findings, intralobular reticular opacities were significantly different between the groups (0% in anti-CADM-140 (+) vs. 84.6% in anti-CADM-140 (−), $P < 0.0001$).

Next, we categorized all 25 cases into four HRCT patterns: lower consolidation/GGA pattern (lower peripheral or peribronchovascular consolidations or GGA); lower reticulation pattern (lower peripheral or peribronchovascular reticulation); random GGA pattern (random peripheral GGA); and others. Lower consolidation/GGA pattern was characterized by nonsegmental consolidations or GGA, with subpleural or peribronchovascular distribution (Figs. 1 and 2). Lower reticulation pattern showed a homogeneous distribution with some subpleural sparing (Fig. 3). In random GGA pattern, small GGAs were seen in a patchy manner in the absence of consolidation (Fig. 4).

The HRCT patterns were significantly different between the anti-CADM-140 (+) and (−) groups (P = 0.002): with

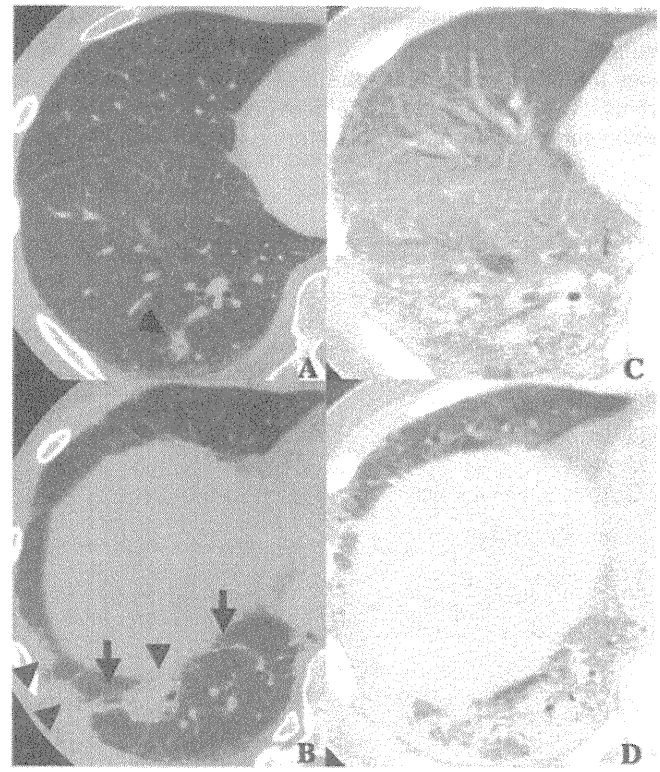

Fig. 1 High-resolution computed tomography (HRCT) images showing lower consolidation/ground-glass attenuation (GGA) pattern in a 44-year-old man positive for anti-CADM-140 antibody (anti-CADM-140). A and B: At diagnosis, peripheral and peribronchovascular consolidations were observed (arrowheads). Interlobular septal thickening and non-septal linear or plate-like opacities were also seen (arrows). C and D: Despite treatment for 6 weeks, severe respiratory failure developed, requiring mechanical ventilation. Diffuse GGA and consolidation with air bronchograms were extended in the whole lungs. Surveillance at this point revealed no evidence of infection. The patient died of respiratory failure 1 week later.

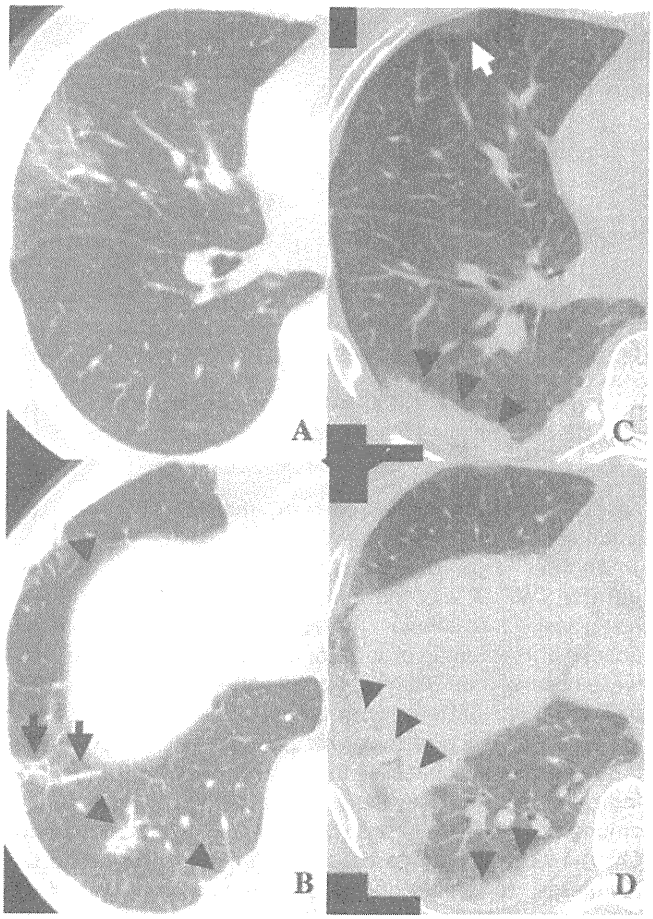

Fig. 2 A and B: HRCT images showing lower consolidation/GGA pattern in a 51-year-old man positive for anti-CADM-140. A: At diagnosis, subpleural nonsegmental GGA was observed. B: Peripheral and peribronchovascular consolidations (arrowheads), and interlobular septal thickening and non-septal linear or plate-like opacities (arrow) were also seen. C and D: HRCT images showing lower consolidation/GGA pattern in a 60-year-old man positive for anti-CADM-140. Subpleural nonsegmental consolidations with air bronchograms were observed (arrowheads). Subpleural nonsegmental GGA was also seen (arrow).

lower consolidation/GGA pattern (50.0%) and random GGA pattern (33.3%) in the anti-CADM-140 (+) group, and lower reticulation pattern (69.2%) in the anti-CADM-140 (−) group. Additionally, the dominant abnormalities were seen in lower lung fields (6/12, 50%) or randomly (4/12, 33.3%) in anti-CADM-140-positive patients, compared to lower lung fields (12/13, 93.2%) in most anti-CADM-140-negative patients ($P = 0.04$). The HRCT patterns in the seven fatal anti-CADM-140 (+) cases were lower consolidation/GGA pattern in four, random GGA pattern in two (including the one patient who died of *Pneumocystis jiroveci* pneumonia and sepsis), and others in one (Table 3). Of 10 patients with anti-ARS antibodies in the anti-CADM-140 (−) group, six (60.0%) had a lower reticulation pattern and two (20.0%) had lower consolidation/GGA pattern. Three patients who were negative for both anti-CADM-140 and anti-ARS showed lower reticulation pattern.

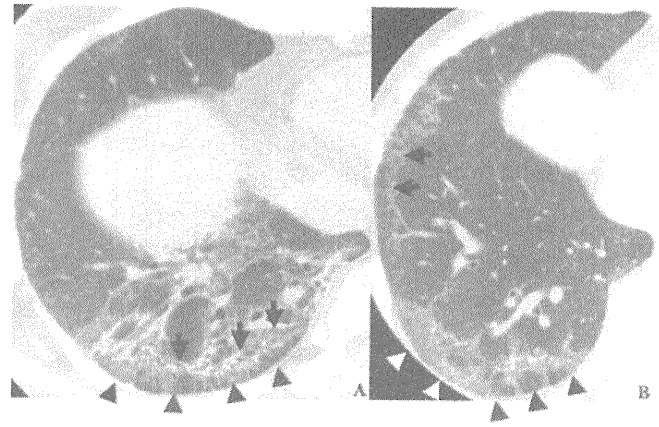

Fig. 3 HRCT images showing lower reticulation pattern. A: A 47-year-old woman negative for anti-CADM-140 (PL-7-positive). Peripheral intralobular reticular opacities with subpleural sparing were the dominant finding (arrowheads). GGAs, interlobular septal thickening, non-septal linear or plate-like opacities, and traction bronchiectasis (arrows) were also observed. The patient remained alive 6 years after diagnosis. B: A 52-year-old woman negative for anti-CADM-140 (Jo-1-positive). Peripheral intralobular reticular opacities with subpleural sparing were the dominant findings (arrowheads). Interlobular septal thickening and non-septal linear or plate-like opacities were also prominent (arrows). The patient remained alive 6 years after diagnosis.

Treatment and outcome

All patients received corticosteroid (CS) therapy, and immunosuppressive (IS) agents; most commonly cyclosporine A (CsA), used in 83.3% and 69.2% in the anti-CADM-140 (+) and (−) groups, respectively.

The median follow-up period from the diagnosis of DM for all patients was 588 days (range, 41—1617 days). Of 12 patients in the anti-CADM-140 (+) group, seven died and five survived, while all 13 patients in the anti-CADM-140 (−) group survived ($P < 0.01$). Of the seven deaths in anti-CADM-140 (+) group, five patients died of progressive ILD that was refractory to initial treatment. The remaining two patients died after the disease had been well controlled for months. One patient died of *P. jiroveci* pneumonia and sepsis, and another of acute exacerbation of ILD without infection. All seven patients were treated with corticosteroids and CsA, whereas cyclophosphamide (CYC) was used in six patients.

Discussion

We demonstrated that radiological features of anti-CADM-140-positive DM-ILD were significantly different from those of anti-CADM-140-negative cases, based on the original classification of HRCT patterns. In our series, anti-CADM-140-positive DM-ILD was characterized by lower consolidation/GGA and random GGA pattern and the absence of intralobular reticular opacities. To our knowledge, this is the first report describing HRCT features of DM-ILD with anti-CADM-140 in comparison with DM-ILD without this antibody.

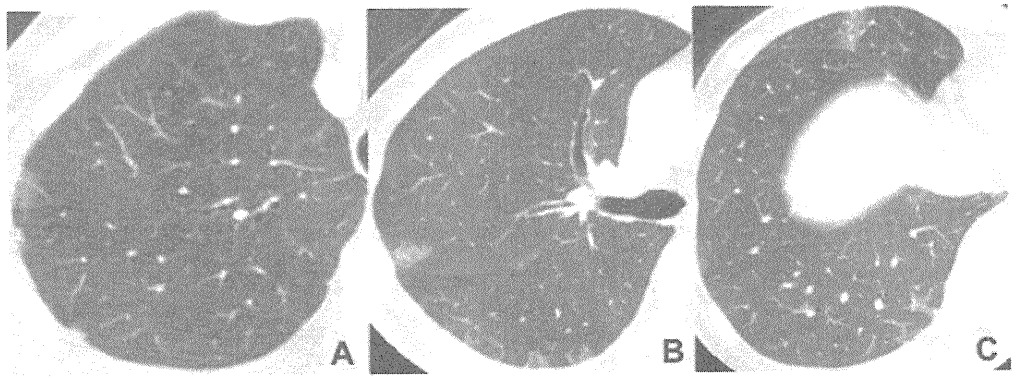

Fig. 4 HRCT image showing random GGA pattern in a 56-year-old woman positive for anti-CADM-140. Small, peripheral, localized GGAs were distributed in a patchy manner, with no consolidation. The patient remained alive 4 years after diagnosis.

The HRCT patterns characterized by the dominant findings and the distributions of such abnormalities were significantly different between the anti-CADM-140 (+) and (−) groups. Lower consolidation/GGA and random GGA patterns predominated in the anti-CADM-140 (+) group, while lower reticulation was more common in the anti-CADM-140 (−) group. Lower reticulation pattern is consistent with idiopathic nonspecific interstitial pneumonia (NSIP)[13–15] and DM/PM-ILD having biopsy-proven NSIP pattern[16]: reticulation, GGAs, lobar volume loss, and lower predominance, but little or no honeycombing. More than half of the anti-CADM-140-negative patients (69.2%, including six anti-ARS-positive patients) in our series had this pattern, suggestive of pathological NSIP pattern. On the other hand, lower consolidation/GGA and random GGA patterns are more difficult to interpret. Lower consolidation/GGA pattern may indicate organized pneumonia (OP)[14,17] or localized diffuse alveolar damage (DAD).[14,17–19] The mortality in patients with this pattern was as high as 50.0% (4/8), suggesting a high prevalence of DAD although radiopathological correlation was not confirmed in our cases. Indeed, Kang et al. reported biopsy-proven DAD, usual interstitial pneumonia (UIP), and NSIP patterns in DM-ILD, while HRCT findings showed OP pattern in most cases.[20] In random GGA pattern, most lesions were too small to speculate pathology.

Another significant characteristic of anti-CADM-140-positive DM-ILD was the absence of intralobular reticular opacities. Intralobular reticular opacities represent abnormal thickening of intralobular interstitial tissue[11] and were observed in 87% of idiopathic NSIP patients[13] and 92% of DM/PM-ILD patients with biopsy-proven NSIP pattern.[16] Thus, the absence of lower reticulation pattern and intralobular reticular opacities in the anti-CADM-140 (+) group indicates a lower prevalence of pathological NSIP pattern among anti-CADM-140-positive cases, in contrast to anti-CADM-140-negative cases. Additionally, the reported responses to treatment and outcomes of DM/PM-ILD patients with biopsy-proven NSIP pattern were much better than those of our anti-CADM-140-positive patients.[16] Although the prognostic value of pathology in DM-ILD have not been established, these differences in both radiological findings and survival suggest that the anti-CADM-140 (+) group includes patients distinct from those with pathological NSIP.

On the other hand, HRCT findings other than intralobular reticular opacities were not significantly different between the anti-CADM-140 (+) and (−) groups. Our results indicate

Table 3 Clinical characteristics of 12 anti-CADM-140-positive cases.

Case No.	Age	Sex	C-ADM	Acute/subacute ILD	HRCT pattern	Duration[a] (days)	Outcome	Cause of death
1	60	M	−	+	Lower consolidation/GGA	64	Death	Respiratory failure
2	51	M	+	+	Lower consolidation/GGA	87	Death	Respiratory failure
3	44	M	−	+	Lower consolidation/GGA	41	Death	Respiratory failure
4	45	F	+	+	Lower consolidation/GGA	52	Death	Respiratory failure
5	41	F	+	−	Lower consolidation/GGA	97	Survival	
6	52	F	+	−	Lower consolidation/GGA	630	Survival	
7	64	F	+	+	Random GGA	133	Death	Acute exacerbation
8	64	F	−	−	Random GGA	92	Death	PCP, sepsis
9	52	M	−	−	Random GGA	952	Survival	
10	56	F	−	−	Random GGA	1237	Survival	
11	70	F	+	−	Other	122	Death	Respiratory failure
12	43	F	−	−	Other	503	Survival	

Abbreviations: C-ADM, clinically amyopathic dermatomyositis; ILD, interstitial lung disease; M, male; F, female; GGA, ground-glass attenuation; PCP, *Pneumocystis jiroveci* pneumonia.
[a] The follow-up period from the diagnosis.

that HRCT patterns may be more helpful in discriminating between anti-CADM-140-positive and negative cases than several nonspecific findings. The HRCT patterns in our study were based on the major abnormalities and the distributions of those abnormalities to describe the overall picture comprehensively and concisely. Thus, the complete picture of HRCT images, rather than the presence of individual abnormalities probably characterized anti-CADM-140-positive cases better.

Among MSAs, anti-ARS has also been reported to be associated with ILD in DM/PM patients.[21] Of 13 anti-CADM-140-negative cases in our study, 10 were positive for anti-ARS, and the HRCT patterns were similar between anti-ARS-positive and negative cases: lower reticulation pattern was predominant (60.0% and 40.0% in anti-ARS-positive and negative patients, respectively). These findings indicate that anti-CADM-140 may be more influential on the HRCT patterns of DM-ILD than anti-ARS.

Notably, the prevalence of C-ADM was not significantly different between anti-CADM-140 (+) and (−) groups. In spite of the designation, half the patients in the anti-CADM-140 (+) group did not fulfill the criteria for C-ADM. Such a discrepancy between anti-CADM-140 and C-ADM was also suggested by Gono and coworkers.[7] In addition, the results of pulmonary function tests and arterial gas analyses at diagnosis were not significantly different. These findings indicate that, while this antibody is a strong predictor of mortality, the initial clinical data cannot necessarily discriminate between anti-CADM-140-positive and negative cases in DM-ILD. In contrast, the HRCT features were significantly different between the two groups, suggesting the clinical utility of HRCT evaluation for predicting the presence of anti-CADM-140.

High mortality in the anti-CADM-140 (+) group suggested the necessity of novel therapies beyond the combination of corticosteroids and immunosuppressive agents, mainly CsA and/or CYC. On the other hand, approximately half of patients with anti-CADM-140 (41.7%) survived with current regimens. Table 3 suggests that the HRCT patterns may not be associated with survival in anti-CADM-140-positive DM-ILD; thus, the prognostic value of HRCT features at diagnosis is the next critical question. A recent study reported the prognostic value of serum ferritin in DM-ILD with anti-CADM-140, although the study population was relatively small.[7] Thus, the predictors of mortality in anti-CADM-140-positive DM-ILD, including HRCT features should be elucidated by analyzing larger numbers of patients. In addition, in the entire spectrum of DM-ILD, the prognostic values of HRCT features should also be compared to that of anti-CADM-140 and other serum biomarkers. As Goh et al. showed in systemic sclerosis-associated ILD,[22] quantitative scoring of disease extent may be helpful in these analyses.

We should mention some limitations of this study. First, this study was a small-sized study in a single center. Second, serial changes in HRCT images were not addressed because follow-up HRCT was performed at rather arbitrary intervals. The effects of treatment on HRCT features and their prognostic values should be further studied in a prospective design. Third, radiopathological correlation was not confirmed. However, the significance of pathological diagnosis or SLB in clinical practice of DM-ILD or CVD-related ILD has not been determined.[23,24] Further, SLB can sometimes induce acute exacerbation in idiopathic pulmonary fibrosis and other ILD patients.[25–27] Fourth, anti-CADM-140 has been reported exclusively in Japanese patients thus far.[5–7] To establish the clinical relevance of this antibody, further studies in other ethnic populations are required.

Despite these limitations, we demonstrated that lower consolidation/GGA pattern and random GGA patterns as well as the absence of intralobular reticular opacities were characteristic of anti-CADM-140-positive DM-ILD. Although HRCT evaluation can be useful in predicting the presence of anti-CADM-140 in DM-ILD, further studies are required to define the prognostic value of HRCT features in anti-CADM-140-positive DM-ILD.

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Conflicts of interest

None of the authors have any financial or personal relationships with other people or organizations that could inappropriately influence (bias) the work reflected in this manuscript.

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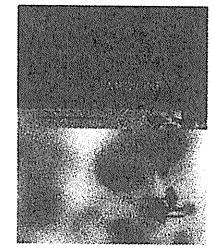

Detection of antisynthetase syndrome in patients with idiopathic interstitial pneumonias

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KEYWORDS
Antisynthetase syndrome;
Aminoacyl-tRNA synthetase;
Idiopathic interstitial pneumonia;
Nonspecific interstitial pneumonia

Summary
Objectives: Antisynthetase syndrome (ASS) is characterized by autoantibodies to aminoacyl-tRNA synthetases (anti-synthetase) and it is frequently associated with interstitial lung disease. The purpose of this study was to elucidate the prevalence and characteristics of the anti-synthetase positive subpopulation among idiopathic interstitial pneumonias (IIPs) and to clarify the importance of screening for these antibodies.
Methods: A retrospective study was performed in 198 consecutive cases with IIPs. Screening for six anti-synthetase antibodies was performed in all cases. Clinical profiles of all cases were compared with reference to the presence of anti-synthetase. High-resolution computed tomography (HRCT) findings of anti-synthetase positive cases were also analyzed.

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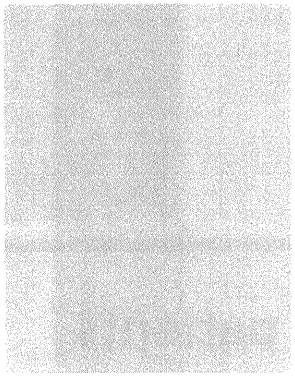

Results: 13 cases (6.6%) were positive for anti-synthetase. Anti-EJ was most prevalent, followed by anti-PL-12. Onset ages of anti-synthetase positive cases were younger than those of anti-synthetase negative cases. Extrapulmonary features of ASS were absent in 6 anti-synthetase positive cases (46.2%). Histologically, among 5 UIP with lymphoid follicles and 11 NSIP cases, the prevalence of anti-synthetase positive cases was 8/16 (50%). On HRCT, ground glass opacity and traction bronchiectasis were the major findings in anti-synthetase positive cases, while honeycombing was absent.
Conclusions: Anti-synthetase positive cases were not rare among IIPs. Anti-synthetase should be screened for in IIPs, especially in pathological NSIP or UIP with lymphoid follicles. These patients should be screened for anti-synthetase even if no suggestive extrapulmonary manifestation exists.

Introduction

Interstitial lung disease (ILD) is caused by both known and unknown etiologies, and idiopathic interstitial pneumonias (IIPs) are the most prevalent type of ILD.[1] Connective tissue disease (CTD) affects a wide variety of organs with the incidence of pulmonary involvement ranging from 19 to 67%.[2] A thorough etiological work-up of CTD and its related conditions is essential in clinical practice for ILD. Difficult-to-diagnose cases exist when they have an incomplete form of CTD that cannot be categorized as CTD using a range of specific criteria. These cases are categorized as idiopathic, or sometimes unclassifiable.

The aminoacyl-tRNA synthetases are a family of enzymes, each of which catalyses the formation of aminoacyl-tRNA from a specific amino acid and its cognate tRNA. Autoantibodies to eight of these synthetases (anti-synthetase) have been reported and they are defined as myositis-specific autoantibodies.[3] Clinical features that occur in anti-synthetase positive cases include myositis, ILD, arthritis, mechanic's hand and often Raynaud's phenomenon. Combination of positive anti-synthetase antibody with any of these findings constitutes a distinct syndrome named anti-synthetase syndrome (ASS).[4] The prevalence of anti-synthetase among PM/DM is 30—40% and characteristics of anti-synthetase positive populations have been established in the past, in several myositis-based large cohort studies. In particular, subpopulations of patients with myositis have higher rates of ILD when they have anti-synthetase than those who have not.[5] ILD in ASS may also be indistinguishable from IIPs when patients have minimal or no myositis. ASS comprises a distinct disease entity and demonstrates a generally good response to corticosteroids, though a number of cases show recurrence after withdrawing or reducing doses of corticosteroids.[6,7] Fisher et al. retrospectively assessed 37 patients with IIPs who had some signs or symptoms indicative of ASS, but were not positive for ANA or anti-Jo-1 antibody, and found that 9 (24%) patients were positive for anti-synthetase.[8] In this previous study, anti-synthetase were measured in patients with clinical signs indicative of ASS, and the decision to perform the test depended upon each physician; thus the overall prevalence of anti-synthetase among IIPs was not clarified. The characteristics of patients with anti-synthetase positive IPs are still unknown together with identification of the population which should be examined for these antibodies. This study aimed to investigate the prevalence of an anti-synthetase positive subpopulation among IIPs. Six anti-synthetase antibodies were measured and aspects of the clinical, pathological and radiological features of anti-synthetase positive cases were investigated to determine which patients should be screened for these antibodies.

Methods

Patient recruitment

In this study, idiopathic interstitial pneumonia (IIP) was defined as interstitial pneumonias of unknown cause where a patient did not fulfill classification criteria for any specific CTD or vasculitides, and in whom lung diseases were not potentially caused by drug or occupational-environmental exposures. Screening for CTD was initially performed by experienced pulmonologists, and also by rheumatologists in patients with serological or clinical features suggestive of CTD.[9–16]Provisionally, undifferentiated connective tissue disease (UCTD)[17] were not excluded from the study population. In all patients diagnosed with idiopathic interstitial pneumonias (IIPs) who visited Kyoto University Hospital from July 2007 through April 2009 and Tenri Hospital, the tertiary care center from April 2006 through April 2009, serum samples were consecutively collected and patients were recruited into this study. The study population comprised 198 cases with IIPs, 53 with idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP) (30 by histological diagnosis; 23 by clinical diagnosis), 11 with nonspecific interstitial pneumonia (NSIP), 3 with histologically unclassifiable interstitial pneumonia, and 131 with non-UIP without histology. Written informed consent was obtained from the participants, and the study was approved by the Review Board of the Ethical Committee of each Institute.

Data collection

Clinical information was retrospectively obtained from medical records. The data included patient's age at onset, gender, pulmonary or extrapulmonary manifestations including signs or symptoms of CTD, laboratory data results including CTD-specific autoantibodies, blood gas analysis, pulmonary function test results, bronchoalveolar lavage

fluid (BALF) findings, treatment regimen, definitive diagnosis of polymyositis/dermatomyositis (PM/DM) during observation, and survival. Clinical diagnosis of PM/DM was made according to the criteria of Bohan and Peter.[16]

Measurement of anti-synthetase

Investigation of anti-synthetase was performed by an RNA immunoprecipitation procedure (IPP) using sera and HeLa cell extracts as previously described.[7] Briefly, 10 μl of sera was mixed with protein-A sepharose beads and incubated with sonicated extracts of HeLa cells. RNAs were extracted with phenol-chloroform and then resolved in urea-10% polyacrylamide gel, which was finally visualized with silver staining (Bio-Rad Laboratories, Hercules, CA, USA). Each antibody was identified by the mobility and pattern of tRNA bands (Fig. 1). Among the eight antibodies established in previous reports, we investigated the following six antibodies; antibodies to histidyl- (Jo-1), threonyl- (PL-7), alanyl- (PL-12), isoleucyl- (OJ), glycyl- (EJ), and asparaginyl-(KS) tRNA synthetases. The other two antibodies have only been reported in case presentations, and are considered to be rare; thus they were not investigated in this study.[3]

Assessment of high-resolution computed tomography (HRCT) findings

Chest high-resolution computed tomography (HRCT) findings were assessed independently by two radiologists (S. N. and T. K.) who were unaware of the clinical or pathological data. The lung fields in HRCT were divided into upper, middle and lower zones at the level of the carina and inferior pulmonary vein, and findings were assessed separately in the three zones of both lungs. The presence or absence of the following nine findings were reported in each subdivided lung zone: pleural irregularities and/or prominent interlobular septa, reticulation, ground glass opacity, consolidation, subpleural lines, centrilobular nodular opacity, irregular peribronchovascular thickening, traction bronchiectasis and bronchiolectasis, honeycombing.[18–20] Initially two readers evaluated the images and recorded results independently. After the completion of separate assessment, unified consensus results were reached through discussion between the two readers.

Statistical analysis

Data were summarized as a median and an interquartile range. We used the Wilcoxon rank sum test to compare the numerical variables and chi-square test or Fisher's exact test as appropriate to the categorical variables. Interobserver variances in the initial assessment of HRCT findings were evaluated using the kappa coefficient for each finding. Kaplan–Meier survival curves were derived for the study population, and comparisons were made using the log rank test. We used JMP (version 6, Japanese Edition. SAS Institute Inc.) in statistical analysis. A p-value of less than 0.05 was considered significant.

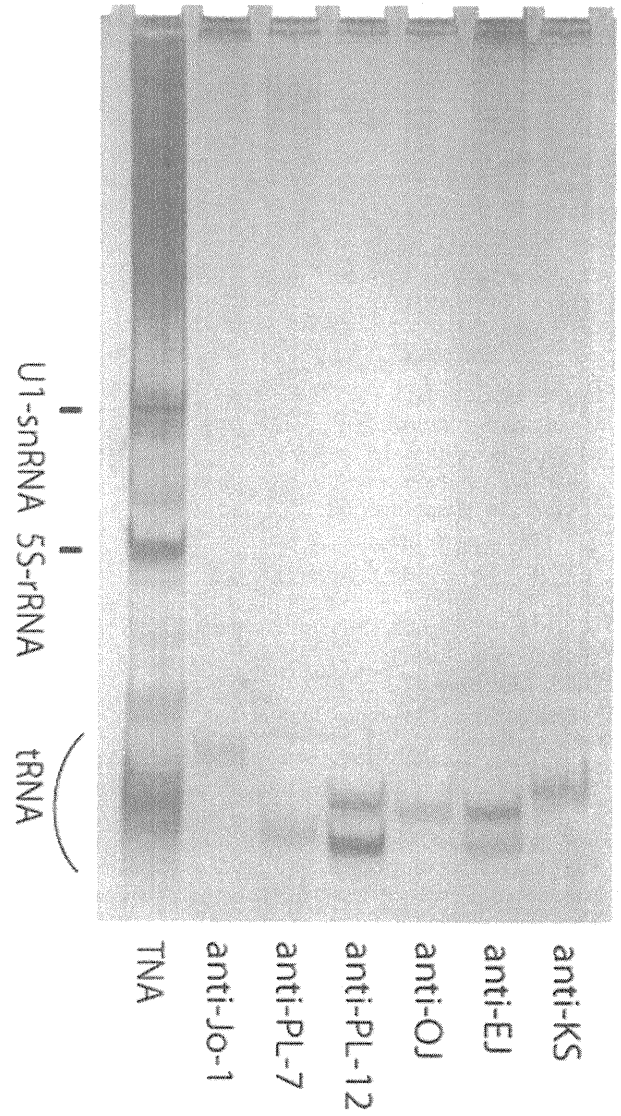

Figure 1 Immunoprecipitation of antibodies to antiaminoacyl-tRNA synthetases (anti-synthetase). The Figure demonstrates urea-polyacrylamide gel electrophoresis (PAGE) of immunoprecipitates, visualized with silver staining. Anti-synthetase antibodies are indicated in 6 lanes; antibodies to histidyl- (Jo-1), threonyl- (PL-7), alanyl- (PL-12), isoleucyl- (OJ), glycyl- (EJ), and asparaginyl-(KS) tRNA synthetases. Each antibody is distinguishable by the mobility and pattern of tRNA bands. TNA denotes total nucleic acids.

Results

Prevalence of anti-synthetase and clinical features

Anti-synthetase was found in 13 (6.6%) of 198 cases; anti-EJ was positive in 6 (3%), anti-PL-12 in 3 (1.5%), and anti-Jo-1, KS, OJ, and PL-7, one in each case (0.5%). No case exhibited reactivity to two or more antibodies. Median age at onset was younger in the anti-synthetase positive group than in the anti-synthetase negative group (55.0 vs. 67.4 years, respectively. $p < 0.001$, Table 1). Significant arthralgia or joint deformity, and cutaneous manifestations were