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## Case report

## Clinically amyopathic dermatomyositis with interstitial lung disease double-positive for anti-MDA5 and anti-PL12 antibodies

Toshiya Hiramatsu<sup>a,\*</sup>, Moeko Murano<sup>a</sup>, Shogo Nakai<sup>a</sup>, Yurina Murakami<sup>a</sup>, Koji Nishimoto<sup>a</sup>, Sayomi Matsushima<sup>a</sup>, Masanori Harada<sup>a</sup>, Tomohiro Uto<sup>a</sup>, Jun Sato<sup>a</sup>, Shiro Imokawa<sup>a</sup>, Takafumi Suda<sup>b</sup>

<sup>a</sup> Division of Respiratory Medicine, Iwata City Hospital, 512-3 Okubo, Iwata, Shizuoka, 438-8550, Japan

<sup>b</sup> Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, 431-3192, Japan

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## ABSTRACT

Anti-melanoma differentiation-associated gene 5 (MDA5) and anti-aminoacyl-tRNA synthetase (ARS) antibodies are two major myositis-specific autoantibodies with distinct clinical features. However, the clinical course remains unclear in patients with clinically amyopathic dermatomyositis (CADM)-interstitial lung disease (ILD) who have co-existing anti-MDA5 and anti-ARS antibodies. Here, we describe the case of a 32-year-old woman with CADM-ILD who had anti-MDA5 and anti-PL12 antibodies. Her serum ferritin level was within the normal range. However, chest computed tomography revealed bilateral lower-lobe consolidation and ground-glass opacities. Treatment with prednisolone and immunosuppressants was successful in improving the skin lesion and ILD, but relapse occurred on reducing the dose of prednisolone. These clinical features match those of anti-ARS antibody-positive dermatomyositis-ILD. Because these two conditions show significantly different clinical features and require different intensities of treatment, clinicians should carefully follow-up these patients throughout the course of the disease.

## 1. Introduction

Anti-aminoacyl-tRNA synthetase (ARS) and anti-melanoma differentiation-associated gene 5 (MDA5) antibodies are myositis-specific autoantibodies (MSAs) [1,2]. These antibodies tend to differ in their pathophysiological profiles and clinical presentations [3–8]. The coexistence of these MSAs is very rare, and only a few such cases have been reported [9–11]. Here, we describe a rare case of clinically amyopathic dermatomyositis (CADM) associated with interstitial lung disease (ILD) with coexisting anti-PL12 and anti-MDA5 antibodies.

## 2. Case report

A 32-year-old woman presented to our hospital with a 3-week history of skin rashes. She had arthralgia and low-grade fever over the previous 2 weeks, and complained of dyspnea on exertion at the initial visit. Fine crackles were audible on auscultation bilaterally. She had Gottron papules in her fingers and elbows (Fig. 1a and b), palmar papules (Fig. 1c) and mechanic hands (Fig. 1d), but she had

\* Corresponding author. Division of Respiratory Medicine, Iwata City Hospital, 512-3 Oookubo, Iwata, Shizuoka, 438-8550, Japan.  
E-mail address: [toshiya\\_hiramatsu1002@yahoo.co.jp](mailto:toshiya_hiramatsu1002@yahoo.co.jp) (T. Hiramatsu).

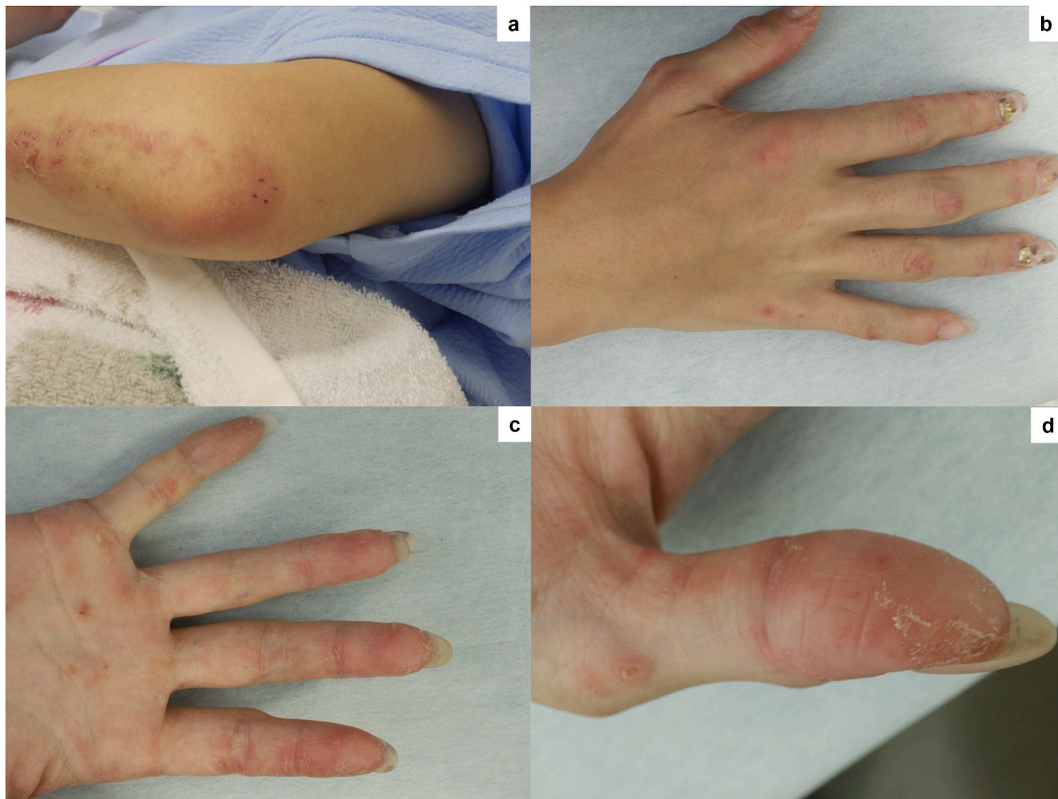
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**Fig. 1.** (a) Elbow erythema (Gottron sign). (b) Gottron papules on the proximal and distal interphalangeal joints. (c) Erythematous papules and macules on the palmar surface of the interphalangeal joints. (d) Cracking and fissuring on the radial side of the digit (mechanic's hand).

never experienced Raynaud's phenomenon. Neither a heliotrope rash nor a shawl sign was observed. Moreover, she had no muscle pain or weakness.

Laboratory tests yielded the following values: white blood cells, 4600/mL; C-reactive protein, 1.25 mg/dL (normal range: 0.00–0.14mg/dL); creatine kinase (CK), 274 U/L (normal range:41–153 U/L); lactate dehydrogenase, 276 U/L (normal range:124–222 U/L); aldolase, 5.5 U/L (normal range: 2.1–6.1 U/L), ferritin, 50 ng/mL (normal range: 10–60 ng/mL). KL-6 and SP-D levels were also within the normal ranges. The patient also tested positive for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies (70 IU/m and 25.6 U/mL, respectively). Anti-ARS and anti-MDA-5 antibodies were detected using an enzyme-linked immunosorbent assay. By using an immunoblot assay, the tRNA component was identified as PL12; anti-Ro52 antibody was also detected. A partial pressure of oxygen was 81.9 mmHg under ambient air by arterial blood gas analysis.

The pulmonary function test showed a slightly restrictive pattern. The results showed that forced vital capacity was 2.23 L (75.1% predicted) and diffusing capacity of the lung for carbon monoxide (DLco) was 19.25 mL/min/torr (101.3% predicted). Chest computed tomography (CT) revealed bilateral consolidation and ground-glass opacification with interlobular septal thickening mainly with bilateral lower-lobe predominance (Fig. 2). The bronchoalveolar lavage fluid was negative for malignant cells and pathogenic organisms, with a total cell count of  $0.93 \times 10^5$  cells/mL and 68.2% alveolar macrophages, 26.8% lymphocytes and 0.6% neutrophils; the ratio of CD4 to CD8 T lymphocytes was 0.87. Transbronchial lung biopsy (right B<sup>8</sup>a and B<sup>3</sup>a) showed lymphocyte infiltration and thickening of the alveolar walls without any vasculitis, granulomas, or necrosis (Fig. 3). Skin biopsy showed keratinization of the epidermis and perivascular inflammatory cell infiltration (Fig. 4).

Accordingly, we diagnosed her as having CADM associated with ILD based on Sontheimer's criteria [12] (Table 1). Treatment with prednisolone (45mg/day; 1mg/kg/day) and tacrolimus (3 mg) was started. This improved the skin lesions and ILD (Fig. 5a). However, after gradually reducing the prednisolone dose to 15 mg/day for five months while continuing tacrolimus, she experienced dyspnea on exertion and the chest CT findings worsened (Fig. 5b). Her oxygen saturation by pulse oximetry was 95% under ambient air. The results of %DLco at one month, three months and five months after the starting of initial therapy were 101%, 87.4% and 69.0%, respectively. Therefore, intravenous cyclophosphamide (700 mg every 4 weeks) was added to the regimen. Her respiratory condition stabilized, and chest CT showed no remarkable deterioration.

### 3. Discussion

The clinical features of MSAs usually differ from one another. Among the MSAs, anti-MDA5 antibody is usually detected in patients with CADM [4,13], which is a subtype of DM with typical skin manifestations but amyopathy or hypomyopathy due to scarce muscle

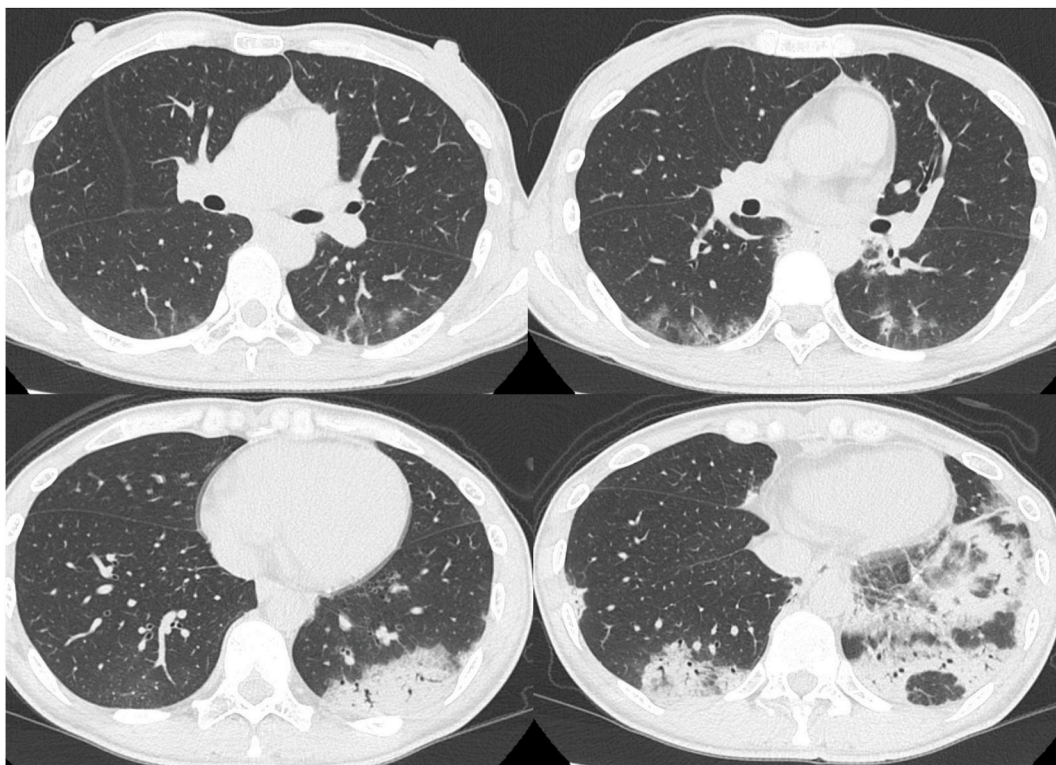


Fig. 2. Chest computed tomography (CT) findings on admission showing subpleural consolidations and ground-glass opacification mainly in the bilateral lower lobes.

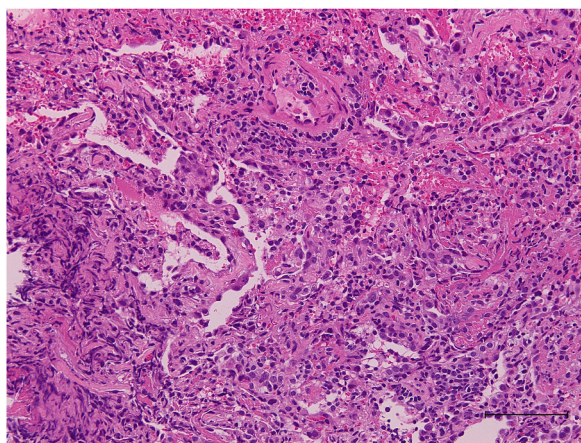
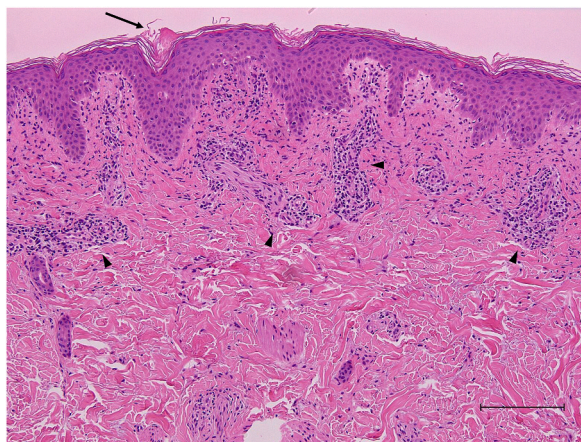


Fig. 3. Transbronchial lung biopsy showing lymphocyte infiltration and thickening of the alveolar walls without any vasculitis, granulomas, or necrosis. Bar indicates 100  $\mu$ m.

inflammation [12,13]. In our case, hallmark cutaneous manifestations were observed with no clinical evidence of proximal muscle weakness, but the serum CK level was slightly elevated. Therefore, we diagnosed her as having CADM (strictly, hypomyopathic DM) on the basis of Sontheimer's criteria [12].

Patients with CADM and anti-MDA5 antibody frequently develop complications of rapidly progressive-ILD, with fatal outcomes within the first 6 months, despite adequate treatment with high-dose steroids and immunosuppressants [3–5]. Therefore, anti-MDA5 antibody is considered a useful indicator for the early diagnosis of fatal and rapidly progressive ILD [4,5,14,15]. In contrast, in patients with DM-ILD and anti-ARS antibody, ILD usually responds to steroid treatment but relapse over the years [3,8]. Although our patient tested positive for anti-MDA5, treatment with steroids in combination with immunosuppressants was effective in inducing the remission of ILD. However, she later experienced ILD-flare-up when the steroid dose was reduced. These clinical features appear to match those of anti-ARS antibody-positive DM-ILD.



**Fig. 4.** Skin biopsy specimen showing keratinization of the epidermis (arrow) and perivascular inflammatory cell infiltration (arrow heads), which is compatible with skin lesions of dermatomyositis (DM). Bar indicates 100 $\mu$ m.

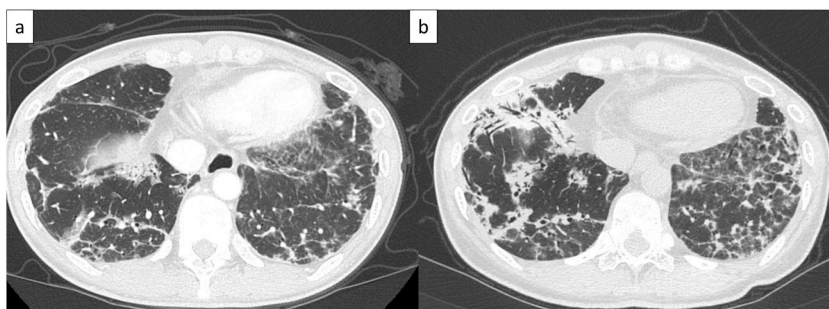
**Table 1**

Sontheimer' criteria for DM, Amyopathic DM, Hypomyopathic DM and CADM [12].

Classical DM	<ul style="list-style-type: none"> <li>- hallmark cutaneous manifestation of DM</li> <li>- proximal muscle weakness</li> </ul>
Amyopathic DM	<ul style="list-style-type: none"> <li>- objective evidence of muscle inflammation characteristic of DM</li> <li>- biopsy-confirmed hallmark of cutaneous manifestations of classic DM occurring for 6 months or longer</li> <li>- no clinical evidence of proximal muscle weakness</li> <li>- no serum muscle enzyme abnormalities</li> </ul>
Hypomyopathic DM	<ul style="list-style-type: none"> <li>If more extensive muscle testing is carried out, the results should be within normal limits.</li> <li>- DM-specific skin disease</li> <li>- no clinical evidence of muscle disease</li> </ul>
CADM	<ul style="list-style-type: none"> <li>- subclinical evidence of myositis on laboratory, electrophysiologic and/or radiologic evaluation</li> <li>- Either amyopathic and/or hypomyopathic DM</li> <li>the predominant clinical problem is skin disease</li> </ul>

DM: dermatomyositis.

CADM: clinically amyopathic dermatomyositis.



**Fig. 5.** Serial chest computed tomography (CT) findings. (a) Chest CT findings one month after start of the treatment showing improvement of consolidations and ground-glass opacifications. (b) Chest CT findings five months after start of the treatment showing newly developed consolidations and ground-glass opacifications in the middle lobe and bilateral lower lobes.

Previous studies have identified several risk factors, including anti-MDA5 antibodies, chest CT findings of lower-lobe consolidation, and high ferritin levels, that are potentially associated with a poor prognosis in patients with DM-ILD [14–19]. In anti-MDA5-positive patients with DM-ILD, the P/F ratio, alveolar-arterial oxygen gradient, and elevation of aspartate transaminase and gamma glutamyl transpeptidase are also associated with poor outcomes [14,16,17]. In our patient, chest CT findings showed lower-lobe consolidations, but the serum ferritin level, P/F ratio, and alveolar-arterial oxygen gradient were within the normal ranges.

A subset of patients with DM has circulating myositis-associated autoantibodies (MAAs) that are often found in other connective tissue diseases [20,21]. Our patient showed RF, anti-CCP, and anti-Ro52 antibodies, which are MAAs. Yamaguchi et al. reported that the coexistence of MAAs could be a biomarker for a favorable prognosis in anti-MDA5-positive patients with CADM; thus, anti-MDA5

**Table 2**  
Clinical features of DM/CADM-ILD with coexistence of anti-MDA5 and anti-ARS antibodies.

Author	Naniwa T [9]	Takeuchi Y [10]	Li ZY [11]	Our case
Age/Gender	43/female	53/female	27/female	32/female
Ethnic group	Asian (Japanese)	Asian (Japanese)	Hispanic	Asian (Japanese)
Type of DM	Classical DM	CADM	CADM	CADM
Type of ILD	RP and relapsing ILD	chronic ⇒ exacerbation	RP-ILD	chronic
Type of anti-ARS ab	Anti-PL7 ab	Anti-EJ ab	Anti-PL7 ab	Anti-PL12 ab
Anti-MDA5 ab	+	+	+	+
MAA	Anti-SS-A ab	ND	ND	Anti-Ro52 ab Anti-CCP ab
Ferritin (ng/ml)	95.1	ND	ND	50
Chest CT findings	Patchy consolidation and GGA with peripheral distribution, Subpleural line and intralobular reticular opacities	Initial: Lower peripheral reticulation and GGA Exacerbation: newly developed random GGA	Extensive GGO	Subpleural consolidation and GGO mainly in the bilateral lower lobes
Follow up period	15 years	Over 32 months	33 days	6 months
Recurrence	+	+	-	+
Outcome	alive	alive	expired	alive

DM: dermatomyositis, CADM: clinically amyopathic dermatomyositis, ND: not described, RP: rapidly progressive, GGA: ground glass attenuation, GGO: ground glass opacifications, ILD: interstitial lung disease, MMA: myositis associated antibody, ab: antibody, CCP: cyclic citrullinated peptide.

antibodies themselves may not be strong predictors of worse outcomes [21]. Our case findings may support this hypothesis.

In fatal cases of rapidly progressive anti-MDA5-positive DM/CADM-ILD, systemic activation of macrophages is potentially related to the pathogenesis [22,23]. However, the pathogenesis and clinical features of double-positive MSAs in DM-ILD are unclear because of the rarity of this condition. To date, only four cases of DM/CADM-ILD with anti-ARS and anti-MDA5 antibody double-positive, including our case [9–11], have been reported (Table 2). MAAs were detected in two patients. Three patients responded to treatment with steroids and immunosuppressants, but recurrence occurred [10]. Moreover, all patients were Asian. Anti-ARS antibody was negative when acute exacerbation of ILD occurred in one patient [10]. This case may indicate that macrophage activation is reduced or blocked by some mechanisms in some certain patients with anti-MDA5 antibody-positive DM/CADM-ILD together with anti-ARS antibody. In contrast, another Hispanic patient died of acute respiratory failure due to DM-ILD [11]. Therefore, whether the clinical course presents as ARS-ILD, MDA5-ILD, or their combination remains unclear. The degree of macrophage activation, ethnic factors, or the type of anti-ARS antibody may contribute to the clinical course. Further investigation is warranted to clarify this. (1090 words).

### Authors' contributions

TH, MM, SN, YM, KN, SM, MH, TU, JS, and SI contributed to the decision of treatment, collecting clinical data, data analysis, and writing the manuscript. TH, MM, SN, YM, KN, SM, MH, TU, JS, SI and TS contributed to the discussion about the patient. All authors read and approved the final manuscript.

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