

[ CASE REPORT ]

## Dermatomyositis Which Was Double Positive for Anti-MDA5 and Anti-ARS Antibodies That Was Successfully Treated by Intensive Immunosuppressive Therapy

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### Abstract:

Myositis-specific autoantibody is associated with the clinical phenotype and prognosis of dermatomyositis. Anti-melanoma differentiation-associated gene 5 (MDA5) and anti-aminoacyl-tRNA synthetase (ARS) antibodies are generally mutually exclusive. We herein present an extremely rare case of dermatomyositis which showed double positivity for anti-MDA5 and anti-ARS antibodies. There have been very few reported cases of double positive anti-MDA5, anti-ARS antibodies. In such cases, the clinical characteristics of each autoantibody can coexist. Thus, we should pay attention to the rapidly progressing features of anti-MDA5 as well as the chronic relapsing features of anti-ARS for the better management of this rare condition.

**Key words:** dermatomyositis, anti-MDA5 antibody, anti-ARS antibody, anti-PL-12 antibody, interstitial lung disease

(Intern Med 61: 1085-1091, 2022)

(DOI: 10.2169/internalmedicine.8579-21)

### Introduction

Myositis-specific autoantibodies (MSAs) are comprised of anti-aminoacyl-tRNA synthetase (ARS), anti-Mi-2, anti-transcriptional intermediary factor 1 $\gamma$ , and anti-melanoma differentiation-associated gene 5 (MDA5) antibodies (1, 2). Anti-ARS antibodies can be further classified into eight subtypes: anti-histidyl (anti-Jo-1), anti-threonyl (anti-PL-7), anti-alanyl (anti-PL-12), anti-glycyl (anti-EJ), anti-isoleucyl (anti-OJ), anti-asparaginyl (anti-KS), anti-phenylalanyl (anti-Zo), and anti-tyrosyl (anti-Ha) antibodies (3, 4). MSAs are expected to be useful for the diagnosis of dermatomyositis since the disease specificity of these autoantibodies is extremely high. In addition, these autoantibodies closely correlate with the clinical disease types and therefore are helpful for predicting any complications and for making a prognosis. Some MSAs are also useful for determining the therapeutic effects and disease activity because they correlate with the disease status (3, 4).

Anti-MDA5-positive dermatomyositis is characterized by cutaneous and oral ulceration, painful palmar papules, and rapidly progressive interstitial lung disease with fatal outcome (5, 6), whereas anti-ARS syndrome is classically known for myositis, fever, Raynaud's phenomenon, arthritis, mechanic's hands, and chronic relapsing interstitial lung disease (1). Previous studies indicated that anti-MDA5 and anti-ARS antibodies rarely coexist because MSAs are, in general, mutually exclusive (1). There have only been three reported cases which were double positive for anti-MDA5 and anti-ARS antibodies (7-9). When anti-MDA5 and anti-ARS antibodies coexist, physicians may therefore be faced with various difficulties regarding clinical judgment since these conditions require a different intensity of immunosuppressive therapy. However, due to the extreme rarity of this condition, the characteristics and prognosis of dermatomyositis which are double positive for anti-MDA5 and anti-ARS antibodies remain unknown, thus necessitating the accumulation of the cases. We herein report a case of anti-MDA5, anti-ARS double-positive dermatomyositis, and also

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Received for publication August 29, 2021; Accepted for publication September 28, 2021

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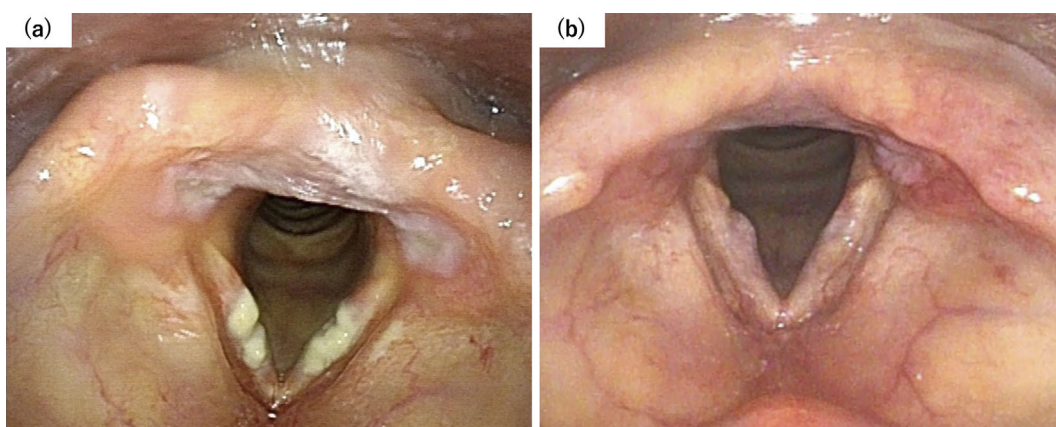
**Figure 1.** Skin findings at the time of hospitalization. (a) Heliotrope rash. (b) Mechanics hands. (c) Painful ulceration of Gottron's papules on the elbows. (d) Painful ulceration of Gottron's papules on the palm of the hands.

review the pertinent literature to increase our understanding of this condition.

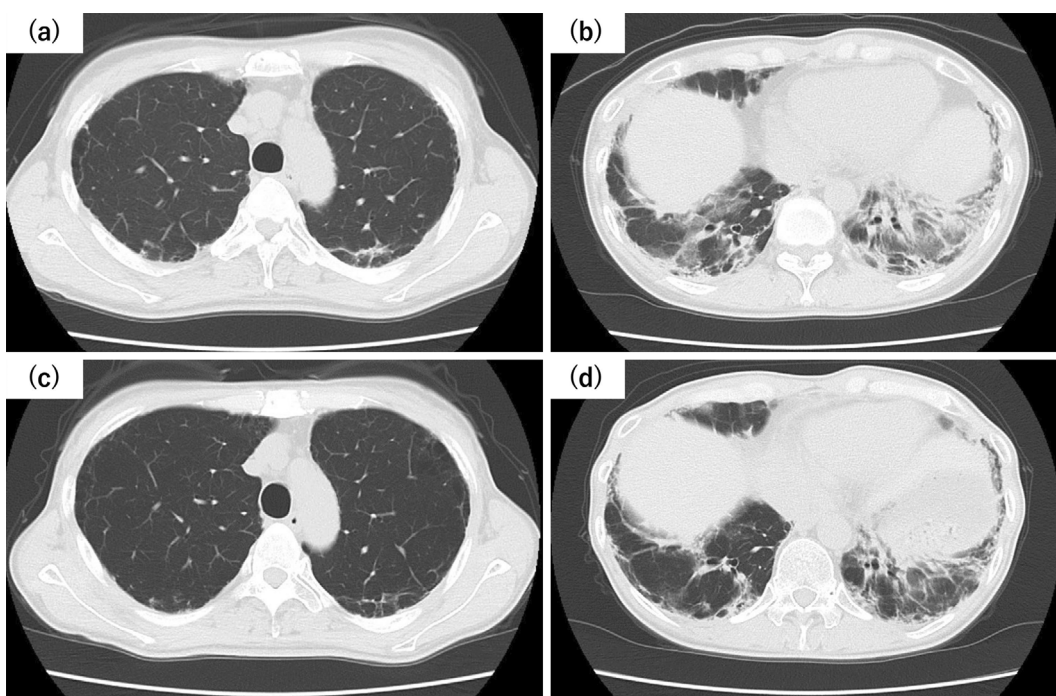
### Case Report

A 51-year-old female who had been suffering from dyspnea, hoarseness, and Gottron's papules presented to our hospital in March 2021. She had been taking a walk along the river every day for 10 years. She had no fever, Raynaud's phenomenon, or joint pain. Her arterial oxygen saturation of pulse oximetry was 88% at room air. Physical examination revealed a heliotrope rash, mechanics hands, and painful ulceration of Gottron's papules on the elbows and palm of the hands (Fig. 1a-d). Lung auscultation showed bilateral fine crackles. No muscle weakness was observed. Blood test showed elevated levels of C-reactive protein (1.83 mg/dL, normal <0.14 mg/dL), ferritin (696 ng/mL, normal <464 ng/mL), and Krebs von den Lungen-6 (1,670 U/mL, normal <500 U/mL). The serum creatinine kinase level was within the normal range (45 U/L, normal 153< U/L). Anti-MDA5 and anti-ARS antibodies were positive with extremely high titers according to the findings of an enzyme-linked immunosorbent assay (anti-MDA5 antibody; 5,000 units, normal <32 units, and anti-ARS antibody; 44.1 units, normal <25 units). MESACUP™ (Medical & Biological Laboratories, Japan) was used to measure the anti-MDA5 and anti-ARS antibodies. We further investigated the autoantigen of anti-ARS antibody by immunoblot assay [EUROLINE

Myositis Antigens Profile 3 (IgG), Euroimmun, Lübeck, Germany], which thus revealed positivity for anti-PL-12 antibody. She had HLA-DR12 (DRB1\*12:02), DR4 (DRB1\*0405), A11, A24, B13, and B35. A laryngoscope examination found the laryngeal ulcer and inflammation (Fig. 2a). Chest computed tomography (CT) revealed upper random ground-glass attenuation (GGA) and lower peripheral consolidation, reticulation and traction bronchiectasis (Fig. 3a-b). A pulmonary function test demonstrated an impaired lung diffusing capacity for carbon monoxide 34.5% (normal >70%), vital capacity (%VC) 79.0% and a forced expiratory volume in 1 second (FEV1%) 58.7%. A skin biopsy showed the vascular fibrin deposition with perivascular inflammation (Fig. 4a-c). We diagnosed her to have clinically amyopathic dermatomyositis (CADM) complicated with interstitial lung disease, showing the characteristics for both anti-MDA5 (reverse Gottron's papules with ulcers, and peripheral consolidations and random ground-glass attenuations on chest CT) and anti-ARS (mechanic's hands, and reticulation and traction bronchiectasis on chest CT) antibodies. She was treated with a nasal canula and intensive combination therapy with methylprednisolone pulse (1 g daily for three days), followed by high dose of prednisolone (60 mg/day), intravenous cyclophosphamide (1,000 mg every 2-3 weeks, 6 times), and tacrolimus (trough concentration: 10 ng/mL). Her dyspnea disappeared soon thereafter and she could thus stop the use of the nasal canula. The painful ulceration of Gottron's papules gradually improved



**Figure 2.** The laryngeal findings obtained from the laryngoscopy examination. (a) The presence of a laryngeal ulcer and inflammation at the time of hospitalization. (b) The complete resolution of laryngeal inflammation after administering intensive immunosuppressive therapy.



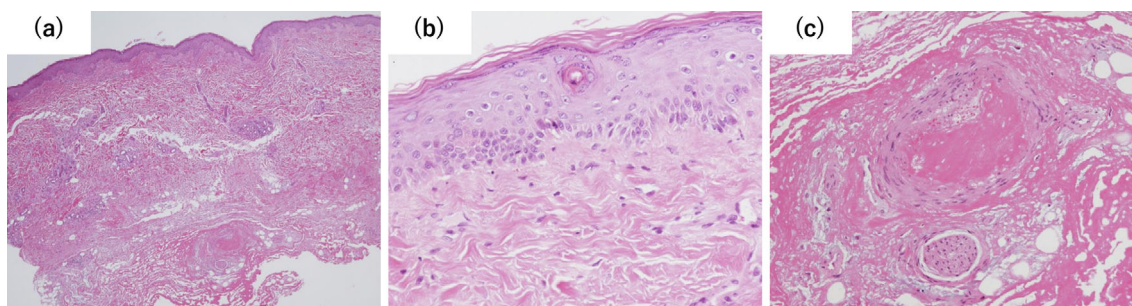
**Figure 3.** The findings of the chest computed tomography (CT). (a) Upper random ground-glass attenuation (GGA). (b) Lower peripheral consolidation, reticulation and traction bronchiectasis. (c, d) The chest CT findings at the 3-month follow-up after treatment. An improvement was observed of the consolidations, and the residual ground glass opacities with reticulation and traction bronchiectasis.

(Fig. 5a-d). A re-examination using a laryngoscope showed the complete resolution of laryngeal inflammation (Fig. 2b). Chest CT at the 3-month follow-up after treatment revealed an improvement of the consolidations but the residual ground glass opacities with reticulation and traction bronchiectasis still remained (Fig. 3c-d). A pulmonary function test showed a marked improvement; lung diffusing capacity for carbon monoxide of 43.8%, %VC of 98.9%, and FEV<sub>1</sub> of 84.2%. Serum C-reactive protein and ferritin levels normalized. The titer of anti-MDA5 antibody also tended to decrease (1,150 units at 3 months after the immunosuppressive

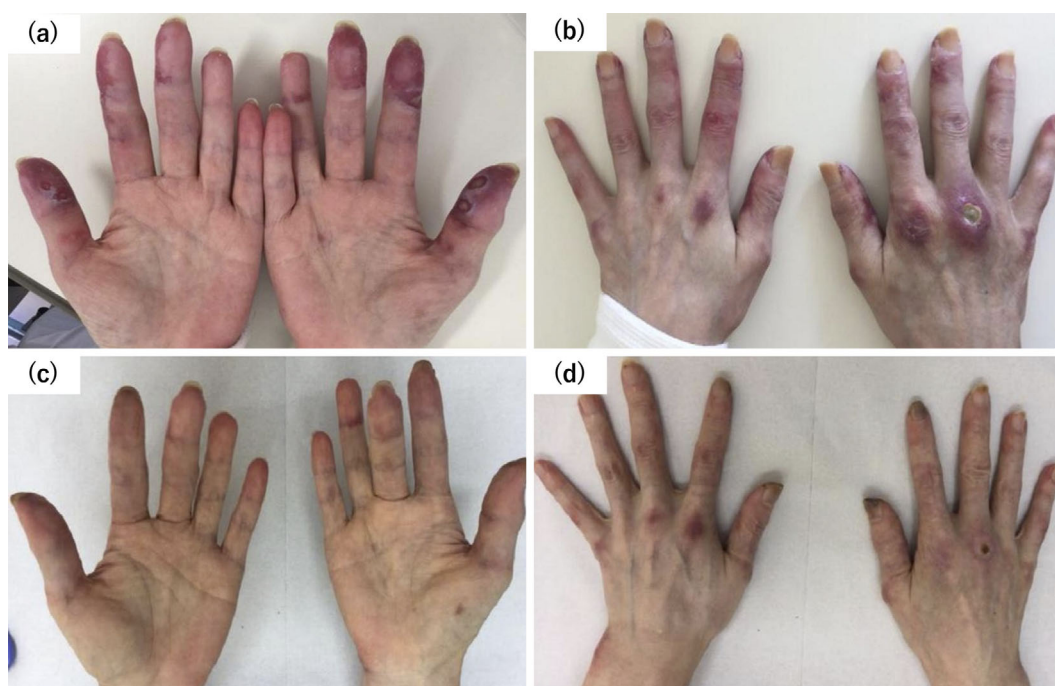
therapy), and anti-ARS antibody was then found to be negative in parallel with the observed clinical improvements. The prednisolone dose was gradually tapered to 10 mg/day, and intravenous cyclophosphamide was switched to oral azathioprine. Currently, her disease status remains stable without any relapse for six months.

## Discussion

Table shows the detailed information of four reported cases of double positive anti-MDA5, anti-ARS antibodies in-



**Figure 4.** The pathological findings of a skin biopsy; Hematoxylin and Eosin staining. (a) The edema of the dermis, and the infiltration of lymphocyte-based inflammatory cell around blood vessels. (b) The perivascular inflammation. (c) The vascular fibrin deposition.



**Figure 5.** Clinical course of the skin findings. (a, b) The worst skin findings were observed on day 45 of hospitalization. (c, d) The painful ulceration of Gottron's papules improved at 6 months after treatment.

cluding our present case. Three cases were Japanese and one case was Hispanic. All cases were female. The mean age was 44 years of age (range: 27 to 53). All cases had poor muscle symptoms and had skin rash such as Gottron's papules. Two cases had anti-MDA5 antibody associated skin ulcerations in addition to the anti-ARS antibody associated skin manifestations such as mechanics hands. The details of four anti-ARS antibodies were as follows: anti-PL-7 (n=2), anti-PL-12 (n=1), and anti-EJ (n=1). Three cases had chest CT findings for both anti-MDA5 (peripheral consolidations and random ground-glass attenuations) and anti-ARS (reticulation and traction bronchiectasis) antibodies. All cases were treated with intensive combination therapy. Two cases experienced disease relapses during the clinical course. One case was refractory to the combination therapy and eventually died.

Anti-MDA5 antibody positive dermatomyositis has a high

mortality rate (41%) due to the onset of rapidly progressive interstitial lung disease within 6 months after the diagnosis, but recurrence rarely occurs once such patients have survived (10). On the other hand, anti-ARS antibody-positive dermatomyositis manifests a chronic relapsing course (11). As shown in Table, the cases of double positive anti-MDA5, anti-ARS antibodies can show not only a rapidly progressing clinical course, but also a chronic relapsing course. Thus, if clinicians encounter cases of double positive anti-MDA5, anti-ARS antibodies, they should pay close attention to the rapidly progressing features of anti-MDA5 antibody positive interstitial lung disease as well as chronic relapsing features of anti-ARS antibody in order to successfully manage this condition.

The characteristics of the chest CT findings of anti-MDA5 antibody positive interstitial lung disease have been reported to show consolidation in the lower lobe, random

**Table. The Characteristics of Four Cases of Anti-MDA-5, Anti-ARS Double-positive Dermatomyositis Including Our Case.**

| Ref.                    | 7  | 8   | 9   | Our case   |
|-------------------------|--|---|---|--|
| Race                    | Japanese   | Japanese  | Hispanic  | Japanese   |
| Sex                     | Female   | Female  | Female  | Female   |
| Age (years-old)         | 43   | 53  | 27  | 51   |
| Anti-ARS antibody       | Anti-PL-7  | Anti-EJ   | Anti-PL-7   | Anti-PL-12   |
| Diagnostic testing tool | Immunoprecipitation assay  | Immunoprecipitation assay   | Immunoblot assay  | ELISA and immunoblot assay   |
| Skin findings           | Heliotrope rash, facial erythema, shawl sign, Gottron's papules, periungual erythema, nail fold bleeding               | Heliotrope rash, facial erythema, Gottron's papules with ulcers, mechanic's hands, periungual erythema  | Gottron's papules   | Heliotrope rash, mechanics hands, Gottron's papules with ulcers  |
| Findings of ILD         | Consolidations and GGA with peripheral distribution, subpleural line, intralobular reticular opacities with subpleural | Initial presentation with anti-EJ and anti-MDA5: Lower peripheral reticulation and GGA. 15 years after onset during acute exacerbation with anti-MDA5: Rapidly progressive course with newly developed random GGA | Extensive GGA bilaterally without bronchiectasis                                    | Upper random GGA, lower peripheral reticulation with consolidation and traction bronchiectasis                                       |
| Treatment               | PSL (1 mg/kg) + TAC + IVCY + IVIg  | High dose steroid + TAC + IVCY + Plasmapheresis   | Methylprednisolone pulse + IVIg + RTX   | Methylprednisolone pulse + TAC + IVCY + IVIg   |
| Respiratory assistance  | Unknown  | High-flow nasal cannula   | VV-ECMO   | Nasal cannula 1L/min   |
| Observation period      | 3 and half years   | 15 years  | 23 days   | 6 months   |
| Clinical course of ILD  | Gradually progressive traction bronchiectasis and volume loss of the lower lobes                                       | Gradually progressive traction bronchiectasis and volume loss of the lower lobes  | Worsening of consolidation and persistent patchy ground glass opacities bilaterally | Improvement of consolidations but the residual lower peripheral ground glass opacities with reticulation and traction bronchiectasis |
| Outcome                 | Surviving with some relapse  | Surviving with some relapse   | Passed away   | Surviving  |

PSL: prednisolone, TAC: tacrolimus, AZP: azathioprine, IVCY: intravenous cyclophosphamide, IVIg: intravenous immunoglobulin, GGA: ground-glass attenuation

ground glass attenuation, and the absence of intralobular reticular opacities (12). On the other hand, the chest CT findings of anti-ARS antibody positive interstitial lung disease are characterized by nonspecific interstitial pneumonia, reticulation, and traction bronchiectasis, which are predominantly distributed in the lower lobe, peripheral and/or peribronchovascular areas (13-15). The findings of our present case had the characteristics of both anti-MDA5 and anti-ARS antibodies; upper random ground glass attenuation and lower consolidation as the characteristics of anti-MDA5 antibody, whereas lower peripheral reticulation with traction bronchiectasis occurred as the characteristics of anti-ARS antibody. Interestingly, the findings of upper random ground glass attenuation and lower consolidation improved after the administration of intensive immunosuppressive therapy, while lower peripheral reticulation with traction bronchiectasis remained refractory. Of note, each subclass of anti-ARS antibodies is associated with the certain clinical features, and anti-PL-7 or anti-PL-12 antibody positive cases are known for being associated with treatment-resistant interstitial lung disease with a poor prognosis (16), and these findings were consistent with our present case.

The titer of anti-MDA5 antibody reflects the severity and disease activity of rapidly progressive interstitial lung disease in patients with CADM (17, 18). Our present case showed an extremely high titer of anti-MDA5 antibody, sug-

gesting a severe type of this condition. The titer of anti-MDA5 antibody decreased after the administration of immunosuppressive therapy, and serial monitoring of this antibody might be useful in order to recognize the early signs of disease relapse in the future.

One study reported that the titer of anti-Jo-1 antibody correlated with the disease activity (19), while another study also reported that anti-EJ antibody became negative after performing immunosuppressive therapy (8). Our case showed the negative conversion of anti-ARS antibody after immunosuppressive therapy during the clinical course. Thus, it is of great interest to examine whether the titer of anti-ARS antibody may reflect the disease activity and thus predict any disease relapse in the future.

Previous studies reported that oral erosion is one of the characteristic features of anti-MDA5-antibody positive CADM (20, 21). To our knowledge, this is the second case describing a laryngeal ulcer in anti-MDA5-antibody positive CADM. In line with the first report (22), the laryngoscopic findings improved after immunosuppressive therapy along with an improvement of the skin ulcers in our case, suggesting that laryngeal involvement was associated with the pathophysiology of anti-MDA5-antibody positive CADM. The pathophysiology of skin lesions in anti-MDA5-antibody positive CADM is considered to be a type of vasculopathy characterized by perivascular inflammation and vascular fi-

brin deposition (21), as shown in our present case. If clinicians encounter cases presenting with hoarseness and skin rash, it is important to consider the possibility of anti-MDA5-antibody positive CADM in order to make an early diagnosis and start treatment in a timely manner due to the potentially fatal nature of the disease.

Regarding host genetic factors, multiple studies have reported the association of HLA-DR12 (HLA-DRB1\*12:01 and HLA-DRB1\*12:02) with anti-MDA5 antibody positive cases (23-25). HLA-DR4 (DRB1\*0405) was reported to be associated with anti-MDA5 (26) or anti-ARS antibody positive cases in Japan (27). Our case showed both HLA-DR12 (DRB1\*12:02) and DR4 (DRB1\*0405), which might be the candidate genetic factors for the cases with double positive anti-MDA5, anti-ARS antibodies. Further studies are required to examine whether specific genetic factors are associated with the onset of double positive anti-MDA5, anti-ARS antibodies in CADM.

In conclusion, we herein presented our case of CADM which was found to be double positive for anti-MDA5, anti-ARS (anti-PL-12) antibodies. It is considered that MSAs are generally mutually exclusive, but there have been some cases of double positive anti-MDA5, anti-ARS antibodies. In those cases, the clinical characteristics of each autoantibody can coexist, thus suggesting the necessity of clinicians to pay particular attention to each of them. Due to the small number of cases of double positive anti-MDA5, anti-ARS antibodies, further investigation is needed in the future.

Written informed consent for publication of this case report was obtained from the patient by the author.

**The authors state that they have no Conflict of Interest (COI).**

Satoshi Hama and Misako Higashida-Konishi contributed equally.

## References

- Hamaguchi Y, Fujimoto M, Matsushita T, et al. Common and distinct clinical features in adult patients with anti-aminoacyl-tRNA synthetase antibodies: heterogeneity within the syndrome. *PLoS One* **8**: e60442, 2013.
- Mimori T, Imura Y, Nakashima R, Toshifuji H. Autoantibodies in idiopathic inflammatory myopathy: an update on clinical and pathophysiological significance. *Curr Opin Rheumatol* **19**: 523-529, 2007.
- Nakashima R. Clinical significance of myositis-specific autoantibodies. *Immunol Med* **41**: 103-112, 2018.
- Hamaguchi Y, Kuwana M, Hoshino K, et al. Clinical correlations with dermatomyositis-specific autoantibodies in adult Japanese patients with dermatomyositis: a multi-centre, cross-sectional study. *Arch Dermatol* **147**: 391-398, 2011.
- Kurtzman D, Vleugels A. Anti-melanoma differentiation-associated gene 5 (MDA5) dermatomyositis: a concise review with an emphasis on distinctive clinical features. *J Am Acad Dermatol* **78**: 776-785, 2018.
- Gono T, Kuwana M. Inflammatory myopathies: choosing the right biomarkers to predict ILD in myositis. *Nat Rev Rheumatol* **12**: 504-506, 2016.
- Naniwa T, Tamechika S, Okazaki Y, Maeda S, Kuwana M. Coexistence of anti-melanoma differentiation-associated gene 5 and anti-aminoacyl-transfer RNA synthetase antibodies in a patient with dermatomyositis and rapidly progressive and relapsing interstitial lung disease. *Mod Rheumatol Case Rep* **1**: 3-8, 2017.
- Takeuchi Y, Hashimoto M, Nakashima R, et al. Anti-EJ, anti-MDA5 double-positive chronic clinically amyopathic dermatomyositis: a case report. *Rheumatol Adv Pract* **2**: rky022, 2018.
- Li ZY, Gill E, Mo F, Reyes C. Double anti-PL-7 and anti-MDA5 positive amyopathic dermatomyositis with rapidly progressive interstitial lung disease in a Hispanic patient. *BMC Pulm Med* **20**: 220, 2020.
- Koga T, Fujikawa K, Horai Y, et al. The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody testing for predicting the prognosis of Japanese patients with DM. *Rheumatology (Oxford)* **51**: 1278-1284, 2012.
- Isoda K, Kotani T, Takeuchi T, et al. Comparison of long-term prognosis and relapse of dermatomyositis complicated with interstitial pneumonia according to autoantibodies: anti-aminoacyl tRNA synthetase antibodies versus anti-melanoma differentiation-associated gene 5 antibody. *Rheumatol Int* **37**: 1335-1340, 2017.
- Tanizawa K, Handa T, Nakashima R, et al. HRCT features of interstitial lung disease in dermatomyositis with anti-CADM-140 antibody. *Respir Med* **105**: 1380-1387, 2011.
- Nakashima R, Hosono Y, Mimori T. Clinical significance and new detection system of autoantibodies in myositis with interstitial lung disease. *Lupus* **25**: 925-933, 2016.
- Waseda Y, Johkoh T, Egashira R, et al. Antisynthetase syndrome: pulmonary computed tomography findings of adult patients with antibodies to aminoacyl-tRNA synthetases. *Eur J Radiol* **85**: 1421-1426, 2016.
- Hervier B, Wallaert B, Hachulla E, et al. Clinical manifestations of anti-synthetase syndrome positive for anti-alanyl-tRNA synthetase (anti-PL12) antibodies: a retrospective study of 17 cases. *Rheumatology (Oxford)* **49**: 972-976, 2010.
- Rohit A, Elaine C, Noreen F, et al. Patients with non-Jo-1 anti-tRNA-synthetase autoantibodies have worse survival than Jo-1 positive patients. *Ann Rheum Dis* **73**: 227-232, 2014.
- Sato S, Kuwana M, Fujita T, Suzuki Y. Anti-CADM-140/MDA5 autoantibody titer correlates with disease activity and predicts disease outcome in patients with dermatomyositis and rapidly progressive interstitial lung disease. *Mod Rheumatol* **23**: 496-502, 2013.
- Matsushita T, Mizumaki K, Kano M, et al. Antimelanoma differentiation-associated protein 5 antibody level is a novel tool for monitoring disease activity in rapidly progressive interstitial lung disease with dermatomyositis. *Br J Dermatol* **176**: 395-402, 2017.
- Kerry B, Oddis CV, Fertig N, et al. Anti-Jo-1 antibody levels correlate with disease activity in idiopathic inflammatory myopathy. *Arthritis Rheum* **56**: 3125-3131, 2007.
- Paige W, David F. Dermatomyositis clinical and pathological phenotypes associated with myositis-specific autoantibodies. *Curr Rheumatol Rep* **20**: 28, 2018.
- David F, Chung L, Zwerner J, Rosen A, Casciola-Rosen L. The mucocutaneous and systemic phenotype of dermatomyositis patients with antibodies to MDA5 (CADM-140): a retrospective study. *J Am Acad Dermatol* **65**: 25-34, 2011.
- Sugimori Y, Yamashita H, Yorifuji H, et al. A case of clinically amyopathic dermatomyositis with hoarseness due to vocal cord necrosis. *J Clin Rheumatol* **24**: 50-51, 2018.
- Kang EH, Go DJ, Mimori T, et al. Novel susceptibility alleles in HLA region for myositis and myositis specific autoantibodies in Korean patients. *Semin Arthritis Rheum* **49**: 283-287, 2019.
- Lin JM, Zhang YB, Peng QL, et al. Genetic association of HLA-

- DRB1 multiple polymorphisms with dermatomyositis in Chinese population. *HLA* **90**: 354-359, 2017.
25. Chen Z, Wang Y, Kuwana M, et al. HLA-DRB1 alleles as genetic risk factors for the development of anti-MDA5 antibodies in patients with dermatomyositis. *J Rheumatol* **44**: 1389-1393, 2017.
26. Gono T, Kawaguchi Y, Kuwana M, et al. Brief report: association of HLA-DRB1\*0101/\*0405 with susceptibility to anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis in the Japanese population. *Arthritis Rheum* **64**: 3736-3740, 2012.
27. Furuya T, Hakoda M, Tsuchiya N, et al. Immunogenetic features in 120 Japanese patients with idiopathic inflammatory myopathy. *J Rheumatol* **31**: 1768-1774, 2004.

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*Intern Med* 61: 1085-1091, 2022