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【 CASE REPORT 】

# Anti-melanoma Differentiation-associated Gene 5 Antibody-positive Dermatomyositis Presenting as Refractory Gingivitis at the First Clinical Manifestation

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**Abstract:**
We herein report a case of melanoma differentiation-associated gene 5 (MDA5) antibody-positive dermatomyositis that developed in a patient with refractory gingivitis. The diagnosis of anti-MDA5 antibody-positive dermatomyositis was made based on a characteristic skin rash, weakness of proximal muscles, interstitial pneumonia, and positivity for anti-MDA5 antibody. The patient was started on triple therapy with high-dose prednisolone, tacrolimus, and intravenous cyclophosphamide. After treatment, the refractory gingivitis disappeared, and the other skin rash and interstitial lung disease also improved. In the diagnosis and treatment of anti-MDA5 antibody-positive dermatomyositis, it is necessary to pay attention to the intraoral findings, including the gingiva.

**Key words:** dermatomyositis, anti-melanoma differentiation-associated gene 5 (MDA5) antibody, gingivitis

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## Introduction

Dermatomyositis (DM) is an autoimmune disease that mainly causes inflammation and damage to the proximal muscles and damage to various organs, such as the lungs, heart, and mucocutaneous lesions (1). Various myositis-specific autoantibodies related to DM have been reported (2). Among these, anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive DM is a subtype of DM that is induced through type 1 interferon and vasculopathy (3-5). Skin ulcers, palmar papules, and rapidly progressive interstitial lung disease (RPILD) are known to be characteristic features of anti-MDA5 antibody-positive DM (1, 2, 6), but other vasculopathy-associated mucocutaneous lesions of oral ulcers/gingival abnormalities are also reported (3, 7).

We herein report a case of anti-MDA5 antibody-positive DM presenting with refractory gingivitis at the first clinical manifestation.

## Case Report

A 53-year-old Japanese woman presented with refractory gingivitis (Fig. 1A). She reported having gum pain that had not responded to traditional dental treatment. No significant infectious agents of the oral cavity were detected, nor was she taking any drugs, including phenytoin and calcium channel blockers, that might induce gingivitis, with no history suggesting nutritional deficiency.

Five months after the onset of the gingivitis, she developed polyarthralgia and erythema of bilateral fingers and was admitted to our hospital for a further examination. Anti-citrullinated protein antibodies and rheumatoid factor were negative, and there were no findings of radiographic erosion. Thus, the diagnosis of rheumatoid arthritis was not made in this patient.

She had no family history of connective tissue diseases.

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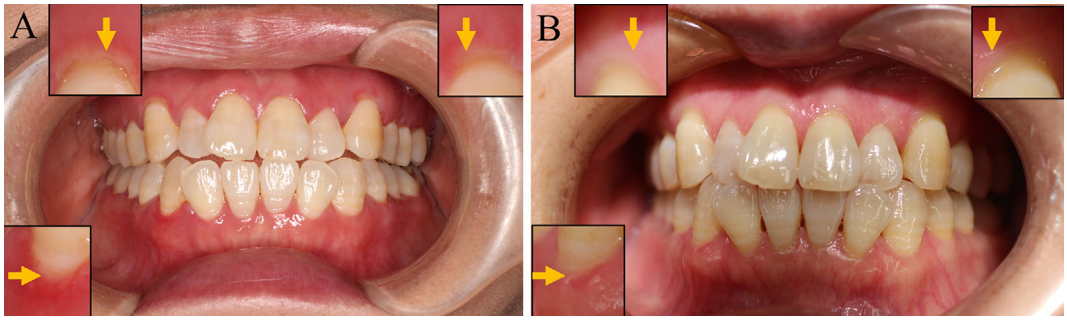


**Figure 1.** **Gingivitis before and after treatment. Painful redness with ulceration at multiple sites of the upper and lower gums (A, highlighted within the squares) was observed before treatment and disappeared after one month of combined immunosuppressive therapy that included prednisolone, tacrolimus, and intravenous cyclophosphamide (B, highlighted within the squares). Arrows show ulceration of the gums.**

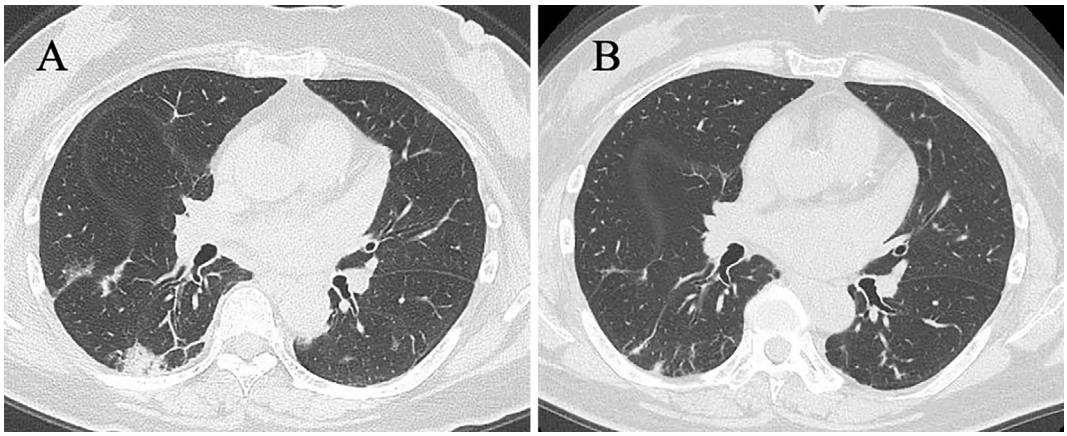


**Figure 2.** **Interstitial lung disease on chest CT before and after treatment. Bilateral linear reticular shadows as well as a patchy shadow just below the pleura were identified by chest CT before treatment (A) and markedly improved after one month of combined immunosuppressive therapy that included prednisolone, tacrolimus, and intravenous cyclophosphamide (B).**

At admission, her vital signs were as follows: blood pressure 93/56 mmHg; pulse rate, 58 beats/min; and temperature, 36.7°C. A physical examination revealed gingivitis manifesting as painful redness with ulceration at multiple sites of the upper and lower gums (Fig. 1A), heliotrope rashes, and Gottron's papules over her knees. Periungual inflammation with ulcers was observed on both fingers and toes. Muscle weakness of the neck, proximal upper limbs, and proximal lower limbs was revealed by manual muscle testing. The patient suffered from polyarthralgia at the joints of both shoulders, wrists, and ankles in addition to the fingers and toes.

Laboratory data showed elevated levels of serum aldolase (11.5 U/L), LDH (328 U/L), ferritin (1,216 ng/mL), and anti-MDA5 antibody (1,600 index). Creatine kinase was within the normal limit (146 U/L). She had not complained of dyspnea or cough, but chest computed tomography (CT) demonstrated bilateral linear reticular shadows as well as a patchy shadow just below the pleura (Fig. 2A). The percentage carbon monoxide diffusing capacity (%DLCO) was 39.9%, and the % vital capacity (%VC) was 74.9% (Fig. 3).

We made a diagnosis of anti-MDA5 antibody-positive DM based on the European League Against Rheumatism/American College of Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and their Major Subgroups (8). The combined use of prednisolone with immunosuppressants was recently recommended for the chronic form of ILD in patients with anti-MDA5 antibody-positive DM (9). In addition, although our patient did not show RPILD, poor prognostic factors of a high titer of anti-MDA5 antibody, high ferritin level, and low %DLCO of anti-MDA5 antibody-positive DM (10, 11) have been described, so we decided to adapt a combined immunosuppressive regimen treatment with prednisolone (60 mg/day), tacrolimus (6 mg/day), and intravenous cyclophosphamide (750 mg/m$^2$ once every 3 weeks) as described (12) (Fig. 3).

After 1 month of this treatment, chest CT showed improvement of ILD (Fig. 2B). The %DLCO and %VC also improved to 54.1% and 100% at 1 month, and these values had further improved to 74.71% and 121.4% at 9 months. The periungual inflammation and muscle weakness also improved. Notably, with this immunosuppressive therapy, the

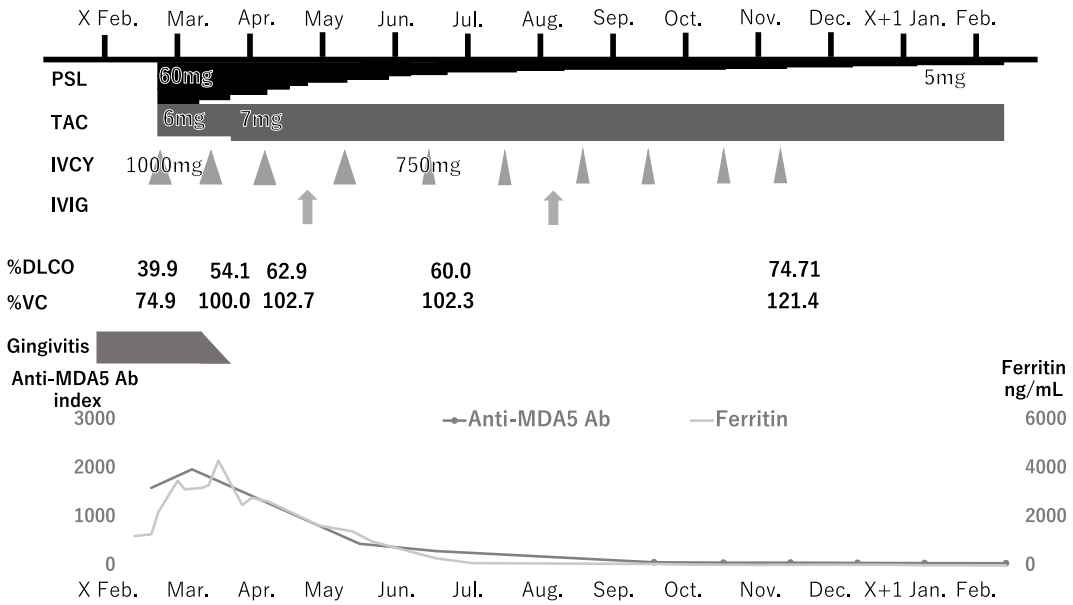


**Figure 3.** **The clinical course of the patient. DLCO: carbon monoxide diffusing capacity, IVIG: intravenous immunoglobulin, MDA5 Ab: melanoma differentiation-associated gene 5 antibody, PSL: prednisolone, TAC: tacrolimus, VC: vital capacity**

patient's gingivitis [ulceration (arrows) and redness of her gums, shown in Fig. 1A] had improved and disappeared by 1 month after treatment initiation (Fig. 1B). Prednisolone was tapered to 5 mg/day, and no relapse, including that of gingivitis or ILD, was observed at 1 year after treatment initiation. The above treatments were well tolerated, and there were no obvious adverse events.

## Discussion

Individuals with anti-MDA5 DM have a distinctive mucocutaneous phenotype that might reflect a severe underlying vasculopathy (3-5). This phenotype includes cutaneous ulceration, alopecia, lateral digit hyperkeratosis or scaling, palmar papules, oral ulcers/gingival abnormalities, and panniculitis (3-5). Our patient exhibited gingivitis as the first clinical manifestation. A rate of oral ulcers/gingival abnormalities up to 50% has been reported in patients with anti-MDA5 DM (3, 7), indicating that oral ulcers/gingival abnormalities are not rare. However, our literature search suggested that the present case was the first case of an individual with anti-MDA5 DM who exhibited gingival abnormalities as the initial clinical manifestation. ILD, especially RPILD, is usually a therapeutic target for patients with anti-MDA5 antibody-positive DM (1, 12, 13), and gingival abnormalities are probably a lesser focus.

It has been demonstrated that painful oral ulcers can affect any site within the oral cavity, including the gingiva, buccal mucosa, tongue, and palate (7). Oral gingivitis was documented in the present patient, and it disappeared after immunosuppressive therapy. Ono et al. demonstrated that anti-MDA5 DM patients exhibited more severe perivascular inflammation in skin lesions on histology than anti-aminoacyl transfer RNA synthetases positive DM patients, along with a strong type 1 interferon signature in their blood and skin, distributed particularly in the vasculature (4). In systemic lupus erythematosus patients, several reports have demonstrated that a type 1 interferon signature causes endothelial dysfunction (14, 15). Although a biopsy of gingival tissues was not performed in our patient, we considered the gingivitis in our patient to have been caused by the strong expression of type 1 interferon because of recovery due to immunosuppressive treatment of prednisolone, tacrolimus, and intravenous cyclophosphamide. Accordingly, the frequency of oral ulcers in anti-MDA5-negative DM patients is significantly lower than in anti-MDA5-positive DM patients (3).

The mortality of patients with anti-MDA5 DM is high (16, 17), making the early recognition of this disease important. Physicians should pay attention to refractory gingivitis because it can be an initial manifestation of anti-MDA5 antibody-positive DM.

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

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