

An Atypical Clinical Course of Anti-MDA5 Antibody-positive Interstitial Lung Disease in a Patient with Three Deteriorations in 9 years

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Abstract

Anti-MDA5 antibody-positive patients with clinically amyopathic dermatomyositis (CADM) are at high risk of developing rapidly progressive interstitial lung disease (ILD), which is associated with a high mortality rate. Approximately half of the patients with ILD recover; however, the long-term clinical course of these patients has not been fully reported and is not completely understood. This report describes the atypical clinical course of an anti-MDA5 antibody-positive CADM patient who experienced three deteriorations of ILD in 9 years. These findings indicate that the ILD in anti-MDA5 antibody-positive patients may not only be rapidly progressive, but may also be chronic and recurrent.

Key words: anti-MDA5 antibody, clinically amyopathic dermatomyositis (CADM), rapidly progressive interstitial lung disease (RP-ILD)

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Introduction

Clinically amyopathic dermatomyositis (CADM), a subtype of dermatomyositis (DM), with little or no muscle involvement, is frequently accompanied by rapidly progressive interstitial lung disease (RP-ILD), which is resistant to aggressive immunosuppressive therapy and often fatal (1-3). The detection of the antibody to CADM-140/melanoma differentiation-associated gene 5 (MDA5) is diagnostic for CADM, and is strongly associated with the pathogenesis, disease activity, and mortality of RP-ILD (4-6). The mortality rate of anti-MDA5 antibody-positive CADM patients who develop RP-ILD is reported to be approximately 50%, with most deaths occurring during the very early stages of the illness (7, 8). To our knowledge, there have been no reports of patients experiencing multiple deteriorations of anti-MDA5 antibody-associated ILD. This report describes the case of an anti-MDA5 antibody-positive CADM patient who experienced three deteriorations of ILD over 9 years.

Case Report

A 59-year-old Japanese woman presented to our hospital with a high fever and erythema on her elbows and knees that had started 2 weeks previously. She had no relevant medical history, and no history of cigarette smoking or allergies. A physical examination revealed Gottron's papules, periungual erythema, the shawl sign, scaling erythema on both knees and elbows, and fine crackles at the bases of both lungs. We did not observe muscle weakness, myalgia, reverse Gottron's sign or skin ulcers. A chest X-ray revealed ground glass opacities (GGO) in both lower lung fields (Fig. 1a). Chest computed tomography (CT) revealed bilateral lower consolidation, non-septal plate-like opacity, intralobular septal thickening, and traction bronchiectasis (Fig. 2a). Laboratory analyses revealed an erythrocyte sedimentation rate of 93 mm/h, a C-reactive protein concentration of 1.9 mg/dL, a KL-6 level of 1,147 IU/L, an SP-D concentration of 250 ng/mL, a creatinine kinase level of 303

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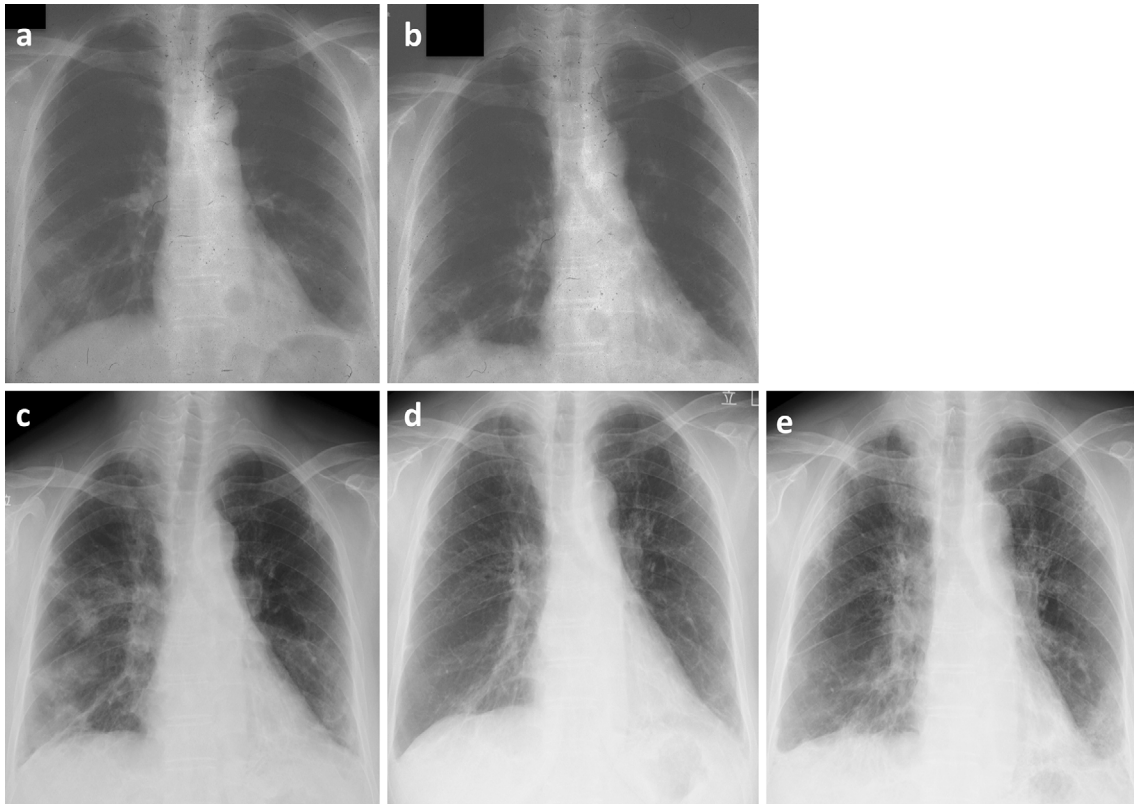


Figure 1. Chest X rays of our patient at the onset (a) and after the first (b), second (c), and third (e) deteriorations of ILD, showing the peripheral infiltration in the lower lung field and volume loss. A chest X ray taken during remission, between the second and third deteriorations, is shown (d) for comparison.

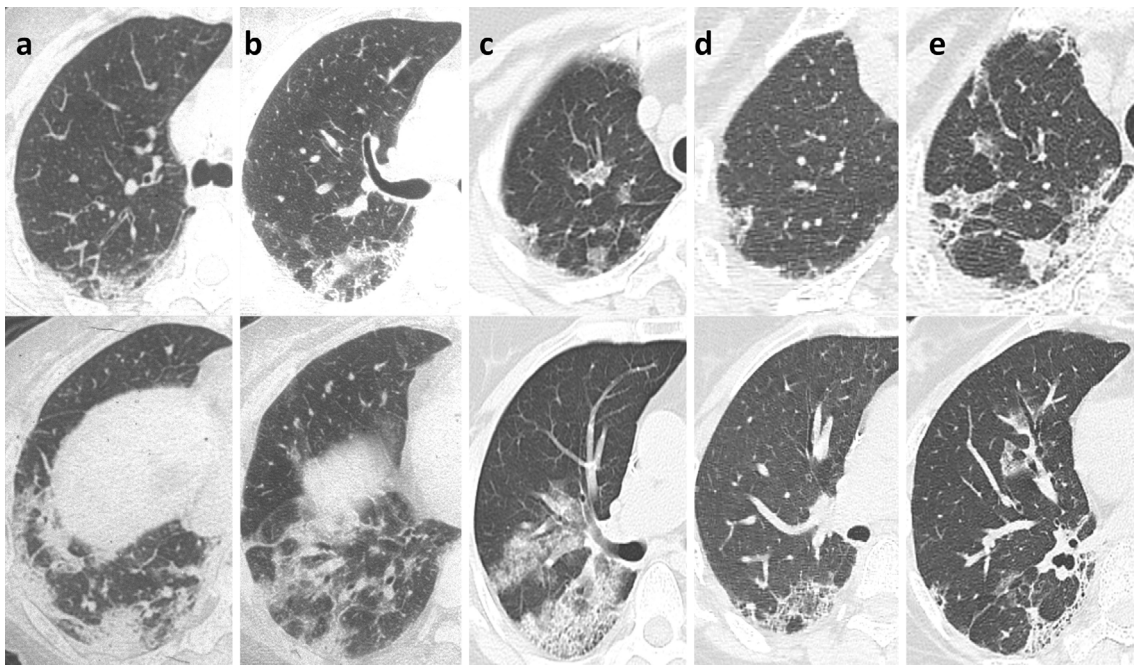


Figure 2. Chest CT scans of our patient at the onset (a) and after the first (b), second (c), and third (e) deteriorations of ILD, showing peribronchovascular consolidation in the dorsal lungs and non-septal plate-like opacities, intralobular septal thickening, traction bronchiectasis, and peripheral intralobular reticular opacities. The longitudinal levels were not the same, because typical patterns are shown in this figure. A chest CT scan taken during remission, between the second and third deteriorations, is shown for comparison (d).

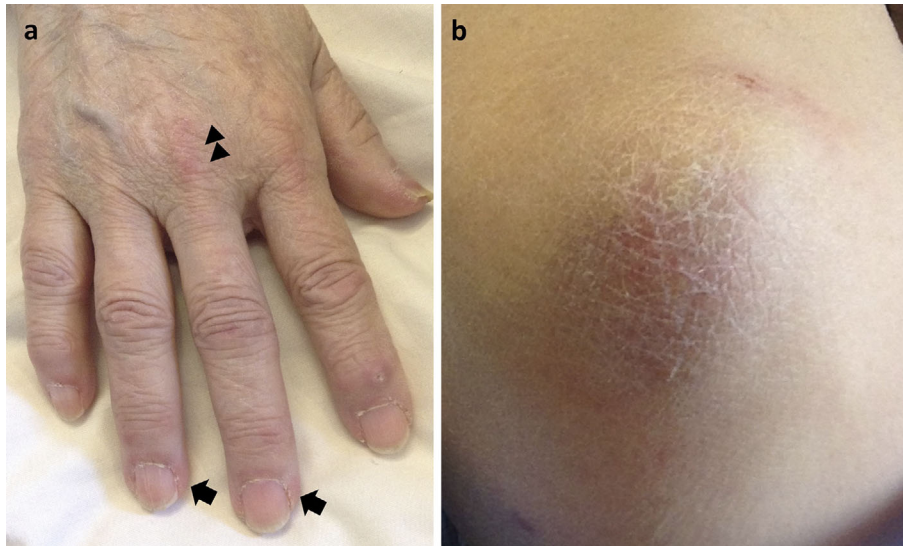


Figure 3. The skin symptoms of this patient, showing (a) periungual erythema (arrows) and Gottron's papules (arrowheads), and (b) scaling erythema on the elbows.

IU/L, and an aldolase level of 5.1 IU/L. Her complete blood cell count and liver and renal functions were normal. Rheumatoid factor, antinuclear autoantibodies, and Jo-1 antibodies were not detected. An electromyogram revealed normal findings, thus we did not perform a muscle biopsy. She was diagnosed with possible dermatomyositis (9) and treatment with oral prednisolone (PSL; 30 mg/day) was initiated. Her fever and dermatological symptoms improved quickly, and her lung GGOs gradually disappeared. The corticosteroid dose was gradually tapered at the outpatient clinic.

One year later, the patient presented with dyspnea on exertion (DOE), low-grade fever, and the worsening of Gottron's papules and scaling erythema. She was taking PSL (10 mg/day). An arterial blood gas (ABG) analysis in ambient air revealed partial pressure oxygen (PaO_2) level of 74.7 Torr in the arterial blood and a partial pressure carbon dioxide (PaCO_2) level of 37.5 Torr. Chest X-ray and CT revealed the worsening of peripheral intralobular reticular opacities, bilateral patchy consolidations, and GGOs, which were dominant along the bronchi in the dorsal lung (Fig. 1b, 2b). Treatment with cyclosporine and PSL (30 mg/day), improved her symptoms and chest X-ray findings, but she developed general malaise and thrombocytopenia. An adverse effect was suspected and the cyclosporine therapy was discontinued. She was maintained on low-dose PSL as an outpatient.

Four years after the first visit, she experienced a second deterioration while taking low-dose PSL (10 mg/day) as a maintenance therapy. She presented with DOE, a high fever, a productive cough, and the worsening of Gottron's papules and the shawl sign. A chest X-ray revealed the worsening of the bilateral GGOs (Fig. 1c), and chest CT showed peripheral intralobular reticular opacities and subpleural non-segmental patchy GGOs (Fig. 2c). She was diagnosed with the deterioration of ILD and started on high-dose methylprednisolone (500 mg/day) for 3 days, followed by PSL (30

mg/day). We recommended that she start taking an immunosuppressive agent, but she refused due to the adverse effects to the drugs that she had experienced at the time of the first deterioration. Moreover, her response to steroid treatment was fairly good, her symptoms improved and she was discharged. Her PSL dose was gradually tapered, and she was maintained on PSL (5 mg/day) as an outpatient. The chest X-ray and chest CT findings showed that she remained in remission at 8 years after the initial visit (Fig. 1d, 2d).

Nine years after the first visit, she again presented with DOE, a high fever, the worsening of Gottron's papules, periungual erythema, the shawl sign, and scaling erythema (Fig. 3). An ABG analysis in ambient air revealed a PaO_2 value of 71.3 Torr and a PaCO_2 value of 42.2 Torr. Her serum levels of KL-6 and ferritin were 652 U/mL and 162 ng/mL, respectively, but her CK and aldolase levels were within the normal limits. The levels of anti-cyclic citrullinated peptide (CCP) and anti-centromere antibodies were also elevated, but arthritis, scleroderma, dysphagia and constipation were not observed. A hand X-ray and echocardiography revealed no bone erosion or pulmonary hypertension. Thus, she was not diagnosed with rheumatoid arthritis or systemic sclerosis. A chest X-ray revealed the worsening of the bilateral GGOs (Fig. 1e), while chest CT showed multiple, random, peribronchial consolidation and GGOs that were dominant in the dorsal lung (Fig. 2e). Assays of her bronchoalveolar lavage fluid showed a cell count of $1.9 \times 10^5/\mu\text{L}$, with a cell differential of 89% macrophages and 11% lymphocytes, but no pathogens. She was again diagnosed with a deterioration of ILD and was treated with high-dose methylprednisolone (500 mg/day) for 3 days, followed by the tapering of the methylprednisolone to 40 mg/day. The patient's rash and dyspnea improved, as did the new consolidations that were observed on her chest CT scans. The outcomes of her two previous deteriorations suggested that low-dose corticosteroid therapy was insufficient.

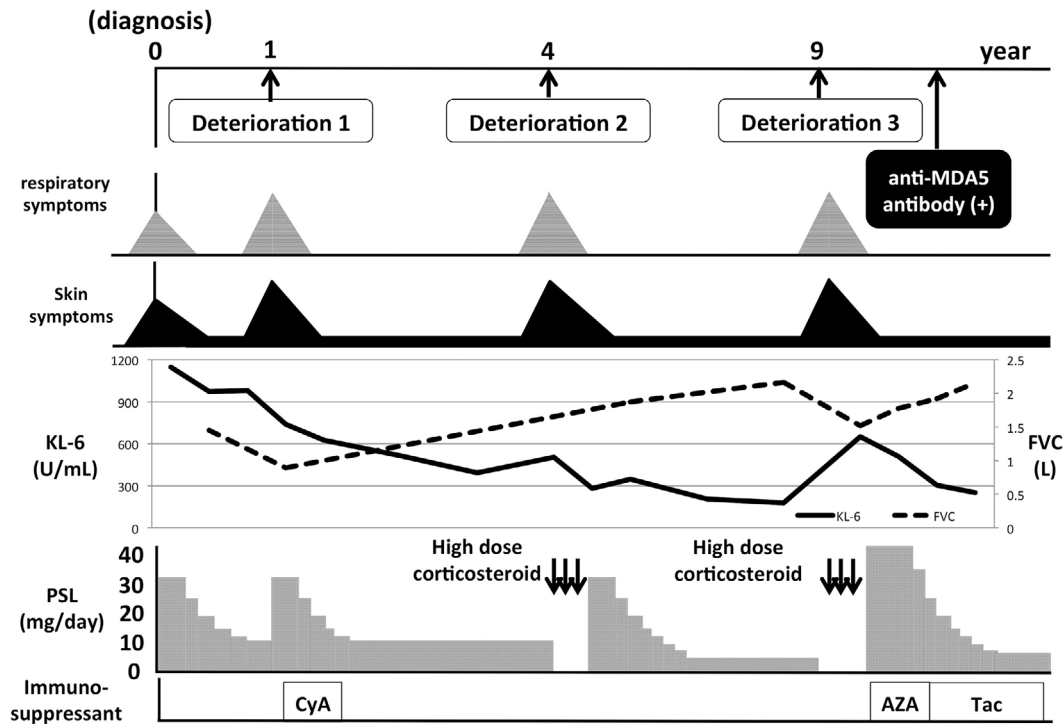


Figure 4. The disease course of our patient over time. She was initially diagnosed with DM at year 0, and experienced acute deteriorations of ILD during years 1, 4, and 9. After the first deterioration, she was treated with cyclosporine (125 mg/day) plus PSL (30 mg/day). After the second and third deteriorations, she was treated with methylprednisolone (500 mg/day). After the third deterioration, she was also treated with azathioprine, but was later switched to tacrolimus. At the third deterioration, anti-MDA5 antibodies were detected. At the present time, 12 months after the third deterioration, she remains well and is continuing treatment with low-dose corticosteroids and tacrolimus. CyA: cyclosporine, AZA: azathioprine, Tac: tacrolimus

Thus, following corticosteroid pulse therapy, she was started on azathioprine (100 mg/day). She developed nausea and vomiting which was suspected to be an adverse effect to azathioprine; thus, she was switched to tacrolimus (1.4 mg/day). Since being discharged 12 months ago, she has remained well and is being maintained on low-dose corticosteroid and tacrolimus without adverse effects.

Her clinical course is shown in Fig. 4. Muscle weakness and myalgia were not observed throughout her clinical course, and her CK and aldolase levels were normal, peaking at 303 IU/L and 7.8 IU/L, respectively. She was diagnosed with CADM and ILD (10). Her clinical course of mild recurrent deteriorations initially suggested that the ILD was associated with an antibody to aminoacyl transfer RNA synthetase (ARS) (1), but she was negative for anti-ARS antibodies, including antibodies to Jo-1, PL-7, PL-12, OJ, and EJ. She was also negative for antibodies to Mi-2, Ro-52, PM75, PM100, signal recognition particle, U1-ribonucleoprotein, and SSA. However, immunoprecipitation assays revealed that she was positive for the anti-MDA5 antibody, which led to a diagnosis of anti-MDA5 antibody-associated ILD.

Discussion

To our knowledge, this is the first description of an anti-MDA5 antibody-positive ILD patient who experienced multiple deteriorations. Following each deterioration, this patient showed a good response to immunosuppressive therapy.

In patients with DM, specific antibodies, including those directed against MDA5 and ARS, have been associated with the development and clinical course of ILD (11). The anti-MDA5 antibody is a useful prognostic marker for this disease, which is associated with RP-ILD, a condition with a high mortality rate. RP-ILD is usually resistant to immunosuppressive therapy, and patients with this condition require early treatment with high-dose corticosteroids and immunosuppressive agents. Most deaths occur during the very early stages of illness, usually within 6 months of diagnosis.

A small retrospective analysis reported that the long-term prognosis of patients with anti-MDA5 antibodies who survive the first 6 months is generally good and that the recurrence rate is very low (7). However, the long-term clinical course and prognosis of CADM patients with anti-MDA5 antibody-associated ILD remain unclear. Anti-ARS antibody-positive ILD patients have a chronic and recurrent clinical course, as well as a more favorable response to treatment

than anti-MDA5 antibody-positive ILD patients (1). The clinical course of our patient suggested that her ILD was associated with anti-ARS antibodies.

The long-term clinical course of our patient indicates that CADM-ILD patients can experience recurrent deteriorations. The reduction of the steroid dose in this patient was not associated with the second and third deteriorations of ILD, since the steroid dose had been tapered more than 2 years before the deterioration. The recurrent deteriorations that were observed in this patient may therefore have been caused by her maintenance therapy, which consisted of low-dose steroid therapy without immunosuppressants.

Two hypotheses may explain this patient's favorable response to treatment. First, genetic variants may have influenced her clinical course. A retrospective study from the United States found that RP-ILD only occurred in 22% of anti-MDA5 antibody-positive patients, a rate that is significantly lower than that in patients of Asian ethnicity (12). Approximately 90% of Japanese patients who are positive for anti-MDA5 antibodies develop ILD, with a mortality rate of approximately 40%. In addition to the antibody itself, the genetic variations among these patients may influence the progression of ILD (13). Our patient was of Japanese descent. Although the phenotyping of DM patients according to their specific antibodies is important in guiding treatment decisions, distinct forms may exist.

Second, the favorable response of this patient to treatment may have been due to the severity of RP-ILD. The general risk factors for RP-ILD in DM patients include high pre-treatment serum levels of ferritin and high alveolar-arterial oxygen gradients (14). At the time of the third deterioration, our patient's serum ferritin level and alveolar-arterial oxygen gradient were both low, suggesting that this patient belongs to a low-risk group.

There is no consensus on the ideal regimen or the intensity of immunosuppressive therapy for CADM-ILD patients who are in remission, nor is there a consensus on the management of patients with stable ILD in association with dermatomyositis. The combination of an immunosuppressive agent and prednisolone has been recommended for maintenance of dermatomyositis-associated ILD, as is the gradual tapering of prednisolone with the careful monitoring of disease activity (15). The findings in our patient indicate that CADM-associated ILD can be chronic and recurrent, suggesting that combination therapy is required in the management of CADM-ILD even during the remission phase.

There are two arguments against these hypotheses. First, our patient was also positive for anti-CCP and anti-centromere antibodies, suggesting that these antibodies may be associated with ILD. However, neither rheumatoid arthritis nor systemic sclerosis was diagnosed, which may have been due to the low-dose steroid therapy (16, 17). The deterioration of ILD in this patient was related to the deterioration of her skin symptoms, including Gottron's papules and the shawl sign, both of which are specific for DM; thus, she was diagnosed with CADM-associated ILD. Moreover, her

chest CT findings revealed lower consolidation, peripheral intralobular reticular opacities, and non-septal plate-like opacities, findings that are typical in patients with anti-MDA5 antibody-positive ILD (18). Second, we only tested the patient for anti-MDA5 antibodies after the third deterioration, which made it difficult to determine whether the anti-MDA5 antibody had been associated with the two prior deteriorations. However, the presence of GGOs, the consolidation patterns, and the exacerbation of her skin symptoms during the three deteriorations were quite similar, suggesting that all three deteriorations were associated with the same etiology.

In summary, we have described the case of a CADM patient with an unusual clinical course who developed three mild deteriorations of ILD over 9 years. Further research is warranted to understand the distinct clinical course of ILD in anti-MDA5 antibody-positive patients.

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

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