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CASE STUDY

Rapidly progressive interstitial lung disease associated with dermatomyositis—Longitudinal course of anti-MDA5 antibody titer in two cases

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Abstract

Antimelanoma differentiation-associated gene 5 antibody (anti-MDA5 Ab)-positive dermatomyositis frequently develops life-threatening rapidly progressive interstitial lung disease (RP-ILD). The longitudinal dynamics of antibody titers reflects treatment responses, and negative conversion of anti-MDA5 Ab leads to the prevention of RP-ILD relapse. Case 1 finally achieved negative conversion of anti-MDA5 Ab after 18-month immunosuppressive therapy despite early diagnosis from skin manifestations. Case 2 showed re-elevation of anti-MDA5 Ab after tacrolimus discontinuation; immediate restart of tacrolimus recovered it without relapse. These cases suggest that anti-MDA5 Ab monitoring is essential to determine therapeutic strategy in dermatomyositis patients with RP-ILD during both initial and maintenance phases.

KEYWORDS
antimelanoma differentiation-associated gene 5 antibody, combined immunosuppressive therapy, cyclophosphamide, intravenous immunoglobulin, negative conversion, tacrolimus

1 | INTRODUCTION

Antimelanoma differentiation-associated gene 5 antibody (anti-MDA5 Ab) is a member of dermatomyositis (DM)-specific autoantibodies newly identified in the recent two decades.[1] Anti-MDA5 Ab-positive DM patients develop rapidly progressive interstitial lung disease (RP-ILD) at a high rate, which is associated with poor prognosis (90-day survival rate; 66.7%).[2] Combined immunosuppressive therapy including systemic corticosteroids, intravenous cyclophosphamide (IVCY), and tacrolimus is highly recommended for RP-ILD,[3] and continuous negative conversion of anti-MDA5 Ab is quite important to avoid relapse of this complication.[4] Herein, we report two cases of DM-associated RP-ILD in which the titer of anti-MDA5 Ab showed unique courses (clinical data of these two patients were included in our previous study with 11 cases).[5]

2 | CASE 1

A 42-year-old woman visited us with a 2-week history of fever, arthralgia, muscle weakness, malaise, and acute erythema on the face, neck, chest, and extremities. Physical examination showed skin rash characteristic of DM, such as heliotrope rash and Gottron's signs on finger joints. Moreover, multiple punched-out skin ulcerations, painful periungual erythema, and inverse Gottron's signs were evident, suggesting the presence of anti-MDA5 Ab (Figure 1A,B). Laboratory examination revealed elevation of lactate dehydrogenase (412 IU/L [normal range, 124-222]), aspartate aminotransferase (55 IU/L [13-30]), creatinine kinase (807 IU/L [41-153]), and aldolase (14.0 IU/L [2.1-6.1]), whereas alanine aminotransferase, C-reactive protein, ferritin, and KL-6 were within normal limits. Though dyspnea was absent, a chest computed tomography revealed ground-glass

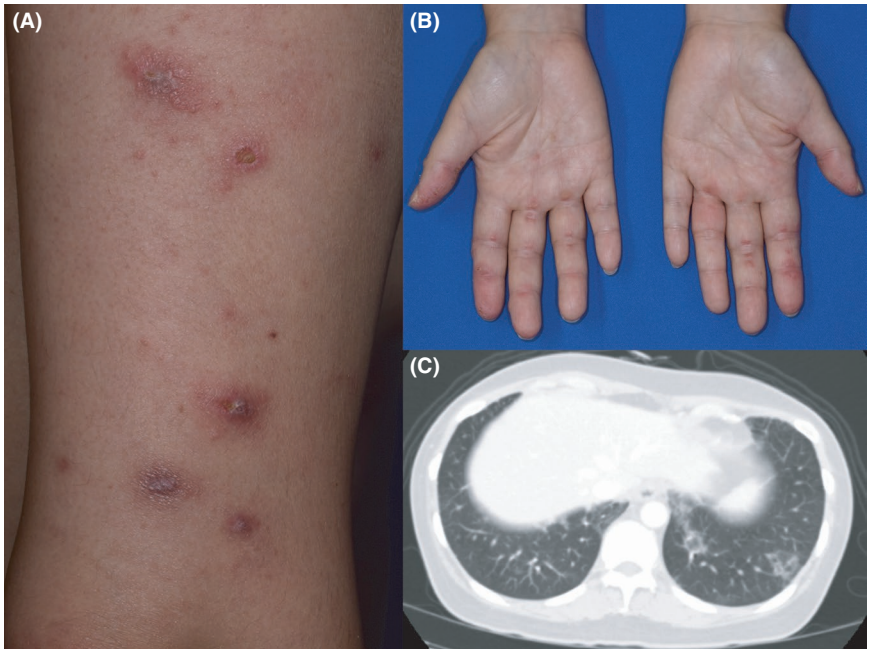

FIGURE 1 Skin manifestations and chest CT findings of Case 1 at first visit. (A) A punched-out skin ulceration on her right upper arm. (B) Inverse Gottron's signs on finger joints. (C) GGO, reticular opacities, and bronchiectasis were observed in bilateral lower lobes. CT, computed tomography; GGO, ground-glass opacities

FIGURE 2 Clinical course and anti-MDA5 Ab titer of Case 1. RP-ILD was successfully treated with combined immunosuppressive therapy, and sustained negative conversion of anti-MDA5 Ab was achieved at 18 months after the initiation of this therapy. % DLco, percent diffusing capacity of lung for carbon monoxide; % VC, percent vital capacity; anti-MDA5 Ab, anti-melanoma differentiation-associated gene 5 antibody; IVCY, intravenous cyclophosphamide; IVIg, intravenous immunoglobulin; PSL, prednisolone; RP-ILD, rapidly progressive interstitial lung disease; TAC, tacrolimus

opacities, reticular opacities, and bronchiectasis in bilateral lower lobes (Figure 1C). Therefore, we suspected her of having DM with RP-ILD. She was admitted to the hospital immediately and underwent screening tests for infectious diseases and malignancies during the inspection of anti-MDA 5 Ab. As soon as anti-MDA-5 Ab turned out to be positive (153 index [<32]), she was subjected to intravenous

methylprednisolone (1000 mg × 3 days), followed by 1 mg/kg of oral prednisolone. Five days after beginning systemic corticosteroids, however, she developed gastrointestinal hemorrhage from a Dieulafoy's lesion in the stomach, which required urgent endoscopic hemostasis twice. Hence, the scheduled combined therapy, namely, IVCY and other immunosuppressants, was postponed for a month. During that time, lung involvement was not relieved and anti-MDA5 Ab titer did not decrease (Figure 2), and her malaise and muscle weakness remained. After initiating biweekly IVCY (500 mg/m^2), tacrolimus and intravenous immunoglobulin (IVIg, 400 mg × 5 days), ground-glass opacities and reticular opacities of the lungs and anti-MDA5 Ab began to decrease, and her physical symptoms were improved. Although those opacities were almost completely disappeared by regular IVCY (every 2 weeks, then reduced to every 4 weeks), her anti-MDA5 Ab remained slightly positive (33 index) after 20 courses of IVCY. Since the cumulative dose and treatment duration of cyclophosphamide reached 15 g and 12 months, regular IVCY was quitted, and she was carefully observed with 9 mg of prednisolone and 10 mg of tacrolimus. Eventually, anti-MDA5 Ab titer became negative at 18 months after the initiation of treatment. At the time of writing, anti-MDA5 Ab-negative conversion was maintained with 5 mg of prednisolone and 8 mg of tacrolimus for the additional 10 months.

3 | CASE 2

A 39-year-old woman was diagnosed as having DM based on characteristic skin symptoms, such as Gottron's signs and shawl sign, abnormal signal intensities within skeletal muscles on gadolinium-enhanced magnetic resonance imaging, and anti-MDA5 Ab positivity detected by immunoprecipitation. A chest computed tomography at diagnosis revealed consolidation in her left lower lung field, suggesting the development of RP-ILD. Combined immunosuppressive therapy completely relieved her symptoms including the consolidation, and her anti-MDA5 Ab titer remained below 15 index over three years under 5 mg of prednisolone and 4 mg of tacrolimus. Four months after stopping tacrolimus, however, her anti-MDA5 Ab titer began to rise and became positive again (44 index). Immediate restart of tacrolimus decreased her anti-MDA5 Ab, and eventually negative conversion was achieved again (Figure 3). Meanwhile, no recurrence of lung involvement was observed.

4 | DISCUSSION

Despite moderate elevation of pretherapeutic anti-MDA5 antibody titer and early intervention with combined immunosuppressive therapy, it took 18 months with 15 g of cyclophosphamide in total to achieve negative conversion of anti-MDA5 Ab in Case 1. Considering our experience in another DM patient with RP-ILD and over 500 index of anti-MDA5 Ab in whom negative conversion of anti-MDA5 antibody was accomplished in 9 months through combined immunosuppressive therapy (unpublished data), Case 1 suggests that relatively low anti-MDA5 Ab titer at diagnosis does not predict early negative conversion of anti-MDA5 Ab. Given that continuous positivity of this antibody is relevant to a higher and earlier recurrence rate of interstitial lung disease (ILD) even though maintenance therapy with corticosteroids and tacrolimus is continued, and that no recurrence had been reported to occur in any of the sustained anti-MDA5 Ab-negative patients at the time of writing,[4] combined immunosuppressant therapy should be performed in anti-MDA-5 Ab-positive ILD patients irrespective of its pretreatment titer.

Cyclophosphamide, a key drug for the treatment of anti-MDA5 Ab-positive ILD,[6] can cause an increased risk of bladder cancer and hematologic malignancy.[7] Knight et al.[8] reported that each 10 g increment in cumulative dose of cyclophosphamide was associated with a doubled risk of bladder cancer, and exposure to cyclophosphamide for longer than 13 months was linked to a near eightfold increased risk of bladder cancer. From this perspective, early diagnosis based on skin manifestations and immediate induction of combined therapy are quite important in anti-MDA5 Ab-positive DM-associated RP-ILD to reduce the cumulative dose of cyclophosphamide. Furthermore, it is critical to prevent the recurrence of ILD because retreatment of recurrent ILD will lead to doubled

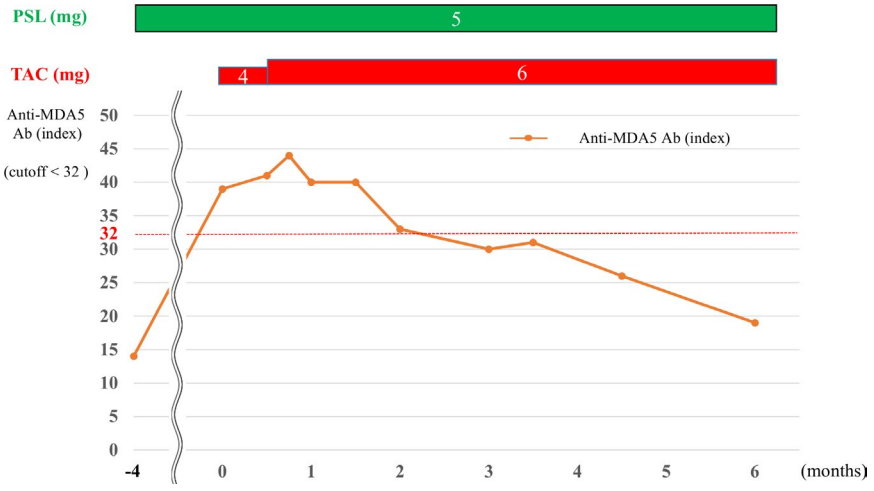

FIGURE 3 Clinical course and anti-MDA5 Ab titer of Case 2. The re-elevated anti-MDA5 Ab titer began to decrease about a month after restarting tacrolimus. anti-MDA5 Ab, anti-melanoma differentiation-associated gene 5 antibody; PSL, prednisolone; TAC, tacrolimus

cumulative dose of cyclophosphamide. In Case 1, negative conversion of anti-MDA5 Ab was fortunately achieved by the acceptable cumulative dose of cyclophosphamide (slightly below the upper limit) with the help of early diagnosis.

In addition to combined immunosuppressive therapy, Case 1 received IVIg because of the refractory muscle involvement. Importantly, Hamada-Ode et al.[9] demonstrated the potential efficacy of IVIg for RP-ILD and anti-MDA5 Ab reduction. Considering the rapid improvement of pulmonary function test results and the decrease in anti-MDA5 Ab titer in Case 1 during concurrent use of IVIg with other immunosuppressants, IVIg may enhance the therapeutic effect of combined immunosuppressive therapy on anti-MDA5 Ab-positive DM-associated RP-ILD. Indeed, there have been several reports supporting this idea.[10,11]

After negative conversion of anti-MDA5 antibody, prednisolone and tacrolimus are generally used continuously as maintenance therapy. The episode of Case 2 clearly indicates that tacrolimus can decrease the titer of anti-MDA5 Ab. Importantly, Matsushita et al.[4] reported that all patients with ILD relapse showed the increase in their anti-MDA5 Ab titers by more than 50 index compared with the titers at the time of remission. In this sense, any symptoms of recurrence were absent in Case 2 (the peak of ant-MDA5 Ab titer; 44 index) likely due to the early restart of tacrolimus. Therefore, careful tapering of tacrolimus should be considered even though long-term remission is achieved. On the other hand, prednisolone seems to have little contribution to reducing the titer of anti-MDA5 Ab considering the transition of its titer in our patients. Further clinical studies with a large number of cases are required to clarify this point in the future.

In summary, we reported two patients with anti-MDA5 Ab-positive DM-associated RP-ILD in which the titer of anti-MDA5 Ab was closely monitored. Their unique clinical courses strongly recommend us to regularly assess the titer of anti-MDA5 Ab not only during the initial therapeutic phase, but even after its long-lasting negative conversion, helping us make a decision on continuation, discontinuation, or restart of immunosuppressive therapies in this clinical entity.

DECLARATION SECTION

Approval of the research protocol: This study was performed according to the Declaration of Helsinki and approved by the ethical committee of the University of Tokyo Graduate School of Medicine (date of issue: May 19, 2019; registration number: 695).

Informed consent: Written informed consent was obtained from the patients.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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REFERENCES

1. Sato S, Hirakata M, Kuwana M, Suwa A, Inada S, Mimori T, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum. 2005;52(5):1571–6.
2. Hozumi H, Fujisawa T, Nakashima R, Johkoh T, Sumikawa H, Murakami A, et al. Comprehensive assessment of myositis-specific autoantibodies in polymyositis/dermatomyositis-associated interstitial lung disease. Respir Med. 2016;121:91–9.
3. Tsuji H, Nakashima R, Hosono Y, Imura Y, Yagita M, Yoshifuji H, et al. Multicenter prospective study of the efficacy and safety of combined immunosuppressive therapy with high-dose glucocorticoid, tacrolimus, and cyclophosphamide in interstitial lung diseases accompanied by anti-melanoma differentiation-associated gene 5-positive dermatomyositis. Arthritis Rheumatol. 2020;72(3):488–98.
4. Matsushita T, Mizumaki K, Kano M, Yagi N, Tennichi M, Takeuchi A, 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. 2017;176(2):395–402.
5. Matsuda KM, Yoshizaki A, Kuzumi AI, Fukasawa T, Ebata S, Yoshizaki-Ogawa A, et al. Combined immunosuppressive therapy provides favorable prognosis and increased risk of cytomegalovirus reactivation in anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis. J Dermatol. 2020;47(5):483–9.
6. Endo Y, Koga T, Suzuki T, Hara K, Ishida M, Fujita Y, et al. Successful treatment of plasma exchange for rapidly progressive interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis: a case report. Medicine (Baltimore). 2018;97(15):e0436.
7. Faurschou M, Sorensen IJ, Mellemkjaer L, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol. 2008;35(1):100–5.
8. Knight A, Askling J, Granath F, Sparen P, Ekbom A. Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. Ann Rheum Dis. 2004;63(10):1307–11.
9. Hamada Ode K, Taniguchi Y, Kimata T, Kawaguchi Y, Shimamura Y, Kuwana M, et al. High-dose intravenous immunoglobulin therapy for rapidly progressive interstitial pneumonitis accompanied by anti-melanoma differentiation-associated gene 5 antibody-positive amyopathic dermatomyositis. Eur J Rheumatol. 2015;2(2):83–5.
10. Koguchi-Yoshioka H, Okiyama N, Iwamoto K, Matsumura Y, Ogawa T, Inoue S, et al. Intravenous immunoglobulin contributes to the control of antimelanoma differentiation-associated protein 5 antibody-associated dermatomyositis with palmar violaceous macules/papules. Br J Dermatol. 2017;177(5):1442–6.
11. Stager K, Wise L. MDA-5 dermatomyositis complicated by interstitial lung disease and cutaneous ulcers: successful treatment with corticosteroids, mycophenolate mofetil and intravenous immunoglobulin. BMJ Case Rep. 2020;13(9):e236431.

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