

# Dermatomyositis with Rapidly Progressive Interstitial Lung Disease Treated with Rituximab: A Report of 3 Cases in Japan

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## Abstract

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We performed a retrospective chart review of three patients with hypomyopathic dermatomyositis and rapidly progressive interstitial lung disease. The patients were Japanese women of 71, 69, and 65 years of age. Two patients were anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibody-positive and 1 was anti-aminoacyl-tRNA synthetase (anti-ARS) antibody-positive. Their respiratory statuses deteriorated despite the administration of glucocorticoid, calcineurin inhibitors, and intravenous cyclophosphamide therapy. We subsequently administered rituximab. The anti-ARS antibody-positive patient survived, while 2 anti-MDA5 antibody-positive patients died.

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

(Intern Med 56: 1399-1403, 2017)

(DOI: 10.2169/internalmedicine.56.7956)

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## Introduction

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Dermatomyositis (DM) is an autoimmune disease that mainly affects the skin and proximal muscles. It is occasionally complicated by interstitial lung disease (ILD). Immunosuppressive agents including glucocorticoids (GCs), calcineurin inhibitors (CNI; e.g. tacrolimus [Tac] and cyclosporine A [CyA]), and intravenous cyclophosphamide (IVCY) have been recommended for the treatment of this condition based on the results of observational studies, which have shown the variable efficacy of these treatments (1, 2). The disease is associated with a high rate of mortality (1).

Anti-aminoacyl-tRNA synthetase (anti-ARS) antibodies, particularly non-Jo-1 (anti-PL-7 and anti-PL-12) antibodies, are strongly associated with the development of ILD (3). Some DM patients with ILD present progressive deterioration in pulmonary disease (rapidly progressive ILD; RP-ILD). The condition of these patients is characterized by mild myositis, palmar papules, fever, a negative or low anti-

nuclear antibody titer, and a very high mortality rate (1). A recent study suggested that RP-ILD is strongly associated with clinically amyopathic DM and the presence of anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibodies (4, 5). In addition, a high ferritin titer is suspected to be a poor prognostic factor in DM patients with RP-ILD (6, 7).

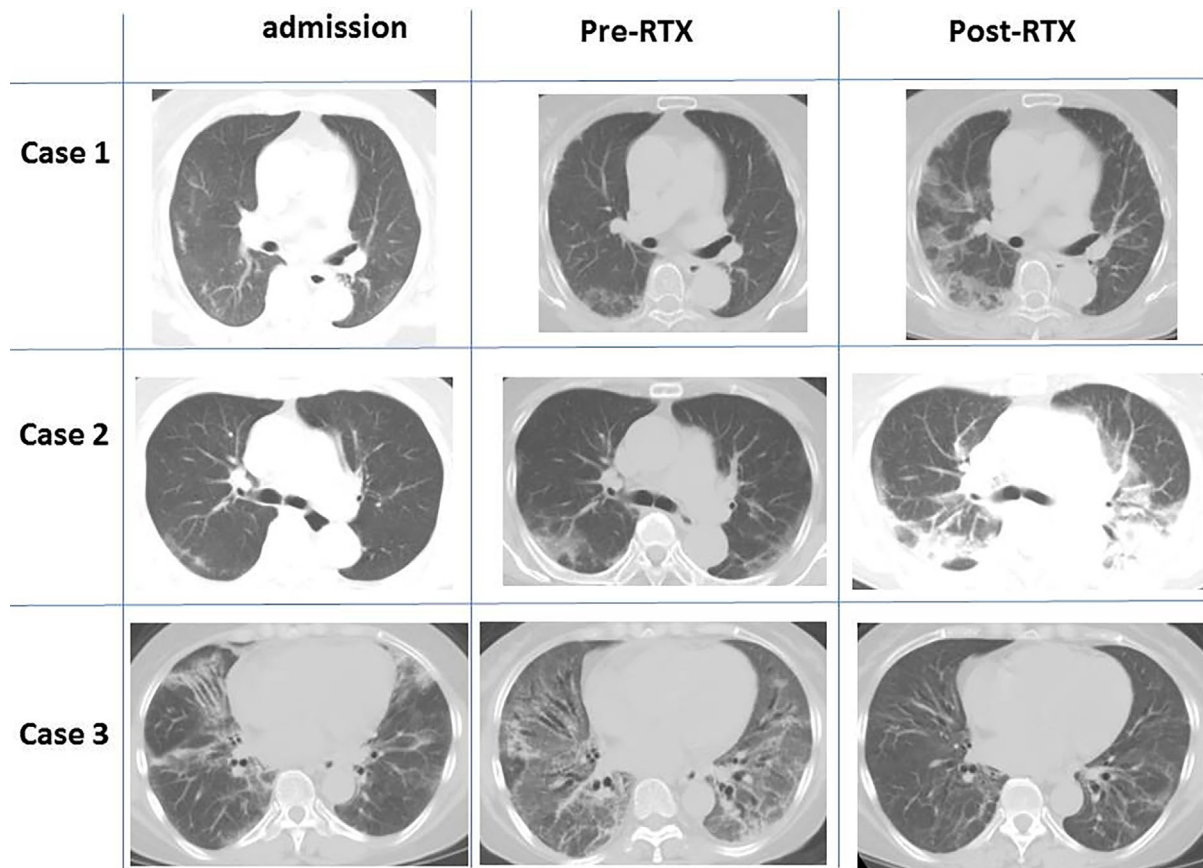
The pharmacological treatment of DM is based on the administration of high doses of GC over long periods, often in combination with another immune-modulating agent (most often methotrexate or azathioprine). Other immunomodulators include CyA, Tac, and mycophenolate mofetil; treatment with high doses of intravenous immunoglobulin has also been described. Despite these treatments, most patients experience persistent muscle weakness or a relapse when the medication is tapered. During the past year, some case series showed the beneficial effects of rituximab (RTX) treatment in anti-ARS antibody-positive DM patients (7-11). In addition, an anti-MDA5 antibody-positive patient displaying the mucocutaneous manifestations of DM who was refractory to IVCY treatment but who improved after the administration

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Received for publication July 6, 2016; Accepted for publication September 26, 2016

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**Figure 1.** Chest computed tomography images of the patients at admission, before the first administration of rituximab (RTX), and after the series of RTX treatments.

of RTX (12), and the successful treatment of 2 anti-MDA5 antibody-positive patients with RTX were recently reported (13, 14). However, the efficacy of RTX treatment in DM patients with RP-ILD, including anti-MDA5 antibody-positive patients is still not clear.

We assessed the clinical and serological responses of DM patients with RP-ILD to RTX.

We performed a retrospective chart review of 3 DM patients with RP-ILD who were treated with RTX in our department from February 2014 to February 2015. The present study was performed in accordance with the Declaration of Helsinki, and informed consent was obtained from all of the patients or their next of kin. We collected clinical data, including the age of onset, sex, disease duration, medications, and respiratory status, their laboratory test results (including the creatine kinase [CK] and ferritin levels and autoantibody type), as well as the chest radiography and computed tomography (CT) findings.

#### **Treatment protocol**

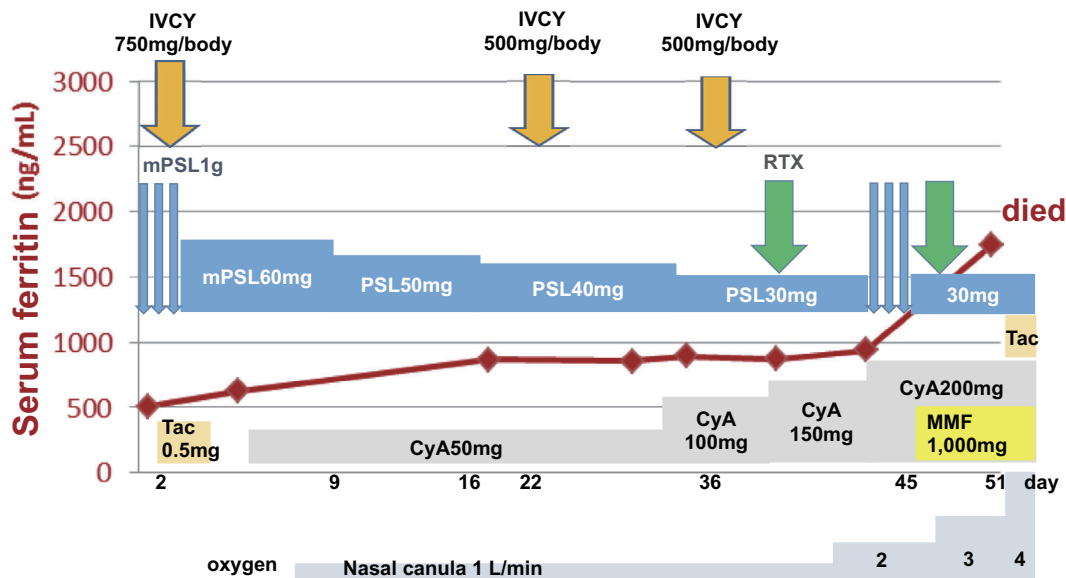
In addition to their pre-existing immunosuppressive therapy (GC, CNi, and IVCY) RTX (375 mg/m<sup>2</sup>) was administered weekly to the patients with a deteriorating respiratory status.

## **Case Reports**

### **Case 1**

A 71-year-old Japanese woman developed fever and dry cough of 2 weeks' duration. Although she was prescribed antibiotics by her physician, her symptoms did not improve and she developed a rash. She was subsequently referred to our clinic.

A physical examination revealed late inspiratory crackles bilaterally in the basilar lung area, purpura on the extensor side of the elbows, and erythema with pruritus on her anterior chest. There was no pain on palpation of her muscles, and her manual muscle test (MMT) parameters were not decreased. Chest CT showed ground-glass opacities (Fig. 1). We administered methylprednisolone (mPSL; 1 g) for 3 days, Tac (Trough level: 5-10 ng/mL) from the 2nd day of hospitalization, and IVCY (750 mg [500 mg/m<sup>2</sup>]) on the 3rd day of hospitalization. However, her respiratory status continued to worsen. We therefore administered IVCY (500 mg) on the 22nd and 36th days and RTX (600 mg [375 mg/m<sup>2</sup>]) on the 38th and 45th days. She did not improve and died on the 51st day of hospitalization. She was anti-MDA5 antibody-positive (Fig. 2).



**Figure 2.** CyA: cyclosporine A, IVCY: intravenous cyclophosphamide, mPSL: methylprednisolone, MMF: mycophenolate mofetil, RTX: rituximab, Tac: tacrolimus

## Case 2

A 69-year-old Japanese woman was admitted with a rash of the extremities, dyspnea on exertion, and polyarthralgia of 3 weeks in duration. She did not have respiratory distress, desaturation, or muscle weakness, but did display hyperkeratosis on the palmar side of her fingers and Gottron's sign. A laboratory analysis revealed a slightly elevated CK level of 225 U/L and a ferritin level of 219 ng/mL. Chest CT showed interstitial lung disease (Fig. 1).

We started intravenous mPSL (1 g pulses) for 3 days and CyA (150 mg/day), followed by prednisolone (PSL; 50 mg daily [1 mg/kg], gradually tapered to 30 mg). Her symptoms improved, and she was discharged on the 17th day after hospitalization. She was anti-MDA5 antibody-positive. At a visit 12 days after her initial discharge, she showed slight respiratory distress with decreased oxygen saturation (SpO<sub>2</sub>) at 95% in ambient air and her cutaneous symptoms had worsened. Her ferritin level of 263 ng/mL was slightly elevated. Chest CT showed worsening interstitial shadows (Fig. 1). Although Gram staining of her sputum revealed no specific findings, empiric antibiotics were administered. Subsequently, intravenous mPSL therapy (60 mg/day) was initiated. In addition, we administered IVCY [650 mg (500 mg/m<sup>2</sup>) on the 2nd day of hospitalization) and RTX [500 mg [375 mg/m<sup>2</sup>] on the 4th day. The patient's condition showed further deterioration and mPSL (1 g/day pulses for 3 days) treatment was initiated from the 6th day. Her respiratory state and chest CT findings continued to worsen. IVCY [1,000 mg (750 mg/m<sup>2</sup>) was therefore administered on the 8th day and the patient was and was intubated and RTX [500 mg (375 mg/m<sup>2</sup>) was administered on the 11th day. On the 12th day, continuous hemodiafiltration was started and tocilizumab (8 mg/kg) was administered; her ferritin level was 1,930 ng/mL. However, the patient did not

respond and died on the 18th day after re-admission to hospital (Fig. 3).

## Case 3

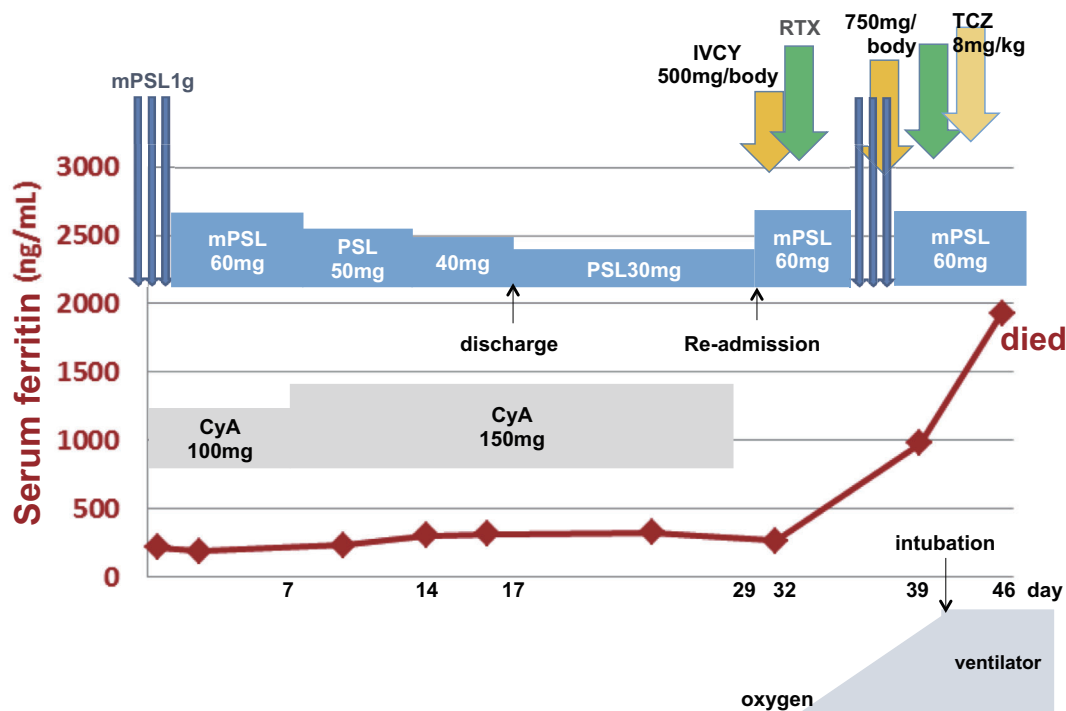
A 65-year-old Japanese woman developed fever, cough, and dyspnea of 6 weeks in duration. She was initially treated with antibiotics for presumed pneumonia by her physician. Her symptoms did not improve. Moreover, a rash and edema appeared on her extremities, and she developed polyarthralgia. She was then referred to our clinic.

Her body temperature was 38.5°C, respiratory rate was 20 breaths/min, and her SpO<sub>2</sub> was 98% in ambient air. A physical examination revealed late inspiratory crackles bilaterally in the basilar lung area, no decreases in her MMT parameters, and urticarial lesions on her trunk and extremities. Laboratory tests revealed a CK level of 399 U/L and a ferritin level of 853 ng/mL. Chest CT showed interstitial shadows (Fig. 1). We started mPSL (1 g pulses for 3 days) from admission, followed by CyA (100 mg/day) from the 2nd day of hospitalization. However, her SpO<sub>2</sub> level began to deteriorate, and we administered IVCY [750 mg (500 mg/m<sup>2</sup>) on the 5th day. On the 5th day, the chest CT findings suggested that her condition had deteriorated (Fig. 1); we therefore administered RTX [500 mg (375 mg/m<sup>2</sup>) on the 7th day, followed by mPSL (1 g for 3 days) from the 8th day. The patient started showing signs of improvement, so mPSL (1 g for 3 days) was administered from the 13th day, and RTX (500 mg) was administered weekly for 4 weeks, IVCY (750 mg) was administered biweekly for 6 treatments, and mPSL was tapered to 20 mg daily and then switched to PSL (20 mg) with a tapering dosage regime. The patient's respiratory status continued to improve and she was discharged with domiciliary oxygen therapy (1 L/min) on the 114th day. She was anti-PL-12 antibody-positive.

**Table. The Clinical Characteristics and Treatments of the 3 Patients.**

Case	Age, sex	Disease duration, weeks	Specific antibody	Previous treatment	RTX cycles, n	Concomitant treatment with different RTX cycles				Serum ferritin (ng/mL), Baseline/Post-RTX	Serum KL-6 (U/mL), Baseline/Post-RTX	Vital status
						1	2	3	4			
1	71, F	2	Anti-MDA5	mPSL 1 g → mPSL 60 mg IVCY Tac → CyA	2	CyA	CyA			507/1,740	991/NA	D
2	69, F	8	Anti-MDA5	mPSL 1 g → mPSL 60 mg CyA IVCY	2	CyA, IVCY	IVCY			219/1,930	922/1,520	D
3	65, F	6	Anti-PL-12	mPSL 1 g → mPSL 60 mg CyA → Tac IVCY	4	Tac, IVCY	Tac, IVCY	Tac, IVCY	CyA, IVCY	853/476	529/987	A

A: alive, Anti-MDA5: anti-melanoma differentiation-associated gene 5 (MDA5) antibody, CyA: cyclosporine A, D: dead, F: female, IVCY: intravenous cyclophosphamide, mPSL: methylprednisolone, NA: not applicable, RTX: rituximab, Tac: tacrolimus



**Figure 3.** CyA: cyclosporine A, IVCY: intravenous cyclophosphamide, mPSL: methylprednisolone, RTX: rituximab, Tac: tacrolimus, TCZ: tocilizumab

## Discussion

We reported the cases of 3 DM patients with RP-ILD (Table); 2 of the patients died, while 1 survived. The patient who survived was anti-ARS antibody (anti-PL-12 antibody)-positive. Both patients who died were anti-MDA5-antibody positive. The outcome of DM with RP-ILD in anti-MDA5 antibody-positive patients was very poor in spite of early intensive care including treatment with GC, CNi, IVCY, and RTX.

Some case series have suggested that RTX had beneficial

effects in anti-ARS antibody-positive DM patients. Our findings were in line with those results in that the anti-PL-12 antibody-positive patient survived. However, there are few reports describing the successful treatment of anti-MDA5 antibody-positive patients with RTX (12-14). In our report, in spite of intensive care, including the administration of RTX, the 2 anti-MDA5 antibody-positive patients died.

The prognosis of anti-MDA5 antibody-positive DM patients with RP-ILD is very poor, in spite of early detection and intensive care. However, the beneficial effects of RTX in the treatment of anti-MDA5 antibody-positive DM patients have been reported. RTX was not administered at the

start of treatment in our clinic; thus, outcome of the two cases in our study cannot be used to definitively characterize the efficacy of RTX in DM patients with RP-ILD.

Although the number of patients in our report is too small to draw definite conclusions, it has some interesting clinical implications. There is a report that the anti-MDA5 antibody titer and ferritin and IL-18 concentrations are useful for the evaluation of the response of anti-MDA5 antibody-positive DM patients to the treatment of ILD (15). The serum ferritin concentrations in the 3 patients in our case series support this hypothesis (Table). Notably, in Case 2, the ferritin level increased as the patient's clinical status deteriorated, after the administration of RTX. In addition, the outcomes of the patients in our study reflected that anti-MDA5 positivity is associated with poor prognosis.

Early and intensive treatment and close monitoring are critical when treating DM patients with RP-ILD. However, new treatments are needed.

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

#### Acknowledgement

We would like to thank Takao Fujii of the Department for the Control of Rheumatic Diseases, Graduate School of Medicine, Kyoto University, and Ran Sasai and Yuji Hosono of the Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, for the measurement of the antibody data.

#### References

1. Kameda H, Nagasawa H, Ogawa H, et al. Combination therapy with corticosteroids, cyclosporin A, and intravenous pulse cyclophosphamide for acute/subacute interstitial pneumonia in patients with dermatomyositis. *J Rheumatol* **32**: 1719-1726, 2005.
2. Kurita T, Yasuda S, Oba K, et al. The efficacy of tacrolimus in patients with interstitial lung diseases complicated with polymyositis or dermatomyositis. *Rheumatology* **54**: 39-44, 2015.
3. Labirua A, Lundberg IE. Interstitial lung disease and idiopathic inflammatory myopathies: progress and pitfalls. *Curr Opin Rheumatol* **22**: 633-638, 2010.
4. Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. *Arthritis Rheum* **52**: 1571-1576, 2005.
5. Gono T, Kawaguchi Y, Satoh T, et al. Clinical manifestation and prognostic factor in anti-melanoma differentiation-associated gene 5 antibody-associated interstitial lung disease as a complication of dermatomyositis. *Rheumatology* **49**: 1713-1719, 2010.
6. Gono T, Kawaguchi Y, Hara M, et al. Increased ferritin predicts development and severity of acute interstitial lung disease as a complication of dermatomyositis. *Rheumatology* **49**: 1354-1360, 2010.
7. Marie I, Dominique S, Janvresse A, Levesque H, Menard JF. Rituximab therapy for refractory interstitial lung disease related to antisynthetase syndrome. *Respir Med* **106**: 581-587, 2012.
8. Sem M, Molberg O, Lund MB, Gran JT. Rituximab treatment of the anti-synthetase syndrome: a retrospective case series. *Rheumatology* **48**: 968-971, 2009.
9. Unger L, Kampf S, Luthke K, Aringer M. Rituximab therapy in patients with refractory dermatomyositis or polymyositis: differential effects in a real-life population. *Rheumatology* **53**: 1630-1638, 2014.
10. Andersson H, Sem M, Lund MB, et al. Long-term experience with rituximab in antisynthetase syndrome-related interstitial lung disease. *Rheumatology* **54**: 1420-1428, 2015.
11. Aggarwal R, Bandos A, Reed AM, et al. Predictors of clinical improvement in rituximab-treated refractory adult and juvenile dermatomyositis and adult polymyositis. *Arthritis Rheum* **66**: 740-749, 2014.
12. Clottu A, Laffitte E, Prins C, Chizzolini C. Response of mucocutaneous lesions to rituximab in a case of melanoma differentiation antigen 5-related dermatomyositis. *Dermatology* **225**: 376-380, 2012.
13. Watanabe R, Ishii T, Araki K, et al. Successful multi-target therapy using corticosteroid, tacrolimus, cyclophosphamide, and rituximab for rapidly progressive interstitial lung disease in a patient with clinically amyopathic dermatomyositis. *Mod Rheumatol* **26**: 465-466, 2016.
14. Yamaguchi K, Yamaguchi A, Uchida M, et al. A case of anti-MDA5-positive rapidly progressive interstitial lung disease in a patient with clinically amyopathic dermatomyositis ameliorated by rituximab, in addition to standard immunosuppressive treatment. *Mod Rheumatol* 2015 (Epub ahead of print).
15. Gono T, Sato S, Kawaguchi Y, et al. Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. *Rheumatology* **51**: 1563-1570, 2012.

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