*Modern Rheumatology Case Reports*, 2025, Vol. 9, Issue 2, rxaf067
doi:10.1093/mrcr/rxaf067
Advance access publication date 10 November 2025
**Case Report**

# Successful methotrexate and rituximab combination therapy for a Taiwanese patient with anti-signal recognition particle antibody-positive immune-mediated necrotizing myopathy: a case report

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## ABSTRACT

We report the successful use of methotrexate (MTX) and rituximab in a Taiwanese patient with anti-signal recognition particle (SRP) antibody-positive immune-mediated necrotizing myopathy (IMNM) refractory to conventional therapy. The patient was a 72-year-old Taiwanese woman. She had facial erythema, bilateral thigh muscle pain, dysphagia, and an abnormally high creatine kinase level and was admitted to our hospital. She tested positive for anti-SRP antibodies, lung ground-glass opacities on computed tomography, and a high signal in the muscle on magnetic resonance imaging of the thigh. Muscle biopsy revealed an absence of inflammatory cell infiltration and prominent necrotic and regenerative tissues. High-dose glucocorticoids, tacrolimus, and intravenous immunoglobulins were administered. Although the creatine kinase levels were temporarily decreased, tacrolimus induced thrombotic microangiopathy. The patient also developed dysphagia and respiratory muscle weakness, which required temporary positive-pressure ventilation. Rituximab was administered on Days 63, 74, 81, and 88, and then MTX was initiated. Dysphagia and respiratory and limb muscle weakness gradually improved, enabling glucocorticoid dose reduction. By Day 200, her creatine kinase level had improved, and she was weaned off the ventilator. Herein, we report the case of a Taiwanese East Asian patient with anti-SRP antibody-positive IMNM who was refractory to conventional therapy and was successfully treated with MTX and rituximab.

**KEYWORDS** Idiopathic inflammatory myopathies; immune–mediated necrotizing myopathy; rituximab; anti-signal recognition particle antibody

## Introduction

Immune-mediated necrotizing myopathy (IMNM) is characterized by progressive subacute proximal muscle weakness and markedly elevated serum creatine kinase (CK) levels. Notably, patients with anti-signal recognition particle (SRP) antibody-positive IMNM have severe muscle weakness, muscle atrophy, cervical muscle weakness, dysphagia, and dyspnoea, and are often refractory to conventional therapies such as glucocorticoids (GCs) [1]. Patients with anti-SRP and anti-3-hydroxy-3-methylglutaryl-coA reductase (HMGCR) antibody-positive IMNM are currently recommended to be initially treated with high-dose GCs. Moreover, early initiation of immunosuppressive agents is recommended depending on the severity and responsiveness to GCs. Methotrexate (MTX) is a second-line treatment for anti-SRP antibody-positive IMNM. Rituximab is a third-line treatment recommended as an alternative to MTX or as an additional concomitant drug in severe cases [1, 2]. However, reports regarding the efficacy of MTX are limited. Rituximab has been reported to be more effective in anti-SRP antibody-positive African-American patients with IMNM than in Caucasian patients with IMNM [3, 4]. Reports on the efficacy of rituximab in Asian patients with anti-SRP antibody-positive IMNM are scarce [5, 6], highlighting the importance of this case report.

## Case presentation

The patient was a 72-year-old Taiwanese woman. Raynaud's phenomenon first appeared several years ago. Two months prior to admission, she developed fatigue, bilateral muscle pain in the thighs, and difficulty swallowing, for which she visited another hospital. She had facial erythema, bilateral muscle pain, swelling of both hands, and an abnormally high CK level of 13,486 U/ml, and was transferred to our hospital. On admission, mild oedematous sclerosis, pale periungual erythema, and mechanic's hands were observed on the fingers. On neurological examination at admission, manual muscle testing showed reduced strength in the iliopsoas (right/left: 3/3) and gluteus medius (3/3) muscles, whereas no muscle weakness was observed in other regions. The main laboratory findings upon admission are shown in

Received 23 June 2025; Accepted 1 October 2025

**Table 1.** Laboratory test on admission.

| ⟨Urine⟩ | | ⟨Others⟩ | |
|---|---|---|---|
| **Protein** | Negative | KL-6 | 418 U/ml |
| **Occult blood** | 3+ | TSH | 10.2 $\mu$IU/ml |
| **White blood cells** | 1+ | FT4 | 0.98 ng/dl |
| **Red blood cells** | Negative | BNP | 15.2 pg/ml |
| ⟨**Blood count**⟩ | | ESR-1HR | 24 mm/h |
| **White blood cells** | 8070 /$\mu$l | IgG | 1411 mg/dl |
| **Haemoglobin** | 13.3 g/dl | CH50 | 47 CH50/ml |
| **Platelet** | $38.4 \times 10^{4}$ /$\mu$l | CRP | 0.15 mg/dl |
| ⟨**Coagulation**⟩ | | HBsAg | 0 IU/ml |
| **APTT** | 26.5 sec | HBsAb | 516.8 mIU/ml |
| **PT(INR)** | 0.96 | HBcAb | 2.3 COI |
| **Fibrinogen** | 411 mg/dl | Anti-nuclear antibody | <40 |
| **D-dimer** | 0.70 $\mu$g/ml | Anti-RNP antibody | Negative |
| ⟨**Biochemistry**⟩ | | Anti-U1 RNP antibody | 1.0 U/ml |
| **Total protein** | 6.7 g/dl | Anti-SSA antibody | 0.4 U/ml |
| **Albumin** | 3.6 g/dl | Anti-ARS antibody | <5.0 |
| **CK** | 17,954 U/l | Anti-TIF-$\gamma$ antibody | <5.0 INDEX |
| **CK-MB** | 845 U/l | Anti-Mi-2 antibody | <5.0 INDEX |
| **AST** | 572 U/l | Anti-MDA5 antibody | <4 INDEX |
| **ALT** | 614 U/l | Anti-Jo-1 antibody | Negative |
| **LDH** | 3197 U/l | Aldolase | 304.7 U/l |
| **ALP** | 46 U/l | myoglobin | 5 299 ng/mL |
| **AMY** | 93 U/l | EUROLINE | |
| **Creatinine** | 0.44 mg/dl | Anti-Ku antibody | Negative |
| **UA** | 4.3 mg/dl | Anti-PM/Scl-100 antibody | Negative |
| **Total cholesterol** | 241 mg/dl | Anti-PM/Scl-75 antibody | Negative |
| **Na** | 139 mmol/l | Anti-SRP antibody | 3+ |
| **K** | 4.2 mmol/l | Anti-PL-7 antibody | Negative |
| **Cl** | 100 mmol/l | Anti-PL-12 antibody | Negative |
| **Ca** | 9.1 mg/dl | Anti-OJ antibody | Negative |
| **IP** | 4.0 mg/dl | Anti-EJ antibody | Negative |
| | | Anti-Ro-52 antibody | ± |

APTT: activated partial thromboplastin time, PT(INR): Prothrombin Time-International Normalized Ratio, CK: creatine kinase, CK-MB: creatine kinase dimer of muscle and Brain chains, AST: Aspartate transaminase, ALT: Alanine transaminase, LDH: lactate dehydrogenase, ALP: Alkaline phosphatase, AMY: amylase, UA: uric acid, Na: sodium, K: potassium, Cl: chlorine, Ca: calcium, IP: inorganic phosphorus, TSH: thyroid stimulating hormone, FT4: free thyroxine 4, BNP: Brain Natriuretic Peptide, ESR-1HR: Erythrocyte Sedimentation Rate 1 hour, IgG: Immunoglobrin G, CH50: homolytic complement activity, CRP: C-reactive protein.

Table 1. There was notable elevation of CK (17 954 U/ml) and aldolase (304.7 U/l) and slight elevation of C-reactive protein (0.15 mg/dl), the erythrocyte sedimentation rate (24 mm/h), and Krebs von den Lungen-6 (KL-6) (418 U/ml). The anti-SRP antibody was positive (3+ on EUROLINE®; 2.5 IU/ml, normal value < 1.0 IU/ml; Cosmic Corporation, Tokyo, Japan). KL-6 levels reached a peak value of 572 U/ml on Day 14 of hospitalization. The NSIP (nonspecific interstitial pneumonia) pattern of mild interstitial lung disease was observed in the basal lung on chest radiography and computed tomography (CT) (Figure 1(a,b)). Regarding cardiac findings, creatine kinase dimer of muscle and Brain chains (CK-MB) levels were 845 U/l and N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) levels were 15.2 pg/ml, with no abnormal findings detected on the electrocardiogram. Echocardiography (UCG) performed on hospital Days 12 and 116 revealed left ventricular hypertrophy; on room air, $PaO_2$ was 85.1 mmHg and $PaCO_2$ was 45.1 mmHg. Due to decreased respiratory muscle function, we assumed that the test results may not be entirely accurate; however, pulmonary function testing on hospital Day 7 showed a % vital capacity (VC) of 44.2% and the percentage of predicted value for Forced Expiratory Volume in one second (ŁV1.0) of 57.1%. Femoral magnetic resonance imaging revealed a strong signal with fat suppression in the adductor magnus (Figure 1(c)). Electromyography revealed myogenic changes in the left biceps brachii and vastus medialis. Histopathological examination of the right rectus femoris muscle biopsy revealed myofibres of different sizes, poor inflammatory cell infiltration, prominent necrotic and regenerative images, and no perifibrillar necrosis or atrophy (Figure 2(a)). Major Histocompatibility Complex (MHC) staining showed some staining along the perimembranous regions of the muscle fibres (Figure 2(b)). No red-ragged fibres or rimmed vacuoles were identified by modified Gomori trichrome staining, indicating no inclusion body myositis. According to these findings, the patient met the Ministry of Health, Labour and Welfare 2015 diagnostic criteria, American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) idiopathic inflammatory myopathy (IIM) classification criteria, and the Bohan and Peter criteria. Based on the myopathological findings, she was comprehensively diagnosed with anti-SRP antibody-positive IMNM and interstitial lung disease. According to the 2013 ACR/EULAR classification criteria for systemic sclerosis [7], the patient presented with finger swelling (2 points), interstitial lung disease (2 points), and Raynaud's phenomenon (3 points), yielding a total score

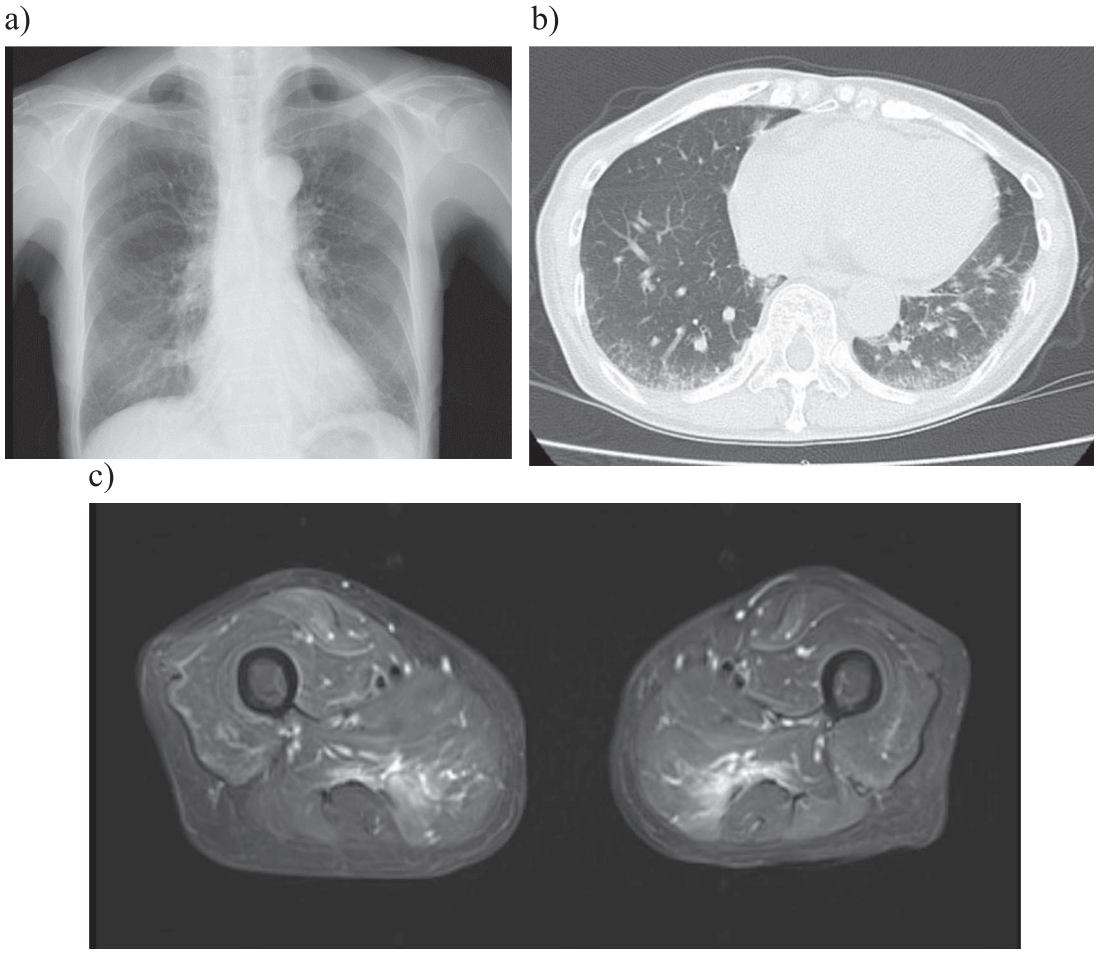


**Figure 1.** Imaging findings. (a) Chest radiography findings on Day 3. (b) Computed tomography (CT) findings of the chest 16 days before admission. (c) Simple magnetic resonance imaging findings of the thigh on Day 6 of admission (fat suppression). High signal intensity was observed in both adductor magnus muscles on Short Tau Inversion Recovery (STIR), consistent with myositis.

of 7 points, which did not meet the classification criteria for systemic sclerosis. A high-dose GC, tacrolimus 3 mg, and intravenous immunoglobulin (IVIG) were initiated on Day 10 (Figure 3). However, the patient's renal disorder progressed on Day 28. Lactate dehydrogenase levels increased to 1 495 U/l, and crushed red blood cells appeared in the peripheral blood. Laboratory findings revealed complement levels of C3 at 107 mg/dl and C4 at 26 mg/dl, a tacrolimus trough level of 13.7 ng/ml, haptoglobin of 86 mg/dl, and an ADAMTS-13 inhibitor level of 0.36 IU/ml with 36% activity. Based on the laboratory findings, we considered thrombotic thrombocytopaenic purpura (TTP) or thrombotic microangiopathy (TMA) due to IIM [8] or tacrolimus. We promptly discontinued tacrolimus. CK levels stopped decreasing, and she developed markedly progressive atrophy of the swallowing and respiratory muscles. On Day 28, positive-pressure ventilation was initiated using positive end-expiratory pressure 5 and pressure support 12. Rituximab, a chimeric anti-CD20 antibody, is reportedly effective in cases of anti-SRP antibody-positive IMNM refractory to GCs [2]. Since our patient was also expected to have TTP complications, we administered rituximab 500 mg/body/week on Days 63, 74, 81, and 88. We later found no decrease in ADAMTS13 activity. The patient was diagnosed with TMA due to IIM [8] or tacrolimus. MTX (7.5 mg/week) was initiated, and the dose was subsequently increased to 10 mg/week. After treatment, KL-6 levels decreased to 391 on day 94, and CT findings showed improvement in interstitial lung disease (Figure 4a, 4b). Muscle weakness in her extremities and respiratory muscles gradually improved, and the patient was weaned off the ventilator on day 111, allowing a reduction in prednisolone dosage to 5 mg/day. Anti-SRP antibody levels decreased to 1.4 IU/ml (<1.0 IU/ml) by Day 146, and CK levels improved to 264 IU/ml by Day 200. The dosage was reduced to 3 mg/day, and no recurrence was noted till Day 314. At the most recent follow-up (Day 868), the patient could ambulate independently without assistance.

## Discussion

Here, we reported the case of a patient with anti-SRP antibody-positive IMNM refractory to high-dose GC, tacrolimus, and IVIG. The patient was successfully treated with a combination of MTX and rituximab.

First, we discuss the current therapeutic guidelines for IMNM, focusing on the positioning of MTX and rituximab within these strategies. Expert opinions from multiple countries on treatment strategies for IMNM were summarized at the 2016 ENMC workshop [2]. The workshop

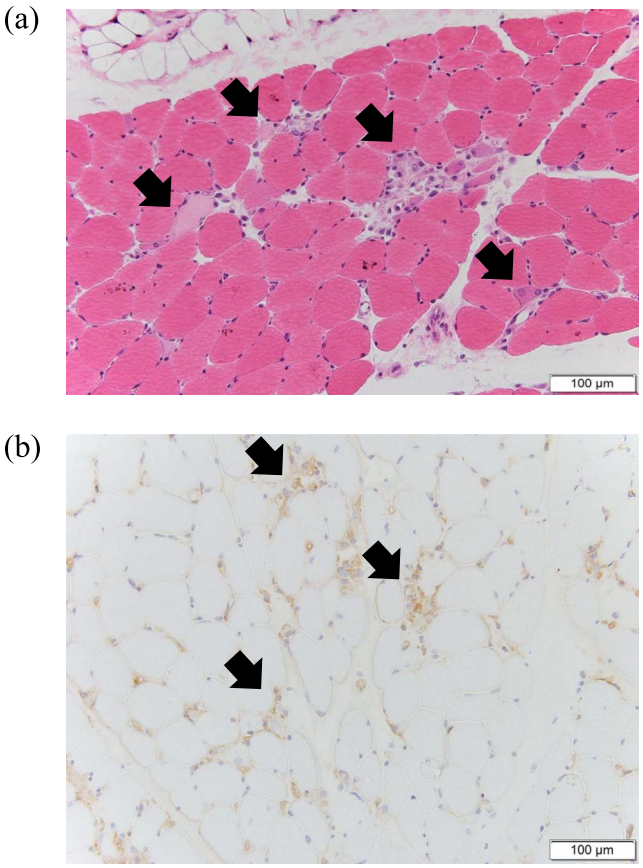


**Figure 2.** Muscle biopsy pathology of the right rectus femoris muscle. (a) HE staining: different sizes of muscle fibre positive, perifibrillar necrosis negative, and perifibrillar atrophy negative. (b) MHC staining: positive staining along the perimembrane of the myofibres in some areas.

recommended initiating treatment with a high-dose GC and, depending on disease severity and response, promptly adding immunosuppressive agents or biological agents, either at treatment onset or within 1 month, for both anti-SRP- and anti-HMGCR-positive IMNM. The workshop mentioned MTX as a second-line treatment for anti-SRP antibody-positive IMNM and recommended starting rituximab within 6 months as an alternative to MTX for third-line therapy or as an additional concomitant drug for severe cases. However, to date, there has been no evidence based on randomized controlled trials. Reports on the effectiveness and safety of immunosuppressive and biological agents in IMNM with GC treatment resistance are currently available only from retrospective observational studies, partly because of the small number of cases [3].

Next, we discuss the treatment in this case using rituximab and MTX. According to current guidelines, MTX is recommended as a second-line agent, whereas rituximab is considered a third-line therapy in severe cases, such as those requiring noninvasive positive-pressure ventilation due to respiratory muscle weakness [1, 2]. However, in the present case, the patient developed clinical symptoms suggestive of TTP after the initiation of tacrolimus. Consequently, we prioritized switching from tacrolimus to rituximab followed by the addition of MTX.

Next, we discuss the differences in the pathogenesis and, in particular, the therapeutic response to rituximab between anti-SRP-positive and anti-HMGCR-positive IMNM. The number of necrotic muscle fibres was higher in patients with anti-SRP antibody-positive IMNM than in those with anti-HMGCR antibody–positive IMNM. Accordingly, compared with anti-HMGCR-positive patients, anti-SRP-positive patients tend to present with more severe muscle weakness and higher CK levels, and are more prone to develop extensive muscle damage [9]. The proportion of patients who respond to GC monotherapy is relatively higher in cases of anti-HMGCR antibody-positive IMNM than in cases of anti-SRP antibody-positive IMNM [10]. In a literature review summarizing reports, rituximab was effective in 14 of 18 (77.8%) cases of anti-SRP antibody-positive IMNM among a total of 34 IMNM cases (decreased CK levels, improved muscle strength, reduced GC, and dose reduction of immunosuppressive agents). Meanwhile, rituximab was effective in 7 of 16 (43.8%) cases of anti-HMGCR antibody-positive IMNM among 34 IMNM cases [3]. These findings suggest that there are differences in the pathogenesis of anti-SRP antibody-positive IMNM and anti-HMGCR antibody-positive IMNM.

Next, we discuss the pathogenic significance of anti-SRP antibodies. In addition to autoimmune reactions, endoplasmic reticulum stress and autophagy are reportedly involved in the pathogenesis of anti-SRP antibody-positive IMNM. However, the exact pathogenesis remains unclear [11]. In IMNM, there is a possibility that anti-SRP antibodies have a high affinity for muscle and direct involvement in muscle atrophy [9]. A positive correlation has been reported between CK levels and anti-SRP antibody [12]. In our case, the anti-SRP antibody titre was 2.5 IU/ml before treatment, and decreased to 1.4 IU/ml after rituximab treatment on Day 146. The pathogenicity of anti-SRP antibodies and importance of memory B cells are related to the effectiveness of rituximab against anti-SRP antibody-positive IMNM. $CD27^{+}$ memory B cells reportedly increase prior to relapse of IMNM [13, 14].

Finally, we discuss the current status of IMNM treatment in Japan. The actual treatment of IMNM in Japan is mainly based on the use of high-dose GCs as the initial treatment, combined with immunosuppressive drugs such as tacrolimus, MTX, and IVIG [10]. However, at present, there are no definite treatment guidelines for IMNM in Japan. In previous studies, rituximab was more effective in African-American patients with anti-SRP antibody-positive IMNM than in Caucasian patients with anti-SRP antibody-positive IMNM [3, 4], suggesting that there may be differences in the efficacy of rituximab for IMNM across racial groups. Reports demonstrating the efficacy of rituximab in East Asian patients with anti-SRP antibody-positive IMNM are available, but they remain scarce [5, 6]. Additional cases from Japan and East Asia need to be evaluated to determine the validity of this finding.

## Conclusion

We reported the case of a patient with anti-SRP antibody-positive IMNM who was refractory to high-dose GC, tacrolimus, and IVIG, and was successfully treated with a combination of MTX and rituximab. Only a few case reports have demonstrated the efficacy of MTX, particularly

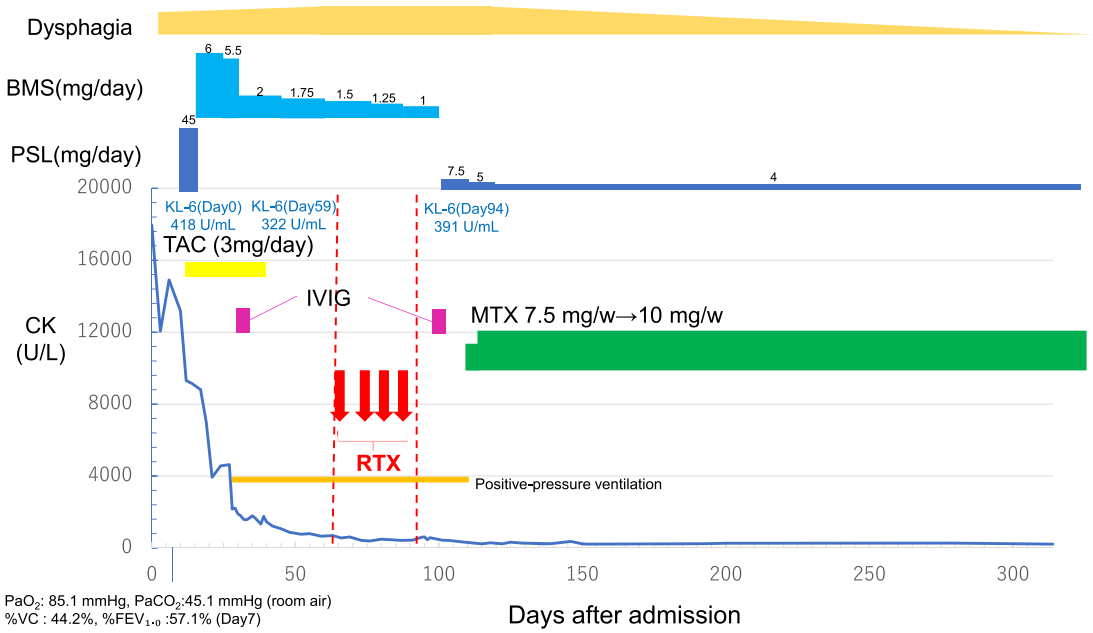


**Figure 3.** Clinical course. The creatine kinase (CK) level was 17,954 IU/ml on the day of admission. Tacrolimus was used in the early stages of treatment with high-dose glucocorticoid therapy and intravenous immunoglobulin (IVIG). However, during the course of the treatment, we changed the therapeutic treatment from tacrolimus to rituximab and methotrexate, with the approval of the hospital ethics committee. Following treatment, CK levels improved to 264 IU/ml by Day 200. Following rituximab treatment, CK levels decreased from 688 to 437 IU/ml. BMS: betamethasone; PSL: prednisolone.

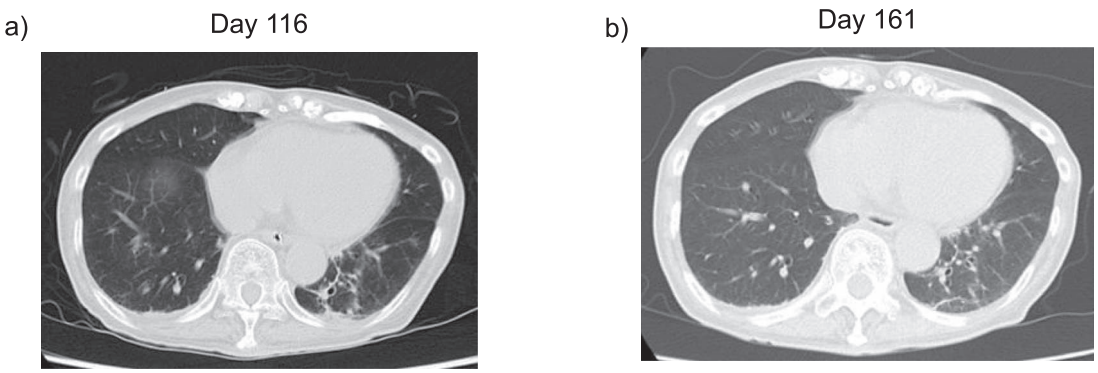


**Figure 4.** (a) Chest radiography findings on Day 116. CT showed improvement of interstitial lung disease. (b) Chest radiography findings on Day 161. CT showed slight improvement of interstitial lung disease.

rituximab, in East Asian patients with anti-SRP antibody-positive IMNM. Not only is combination therapy with MTX and RTX effective in improving myositis in treatment-resistant anti-SRP antibody-positive IMNM cases, but it also holds significant potential for preventing muscle atrophy through its GC-sparing effect. Therefore, this case is clinically meaningful.

## Acknowledgement

We acknowledge proofreading and editing by Benjamin Phillis at the Clinical Study Support Centre at Wakayama Medical University.

## Conflict of interest

None declared.

## Funding

None declared.

## Patient consent

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

## Ethical approval

Rituximab and MTX treatments were approved by the ethics committee of our university (4462).

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doi:10.1093/mrcr/rxaf067
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