Immune-mediated necrotizing myopathy which showed deposition of C5b-9 in the necrotic muscle fibers and was successfully treated with intensive combined therapy with high-dose glucocorticoids, tacrolimus, and intravenous immunoglobulins

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ABSTRACT
Currently, no standard treatment strategy has been established for immune-mediated necrotizing myopathy (IMNM). Here we present a case of IMNM which was successfully treated with intensive combined therapy with high-dose glucocorticoids, tacrolimus, and intravenous immunoglobulins. Her muscle weakness was rapidly progressive and severe so that she became bedridden one week after admission. She was complicated with dysphagia and had serum myogenic enzymes elevation, ventricular diastolic dysfunction, and interstitial lung disease. Serum anti-SRP antibody was positive and her muscle biopsy revealed many necrotic fibers with minimal inflammation. Further histological analysis demonstrated infiltration of phagocytic macrophages with deposition of membrane attack complex (C5b-9) in the necrotic muscle fibers, suggesting activation of complement pathway and macrophages as a pathomechanism of this disease. She was diagnosed as IMNM and was immediately initiated a combination therapy described above, which led to dramatic clinical improvements. Recent studies suggest that intravenous immunoglobulins and tacrolimus can inhibit the activation of complement pathway and macrophages. Our present case suggests that early initiation of intensive combined therapy including intravenous immunoglobulins and tacrolimus might be effective for preventing irreversible muscle damages by disrupting a pathogenic activation of complement and macrophages in IMNM.

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1. Introduction
Immune-mediated necrotizing myopathy (IMNM) is one of the distinct groups of idiopathic inflammatory myopathies [1–3]. Two disease-specific autoantibodies for IMNM have been identified: anti-signal recognition particle (SRP) and anti-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies. Anti-SRP antibody positive IMNM usually develops in an acutely progressive pattern of symmetric proximal-dominant limb weakness [1]. It is not uncommon for the patients to become bedridden in a few weeks after disease onset. Dysphagia can be observed in about half of the cases as a fatal complication [4,5]. In addition, cardiac and lung involvements such as diastolic dysfunction and interstitial lung disease can be found in this disease [4,5].

Currently, no standard treatment strategy has been established for anti-SRP antibody positive IMNM due to the absence of randomized controlled trials. In general, glucocorticoid is used as a first-line therapy, but glucocorticoid monotherapy often results in poor control of the condition [6]. As additional immunosuppressive drugs, methotrexate and azathioprine are often used, but even with these immunosuppressive drugs, the disease often shows treatment resistance [7]. Therefore, establishment of effective treatment strategy is desired in this disease. In recent years, activation of macrophages and complement has been assumed as a central pathophysiology causing muscle necrosis in IMNM because infiltration of phagocytic macrophages and deposition of membrane attack complex (C5b-9) were confirmed in inflamed necrotic muscle fibers [1]. Tacrolimus, a calcineurin inhibitor, has been reported to suppress macrophage activation [8,9] and intravenous immunoglobulins can inhibit a
complement activation pathway [10]. In this regard, early initiation of combined therapy with high-dose glucocorticoids, tacrolimus, and intravenous immunoglobulins might be effective for IMNM. Here we report a case of IMNM which showed infiltration of phagocytic macrophages with deposition of C5b-9 in the necrotic muscle fibers and was successfully treated with early combined therapy with high-dose glucocorticoids, tacrolimus, and intravenous immunoglobulins.

2. Case presentation
A 54-year-old woman experienced weakness of her proximal upper and lower extremities in April 2021. Two weeks later, she noticed dysphagia and was admitted to our hospital for further investigations. She had no history for statin use and no family history of neuromuscular and connective tissue diseases. Manual muscle test (MMT) scores were as follows; 3/3 in deltoid and 4/4 in iliopsoas muscles. There was no Gottron papules, Heliotrope rash, and mechanic’s hands. Bilateral fine crackles were audible on her lower chest. Serum levels of creatine kinase (CK, 12102 U/L, normal <153 mg/dL), aldolase (237 U/L, normal <6.1 U/L), troponin-T (3.510 ng/mL, normal <0.014 ng/mL), and C-reactive protein (0.42 mg/dL, normal <0.14 mg/dL) were elevated. There were not hypothyroidism or hypokalemia. Serum antinuclear antibody test by immunofluorescence method was negative (<1:40). Serum anti-SRP antibody was positive by immunoblot assay (EUROLINE Myositis Antigens Profile 3 [IgG], Euroimmun, Lübeck, Germany), while other autoantibodies such as anti-HMGCR, anti-ARS, anti-MDA5, anti-Mi2, anti-TIF1γ, anti-dsDNA, anti-Sm, anti-mitochondrial M2, and anti-neutrophil cytoplasmic antibodies, and rheumatoid factor were all negative. Types of human leukocyte antigen were as follows; A22, A33, B44, B51, DRB1*12:01:01, and DRB1*13:02:01. Electromyography performed on the proximal upper extremities showed the myopathic changes (low amplitude with a short duration). Magnetic resonance imaging (MRI) demonstrated gadolinium enhancement of triceps and proximal lower extremities (Figure 1). The biopsy of her left triceps brachii muscle revealed many necrotic fibers, in which phagocytes and deposits of membrane attack complex (C5b-9) were observed (Figure 2). Electrocardiogram showed negative T wave at V1, V2, V3, and V4, in addition to poor R progression. Transthoracic echocardiography revealed impaired relaxation (E/A ratio of 0.77), with the preservation of left ventricular ejection fraction (66%). Percutaneous coronary angiography showed no stenotic lesions. Contrast-enhanced computed tomography (CT) of whole body showed no evidence of malignancies but the ground-glass opacities (GGO) with reticular shadow was found on both sides of inferior lobes of lungs (Figure 3(a)). Respiratory function test revealed restrictive ventilatory defect, with decreased vital capacity (%VC of 68.4%). We diagnosed her with anti-SRP antibody positive IMNM, complicated with dysphagia, ventricular diastolic dysfunction, and interstitial lung disease.

Rapidly progressive deterioration of her proximal muscle weakness (MMT scores, 2/2 in deltoid and in 2/2 iliopsoas muscles) occurred within one week after admission, resulting in the bedridden state. Early intensive combined therapy with high-dose prednisolone (70 mg/day), tacrolimus (trough concentration: 10 ng/mL), and intravenous immunoglobulins (400 mg/kg/day for 5 consecutive days) was initiated. Two weeks later, remarkable improvements were observed both in MMT scores (4/4 in deltoid and 3/3 in iliopsoas) and in serum CK level (2736 U/L). Serum troponin-T level was decreased to 0.794 ng/mL, negative T wave on electrocardiogram disappeared, and diastolic function (E/A ratio

Figure 1. Magnetic resonance imaging findings of upper and lower proximal extremities. Magnetic resonance imaging shows the gadolinium enhancement of triceps (a) and quadriceps (b) (yellow arrows).
of 0.84) was improved. In addition, the density of GGO on chest CT and pulmonary function (%VC of 82.6 %) were both improved (Figure 3(b)). She was also recovered from dysphagia. Prednisolone dose was gradually tapered to 10 mg/day and her muscle weakness improved further to independent walking within 3 months after initiation of the above combined therapy (Figure 4).

3. Discussion

Anti-SRP antibody positive IMNM is characterized by severe proximal muscle weakness, which often shows poor response to glucocorticoid treatment alone. However, currently there is no established treatment strategy for this disease. Our present case and one case report [11] have shown dramatic clinical response to an early combined therapy with high-dose glucocorticoids, tacrolimus, and intravenous immunoglobulins, suggesting that early initiation of these combination therapy could be a new treatment strategy for IMNM and be important to prevent irreversible muscle damages.

Anti-SRP antibody is considered to be pathogenic in IMNM [1]. Anti-SRP antibody binds to an ectopically expressed SRP antigen at a surface of muscle fiber, leading to a subsequent activation of complement [1]. Then, complement activation triggers muscle necrosis by deposition of membrane attack complex (C5b-9) and myophagocytosis by recruiting activated macrophages [1]. In fact, both in vitro and in vivo experiments have shown that...
anti-SRP antibody induced muscle necrosis in the complement- and myophagocytosis- dependent manner [12–15]. Furthermore, C5b-9 deposits have been reported in inflamed necrotic muscle fibers of anti-SRP antibody positive IMNM [6,11,12,15–18]. To our knowledge, our case is the second Japanese case which demonstrated C5b-9 deposits and myophagocytosis in the necrotic muscle fibers of anti-SRP antibody positive IMNM [11], and more accumulation of cases are required to confirm an involvement of C5b-9 in Japanese patients with IMNM.

The prevalence of cardiac dysfunction in anti-SRP-antibody positive IMNM is ranging from 2 to 30% according to the previous reports [19]. Left heart diastolic dysfunction of our case and other case reports [11,19] have shown favorable responses to immunosuppressive therapies including tacrolimus and intravenous immunoglobulins, suggesting that cardiac injury was caused by an immune-mediated mechanism. Although precise mechanisms leading to cardiac injury remain unclear in IMNM, the similar pathological findings between myocardium and skeletal muscle in an identical case [11] indicate that anti-SRP antibody mediated activation of complement and macrophage is commonly involved in the pathogenesis of cardiac and skeletal muscle injury.

Interstitial lung disease can be found in 10–50% of patients with anti-SRP antibody positive IMNM [5,20]. Non-specific interstitial pneumonia pattern on high resolution CT is a most common finding in patients with IMNM and their respiratory symptoms are not severe and remain stable throughout their clinical course [20], in contrast to patients with anti-MDA5 or anti-ARS antibody positive interstitial lung disease. Interestingly, as shown in our present case, IMNM patients with interstitial lung disease had a higher frequency of dysphagia [20], suggesting a potential contribution of gastroesophageal reflux in developing interstitial lung disease of IMNM. As for treatment, Kusumoto T et al. have reported favorable efficacy of combination therapy consisting of prednisolone, cyclosporine and intravenous immunoglobulins for interstitial lung disease in a patient with IMNM [21], in line with our present case.

As one of the mechanisms implicated in intravenous immunoglobulins-mediated immunomodulation, intravenous immunoglobulins have been shown to disrupt an activation of complement pathway [10,22]. Mechanistically, infused immunoglobulins make the complexes with C3b and inhibit the incorporation of activated C3 molecule into C5 convertase [10,22]. Our present case had the evidence of complement activation as shown by the presence of C5b-9 deposits in the necrotic muscle fibers and showed good clinical response to intravenous immunoglobulins, supporting a potential of this treatment on treating anti-SRP antibody positive IMNM by inhibiting complement activation.

In addition to T cells, tacrolimus has been reported to inhibit phagocytosis and inflammatory molecules production by activated macrophages [8,9]. Therefore, tacrolimus could be effective to prevent myophagocytosis by macrophages in our case. Also, tacrolimus has been reported to be efficacious for treating interstitial lung disease in patients with idiopathic inflammatory myopathies [23,24]. In line with those studies, our present case showed the radiological improvements of interstitial lung disease.
on chest CT. Thus, tacrolimus can be appropriate for the cases with anti-SRP antibody positive IMNM and interstitial lung disease.

In conclusion, an early intensive combined therapy with high-dose glucocorticoids, tacrolimus, and intravenous immunoglobulins might be an effective treatment strategy in patients with anti-SRP antibody positive IMNM in future. Accumulation of cases and further randomized controlled studies are required to confirm our results.

**Ethical approval**

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

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

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