

[CASE REPORT]

Marked Respiratory Failure in an Ambulant Patient with Immune-mediated Necrotizing Myopathy and Anti-Kv1.4 and Anti-titin Antibodies

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Abstract:

We herein report a case of seronegative immune-mediated necrotizing myopathy (IMNM) concurrent with anti-Kv1.4 and anti-titin antibodies. A 72-year-old Japanese woman presented with a 29-year history of fluctuating high serum creatine kinase (CK) levels followed by intermittent ptosis and respiratory muscle weakness. This case highlights the fact that marked respiratory muscle weakness requiring intubation can be seen in an ambulant patient with IMNM. Marked respiratory muscle weakness, rhabdomyolysis-like acute elevation of CK levels, and anti-striational muscle antibodies may be a characteristic constellation of findings in a distinct subgroup of patients with inflammatory myopathy with myasthenia gravis or similar symptoms.

Key words: respiratory paralysis, muscular diseases, creatine kinase, blepharoptosis

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Introduction

Weakness of the respiratory muscles typically occurs late in the course of a broad variety of muscle disorders that present with diffuse muscle weakness. Musculoskeletal diseases that present with marked respiratory muscle weakness but a preserved limb muscle strength or ambulation are a distinct entity. This group includes metabolic myopathies, such as adult-onset Pompe disease, as well as mitochondrial, hereditary, inflammatory, and adult-onset nemaline myopathies (1).

Immune-mediated necrotizing myopathy (IMNM) is a relatively new entity within the spectrum of idiopathic inflammatory myopathies manifesting as proximal muscle weakness and a high serum creatine kinase (CK) level, along with specific histopathological findings. IMNM is divided into three groups: anti-signal-recognition particle (anti-SRP) myopathy, anti-3-hydroxy-3-methylglutaryl-CoA reductase (anti-HMGCR) myopathy, and seronegative

IMNM (2). Although neuromuscular respiratory dysfunction has been reported as a relatively common complication in seronegative IMNM (3), marked respiratory muscle involvement requiring intubation in cases with a preserved muscle strength of the limbs has rarely been reported.

Anti-striational antibodies were first described as serum immunoglobulins reacting with cross-striations of skeletal muscle in myasthenia gravis (MG) patients (4). Anti-striational antibodies, including autoantibodies to titin, ryanodine receptor, and muscular voltage-gated potassium channel Kv1.4, are frequently detected in MG patients with myositis and/or myocarditis (5-7). In addition, these antibodies are detectable in the serum of patients with immune checkpoint inhibitor-related inflammatory myopathies with or without MG (8). A few cases of immune checkpoint inhibitor-induced necrotizing myopathy and MG with anti-striational antibodies have been reported (9, 10).

We herein report a patient with seronegative IMNM concurrent with anti-striational antibodies who developed severe

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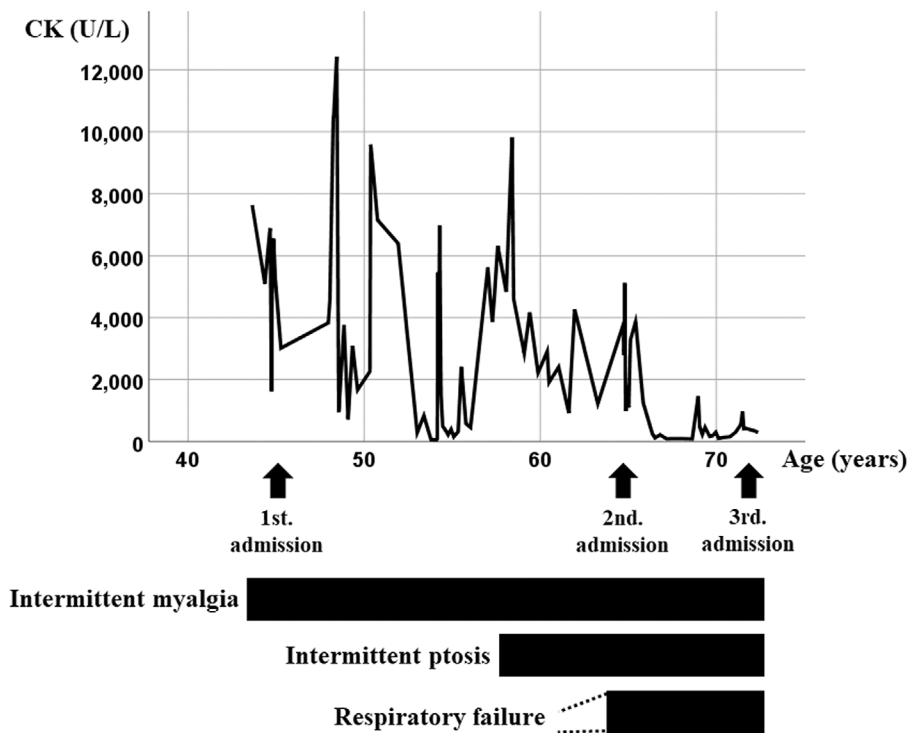


Figure 1. Clinical course of the patient. CK: creatine kinase

respiratory failure requiring intubation despite a preserved limb muscle strength with rhabdomyolysis-like acute elevation of serum CK levels without the use of immune checkpoint inhibitors.

Case Report

A 72-year-old woman with a medical history of appendicitis presented with an 8-year history of severe respiratory failure and a 29-year history of fluctuating high serum CK levels. No family history of neuromuscular disorders was reported.

At 43 years old, the patient presented with myalgia of the lower extremities that lasted a couple of days, with concomitant elevation of serum CK levels to 7,634 U/L. Subsequently, similar episodes of myalgia of the lower extremities that lasted a couple of days recurred every few months. At 45 years old, the patient was admitted to our hospital for the first time with complaints of recurrent myalgia.

A neurological examination on admission found no abnormalities. No muscle weakness was observed. Routine laboratory tests showed an elevated CK level of 3,015 U/L. A normal response was observed upon nonischemic forearm exercise testing. A needle electromyogram (EMG) of the right bicep and gastrocnemius showed decreased amplitude polyphasic motor unit potentials, indicating the presence of myogenic changes. A muscle biopsy of the left gastrocnemius showed moderate variation in fiber size. Only a necrotic fiber and a few regenerating fibers were present. Additional dystrophin immunostaining patterns were normal, and a final diagnosis could not be reached.

After discharge, her elevated CK level was followed by a local clinic. The CK levels fluctuated, with an acute elevation to levels up to 12,430 U/L (Fig. 1). In addition to intermittent mild myalgia, one-sided ptosis that lasted for several days without diplopia or fatigability began to occasionally appear from 58 years old. At 64 years old, the patient presented with mild dyspnea and daytime sleepiness and was referred to another hospital. The patient's oxygen saturation was observed to be 93% on room air, and respiratory function testing showed a restricted pattern with a marked decrease in the vital capacity (VC; 1.1 L, 46.3% of predicted). Computed tomography (CT) of the chest showed no remarkable findings except for mild atrophy of the paraspinal muscles. Shortly after undergoing muscle CT, the patient developed severe dyspnea, and an arterial blood gas analysis revealed hypercapnia (PaCO_2 , 85.7 mmHg) and hypoxemia (PaO_2 , 42.7 mmHg), which suggested type 2 respiratory failure. Due to CO_2 narcosis, intubation was performed, and artificial ventilatory assistance was started. The patient was transferred to our hospital for the investigation of the underlying neuromuscular disease that had led to her respiratory failure.

A neurological examination on this second admission revealed a normal cranial nerve function. No ptosis, external ophthalmoplegia, diplopia, or facial weakness was noted. Manual muscle testing revealed a normal neck and limb muscle strength. The patient's abdomen looked very thin, and she was unable to sit up from the supine position. Ambulation was still possible, and Gowers' sign was negative. All deep tendon reflexes were present, and the patient demonstrated normal sensory functions.

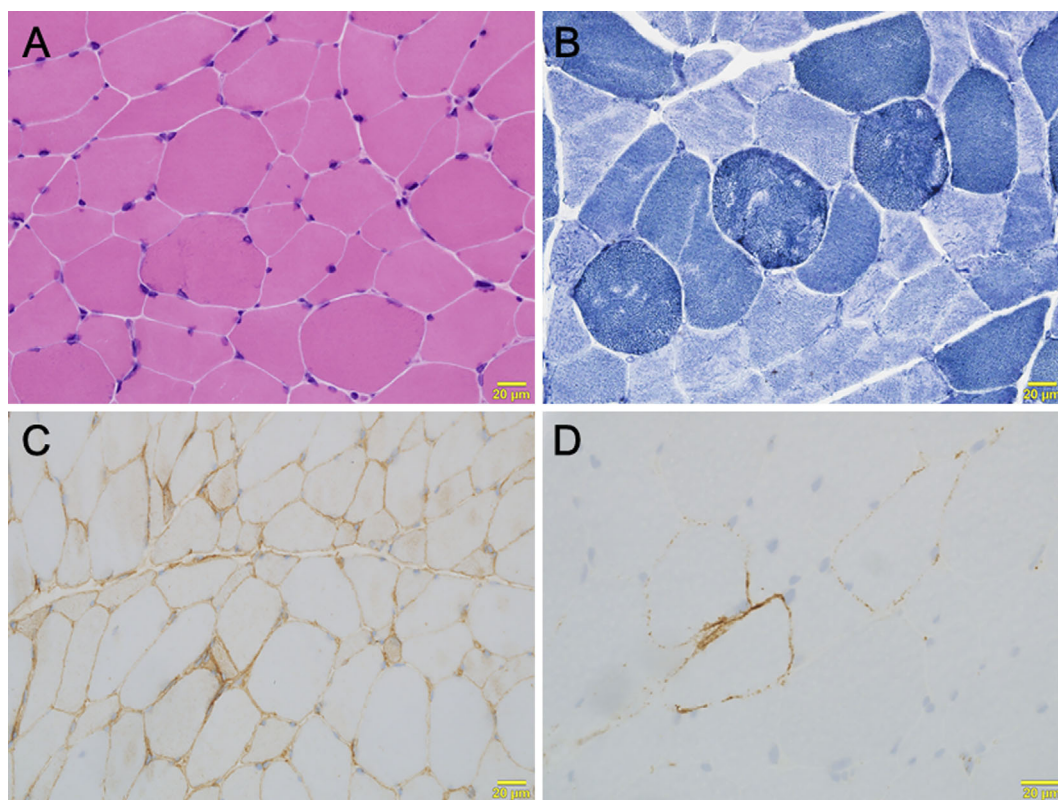


Figure 2. Histopathological findings of the left biceps brachii muscle. Hematoxylin and Eosin staining section showed a moderate variation in fiber size and scattered regenerating muscle fibers (A). Nicotinamide adenine dinucleotide (NADH) staining showed that the intermyofibrillar networks were mildly disorganized in some fibers with a moth-eaten appearance (B). Immunohistochemical staining showed the focal expression of human leukocyte antigen ABC (HLA-ABC) (C) and membrane attack complex (MAC) deposition on sarcolemma in some fibers (D).

Laboratory tests showed increased serum levels of muscle enzymes including CK (5,118 U/L) and aldolase (68.4 U/L; normal 2.1-6.1 U/L). Serum anti-acetylcholine receptor antibodies and anti-muscle-specific tyrosine kinase antibodies were negative. The acylcarnitine profile was normal, while total carnitine was 66.1 $\mu\text{mol/L}$ (normal, 45-91 $\mu\text{mol/L}$), free carnitine was 56.8 $\mu\text{mol/L}$ (normal, 36-74 $\mu\text{mol/L}$), and acylcarnitine was 9.3 $\mu\text{mol/L}$ (normal, 6-23 $\mu\text{mol/L}$). Anti-mitochondrial M2 antibody was negative. A dried blood spot test showed normal acid alpha-glucosidase activity (23.04 pmol/punch/h). An electrocardiogram showed a normal sinus rhythm with a heart rate of 81/min. Echocardiography revealed a good ejection fraction (80.4%) and no asynergy in the left ventricular wall motion. A study of the phrenic nerve conduction of the right side showed mildly decreased compound muscle action potential (130 μV) and normal latency (7.7 ms). A needle EMG of the right deltoid showed low amplitude polyphasic motor unit potentials, indicating myogenic changes. Magnetic resonance imaging (MRI) of the thigh muscles showed no signs of fatty replacement or a high intensity on short tau inversion recovery, which are reflective of inflammation. Genetic testing revealed no pathogenic or likely pathogenic *TTN* gene variants. Although a final diagnosis could not be reached, the serum level of CK was found to have decreased to 1,571 U/L without any

treatment, which led to her discharge with intermittent assistance by non-invasive positive pressure ventilation (NPPV).

After discharge, the patient remained independent in her daily home activities with intermittent NPPV assistance. No muscle weakness progression was observed, and the degree of fluctuation in the CK levels was milder than previously (Fig. 1). At 72 years old, the patient was admitted for a further evaluation, including a second muscle biopsy. No waxing or waning was found upon repetitive nerve stimulation test (right facial, accessory, and ulnar nerves). On a single fiber EMG, jitter was normal in the right frontalis. Chest CT was negative for thymoma. A muscle biopsy from the left biceps brachii showed moderate variations in fiber size and scattered regenerating muscle fibers without mononuclear cell infiltration in the endomysium (Fig. 2). Perifascicular atrophy was not seen. A few fibers with internal nuclei were observed. Intermyo-fibrillar networks were mildly disorganized in some fibers with a moth-eaten appearance upon nicotinamide adenine dinucleotide (NADH) staining. Immunohistochemical staining showed the expression of human leukocyte antigen ABC (HLA-ABC) in some muscle fibers. Membrane attack complex deposits were observed on the sarcolemma of some muscle fibers. The anti-signal recognition particle (SRP), anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), anti-aminoacyl transfer

RNA synthetase (ARS), anti-U1 ribonucleoprotein (anti-U1 RNP), and anti-Ku antibodies were negative. Cell-based assays (7) revealed seropositivity for anti-voltage-gated potassium channel Kv1.4 and anti-titin antibodies.

Based on the above results, a diagnosis of seronegative IMNM concurrent with anti-striational muscle antibodies was made. Immunotherapy was not initiated because no progression of muscle weakness was observed, and the patient was concerned about infection of coronavirus disease 2019. The patient remained ambulant and independent in her daily activities at home with intermittent assistance of NPPV at the time of the final follow-up.

Discussion

Two unique presentations were found in this case. First, marked respiratory muscle weakness requiring intubation presented in an ambulant patient with seronegative IMNM. Second, an MG-like symptom (intermittent ptosis), repeated rhabdomyolysis-like elevation of CK levels, and anti-Kv1.4 and anti-titin antibodies were concurrent with IMNM in the absence of immune checkpoint inhibitor use.

Marked respiratory muscle weakness requiring intubation was observed in an ambulant patient with seronegative IMNM. In the present case, severe respiratory muscle weakness requiring intubation was observed despite the absence of weakness of the limb muscles. Furthermore, the patient remained ambulant over eight years after the onset of symptoms associated with respiratory muscle weakness. Although the clinical course of the present case was not typical for IMNM, our final diagnosis was seronegative IMNM based on histopathological findings and the careful exclusion of diseases that require differentiation. Given the fixed muscle weakness, elevated serum CK levels, and myopathic changes of EMG findings, we made a diagnosis of muscle disease as the main cause of the marked respiratory muscle weakness. Muscle biopsies revealed sarcolemmal membrane attack complex (MAC) deposition alongside mild HLA-ABC expression in the muscle fibers, which suggested that the disease was associated with immune-mediated myofiber necrosis. We therefore measured the antibodies against SRP and HMGCR, and the results were negative. In addition, anti-mitochondrial M2 and anti-ARS antibodies, which are associated with IMNM (11, 12), were also negative. Therefore, we considered the case to be one of seronegative immune-mediated necrotizing myopathy. Selective involvement of the semitendinosus muscle, which would have suggested a hereditary myopathy with early respiratory failure, was not observed on MRI of the thigh muscles. Genetic testing showed no pathogenic *TTN* gene variant in the present case. Her normal acid alpha-glucosidase activity did not suggest Pompe disease. Although intermittent ptosis and positive results of anti-striational muscle antibodies were observed in the disease course of the present case, there was no ptosis, external ophthalmoplegia, diplopia, or fatigability when respiratory muscle weakness became apparent. Considering the

clinical course, the negative results of serum anti-acetylcholine receptor antibodies and anti-muscle-specific antibodies, as well as the results of electrophysiological tests, including repetitive nerve stimulation tests and a single-fiber EMG, IMNM was identified as a possible cause of respiratory muscle weakness over any neuromuscular junction disorders.

An IMNM case with respiratory failure as the presenting symptom has been previously reported (13). In that case, although marked respiratory muscle weakness requiring intubation was observed, as in the present case, severe limb weakness was also observed simultaneously in this previous case (13). Marked fluctuation of serum CK levels and spontaneous stabilization of respiratory muscle weakness and serum CK levels without treatment are not typical for the clinical course of IMNM. However, spontaneous symptomatic improvement lasting for longer than four years has been reported previously in a patient with anti-HMGCR myopathy (14). Furthermore, a previous report of three idiopathic inflammatory myopathy patients showed spontaneous clinical improvement without the administration of immunosuppressants (15).

Marked respiratory muscle weakness, rhabdomyolysis-like acute elevation of CK levels, and anti-striational muscle antibodies may be a characteristic constellation of findings in a distinct subgroup of patients with inflammatory myopathy with MG or MG-like symptoms. In the present case, transient ptosis and severe respiratory muscle weakness were observed over the long disease course of repeated rhabdomyolysis-like elevation of CK levels and positivity for anti-voltage-gated potassium channel Kv1.4 antibody and anti-titin antibody. Uchio et al. noted that 5 of 10 patients with idiopathic inflammatory myopathy with myasthenia gravis showed rhabdomyolysis-like acute elevation of serum CK levels and marked respiratory failure requiring ventilator support with and without thymoma (16). Anti-titin antibodies were positive in four of the five patients (16). A previous case report described a patient that was positive for anti-striational muscle antibodies who developed acute rhabdomyolysis and polymyositis with marked respiratory muscle weakness and ptosis after treatment with immune checkpoint therapy (17). Aside from this previous case, immune-related adverse events caused by treatment with immune checkpoint inhibitors share clinical features with the present case. Previous reports have shown that anti-striational antibodies are often positive in immune checkpoint inhibitor-induced myopathy or MG (18, 19). Similar to the findings in the present case, immune checkpoint inhibitor-induced myopathy was observed to overlap with MG-like symptoms (8, 20-23). In addition, rhabdomyolysis is an adverse event reported to be caused by immune checkpoint inhibitor therapy. Cases with rhabdomyolysis and MG or myositis have been previously reported (24, 25). Therefore, the present case and the known immune checkpoint inhibitor-induced immune-related adverse events may have a common autoimmune mechanism as their underlying pathophysiol-

ogy.

In the present case, both anti-titin and anti-voltage-gated potassium channel Kv1.4 antibodies were positive. A previous study showed that MG patients with positivity for both antibodies had more severe manifestations and more frequent concomitant myocarditis and/or myositis than MG patients with positivity for anti-titin antibodies only (26). Additional cases similar to ours are needed to clarify the different roles played by both antibodies in inflammatory myopathy.

In conclusion, marked respiratory failure requiring intubation with preserved limb muscle strength was seen in a seronegative IMNM patient. Marked respiratory muscle weakness, rhabdomyolysis-like acute elevation of CK levels, and anti-striational muscle antibodies may be a characteristic constellation of findings in a distinct subgroup of patients with inflammatory myopathy with MG or MG-like symptoms.

Author's disclosure of potential Conflicts of Interest (COI).

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