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Case Report

Influenza A (H3N2) infection followed by anti-signal recognition particle antibody-positive necrotizing myopathy: A case report

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ABSTRACT

A 60-year-old Japanese woman presented with subacute progressive muscle pain and weakness in her proximal extremities. She was diagnosed with influenza A (H3N2) infection a week before the onset of muscle pain. At the time of admission, she exhibited weakness in the proximal muscles of the upper and lower limbs, elevated serum liver enzymes and creatinine kinase, and myoglobinuria. She did not manifest renal failure and cardiac abnormalities, indicating myocarditis. Electromyography revealed myogenic changes, and magnetic resonance imaging of the upper limb showed abnormal signal intensities in the muscles, suggestive of myopathy. Muscle biopsy of the biceps revealed numerous necrotic regeneration fibers and mild inflammatory cell infiltration, suggesting immune-mediated necrotizing myopathy (IMNM). Necrotized muscle cells were positive for human influenza A (H3N2). Autoantibody analysis showed the presence of antibodies against the signal recognition particle (SRP), and the patient was diagnosed with anti-SRP-associated IMNM. She was resistant to intravenous methylprednisolone pulse therapy but recovered after administration of oral systemic corticosteroids and immunoglobulins. We speculate that the influenza A (H3N2) infection might have triggered her IMNM. Thus, IMNM should be considered as a differential diagnosis in patients with proximal muscle weakness that persists after viral infections.
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Case presentation

A 60-year-old Japanese woman visited the local clinic 23 days before being admitted to the Nagasaki University Hospital with a sore throat and fever (39 °C) that lasted for 2 days. She had been taking statins for 6 years to treat her dyslipidemia. She was diagnosed with influenza A infection by immunochromatographic testing and was prescribed oseltamivir for 5 days. Her fever reduced after a day, although her fatigue persisted throughout the course of medication. Seven days before admission, she noticed muscle pain and edema in her proximal extremities along with shortness of breath. Muscle symptoms worsened, and she was unable to walk a week later and therefore visited another clinic. The physician detected symmetrical proximal muscle weakness in the extremities and elevated serum levels of creatine kinase (CK)

Abbreviations: CK, creatine kinase; SRP, signal recognition particle; IMNMs, immune-mediated necrotizing myopathies; HMGCR, anti-3 hydroxy-3 methylglutarylcoenzyme A reductase.

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(7,695 U/L). She was suspected of developing subacute myositis and was referred to the Nagasaki University Hospital on the same day.

She was alert and had the following vitals on admission: body temperature, 36.7 °C; blood pressure, 135/87 mm Hg; pulse rate, 101 beats/min; respiratory rate, 18 breaths/min; and oxygen saturation, 98% in room air. She had no family history of muscular diseases. Manual muscle testing showed a score of 3/3, 4/4, 4/4, 3/3, and 4/4 (right/left) for the shoulder and arm, elbow, forearm, hip, and knee muscles, respectively. She had pain in her shoulders and thighs on motion. Pretibial pitting edema was also noticed. The findings of chest and abdominal examinations were unremarkable. Neurological examination confirmed that her cranial and peripheral nerves were normal. She did not have a rash or erythema. Supplementary Table 1 shows the data from her laboratory tests. Her blood cell counts were normal, and biochemistry tests showed elevated levels of liver enzymes [(aspartate transaminase, 358 U/L; alanine transaminase, 395 U/L; lactate dehydrogenase, 1,367 U/L (normal, 124–222 U/L)]. Serum CK was elevated at 8,429 U/L (normal, 41–153 U/L) with CK-MB at 469 U/L (normal, 0–15 U/L). Urine myoglobin level was 160 ng/mL (normal, <10 ng/mL). Rosuvastatin was discontinued after admission as statin-induced myopathy was a possible differential diagnosis. Elevated levels of N-terminal-pro hormone BNP (107.0 pg/mL; normal, <55 pg/mL) and troponin T (1,520 ng/mL; normal, <0.014 ng/mL) suggested the presence of myocarditis. However, electrocardiograms, transthoracic echocardiography, and gallium-67 myocardial scintigraphy revealed no abnormal findings. The nerve conduction study performed by a neurologist revealed normal peripheral nerves. Electromyography revealed myogenic changes in her biceps and triceps. Serum hemagglutination inhibition assay detected antibodies against influenza A (H3N2) at 1:160 titer, whereas that for H1N1pdm09 was negative (<1:10), confirming influenza A (H3N2) viral infection.

Subsequently, she was administered intravenous saline (1,000 mL/day) and oral furosemide (20 mg). However, the levels of muscular enzymes in her serum remained high, and she had progressive muscular symptoms that made it difficult for her to get up without help. Magnetic resonance imaging of the left upper limb revealed areas of high signal intensity in the shoulder and upper arm muscles on day 14; the findings were nonspecific, but indicative of myopathy (Supplementary Figure S1). Muscle biopsy of the left biceps brachii showed necrotizing myopathy with numerous necrotic regeneration fibers and mild inflammatory cell infiltration on day 16 (Figure 1A), suggesting immune-mediated necrotizing myopathy (IMNM). Immunohistochemistry of fresh-frozen biopsy specimens revealed influenza A (H3N2)-positive necrotizing muscle cells (Figure 1B). Commercial line immunoassay using serum on day 13 was positive for the anti-SRP antibody against multiple myopathy-related autoantibodies (Supplementary Table S2). Antinuclear antibody test by immunofluorescence showed cytoplasmic staining, consistent with the pattern by anti-SRP antibodies (Figure 1C). Additionally, radioimmunoprecipitation using ^{35}S-methionine-labeled human cells clearly confirmed the typical patterns of anti-SRP antibody components (Figure 1D). These tests were confirmed using serum on day 65. Thus, she was diagnosed with anti-SRP antibody-positive IMNM following the influenza A (H3N2) infection. She underwent three courses of

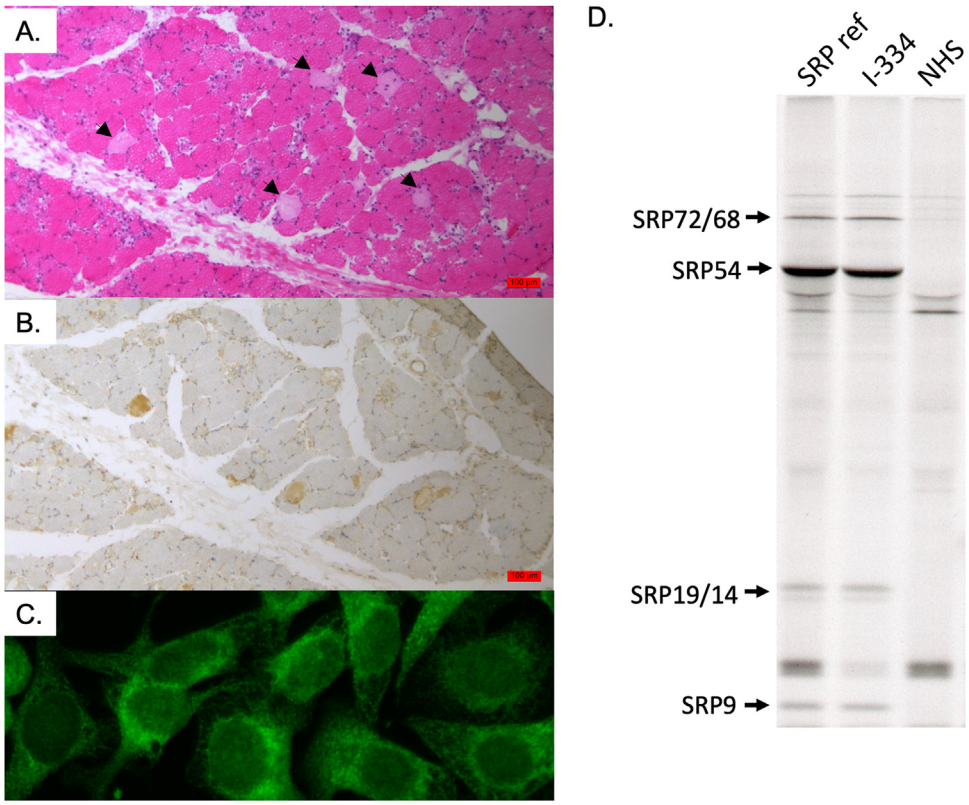

Figure 1. A. Hematoxylin-eosin staining of the muscle biopsy tissue. Necrotic regeneration fibers (arrows) and mild inflammatory cell infiltration were observed. Scalebar, 100 μm; Magnification, 40×. B. Immunostaining of muscle biopsy tissue using anti-human influenza A (H3N2) monoclonal antibody (Clone F49, code No. M146, Takara Bio Inc.). Scalebar, 100 μm; Magnification, 40×. The lung tissue from an autopsy of influenza A (H3N2) served as the positive control (Takahashi et al., 2000) and confirmed that type II lung epithelial cells were stained with the anti-influenza A (H3N2) antibody. A tissue microarray was used as a negative control. The muscle biopsy tissue was negative for mouse IgG isotype control. C. Antinuclear antibody test by immunofluorescence was positive in a cytoplasmic pattern. D. Immunoprecipitated anti-SRP reference serum, patient serum, and normal human serum (NHS) were fractionated by 12.5% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Components of SRP (SRP9, SRP14, SRP19, SRP54, SRP68, and SRP72) have been indicated.

methylprednisolone pulse therapy from day 23. However, she exhibited dysphagia, and her muscular enzyme levels remained high. Immunoglobulins (400 mg/kg) were administered for five days from day 40 to treat the steroid-resistant myopathy, and oral corticosteroids (40 mg/day) were initiated on day 44. Her muscle strength gradually improved and her muscle enzyme levels reduced (Supplementary Figure S2). She could walk using a walker on day 58, following which she was transferred to a rehabilitation hospital on day 67 and was able to walk on her own on day 72.

Discussion

Influenza virus infections typically induce pain in the joints and muscles along with respiratory symptoms. Myositis was first described in 1957 as a complication of infection by the influenza virus (Lundberg, 1957). It is commonly found in children recovering from acute illness (5.5% and 33.9% infected with influenza A and B, respectively) (Hu et al., 2004). In adults, muscle symptoms are less frequent, although myositis was detected in 13.3% in the elderly during the influenza A (H3N2) epidemic (Yoshino et al., 2000). Half of the adult cases of influenza-associated myositis are females over the age of 60. The majority of these patients were infected with influenza A, among which 37% were positive for influenza A (H3N2) (Sellers et al., 2017). Myopathy typically begins within one week of the onset of respiratory symptoms (Sellers et al., 2017). However, the pathogenesis of influenza-associated myositis is unclear. The influenza virus has been isolated from muscle tissues, suggesting that direct viral invasion of muscle fibers accounts for some cases of myositis (Gamboa et al., 1979; Kessler et al., 1980). Symptoms typically resolve within a week. However, fatal cases with rhabdomyolysis and renal failure have also been reported (Sellers et al., 2017).

IMNMs are a class of acquired autoimmune muscle disorders caused by various etiologies, including a subset associated with anti-SRP antibodies, statin-induced myopathy with antibodies against 3 hydroxy-3 methylglutaryl-coenzyme A reductase (HMGCR), connective tissue diseases, cancer, and viral infections, including HIV and hepatitis C (Quinn et al., 2015). IMNMs are clinically characterized by proximal muscle weakness, high levels of CK, and myopathic findings using electromyography. Pathologically, IMNMs include muscle fiber necrosis in the absence of substantial lymphocytic inflammatory infiltration (Stenzel et al., 2012). Recent studies revealed an increase in the incidence of IMNMs (Klein et al., 2015) and presence of anti-SRP or anti-HMGCR antibodies in two-thirds of IMNM patients (Mohammed et al., 2019). INMNs associated with anti-SRP or anti-HMGCR occur frequently in women aged between 40 and 60 years (Watanabe et al., 2016). Anti-SRP IMNM presents with severe muscle weakness and resistance to immunotherapy compared to anti-HMGCR positive ones.

In this case, the onset, clinical course, and pathological findings made it difficult to differentiate among influenza-related myositis, statin-induced IMNM, and anti-SRP associated IMNM. Anti-SRP-positive IMNM was reported to show a seasonal trend in winter (Leff et al., 1991). Prior infection (most commonly viral infection) or vaccinations (usually influenza vaccination) were also noted in more than 20% of patients with idiopathic inflammatory myopathies (Limaye et al., 2017). A woman was recently reported to have developed anti-SRP-positive IMNM two weeks after being administered influenza vaccination (Mamarabadi et al., 2018). In this case, the disease process and immune response against the influenza A (H3N2) virus may have induced the production of anti-SRP antibodies and worsened her myositis. Rhabdomyolysis caused by influenza virus itself or a drug (statin or oseltamivir (Puttagunta et al., 2018)) could be another differential diagnosis for the present case. However, renal dysfunction, which is usually correlated with a greater degree of rhabdomyolysis with severe muscular symptoms (Borgatta et al., 2012), was not observed in this patient; moreover, she did not respond to hydration treatment. To the best of our knowledge, this is the first report of anti-SRP antibody-positive myopathy following infection with influenza virus. This case report highlights the importance of considering IMNM as a differential diagnosis in patients with progressive proximal myositis that persists after influenza infection.

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Conflict of interest

The authors do not have any competing interests to declare.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.11.153.

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