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COVID-19 and immune-mediated necrotizing myopathy in a filipino female: A case report

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Introduction

Autoimmune myopathies are complex groups of diseases arising from insult to one or more muscle groups. These are characterized by symmetric muscle weakness with evidence of muscle injury on laboratory findings, myopathic changes on electromyography, and typical findings histologically. Depending on the subtype, the skin may also be affected. These are commonly associated with medication use, viral infections, malignancies, and other rheumatologic and connective tissue diseases.

As such, infectious agents have been implicated in the pathogenesis of autoimmune disorders for decades. Coronavirus Disease (COVID-19), which is an infectious disease caused by the SARS-CoV-2 virus is no exception. Patients with idiopathic inflammatory myopathies and other autoimmune diseases are at higher risk of developing complications.

Although the exact cause for muscle injury in the setting of COVID-19 is not well-established, autoimmune inflammatory damage is the most accepted mechanism as it can cause direct muscle damage and indirect damage through cytokine storm. In developing countries like the Philippines, inflammatory myositis in relation to COVID-19 has rarely been reported.

Here, we present a case of a 77-year-old female who is a known case of Immune-Mediated Necrotizing Myopathy for more than a decade, already recovered and is independent on all activities of daily living, presenting with gradual progressive proximal muscle weakness of all extremities after the onset of her mild COVID-19 infection.

Case presentation

Patient is a 77-year-old female, right-handed, known case of Immune-Mediated Necrotizing Myopathy since June 2015, initially presenting as 2-month history of proximal muscle weakness of bilateral lower extremities more than bilateral upper extremities. She underwent muscle biopsy of quadriceps femo-

ris, and was tested for myositis markers which revealed positive for HMG CoA reductase antibodies (value of 202.7 compared to the normal value of <20). The patient received a total of 1 dose IVIG and 10 doses of Rituximab from 2015 to 2021. She is independent in almost all activities of daily living, able to ambulate without support but would take more time in activities involving the proximal muscles of the bilateral lower extremities such as climbing up the stairs and sitting up. Patient is on regular monitoring of total Creatine Phosphokinase (CPK) levels and liver enzymes which is noted to be within normal levels since 2021. However, in February of 2022, at the peak of COVID19 surge in the Philippines, the patient tested positive for COVID19 as confirmed by RT-PCR. The severity of COVID-19 was mild as per the World Health Organization (WHO) criteria and her symptoms were just fever, cough and colds, with no supplemental oxygen requirement. The patient underwent home quarantine and was on supportive treatment. She had no significant relevant medical or surgical history, and she was not taking any regular medications except paracetamol. She did not have any recent travel history. She was vaccinated against COVID-19. Since the onset of the COVID19 symptoms, the patient also progressive weakness of her proximal muscles on all extremities but more on the bilateral upper extremities, eventually causing debilitation on her daily activities of living, needing a wheelchair on long walks. There were no associated numbness, urinary or fecal incontinence, headache, dizziness nor changes in sensorium.

On examination, vital signs were stable. She was awake, coherent with no signs of cardiorespiratory distress. There were no cortical abnormalities as well as cranial nerve abnormalities on the neurologic exam. However, she had weakness involving proximal muscle groups of upper and lower extremities bilaterally, with a grade of 3-/5 on all proximal muscles of all limbs on manual muscle testing. There was no rash on the hands or face. The rest of her examination was unremarkable. The patient received pulse steroid therapy at the end of February 2022 right after she was cleared out of her quarantine from COVID19. The patient was assessed daily during her in-patient stay for muscle strength with noted daily improvement of proximal muscle strength daily. On the 3rd and last day of pulse steroid therapy, the proximal upper extremities were already graded 4/5 as she can already hold against moderate resistance, while the proximal bilateral lower extremities improved to 4-/5 and she can already walk with one-man assist on short distance. The patient was discharged and advised to follow up in the outpatient clinic to assess her motor system and titrate the steroid accordingly. The patient had monthly creatine phosphokinase monitoring which has been severely elevated since the onset of her COVID19 symptoms, but has been decreasing gradually after the onset of COVID19 infection as summarized in Tables 1 and 2.

Table 1: During the first episode of Polymyositis.

Month	CPK-Total level (Reference range: 26-192 U/L)
July 2015	22,896 U/L
November 2015	4,074 U/L
July 2016	2,028 U/L
July 2017	747 U/L
July 2018	242 U/L
July 2019	220 U/L

Table 2: During COVID.

Month	CPK-Total level (Reference range: 26-192 U/L)
January 2022	1,898 U/L
February 2022	7,397 U/L
March 2022	1,704 U/L
April 2022	933 U/L
June 2022	374 U/L
July 2022	279 U/L

Pathophysiology

Although the triggering factor is still unknown, there is an active interaction between the MHC+ fibers and T lymphocytes. The degeneration and necrosis of muscle fibers are predominantly due to the release of cytotoxic enzymes such as perforins and granzymes. Lytic granules polarize towards the target cell when the cytotoxic T cells recognize the antigen. Fusion with the cell membrane of the target cell will cause focal release of soluble lytic proteins to induce target cell death.

Clinical features

The pattern of weakness of IMNM is progressive proximal weakness, with a creatine kinase of usually more than 1,000-10,000 u/L. Electromyography would show fibrillations and sharp waves, while muscle biopsy and muscle imaging will show necrotizing myopathy and T1 hyperintensity and increased STIR signal respectively. Diagnostic criteria for anti-HMGCR IMNM include elevated serum Creatine Kinase (CK) levels, presence of anti-HMGCR autoantibodies and proximal muscle weakness mainly in the lower limbs. Muscle biopsy is not a requirement for diagnosis if autoantibodies are present, nevertheless distinctive histopathological features are the presence of scattered myofibers at various stages of necrosis, fibers regeneration and macrocytes infiltration, lymphocytic infiltrate is usually absent or poorly seen, and staining for MHC I and C5b-C9 molecules can be positive.

Discussion

Immune Mediated Nectorizing Myopathy (IMNM) is a complement-mediated muscle disease. It can present much like polymyositis and causes muscle necrosis that leads to weakness of the skeletal muscles on the both sides of the body, commonly those closest to the body's core such as the hips, upper arms, shoulders, neck, and thighs. Muscle weakness, which is often severe, can develop within days, weeks, or months. This type of weakness often leads to difficulty climbing stairs, rising from a chair or from the floor, turning in bed, combing hair, and brushing teeth. Ocular muscles are not affected, and distal muscles are spared in 75% of cases. Atrophy and hyporeflexia, if present, are less pronounced. Causes of IMNM can be associated with certain medications, especially statins used to manage cholesterol, anti-HMGCoAR and anti-SRP auto antibodies, cancer, viral infections, or other connective tissue diseases. Women and men are affected equally, with an average age of onset between ages 40-60.

Fatigue is one of the most common symptoms post COVID infection, potentially by direct infection of the muscle or as an

inciting environmental event triggering autoimmunity. Case reports describe worsened disease activity after COVID-19 infection, both in dermatomyositis and immune-related necrotizing myositis. Previous reports have pointed to myopathy based on electromyography of post COVID patients. Muscle biopsies analyzed also showed histological changes such as capillary injury, inflammation, and mitochondrial changes associated with the disease duration. Some studies also showed more pronounced skeletal muscle inflammation compared to cardiac muscles, mostly seen in chronic COVID courses. However, there has been no evidence of direct viral infection of myofibers based on immunochemistry and electron microscopy.

Conclusion

COVID-19 pandemic has sustained an unfavorable effect on continuity of medical care on patients with autoimmune myopathies in general. COVID-19 can trigger their autoimmune myopathies since their immune response is compromised due to immunosuppressive therapies. The clinical profile of patients is highly variable, which warrants a high index of suspicion for myositis in any COVID-19 patient, hence, the best management should be anticipatory since delays and omissions in clinical care may potentially translate to poorer outcomes in the future.

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