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COVID-induced Immune-mediated Necrotizing Myositis: an Atypical Presentation of Rhabdomyolysis with Breakthrough COVID-19 Infection – A Case Report

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Abstract Immune-mediated necrotizing myopathy (IMNM) is an inflammatory myopathy characterized by proximal muscle weakness and significantly elevated creatinine kinase levels. IMNM occurs primarily in adults and is usually rapidly progressive in nature. It can be seronegative or associated with antibodies against signal recognition peptide (SRP) or hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). Scarce and rare cases of Immune-mediated necrotizing myopathy have recently been observed in muscle biopsy of COVID-19 patients with similar histological and clinical features of other IMNM with profound proximal muscle weakness and elevated CPK levels. We present a very interesting case of an atypical presentation of IMNM in the presence of COVID-19 infection. Treatment with Remdesivir and dexamethasone resulted in improvement of her symptoms.

Keywords: *COVID-19, necrotizing myositis, rhabdomyolysis, breakthrough infection*

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1. Learning Points

1) Immune-mediated necrotizing myopathy (IMNM) is a subtype of inflammatory myopathies characterized by necrosis of the myofibers. It can be associated with anti-SRP, and anti-HMGCR, a statin-associated myopathy, both of which have histologically predominant-macrophage infiltrates.
2) It can be seronegative or associated with antibodies against signal recognition peptide (SRP) or hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). It is distinguished from other inflammatory myopathies by the extent of muscle necrosis and relative paucity of lymphocyte seen on muscle biopsy.
3) IMNM can be the presenting symptom of COVID 19 infection in the absence of respiratory symptoms as in our case.
4) Viral infections associated with IMNM include coxsackie B, parvovirus, enterovirus, human T cell-lymphotropic virus, human immunodeficiency virus and COVID-19.
5) Statin-use can result in spectrum of myopathies, the most severe forms include IMNM, which is predominantly associated with anti-HMGCR antibodies, and non-immunogenic Rhabdomyolysis; the latter form is distinct as it has no macrophage infiltrate on histopathology.

2. Background

Immune-mediated necrotizing myopathy (IMNM), sometimes referred to as necrotizing autoimmune myopathy (NAM) is a type of inflammatory myopathy characterized by proximal muscle weakness and significantly elevated creatinine kinase levels. It is distinguished from other inflammatory myopathies by the extent of muscle necrosis and relative paucity of lymphocyte seen on muscle biopsy. IMNM occurs primarily in adults and is usually rapidly progressive in nature [1]. It can be seronegative or associated with antibodies against signal recognition peptide (SRP) or hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), but the exact pathophysiology is unknown [2]. IMNM can present as an acute part of initial infection or may present late in the disease course. It can be associated with viral infection, malignancy, connective tissue disorders such as scleroderma and, statin use [2]. Statin-use can result in spectrum of myopathies, the most severe forms include

IMNM, which is predominantly associated with anti-HMGCR antibodies, and non-immunogenic Rhabdomyolysis; the latter form is distinct as it has no macrophage infiltrate on histopathology. Among viral infections, reports have shown an association of IMNM with coxsackie B, parvovirus, enterovirus, human T cell-lymphotropic virus, human immunodeficiency virus and COVID-19 lately [3,4]. We present a very interesting case of an atypical presentation of IMNM in the presence of COVID-19 infection.

3. Case Presentation

An 80-year-old female history of type 2 diabetes mellitus on chronic high-intensity rosuvastatin therapy and stage IIIB-IV chronic kidney disease presented with several weeks of worsening shortness of breath and decreasing urine output despite incremental increase in loop diuretic use. History was significant for administration of Johnson & Johnson COVID-19 vaccine 4-weeks prior to presentation. Vitals signs on presentation were blood pressure 102/56 mmHg heart rate of 70/minute, temperature of 100.2 F and oxygen saturation of 96% on room air. Physical examination and Review of systems was otherwise unremarkable. Initial laboratory work-up revealed D-dimer 2438 ng/ml (normal < 230 ng/ml), creatinine of 4.4 mg/dl, with her baseline around 2 mg/dl, and BUN of 71 mg/dl (normal 8-10 mg/dl). CT Chest without contrast was remarkable for bilateral ground-glass with streaky opacities predominant at the peripheral lung fields and RT-PCR was positive for COVID-19. As part of hypercoagulable work-up a V/Q scan was performed that indicated a low probability of pulmonary embolism, however a venous duplex of the lower extremities was positive for a right peroneal deep venous thrombosis managed appropriately with unfractionated heparin infusion. Due to persistently increasing levels of creatinine and oliguria despite fluid resuscitation, further work-up with a urinalysis revealed large blood with only 4-6 red blood cells and few granular casts. Serum Creatinine Phosphokinase (CPK) levels were also found to be elevated at 4090 U/L (Normal: 26-140) along with an Aspartate aminotransferase (AST) of 220 U/L. At this time her statin therapy was discontinued, and although she was hydrated with 0.45% normal saline at 70 cc/hr after consultation with Nephrology, her CPK continued to rise, peaking at 57099 U/L on day 6, while creatinine peaked at 3.17 on day 12 of admission. Renal ultrasonography revealed echogenic kidneys and asymmetrically small right kidney at 8.6 cm suggestive of medical renal disease. Her screening anti-nuclear and anti-Jo-1 antibody was negative. In order to exclude other forms of myopathies, muscle biopsy from the left anterior quadriceps was done and was positive for numerous necrotic/regenerating myofibers abundant with CD68 + Macrophages and very rare CD3 T-cells consistent with necrotizing myopathy (Figure 1). With continued IV hydration at the same rate and treatment with Dexamethasone and Remdesivir in light of acute tubular necrosis from rhabdomyolysis presumptively in the setting of COVID-19 disease her urine output improved gradually along with reduction in her CPK to 605 on day 12 as well as stabilization of her creatinine to 2.6 mg/dl on day 15.

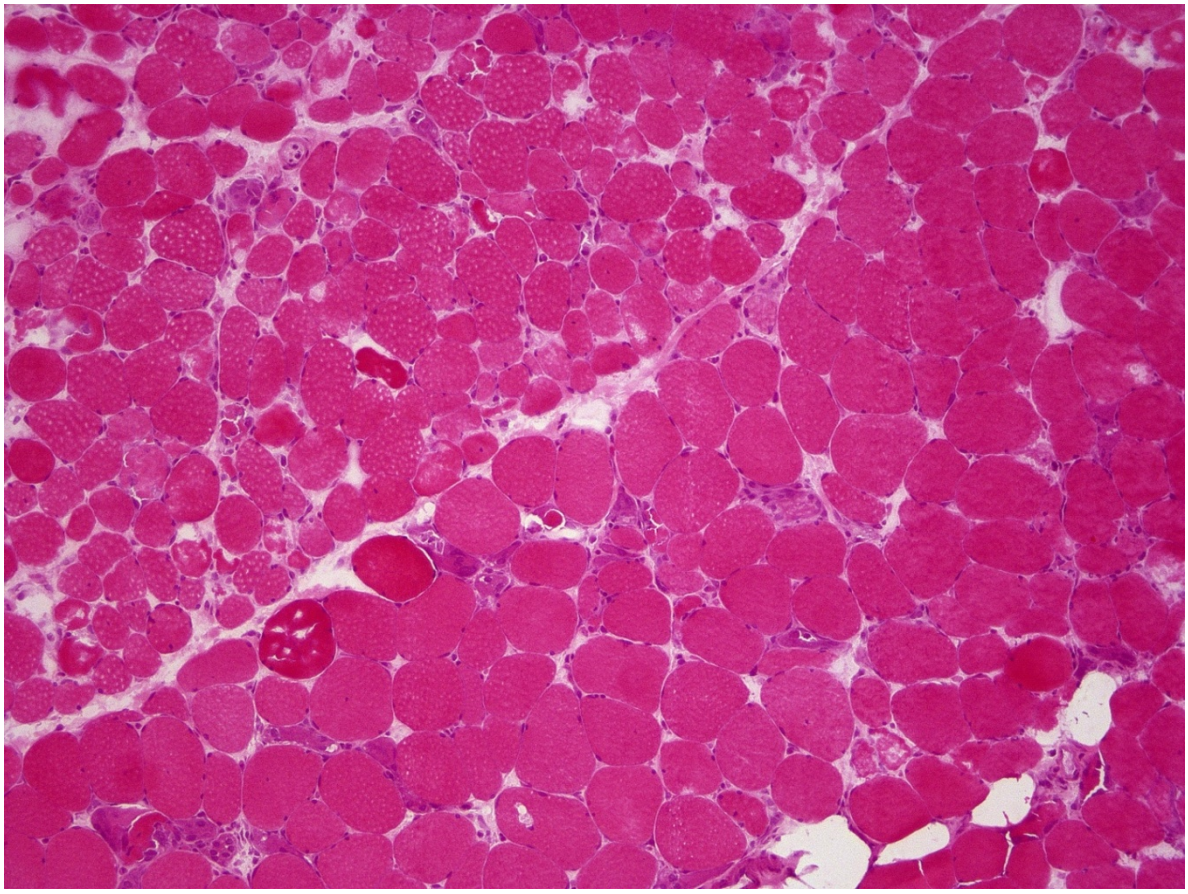

Figure 1. H&E Stain showing necrotic fibers (*), increasing variation in size of myofibers and no lymphocytic infiltrate

4. Discussion & Conclusion

Immune-mediated necrotizing myopathy (IMNM) is a subtype of inflammatory myopathies characterized by necrosis of the myofibers. It can be associated with anti-SRP, and anti-HMGCR, a statin-associated myopathy, both of which have histologically predominant macrophage infiltrates [3]. All forms of the abovementioned myopathies typically present with severe proximal muscle weakness along with elevations in serum CPK > 100 x the upper limit of normal (around 20,000 U/L) [4]. Scarce and rare cases of IMNM have recently been observed in muscle biopsy of COVID-19 patients with similar histological and clinical features of other IMNM with profound proximal muscle weakness and elevated CPK levels [5]. There are a few case reports of COVID-19 induced IMNM: in case reports from Veyesh et. al and Lokineni et. al, COVID-19 induced IMNM was noted to be a delayed presentation 4-weeks after the initial COVID-19 infection [6,7]. Our case demonstrates extremely atypical features as there was no clinical myalgia on review of symptoms or physical examination. Additionally, our patients IMNM was the presenting feature of the COVID-19 disease rather than a delayed effect.

Statin-induced IMNM was also unlikely to exist in our patient as prompt withdrawal of statin along with treatment for COVID-19 resulted in clinical improvement, which is not typical of the Statin-induced IMNM [4]. The peak CPK elevation of 57, 009 U/L in our patient was noted to be dissimilar to the case reports by Veyesh et. al (15, 000 U/L) and Lokineni et. al (27,000 U/L). However, COVID-19 induced IMNM may be seronegative, as is in our case along with Veyesh et. al and Lokineni et. al, or seropositive as seen in another case report by Zhang et. al [8].

Management strategies in IMNM appear variable as exemplified in other cases. Since COVID-19 related IMNM is extremely rare and novel, appropriate treatment regimen has not been established. Our patient was responsive to supportive care along with systemic steroids, whereas other cases have utilized immunosuppressants or high-dose steroids as well [6,7]. Since IMNM was the presenting feature of COVID-19 in our patient, it is reasonable to assume that treatment of the infection itself was therapeutic in the resolution of IMNM and acute tubular necrosis. What does appear unique in our case is that the treatment regimen consisting of Systemic Steroids and Remdesivir has been exclusively studied in the pulmonary disease resulting from COVID-19 disease. As to why this regimen was effective despite the absence of any respiratory manifestations in our patient remains unknown.

Musculoskeletal sequalae in COVID-19 disease are not well studied owing to the scarcity of case reports and independent studies. The few established case reports all appear to share similarities to their clinical and histological features to established forms of IMNM unrelated to COVID-19. However, our case remains distinct with its atypical clinical presentation and disproportionately high elevation in CPK. In addition, it was also noted to be the presenting feature of COVID-19 in our patient, and highly responsive to the same Steroid regimen used to treat pulmonary manifestation of COVID-19. This may indicate that the same pathophysiological mechanism that causes respiratory failure in COVID-19 is also responsible for IMNM in COVID-19 patients at a cellular level without direct viral invasion. It remains to be seen if there is any long-term sequalae with respect to physical disability and progression of chronic kidney disease in our patient as a result of her hospital course.

List of Abbreviations

Immune-mediated necrotizing myopathy - IMNM
necrotizing autoimmune myopathy - NAM
Signal recognition peptide - SRP
Hydroxy-3-methylglutaryl-coenzyme A reductase - HMGCR
Creatinine Phosphokinase - CPK
Aspartate aminotransferase – AST

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