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Severe Rhabdomyolysis In A Patient With Concomitant Covid-19 And Influenza Infections

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Abstract
Though rare, rhabdomyolysis and myositis have been reported following viral infections. Some of those viruses include Influenza A, Influenza B, Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), and H1N1 infection. Amid the onset of the COVID-19 pandemic, sporadic instances of rhabdomyolysis complicating the Coronavirus 2 (SARS-COV-2) infection have been reported. If untreated, rhabdomyolysis can be associated with several complications including electrolyte imbalance, acute renal failure, and cardiac complications. Therefore, early signs of rhabdomyolysis following (SARS-COV-2) should be treated aggressively to avoid such complications.
Keywords: *Covid-19 Infection; Rhabdomyolysis; Myositis; Steroid Therapy*

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I. Introduction

Complications resulting from COVID-19 or SARS-CoV-2 infection have been linked to increased mortality and morbidity rates. One of these complications is severe rhabdomyolysis, which can be life-threatening. We report a case of a 33-year-old lady who presented with severe rhabdomyolysis 3 days following an upper respiratory tract infection secondary to Influenza B and COVID-19 infections which was resistant to both hydration and urinary alkalinization. The patient was eventually started on systemic steroid therapy after which symptoms and laboratory results improved.

II. Case Report

A 33-year-old lady with a medical history notable only for class 2 obesity and a BMI of 39 kg/m^2 presented to the emergency room 3 days following an upper respiratory tract infection with low-grade fever with generalized myalgia and weakness in both upper and lower extremities. Initial evaluation using a PCR test on a nasopharyngeal swab was positive for both Influenza B and COVID-19 infections. Initial vital signs revealed a blood pressure of 127/70 with a pulse of 75 beats/min and a temperature of 99 degrees Fahrenheit. Physical examination was remarkable only for diffuse weakness in both upper and lower extremities as well as diffuse muscle tenderness. CBC showed a WBC count of 8.0 E3/uL and a normal platelet count. Liver enzymes were elevated with an AST level of 1068 E3/uL (normal range 130-350) and an ALT of 329 u/L (normal range 0-35). Further, her phosphorus was 3.8 mg/dL (normal range 2.5-4.9), calcium was 8.1 mg/dL (normal range 8.4-10.2), and total protein was 7.8 g/dL (normal range 6.3-8.2). ANA antinuclear antibody was negative, and (anti-DS-DNA) anti-double-stranded DNA antibody was also negative. Sodium was 134 mmol/L(range 137-145), potassium was 4.7 mmol/L (range 3.5-5.1), blood urea nitrogen (BUN) was 12 mg/dL (range 7-20), and creatinine was 0.62 mg/dL (range 0.52-1.04). Creatine kinase (CPK) was >160,000 U/L (normal range 26-192 U/L) and myoglobin was 8048 ng/mL (range<62 ng/mL). Urine myoglobin was >5000 mcg/L (range<65 mcg/L). Urine pH was 7.0 (range 4.6-8) with negative red blood cells (RBC) per high power field. Urine dipstick was positive for occult blood. To avoid developing renal failure, the patient was started on aggressive intravenous fluid hydration using 150 milliequivalent of sodium bicarbonate mixed in a liter of D5W fluid, running at a rate of 200 ml/hour. Despite 72 hours of aggressive hydration and alkalinization of the urine, the creatine kinase remained elevated. A decision was then made to proceed with a muscle biopsy and start bolus steroid therapy using intravenous methylprednisolone. On the second day after starting steroid therapy, the creatine kinase began dropping significantly [Figure 1]. The patient continued to improve on tapering doses of steroids with remarkable improvement in her myalgias and muscle weakness.

Muscle biopsy revealed acute monophasic necrotizing myopathy with muscle fiber necrosis and regeneration. Genetic tests were negative.

FIGURE 1

Day	Serum Creatine Kinase U/L	Serum Myoglobin ng/mL	Urine Myoglobin mcg/L	Serum Creatinine mg/dL
1	>160,000	8048	>5000	0.63
2	>160,000	8000	>5000	0.73
3	>160,000	7072	>5000	0.76
4	>160,000	74000	>5000	0.91
5	>160,000	6946	>5000	0.72
Steroids Started				
6	83123	3391	2200	0.68
7	25601	2694	1400	0.56
8	9974	1480	700	0.53
9	4998	470	250	0.55

III. Discussion

Rhabdomyolysis is a complex condition characterized by damage to the cells of skeletal muscle. During resting position, the plasma membrane of muscle cells contains several ionic channels that regulate the exchange of Na^+ (sodium ion) with Ca^{+2} (calcium ion) as well as K^+ (potassium ion). Both the Na^+ and Ca^{+2} are stored in the sarcoplasmic reticulum, whereas K^+ is intracellular. During muscle action potential, adenosine triphosphate (ATP) is the energy source that allows the activation of the above channels across the muscle membrane, causing the Na^+ and Ca^{+2} ions to move intracellularly in exchange for K^+ ions. When there is an injury to muscle cells, whether due to crush injury or rhabdomyolysis, there is a disruption in such ionic equilibrium causing an abnormal influx of Na^+ and Ca^{+2} intracellularly. This leads to an osmotic influx of water into the cell, causing cellular swelling and activation of proteases that lead to cellular destruction, necrosis, and apoptosis [1–3].

Several causes for rhabdomyolysis range from hereditary diseases like McArdle's syndrome [4], lipid storage disease [5], neuroleptic syndrome, and malignant hyperthermia [6]. Commonly seen acquired diseases include crush injuries which can be witnessed in earthquakes and war traumas as well as inflammatory diseases like myositis in connective tissue disorders [7–9]. Infections, including viruses such as Influenza A and B, HIV, H1N1, Epstein-Barr Virus (EBV), and Cytomegalovirus (CMV), can trigger rhabdomyolysis [10–12]. Since the emergence of the COVID-19 pandemic, there have been several reported cases of rhabdomyolysis. However, most of those cases had a mild to moderate degree of rhabdomyolysis with creatine kinase less than 100,000 U/L and there was usually a degree of renal impairment [13]. Acute renal failure represents one of the most perilous outcomes associated with rhabdomyolysis. Myoglobin, which has a molecular weight of 17500 Daltons, is considered to be the main cause of tubular injury. The damaged muscles cause an increased leakage of fluids from the extracellular space into the muscle cells, triggering the activation of the renin-angiotensin system, and causing renal vasoconstriction. This relative ischemic state favors the production of more acidic urine which prefers the binding of myoglobin and its degradation product to the Tamm-Horsfall tubular protein. This causes further tubular injury and acute tubular necrosis [14]. In addition, the iron in the myoglobin is transported by the cubilin and megalin endocytic receptors of the proximal convoluted tubules, leading to a higher delivery of oxidized iron to tubular cells and further tubular injury [15].

The treatment of rhabdomyolysis starts with addressing the primary causative factor. If it is secondary to medications like statins, the medication should be stopped immediately. Intravenous fluids and volume resuscitation are the main course of therapy. Some studies prefer the use of Lactated Ringer's for fluid replacement rather than normal saline as Lactated Ringer's can maintain a more alkaline pH urine while saline can cause some element of hyperchloremic metabolic acidosis. However, this has been controversial since other studies that were conducted have not shown a difference [16,17]. Even though many experts use bicarbonate drip in rhabdomyolysis in an attempt to increase the alkalinity of the urine, this issue remains debatable and there is a need to conduct more research [18]. Aggressive hydration and intravascular volume repletion remain the main course of treatment, with normal saline still being the most preferable fluid. With acute renal failure including electrolyte imbalance and acid-base disorder, high permeability dialysis as well as continuous renal replacement therapy (CRRT) can help remove the myoglobin molecule and decrease the load burden on the nephrons [19,20]. There have been few reported cases showing the effectiveness of plasmapheresis in treating severe rhabdomyolysis [21]. In the presented case, the patient responded to steroid therapy, which was consistent with the fact that the patient had an element of viral-induced myositis. Because there was muscle cell necrosis, it was difficult to see pathological support at that stage and the yield was not accurate.

IV. Conclusion

Though uncommon, rhabdomyolysis can still be seen as a complication of viral infection due to Influenza B as well as COVID-19 infections. Early diagnosis and treatment are vital to avoid end-organ damage.

Compliance with ethical standards

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Disclosure of conflict of interest
There was no conflict of interest among corresponding authors.

Statement of informed consent
Proper informed consents were obtained.

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