


Clostridioides difficile Induced Rhabdomyolysis Associated With Decompensated Cirrhosis

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Abstract

Rhabdomyolysis (RBD) occurs secondary to tissue injury, resulting in (muscle) cell lysis and release of intracellular electrolytes and proteins into circulation. An elevation in the muscle enzyme, creatine kinase (CK), is a diagnostic marker and indicates muscle breakdown. Symptoms include dark urine caused by release of myoglobin, myalgias, and acute kidney injury (AKI). RBD is categorized as (1) traumatic, (2) nontraumatic exertional (ie, metabolic myopathies), or (3) non-exertional and non-traumatic. *Clostridioides difficile* (CD) has been previously reported to cause RBD, but the risk factors, pathogenesis, and recommended treatment regimen remain unclear.

Keywords

Clostridioides difficile, rhabdomyolysis, acute kidney injury, decompensated cirrhosis, gastroenterology

Background

The diagnosis of rhabdomyolysis (RBD) is made in the appropriate clinical setting with a confirmatory elevation in creatine kinase (CK). An elevation of CK above 5x upper limit of normal is considered diagnostic. Patients most often present with RBD after some form of trauma with symptoms ranging from asymptomatic dark urine to severe myalgias and acute kidney injury (AKI). Common causes include trauma, toxin ingestion, immobility, and sepsis.¹ Sepsis is most commonly linked to viral and bacterial infections with *Legionella*, *Streptococcus*, and *Salmonella*.^{2,3} *Clostridioides difficile* (CD) colitis has been reported to cause RBD in 10 patients, including 1 patient who had concomitant chronic liver disease. Here, we present what appears to be the second case of CD induced RBD in a patient with decompensated cirrhosis, raising the possibility that decompensated cirrhosis is a risk factor for CD-induced RBD.

Case

A 57-year-old male with alcohol-related cirrhosis presented with 3 days of myalgias, weakness, and watery diarrhea. The myalgias began in the proximal extremities and rapidly progressed. He denied recent falls or trauma. He complained of having 4 episodes of loose watery stools daily. He denied recent ETOH or drug use, fever, rash, joint swelling, or abdominal

pain. Two weeks previously, he was prescribed furosemide and spironolactone for treatment of ascites. Other medications included atorvastatin and omeprazole. His physical examination revealed that he was afebrile, with a heart rate of 82 and blood pressure of 131/79. His abdomen revealed no evidence of sifting dullness, and he had 2/5 strength in the proximal extremities. Laboratory data included white blood cells 13,000/mm³, creatinine 0.97 mg/dL, albumin 2.6 g/dL, total bilirubin 1.8 mg/dL, aspartate aminotransferase (AST) 1230 U/L, alanine aminotransferase (ALT) 171 U/L, alkaline phosphatase (ALP) 202 U/L, creatine kinase (CK) 13,000 U/L, urinalysis +blood/absent red blood cells, positive CD polymerase chain reaction, normal abdominal x-ray and ascitic fluid absolute neutrophil count. He developed an AKI with peak Cr of 1.92. His diuretics and statin were held. He was treated with IV fluids and a 10-day course of oral vancomycin. Anti-HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase) antibody-

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ies were absent. He was discharged 10 days later with normalization of his creatinine, CK, and aminotransferases.

Discussion

The differential diagnosis for RBD in this patient included infection, hypovolemia, and autoimmune causes. Given the patient's myalgias and profound weakness, our initial impression was that he had an inflammatory myopathy, such as statin-induced necrotizing myositis or polymyositis. However, the time course for these diagnoses is usually subacute—weeks to months. The lack of anti-HMGCR also suggested that this was not statin-induced myopathy. Finally, his weakness drastically improved with rehydration. Given the absence of evidence for primary muscle injury, his substantial hypovolemia from diarrhea and diuretic use and the prominent clinical CD colitis presentation, we believe that this patient had CD induced RBD. *C. difficile* is an uncommon, infectious cause of RBD and the mechanism by which CD induces RBD is unclear, but a direct cytotoxic effect of CD toxins on muscle has been proposed.⁴

Current evidence suggests that patients with cirrhosis may be more susceptible to CD due to frequent hospitalizations, altered gut flora, proton pump inhibitor use, and use of antibiotics.⁵ Patients with cirrhosis and CD also appear to have an increased risk of mortality compared to patients without cirrhosis (by at least 5%).⁵ Furthermore, patients with CD and decompensated cirrhosis with higher Model for End-Stage Liver Disease (MELD) scores had poorer outcomes.^{6,7} Although, our patient had decompensated cirrhosis, his MELD score of 14 on admission and clinical recovery with treatment is consistent with somewhat compensated liver function. Interestingly, CD thrives in the setting of gut inflammation and patients with inflammatory bowel disease are four times more likely to acquire CD than the general population.⁸ We speculate that portal hypertension in decompensated cirrhosis allows for bacterial translocation and delivery of CD toxins to the blood stream and muscle tissue, leading to an inflammatory response that in turn leads to RBD. Therefore, we speculate that CD may be a risk factor for severe RBD in patients with decompensated cirrhosis.

Some evidence suggests that cirrhosis itself may be a risk factor RBD, with an increased mortality risk associated with a higher Child-Pugh score.⁹ A separate study revealed that infection was the most common etiology of RBD in patients with cirrhosis and the likelihood of renal failure was greater in patients with cirrhosis compared to those without.¹⁰ Cirrhosis is known to cause muscle injury and inflammation, with subsequent reduction in muscle mass and sarcopenia.¹¹ Sarcopenia from cirrhosis results in a hypermetabolic state due to impaired glycogen storage, breakdown of fatty acids, and release of catabolic cytokines.¹¹ This process triggers fatty replacement of muscle fibers and is further exacerbated by malnutrition, hormonal imbalance and perhaps gut dysbiosis.¹¹ Chronic inflammation with release of pro-inflammatory cytokines, such as tumor necrosis factor- α and interleukin-6, along with

the upregulation of myostatin via hyperammonemia and proteolysis induced by mitochondrial dysfunction and reactive oxygen species, further exacerbate muscle injury.^{12,13} Altogether, the predisposition for RBD in decompensated cirrhosis is likely multifactorial—due to the aforementioned muscle injury, persistent inflammation, and systemic fluid shifts.

The risk of AKI in patients with cirrhosis who develop RBD may be increased. Even in patients without cirrhosis, AKI in RBD is relatively common.¹⁴ Some 33% to 50% of patients with RBD secondary to infection develop AKI.¹⁵ Muscle injury in RBD results in the release of nephrotoxic, heme-pigment containing proteins, inducing a cascade of renal vasoconstriction, oxidative epithelial injury, and tubular obstruction.¹⁵ Cirrhosis may increase the risk for AKI development by a variety of factors. In patients such as ours, decompensated cirrhosis leads to renal impairment for many reasons including, in particular, functional hypovolemia and activation of the renin-angiotensin-aldosterone system with systemic and splanchnic vasodilation resulting in decreased renal perfusion.

Conclusion

In summary, a variety of factors in decompensated cirrhosis predispose these patients to CD induced RBD, and our case provides additional support for this association. Although the exact pathophysiology of CD-induced RBD remains to be determined, current treatment remains supportive, with appropriate hydration and elimination of underlying disorders. Additionally, the prevalence of RBD in decompensated cirrhosis is likely underreported given the frequent association with severe comorbidities and the multiple factors previously mentioned that may increase the susceptibility of RBD development. Furthermore, since patients with chronic liver disease often have abnormal AST and LDH (lactate dehydrogenase) levels at baseline, which typically increase suspicion for RBD, the diagnosis of RBD in patients with cirrhosis is almost certainly often missed. Further studies evaluating the prevalence of RBD in cirrhosis are needed to aid in our understanding of this disease process and physicians must be mindful of the association between decompensated cirrhosis and each CD and RBD and the risk for increased mortality.

Author's Note

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

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