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Case Report
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The Not-So Benign Sickle Cell Trait: Exertional Rhabdomyolysis, Hyposthenuria, and Acute Kidney Injury

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Abstract

Sickle cell trait (SCT) is largely understood to be a clinically silent disease that typically does not require intensive clinical monitoring or counselling of patients. In fact, many patients with SCT are unaware that they have this genetic condition. However, as more studies, case reports, and reviews are published, the understanding of severe clinical pathology that can be associated with SCT, and the need for further counselling and education for our patients increases. We present the case of a baseline healthy young male, who was admitted to the hospital with severe rhabdomyolysis, acute liver injury, extreme electrolyte disturbances, and renal failure necessitating emergent hemodialysis. An otherwise healthy athlete with minimal risk factors other than a precipitating physical competition the week prior, the gravity of his presentation led our team to question why he had such a severe presentation. Further work up revealed sickle cell trait (SCT). SCT has been linked to increased risk of exertional rhabdomyolysis, which causes muscle damage via microvascular occlusion as well as tissue ischemia caused endothelial damage [1,2]. The previously mentioned predisposes to a decreased ability to concentrate urine in those with sickle cell trait and further increases the risk for dehydration and more serious clinical presentations [3-5]. The potential links between SCT and exertional rhabdomyolysis support the hypothesis that SCT is not a clinically silent condition.

Introduction

Sickle cell trait (SCT) is usually interpreted as a genetic finding with few apparent clinical correlations. However, recent studies and reports have shed light on not only the risks of exercise associated-SCT, but also a relationship to hyposthenuria and acute kidney injury. In this case presentation of a patient that was found to have SCT incidentally after an athletic competition, we explore the correlations between SCT, exertional rhabdomyolysis, hyposthenuria, and acute renal injury.

Case Presentation

A previously healthy 24-year-old male presented to the emergency room with severe myalgias, weakness, and bilateral lower extremity numbness, two days after a week of intensive exercise with minimal hydration. He initially presented to an outside hospital, received an MRI of his lumbar spine, which was unrevealing, and discharged home with muscle relaxants. He represented two days later to our hospital with increased bilateral lower extremity pain, numbness, weakness, and dark urine. Vital signs and physical exam were unremarkable other than mild hypertension, non-focal diffuse weakness, and a hyper-pigmented rash on the dorsum of his

hands and feet. His presenting labs were consistent with a severe AKI (creatine of 6 though unknown baseline), hyperkalemia (potassium of 8.6), hyperphosphatemia (phosphorus of 13.9), and hypocalcemia (ionized calcium of 0.74). His liver enzymes were consistent with acute liver injury (aspartate aminotransferase of 8,420 and an alanine aminotransferase of 2,506), His complete blood count was notable for a hemoglobin of 19.5, and white blood cell count of 30,600. His initial CK was 51,000, repeat four hours after was 316,000. An initial sickle cell

screen in the emergency room was positive, most likely collected due to mention of family history of sickle cell. Pathology review of a peripheral smear revealed normal red blood cell morphology and no evidence of sickled cells. The urinalysis showed dark urine, red blood cells, and elevated urine myoglobin.

After several unsuccessful strategies at improving hyperkalemia, the patient underwent

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emergent dialysis. Throughout his week-long hospital stay, he remained on intermittent HD with little to no sign of renal recovery. Given the severity of his presentation, including acute liver injury and a hyperpigmented rash, gastroenterology and rheumatology were consulted. Through further workup and monitoring, no evidence of other etiology of acute liver injury or myopathy was discovered.

Hemoglobin electrophoresis resulted during his stay and was consistent with sickle cell trait. He was discharged home on outpatient hemodialysis, and renal function began to improve a week after discharge.

Discussion

Sickle Cell Trait (SCT) is typically thought of as a clinically benign condition, especially when compared to its homozygous counterpart, Sickle Cell Disease (SCD). SCT is a heterozygous condition where individuals inherit one sickle cell gene and one normal gene -- under typical circumstances and even in instances of low to moderate physiological stress, SCT generally does not result in clinically significant sickling or outcomes [3]. However, in circumstances of more severe cellular stress, detrimental health outcomes in those with SCT – i.e. exertional rhabdomyolysis and acute renal failure – can occur [3-6]. In our case presentation, exertional rhabdomyolysis led to a severe, sustained acute kidney injury (AKI) with subsequent renal failure, necessitating hemodialysis.

There have been several case reports and multiple studies, dating at least back to the 1970s, that document a link between sickle cell trait and an increase in patients' risk of exertional rhabdomyolysis [1-2, 7-11]. A large 2016 retrospective cohort study of US Army soldiers determined that there was a significantly higher risk of exertional rhabdomyolysis among soldiers with SCT [2]. A 2018 systematic review found there be a positive direct correlation between SCT and exertional rhabdomyolysis [1]. Given this, sickle cell trait and its association with exertional rhabdomyolysis is now a more commonly known association. The exact mechanism of why those with SCT are at increased risk of exertional rhabdomyolysis is not completely understood, though some reports have theorized the pathophysiology to include exertional sickling [8-9, 12]. The sickling process in SCT remains not nearly as common as in sickle cell disease, and typically only occurs in periods of excessive or extreme physiologic stress [13]. In all patients with or without SCT, rhabdomyolysis results from increased cytoplasmic and mitochondrial calcium, which releases proteases and causes other cellular dysfunction, with resultant depletion of intracellular ATP and/or direct rupture of cell membranes [14-15]. This cellular breakdown leads to severe pain, myoglobinuria, rising CK levels, electrolyte disturbances and in some cases, acute renal failure [14,16]. The renal failure in patients with exertional rhabdomyolysis, is thought to be secondary to the nephrotoxic myoglobin and acids produced and released from the breakdown of muscle tissue as well as hypoperfusion to the kidneys [17].

In the adult population, common causes for rhabdomyolysis include acute illness or infection, alcohol, illicit drugs, medications, surgery, trauma or crush injury, and exercise [15]. Underlying risk factors for rhabdomyolysis (either traumatic or non-traumatic) include male sex, black race, dehydration, body mass index over 40, lipid lowering medications, age extremes (age less than 10 years or over 60 years), to name a few [15]. Exertional rhabdomyolysis does not have a formal definition though it is typically diagnosed by elevated CK and muscle tenderness/pain after recent vigorous exercise (without recent trauma or other direct injury) [16]. Non-traumatic exertional rhabdomyolysis is even more likely to occur when exercise is prolonged, eccentric type exercises, hot and humid environments, increased sweating which can lead to hypokalemia [14]. Sickle cell trait is now more commonly known as a risk factor for exertional rhabdomyolysis.

This patient was a previously healthy, young, athletic male; his only known (at the time of presentation) non-modifiable risk factors for rhabdomyolysis were male gender and black race. His only modifiable risk factors were dehydration and an intense athletic competition the week prior. Due to the severity of his presentation, which included not only renal failure, but also acute liver injury, a broad diagnostic evaluation was done and was unremarkable. Given his severe pain and mention of family history of sickle cell disease or trait, a screen for sickle cell disease was also performed on presentation and was positive. Hematology was consulted, though had lower suspicions for SCD given his lack of anemia, and no previous presentations for acute pain episodes. Hemoglobin electrophoresis was therefore sent to rule out sickle cell disease, and in turn revealed a diagnosis of sickle cell trait. Due to the severity of rhabdomyolysis and the multi-organ involvement, our team questioned whether this diagnosis of SCT played a role in his clinical outcomes, specifically whether SCT could lead to an increased risk of not only exertional rhabdomyolysis but also acute renal failure.

SCT at baseline has also been hypothesized to be associated with an increased risk of chronic kidney disease, a faster decline in GFR, and an increased risk of AKI, specifically severe and sustained AKIs [6,18]. It is also well established that those with SCT are at increased risk of dhyposthenuria and have an impaired ability concentrate their urine [19]. The concentration of urine occurs in the renal medulla, which is a sensitive and delicate region of the kidney, made up of the vasa recta, tubules, and thin inter-tubule capillaries [19-20]. Under times of severe stress, (i.e. acidosis, damaging proteins) damage to the medulla can occur, which leads to a reduction in the concentrating capacity leading to further dehydration and renal dysfunction [19]. Previous case reports and articles have alluded to a potential link between hyposthenuria and the severity of the rhabdomyolysis [9]. Given the severe nature of our patient's presentation we questioned whether sickle cell trait also led to an increased risk of acute renal injury.

In those with SCT, there is an underlying risk of hyposthenuria, which leads to dehydration through excess water losses in the urine, leading to further dehydration, and facilitates the development of acute renal injury [18]. This is in part to the low flow state of the medulla, which has been postulated as an ideal condition for sickled HbS to form further exacerbating hyposthenuria [5,19]. The combination of dehydration, inability to concentrate urine, and physiologic stress induced by severe rhabdomyolysis, all likely led to the severe renal presentation seen in this patient. Given this, hydration, and patient education regarding risks with intense physical activity are key factors in preventing severe renal failure and dehydration that occurs in those with SCT.

Conclusion

This report adds to existing literature about the clinically significant outcomes associated with SCT and posits several possible mechanisms for why these occur. We recommend counselling patients with sickle

cell trait about the risks of exertional rhabdomyolysis, specifically the risks of dehydration during times of moderate to intense exercise. Further, those with sickle cell trait may be particularly vulnerable to more severe acute renal failure in these times of cellular stress due to underlying hyposthenuria and decreased ability to concrete urine.

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