Case Report

An elevated creatine kinase in the context of influenza A infection and sickle cell trait

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Summary

We describe the case of a 37-year-old normally fit and well man who presented to hospital with fever, lethargy and myalgia. He was found to have a creatine kinase level of over 1 million IU.L⁻¹. He initially underwent fluid resuscitation, but despite this his renal function declined and he required continuous veno-venous haemodiafiltration. Subsequent testing revealed a positive viral swab for influenza A and that he was a carrier of sickle cell trait. We review the literature for previous reports describing this association and demonstrate the rarity of such a presentation.

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Introduction

Creatine kinase (CK) is an enzyme that catalyses the phosphorylation of creatine with adenosine triphosphate to form phosphocreatine. Its three isoenzymes exist in the brain (CK-BB), heart (CK-MB) and skeletal muscle (CK-MM). Elevated levels can indicate damage to these tissues, and consequently may be used alongside other investigations to detect pathological processes, such as myocardial infarction and rhabdomyolysis. Rhabdomyolysis is a complex syndrome characterised by the rapid breakdown of muscle, with release of intracellular contents such as myoglobin, CK and lactate dehydrogenase. The aetiology of rhabdomyolysis can be broadly divided into traumatic and atraumatic, with atraumatic causes including viral infections such as influenza A.

Acute kidney injury (AKI) is defined by Kidney Disease Improving Global Outcomes as an increase in serum creatinine concentrations by greater than or equal to 26.5 $\mu\text{mol.L}^{-1}$ within 48 h, or an increase in creatinine by greater than or equal to 1.5 times the baseline creatinine [1]. Its aetiology can be broadly divided into pre-renal (renal hypoperfusion), intrinsic renal disease and post-renal (obstruction to the excretion of urine). Complications of AKI include acid-base disturbance, electrolyte derangement, the accumulation of toxins, and hypervolaemia which may result in organ dysfunction. Rhabdomyolysis is a recognised cause of AKI secondary to acute tubular necrosis from intravascular volume depletion and myoglobinuria. The treatment of AKI is largely directed towards the causative agent, whilst preventing further injury (e.g. by stopping nephrotoxic medications) and managing any complications. Renal replacement therapy, often in an intensive care unit (ICU) setting, may be indicated if initial management proves unsuccessful.

We describe the case of an exceptionally raised CK level in the context of influenza A infection leading to rhabdomyolysis and subsequent AKI.

Report

A 37-year-old Afro-Caribbean man presented to the hospital with a five-day history of fever, lethargy, severe proximal myalgia rendering him unable to walk, and brown/black urine. He denied any rashes or foreign travel in the previous 12 months, as well as any illicit drug use, excessive alcohol ingestion or intense exercise. He had a past medical history of sickle cell trait. He took no regular medication, had no significant family history and was employed as a social worker.

On presentation, he was haemodynamically stable and had a normal respiratory, cardiac and abdominal examination. He was clinically euvoelaemic. He was unable to walk due to pain and his deltoids, and his proximal arms and thighs were tender to palpation. Movements of his upper limbs against gravity were painful. No rashes were identified. His urine dipstick was strongly positive for protein and blood, contained leucocytes and was negative for nitrites. His chest radiograph and ECG were unremarkable. Admission blood tests revealed normal sodium and potassium, a possible AKI with serum creatinine of $132 \mu\text{mol.l}^{-1}$ (no baseline obtainable) and an elevated CK of $870,000 \text{ IU.l}^{-1}$. He also had a raised aspartate transaminase (AST) of 2428 IU.l^{-1} and a viral swab was positive for influenza A. He was admitted to a medical ward for intravenous fluid therapy and observation of his kidney function, as he was at risk of worsening AKI.

He was initially treated with 6 l of compound sodium lactate infusion (Hartmann's solution) over 6 h with 1 l of 1.26% sodium bicarbonate over 10 h and was commenced a five-day course of oseltamivir 75 mg twice daily. Repeat blood tests the following day showed a rising creatinine concentration of $369 \mu\text{mol.l}^{-1}$ with a serum pH of 7.30, potassium concentration of 5.2 mmol.l^{-1} and lactate concentration of 1.5 mmol.l^{-1} . His AST also rose to 5474 IU.l^{-1} and lactate dehydrogenase was $41,000 \text{ IU.l}^{-1}$. A repeat CK was $1,172,440 \text{ IU.l}^{-1}$, and he was therefore transferred to the ICU for continuous veno-venous haemodiafiltration (CVVHDF). To determine if there was myocardial involvement, he underwent an echocardiogram, which was unremarkable. A computed tomography scan of his chest, abdomen and pelvis was negative for overt malignancy. Subsequent virology testing for hepatitis, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, auto-antibodies and several respiratory viruses all returned negative. He improved clinically and biochemically on a daily basis and received a total of seven days of CVVHDF. He was stepped down to the renal ward with normal serum sodium and potassium levels, and an acceptable urine output after cessation of CVVHDF. However, in subsequent days he became oligo-anuric and fluid overloaded, with pulmonary oedema and widespread peripheral oedema. He therefore underwent once-daily haemodialysis for three days to augment fluid removal and was observed on the ward for a further week. At discharge, his creatinine was $787 \mu\text{mol.l}^{-1}$, CK 393 IU.l^{-1} with normal sodium, potassium and AST concentrations and an acceptable urine output. He was followed up in the renal outpatient clinic where his serum creatinine continued to decline, his potassium concentration was within normal range and his urine output was approximately $2-4 \text{ l.day}^{-1}$.

Discussion

This patient had AKI secondary to rhabdomyolysis. Rhabdomyolysis is a condition caused by the rapid breakdown of skeletal muscle and has a variety of causes including strenuous exercise, pharmacological agents, acquired metabolic disorders and infections. It is characterised by the release of myoglobin and elevated levels of enzymes such as lactate dehydrogenase and CK. AKI can develop secondary to acute tubular necrosis as a result of intravascular volume depletion and myoglobinuria [2]. When considering the aetiology of rhabdomyolysis in the above case, the patient took no prescribed medications and there was no history of strenuous exercise or recreational drug use. This was his first episode of rhabdomyolysis and he had no past medical history of inherited or acquired metabolic disorder. The cause of rhabdomyolysis in this patient was therefore attributed to his current infection with the influenza A virus.

Influenza A is a ribonucleic acid virus and is a member of the Orthomyxoviridae family [3]. It primarily affects the epithelium of the human respiratory tract, and its clinical presentation and course can vary from a mild, self-limiting upper respiratory tract infection to acute respiratory distress syndrome meriting mechanical lung ventilation. Influenza A can cause myositis, but this is generally mild, self-limiting and without complications. Occasionally, excessive muscle breakdown secondary to myositis can lead to rhabdomyolysis, but the frequency is not well defined in the literature. The highest associated CK level reported in the literature is $4,312,211 \text{ IU.l}^{-1}$ in a 30-year-old male with a background of asthma but no clinical explanation for the unprecedented level. Very few reported levels exceed 1 million IU.l^{-1} [4]. The pathophysiology of rhabdomyolysis secondary to influenza is thought to be multifactorial. Mechanisms implicated include elevated concentrations of circulating cytokines damaging myocytes in conjunction with viral toxins and direct viral invasion of muscle tissue. In vitro studies have shown that the virus can replicate and cause direct myocyte lysis [5]. As the CK concentrations in

this patient were exceptionally elevated and he had a background of sickle cell trait, we reviewed the literature to determine if a link between the two was reported or described.

Sickle cell trait is an inherited haemoglobinopathy. Affected individuals are broadly asymptomatic, and the condition is generally considered benign. There is, however, evidence that it can contribute to pulmonary embolism, renal disease, splenic infarction and exertional rhabdomyolysis [2, 6, 7]. Exertional rhabdomyolysis was well described by Kark et al. as a cause of increased exercise-related deaths in U.S. army recruits with sickle cell trait versus those without [6]. However, our patient had no history of recent or regular intense exercise to explain his profound rhabdomyolysis. This case may therefore represent a previously unreported example of sickle cell trait augmenting the myositis caused by influenza A, resulting in severe non-exertional rhabdomyolysis.

The aetiology of rhabdomyolysis is broad and includes strenuous exercise, pharmacological agents, acquired metabolic disorders and infection. With this case in mind, clinicians should be alert to the possible interaction of influenza A and sickle cell trait as a potential rarer cause and suspect an association if patients with sickle cell trait develop AKI. Treatment of rhabdomyolysis aims to correct causative factors and minimise complications such as AKI. Here, influenza A infection was managed expectantly and associated AKI corrected with intravenous fluids and CVVHDF. More investigation is required to establish whether there is a predisposition towards myositis and/or rhabdomyolysis in those with sickle cell trait infected with influenza A.

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References

1. KDIGO AKIWG. Kidney disease improving global outcomes (KDIGO) clinical practice guideline for acute kidney injury. *Kidney International Supplements* 2012; **2**: 1–141.
2. Naik R, Smith-Whitley K, Hassell K, et al. Clinical outcomes associated with sickle cell trait. *Annals of Internal Medicine* 2018; **169**: 619.
3. Peteranderl C, Schmoldt C, Herold S. Human influenza virus infections. *Seminars in Respiratory and Critical Care Medicine* 2016; **37**: 487–500.
4. Kullar R, Fitelson D, O'Brien S. A case of influenza A presenting with rhabdomyolysis and creatine kinase above 4 million. *Chest* 2013; **144**: 273A.
5. Fadila M, Wool K. Rhabdomyolysis secondary to influenza a infection: a case report and review of the literature. *North American Journal of Medical Sciences* 2015; **7**: 122.
6. Kark J, Posey D, Schumacher H, Ruehle C. Sickle-cell trait as a risk factor for sudden death in physical training. *New England Journal of Medicine* 1987; **317**: 781–7.
7. Nelson D, Deuster P, Carter R, Hill O, Wolcott V, Kurina L. Sickle Cell Trait, Rhabdomyolysis, and Mortality among U.S. Army Soldiers. *New England Journal of Medicine* 2016; **375**: 435–42.