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Pigment cast nephropathy; time to revisit the diagnosis

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ABSTRACT

Pigment cast nephropathy is one of the most severe complications of rhabdomyolysis. It is an important cause of renal failure requiring renal replacement therapy. We report the case of a 23-year-old man who presented with short febrile illness with hyperpyrexia and altered sensorium. Non-contrast CT-brain and CSF analysis were normal. He later developed petechial rashes with thrombocytopenia followed by frank hematuria and worsening renal functions. A kidney biopsy was performed, which revealed findings of myoglobin cast nephropathy.

Brief Report

Implication for health policy/practice/research/medical education:
In this study we report a case of a 23-year-old man who presented with hyperpyrexia, altered sensorium and developed deranged renal function. A kidney biopsy was performed, which revealed findings of myoglobin cast nephropathy. Pigment cast nephropathy is a rare disorder and is often misdiagnosed. Our case was unique as he had varied clinical presentation with an underlying pigment cast nephropathy. A timely diagnosis and management lead to a good outcome in this case.

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Introduction

Pigment cast nephropathy is a syndrome complex associated with an abrupt decline in the renal function as a result of the toxic action of pigments on the kidney (1). The major endogenous pigments responsible for this condition are myoglobin (released during rhabdomyolysis), hemoglobin (released during intravascular haemolysis) and bile (released into the circulation during cholestasis). Rhabdomyolysis induced pigment nephropathy accounts for 7%-15% of all cases of acute kidney injury (AKI) (2). Rhabdomyolysis is typically characterised by muscle pain, red to brown urine due to myoglobinuria and elevated muscle enzymes, including creatine kinase in the blood.

Here, we report the case of a patient presenting with fever and myalgia who later began passing red-brown coloured urine with a special focus on his blood picture and renal biopsy findings. A 23-year-old male presented with fever of 2 days duration, which was high grade, intermittent and associated with chills and rigors. There was no evening rise of temperature or associated night sweats. Additionally, he also complained of profound myalgia and severe prostration. The patient denied any past history of similar complaints or any medical/surgical illness. There was no history of recent travel to any endemic areas or use of any recreational drugs. However, he had undergone unaccoustomed physical exertion about four days prior to admission.

On examination, the patient was febrile, had tachycardia but was normotensive. Though the patient had myalgia, there was no muscle tenderness associated with it. His general and systemic examination findings were within normal limits. He was managed symptomatically and was evaluated for tropical infections which in turn were all negative. The following day he developed hyperpyrexia (106°F) complicated with seizure and altered sensorium with neck stiffness. Non-contrast CT-brain and CSF

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analysis were normal.

Over the next five days, the patient continued to remain febrile, had a persistently raised blood pressure and developed ecchymotic lesions over his body and also had bleeding from the site of his IV cannulation. He started having frank hematuria. Investigation revealed a drop in haemoglobin with thrombocytopenia. Peripheral blood smear examination revealed 1%-2% schistocytes suggesting evidence of hemolysis. He had elevated blood urea and creatinine levels at 82 mg/dL and 4.4 mg/dL respectively, with CPK and LDH of 1784 and 500 IU/L respectively. Urine examination showed the presence of red blood cells while myoglobin was absent. On further work-up, his serum procalcitonin level was 2 ng/mL, indicating moderate to severe sepsis. His coagulation profile (aPTT/PT/INR), D-dimer and fibrin degradation product was within normal limits though serum fibrinogen levels were 440 mg/dL. USG abdomen revealed bilateral pleural effusion with hepatomegaly and minimal ascites. Kidneys were normal in size, but showed increased echogenicity. In view of the rapidly worsening azotemia (subsequent days blood urea and creatinine were 220 and 8.5 mg/dL respectively), hypertension, thrombocytopenia with schistocytes on peripheral blood smear, a possibility of atypical haemolytic uremic syndrome was entertained. The etiology suspected was viral febrile illness triggering an aberrant complement pathway abnormality with microangiopathic hemolytic anemia (MAHA). Fundus examination, electrocardiogram (ECG) and 2D echocardiography did not reveal any evidence of chronic hypertension. In view of rapid worsening of renal functions and MAHA, the patient was subjected to renal biopsy. Renal biopsy showed presence of coarse granular orange red coloured casts in the H&E stain while it appeared polychromatic in Masson's trichrome stain (Figures 1A and 1B). These casts were tinctorially different from the RBC casts (by the absence of RBCs) and myeloma casts (PAS positive, No fracturing of cast). There was obstructive cast in another focus eliciting inflammatory reaction in the surrounding interstitium. However no giant cells, granuloma or any fungal structures were seen. The tubular lining cells appeared sloughed at places but no intranuclear inclusions were noted (Figure 1C). There was no evidence to suggest vascular endothelial cell injury or thrombotic microangiopathy. On immunohistochemistry (IHC), these casts were positive for myoglobin thereby confirming the diagnosis of myoglobin pigment cast nephropathy with acute tubular necrosis, secondary to rhabdomyolysis (Figure 1D). The patient was managed conservatively with IV fluids and rapid cooling therapy. He also received empirical antibiotics, anti-malarial and anti-virals (acyclovir) which were stopped once infections were ruled out. Subsequently anti-hypertensive (needed three anti-hypertensive medication) were added. Despite worsening of haematological and metabolic parameters the patient showed rapid clinical improvement. The patient was discharged on day 21 of admission with renal function returning to baseline. On follow-up after 6 months, the patient was normotensive with normal renal functions, no proteinuria and no haematological abnormality.

The probable cause was delayed presentation of heat stroke (history of unaccustomed physical exertion) also known as exertional heat stroke. It was complicated with multi-organ dysfunction, rhabdomyolysis and pigment cast nephropathy.

Discussion

Rhabdomyolysis refers to rupture of the striated muscle leading to discharge of the cellular constituent into the blood circulation. The cause could be as trivial as exertion/prolong bed rest to more common ones like muscle injury, drugs and toxins as well as the sinister ones like the neuroleptic malignant syndrome and malignant hyperthermia due to tropical infections, heat stroke or due to channelopathy triggered by anaesthetic agents (3). The presentation can be myriad ranging from mild asymptomatic illness to multi-organ involvement with dyselectrolytemia, disseminated intravascular coagulopathy, acute renal failure resulting in a potentially fatal outcome. Clinically, myoglobinuria which is characteristically described as tea-coloured urine; along with muscle pain and weakness, defines rhabdomyolysis (4). This triad, however, is seen in <10% of patients. Elevated creatine kinase, level remains the most sensitive laboratory test for assessment of rhabdomyolysis as serum myoglobin though rises rapidly, has a very short half-life and hence becomes undetectable within 24 hours (5).

Rarely, rhabdomyolysis may occur with high grade fever resulting in malignant hyperthermia like syndrome, as seen in our case. The mechanism of hyperthermia is not clearly known. According to Hollander et al who studied malignant hyperthermia like syndrome with rhabdomyolysis among diabetic adolescents; a high grade fever resembling malignant hyperthermia occurs when the calcium equilibrium alters in the myocytes resulting in markedly decreased levels in the sarcoplasmic reticulum and an influx of calcium in the myoplasm (6). The known triggers include the anesthetic agents like halothane and succinylcholine, neuroleptics and heat stress.

Treatment for rhabdomyolysis, at least initially, is mainly supportive, focusing on the management of the ABCs (airway, breathing and circulation) and measures to preserve renal function, including vigorous rehydration (7).

Pigment cast nephropathy is one of the most severe complications of rhabdomyolysis. Approximately 10% of

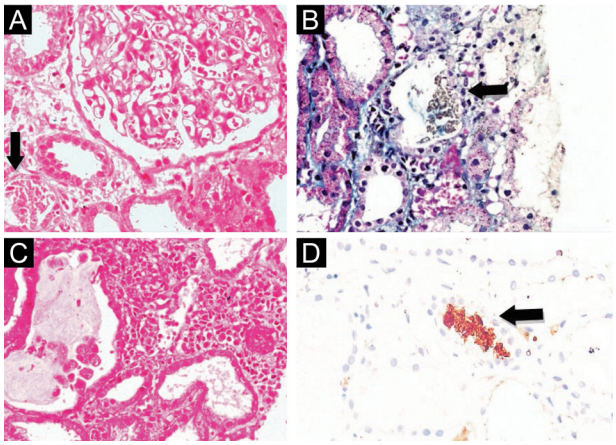

Figure 1. (a,b) The granular and orangeophilic tinge of the tubular cast can be appreciated in the H&E stain while these casts appear polychromatic in Masson's trichrome stain (Black arrow in a,b respectively, x400). (c). Areas of acute tubular necrosis highlighted by shedding of tubular lining epithelial cells and interstitial inflammation. (d). Immunohistochemistry depicting the casts to be positive for myoglobin (Black arrow, x400).

patients with acute renal failure have rhabdomyolysis and myoglobinuria (8). Myoglobin is a member of the group of low molecular weight proteins with a molecular weight of 17800 Da. Myoglobinuria occurs when the plasma concentration of myoglobin exceeds 100 mg/d or the renal threshold of myoglobin exceeds beyond 0.5-1.5 mg/dL (8).

Myoglobin exerts its toxic effect on the kidney both directly as well as indirectly. Whereas the heme molecule (produced as a result of the breakdown of myoglobin) causes a direct tubule-toxic effect, its precipitation along with Tamm Horsfall protein leads to obstruction of the distal tubule. Additionally the vasoconstrictor effect of myoglobin is also known thereby further aggravating the renal toxicity (5). In presence of precipitating factors like volume depletion, acidosis and ischemia the nephrotoxic potential of myoglobin increases manifold thereby causing AKI. The definitive diagnostic modality for diagnosis of myoglobin nephropathy induced AKI is renal biopsy.

Light microscopy reveals features of acute tubular injury with loss of brush border, sloughing of the tubular epithelial cells and presence of myoglobin casts in the tubular lumen. These casts are composed of round granules lining up in chains or aggregating in clusters. Their colour ranges from pink to red brown (orangeophilic tinge) with hematoxylin and eosin stain (Figure 1A), bright magenta on PAS stain and appear polychromatic on trichrome stain (Figure 1B). IHC staining with antibody specific to myoglobin is strongly positive (Figure 1D) in these casts. No specific finding is noted on immunofluorescence microscopy; however, electron microscopy reveals globular myoglobin casts having an electron dense core with a less intense periphery with an absent substructure.

The differential diagnosis of pigment cast is hemoglobin cast and RBC cast in this setting, bile cast remains another entity produced under different circumstances (usually associated with high serum bilirubin levels >20 mg/dL. Differentiating myoglobin, hemoglobin and RBC casts on light microscopy is very difficult. Presence of ghost RBC's within the cast gives a clue to the presence of RBC cast. Other than it no single feature can confidently distinguish these casts. Therefore, herein lies the importance of immunohistochemical test. The specific antibodies to both hemoglobin and myoglobin are now commercially available but not widely used. In our case we could confidently distinguish between these casts based on the positivity for myoglobin stain. However one should remember that coexistence of both hemoglobin and myoglobin casts is a remote possibility. Another thing to remember is that Perls Prussian blue staining, which is used to detect presence of iron in the tissue cannot identify the haemoglobin casts as this stain identifies the Fe^{3+} iron molecule and not Fe^{2+} which is present in hemoglobin cast (9). Bile casts which are seen in bile cast nephropathy, are yellow brown in colour and appear dark green and emerald green on Hall's and Fouchet's stains respectively (10).

Most of the patients with myoglobin pigment cast nephropathy recover their kidney function if the underlying cause can be treated, although renal replacement therapy may be required. It has a relatively good prognosis depending upon the underlying cause. However, a long term follow up is needed to ascertain the burden of pigment induced nephropathy to chronic kidney disease incidence in the future.

Conclusion

Our patient had delayed effect of heatstroke. Hematologic disorders like hemolysis and thrombocytopenia are commonly seen such cases (11). Although rhabdomyolysis is a rarely reported complication in heatstroke, it should be considered in patients who present with severe myalgia and markedly elevated creatine kinase levels. IHC remains the gold standard to classify and diagnose the cases of pigment cast nephropathy. Timely diagnosis and treatment leads to a good outcome in this otherwise potentially fatal disease.

Authors' contribution

AWK and TJ reviewed the sample, reported pathology results and wrote the paper. SKP was the treating physician of the patient, followed up the case and helped in writing the draft. All authors read and signed the final paper.

Conflicts of interest

There is no conflict of interest in this study.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the author. The patient gave the consent to publish as a case report.

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