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“Double whammy” to the kidneys: an unusual etiology of acute kidney disease

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ABSTRACT

Severe rhabdomyolysis could lead to myoglobinuria and acute kidney injury (AKI). Acute interstitial nephritis (AIN) is commonly caused by drugs. AIN *per se* can cause ‘severe’ AKI. Renal recovery is delayed when several factors are involved in the pathogenesis of AKI. Survivors of AKI require long-term follow-up. Here, we report a case where both severe rhabdomyolysis and drug-induced AIN contributed to ‘severe’ dialysis-requiring AKI. Renal biopsy was diagnostic and showed characteristic features. Steroid therapy for AIN resulted in partial recovery.

Keywords: Acute kidney disease, Rhabdomyolysis, Acute interstitial nephritis

Implication for health policy/practice/research/medical education:

AKI is severe when two or more etiologies are implicated. Renal biopsy should be done when AKI does not recover in two weeks or earlier if AIN is suspected. Immunohistochemistry for myoglobin should be conducted in renal biopsy specimen if rhabdomyolysis is suspected. Survivors of dialysis-requiring ‘severe’ AKI require long-term follow up.

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Introduction

Strenuous exercise is a common cause of rhabdomyolysis. Myoglobinuria occurs in severe rhabdomyolysis. Rhabdomyolysis is a common cause of acute kidney injury (AKI). Acute interstitial nephritis (AIN) is commonly caused by non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics. Severe AIN can lead to dialysis-requiring AKI. Renal biopsy is indicated when AKI recovery is delayed or when AIN is suspected.

The term acute kidney disease (AKD) was proposed in KDIGO (Kidney Disease Improving Global Outcomes) AKI classification to define the course of disease after AKI (1). Subsequently, Acute Disease Quality Initiative (ADQI) 16 workgroup proposed a definition for AKI recovery and AKD (2).

Case Presentation

A 28-years-old gentleman presented with complaints of pedal edema and oliguria of three days duration. He gave history of passing ‘reddish brown’ urine once. He revealed an unaccustomed swimming activity followed by

myalgia a week back, and for which he had consumed few nimesulide tablets. Nine months earlier, he was diagnosed with diabetes mellitus and acute coronary syndrome, for which a coronary stent to right coronary artery was placed elsewhere. Serum creatinine value was 0.85 mg/dL. His daily medicines included aspirin 75 mg, ticagrelor 180 mg, atorvastatin 40 mg, rabeprazole 20 mg, vildagliptin 50 mg and metformin 500 mg. Admission labs included the following; blood urea 119 mg/dL, serum creatinine 12.4 mg/dL, serum sodium 129 mmol/L, potassium 6 mmol/L and bicarbonate 15 mmol/L. Serum calcium and phosphorus levels were normal. Urinalysis revealed trace protein. Complete hemogram and fasting lipid profile were normal. Liver function tests revealed transaminitis. Aspartate aminotransferase (AST) was 1128 U/L and alanine aminotransferase (ALT) was 673 U/L. Rest of the liver function tests were within normal limits. Serum creatine phosphokinase (CPK) was 25201 U/L and lactate dehydrogenase (LDH) was 2879 U/L. Echocardiogram was unremarkable. Ultrasound abdomen revealed normal sized kidneys.

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In view of oliguria and azotemia, hemodialysis (HD) was initiated. Within a week after admission, liver enzymes, CPK and LDH became normal. Urine output improved but azotemia persisted even after 2 weeks and intermittent HD was required. In view of non-recovery of renal failure, renal biopsy was done after stopping antiplatelets for 5 days. Unfractionated heparin was administered in this period to prevent stent thrombosis.

Light microscopy (LM) study using haematoxylin and eosin (H & E), periodic acid-Schiff (PAS) and Masson's trichrome stains was performed (Figure 1). LM sections showed unremarkable glomerular pathology. In the tubulointerstitial compartment, interstitial edema was prominent. Interstitial infiltrates consisting of lymphocytes and plasma cells were seen in many areas of interstitium. There was evidence of tubular epithelial cell injury. Occasional tubules showed pigment casts. There was no interstitial fibrosis and tubular atrophy. Immunofluorescence study was negative. Since the patient was admitted with rhabdomyolysis, immunohistochemistry (IHC) for myoglobin was done. IHC conducted on paraffin block for myoglobin was positive on some casts. It was also positive within the cytoplasm of some of the tubular epithelial cells, suggesting myoglobin mediated tubular injury (Figure 2).

Since biopsy showed features of AIN, injection methylprednisolone 250 mg intravenously was given for 3 days, followed by oral prednisolone at 0.5 mg/kg body weight. His renal function gradually improved and became dialysis independent. Serum creatinine level was 2.7 mg/dL at the time of his discharge from the hospital. His serum creatinine was 1.8 mg/dL, 3 months after his discharge from the hospital during his last follow-up. AKD had progressed to chronic kidney disease (CKD).

Discussion

Strenuous exercise is a common cause of rhabdomyolysis.

The incidence of AKI in rhabdomyolysis is up to 50%. The risk of AKI is more when serum CPK level at admission is more than 20 000 U/L. Myoglobinuria occurs in severe rhabdomyolysis. Mechanisms of AKI include dehydration, intra-renal vasoconstriction, precipitation of myoglobin with the Tamm-Horsfall protein in acidic urine, intratubular obstruction and direct tubular injury. Majority of patients who develop AKI due to rhabdomyolysis recover (3).

Drug-induced AIN is the common etiology of AIN, with NSAIDs (nonsteroidal anti-inflammatory drugs) and antibiotics being the most frequent offending agents (4). Pathogenesis involves an immunologic reaction either against endogenous nephritogenic antigen or an exogenous antigen processed by tubular cells. Cell-mediated immunity plays role in recruiting T-lymphocytes and macrophages. They secrete cytokines, which increase the production of extracellular matrix and fibroblasts, ultimately leading to areas of interstitial fibrosis (5). This is the reason why a significant proportion of patients (30 to 70%) with AIN, do not recover completely to achieve their baseline renal function (6).

AKI could lead to deleterious consequences in the long-term including increased incidence of CKD, increased risk for recurrent AKI and cardiovascular morbidity (7). The pathophysiologic processes that happen during the underlying transition include nephron loss and glomerular hypertrophy, interstitial inflammation and subsequent fibrosis, endothelial injury, cell cycle arrest and maladaptive repair, vascular rarefaction and renin-angiotensin-aldosterone-system activation (8). Hence, AKI and CKD are now considered 'interconnected' syndromes. Acute Disease Quality Initiative (ADQI) 16 workgroup proposed a definition for AKI recovery recently. It was defined as the absence of AKI by both serum creatinine and urine output criteria (KDIGO) within seven days after

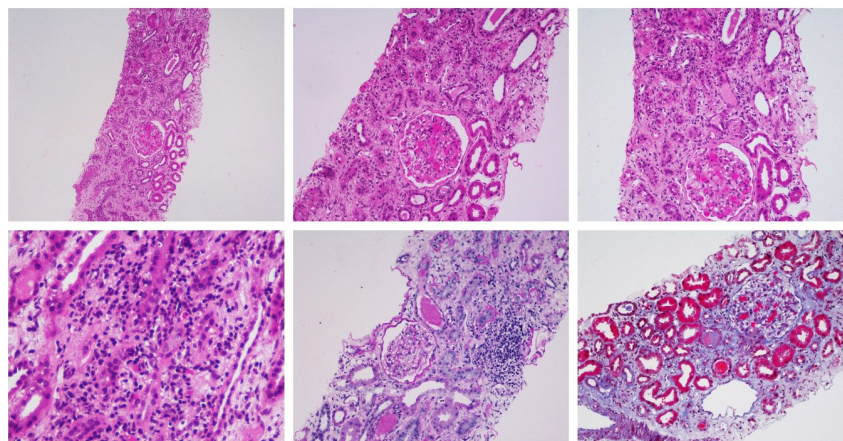


Figure 1. Haematoxylin and eosin stains showing normal glomeruli. There is interstitial oedema. Interstitial infiltrate, consisting of lymphocytes and plasma cells, is seen in many areas of interstitium. There is tubular epithelial cell injury. Occasional tubules show pigment casts. There is no interstitial fibrosis and tubular atrophy. PAS (periodic acid-Schiff) stain showing inflammatory infiltrate in the interstitium. Last section stained with MT (Masson's trichrome) stain.

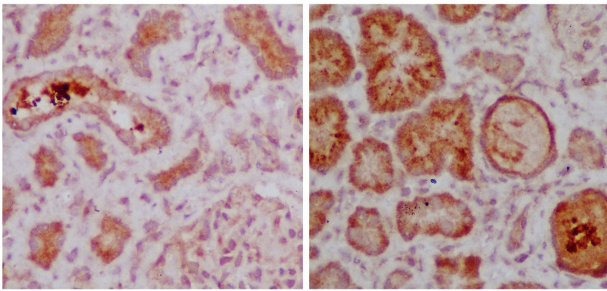


Figure 2. Immunohistochemistry on paraffin block for myoglobin is positive on some casts. It is also positive within the cytoplasm of some of the tubular epithelial cells.

AKI onset. ‘Transient AKI’ was defined by rapid reversal of AKI within 48 hours. Late reversal in the timeframe of 48 hours and seven days was defined as ‘persistent AKI’. AKI that did not recover within a week was termed as AKD (2).

The initial working diagnosis for this case was severe rhabdomyolysis with AKI. Because the recovery of renal function was not as quick as expected, renal biopsy was planned at the end of two weeks. To avoid bleeding risks, it was required to stop anti-platelets for five days prior to biopsy. Otherwise, biopsy would have been done few days earlier. Additional findings of AIN in biopsy necessitated treatment with steroids (9).

Although many of the drugs consumed by the patient including aspirin, ticagrelor and rabeprazole could cause AIN, the temporal association suggests nimesulide as the etiology for AIN in this case. It is possible that high dose statins, which this patient was taking for coronary artery disease could have contributed to severe rhabdomyolysis (10).

To our knowledge, this is the first reported case with histopathologic evidence, where two independent factors, rhabdomyolysis and AIN were involved in the pathogenesis of AKI. The severity of AKI could be attributed to this “double whammy” on kidneys. He has already progressed to CKD and regular follow-up is mandatory.

Conclusion

AKI is ‘severe’ when two different etiologies are implicated in the pathogenesis. Clinicians should have high index of suspicion for AIN, so that renal biopsy could be planned in timely manner and steroids administered earlier in the course of disease. In survivors of ‘severe’ AKI, probability of progression to AKD and CKD is high. Long term follow-up of such AKI survivors is desirable.

Authors’ contribution

VJ was involved in preparation of manuscript and patient

care. MS, DK and RP were involved in patient care and helped in drafting manuscript. AK reported biopsy findings. All authors have reviewed and agreed on the final version of this manuscript prior to submission.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors. Informed consent was obtained from the patient for the publication of this report.

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