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Kidney Biopsy Teaching Case

Intratubular Hemoglobin Casts in Hemolysis-Associated Acute Kidney Injury

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Kidney injury is a complication of intravascular hemolysis associated with many forms of hemolytic disease. Reports of kidney biopsy findings in patients with hemolysis-related kidney injury have focused primarily on the accumulation of hemosiderin pigment within proximal tubular epithelial cells (hemosiderosis), a feature of chronic hemolysis. The nephrotoxic effects of hemoglobin include direct cytotoxicity to tubular cells, but hemoglobin also can precipitate in distal nephron segments, forming obstructive casts. We present a case of hemolysis-associated tubular injury, characterized by acute onset of intravascular hemolysis followed by acute kidney injury with acute tubular injury and abundant intratubular casts containing hemoglobin.
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INDEX WORDS: Acute kidney injury (AKI); acute tubular injury; hemoglobin casts; intravascular hemolysis; renal biopsy; acute tubular necrosis.

INTRODUCTION

Acute intravascular hemolysis results in large amounts of free hemoglobin that can be toxic to the kidney. The toxic effects of heme-containing proteins, including hemoglobin and myoglobin, are multiple, and histopathologic changes are variable. Reports of kidney injury in the setting of intravascular hemolysis and hemoglobinuria have long focused on the presence of excess hemosiderin within proximal tubular epithelial cells, which is seen predominantly in patients with persistent or recurrent bouts of hemolysis and hemoglobinuria. We present an unusual case of acute kidney injury in the setting of intravascular hemolysis in which the biopsy specimen showed extensive intratubular hemoglobin casts in the distal nephron without detectable intracellular hemosiderin.

CASE REPORT

Clinical History and Initial Laboratory Data

A 43-year-old African American woman presented with fevers, weakness, and difficulty ambulating. Prior to presentation, she was in her usual state of health and had no significant medical history. She reported recent heavy menstrual bleeding and on presentation was anemic with hemoglobin level of 5 g/dL. Haptoglobin levels were elevated at 371 (reference range, 51-192) mg/dL, and direct agglutination test results were negative. Physical examination was significant for a right lower-extremity deep vein thrombosis, which was confirmed on imaging studies. A left-sided pulmonary embolus also was identified. Gynecologic assessment revealed an enlarged fibroid uterus.

Serum creatinine level at presentation was 0.6 mg/dL, corresponding to estimated glomerular filtration rate (eGFR) of 138 mL/min/1.73 m^2 calculated by the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation. The patient received 2 units of packed red blood cells (RBCs), with an increase in hemoglobin level to 7 g/dL. During her hospitalization, colonoscopy and esophagogastroduodenoscopy results were normal, and an infectious workup was negative, including serologic studies for hepatitis C virus, hepatitis B virus, HIV (human immunodeficiency virus), and *Mycoplasma pneumoniae*. Testing for antinuclear antibody gave positive results (with a titer of 1:160), but results of serologic studies for anti–double-stranded DNA, anti-Smith, anti-SSA, and anti-SSB antibodies were negative and complement levels were normal. Because of the patient's severe anemia and venous thrombosis, testing was performed for paroxysmal nocturnal hemoglobinuria. Flow cytometry revealed the appropriate presence of CD55 and CD59 on peripheral-blood granulocytes, excluding paroxysmal nocturnal hemoglobinuria. An inferior vena cava filter was placed and the patient was started on prednisone treatment, with reduction of fevers and improvement of generalized symptoms. She was discharged 11 days after the initial presentation.

One day following the patient's discharge, she returned to the emergency department with recurrent fever and hemoglobin level $<$ 6 g/dL. She received 4 additional units of packed RBCs over 2 days and subsequently developed shortness of breath, darkened urine, and acute kidney injury, with serum creatinine level of 3 mg/dL (eGFR, 22 mL/min/1.73 m^2). Urinalysis showed protein (2+) and blood (3+), with 5 to 10 RBCs per high-power field. A kidney biopsy was performed.

Kidney Biopsy

Forty-three glomeruli were sampled, of which one showed ischemic obsolescence. The other glomeruli were without abnormalities. Proximal tubules showed diffuse loss of brush borders, sloughing of cytoplasm into tubular lumina, and reactive nuclear atypia with occasional mitotic figures. Numerous intratubular globular and granular casts were seen within distal tubular lumina, which were eosinophilic on the hematoxylin and eosin–stained

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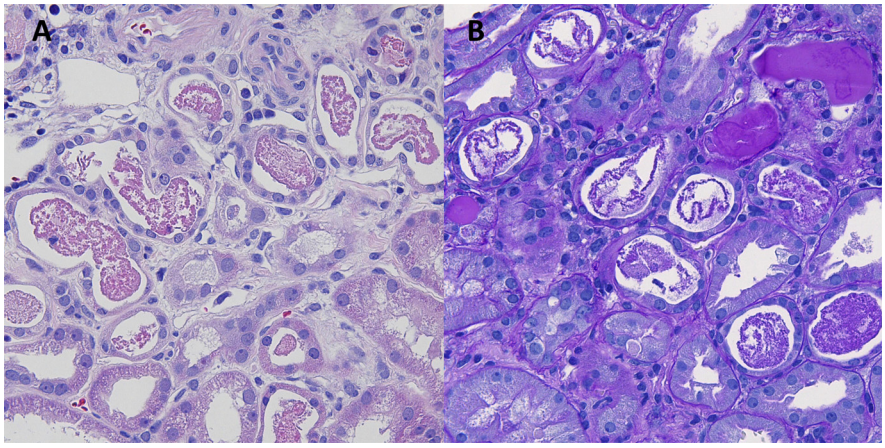

Figure 1. (A) Distal tubules show abundant globular to granular eosinophilic casts on hematoxylin and eosin–stained sections, (B) which are periodic acid–Schiff reagent positive (A, B: original magnification, ×40).

section (Fig 1A), periodic acid–Schiff reagent positive (Fig 1B), fuchsinophilic on trichrome stain, and silver negative. There was no significant interstitial fibrosis or tubular atrophy. Immunohistochemical staining for myoglobin was negative in tubular casts (Fig 2A); however, these casts stained strongly for hemoglobin A (Fig 2B). Prussian blue stain was negative for hemosiderin deposition (Fig 2C).

By direct immunofluorescence microscopy, there was no glomerular, tubular basement membrane, or interstitial staining for immunoglobulin G (IgG), IgA, IgM, C3, C1q, κ light chain, λ light chain, fibrinogen, or albumin. A few proteinaceous tubular casts stained for IgA, κ light chain, and λ light chain. Ultrastructural examination of glomeruli showed no abnormalities. Examination of tubules revealed markedly electron-dense material within distal tubular lumina (Fig 3). Hemosiderin granules were not identified within tubular epithelial cells.

Diagnosis

The biopsy was interpreted as acute tubular necrosis with diffuse intratubular hemoglobin casts, indicative of toxic injury from intravascular hemolysis.

Clinical Follow-up

Following the patient's kidney biopsy, she underwent further workup for acute hemolysis. Repeat testing revealed haptoglobin level < 20 mg/dL, lactate dehydrogenase level of 2,557 (reference

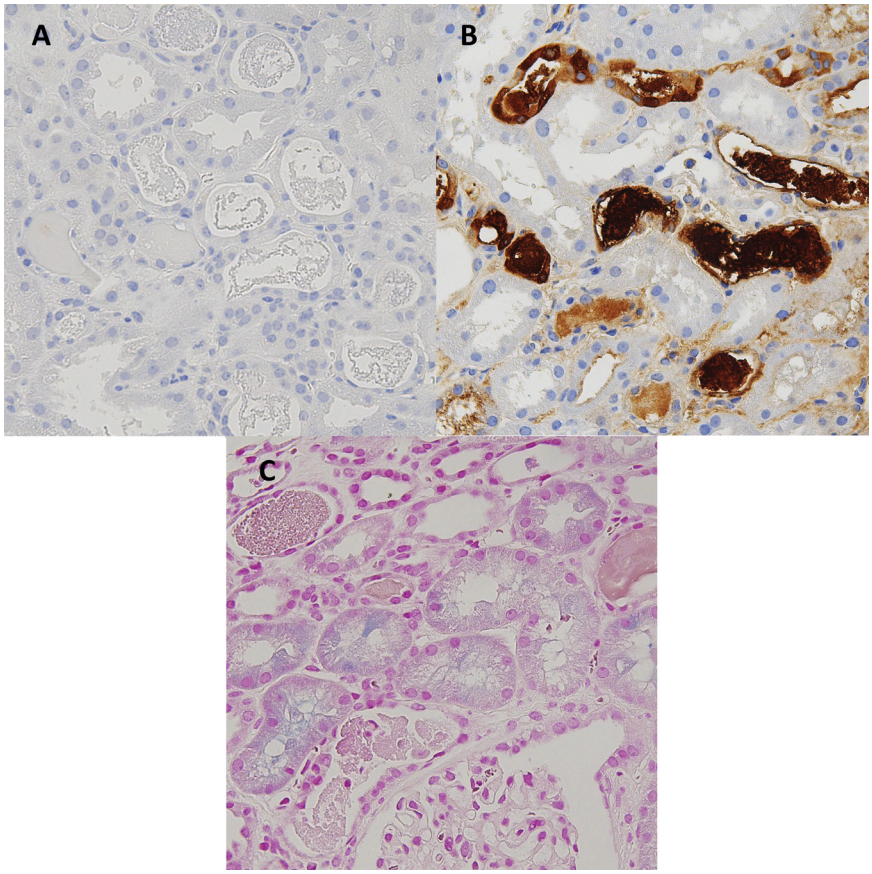

Figure 2. (A) The identified casts did not stain for myoglobin by immunohistochemistry, (B) but showed diffuse and strong staining for hemoglobin A. (C) Intracytoplasmic hemosiderin was not identified within tubular epithelial cells (Prussian blue stain; A-C: original magnification, ×40).