

# Hemoglobin Cast Nephropathy



Saqib Mahmud<sup>1</sup>, Carl Dernell<sup>2</sup>, Naveet Bal<sup>1</sup>, Alexander J. Gallan<sup>2</sup>, Samuel Blumenthal<sup>1</sup>, Abhilash Koratala<sup>1</sup> and Daniel Sturgill<sup>1</sup>

<sup>1</sup>Division of Nephrology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA; and <sup>2</sup>Department of Pathology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

**Correspondence:** Saqib Mahmud, Division of Nephrology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226, USA. E-mail: [smahmud@mcw.edu](mailto:smahmud@mcw.edu)

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## INTRODUCTION

Intravascular hemolysis is a rare, life-threatening cause of anemia that results in the breakdown of red blood cells (RBCs) within the vasculature releasing hemoglobin into the circulation.<sup>1</sup> Hemoglobin is a toxic molecule to renal tubules and can cause injury by various mechanisms. Hemoglobin cast nephropathy can resemble other etiologies of acute kidney injury (AKI), including acute tubular necrosis, acute interstitial nephritis, and thrombotic microangiopathy. Few studies have demonstrated immunohistochemically proven hemoglobin casts on kidney biopsy associated with intravascular hemolysis.<sup>2,3</sup> We present 2 distinct cases of hemolysis-associated hemoglobin cast nephropathy related to the use of rifampin and autoimmune hemolytic anemia.

## CASE PRESENTATION

### Case 1

A 64-year-old woman with a history of bronchiectasis and pulmonary *Mycobacterium avium* complex infection presented with nausea and vomiting over 3 days. She had a pulmonary *M. avium* complex infection 3 years earlier and received rifampin, azithromycin, and ethambutol for 1 year. Two months before presentation, a persistent cough developed and a computed tomography scan was suggestive of recurrent *M. avium* complex infection. She again began a regimen of rifampin, ethambutol, and azithromycin and a few days later nausea, vomiting, chills, fevers, and back pain developed.

On physical examination, she was afebrile, blood pressure was 153/82 mm Hg, heart rate 54 beats/min, respiratory rate 18 breaths/min, and oxygen saturation was 97% on room air. She was alert and in no distress,

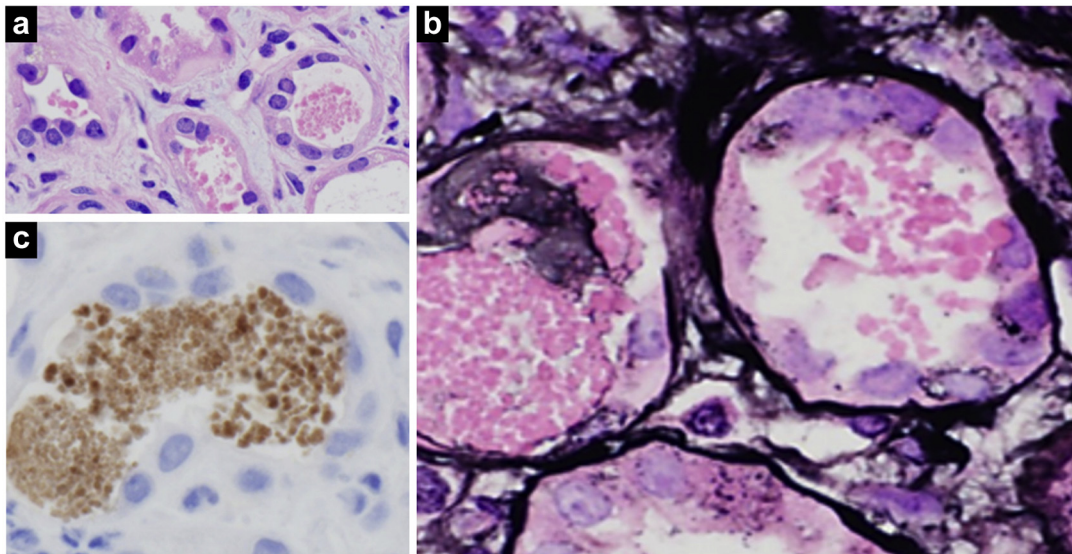
and the examination was otherwise unremarkable except for 3 new small purpuric lesions on the back.

Pertinent laboratory data demonstrated a serum creatinine level of 6.6 mg/dl (baseline, 0.9 mg/dl), blood urea nitrogen level of 66 mg/dl, and hemoglobin level of 11.1 g/dl (baseline, 15 g/dl). The platelet count was low at 9000/ $\mu$ l and the lactate dehydrogenase level was elevated at 507 units/l. Plasma fibrinogen level, haptoglobin, aspartate aminotransferase, alanine aminotransferase, bilirubin, prothrombin time, partial thromboplastin time, and international normalized ratio were normal, and a direct antibody test result was negative. Urinalysis demonstrated 3+ blood, no albumin, and a specific gravity <1.005. Urine microscopy demonstrated 2 to 5 RBCs per high-power field and dark, granular casts. A renal sonogram was performed and was unremarkable.

### Hospital Course

Given the concern for the possibility of thrombotic thrombocytopenic purpura perhaps related to rifampin, plasma exchange was initiated but discontinued when the ADAMTS13 level returned as normal. Rifampin had been discontinued on admission. A peripheral blood smear demonstrated no schistocytes. A rifampicin-induced platelet-reactive antibody was identified.

The patient remained nonoliguric and the serum creatinine level rose to 8.1 mg/dl on day 4 of admission. However, her platelet count improved to 120,000/ $\mu$ l. Given concern for rifampin-associated acute interstitial nephritis, she received methylprednisolone 120 mg/d for 3 days. Hemodialysis was performed to optimize platelet function before proceeding with a nephrologist-performed, percutaneous ultrasound-guided kidney biopsy.



**Figure 1.** Kidney biopsy findings in case 1. (a) The tubules contain densely eosinophilic intraluminal casts with a granular to globular appearance (hematoxylin and eosin stain). (b) The casts are non-argyrophilic and sometimes distend the tubular lumen (Jones methenamine silver stain). (c) Hemoglobin A immunohistochemical stain is strongly positive in the casts.

### Kidney Biopsy Diagnosis

The biopsy demonstrated several intratubular pigmented casts that were eosinophilic on hematoxylin and eosin stain, non-argyrophilic, and negative to weakly positive on periodic acid–Schiff stain. The casts were composed of aggregates of rounded, globular structures. Red cell “ghosts” were not identified. The casts were strongly positive for hemoglobin A immunohistochemical stain, confirming the diagnosis of hemoglobin cast nephropathy (Figure 1). There was also mild interstitial edema with a few scattered inflammatory cells, raising the possibility that a component of acute interstitial nephritis was also present before steroid therapy, but significant ongoing interstitial nephritis was not present and hemoglobin casts were considered to be the predominant cause of AKI. The glomeruli, arteries, and arterioles showed no pathologic abnormalities, and no interstitial fibrosis or tubular atrophy was present. Immunofluorescence microscopy was negative for an immune complex–mediated disease, and the intratubular casts did not show monoclonal staining. Electron microscopy was not performed.

### Follow-up

After establishing the diagnosis of hemoglobin cast nephropathy, the patient continued to receive supportive care with kidney function gradually improving and a creatinine level of 2.87 mg/dl on discharge. The serum creatinine level 4 weeks after hospital discharge was 1.18 mg/dl.

### Case 2

A 21-year-old woman with a medical history of a seizure disorder and hypothyroidism presented with

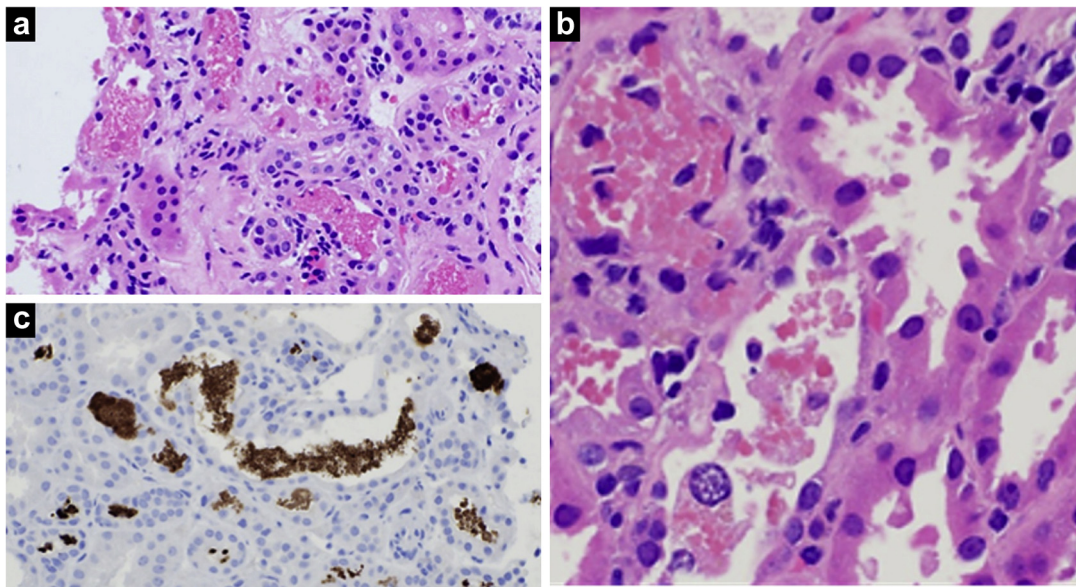
symptoms of dark-colored urine and abdominal pain. She had noticed dark urine 2 weeks before presentation and a week later noticed right upper quadrant abdominal pain and yellow discoloration of the skin.

On physical examination, she was awake and alert but appeared jaundiced. Pulmonary and cardiac examinations were unremarkable. The abdominal examination revealed mild tenderness in the right upper quadrant and no skin lesions were seen.

Laboratory data revealed a hemoglobin level of 5.8 g/dl, hematocrit 16%, platelet count 363/ $\mu$ l, lactate dehydrogenase 710 units/l, and total bilirubin 7.3 mg/dl. A direct antiglobulin test result was positive. Peripheral smear did not reveal schistocytes. Other pertinent laboratory data included a blood urea nitrogen level of 20 mg/dl and a serum creatinine level of 0.85 mg/dl.

### Hospital Course

The patient was admitted with an initial working diagnosis of autoimmune hemolytic anemia and received blood transfusion and intravenous methylprednisolone 125 mg every 6 hours. Over 1 day, the serum creatinine level increased to 3.12 mg/dl from a baseline of 0.82 mg/dl and peaked at 7.91 mg/dl after 48 hours. The initial workup of AKI included urinalysis, which was significant for large blood, and urine microscopy showed 0 to 2 RBCs per high-power field, multiple dark-pigmented casts without dysmorphic RBCs or cellular casts. A renal sonogram was unremarkable. She started hemodialysis for uremic symptoms. The initial nephrology consultant at an outside hospital diagnosed acute tubular necrosis given the presence of dark granular casts on urine microscopy,



**Figure 2.** Kidney biopsy findings in case 2. (a) Numerous eosinophilic intratubular casts are present, some of which have a granular appearance (hematoxylin and eosin stain). (b) Other casts are composed of larger eosinophilic globules (hematoxylin and eosin stain). (c) Hemoglobin A immunohistochemical stain demonstrates that both the granular and globular casts are composed of hemoglobin.

although the concern for an alternative diagnosis related to hemolysis prompted a nephrologist-performed, ultrasound-guided, kidney biopsy, as described in the following section.

#### Kidney Biopsy Diagnosis

The biopsy showed numerous tubules distended by intraluminal pigmented casts that were granular to globular in appearance. This cast material was densely eosinophilic on hematoxylin and eosin stain, non-argyrophilic, and negative to weakly positive on periodic acid–Schiff stain. Red cell ghosts were not identified. The casts were strongly positive for hemoglobin A immunohistochemical stain, confirming the diagnosis of hemoglobin cast nephropathy (Figure 2). The affected proximal tubules also demonstrated extensive acute tubular injury, including loss of the brush borders and cytoplasmic sloughing. The glomeruli, arteries, and arterioles showed no pathologic abnormalities. There was no significant interstitial fibrosis, tubular atrophy, or interstitial inflammation. Immunofluorescence microscopy was negative for an immune complex-mediated disease, and the intratubular casts did not show monoclonal staining. Electron microscopy was noncontributory.

#### Follow-up

The patient continued to receive high-dose intravenous methylprednisolone for autoimmune hemolytic anemia. After kidney biopsy, she received rituximab for ongoing treatment of autoimmune hemolytic anemia and required hemodialysis for two weeks. As her urine output and renal function started to improve, she did not require further renal replacement. Her serum

creatinine level 1 month after the initial injury improved to 1.41 mg/dl.

## DISCUSSION

Hemolytic anemia can be caused by multiple etiologies but is broadly classified into intravascular and extravascular hemolysis.<sup>1</sup> Drug-induced hemolysis (such as with rifampin), microangiopathies, autoimmune causes, and infections are all causes of intravascular hemolysis. Hemolysis results in hemoglobinuria, which can lead to acute and chronic kidney injury.<sup>2,4,5</sup> Hemoglobin released into the circulation binds to haptoglobin, which is not filtered by the glomerulus owing to its large size, and is degraded in the reticuloendothelial system. During overwhelming hemolysis, haptoglobin molecules are saturated and free hemoglobin levels rise in the blood. Hemoglobin is filtered by the glomerulus and enters the tubules, where it dissociates into heme and globin. Heme can cause nephrotoxicity by multiple

**Table 1.** Comparison of clinical and laboratory data between the 2 patients

Characteristics	Patient 1	Patient 2
Etiology of hemolysis	Rifampin	AIHA
Serum creatinine baseline, mg/dl	0.9	0.82
Serum creatinine on admission, mg/dl	6.6	3.12
Serum creatinine at discharge, mg/dl	2.87	1.76
Serum creatinine at 4 wk after AKI, mg/dl	1.14	1.41
Dialysis requirement before kidney biopsy	Yes	Yes
Dialysis requirement at discharge	No	No
Heme casts on kidney biopsy	Yes	Yes
Steroid therapy before kidney biopsy	Yes	Yes

AIHA, autoimmune hemolytic anemia; AKI, acute kidney injury.

**Table 2.** Teaching points

- Hemoglobin cast nephropathy is a rare cause of acute kidney injury and can mimic other causes of acute kidney injury (e.g., acute tubular necrosis, acute interstitial nephritis).
- Usually seen in the presence of intravascular hemolysis
- Hemolytic anemia and acute kidney injury should raise the suspicion of hemoglobin cast nephropathy.
- Final diagnosis requires kidney biopsy
- It is differentiated from red blood cell casts containing hemoglobin of glomerular hematuria by the absence of red blood cells by hemoglobin immunostain.
- Treatment is supportive and aimed at treating the underlying cause of hemolysis.

mechanisms, including decreased renal perfusion, tubular cytotoxicity, and the formation of casts.<sup>6</sup> Rifampin-induced hemolysis and autoimmune hemolytic anemia can both result in hemoglobin casts and severe AKI necessitating hemodialysis, as seen in our 2 cases.<sup>1,7</sup>

The presentation of hemoglobin cast nephropathy secondary to hemolysis can mimic many other disease patterns as in the 2 cases presented. Clinical hallmarks of anemia can be evident, including symptoms of weakness, fatigue, dyspnea, jaundice, and dark urine. Laboratory findings of hemolysis are often present, including an elevated lactate dehydrogenase level, total bilirubin, and low haptoglobin. Other possible laboratory findings can include a positive Coombs test result, increased reticulocyte count, and spherocytes on peripheral blood smear. Electrolyte abnormalities can include hyperkalemia, hyperphosphatemia, hyperuricemia, and metabolic acidosis owing to lysing RBCs. Urinalysis often demonstrates blood but no or minimal RBCs with varying degrees of albuminuria. Urine microscopy can reveal dark-pigmented casts, which can mimic acute tubular necrosis as occurred in the case of autoimmune hemolytic anemia described earlier. Fractional excretion of sodium in such cases can be <1%, which is more consistent with cast nephropathy.<sup>8</sup> Renal imaging is not usually diagnostic in such instances and can only help rule out other anatomic causes of AKI. Ultimately, the diagnosis of hemoglobin cast nephropathy requires a kidney biopsy.

On the kidney biopsy, the finding of eosinophilic granular casts raises a differential diagnosis of RBC casts, myoglobin cast nephropathy, bile cast nephropathy, hemoglobin cast nephropathy, and acute tubular injury or necrosis. RBC casts develop in the setting of glomerular hematuria, most commonly owing to glomerulonephritis. Because hemoglobin is present within RBCs, hemoglobin immunostain highlights RBC casts as well as the hemoglobin casts. Conversely, hemoglobin cast nephropathy owing to intravascular hemolysis does not contain fragments of RBCs because they have been cleared in circulation before entering

the kidney. Therefore, assessing for the presence of old RBC fragments (ghosts) is helpful in the distinction between RBC casts and hemoglobin casts. Myoglobin cast nephropathy develops in the setting of rhabdomyolysis. The casts are essentially identical in appearance to hemoglobin casts but stain with myoglobin immunostain and are negative for hemoglobin immunostain. Bile cast nephropathy develops in the setting of hyperbilirubinemia and is typically secondary to cirrhosis. Although the casts may have a yellow-green appearance, they can also appear eosinophilic and nearly identical to hemoglobin and myoglobin casts. Granular casts associated with acute tubular injury or necrosis often contain fragments of sloughed epithelial cells and are negative for myoglobin and hemoglobin immunostains. Finally, the possibility of light-chain cast nephropathy should always be considered and excluded by immunofluorescence in the setting of atypical-appearing casts, although light-chain casts only rarely take on a granular appearance.

The treatment of hemoglobin cast nephropathy requires the halting of ongoing hemolysis, which in these cases involved stopping the offending drug (rifampin) and immunosuppression to reduce autoimmune hemolysis, respectively. Nephrology management is primarily supportive and revolves around maintenance of appropriate volume status, the correction of electrolyte abnormalities, and the prevention of any further renal insults.<sup>9</sup> Dialysis may become indicated if such abnormalities cannot be managed medically. The key clinical and laboratory differences between these 2 cases are summarized in [Table 1](#).

## CONCLUSIONS

Hemoglobin cast nephropathy should be strongly suspected in patients presenting with hemolysis and AKI. The diagnosis is multifaceted, requiring a high

**Table 3.** Reported causes of hemoglobin cast nephropathy

### Extrinsic and intrinsic red blood cell defects

- Autoimmune hemolytic anemia
- ABO incompatibility
- Paroxysmal nocturnal hemoglobinuria
- Sickle cell disease
- Evans syndrome

### Drugs

- Rifampin
- Trimethoprim/sulfamethoxazole
- Vancomycin
- Bevacizumab

### Infections

- Mycoplasma

### Mechanical

- Cardiopulmonary bypass
- Prosthetic heart valves

### Other

- Sodium nitrite ingestion
- Disseminated intravascular coagulation

index of suspicion, clinical history, examination, laboratory findings, and ultimately a kidney biopsy (Tables 2 and 3).

## DISCLOSURE

All the authors declared no competing interests.

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