Interesting Histology in Tropical Acute Kidney Injury

To the Editor: We read with interest the article titled 'Molecular mechanisms of rhabdomyolysis-induced kidney injury: from bench to bedside' by Hebert JF *et al.*[1] published in *Kidney Int Rep*. The authors have in detail described a variety of etiologies and the mechanisms of rhabdomyolysis-induced acute tubular injury.[1] We would like to highlight that snake venom is also an important cause for rhabdomyolysis.[2] Certain bacterial, viral, fungal, and protozoal infections can also lead to rhabdomyolysis.[3] Here we would like to present a case of rhabdomyolysis-induced by leptospiral infection, a rare but documented cause.

A 46-year-old male was admitted with a short febrile illness, oliguria, and myalgia for 4 days. Fever was high grade, continuous, and associated with rigor. On examination, he was febrile, hypotensive, had pallor, and no icterus or hepatosplenomegaly. His laboratory measurements were as follows: (i) urea 250 mg/dl, (ii) serum creatinine 9.1 mg/dl, (iii) and potassium 5.5 mEq/l. He was initiated on slow low efficiency dialysis. His hypotension was managed with dual inotropes and he was converted to regular hemodialysis after 48 hours. Because the etiology of acute kidney injury was unclear and he remained oligoanuric for 10 days, a renal biopsy was performed.

The biopsy revealed glomeruli with normal morphology. The tubular epithelial cells showed features of acute tubular injury. Some of the tubules had granular reddish brown pigment casts (Figures 1 and 2). The differential diagnoses of pigment casts include

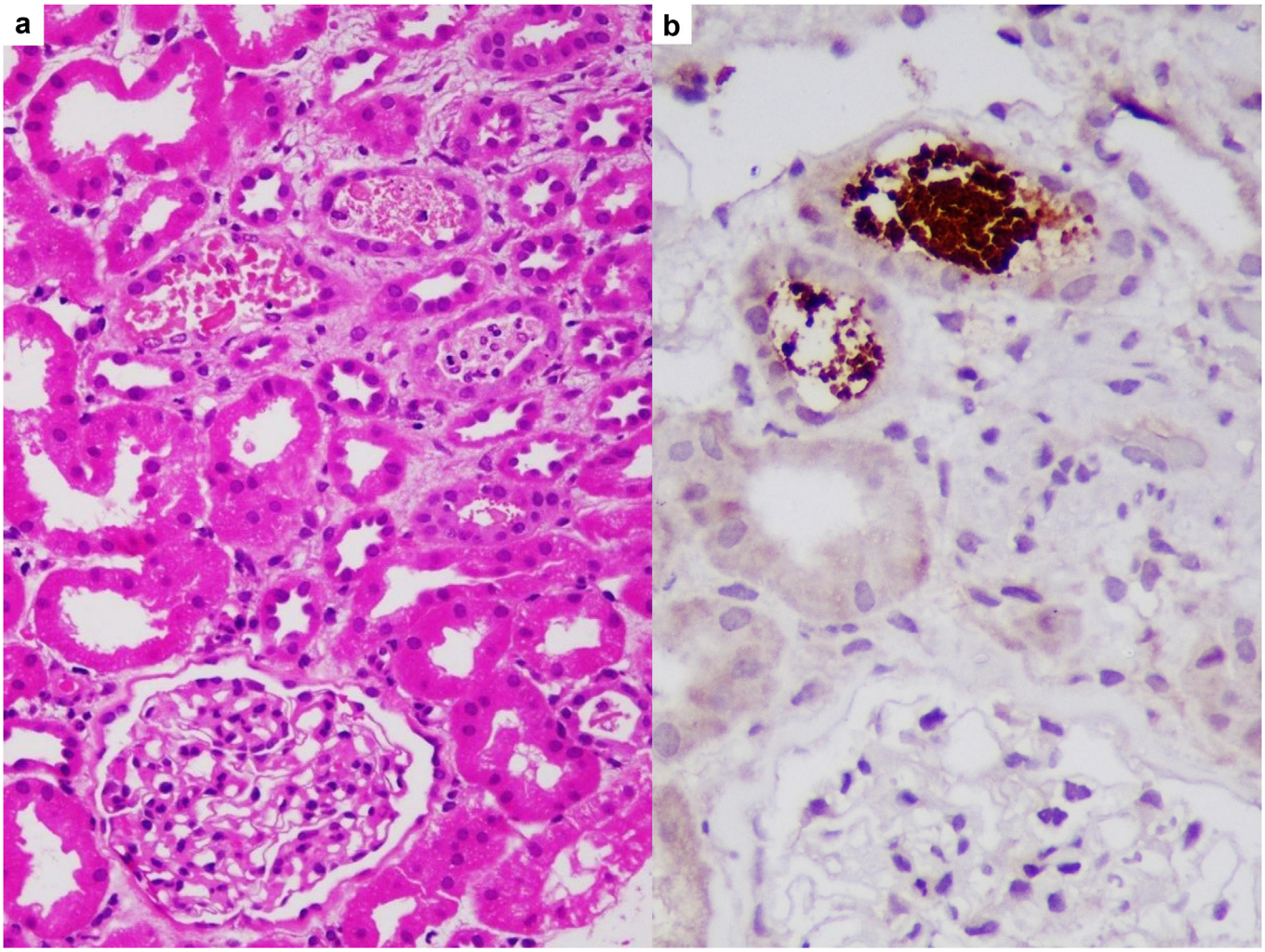

Figure 1. (a) Granular pigment casts were seen in some of the tubules. There was tubular epithelial injury and interstitial edema. (b) Immunohistochemical stain for myoglobin showed positive staining on the casts.

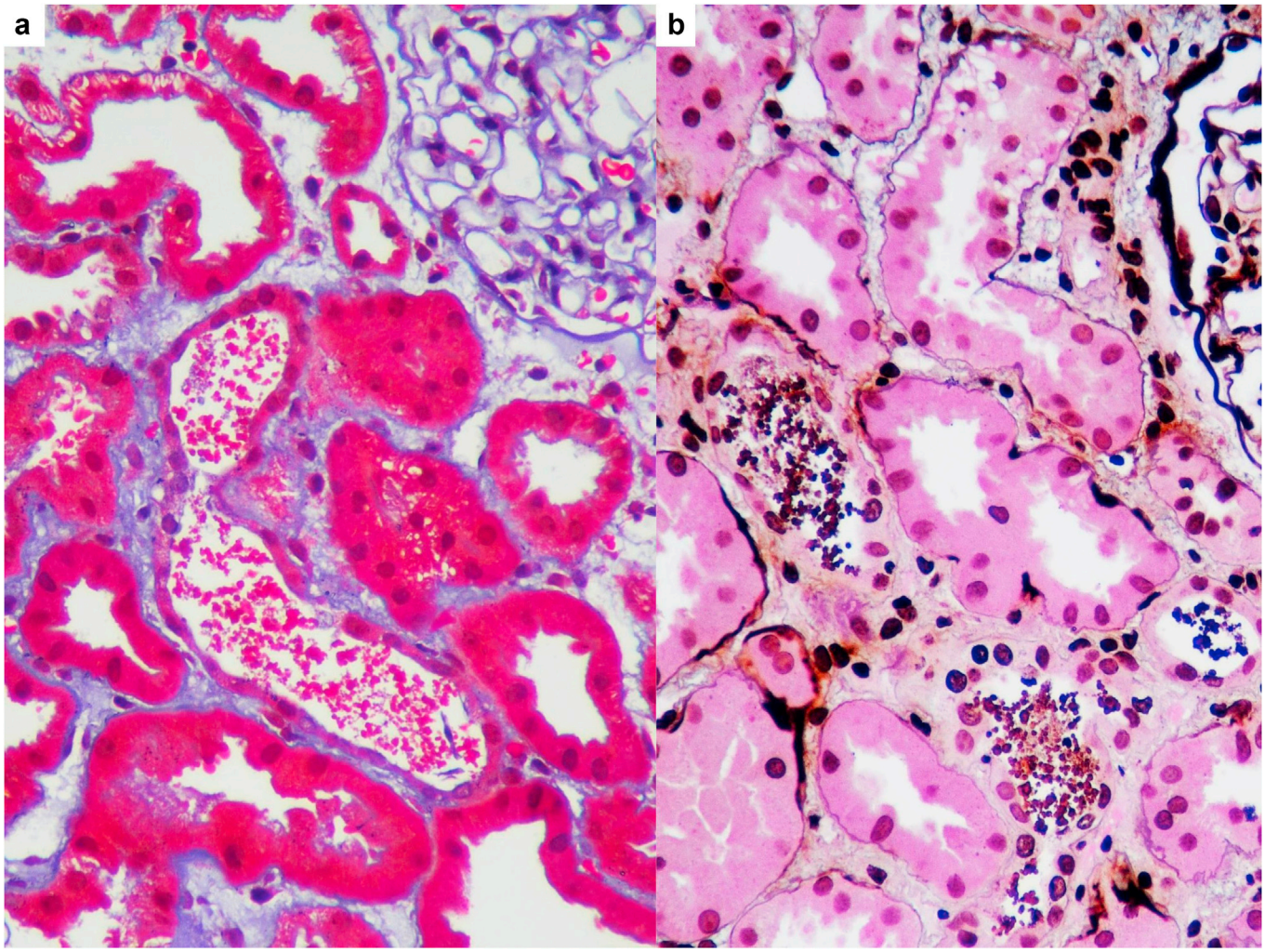

Figure 2. (a) Masson trichrome stain showed granular red casts. (b) These casts appeared brown-black on Jones silver stain.

hemoglobin casts, myoglobin casts, red blood cell casts, light chain casts, and cellular debris. Using light microscopy, hemoglobin and myoglobin casts are indistinguishable. Immunofluorescence study for routine antisera, including light chains, was negative on this biopsy. Immunohistochemical staining for hemoglobin and myoglobin was performed. The tubular casts were positive for myoglobin (Figure 1b) and negative for hemoglobin, confirming the diagnosis of rhabdomyolysis-induced acute tubular injury.

In view of the background of a short febrile illness with oligoanuric renal failure, he was investigated for malaria, leptospirosis, dengue, and scrub typhus, which revealed positive IgM enzyme-linked immunosorbent assay for leptospirosis. His creatine phosphokinase, which was 8880 IU/l gradually declined with recovery. He was managed with parenteral piperacillin and tazobactam in appropriate doses. He underwent 10 sessions of hemodialysis after which he recovered. His last creatinine done 40 days after discharge was 1.2 mg/dl.

Leptospirosis, a disease caused by a species of spirochetes, is a widespread reemerging zoonotic disease of global public health importance.[4] *Leptospira* invade the human body through cuts or abraded skin, mucous membranes, or conjunctivae when it comes in contact with infected urine or contaminated water or soil. It then enters the bloodstream, causing high fever, headache, and myalgia. Although most cases are mild, some can be severe with a high mortality rate when associated with jaundice, renal failure, and hemorrhage (Weil's disease) and pulmonary hemorrhagic syndrome.

Renal involvement can range from a mild prerenal azotemia to renal failure requiring dialysis. Several mechanisms are implicated in acute tubular injury associated with leptospirosis. Hypotension and hypovolemia causing decreased renal blood flow are the common causes.[5,S1,S2] Rhabdomyolysis is a rare

complication of leptospirosis. It occurs when there is a hemodynamic alteration causing tissue hypoxia with high lysosomal enzymatic activity in the skeletal muscle tissue. Leptospiral surface protein is known to act as a toxin, which can directly damage muscle tissue with release of myoglobin, giving rise to rhabdomyolysis-induced acute tubular injury.[3,S2]

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

1. Hebert JF, Burfeind KG, Malinoski D, Hutchens MP. Molecular mechanisms of rhabdomyolysis induced kidney injury: from bench to bedside. *Kidney Int Rep*. 2023;8:17–29. https://doi.org/10.1016/j.ekir.2022.09.026
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Authors' Reply: Rhabdomyolysis-Induced Acute Kidney Injury in Austere Environments Highlights Need for Specific Treatment

The Author Replies: We would like to thank Drs. Govindan, Fernando, and Kurien for their interest in our review of the mechanisms and emerging therapies for rhabdomyolysis-induced acute kidney injury (RIAKI).[1] Rhabdomyolysis has multiple etiologies, including crush injury[S1], overexertion[S2], viral infection (including COVID-19)[S3,S4], or drug use[S5]; however, any injury resulting in the destruction of skeletal muscle can be an attributable cause of RIAKI. We agree with their assertion that venom from multiple animal species, including snakes and wasps, can cause rhabdomyolysis and subsequent acute kidney injury (AKI).[S6,S7] Because of the critical and urgent nature of the injury and frequency in austere medical environments such as rural areas, venom-induced RIAKI is an important etiology that should inform efforts to derive novel treatment.

The authors describe a 46-year-old male patient presenting with acute tubular injury secondary to leptospirosis infection, which has been previously linked to AKI in humans,[2] and RIAKI in a guinea pig model.[3] AKI associated with hypotension, was identified by elevated serum creatinine and renal biopsy before the etiology was confirmed. Tubular casts observed by immunohistochemistry and Masson's trichrome are cited as principal observations for the resultant RIAKI. Their finding of tubular epithelial injury in Figure 1 is very interesting because, as our review discusses, muscle metabolites released in the bloodstream are readily filtered by the glomerulus and enter the proximal tubule. Lining the tubule are megalin-expressing epithelial cells which endocytose myoglobin.[4,S8] Intracellularly, injury results from free iron-mediated production of reactive oxygen species.

This case of a reproductive-age male highlights essential facets of AKI care which may be