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On the Cover
What is the diagnosis?
A 40-year-old female without a history of diabetes presented with pallor, fatigue, vomiting, loss of appetite, and oliguria for the past 10 days. She denied any similar history in the past, and there were no systemic symptoms such as arthralgia, rash, hair loss, or sore throat. There was no history of spontaneous abortion. Blood pressure readings were within normal limits. Routine urine examination showed a bright red color, trace protein, and 2–3 RBCs/hpf. Serum creatinine was 8.3 mg/dL. Complete blood count revealed a hemoglobin of 8.4 gm/dL and total leucocyte count of 3800 cells/mm3, platelets 140 × 10^3/microL. Viral markers for hepatitis B and C, human immunodeficiency virus, as well as autoimmune serologies (such as antinuclear antibody and antinuclear cytoplasmic antibody) were negative.

Image Description:
Kidney biopsy was for diagnosis of AKI. Biopsy comprised 18 glomeruli and four arteries. Predominant findings were: tubules containing brownish coarse pigment alongside denudation of brush border indicative of AKI. These pigments were positively stained with Prussian blue stain for iron. Iron pigment was dominantly seen in proximal tubules over distal tubules. The interstitial space revealed subtle evidence of edema, however lacked inflammatory cells and fibrosis. The glomerular and arterial compartments were unremarkable. Direct immunofluorescence was negative with a panel of antisera (IgG, IgA, IgM, C3, C1q, Kappa & Lambda). These findings suggested intravascular hemolysis and led to a subsequent workup for red blood cell membrane defects. Coomb’s test and sickle test were negative. Testing for Malaria parasite was negative by card test. Flow cytometric evaluation revealed CD14-negative leucocytes and CD55-negative/CD59-negative population on red blood cells in 70% of the population.

Thus, testing confirmed paroxysmal nocturnal hemoglobinuria-induced secondary hemosiderosis causing acute tubular injury. Bone marrow examination showed normal representation of all hematopoietic elements with normal iron stores.

Teaching Points:
Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal disorder due to an intrinsic membrane defect. Stem cell mutation results in either partial or complete absence of cell membrane protein, glycosyl phosphatidylinositol (GPI)-anchored proteins. In view of the mutation found in PNH, there is reduced or absent expression of GPI-linked complement regulator molecules on all cells derived by bone marrow (such as CD55, CD59, and CD14). As a result, there is uncontrolled complement-mediated hemolysis and thrombosis. Kidney disease in PNH is mainly related to intravascular hemolysis, which may be due to direct tubular toxicity of heme released from hemoglobin. Kidney biopsy demonstrating brownish pigment in the proximal tubules, which stain for iron, should lead to a diagnostic workup for PNH. Supportive hemodialysis is recommended for managing kidney injury, along with iron supplements and steroids. The mainstay of therapy for PNH includes blockage of alternative complement pathways with drugs such as eculizumab, ravulizumab, and allogeneic hematopoietic stem cell transplantation. Outcome of kidney injury is based on the containment of ongoing hemolysis. Our patient was managed conservatively with temporary hemodialysis for 8 weeks. Serum creatinine had stabilized to 1.3 mg/dL at the end of 8 weeks.

(Images and text provided by Mahesh Vankalakunti, Manipal Hospital, Bengaluru, India; Manjunath Doshetty, Chirayu Hospital, Kalaburagi, India; and Venkatesh Moger, Karnataka Institute of Medical Sciences, Hubli, India)