

## **Image Quiz 9**

### **CLINICAL HISTORY:**

Previously healthy 23 year male, athlete by profession, presented with high grade fever associated with chills and rigor, myalgia, reduced urinary output, anorexia and vomiting since one week. No history of sore throat or joint pains. Reports intake of NSAID's briefly for myalgia, antipyretics for fever and a course of oral broad spectrum cephalosporin's over last one week. Not a known hypertensive or diabetic. No history of bleeding diathesis. On examination BP 160/94 mmHg, Anaemia +, No skin rash.

### **INVESTIGATIONS:**

Urine albumin 1+, RBC 8-10/hpf, WBC 6-8/hpf, Serum creatinine 4.5 mg% (397.8 micro mol/L)

Haemoglobin 7.5 g% (75g/L), TLC 11,600 mm<sup>3</sup> (71% polymorphs), platelets 1, 25,000/mm<sup>3</sup>, peripheral smear: RBC hypochromia, anisocytosis, polychromatophilia, schistocytes and several trophozoites of *Plasmodium falciparum* +.

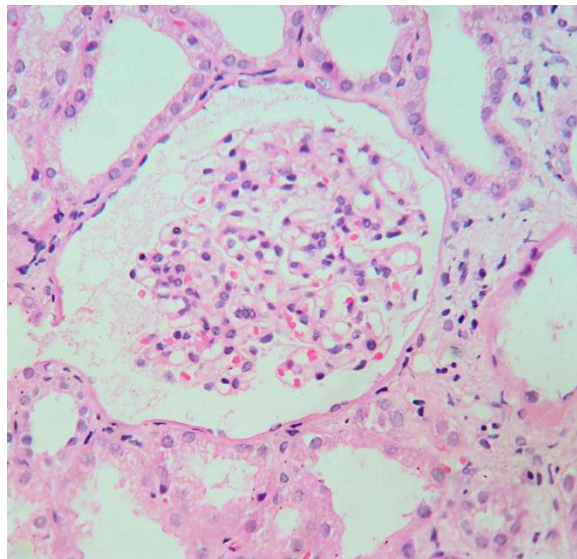
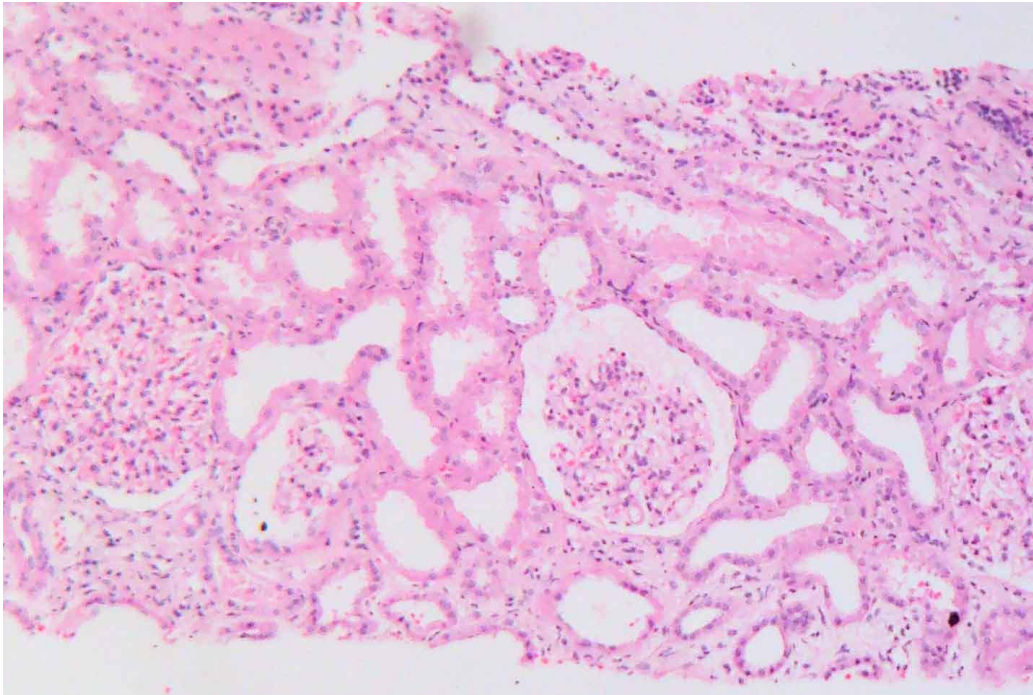
Serum LDH : 325 IU/L(range 0-250 U/L), C3 and C4 levels - within reference ranges, ANA & anti-ds DNA- negative, Viral markers (HCV, HBsAg, HIV)- negative.

### **CLINICAL IMPRESSION:**

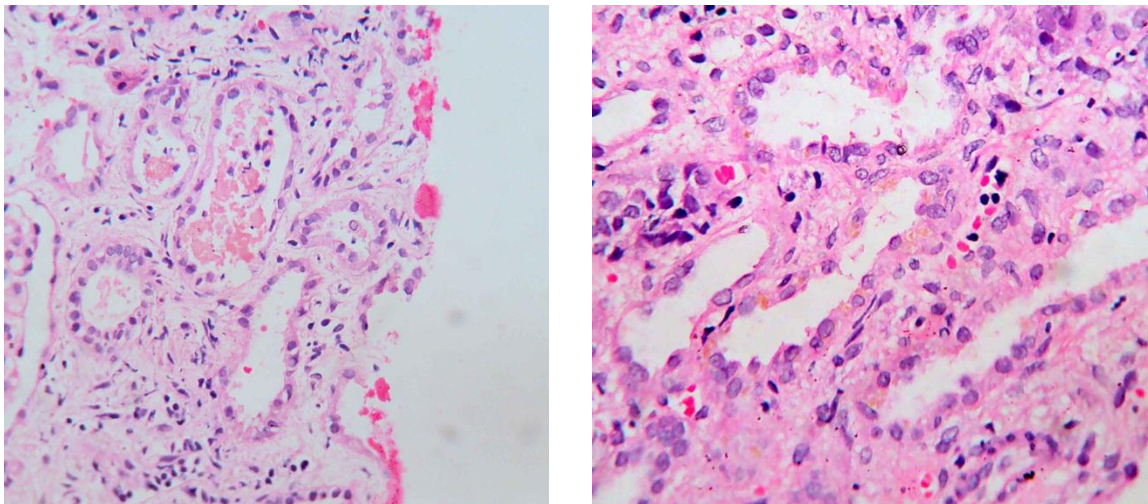
AKI secondary to? Acute tubular injury/? Acute tubulointerstitial nephritis /? HUS  
(thrombotic microangiopathy)

*A renal biopsy was performed to ascertain the cause of AKI. DIF studies were negative for IgA, IgG, IgM, C3, C1q and kappa & lambda light chains*

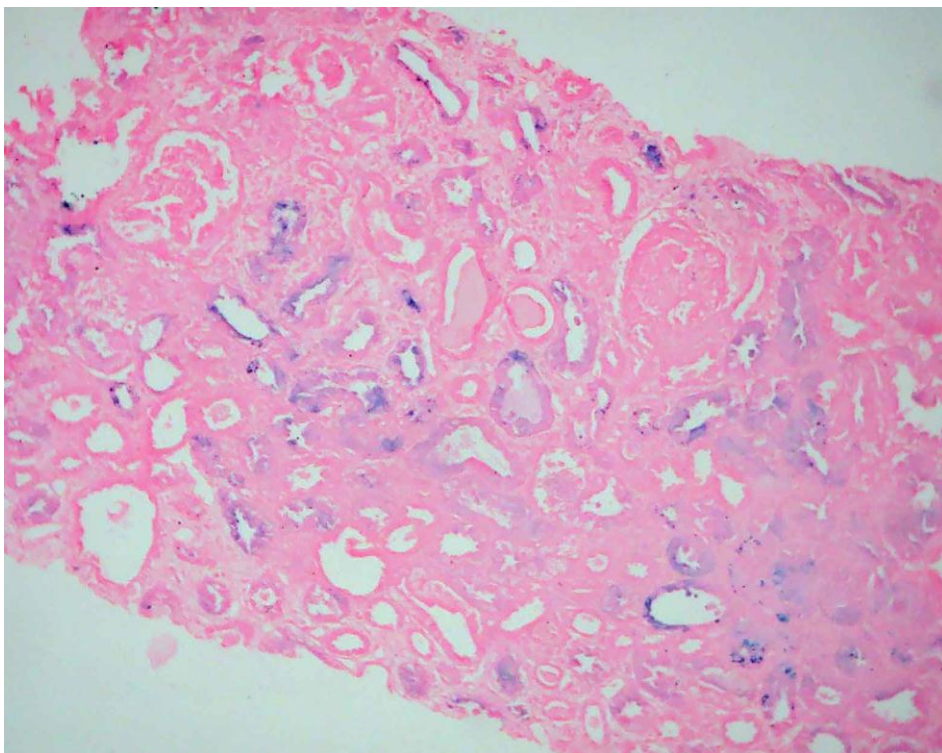
**MICROSCOPY:**



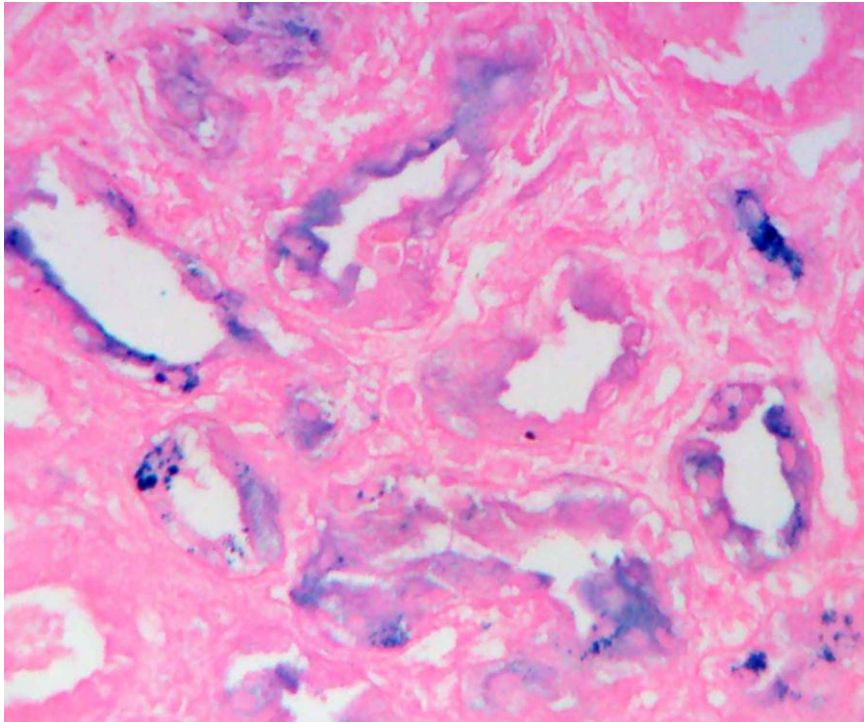
Low magnification photomicrograph from the biopsy shows features of acute tubular injury in the form of epithelial simplification and loss of brush borders. The glomeruli appear unremarkable. (Fig a &b)



Few injured tubules show granular and pigmented casts in lumina, accompanied by few sloughed tubular epithelial cells and polymorphs. Few tubules also revealed cytoplasmic granular golden – brown pigment. (Fig c & d)







Perls stain revealed widespread positivity in the tubular epithelial cell cytoplasm, indicating iron/hemosiderin deposition at these sites. (Fig e & f)

**FOLLOW UP:**

Bilirubin 2.8 mg%; indirect 2.1, Direct 0.7 mg%, SGOT & SGPT- within reference range,

Urine for hemoglobinuria: positive

Glucose 6 phosphate Dehydrogenase (G6PD) enzyme levels: Deficient (mild deficiency : 30% enzyme activity)

**DIAGNOSIS:**

Acute kidney injury (AKI) due to unmasking of G6PD deficiency by *P. falciparum* malarial infection leading to intravascular hemolysis, hemoglobinuria and heme pigment deposition in renal tubules (pigment nephropathy)

**DISCUSSION:**

Clinically, there are two major renal syndromes associated with malarial infection [1]:

(1) An immune complex mediated progressive glomerulopathy , most commonly, mesangiocapillary or membranoproliferative glomerulonephritis (MPGN) & mesangioproliferative glomerulonephritis, and less commonly other non-immune complex mediated forms including focal & segmental glomerular sclerosis (FSGS) and minimal change disease.[2] The MPGN pattern of injury is most often seen in African patients and classically complicates quartan malaria (caused by *Plasmodium malariae*)

(2) Acute Kidney Injury (AKI), with predominantly tubulointerstitial & vascular involvement and predominantly associated with *Plasmodium falciparum* malaria. This is more commonly seen in Southeast Asia, India, and sub-Saharan Africa.

Renal involvement in falciparum malaria can present as electrolyte abnormalities, abnormal urinary sediments, proteinuria, hematuria, liver dysfunction and jaundice (hyperbilirubinemia), hemolysis, etc. [3].

Malarial AKI is usually associated with oliguria and in severe cases may progress to anuria.

Non oliguric AKI is relatively uncommon. Pre-renal azotemia usually presents with clinical signs of severe dehydration; however, prolonged anuria or oliguria may lead to inevitable expansion of extracellular fluid volume because of diminished salt and water excretion.

Malarial AKI is catabolic in type and characterized by rapid rise of plasma urea and creatinine due to increased catabolism, presenting clinically as the syndrome of rapidly progressive renal failure (RPRF).[4]

Predisposing Factors for AKI in malaria include volume depletion, gastrointestinal bleed, sepsis, use of nephrotoxic drugs (aminoglycosides and NSAID), hyperbilirubinemia etc.

The association between renal failure and jaundice is a recurrent finding in studies on severe

malaria [5,6]. Other studies have also indicated that most patients of AKI with jaundice had conjugated hyperbilirubinemia with cholestasis which contributes to the reduction of GFR and development of ATN [7]. ARF associated with jaundice had high mortality in comparison to non-jaundiced ARF patients [8,9].

Precise mechanisms of renal failure in falciparum malaria are not clearly known. Several hypotheses including mechanical obstruction by infected erythrocytes, immune mediated glomerular pathology, fluid loss due to multiple mechanisms and alterations in the renal microcirculation etc. have been proposed [10-12].

While hemolysis (mainly extravascular) is a common feature in *P falciparum* infection; occurring in about 46% cases, acute kidney injury (AKI) is relatively uncommon and seen in only about 3% of patients [12]. In extravascular hemolysis, the parasitized red blood cells are destroyed by 'pitting' of the parasites from the red blood cells by macrophages in the spleen.[13] Following this, the erythrocytes are destroyed by various mechanisms including increased activity of macrophages in spleen and alterations of the red cell membrane caused by immune and non-immune mechanisms [14,15].

Intravascular hemolysis was earlier known as "black water fever". This occurs mostly in *P. falciparum* infection and the important factors involved in pathogenesis include the use of antimalarial drugs, particularly irregular ingestion of quinine; G6PD deficiency; and malarial fever [16-18].

The histologic picture in malaria associated AKI shows a variable mixture of acute tubular injury/ necrosis (ATN), interstitial nephritis, and glomerulonephritis. ATN is the most consistent histologic finding. Tubular changes include cloudy swelling, hemosiderin granular deposits and tubular lumina often contain haemoglobin casts. In cases with intravascular hemolysis and hemoglobinuria [19], the hemosiderin deposits in renal tubules can be demonstrated with the Perls iron reaction. The interstitium is usually edematous and the venules may show clumps of parasitized erythrocytes in cases with high parasite load [1].

## **REFERENCES**

1. Barsoum R: Malarial nephropathies. [\*Nephrol Dial Transplant\* 13: 1588–1597, 1998](#)
2. Doe JY, Funk M, Mengel M, Doehring E, Ehrich JH. Nephrotic syndrome in African children: lack of evidence for ‘tropical nephrotic syndrome’? [\*Nephrol Dial Transplant\* 2006; 21: 672–6.](#)
3. Maheshwari A, Singh AK, Sinha DK, Tripathi K, Prakash J. Spectrum of renal disease in malaria. *J Indian Med Assoc* 2004; 102: 143–6.
4. Das BS. Renal failure in malaria. [\*J Vector Borne Dis\* 2008; 45: 83–97](#)
5. Mukherjee AP, White JC, Lau KS. Falciparum malaria associated with jaundice, renal failure and anemia. [\*Trans R Soc Trop Med Hyg\* 1971; 65: 808–14.](#)
6. Marsh K. Malaria: a neglected disease. [\*Parasitology\* 1992; 104: S53–S69.](#)
7. Naqvi R, Ahmad E, Akhtar F, Naqvi A, Rizvi A. Outcome in severe acute renal failure associated with malaria. [\*Nephrol Dial Transplant\* 2003; 18: 1820–3.](#)

8. Pati SS, Mishra SK, Mohanty S, Patnaik JK, Das BS. Influence of renal impairment on plasma concentrations of conjugated bilirubin in cases of *Plasmodium falciparum* malaria. [Ann Trop Med Parasitol 2003; 97: 581–6.](#)
9. Burchard GD, Ehrhardt S, Mockenhaupt FP, Mathieu A, Agana-Nsiire P, Anemana SD, et al. Renal dysfunction in children with uncomplicated *Plasmodium falciparum* malaria in Tamale, Ghana. [Ann Trop Med Parasitol 2003; 97: 345–50.](#)
10. Eiam-Ong S, Sitprija V. Falciparum malaria and the kidney: a model of inflammation. [Am J Kidney Dis 1998; 32: 361–75.](#)
11. Sitprija V. Nephropathy in falciparum malaria. [Kidney Int 1988; 34: 867–77.](#)
12. Barsoum R. Malarial Acute Renal Failure. [J Am Soc Nephrol 2000; 11: 2147–2154](#)
13. Schnitzer B, Sodeman T, Mead M, Contacos P. Pitting function of the spleen in malaria. Ultrastructural observations. [Science 1972;177:175-7.](#)
14. Looareesuwan S, Ho M, Wattanagoon Y, et al. Dynamic alteration in splenic function during falciparum malaria. [N Engl J Med 1987; 317:657-9.](#)
15. Mohan K, Dubey ML, Ganguly NK, Mahajan RC. Plasmodium falciparum role of activated blood monocytes in erythrocyte membrane damage and red cell loss during malaria. [Exp Parasitol 1995;80:54-63.](#)
16. Reeve P, Toaliu H, Kaneko A, et al. Acute intravascular hemolysis in Vanuatu following a single dose of primaquine in individuals with G6PD deficiency. [J Trop Med Hyg 1992;95:349-54.](#)



17. Sarkar S, Prakash D, Marwaha R, et al. Acute intravascular hemolysis in G6PD deficiency.

[Ann Trop Pediatr 1993; 13:391-4.](#)

18. Hong chau TT, Day NPJ, Chuong LV, et al. Black water fever in southern Vietnam: a

prospective descriptive study of 50 cases. [Clin Infectious Dis 1996;23:1274-81.](#)

19. Ajetunmobi WA, Adebola OE, Brown BJ et. al. Haemoglobinuria among children with

severe malaria attending tertiary care in Ibadan, Nigeria. [Malaria Journal 2012, 11:336](#)