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Original Article

Novel presentation of *Plasmodium vivax* malaria with acute kidney injury and hemolytic uremic syndrome

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ABSTRACT

Background: In India, epidemiologically, *Plasmodium vivax* predominates over *Plasmodium falciparum* malaria, and this produces a major public health problem due to the recent increase in severe vivax malaria. Malaria-related renal failure is usually ascribed to acute tubular necrosis (ATN) and interstitial nephritis, and rarely to cortical necrosis. Clinical features of hemolytic uremic syndrome (HUS) and thrombotic microangiopathy (TMA) on renal histology have not been described conclusively in relation to malaria.

Methods: This prospective observational study includes patients of vivax malaria with renal failure admitted to a tertiary care hospital during November 2011 to April 2012 with features of HUS (anemia, thrombocytopenia, and acute kidney injury). The diagnosis of *P. vivax* malaria monoinfection was established with detection of parasite in peripheral smear and malaria card test. Renal biopsies were performed after three weeks for nonrecovering renal failure and evaluated with light and immune-fluorescence microscopy.

Results: Five patients (2 males and 3 females) had clinical constellation of HUS associated with vivax malaria. All the patients required dialysis [1 peritoneal dialysis and 4 hemodialysis (HD)]. Renal biopsy performed in all the patients showed characteristic features of TMA like mucointimal proliferation, subintimal fibrin deposits with luminal thrombi along with ATN, and cortical necrosis. Three patients were dependent on dialysis [1 continuous ambulatory peritoneal dialysis (CAPD) and 2 HD]. The rest of the two patients had partial recovery at the end of 3 months. The patient on CAPD died due to pneumonia-related sepsis.

Conclusion: Clinical association of vivax malaria with TMA leading to HUS is novel and suggests parasite-related severe endothelial injury. Future studies are needed to demonstrate interaction of parasite with endothelium and factors related to it.

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1. Background

According to the World Malaria Report 2011, *Plasmodium vivax* (*P. vivax*) accounts for up to 50% cases of malaria in south-east Asia and the unique epidemiology of malaria in India includes predominance of *P. vivax* over *Plasmodium falciparum* (*P. falciparum*).[1–4] *P. falciparum* is well recognized for its disastrous complications and disease course with renal failure and multi-organ failure leading to significant mortality, and represents the usual cause of severe malaria.[5–7] Although vivax malaria was formerly described as "benign tertian malaria," many recent reports described its deadlier image in the form of complications like cerebral malaria, acute kidney injury (AKI), severe anemia, acute respiratory distress syndrome, shock, abnormal bleeding, and multiorgan dysfunction.[8–11] With such background of significant morbidity and mortality related to vivax malaria, some authors raised questions about the "benign" nature of it.[12,13] This emergence of clinical severity and chloroquine resistance are the

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major factors leading to increasing burden of vivax malaria and represent a global health menace, which needs focused efforts for its resolution. Though *P. falciparum* related AKI has been attributed to volume depletion, sepsis, and intravascular hemolysis leading to acute tubular necrosis (ATN)/cortical necrosis,[4,14] mechanism and management strategy of *P. vivax* related AKI is largely unclear. The coexistence of thrombotic microangiopathy (TMA) with vivax malaria has occasionally being reported in the literature,[15,16] but the exact association of vivax malarial infection with TMA leading to hemolytic uremic syndrome (HUS) has not been established. This scarcity of data prompted us to review cases of AKI associated with vivax malaria and having renal histological features of TMA to find out possible mechanisms. The present case series describes five cases of vivax malaria that presented within short period with AKI along with features of TMA on renal histology.

2. Material and methods

We have prospectively followed cases of vivax malaria with AKI admitted to our hospital during November 2013 to August 2015 to describe the clinical characteristics, laboratory parameters, and outcomes at the end of 3 months. The vivax malaria monoinfection was diagnosed on the basis of direct visualization of various forms of parasite in a peripheral blood smear and also by rapid diagnostic test [negative PfHRP-II assay of *P. falciparum* and positive *P. vivax* specific lactate dehydrogenase (LDH)]. Other causes of fever and AKI (enteric fever, leptospirosis, typhus fever, urinary tract infection sepsis, and dengue fever) were ruled out by clinical history and relevant additional investigations. Additional investigations included complement levels (C3/C4), LDH, tests for antinuclear antibody (ANA), antidouble-stranded DNA (ds-DNA), antineutrophil cytoplasmic antibody (c-ANCA/p-ANCA), antiglomerular basement membrane antibody, Coomb's test, and C-reactive protein along with renal ultrasound. The patients were treated with IV artesunate (2.4 mg/kg stat followed by 2.4 mg/kg at 12 and 24 h and then daily for 7 days), doxycycline (3 mg/kg for 7 days) in adults, and clindamycin (20 mg/kg/day in three divided doses) in children. Till the exclusion of bacterial infection (e.g. *Salmonella*), the patients were given intravenous ceftriaxone 1 gm twice daily. AKI was considered if serum creatinine was >3 mg/dL and urine output was <400 mL/24 h with normal kidney size as per ultrasonography. Renal replacement therapy (RRT) in the form of intermittent hemodialysis (HD) or peritoneal dialysis (PD) was initiated for uremic symptoms, azotemia with metabolic acidosis, fluid overload, and hyperkalemia. RRT continued until the patient's renal function improved (increase in urine output or progressive decrease in creatinine). We considered renal biopsy in patients requiring RRT for longer than three weeks and not showing any improvement in urine output. The renal tissue was sent for standard light and immunofluorescence (IF) microscopic evaluation. The tissue sections were stained with hematoxylin and eosin (H&E), periodic acid Schiff (PAS), Gomori's trichrome, and Jones methenamine silver. IF microscopy was done with antibodies to C3, IgM, IgG, IgA, and C1q.

3. Results

Five patients who had vivax malaria associated AKI due to biopsy proven TMA are discussed here. The age of patients varies between 9 and 24 years. All the patients had history of fever, oliguria, and pedal edema. Jaundice was observed in two patients. One patient (patient 2) had generalized seizures related to electrolyte imbalance. Peripheral smear was showing parasitic forms of vivax in all the cases (trophozoites in four patients and schizonts in one case), of which three cases were referred from elsewhere with positive smear. All the patients had evidence of hemolysis in the form of schistocytes on the peripheral smear. None of the patients had hypotension and evidence of sepsis.

As observed from Table 1, all the five patients had significant anemia, thrombocytopenia, and renal failure along with raised LDH suggestive of active hemolysis. The median level of hemoglobin was of 7.9 g/dL (range 6.7–8.4 g/dL), platelet count of 24,000/mm^3 (16,000–93,000/mm^3), serum creatinine of 6.4 mg/dL (range 4.5–9.2 mg/dL), and LDH of 1450 U/l (range of 1136–2838 U/l). All the patients had microscopic hematuria with dipstick positive proteinuria up to 3+. Other investigations, including coagulation assays (prothrombin time, partial thromboplastin time), complement levels, antibodies like ANA, ds-DNA, ANCA, anticardiolipin antibodies, and Coomb's test were negative. Blood culture, Widal test, IgM antibody to dengue, and leptospirosis were inconclusive. Chest X-ray and renal ultrasound were unremarkable.

Renal histological changes are shown in Table 2 and photomicrographs of patients 4 and 5 are shown in Figs. 1 and 2. Renal biopsy was done with median interval of 28 days (range 22–30 days). All the needle core biopsy samples were adequate. In two

Table 1
Laboratory parameters on initial evaluation.

Patient no.	Age (years)/sex	Urine (protein; RBCs/hpf)	Hb (g/dL)	TLC (cells/mm^3)	Platelets (cells/mm^3)	Urea (mg/dL)	Creatinine (mg/dL)	LDH (U/l)
1	13/M	1+, 8–10	6.7	9700	23,000	118	5.6	1450
2	9/F	1+, 5–6	7.9	11,400	24,000	96	4.5	1145
3	16/M	2+, 10–15	7.2	9670	16,000	176	6.4	1660
4	20/F	3+, 10–15	8.2	8400	53,000	185	7.3	2838
5	24/F	1+, 5–6	8.4	11,200	93,000	214	9.2	1136

TLC, total leukocyte count; LDH, lactate dehydrogenase.

Table 2
Renal histopathological changes and outcome.

Patient no.	Renal histology			Outcome
	Glomeruli/tubules	Arteries and arterioles	IF microscopy	
1	Mild ATN	Mucointimal proliferation, subintimal fibrin deposits	Negative	Maintenance HD
2	Mild ATN	Subintimal fibrin deposits with luminal thrombi	Negative	CAPD/expired
3	Mild ATN	Mucointimal proliferation, luminal narrowing	Negative	Partial recovery (creatinine-2.2)
4	PCN	Mucointimal proliferation, subintimal fibrin deposits, organizing thrombi	Negative	Partial recovery (creatinine-3.0)
5	PCN	Subintimal fibrin deposits, endothelial swelling	Negative	Maintenance HD

IF, immunofluorescence; ATN, acute tubular necrosis; PCN, patchy cortical necrosis; HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis.

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