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Acute Kidney Injury and Pancytopenia, A Rare Case Presentation of Vivax Malaria

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Abstract

Plasmodium vivax malaria is a common cause of fever in malaria-endemic country like India. Acute kidney injury and Pancytopenia both are recognized in complicated falciparum malaria but rarely found in vivax malaria.

We present a case of vivax malaria having pancytopenia in complete blood count and progressive rise of serum creatinine. After confirmation of plasmodium vivax trophozoites in blood smear, he was given a standard dose of chloroquine and primaquine. After 3 days the patient was afebrile and cytopenia and kidney function started improving. At day seven pancytopenia resolved and serum creatinine normalized. The patient was discharged from the hospital. Though rare, vivax malaria should be included in the differential diagnosis of patients having fever, pancytopenia, and acute kidney injury, especially in a malaria-endemic region.

Keywords: vivax malaria; acute kidney injury; pancytopenia

Case Description

A 43 years old male patient was admitted to the general ward with a history of intermittent fever with chill and rigor for the last 7 days. He was initially treated by his GP with paracetamol SOS for fever. He started feeling dizzy and nausea with a decrease in urine output despite taking adequate fluid. He has no history of cough, expectoration, rash, joint pain, weight loss, bleeding gum, bleeding per rectum. His bowel and bladder habits are normal. Neither he had any significant past medical history, nor he was taking any medicines on a regular basis. His home temperature chart shows a twice-daily spike of fever without any diurnal variation, the maximum recorded temperature being 102 °F. On examination, he had a fever, pallor without any icterus, and mild splenomegaly. No neck rigidity could be demonstrated. Other systemic examination reveals no abnormality. After sending blood for culture – aerobic Bactec, CBC, LFT, Urea and creatinine, malarial parasite, malaria antigen, IgM dengue antibody, IgM typhoid antibody, he was put on intravenous fluid and paracetamol SOS. Urine was collected and sent for routine and culture. The chest X-ray was normal, and the ultrasonography of the abdomen revealed splenomegaly. The patient was adequately hydrated as no collapse of the inferior vena cava demonstrated in bedside ultrasonography. After six hours of admission in the hospital, his urine output started to decline. Initial laboratory reports suggest Haemoglobin - 8.7 g %, Total WBC count – 3000/cc, platelet count – 1.1 lac/cc, serum urea - 28 mg/dl, serum creatinine - 0.87 mg/dl, LFT with GGT – normal. Peripheral thick and thin blood smear revealed schizont and trophozoite ofplasmodium vivax **(Figures 1 and 2).** The pathologist's comment on peripheral smear suggests anemia to be normocytic and normochromic (MCV - 86 fl, MCH - 27 pg, MCHC - 30.6 gm/dl). Blood for malaria antigen- positive for vivax, negative for falciparum. IgM dengue and typhoid antibody were negative. Urine routine examination shows pus cells 1- 2/hpf, no RBC, no cast, no protein. The patient was given tablet chloroquine 600 mg on day 1,600 mg on day 2 and 300 mg on day 3. Tablet primaquine started at a dose of 15 mg daily from the next day after getting normal blood for the G6PD result. The patient was hemodynamically stable and did not complain of nausea and vomiting. But his urine output was at the range of 15-20 ml/hour. The total urine output on day 1 was 380 ml. The possibility of co-existent sepsis was considered because the initial C-reactive protein was 136 mg/dl (Normal up to 6 mg/dl). But initial blood culture and urine culture did not show any growth of bacteria. Blood for LDH and haptoglobin – normal, reticulocyte count was 1.5 %. Serum vitamin B12 & folate level – normal. Blood for serum ferritin and fibrinogen was normal and there was no schistocyte in a peripheral blood smear. On day 2 the patient was febrile, but the range of temperature was gradually declining. His urine output showed marginal improvement to 600 ml in the last 24 hours. But the serum creatinine level increased to 1.7 mg/dl though serum urea decreased to 24 mg/dl. Clinically there were no signs of uremia like a pericardial rub. Fractional excretion of sodium in urine was calculated and found to be 1.4 suggestive of an intrinsic renal cause of acute kidney injury. On day 3, he had one episode of fever and his urine output started to rise, total 860 ml in the last 24 hours. Foley's catheter was removed. His total intake was maintained as previous days output plus 500ml.On day 3 serum creatinine was 1.6 mg/dl. He was

completely afebrile from day 4 onwards. His hemoglobin level, total leucocyte count and platelet count has started to improve from day 4 onwards. His final report of blood and urine culture did not reveal any growth. He was discharged on day 7 after satisfactory improvement of the haematological and renal profile. Serial laboratory parameters were shown in the following **table 1**.

Table 1: Laboratory parameters during hospital stay

Parameters	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Total leucocyte count per microliter	3000	3200	3600	3800	4200	4400	4800
Differential count	N57 %, L38 %, M3 %, E2 %	N64 %, L32 %, M2 %, E2 %	N62 %, L34 %, E2 %, M2 %	N60 %, L36 %, M3 %, E1 %	N60 %, L36 %, E2 %, M2 %	N64 %, L33 %, E2 %, M1 %	N64 %, L30 %, E2 %, M3 %
Platelet count in lac per microliter	1.1	1.2	1.2	1.4	1.4	1.5	1.6
Hemoglobin (gm %)	8.7	8.8	8.9	9.2	9.2	9.2	9.4
Serum urea (mg/dl)	28	24	25	26	26	25	24
Serum creatinine (mg/dl)	0.87	1.7	1.6	1.5	1.4	1.4	1.2
Serum sodium (mmol/l)	130	133	132	138	140	136	138
Serum potassium (mmol/l)	4.2	4.8	4.5	4.6	4.8	4.6	4.3

N - neutrophil, L - lymphocyte, M - monocyte, E - eosinophil

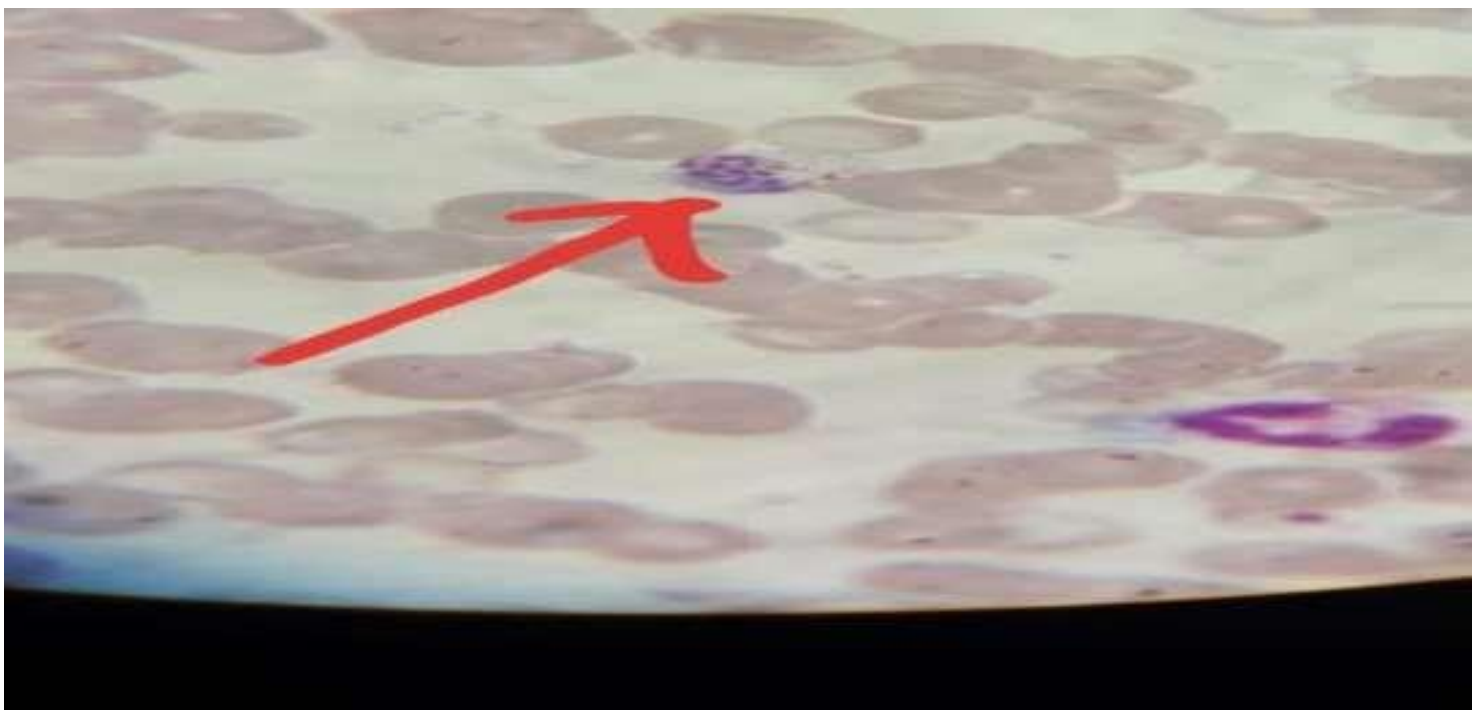

Figure 1: Schizont form of plasmodium vivax

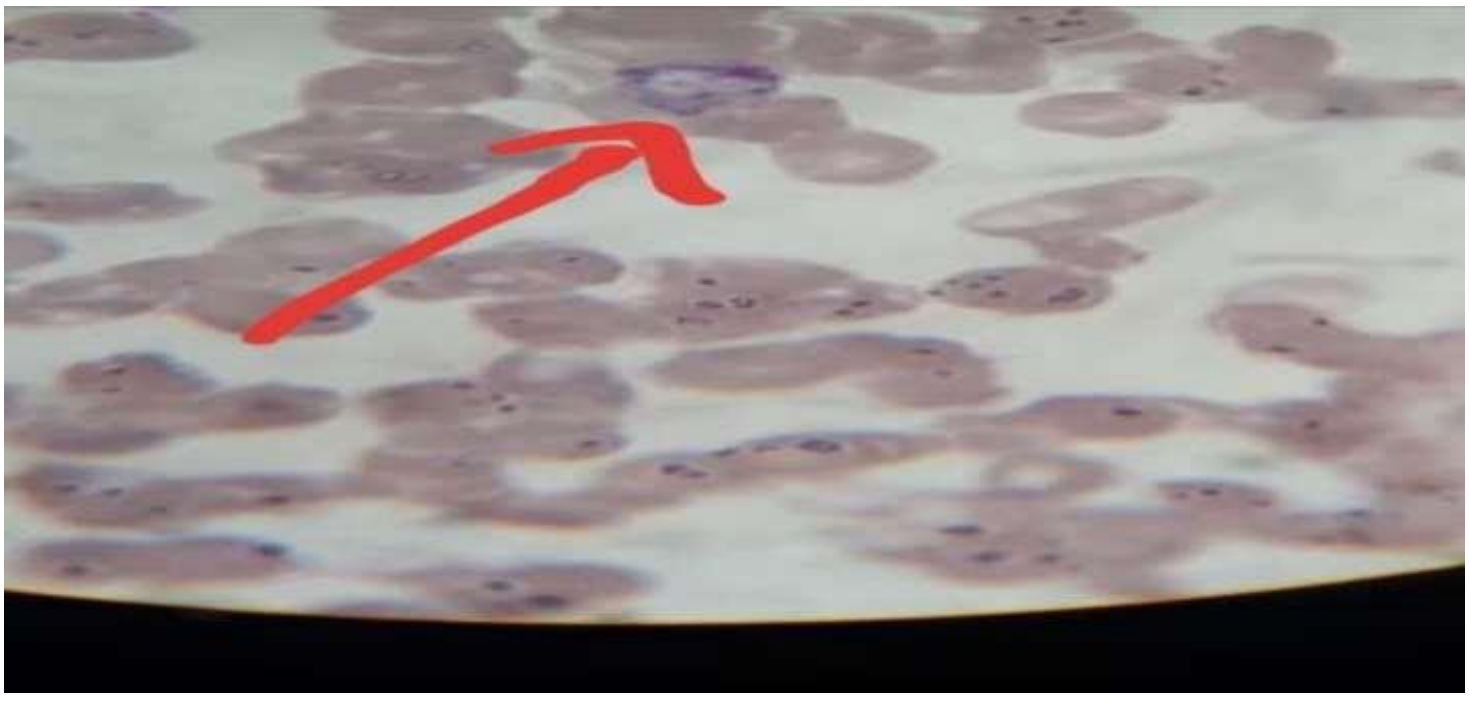

Figure 2: Trophozoite form of plasmodium vivax

Discussion

P. Vivax is the most widely distributed human malaria, with a global burden of 70 - 80 million new cases every year **[1].** Severe infection, as recognized with multi-organ involvement, with P. Vivax has been reported by *Kochar et al.* **[2]** It has been observed that in comparison to falciparum, vivax has a lower pyrogenic threshold, more pronounced inflammatory response, and higher cytokine production **[3].** Traditionally, thought to be a benign agent with a low fatality, P. vivax can also cause severe diseases like P. falciparum. Multiple studies have shown that vivax malaria can be complicated by thrombocytopenia, severe anemia, renal involvement, and ARDS **[4,5].** Approximately 10 % - 20 % of malaria-related AKI has been linked to infection with P. vivax **[2,4,5]** Symptomatology from Vivax malarial AKI reported from different centers share many symptoms in common. The decline in urine output has been reported from 47 % to 84 % **[6,7]** Cerebral involvement, which varies in reports from altered sensorium to coma, has been reported from 36 % to 58 % **[6,7].** Hyponatremia is a typical biochemical finding, being reported in up to 15.8 % of cases with severe Vivax malaria **[6].** Hyperbilirubinemia is a common finding of vivax malaria and mostly due to hemolysis. Hyperkalaemia is a striking feature, and often fatal with its cardiac arrhythmia's complication. It is attributed to hemolysis and acidosis, particularly in the setting of renal failure **[6].** The whole spectrum of morphological changes on renal histology has been reported in malarial nephropathy, acute tubular necrosis resulting from hemodynamic changes, acute interstitial nephritis refractory to tubular injury, or resulting from acute inflammatory response, then glomerular changes as part of the acute post-infectious process or indicating immune-mediated changes. These are well described in previously published review articles **[8,9].**

Mortality in cases with vivax malaria and AKI has been reported from 11 to 16 % **[2,6,10].** Prolonged disease duration, low hemoglobin counts, oliguria or anuria on admission, hyponatremia, hypotension, metabolic acidosis, acute respiratory distress syndrome were the more predictors of mortality. Haemodialysis is an effective treatment for malarial AKI. Early referral of malarial AKI patients to dialysis facility units and early institution of hemodialysis in complicated *P.vivax* malaria may further reduce mortality and enhance recovery of kidney functions. Anuria, refractory metabolic acidosis, refractory Hyperkalaemia, rising trend of serum creatinine, uremic encephalopathy, and uremic pericarditis are indications for renal replacement therapy **[11].** In our case, because of early diagnosisand prompt treatment, the patient recovered spontaneously without renal replacement therapy.

Pancytopenia- It is a rare complication of vivax malaria. There are several mechanisms including microangiopathic hemolytic anemia, hemophagocytic syndrome **[12]** hypoplasia of bone marrow **[13].** Hemophagocytic syndrome (HPS) starts because of inappropriate or excessive immunologic responses of T cells. In HPS, high levels of IFN-gamma, soluble IL - 2 receptors, TNF - a IL-1, and IL - 6 have been demonstrated, suggesting that elaboration of activating cytokines by T helper cells promotes activation of macrophages in this disease. These cytokines depress the proliferation of progenitor cells, which aggravate the pancytopenia because of phagocytosis of the blood cell **[12]**. Wickramasinghe and colleagues proposed that P. vivax has a direct toxic effect on erythroblasts or their precursors **[13]**. Alternatively, P. vivax may exert its effect on bone marrow macrophages leading to increased phagocytic activity and/or release of locally cytotoxic molecules damaging surrounding hematopoietic cells **[13]**. Whatever the cause, some degree of impaired erythropoiesis has been shown to persist for at least two weeks after treatment of vivax malaria and therefore the effects of these putative factors must be long-lasting **[13]**.

The bone marrow in P. vivax malaria is also characterized by dyserythropoietic, increased macrophages (some showing hemophagocytosis), increased plasma cells, and sometimes increased eosinophils. In hyper-reactive malarial splenomegaly, there may be a marked increase in bone marrow lymphocytes **[14]**.

Conclusion

Benign tertian malaria caused by plasmodium vivax is a common cause of fever in malaria-endemic regions. Though it is less virulent than falciparum malaria, the course of the disease may not be entirely benign. It has a diverse clinic-pathological presentation like fever, anemia, jaundice, hepato-splenomegaly. Acute kidney injury and pancytopenia may happen as a rare manifestation of vivax malaria, which is reversible with prompt antimalarial therapy.

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