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Malaria Causing Cardiomyopathy and Thrombotic Microangiopathy: A Rare Association

CASE REPORT

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ABSTRACT

We report a case of dual comorbidities of thrombotic microangiopathy (TMA) and cardiomyopathy associated with Plasmodium vivax malaria. A 20-year-old girl presented with worsening anemia, persistent thrombocytopenia, acute kidney injury, and sinus bradycardia with ST–T changes. Hemolytic uremic syndrome was diagnosed based on schistocytes on peripheral blood film, increased serum lactate dehydrogenase, and elevated reticulocyte production index. Kidney biopsy revealed TMA. Echocardiography initially revealed dilated cardiomyopathy with low ejection fraction that improved to normal on follow-up. The patient was kept on maintenance hemodialysis during acute illness, and later she became dialysis dependent. She has now been advised for renal transplantation.

Keywords: *Plasmodium vivax* malaria, thrombotic microangiopathy, cardiomyopathy

INTRODUCTION

Complicated malaria is usually associated with *Plasmodium falciparum*, whereas *Plasmodium vivax* infection is usually considered as benign. However, it is increasingly being reported as a cause of severe malaria, and its association with acute kidney injury (AKI) has been observed (1, 2). Thrombotic microangiopathy (TMA) is usually hereditary and due to acquired causes that lead to severe a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) deficiency. TMA as a complication of malaria, although described in the literature, is a rare manifestation of *P. vivax* infection. It has been exclusively described in children (3). Similarly, myocarditis due to *P. vivax* is extremely rare, limited to only few case reports (4). We report a case of non-recovering intrinsic renal failure secondary to TMA in glomerular vessels associated with dilated cardiomyopathy in a young female due to *P. vivax* malaria. Her AKI progressed to chronic kidney disease (CKD), and later she became dialysis dependent. However, there was spontaneous improvement in cardiomyopathy.

CASE REPORT

A 20-year-old previously asymptomatic girl presented in the emergency department with complaints of high-grade fever with chills and rigors for 1 week and anuria for 1 day. Fever was of tertian pattern without any rash but associated with nausea and vomiting. After 1 day, she also developed generalized body swelling and shortness of breath. She had normal blood pressure (110/80 mm Hg), tachycardia (pulse rate 104 beats/min), tachypnea (respiratory rate 32 breaths/min) with normal saturation (SpO_2 97% on room temp of 29°C air), pallor, and bilateral pitting pedal edema. Systemic examination was normal. Complete blood count revealed anemia (hemoglobin 9.9 g/dL), thrombocytopenia (platelet count 20,000) with microcytic hypochromic picture, and schistocytes on peripheral blood film. Rapid card test for malaria was positive with *P. vivax* seen on smear examination. Dengue serology and viral markers were negative. Kidney function tests showed AKI (blood urea 60 mg/dL and serum creatinine 1.7 mg/dL). Hemoglobin progressively decreased to 6.8 g/dl in 1 week; however, platelets increased to normal. There was a constant increase in blood urea (162 mg/dL) and serum creatinine (8.1 mg/dL) with blood urea nitrogen and serum creatinine ratio (BUN: S.cr.) <20:1 suggestive of some intrinsic cause of AKI. In liver function tests, there were transaminitis (aspartate transaminase 254 U/l and alanine transaminase 393 U/l), indirect hyperbilirubinemia (total bilirubin 2.8 mg/dL and indirect bilirubin 0.9 mg/dL), and deranged international normalized ratio (1.62), which normalized over the next 1 week. Urine examination showed albuminuria with total proteins of 894 mg/dL (normal <300 mg/dL). Lactate dehydrogenase was 1052 U/l (normal 140-280 U/l), and reticulocyte production index was 2.8% (normal 0.5%-1.5%); therefore, both were high, whereas serum haptoglobins were very low (9 mg/dL, normal 30-200 mg/dL). Blood gas analysis revealed metabolic acidosis (pH 7.29, bicarbonates 15.6 mmol/l). Ultrasonography (USG) of the abdomen

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showed the presence of 2+ free fluid, without any organomegaly. Chest X-ray (Figure 1) and USG of the thorax showed bilateral pleural effusion. After 1 day of admission, electrocardiography (ECG) (Figure 2) had features of myocarditis in the form of sinus bradycardia, and creatine kinase-MB was increased (213 U/l, normal 25 U/l) then returned to normal after 3 days. Echocardiography (ECHO) revealed severe global hypokinesia of the left ventricle and dilated cardiomyopathy with ejection fraction of 25%. Serum IgM for typhidot, leptospira, and scrub typhus was negative. Stool complete examination was normal, and stool culture was sterile. Serum procalcitonin was increased (95.63 ng/mL, normal <0.5 ng/mL), but no growth was observed in blood cultures. Erythrocyte sedimentation rate (50 mm/h) and C-reactive protein (50.2 mg/dL, normal <5 mg/dL) were increased. Antinuclear antibodies by immunofluorescence assay were negative; extractable nuclear antigen profile was non-contributory. Direct Coombs test and serum IgA tissue transglutaminase were negative, and thyroid profile was within normal limits. Antiphospholipid antibody profile was also normal. Complement profile initially revealed normal C4 and low C3 and CH50 (C3 84.1 mg/dL, normal 90-180 mg/dL and CH50 32%, normal 70%-130%). Later, C3 and C4 returned to normal. There was no hypertension, and magnetic resonance angiography of renal vessels was also normal. The patient was kept in the intensive care unit with a working diagnosis of complicated malaria. Treatment included intravenous artesunate, broad spectrum antibiotics, antipyretics, and diuretics. In view of progressive and non-resolving AKI with metabolic acidosis and symptoms of uremia and fluid overload, hemodialysis was initiated and continued every 24 h for the next few weeks. Fever gradually improved, but uremia, fluid overload, and other biochemical derangements persisted. The patient refused plasmapheresis and was maintained on hemodialysis twice per week. She was discharged on oral diuretics and hematinics with regular follow-up. After 1 month, on repeat investigations, all biochemical parameters were similar to previous reports except that serum calcium was decreased (6.4 mg/dL, normal 8.5–10.4 mg/dL) and serum phosphorus was increased (5.6 mg/dL, normal 2.5-4.5 mg/dL). Vitamin D was low (10.73 ng/mL, normal 20-100 ng/mL), and intact parathyroid hormone was high (125 pg/mL, normal 10–65 pg/mL). Chest X-ray showed left ventricular type cardiomegaly (Figure 1), and ECG revealed left axis deviation with left ventricular hypertrophy (Figure 2). Fundus was normal. ECHO showed an ejection fraction of 40%. USG abdomen showed normal kidney size with maintained corticomedullary differentiation, and renal biopsy (Figure 3) was performed, revealing acute cortical necrosis with TMA and tubular necrosis with mild chronic interstitial activity. No immune deposits were seen on immunofluorescence study. Plasmapheresis was advised for treatment, but the patient refused. On the following months, repeat USG revealed a decreased kidney size (right kidney 7.8×2.2×2.1 cm and left kidney 8.7×2×1.9 cm). She had become hypertensive, though her left ventricular ejection fraction improved to 57% on repeat ECHO. On the next follow-up, renal transplantation was presented as an option to the patient.

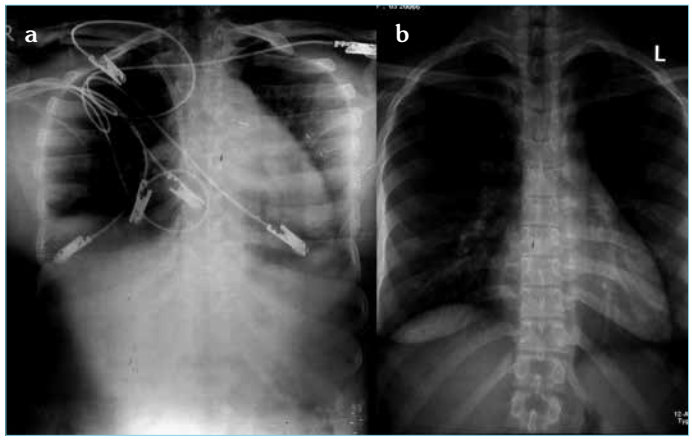

Figure 1. a, b. Chest X-Ray of patient.

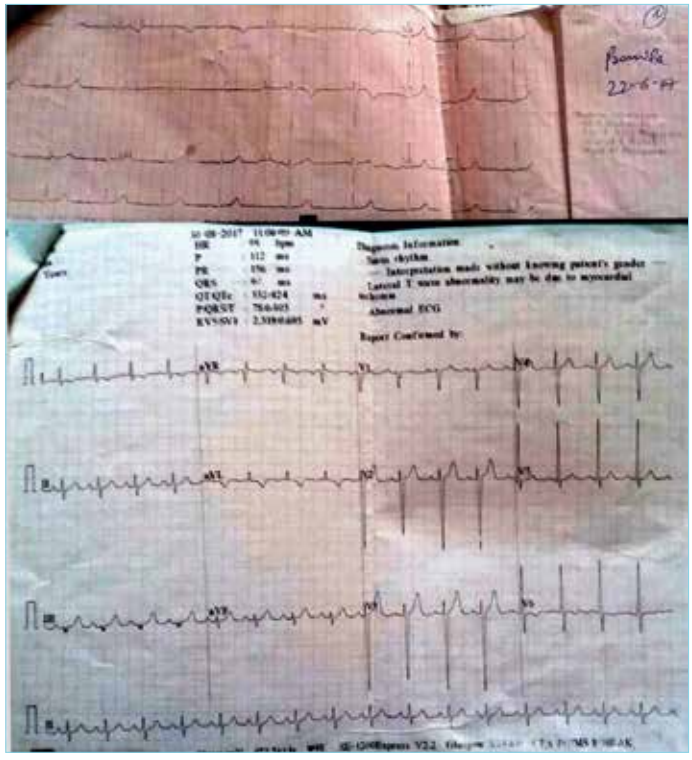

Figure 2. ECG of patient.

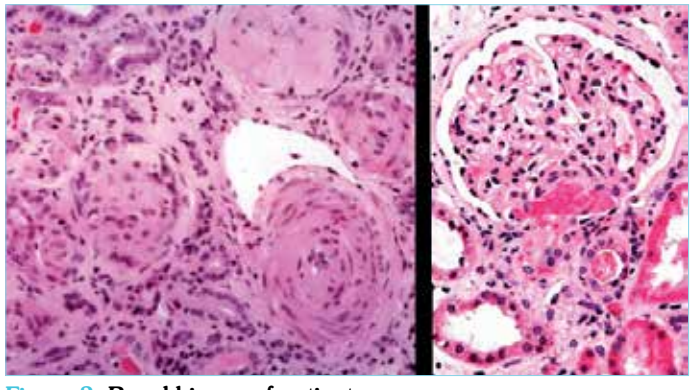

Figure 3. Renal biopsy of patient.

DISCUSSION

P. falciparum is a known cause of severe malaria, but now, *P. vivax* malaria is increasingly being diagnosed in cases of severe disease, especially causing AKI (5). The etiologies of AKI are categorized as prerenal (decreased renal perfusion), intrinsic renal (pathology affecting vessels, glomeruli, tubules, or interstitium),

and post-renal (obstruction of urinary flow). TMA-hemolytic uremic syndrome (TMA-HUS) and renal cortical necrosis are the most important intrinsic causes of AKI associated with *P. falciparum* and *P. vivax*. Though the pathogenic mechanism is well described for *P. falciparum* malaria, it is still unanswered in the case of *P. vivax* malaria. Hemolysis, disseminated intravascular coagulation, and sepsis may play important roles in the pathogenesis. Endothelial dysfunction, which is known to occur in *P. falciparum* malaria, may play a role in AKI seen with *P. vivax* malaria. de Mast et al. (6) in their study of patients with malaria observed reduced levels of ADAMTS13 activity and antigen in both *P. falciparum* and *P. vivax* malaria infections with the presence of unusually large von Willebrand factor polymers in the plasma causing platelet aggregation (7). These prothrombotic polymers may also be a reason of TMA in our case. Antimalarial drugs, such as quinidine and mefloquine, can cause TMA in malaria, but the girl had no history of intake of any of these drugs (8). Low C3 and normal C4 were suggestive of the activation of alternate complement pathway; however, malaria triggering it is not yet reported. Low CH50 was suggestive of classic complement pathway deficiency, but any specific cause for it could not be elucidated. *P. vivax* malaria also has pathogenic mechanisms, such as increased inflammatory response and cytokine production, Weibel-Palade bodies exocytosis, altered thrombosis, platelet activation, and impairment of vasomotor responses as seen with *P. falciparum* malaria. Some autopsy reports have also suggested endothelial "stimulation" in *P. vivax* malaria; however, the reason for increased complications with *P. vivax* malaria particularly in the Indian subcontinent is still not known (9). The occurrence of TMA may be coincidental with *P. vivax* malaria, and it might be a part of primary thrombotic thrombocytopenic purpura or atypical HUS; however, the possibility of atypical HUS due to congenital complement dysregulation was eliminated by the fact that the complement levels were only transiently decreased. Though a positive response to plasmapheresis has been reported in some studies, its role after established CKD is not very clear; this option had been already given to our patient (10). Cardiac complications caused by *P. vivax* malaria are extremely rare in the literature, and nearly all reported cases of malaria with cardiac complications, such as pericardial effusion, bundle branch block, cardiomyopathy, and myocarditis, have been limited to *P. falciparum*. Though the exact mechanism of cardiac complications associated with malaria is not known, various proposed pathogeneses include (1) mechanical blockage of capillaries by malaria parasite and parasitized red blood cells, (2) myocardial damage by macrophages containing malaria pigment, (3) myocardium damage by tumor necrosis factor, and (4) hypoglycemia and acidosis caused by severe malaria may affect myocardial function. A regional wall motion abnormality is suggestive of myocarditis or coronary artery disease. Treatment of myocarditis due to malaria is rest and to avoid exertion. In our case, severe global hypokinesia was seen suggestive of myocarditis, and it improved with supportive treatment alone.

CONCLUSION

P. vivax malaria is not as benign as it was previously considered. TMA should be suspected in a patient infected with malaria who has non-recovering AKI with persistent anemia and thrombocytopenia even after clinical recovery from malaria. Heart failure should raise suspicion of myocarditis and cardiomyopathy. Early institution of plasmapheresis is considered beneficial, though its role in established CKD is yet to be confirmed.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: DJ, NN. Performed the experiments or case: DJ, PV, DS. Analyzed the data: PV, PJ. Wrote the paper: DS, PV. All authors have read and approved the final manuscript.

Conflict of Interest: The authors have no conflicts of interest to declare.

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