Hemolytic uremic syndrome associated with *Plasmodium vivax* malaria successfully treated with plasma exchange

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ABSTRACT

We report a case of hemolytic uremic syndrome (HUS) in an adult patient with *Plasmodium vivax* malaria. The patient presented with worsening anemia, persistent thrombocytopenia and acute kidney injury. HUS was diagnosed based on the high serum lactate dehydrogenase, elevated reticulocyte count and presence of schistocytes on peripheral blood smear. Kidney biopsy showed features of thrombotic microangiopathy. Complete hematological remission was achieved after five sessions of therapeutic plasma exchange. Renal function partially recovered and stabilized at discharge. *Vivax* malaria, generally considered benign, may be rarely associated with HUS.

Key words: Acute kidney injury, hemolytic uremic syndrome, *vivax* malaria

Introduction

Plasmodium vivax malaria is increasingly being reported as a cause of severe malaria associated with acute kidney injury.[1,2] Thrombotic microangiopathy is a rare manifestation of *P. vivax* malaria described mainly in children.[3-5] We report a case of acute kidney injury secondary to hemolytic uremic syndrome (HUS) in an adult patient with *P. vivax* malaria.

Case Report

A 29 year old previously asymptomatic male was admitted in a peripheral hospital with fever and jaundice of 1 week duration. He had anemia (hemoglobin [Hb] 8.8 g/dl), thromocytopenia (platelet count 55,000/µl), renal impairment (serum creatinine [s. creatinine] 1.5 mg/dl) and direct hyperbilirubinemia (total bilirubin 3.9 mg/dl, direct 1.9 mg/dl). Peripheral smear showed the presence of schizonts of *Plasmodium vivax*. Antigen test for *Plasmodium falciparum* was negative. He was treated with Artesunate and Clindamycin for 7 days and was discharged when asymptomatic, although improvement in thrombocytopenia or renal impairment was not observed. Two week later (1 week after being afebrile and getting discharged) he presented to us with vomiting and pain in the abdomen for 3 days and decreased urine output. He did not have fever, loose motions, rash, bleeding or alteration in sensorium. There was no history of treatment with quinine. He was hypertensive, pale, did not have edema and had unremarkable systemic examination except for the presence of haemic murmur. Severe anemia (hemoglobin 4.8 g/dl), thrombocytopenia (platelet count 61,000/µl) and azotemia (s. creatinine 8.3 mg/dl) were noted. Presence of schistocytes on peripheral smear, elevated reticulocyte count (13%), elevated serum lactate dehydrogenase (LDH 1242 U/L) and indirect hyperbilirubinaemia indicated ongoing microangiopathic hemolytic anemia. Urinalysis showed microhematuria and proteinuria of 3.75 g/day. Coagulation profile was normal. Serum C3 level was low (50 mg/dl), C4 level being normal. Antinuclear antibodies and enzyme-linked immuno sorbent assay for human immunodeficiency virus were negative. Hepatitis B surface antigen and anti-hepatitis C antibodies were negative. He underwent five sessions of 1.5 volume plasma exchanges with

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replacement with fresh frozen plasma. Hypertension was controlled. Intermittent hemodialysis was done. Anemia was corrected with packed red cells transfusion. After five sessions of plasma exchanges, platelet count increased to 150,000/µl Hb stabilized at 6 g/dl and then increased. S. LDH decreased to 206.3 U/L and s. creatinine stabilized at 5.5 mg/dl, patient being dialysis-independent. This hematological remission persisted at 4th week (Hb 9.1 g/dl, platelet count 163,000/µl) with C3 level being normal. Kidney biopsy was performed at this time. Enlarged glomeruli had capillary wall thickening, with double contours seen on silver Methanamine stain, endothelial swelling and increased mesangial cellularity. Arterioles with onion peel appearance were seen [Figures 1 and 2]. No immune deposit was seen on immunoflorescence study.

At the end of 4 months, he requires two antihypertensive drugs, has Hb 13.5 g/dl, platelet count 229,000/µl, s. creatinine 1.4 mg/dl and poteinuria 1.2 g/day.

Discussion

Although severe malaria is known to be caused by *Plasmodium falciparum*, *vivax* malaria is increasingly being observed to result in severe disease with involvement of multiple organ systems[6] and particularly, acute kidney injury.[2,7]

Pathogenesis of acute kidney injury and dysfunction of other organs in *vivax* malaria is not well elucidated. Volume depletion, hemolysis, disseminated intravascular coagulation and sepsis may contribute to the pathogenesis.[2,8] Thrombotic microangiopathy has been reported in children in association with malaria.[3-5] Endothelial dysfunction, which is known to occur in falciparum malaria may have a role in organ failure seen infrequently in the course of *vivax* malaria. de Mast *et al*.,[9] observed that A Disintegrin and Metalloproteinase with Thrombospondin Motifs13 (ADAMTS 13) activity and antigen levels were reduced in patients with falciparum as well as *vivax* malaria with the appearance of prothrombotic unusually large von Willebrand factor polymers in plasma. This endothelial cell perturbation may be a reason for thrombotic microangioathy as seen in our case.

The presence of hypocomplementaemia on presentation may point towards underlying disorder of complement dysregulation, but complement level had normalized during the recovery, suggesting secondary cause of complement depletion. Although, infections have been described to trigger episodes of HUS in disorders of complement dysregulation, malaria triggering such an event is not yet reported.

Unusual association of HUS with *vivax* malaria in our case underlines the need to understand molecular mechanisms in endothelial dysfunction associated with *vivax* malaria.

Conclusion

This report highlights importance of recognition of *P. vivax* malaria as a cause of atypical HUS. Persistent thrombocytopenia with worsening renal function in spite of otherwise recovery from the febrile illness should be investigated to look for the presence of HUS. Plasma exchange may be helpful in the management. Further research is warranted to elucidate the role of the complement system and endothelial dysfunction in the pathogenesis of acute kidney injury following *P. vivax* malaria.

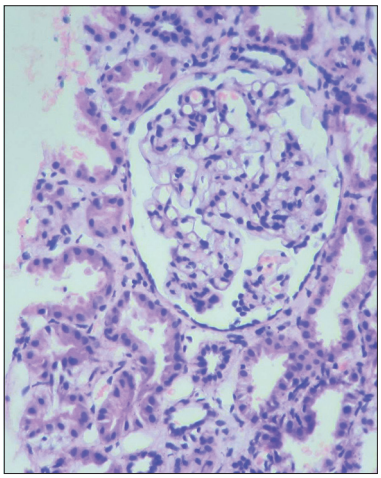

Figure 1: Renal biopsy showing hypercellular glomerulus with thickened capillary walls. (H and E, ×400)

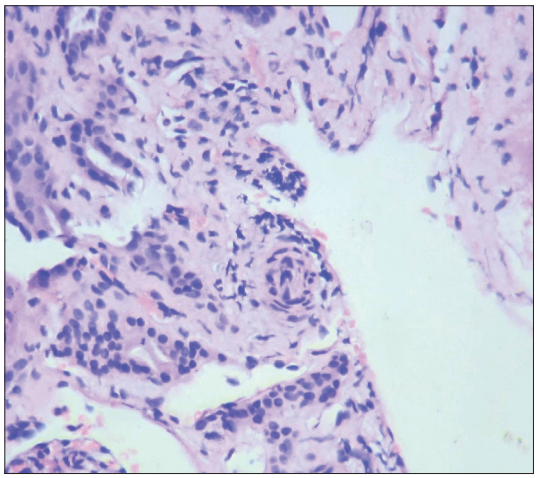

Figure 2: Onion-peel appearance of the arteriole. (H and E, ×400)

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