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CASE REPORT

Glomerular thrombotic microangiopathy caused by *Plasmodium vivax* infection

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Abstract:
Acute renal failure, although less commonly seen in P. vivax than P. falciparum infection, may be associated with significant morbidity and even mortality. The exact pathogenesis of vivax related renal failure is unknown as renal biopsies are done infrequently. We report a 10 year old boy with renal failure and severe thrombocytopenia due to vivax infection wherein the renal histopathological examination revealed thrombotic microangiopathy. We suggest this as one of the important underlying mechanisms of vivax-induced renal failure.

Keywords: *vivax malaria, renal failure, thrombocytopenia, thrombotic microangiopathy*
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Introduction

Malaria is an important cause of acute renal failure (ARF) in children in developing regions of the world [1]. Even vivax malaria which was hitherto considered benign may result in various severe manifestations including renal failure [1-3]. Cytoadherence of *P. falciparum* infected red blood cells to the vascular endothelial cells of different host organs along with rosette formation is considered to be an important pathogenic mechanism in severe malaria [2]. However, this is not usually seen in *P. vivax*. Though various mechanisms have been postulated, the pathogenesis of vivax induced renal failure still remains an enigma.

Case report

A 10 year old boy was referred to our hospital with a history of high grade fever for 5 days followed by vomiting and drowsiness for 3 days. He had also developed progressive oliguria with generalized body swelling over the previous 3 days. Physical examination revealed weight 25kg (10^{th} centile for age) and height 120cms (3^{rd} centile for age). His heart rate was 80/min and respiratory rate 20/min. Blood pressure was 130/100 mm Hg. The child was drowsy with no focal neurological deficits. Abdominal examination did not reveal any organomegaly. The rest of the systemic examination was unremarkable.

Investigations showed a hemoglobin level of 690 gm/L, leukocyte count of 4.2×10^9/L (neutrophils 56%, lymphocytes 42%, eosinophils 2%) and platelet count of 46×10^9/L. Lowest platelet count during hospital stay was 31×10^9/L. Peripheral blood smear showed red cells parasitized with trophozoites of *P. vivax* with predominantly normocytic, normochromic and few microcytic, hypochromic cells. No immature cells or fragmented red cells were seen. A rapid card test (QDx Malaria Pv/Pf, Nicholas Piramal, India) which is based on detection of *P. falciparum* specific histidine-rich protein-2 and *P. vivax* specific lactate dehydrogenase antigen was positive for *P. vivax* and negative for *P. falciparum*. Glucose-6-phosphate dehydrogenase levels were normal. Plasma hemoglobin was 43 mg/dL (normal 0-15 mg/dL) and urine hemoglobin was nil. The blood level of urea was 105 mg/dL and creatinine 7.1 mg/dL, these rose to a maximum of 191 mg/dL and 10.1 mg/dL respectively on day 2 of hospital stay. Blood glucose was 100 mg/dL, arterial pH 7.12, bicarbonate 15 mEq/L, sodium 140 mEq/L and potassium 3.5 mEq/L. Urinalysis showed trace proteinuria with no red cells, casts or crystals. Serum complement C3 level was 41 mg/dL (normal 50-150

mg/dL). Coagulogram showed PTI 86% and aPTT 28sec (control 25-32 seconds). Serum bilirubin was 1.25 mg/dL. Repeated blood cultures were sterile and IgM ELISA for Leptospira as well as Dengue serology was negative. Ultrasonography of the abdomen showed edematous kidneys (right measuring 10.0 x 5.2 cm and left 10.2 x 4.9 cm) with loss of cortico-medullary differentiation suggestive of renal parenchymal disease and mild ascites. A renal biopsy was performed during third week of hospitalization. The histopathological examination revealed that 2 out of 9 glomeruli examined were entrapped in a patch of healed cortical necrosis and had a fibrillary appearance. Tubulo-interstitial compartment showed regenerating acute tubular necrosis along with patchy mild lymphomononuclear inflammation (Fig 1). Few tubules showed RBC casts. Some glomeruli showed endothelial cell swelling and focal duplication of the basement membrane (Fig 2). These features were consistent with thrombotic microangiopathy (TMA) along with acute cortical necrosis. Immunofluorescence microscopy showed traces of immunoglobulin IgM, IgG, IgA and fibrinogen in the mesangium. Only 1 out of 9 glomeruli had segmental C3 deposition. Electron microscopy (EM) did not reveal any immune complex deposits or evidence of TMA in the two glomeruli examined.

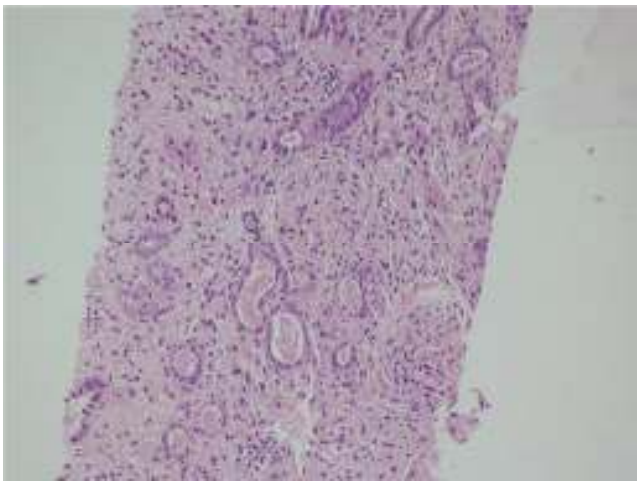

Fig 1: Photomicrograph shows acute tubular necrosis and bloodless glomerulus of thrombotic microangiopathy [H&E x 20]

He had received a course of chloroquine before referral to our institute. He was subsequently treated with Artemisinin-based combination therapy ACT (Artesunate and doxycycline) for 7 days. Hemodialysis was initiated on day 2 of his hospital stay in view of anuria, encephalopathy, worsening azotemia, fluid overload and metabolic acidosis. He also received transfusions of packed red cells and platelets as supportive therapy during dialysis. Hypertension was controlled with calcium channel blockers (amlodipine 0.4 mg/kg/day). A total of 8 cycles of hemodialysis were instituted following which the patient gradually showed improvement in encephalopathy, renal and metabolic parameters (pH 7.4, HCO_3 24 meq/L, serum urea 86 mg/dL, serum creatinine 1.9 mg/dL and urine output >1ml/kg/hour) and was discharged after 3 weeks of the hospital stay. At follow-up 2 weeks later, serum urea and creatinine had returned back to normal.

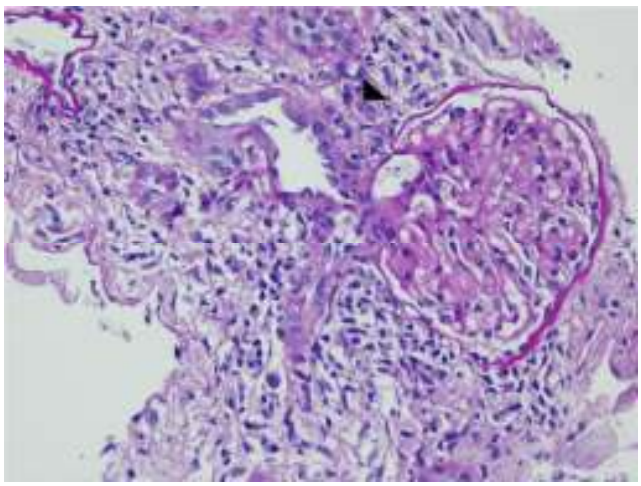

Fig 2: Photomicrograph shows sub-endothelial widening in glomerular capillary (arrow) and endothelial swelling in the afferent arteriole (arrow head) [PAS x 40]

Discussion

P. vivax malaria, conventionally considered benign with low fatality, can also cause severe disease like falciparum. Studies indicate that vivax malaria may be complicated by thrombocytopenia, severe anemia, hepatic dysfunction, renal involvement, acute intermittent porphyria and acute respiratory distress syndrome [1, 3]. Though falciparum malaria is a well established cause of renal failure, the literature suggests that *P. vivax* is the causative agent for acute renal failure in 10-20% of malaria related acute renal failure [1-3]. The pathogenetic mechanisms underlying vivax induced ARF, however, remain less clearly defined.

The histolopathological picture in malarial ARF shows a variable mixture of acute tubular necrosis (ATN), interstitial nephritis and glomerulonephritis. Kanodia et al studied renal biopsies performed in 10 out of 100 patients of malarial ARF, amongst which 70% had patchy cortical necrosis, 20% had mesangial proliferative glomerulo-nephritis without any immune deposits and ATN, and 10% had idiopathic membranous glomerulonephritis [2]. Most of the biopsy based studies have been done in falciparum associated ARF. Unlike falciparum, *P.vivax* was previously believed to be incapable of causing cytoadherence or microvascular sequestration, endothelial dysfunction/activation and subsequent organ dysfunction. It has now been shown that concentrations of circulating endothelial activation markers are also high in vivax malaria as in falciparum [4]. Hence, endothelial injury may be considered to be one of the important mechanisms in renal failure due to vivax.

Similar to our case, Saharan et al reported thrombotic microangiopathy on renal biopsy in a patient with renal

failure due to vivax [5]. They suggested that endothelial injury to the renal microvasculature, possibly due to elevated levels of tumor necrosis factor-α and other cytokines, might result in thrombotic microangiopathy. Sharma et al reported a similar case of vivax presenting as hemolytic uremic syndrome (HUS) [6]. They postulated that a malarial toxin, like Shiga toxin, might alter endothelial cell integrity and provoke a sequence of events leading to extensive microvascular damage and subsequently resulting in HUS. In our patient also, the histopathological examination supports thrombotic microangiopathy as the cause of ARF. We could not, however, estimate the levels of endothelin-based biomarkers due to non-availability at our institute. The absence of pathological changes on EM was probably due to patchy involvement of the glomeruli.

None of the possible etiological factors described previously viz. hypotension, hyperbilirubinemia, disseminated intravascular coagulation or sepsis were seen in our patient [7]. The possibility of the child having suffered hypotension during the initial phase of his illness, however, cannot be totally excluded. Our patient also had severe thrombocytopenia and this rare combination of renal failure and severe thrombocytopenia, previously reported by us, is now well recognized [3, 8]. The atypical HUS-like clinical presentation and the histopathological findings of TMA suggest that TMA may be an important underlying mechanism in severe vivax malaria associated with ARF. The link between HUS and TMA is well established [9-11]. *P. vivax* may indeed be one of the many etiological agents for non-genetic atypical HUS. The marginally low serum C3 levels in our patient could also be explained by the complement dysregulation associated with atypical HUS[11-12]. Prospective histopathological studies are urgently required at centers where malaria is commonly reported to further elucidate the pathogenesis of associated ARF. Plasma manipulation (infusion or exchange), known to reduce mortality in atypical HUS, and the humanized monoclonal antibodies (e.g. eculizumab) which are currently undergoing trials in atypical HUS may then also become part of supportive therapy in severe malaria related ARF also [9, 11-12].

With the emergence of chloroquine resistant vivax malaria, a unified ACT-based strategy for treatment is recommended in regions where both vivax and falciparum malaria are endemic [13]. We used ACT keeping in view the severity of illness and prior treatment with chloroquine. The possibility of mixed infection in our patient was excluded by microscopic diagnosis of species and negative malaria card test which is highly sensitive and specific for the exclusion of falciparum infection [14].

In conclusion, the attempts to study the underlying mechanisms in vivax related renal failure are rare. Thrombotic microangiopathy as seen in our patient may be proposed as one of the mechanisms, hence emphasizing the need for histological diagnosis in all such cases to optimize therapies and to prevent associated morbidity and mortality.

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