Plasmodium Vivax Malaria Presenting as Hemolytic—Uremic Syndrome

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The atypical manifestations of malaria are frequently seen in highly endemic area like ours, *i.e.,* South Gujarat (unpublished data). The disturbances of renal function in malaria include transient proteinuria, immune complex nephritis presenting with nephrotic syndrome and acute renal failure(1). Hemolytic uremic syndrome (HUS) may occur as a part of many disease processes and has been noted to follow a wide range of associated conditions(2). The association between malaria and HUS is not reported in literature but their temporal relationship can be established retrospectively from our case report.

Case Report

A four-year-old girl, without significant past medical history, was admitted with chief complaints of high grade intermittent fever with rigors for a week. She became anuric and drowsy, developed edema on legs and face and had bloody stool since four days. She was treated with IV fluids by general practitioner for two days before hospitalization.

Physical examination on admission revealed a drowsy febrile child with severe pallor and multiple ecchymotic spots at venipuncture sites. The remaining systemic examination was unremarkable. She was catheterized with proper precaution and initial output was 40 ml of urine. She was given single bolus of fluid challenge, followed by loading dose of loop diuretic but did not have any urine output in next six hours.

Her Hb was 6 g/dl. The total leucocyte count was 5400/cu mm with DC P : 36, L : 62, M : 1 and E : 1. Platelet count was 80,000/cu mm. Peripheral smear revealed the picture of hypochromic microcytic anemia with presence of target cells, helmet cells, fragmented RBCs and normoblasts. Blood film for malarial parasite was positive for *P. vivax.* Urine analysis was suggestive of mild proteinuria and plenty of RBCs without significant sediments or pyuria. Prothrombin time was within normal range (22/18 sec). Serum bilirubin was 0.8 mg/dl. Blood, urine and stool specimen were sent for culture. Blood urea and serum creatinine were 192.9 mg/dl and 6.4 mg/dl, respectively. Serum electrolytes were Na^+ 130 mEq/L, K^+ 5.8 mEq/L, Cl^- 92 mEq/L. *X*-ray abdomen (KUB) and ECG were unremarkable.

With the provisional diagnosis of HUS with malaria, she was treated with injections. Chloroquine, ampicillin, calcium gluconate, sodium bicarbonate, mannitol and frusemide with restricted intravenous fluids. As she remained anuric for twelve hours after conservative treatment peritoneal dialysis was started and total 30 cycles were completed. She became afebrile with regression of splenomegaly and started to have liberal urine output three days after

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institution of dialysis. Blood, urine cultures were sterile and stool culture did not grow any pathogenic organisms. Renal sonogram was normal. Her azotemia and thrombocytopenia persisted for next two weeks with gradual improvement. By the end of three weeks her platelet count was 2,00,000/cu mm. BUN and serum creatinine were 52 mg/dl and 1.1 mg/dl. She was discharged on 25th day and remained well on follow-up.

Discussion

Intravascular coagulation occurs as a pathogenic mechanism in diverse number of clinical syndromes. HUS is the most striking example in infants and children(1). Gasser *et al.* initially described this syndrome of acute renal failure, hemolytic anemia and thrombocytopenia in five children, all of whom, had progressively deteriorating course culminating in death(3). A breakthrough in understanding the pathogenesis of HUS came when Karmali *et al.* in 1983 reported isolation of cytotoxin producing *E. coli* in stools from patients with HUS(4). The dysentery associated form of HUS has been chiefly observed in Indian subcontinent(5), but we don't have enough data on epidemiological and microbiological aspects of HUS from developing countries(6).

The complex issue of HUS is better elucidated with increasing knowledge but still our understanding of the condition is only in infancy. HUS was initially believed to be a renal disorder with secondary hematological manifestations but recent studies indicate that the syndrome should be regarded as systemic disease(7). The basic underlying abnormality is an angiopathy, predominantly in renal microvasculature. Vascular endothelial injury is followed by localized coagulation. Mechanical trauma to red cells and platelets during their passage through these abnormal vessels leads to their destruction and eventually removal by RE cells(6). The role of shiga toxin, verotoxin and shiga like toxins in HUS is well established. The glycolipid globotriosyl ceramide (Gb3) is cell surface receptor for such toxins. Human kidney contains these receptors which is in higher concentration in cortex than in medulla(8). The role of other possible toxins is still ill defined but such toxin can alter the endothelial cell function, leading to increase in procoagulant activity.

The invasion, alteration and destruction of red cells by malarial parasites, systemic circulatory changes and immune phenomenon are all important in pathophysiology of malaria. The role of malarial toxin is still ill defined(9). The protean manifestations of malaria in endemic area is multifactorial complex issue but is mainly attributed to the partial loss of immunity and increased sensitivity of the host on repeated exposure to plasmodium reinfection(1). Azotemia is frequent finding in malaria and may be attributed to the hypercatabolism and dehydration secondary to the high grade fever. But for the development of classical ARF contributory factors are(10): (*i*) High parasitemia; (*ii*) Decrease in extracellular fluid volume secondary to dehydration due to fever, vomiting and diarrhea, often present in acute malaria; (*iii*) Delay in institution of treatment with antimalarials; Hemoglobinurea, which may be of varying degrees and can in and by itself cause tubular injury; and (*v*) Disseminated intravascular coagulation that occurs in some patients.

The predominant pathology in intrinsic renal failure associated with malaria lie in tubules but clinical presentation and subsequent investigative workup suggest vascu-

lar lesion in this case. The temporal relationship between malaria and HUS is established after exclusion of common possible etiologies of HUS, well supported by clinical course and therapeutic response in present case. The lesion in the renal microvasculature may be an initial event for HUS associated with malaria which can be explained on the basis of: (*i*) The infected RBCs adhere to the endothelium of small vessels via 'knobs' on the erythrocytic membrane and with aggregation of parasitized RBCs, flow becomes sluggish and local hypoxia ensues. The pathologic chain of events may manifest clinically as renal cortical disruption and failure(11); (*ii*) Malarial toxin just like shiga toxin can alter endothelial cell integrity and provoke the sequence of events, leading to extensive microvasculature damage which subsequently results in HUS; and (*iii*) Disseminated intravascular coagulopathy associated with malaria.

Thus, HUS can be a presenting feature of malaria. With changing epidemiological pattern of malaria especially in endemic areas; such complications can be noted with *P. vivax* infections. The therapeutic response is dramatic after institution of antimalarial treatment with supportive care for renal failure. The long term morbidities associated with HUS include progressive renal impairment, late onset hypertension and neurological sequelae(12). Such long term complications are less likely in HUS associated with malaria, assuring good prognosis with prompt effective treatment of plasmodium infection.

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