PERIPHERAL GANGRENE IN NONFATAL PEDIATRIC CEREBRAL MALARIA: A REPORT OF TWO CASES

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Abstract. Two Thai girls aged 10 and 13 years from the same rural area were admitted to Paholpolpayuhasena Hospital, Kanchanaburi, Thailand during the rainy season of 1989 with cerebral malaria. After several days of conventional treatment, both developed gangrene involving the feet and toes, but the lesions healed and no other complications were seen. In the absence of convincing clinical and laboratory evidence of vasculitis or coagulopathy, it seems likely that host factors (dehydration, sluggish peripheral circulation, platelet activation, subclinical intravascular coagulation) combined with strain-specific parasite factors (tissue sequestration of mature forms, rosette formation) may predispose to peripheral microvascular occlusion sufficient to produce infarction of tissue in susceptible children. However, despite the apparently ominous appearance of such lesions in a comatose child, the prognosis seems good.

INTRODUCTION

Although endothelial adherence of erythrocytes containing mature forms of *Plasmodium falciparum* within capillaries and post-capillary venules of vital organs has been recognised for almost 100 years (Marchiafava and Bignami, 1894), controversy still exists as to the exact pathophysiological effects of this phenomenon in man (White, 1986). There is little evidence that extensive erythrocyte sequestration leads directly to tissue hypoxia severe enough to cause infarction (Rigdon, 1944; MacPherson *et al,* 1985), but it is likely that the sequestered biomass exerts its primary pathological effect through parasite-mediated metabolic disturbances in the microvasculature of organs such as brain, liver and kidney (White 1986). Disseminated intravascular coagulation (DIC) leading to microvascular occlusion would appear to be an uncommon occurrence even in severe infections (Sheagren *et al,* 1970; Perrin *et al,* 1982). Immune-mediated vasculitis in malaria is also a rare and controversial complication (Tora and Roman, 1978; MacPherson *et al,* 1985). Despite the fact that evidence of a direct effect of microvascular occlusion on tissue viability is rare, we report two cases of young children with slide-positive falciparum malaria who presented in unrousable coma and subsequently developed peripheral gangrene. Both children received conventional treatment for severe falciparum malaria and survived with complete healing of all lesions.

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CASE REPORTS

Case 1: A 13 year old Thai girl was admitted unconscious to Paholpolpayuhasena Hospital, Kanchanaburi, Thailand during June 1989. She had complained of intermittent fever and rigors for four days before presentation. On the day of admission she suffered a convulsion and did not regain consciousness. Her past medical history was otherwise unremarkable and she had not had malaria previously. On examination, she did not respond to painful stimuli. Her oral temperature was 37.7°C, pulse rate 120 bears/minute, supine

blood pressure 100/70 mmHg and respiratory rate 26/minute. She had pale conjunctivae but no jaundice. Cardiovascular examination was normal, and all peripheral pulses were full and symmetrical. The liver and spleen were impalpable. She had no neck stiffness and no focal neurological signs, and fundoscopy was normal.

Her hemoglobin was 7.6 g/l and white cell count 5.2 × 10^9/l with 64% neutrophils and 36% lymphocytes. Microscopic examination of a thick blood film revealed asexual forms of *P. falciparum* at a parasite density of 75,000/μl. Red cell morphology was normal on blood film but there were occasional nucleated erythrocytes and some polychromasia, and platelet numbers were reduced. The urine specific gravity was 1.020 with 1+ albuminuria but urine microscopy was normal. A routine biochemical screen revealed a serum BUN of 44.0 mg/dl, creatinine 1.13 mg/dl, glucose 167 mg/dl, SGOT 54 iU/l (normal range 0-40 iU/l), SGPT 40 iU/l (0-40 iU/l), sodium 127 mmol/l, chloride 95 mmol/l, potassium 4.4 mmol/l and bicarbonate 13 mmol/l. A chest X-ray was normal, and blood and urine cultures were taken.

Intravenous quinine at 10 mg salt/kg body weight over four hours at 8 hourly intervals was started through a forearm venous cannula and she received a transfusion of two units of packed red cells. On the second day she remained in deep coma with intermittent decerebrate posturing but had developed hyperpigmented macules on both feet. A proportion of these lesions progressed to dry gangrene after three days of treatment (see Fig 1), but her conscious level had improved by this time and she was responding appropriately to verbal commands. A further blood smear on the third day revealed normal red cell morphology without fragments and continuing thrombocytopenia (46,000/μl). Whole blood clotting time was 12 minutes. Blood cultures were negative after 72 hours. Her subsequent clinical course was uneventful and quinine treatment was discontinued after 7 days. Limited surgical debridement of toes on both feet was performed subsequently, but all lesions healed well and she was discharged from hospital one month after admission.

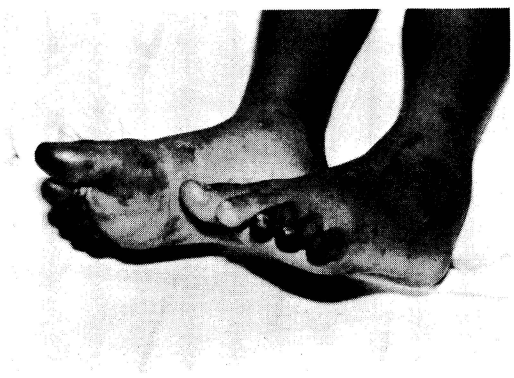

Fig 1—Gangrene involving the toes of both feet, with areas of cutaneous involvement extending above the ankles (Case 1).

Case 2: A 10 year old Thai girl with no previous history of malaria presented in coma Thong Pha Phum Hospital, Kanchanaburi, Thailand, during September 1989. She had a 7 day history of fever, headache and abdominal pain, and had become restless and drowsy on the day of admission. On examination she responded nonpurposively to painful stimuli but had no neck stiffness, photophobia or focal signs. A peripheral blood smear showed asexual forms of *P. falciparum* with a parasitemia of 88,000/μl. Urinalysis revealed 50-100 red blood cells per high power field with scattered red cell casts but no albuminuria. Her serum creatinine was 2.0 mg/dl. Intravenous quinine and supportive treatment were given and she maintained a satisfactory urine output. On the third day of admission she developed peripheral edema and erythematous macules of up to 3 cm in diameter on both feet. Some of these lesions progressed to areas of dry gangrene after 24 hours. She was started on intravenous co-trimoxazole and then transferred to Paholypolpayuhasena Hospital.

On admission to Paholpolpayuhasena Hospital, her oral temperature was 38.5°C, her pulse rate 100 beats/minute and respiratory rate 28/minute. She was drowsy but responded purposively to verbal commands. She had pale conjunctivae and moderately icteric sclerae. Examination of the cardiovascular system revealed no abnormalities. The liver was tender and palpable 2 cm below the right costal margin but the spleen was impalpable. There were multiple erythematous and gangrenous maculae on both feet, with peripheral gangrene of some toes (see Fig 2). There were no lesions on the hands or splinter hemorrhages, and fundoscopy was normal.

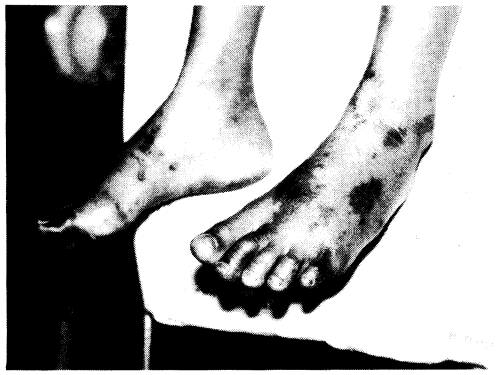

Fig 2—Peripheral gangrene in Case 2, with a similar pattern of distribution to that in Case 1.

Investigations revealed a venous hematocrit of 32% with normal red cell morphology, a white cell count of 12.3 × 10^9/l (73% neutrophils, 18% lymphocytes, 4% eosinophils and 4% monocytes), and thrombocytopenia (platelet count < 50,000/μl). She was slide-negative for malaria. Urinalysis showed a trace of albumin with 0-1 red blood cells and 3-5 white blood cells/high power field. No red cell casts were seen. Her BUN and creatinine had fallen to 22 mg/dl and 0.6 mg/dl respectively, but she was still jaundiced (total serum bilirubin 8.5 mg/dl). Her serum albumin was 2.03 g/dl, globulin 3.73 g/dl, alkaline phosphatase 68.5 iU/l, SGOT 47 iU/l, SGPT 59 iU/l and she was normoglycemic. Blood and urine cultures were taken. Lumbar puncture revealed clear and colorless CSF with 4 leukocytes/μl, a protein of 24.0 mg/dl and glucose of 44 mg/dl. Her admission plasma fibrinogen concentration was decreased at 1.2 g/l and fibrinogen degradation products (FDP) were mildly raised (80-160 μg/ml).

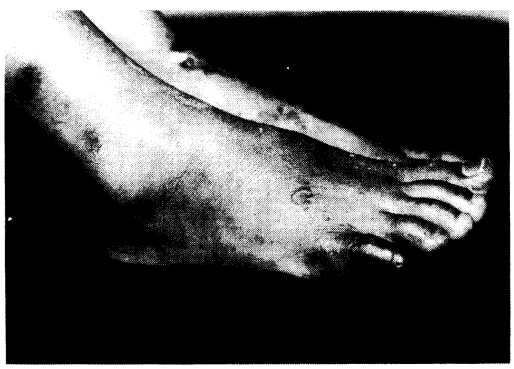

Fig 3—Gangrenous lesions three weeks after presentation in Case 2. The patient lost distal tissue from the right 1st and 5th toes but surgical debridement and antibiotic cover were not required.

Intravenous quinine was continued for 2 days and she was changed to oral quinine to complete a 10-day course of this drug. Co-trimoxazole was stopped and penicillin G and gentamicin were given for 72 hours until the results of admission cultures proved negative. A full-thickness punch skin biopsy at the site of an erythematous macule revealed focal epidermal necrosis without evidence of vasculitis. The gangrenous areas on both feet resolved with conservative management over the week following admission (see Fig 3), at which time the patient was discharged.

DISCUSSION

The patients described in this report exhibit many similarities. Both were young Thai girls from the same rural area who presented with cerebral malaria during the rainy season months of 1989. Both received, and responded appropriately to, conventional antimalarial therapy but each developed peripheral gangrene after 2-3 days of treatment. The gangrene was confined to the feet, was not associated with definite clinical evidence of coagulopathy, sepsis or vasculitis, and resolution of the lesions was complete.

The cause of peripheral gangrene in these two young girls remains uncertain. Although case 2 had decreased plasma fibrinogen concentrations, raised FDP levels and a depressed platelet count when the lesions were most marked, clinically significant bleeding and blood film evidence of a microangiopathic hemolytic anemia were not seen in either patient. Both thrombocytopenia and laboratory evidence of mild activation of the coagulation cascade are common findings in Thai adults with cerebral and severe malaria in the absence of DIC (Phillips *et al,* 1986; Pukrittayakamee *et al,* 1989), Furthermore, intravascular fibrin deposition is not a prominent feature in post-mortem histological studies of patients who died in coma (MacPherson *et al,* 1985). These considerations suggest that intravascular coagulation was not the primary factor underlying peripheral gangrene in our patients.

Proliferative glomerulonephitis is a rare complication of acute falciparum malaria (Berger *et al,* 1967; Hartenbower *et al,* 1972) but there is usually no evidence of a renal vasculitis in such cases (Sitprija, 1988). Although case 2 had presumptive evidence of glomerulonephritis when she first presented, her renal function had improved and urine microscopy was normal at the time of her transfer to Paholpolpayuhasena Hospital, and neither case developed acute renal failure or nephrotic syndrome. In addition, there was no evidence of vasculitis on skin biopsy in the second case. The implication that cerebral malaria is caused by an immune-mediated vasculitis (Toro and Roman, 1978) has no histological support (MacPherson *et al,* 1985), and in neither of our patients was coma prolonged or did focal neurological signs develop. Thus, there is no convincing evidence that vasculitis was the cause of peripheral gangrene in these two young girls.

Reports of malaria-associated peripheral gangrene are rare. Thapa *et al* (1987) described a case of peripheral gangrene in an Indian child with falciparum malaria. The age, sex and associated clinical features in this case were not provided. The patient was reported to have lost terminal portions of fingers and toes, and to have received immunosuppressive therapy which was also administered during several subsequent hospital admissions with peripheral gangrene not always associated with malaria. In a second case report from India (Sharma, 1987), a 22 year old man with otherwise uncomplicated falciparum malaria developed cutaneous gangrene involving the nose, cheeks, earlobes and all fingers and toes, a distribution reminiscent of Raynaud's phenomenon. He was treated with high-dose corticosteroids, aspirin and vasodilator drugs in addition to conventional antimalarial and supportive therapy, and all lesions healed. Paradoxically, malariotherapy has been used successfully to treat the peripheral gangrene of Buerger's disease (Corelli 1973). However, the species used was *P. vivax,* an infection in which sequestration of parasitised erythrocytes is not observed.

Although sequestration of erythrocytes containing mature forms of *P. falciparum* does not, on its own, lead to infarction of tissue, recent studies have identified two factors which may amplify the effect of sequestration on microvascular blood flow; the formation of 'rosettes' around parasitised red cells (David *et al,* 1988) and the reduction in deformability that accompanies intracellular maturation of the parasite (Cranston *et al,* 1984). It is possible that, in a patient infected with a strain of *P. falciparum* whose developmental characteristics favor these possible mechanisms of microvascular obstruction, significant tissue hypoxia could result. This would be especially true in the sluggish peripheral circulation of an unconscious, dehydrated patient. With the addition of even a mild degree of fibrin deposition and release of vasoconstrictor substances such as thromboxane A_2 from activated platelets (Essien, 1989), tissue viability could be impaired sufficiently to produce the localized pattern of gangrenous lesions seen in our cases.

The physician managing children with cerebral malaria should be aware of this complication. Exclusion and treatment of other causes of focal ischemia (such as frank DIC) and institution of measures which ensure adequate peripheral perfusion (such as prompt rehydration) should be carried out without delay. Where no obvious cause can be found, the prognosis of peripheral gangrene in such patients seems good, despite its apparently ominous appearance in a severely-ill child.

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