CASE REPORT

Symmetrical Peripheral Gangrene as a Rare Complication of Malaria: A Case Report from the Arthur Davison Children's Hospital in Ndola, Zambia

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ABSTRACT

Malaria is a common parasitic disease with very high mortality in tropical countries including Zambia. Symmetrical Peripheral Gangrene (SPG) is a rare complication of malaria, associated with Plasmodium falciparum infection. Reported here is a case of SPG in a 2 year3-month-oldZambian toddler and highlight the need for awareness and prompt diagnosis and treatment.

BACKGROUND AND LITERATURE REVIEW

Malaria is a major cause of morbidity and mortality in Zambia particularly in the under 5 year old children.[1] Children under 5 years of age are one of the most vulnerable groups affected by malaria.[1]In Africa about 285,000 children died before their fifth birthday in 2016.[2]In Mozambique malaria accounted for 27,612 childhood mortality in 2010 with the disease accounting for a large population of both in patient and out patients visits.[3]In Zambia malaria accounts for up to 40% of all childhood mortality of which 15-20% of deaths occur in children under 5 years of age.[4]Most of the mortality from malaria in children aged 6 months to 3 years is due to cerebral malaria and has a mortality rate of 25% even with the best treatment.[5]SPG is a rare and severe complication of malaria in which there is distal ischemic damage without the presence of a vascular disease in two or more extremities.[6]The first reported case series of malaria associated gangrene in young African children was in Mozambique in 2014.[3]The reported mortality rate for malaria complicated by peripheral gangrene may be as high as 35%, with an amputation rate of 70-90%.[3] We describe a case of confirmed *Plasmodium falciparum* malaria and SPG that presented to the paediatrics emergency room at Arthur Davison Children's Hospital in Ndola, Zambia.

CASE PRESENTATION

A 2 year 3-month-oldfemale toddler was referred from a district hospital with malaria complicated by severe anaemia for blood transfusion. She presented to the emergency room with a three days complaint of fever and vomiting. She was diagnosed with malaria by a rapid diagnostic test (RDT) (SD BIOLINE malaria Ag, Standard Diagnostics inc, India) for malaria and severe anaemia and had received one dose of Coartem.

She had previously been well and had not received any medication in the recent past. On examination, she was fully conscious, and febrile with a

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temperature of 38.5°C and weighed 9.0 kg. The abdominal, cardiovascular and respiratory systems were normal. Blood pressure was normal, around 50th centile for age. She was positive for *P.falciparum* with heavy parasitaemia of 2000/ul parasites on blood slide and blood sugar profile bydextrostix was in the range of4.9mmol/l to 10.2 mmol/l. Urinalysis had haematuria of 3+. Table 1 shows the investigations that were done and the clotting profile was deranged with severe thrombocytopaenia.

After three days in hospital she was noted to have gangrenous changes in the distalends of both hands, figures 1 and 2;left foot toes, figure 3; left ankle, figure 4; normal right leg, figure 5.

Table 1: Investigations done on a toddler with Malaria associated SPG

Laboratory Test	Result
Full blood count	Haemoglobin - 2.1 g/dl White blood cell count-22 000/ul (polymorphs - 75%, lymphocytes-25%, Eosinophils-0.47%) Platelet count-35 000/ul Red blood cell count-0.7 $X10^6$/ul HCT-6.4% MCV-125.3Fl MCH-35.3pg MCHC-28.1g/dl
Clotting profile	INR-4.2 (2.5-4.0) APPT-58seconds (25-38 seconds) PT-51 seconds (11-18 seconds)
Liver function tests	ALT-45U/L AST-32U/L
Renal function tests	Urea-2.1mmol/l,Creatinine–65mmol/l Electrolytes: Sodium - 138mmol/l, Potassium-3.5mmol/l,Chloride- 97mmol/l,
Blood culture	Negative
Urine Microscopy	2-3 red blood cells No casts cells
Urine culture	No growth after 24 hours
HIV test	Negative

Figure 1: Right hand - gangrenous changes of index, middle, ring fingers up to distal phalanges and little finger affecting the nail region

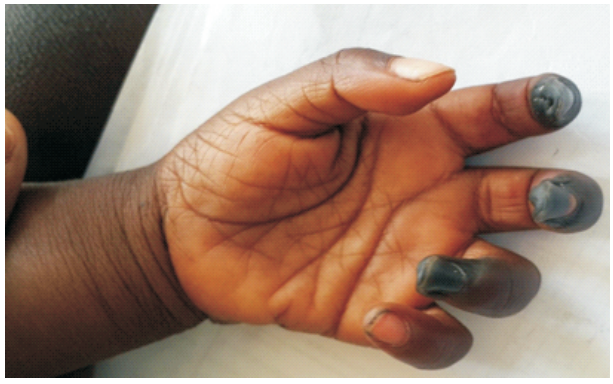

Figure2: Left hand - gangrenous changes of the index, middle, ring fingers up to the distal phalanges

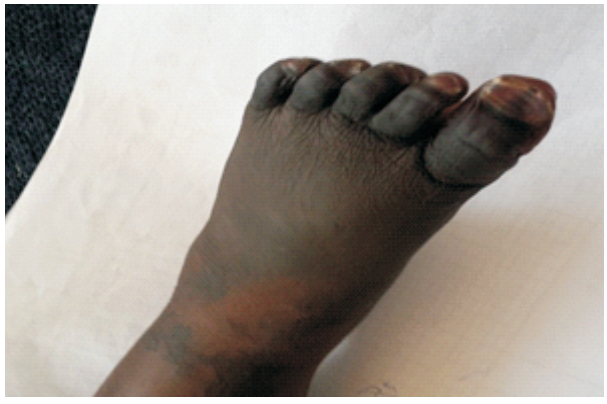

Figure 3: Left Leg - gangrenous changes on the dorsum of the foot

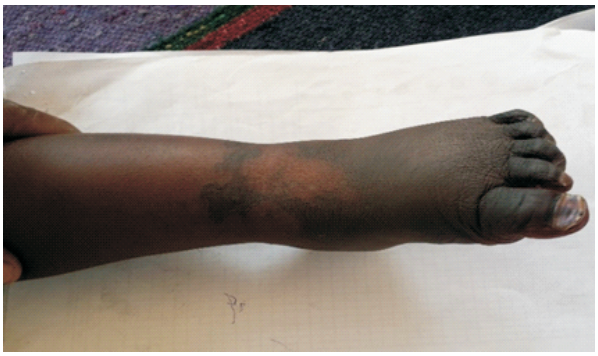

Figure 4: Left Leg - gangrenous changes up to the level of the ankle

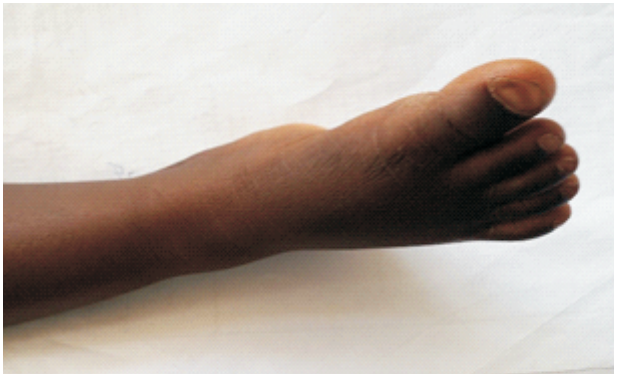

Figure 5: Right leg - Normal

The patient was treated with Artesunate 27mg OD IV for 7 days and Cefotaxime 450mg QID IV for 14 days. She was transfused a total of 60ml/kg fresh whole blood over two weeks. Surgeons advised amputation to be done after the gangrene had demarcated but the patient left against medical advice while waiting for surgery.

DISCUSSION

SPG is an extremely rare complication of malaria, reported more commonly in adults than in children.[5]Malaria remains a major cause of morbidity worldwide.[7]It has been implicated rarely as a cause of SPG.[8]About 18-40% mortality due to malaria has been reported in India and survivors have high frequency of multiple limb amputations.[9]

Of the four species of plasmodium recognised to infect humans, *P.falciparum* causes 95% of all the cases of complicated malaria.[10] SPG is associated with ahigh rate of amputation of the limbs in the survivors and no specific treatment has been shown to consistently prevent progression or to reverse the gangrene.[11]

One of the theories to explain the pathogenesis of malaria associated peripheral gangrene is that heavy parasitaemia results in the activation of the intrinsic coagulation pathwayor complement system to cause thrombosis.[12]Our patient had heavy parasitaemia and this may have contributed to the development of SPG. The microthrombosis associated with disturbed procoagulant-anticoagulant balance is the hallmark of SPG and early recognition with prompt management of disseminated intravascular coagulation and underlying condition may halt the progression of the disease.[9]

Erythrocytes infected with parasites interact with endothelium receptors leading to adherence and sequestration of the red blood cells (RBCs) and further obstruction of thesmall vessels.[13] Furthermore,changes in the membrane that occur in *P.falciparum* infectedRBCs cause activation of the blood coagulation cascade to cause thrombosis.[13]Another theory is that parasitized RBCs which are less deformable experience mechanical sludging in the microvasculature and microvascular occlusion propagates proximally causing distal ischaemia and necrosis.[13] The blockage of the terminal arterioles could be the important reason for gangrene.[14] Microthrombi which has been found in the amputated specimens is a result of these possible mecahanisms.[13]

Microcirculation is compromised in *P. falciparum* as a result of adhesion of the infected erythrocytes to the vascular endothelium, cytoadherence and due to resorting of infected RBCs around the parasitized RBCs.[15] Microvascular occlusion may propagate proximally and result in distal ischaemia and necrosis.[9] Heavy parasitaemia may alter the lipid distribution across the cell membrane of parasitized erythrocytes worsening the clinical picture resulting in the activation of intrinsic coagulation cascade and

the complement system.[16]Several vascular receptors for the adhesive surface protein of infected RBCs have been identified such as cluster of differentiation(CD 36),intracellular adhesion molecule 1,thrombospondin,vascular cell adhesion molecule 1,endothelial leucocyte adhesion molecule and histidine rich protein.[17]

Presence of SPG portends a poor prognosis with high mortality and amputation rate.[15]

Prompt diagnosis of SPG is necessary to minimise proximal progression of the disease and malaria treatment should be initiated immediately. Treatment of SPG is largely empirical with treating of malaria infection.

Severe *P. falciparum* infection is associated with activation of the coagulation cascade with prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) with no typical bleeding and /or haemorrhage. Although our patient had deranged clotting profile with severe thrombocytopaenia, she had no evidence of bleeding. This patient was a candidate for amputation, but the toddler was taken away from hospital by the parents against medical advice.

CONCLUSION

This is the first paediatric case ever reported in Zambia with severe Malaria associated peripheral gangrene and needed amputation. SPG though rare, should be looked for in children with deranged clotting profile in Malaria endemic areas.

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Conflict of interest

The authors declare that they have no conflict of interest.

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