Symmetrical peripheral digital gangrene following severe Plasmodium falciparum malaria-induced disseminated intravascular coagulopathy

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ABSTRACT
Symmetrical peripheral digital gangrene is a life-changing complication, caused by a pro-thrombotic life-threatening disease, such as disseminated intravascular coagulopathy (DIC) secondary to systemic infection. We describe the unusual case of a woman who developed symmetrical peripheral digital gangrene following DIC because of malaria. While initial treatment led to cure of the infection, in this report we describe also the subsequent management of symmetrical peripheral digital gangrene.

Key words: Disseminated intravascular coagulopathy • malaria • symmetrical peripheral digital gangrene

Symmetrical peripheral digital gangrene is an unusual complication of a number of different life-threatening thrombotic states, often as a sequela of purpara fulminans, such as disseminated intravascular coagulopathy (DIC) secondary to septicaemia from either group A streptococci, S. Pneumoniae, Neisseria meningitidis or staphylococci infection (1,2). In this situation there is often excessive disproportionate consumption of one or more anti-coagulant factors, such as protein C or S, leading to the hypercoagulable state (3). Rarely an inherited deficiency of an anti-coagulant factor, or in the case of antiphospholipid syndrome an acquired state, can manifest with symmetrical peripheral digital gangrene following infection or trauma (3,4). Here we describe an unusual case of severe malaria that resulted in symmetrical peripheral digital gangrene and highlight the management issues that arise after the acute illness has resolved.
CASE

Three days after returning from a trip to visit her family in Nigeria, a 44-year-old African female developed fever, abdominal pain, lethargy, constipation, oliguria, nausea and vomiting. She had taken doxycycline anti-malarial prophylaxis during her trip and had been previously well. On admission she was conscious, alert, orientated, but in discomfort. Her temperature was 37.8°C, heart rate was 107 beats per minute and blood pressure was 106/54. Of note, abdominal examination showed epigastric and bilateral loin tenderness.

The BINAX test for malarial antigens was positive and the subsequent blood film showed 24% parasitaemia with schizonts. Urine analysis showed haematuria (++++) and proteinuria (+). Investigations also showed acute haemolysis (haemoglobin 11.8 g/dl and bilirubin 127 μmol/l), acute hepatorenal failure (albumin 33 g/l, aspartate transaminase 161 IU/l, amylase 90 IU/l, urea 37.2 mmol/l, creatinine 852 mmol/l) and DIC (platelets $48 \times 10^9$/l, prothrombin time 13 seconds, activated partial thromboplastin time 40 seconds, fibrinogen 6.2 g/l and elevated fibrinogen degradation products). She also had elevated inflammatory markers (C-reactive protein 324 mg/l and erythrocyte sedimentation rate 39 mm/hour), but normal plasma glucose level (5.6 mmol/l) and chest X-ray.

Consistent with a diagnosis of severe malarial infection, defined as parasitaemia >5% with complications, she received intravenous resuscitation with crystalloids, packed red cells and fresh frozen plasma, and was transferred to the intensive care unit. In response to the extremely high parasite burden, initial malarial treatment consisted of exchange blood transfusion and intravenous artesunate, which led to a rapid drop in parasitaemia such that there were no detectable parasites by blood film after 3 days; after which she was switched to doxycycline treatment. Despite the rapid reduction in parasite burden, the patient remained hypotensive necessitating continued administration of vasopressors (vasopressin, adrenaline and noradrenaline) for 9 days in total. During this time and despite maintaining a mean arterial pressure of >60 mmHg, together with administration of heparin and fresh frozen plasma, she developed peripheral cyanosis, with subsequent evolution to frank necrosis (Figure 1). She made an otherwise full recover and was discharged from the hospital.

Figure 1. Symmetrical peripheral digital gangrene affecting hands and feet. Taken 1 month after admission, these photographs show the extent of the cutaneous necrosis because of severe malaria. Necrosis is evident upon the distal-most tips of the patient’s digits, sparing the proximal tissues.
Symmetrical peripheral digital gangrene

Figure 2. Post-operative photographs of hands and feet. Taken 1 month after surgical debridement of the necrotic tissue, these photographs show the extent of tissue necrosis that had occurred. The necrosis had affected both soft tissue and bone.

while attending clinic for regular assessment of necrotic tissues and intermittent treatment of local wound infection. Because of the potential risk of wound infection, primary moisture-retaining wound dressings were not used. The patient was formerly assessed by occupational therapists and physiotherapist; it was established that the patient was able to carry out activities of daily living. Because of the extent of tissue necrosis, the patient was unable to return to work as a nurse. Despite patiently waiting for auto-amputation of her necrotic digits to occur for 6 months, the patient eventually underwent surgical debridement of the necrotic tissue. Surgery involved removal of distal phalanges to facilitate primary closure with sutures and so rapid healing (Figure 2).

DISCUSSION
Malaria is still a major cause of worldwide infection and mortality, causing over 1 million deaths each year (5). Up to 30 000 travellers returning from endemic areas contract malaria each year, 2000 of whom are returnees to UK (6,7). Of the four *Plasmodium* species responsible for malaria, *Plasmodium falciparum* infection is the most common (95%), and almost all of the cases of severe malaria and associated mortality are caused by *P. falciparum* infection. Severe malaria, as defined by the World Health Organisation (WHO) for adults (8,9), is based upon the presence of one or more of the following clinical and laboratory criteria: cerebral malaria (impaired consciousness or prostration with a Glasgow Coma Scale score <9), repeated generalised convulsions, hyperpyrexia (core body temperature >40°C), pulmonary oedema or respiratory distress syndrome, circulatory collapse (systolic blood pressure <70 mmHg), severe anaemia (haemoglobin <5 g/dl or haematocrit <15%), renal failure (serum creatinine >265 mmol/l or urine output <400 ml per 24 hours), acidosis (arterial pH <7.25), hyperbilirubinaemia (total bilirubin >43 μmol/l), hypoglycaemia (blood glucose <2.2 mmol/l), abnormal bleeding or DIC and or hyperparasitaemia (>5% parasitised erythrocytes). Parasitaemia levels greater than 5% and or the presence of more mature parasite forms such as schizonts on blood film are associated with worse prognosis (10). Overall severe malaria has a mortality rate >10%, even among patients who are repatriated and managed within an intensive care unit (11).

The management of malaria involves the eradication of the *Plasmodium* species and simultaneous treatment of complications. In the case of Sub-Saharan Africa, which has the highest rate of malarial infection, quinine resistance is prevalent (5). However, the choice
of anti-malarial is also dependent upon the level of parasitaemia. For patients with greater than 10% parasitaemia, improved survival with rapid clearance of parasites has been observed with parenteral administration of artesunate (12,13). While artesunate is widely considered an effective anti-malarial therapy, it remains without a European drug licence because of concerns about Good Manufacturing Practice (7). As for our patient, exchange transfusion can rapidly remove infected erythrocytes and thus decrease intravascular haemolysis and may be considered as adjunctive therapy when hyperparasitaemia is greater than 20% (7,8).

DIC or consumption coagulopathy is a common complication of malaria, affecting 5–30% of tourists returning with severe malaria (11,14). Consistent with diagnosis of DIC, our patient had a reduced platelet count, activated partial thromboplastin time and elevated fibrinogen degradation products. Although the fibrinogen level was raised, this would be expected as it is an acute phase protein. In a study of 533 patients with DIC, only 8.6% of patients had a reduced fibrinogen level, leading the authors also suggest that a C-reactive protein to fibrinogen ratio is a more sensitive indicator of ongoing DIC (15). DIC is one of the WHO criteria for severe malaria, as an independent marker of poor prognosis (9).

DIC in the situation of severe malaria leading to symmetrical peripheral digital necrosis is a rare phenomenon, and there are only a few reported cases in the literature (16–20). This phenomenon is believed to be multifactorial, precipitated by sequestration of infected erythrocytes in the vasculature, increased erythrocyte adhesiveness, together with platelet consumption and coexistent haemodynamic collapse (21). Also the infected erythrocytes become increasingly adhesive in malaria because of cell surface expression of parasitic antigens, as well as other cryptic epitopes and associated cell membrane phospholipid asymmetry (22,23). In addition, the vascular endothelium is activated, leading to secretion of pro-coagulant factors such as von Willebrand factors (24). This can be compounded, as in our case, by haemodynamic collapse and administration of vasopressors.

As in our case, symmetrical peripheral digital necrosis is often a manifestation of a life-threatening illness (1–4). For those who survive the acute illness, symmetrical peripheral digital necrosis is a major debilitating complication. As with ‘dry gangrene’ from other causes, in the short-term, necrotic digits are often left in order to maximise recovery of viable tissue. However, the period of time to auto-amputation varies substantially between patients. During this period it is essential that the functional capabilities of the patient are assessed by both questionnaire and occupational therapist interview (25–27). Surprisingly, questionnaires are extremely effective tools to accurately assess the patient’s functional ability and highlight the need for support (25,28). Also during this time, physical exercise with the help of a physiotherapist can stimulate collateral blood flow, increasing tissue preservation and maintain joint function (29). As with symmetrical peripheral digital necrosis, the successful rehabilitation of hands following trauma, burns or rheumatoid arthritis is very much dependent upon maintenance of small joint function and grip strength (29,30). Occasional courses of antibiotics may be necessary during this time to treat underlying wound infection. If, however, auto-amputation does not occur in a timely fashion, surgical debridement may be necessary to remove the necrotic tissue.

In summary, malaria remains a major worldwide threat to human health; including UK national travelling abroad. We have presented the unusual case of symmetrical peripheral digital necrosis secondary to severe malarial infection with DIC. This case report outlines an approach to evaluate and manage patients with symmetrical peripheral digital necrosis in the period after resolution of their acute illness.

REFERENCES