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CONCISE ARTICLE

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Plasmodium falciparum Cerebral Malaria Complicated by Disseminated Intravascular Coagulation and Symmetrical Peripheral Gangrene: Case Report and Review

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Abstract The case of a 56-year-old female tourist who survived cerebral *Plasmodium falciparum* malaria with disseminated intravascular coagulation and symmetrical peripheral gangrene, ultimately requiring amputation of her left-sided fingertips and toes, is reported. While symmetrical peripheral gangrene has been described rarely in Asian, African, and American patients with *Plasmodium falciparum* malaria and disseminated intravascular coagulation, no such case has been reported in travelers returning from endemic areas.

Introduction

During recent decades, malaria has become an increasingly important and serious health problem among Europeans traveling to endemic areas [1]. The number of patients who contract *Plasmodium falciparum* malaria is about 8,000 per year in countries of the European Union, and about 60% of these are infected in West African countries [1]. We report the first case of a Caucasian traveler returning from Africa with cerebral falciparum malaria complicated by disseminated intravascular coagulation (DIC) and symmetrical peripheral gangrene (SPG). Both cerebral malaria and SPG are linked pathogenetically to vascular occlusion, which results either from adhesive properties of the infected erythrocytes [2] or from DIC [3]. Therapeutic options are briefly discussed.

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Case Report

A 56-year-old woman was admitted to the intensive care unit in January 2002 after she had been found nonresponsive in her flat. Two days previously, she had returned from a trip to Sao Tome and Principe, West Africa. She had had no antimalarial chemoprophylaxis. The day before admission, she took acetylic salicylate because of fever up to 39°C. Her personal history was unremarkable except for nicotine (60 pack-years) and alcohol use.

On examination, she was stuporous, with a Glasgow coma scale rating of 8. Her temperature was 39.4°C, pulse rate 140/min, and blood pressure 135/60 mmHg. Cardiopulmonary examination was normal except for tachypnea (24/min). All peripheral pulses were palpable. There was no focal neurological deficit, and meningism was absent. Examination of the abdomen was normal. A stick test was positive for *Plasmodium falciparum*. A peripheral blood smear revealed high parasitemia, with 10.3% of erythrocytes infected with *Plasmodium falciparum*. A total of eight bacterial blood cultures drawn on days 1, 3, 5, and 9 remained sterile. Blood tests showed severe thrombocytopenia ($13\times10^3/mm^3$), absence of leukocytosis ($8\times10^3/mm^3$), mild anemia (hemoglobin 10.9 g/dl), an elevated C-reactive protein (175 mg/l, normal<5), and severe lactic acidosis (lactate, 8 mmol/l; normal, 0.6–1.7; pH 7.33). There was no hypoglycemia. Creatinine concentration was increased (140 μmol/l; normal, 58–96 μmol/l).

Treatment with intravenous quinine and doxycycline was initiated. On the next day, the patient was responsive but disoriented, parasitemia decreased to 2.4% at 24 h and to 0.5% at 36 h after the start of treatment. Mechanical ventilation was initiated because of respiratory insufficiency and worsening lactic acidosis (14 mmol/l, pH 7.16). No vasopressors had to be administered. On day 3, acral discolorations of her fingers and toes on the left were observed. Low fibrinogen concentration (1.2 g/l; normal, 2–4 g/l), elevated D-dimers (>8,000 μg/l; normal, <500 μg/l), prolonged prothrombin time (international normalized ratio [INR] value, 1.7), and a persistently low platelet count ($9\times10^3/mm^3$) suggested disseminated intravascular coagulation (DIC). Low doses of heparin (5,000 U/24 h), platelets, and fresh frozen plasma were repeatedly administered. Eight days after admission, the patient was extubated. Thirty days after admission, she was transferred to a neurorehabilitation clinic because she had various neuropsychological deficits. The tips of her second, third, and fourth fingers of her left hand and all toes of her left foot (Fig. 1) remained gangrenous and were amputated 6 months later. Further

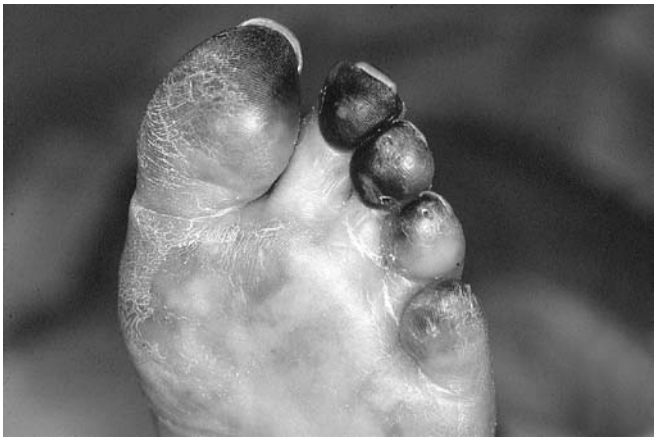

Fig. 1 Left foot of the patient on day 20 of hospitalization

evolution was uneventful, and after 1 year the patient had fully recovered and took another trip to Africa.

Discussion

According to the current World Health Organization definition, the presence of one or more of the following clinical or laboratory findings is diagnostic for severe *Plasmodium falciparum* malaria [4]. Clinical findings include an impaired level of consciousness, respiratory distress and pulmonary edema, multiple convulsions, circulatory collapse with hypotension refractory to treatment, abnormal bleeding, and jaundice. Relevant laboratory findings include severe anemia, hypoglycemia, acidosis, hyperlactatemia, hyperparasitemia (>5%), and renal impairment. In nonimmune subjects, mortality from severe *Plasmodium falciparum* malaria is about 11% in an intensive care setting [5]. DIC is observed in up to 30% of nonimmune patients with imported malaria in the temperate zone [5, 6, 7], and indicates poor outcome [5, 7]. Development of SPG has been described in few Asian, African, and American patients with *Plasmodium falciparum* malaria and DIC [8, 9, 10, 11, 12, 13, 14] (Table 1), but not in travelers returning from endemic areas.

Several factors play a role in the development of tissue necrosis and SPG. Fibrin thrombi were found in skin biopsy specimens of patients with SPG [8, 14] and, postmortem, in the capillaries of various organs, suggesting DIC [3]. Laboratory markers consistent with DIC include increased concentrations of fibrin degradation products such as D-dimers [15], low fibrinogen concentration, prolonged prothrombin time (increased INR value), and low platelet counts. The blood coagulation cascade is activated by changes in the erythrocyte membrane that occur during infection with *Plasmodium falciparum* [6, 16, 17, 18]. During hemolysis, negatively charged phosphatidylserines are exposed from the inner leaflet of the erythrocyte membrane bilayer, which trigger the formation of prothrombinase [19]. In addition,

Table 1 Clinical features of reported cases of *Plasmodium falciparum* malaria associated with disseminated intravascular coagulation (DIC) and peripheral gangrene

Case no. [ref.]	Age in years, gender	Country	Parasitemia (%)	Hemoglobin (g/dl)	Platelet count ($\times 10^3/\mu l$)	Clinical features	Antimalarial therapy	Anticoagulants
1 [8]	21, M	India	NA	6.8	210	DIC, gangrene of fingers and toes on day 3	artesunate	none
2 [8]	59, M	India	NA	5.5	100	DIC, gangrene of fingers and toes on day 3	quinine	none
3 [8]	35, F	India	NA	7.1	110	DIC, gangrene of both feet	quinine	none
4 [9]	11, M	Zimbabwe	NA	11.6	21	DIC, necrotic area on right hand	chloroquine, quinine	heparin
5 [9]	9, M	Zimbabwe	NA	12.9	10	cerebral malaria, DIC, purpura fulminans of both feet on day 3	quinine, chloroquine	heparin, streptokinase
6 [10]	46, F	India	6.0	5.0	160	DIC, gangrene of both feet	quinine	none
7 [11]	13, F	Thailand	NA	7.6	46	cerebral malaria, gangrene of toes on day 3	quinine	NA
8 [11]	10, F	Thailand	NA	NA	<50	cerebral malaria, DIC, gangrene of toes on day 3	quinine	NA
9 [12]	26, F	India	NA	10.0	NA	gangrene of fingers and toes	quinine	NA
10 [13]	22, M	India	NA	13.0	190	gangrene of fingers and toes	quinine	NA
11 [14]	44, F	Haiti	NA	7.5	28	DIC, gangrene of toes on day 3	chloroquine	heparin
12 [present report]	56, F	European tourist, Sao Tome	10.3	13.9	13	cerebral malaria, DIC, gangrene of fingers and toes on day 3	quinine, doxycycline	heparin

NA, not available

inflammatory cytokines, especially TNF-α and interleukin-6 [20, 21], increase tissue factor expression on mononuclear cells, leading to thrombin formation.

When merozoites mature to the trophozoite and schizont stages, the infected erythrocytes change their membrane composition, and knobs appear on their surfaces [2]. The altered erythrocyte surface mediates both cytoadherence to host receptors on endothelial cells and adhesion to noninfected and other infected erythrocytes. By acquiring these adhesive properties, parasitized erythrocytes are sequestered in the microcirculation, and vascular obstruction occurs [2, 8]. This potentially reversible mechanism was reported to be of importance in the pathogenesis of cerebral malaria.

DIC due to bacterial infections is the major cause of symmetrical peripheral gangrene [8, 22]. However, the negative blood cultures obtained serially in the present patient practically ruled out a concomitant bacterial infection. Nevertheless, the irreversible gangrene of fingers and toes was likely due to DIC and probably was not solely a consequence of erythrocyte sequestration because laboratory markers were consistent with DIC at the time tissue necrosis developed. Moreover, in the present case and in most of the cases reported (Table 1), signs of tissue necrosis were first observed after 3 days of effective antimalarial therapy, at which time the proportion of infected erythrocytes had fallen to below 5% of its initial value. Patients treated with high doses of norepinephrine and those with peripheral arterial disease or vasculitis are at particular risk of developing SPG.

While the management of severe *Plasmodium falciparum* malaria is well established [4], effective treatment options for patients with malaria and DIC are limited [7] except for the use of antimalarial chemotherapy. The clinical course of *Plasmodium falciparum* malaria is not positively influenced by the use of heparin [23], but low doses of heparin (300–500 U per hour [21]) are recommended in patients with DIC and extensive deposition of fibrin, as occurs with purpura fulminans or acral ischemia. If tissue necrosis is extensive, the use of thrombolytic agents may be considered [9]. However, the risk of bleeding associated with such therapy in severely thrombocytopenic patients is high; thus, these agents cannot be generally recommended. Depending on the final extent of the necrotic areas, surgical options should be considered [8, 10, 12]. The potential benefit of blood transfusions in patients with severe falciparum malaria is discussed controversially [24]. Excessive hydration must be avoided to prevent pulmonary edema [7]. On the other hand, overzealous fluid restriction may contribute to renal failure and may further impair tissue perfusion. Careful monitoring of fluid balance, therefore, is mandatory [7]. It is recommended that the central venous pressure be maintained at about 5 cm of water after rehydration.

In summary, the outcome of severe falciparum malaria depends on early diagnosis, rapid initiation of antimalarial chemotherapy, and supportive intensive care. In addition, as emphasized by the present case report, adequate antimalarial chemoprophylaxis is essential to prevent such severe complications.

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