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Case Report

Cerebral Malaria Treated with Artemisinin in the Intensive Care Unit: A Case Report

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Abstract

Malaria is a parasitic disease that is starting to be encountered in intensive care units (ICU) worldwide, owing to increasing globalisation. Severe malaria caused by *Plasmodium falciparum*, is characterised by cerebral malaria, acute renal failure, hypoglycaemia, severe anaemia, splenomegaly and alveolar oedema. We present the case of a 25-yr old male patient who presented to the Emergency Department of Uludag University in Bursa, Turkey in the winter of 2014 with complaints of fever for three days. His medical history revealed a 14-month stay in Tanzania. Staining of blood smears revealed characteristic gametocytes in accordance with *P. falciparum* infection. The day after admission, he had an epileptic seizure after which his Glasgow Coma Scale was 6, so he was intubated and transferred to the ICU. A computerized tomography scan revealed findings of cerebral oedema. Intravenous mannitol was administered for 6 days. Intravenous artemisinin was continued for 10 days. Due to refractory fevers, anti-malarial treatment was switched to quinine and doxycycline on the 14th day and on the 16th day the fevers ceased. This case emphasizes that cerebral malaria should be suspected in cases of seizures accompanying malaria, and treatment should be initiated in the ICU. Furthermore, resistance of *P. falciparum* to artemisinin should be in mind when a response to therapy is lacking.

Introduction

It is predicted that with increasing globalisation, unexpected cases of particular epidemiology will be encountered in intensive care units (ICU) worldwide. It is the responsibility of an intensivist to be up to date on these diseases and their management.

Malaria is a parasitic disease characterized by intermittent fever, anaemia and splenomegaly. In 2010, it is estimated to have caused the death of 1,240,000 people worldwide (1, 2). More than two-thirds of malaria cases come from the African continent. Severe malaria cause by *Plasmodium falciparum*, is characterised by cerebral malaria, acute renal failure, hypoglycaemia, severe anaemia, splenomegaly and alveolar oedema (3). Classic therapy includes quinine/quinidine but due to concerns for resistance, new regimens such as artemisinin derivatives have gained popularity. Their ability to clear parasitaemia rapidly and to act against more life-cycle stages of the pathogen (4, 5) are cause for their preference for rapid treatment of severe malaria cases, where treatment in the intensive care unit is required. Herein, we present a case of severe falciparum malaria managed in the ICU and treated consecutively with artemisinin and quinine. Permission to share this information has been granted by the patient.

Case Presentation

A 25-yr old male patient presented to the Emergency Department of Uludag University in Bursa, Turkey in the winter of 2014 with complaints of fever and chills for the past three days. His medical history revealed that his fever started upon return from a 14-month stay in Tanzania. Physical examination was normal except for mild sensitivity in the upper right quadrant of the abdomen and a fever of 37.8 °C. Laboratory results showed counts of white blood cells (WBC): 3230/ μ L, platelets: 26.800/ μ L, and haemoglobin (Hb): 14.3 g/dL. Other remarkable measurements included as-

partate aminotransferase (AST): 145 IU/L, alanine aminotransferase (ALT): 142 IU/L, total bilirubin: 3.4 mg/dL, direct bilirubin: 2.1 mg/dL, and C-reactive protein (CRP): 13.8 mg/dL. The chest radiogram was unremarkable. The patient was admitted after consultation with an infectious diseases specialist with a suspicion of malaria. Staining of thick and thin blood smears revealed characteristic gametocytes (Fig. 1, 2a and 2b) in accordance with *P. falciparum* malaria infection and he was commenced on a course of intravenous artemisinin (2.4 mg/kg).

Upon admittance, he had two episodes of fever reaching 39 °C for which he was treated with IV paracetamol. The day after admission, he had an epileptic seizure, which was treated with IV diazepam. A computed tomography (CT) scan of the brain was performed with a suspicion of intracranial bleeding or cerebral malaria. The result was unremarkable owing to major artefacts. A 10% glucose infusion was commenced for hypoglycaemia. The results of laboratory tests were as follows; WBC: 8140/ μ L, Hb: 12 g/dL, platelets: 22.000/ μ L ALT: 302 IU/L, AST: 192 IU/L, CRP: 21.67 mg/dL, and International normalized ratio (INR): 2.45. The patient's Glasgow Coma Scale was 6 and he was intubated and transferred to the ICU.

Another CT scan upon admission to the ICU revealed findings concordant with cerebral oedema. Intravenous mannitol was administered for a total of 6 days. Midazolam was preferred for sedation owing to presence of seizures. Intravenous artemisinin was continued at a dose of 1.2 mg/kg twice daily for 10 days, after which artesunate and lumefantrine was administered through a feeding tube for 3 days. Due to refractory fevers, anti-malarial treatment was switched to quinine and doxycycline on the 14th day (although the parasite load was nil) and on the 16th day the fevers ceased.

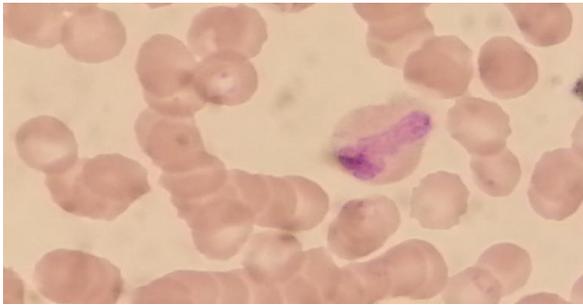


Fig. 1: Gametocyte of *P. falciparum* in a thin blood smear (Original picture)

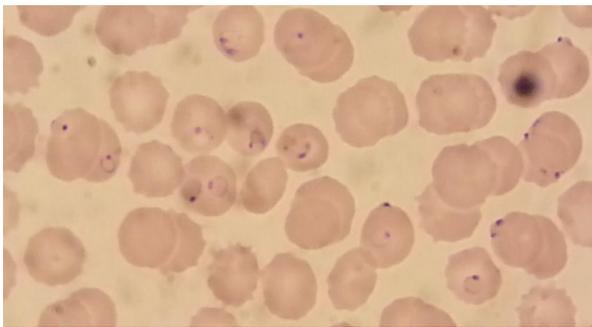


Fig. 2a: Ring-form trophozoites of *P. falciparum* in a thin blood smear (Original picture)

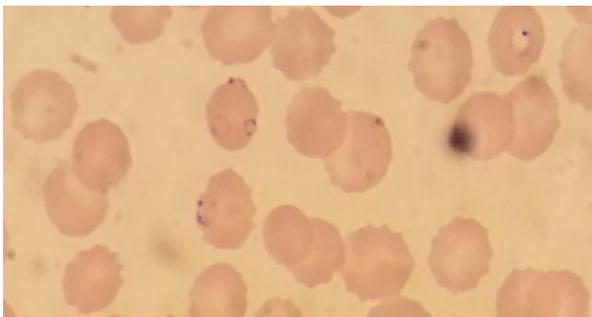


Fig. 2b: Ring-form trophozoites of *P. falciparum* in a thin blood smear (Original picture)

The patient was treated in the ICU for 19 days. He remained on ventilator therapy for 18 days and developed ventilator associated pneumonia (VAP) for which he was treated with meropenem for 10 days. He had a peak of hepatic enzymes on day 4 of ICU stay (ALT: 171 IU/L, AST: 247 IU/L). He had an episode of diarrhoea lasting 3 days, leading to a suspicion of Salmonellosis (later uncon-

firmed) for which he was treated with ceftriaxone for 9 days. High serum urea and creatinine levels during ICU stay normalized without intervention.

On examination of blood smears, total parasite load for *P. falciparum* was 8% at admission and nil after 13 days of IV artemisinin and 3 days of oral artemisinin and lumefantrine. After cessation of all antibiotic therapy, he was discharged after 25 days with no sequelae.

Discussion

We presented a case of severe malaria manifesting as cerebral malaria, managed successfully in the ICU. The patient had a recent history of travel to Tanzania without prophylactic precautions. *P. falciparum* is the commonest species of Plasmodium in Tanzania and 73% of the population live in a high transmission (>1 case per 1000) area (6). Any travellers to endemic regions for malaria are recommended to begin prophylaxis prior to departure with mefloquine and atovaquone/proguanil or doxycycline, and continue this treatment for some time after.

Severe malaria must be followed up closely due to risks of progression to a complicated case. The WHO criteria for severe disease are parasitaemia >5%, development of ARDS, impaired consciousness (seizures or GCS <11), multiple convulsions, shock, abnormal bleeding or coagulopathy, macroscopic hemoglobinuria, development of acute kidney injury (AKI), jaundice, hyperlactataemia, acidosis, hypoglycaemia, and severe anaemia (haemoglobin <5 g/dL) (7). Such patients must be transferred to the ICU if any suspicion of these conditions arises. In our patient, convulsions were the first sign and 7 of the above criteria for severe malaria were fulfilled during his stay in the ICU.

Malaria kills approximately one million people per year. Half of these deaths occur in those with cerebral malaria. Worldwide, cerebral malaria occurs primarily in African chil-

dren and Asian adults, with greater than 90% of cases occurring in children ≤ 5 years of age in sub-Saharan Africa (8). Nearly all cases of cerebral malaria are attributed to *P. falciparum* (9). In a study of children in Kenya, of 19,560 patients admitted with a diagnosis of malaria, 9,313 (47.6%) had neurological involvement. In children under 5 years of age, annual incidence of cerebral malaria was reported to be 1,156 in 100,000 (10). Cerebral malaria is characterized macroscopically by oedema, congestion and white-matter petechial haemorrhages. While congestion and haemorrhages are more difficult to actively treat, treatment of cerebral oedema is possible with corticosteroids and mannitol but the use of both these drugs in cerebral malaria are controversial. Warrell et al. (11) randomized patients into two groups, to receive either dexamethasone or placebo. There was no difference between groups as to their mortality, meanwhile complications such as pneumonia and gastrointestinal bleeding were more common in patients receiving dexamethasone. Mohanty et al. (12) studied patients with cerebral malaria related cerebral oedema on CT scans. Although not statistically significant, patients receiving mannitol had a higher mortality. A recent Cochrane database systemic review (13) does not recommend the routine use of mannitol or other osmotic diuretics in the adjunctive treatment of cerebral malaria. In our case, we prescribed IV mannitol for the treatment of cerebral oedema. The reasoning behind this decision was in accordance with the recent literature results mentioned above, therefore leaving the decision to our clinical judgment. Glucocorticoids were omitted from treatment due to the patient having developed VAP, and a decision was made to avoid further infections.

Today, WHO recommends the use of parenteral artemisinin derivatives as the first-line treatment of severe malaria (7); however, resistance to artemisinin is an emerging problem (14). This problem may start to reverse the substantial recent advances in malaria control. Parasite clearance is the criteria for determin-

ing resistance to this drug, and is determined through parasite counts in blood smears. The patient in this case had refractory fevers after treatment with artemisinin derivatives for 13 days, raising suspicion for artemisinin resistance. Although a count was performed and revealed no parasites on the 14th day, treatment was switched to quinine at this time because of a multitude of ongoing diagnoses accompanying persistent fevers, such as pneumonia, and salmonellosis. The decision to continue anti-malarial treatment was made in order to guarantee that all ongoing diagnoses were treated completely.

Because a broad range of disorders can mimic malaria, patients returning from travels to the tropics should also be evaluated for other diseases. Within these, yellow fever and typhoid fever are the two most prominent alternatives. Besides, fever associated with neurological symptoms can bring to mind diagnoses such as meningitis and encephalitis. Putting these aside, a combined presentation of fevers and neurological symptoms with a specific travel history can only lead to a few diagnoses. Our patient presented with fevers and a travel history to sub-Saharan Africa and malaria was quickly confirmed with blood smears.

Increasing travel in endemic countries and rapidly developing drug resistance will guarantee that malaria continues to be an important disease worldwide. This case demonstrates the importance of informing travellers of the rapid fatal outcome and the need for prophylaxis. It also emphasizes that cerebral malaria should be suspected in cases of seizures accompanying malaria, and supportive treatment in the ICU should be initiated in addition to anti-malarial therapy. Lastly, resistance of *P. falciparum* to artemisinin should be remembered when a response to therapy is lacking.

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