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Fever in a Traveler Returning From Africa

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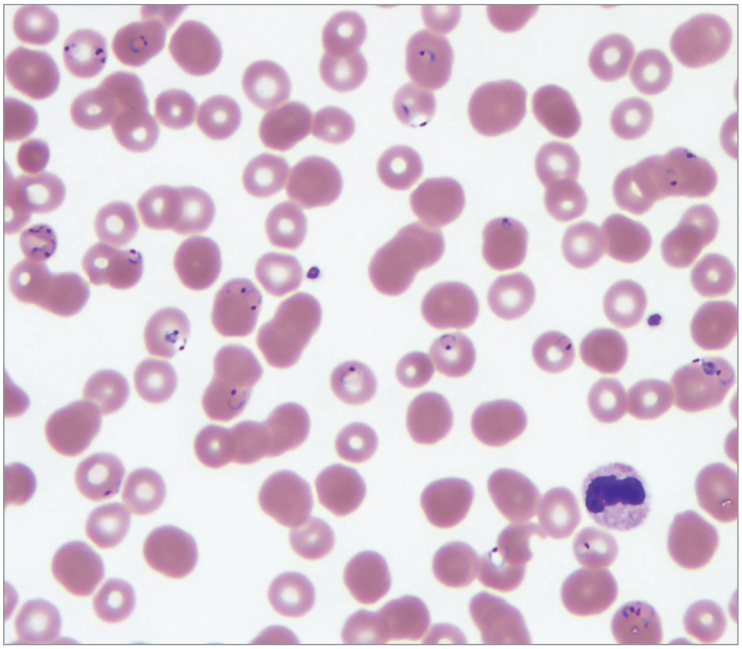

Figure. Thin preparation smear of blood obtained from patient (Wright-Giemsa, original magnification ×100).

A 35-year-old man presented to the emergency department with 4 days of fever (temperature up to 39°C), extreme weakness, fatigue, and 1 to 2 days of progressive confusion. He was born in the United States but had traveled to Sierra Leone for a period of 3 weeks and had returned 1 week prior to presentation. He did not take any form of malaria prophylaxis, nor did he use insect repellent while traveling. He previously received the yellow fever vaccine but not hepatitis A or typhoid vaccination.

Physical examination revealed a temperature of 39.3°C, heart rate of 120/min, blood pressure of 119/60 mm Hg, respiratory rate of 32/min, and oxygen saturation of 98% on room air. The patient was jaundiced, with scleral icterus, and was alert and oriented, although he had a fluctuating attention span and was unable to complete basic tasks. He was able to localize painful stimuli. No retinal lesions were present on dilated ophthalmologic examination. Laboratory tests were notable for a white blood cell count of 5000/μL with 88% polymorphonuclear leukocytes, 1% bands, 5% lymphocytes, 5% monocytes, and 0% eosinophils; hemoglobin level of 9.5 g/dL, and platelet count of 25 $\times 10^3$/μL. Sodium level was 132 mEq/L; potassium, 4.0 mEq/L; chloride, 100 mEq/L; carbon dioxide, 15 mEq/L; blood urea nitrogen, 40 mg/dL; and creatinine, 1.5 mg/dL. Total bilirubin level was 23.9 mg/dL; aspartate aminotransferase, 252 U/L; and alanine aminotransferase, 100 U/L. Venous lactate level was 49.6 mg/dL. A computed tomography scan of the head was unremarkable. A thin preparation blood smear was obtained (**Figure**).

WHAT WOULD YOU DO NEXT?

A. Start artemether-lumefantrine

B. Start chloroquine

C. Start intravenous quinidine gluconate and doxycycline

D. Perform an exchange transfusion

Diagnosis

Severe *Plasmodium falciparum* malaria

What to Do Next

C. Start intravenous quinidine gluconate and doxycycline

The key to the correct diagnosis was a thin preparation smear showing numerous normal-sized red blood cells with malarial ring forms, including some red blood cells with multiple parasites consistent with *P falciparum*. Ring forms included single and double "classic headphone" chromatin dots as well as peripheral applique forms. Banana-shaped gametocytes, which are pathognomonic for *P falciparum*, were not present. Symptoms and laboratory findings were consistent with severe malaria. The absence of cerebral edema on computed tomography scan and absence of coma or convulsions decreases the likelihood of cerebral malaria, which is more common in children.[1]

The current CDC-recommended treatment for severe *P falciparum* malaria in the United States is parenteral quinidine and doxycycline to rapidly reduce red blood cell parasitemia.[2] Choice A is incorrect because an oral agent is not the treatment of choice in cases of severe malaria. All malaria cases from Africa should be considered chloroquine resistant; therefore, B is not correct. Choice D is incorrect because no benefit has been observed for exchange transfusion in multiple studies.

Discussion

Approximately 1700 cases of malaria are diagnosed in the United States each year, mostly from travelers returning from sub-Saharan Africa, with 61% of cases identified as attributable to *P falciparum*. Sixteen percent are severe cases, which have a significantly higher attributable mortality.[3] Patients with severe malaria are found to have significant anemia, renal insufficiency, thrombocytopenia, elevated transaminase levels, coagulopathy, acidosis, hypoglycemia, and hyperparasitemia (defined as ≥10% by the World Health Organization [WHO] and ≥5% by the CDC). Cerebral malaria may be a component of severe malaria, with symptoms that include coma, seizures, or both.[1] Retinopathy can often be observed when cerebral malaria occurs in children; however, retinal changes are not always present in adults. The mortality rate associated with cerebral malaria is 15% to 20% with appropriate therapy and can increase to more than 30% with associated organ dysfunction.[1]

The currently recommended therapy in the United States for severe malaria is parenteral quinidine gluconate. A loading dose (6.25 mg base/kg or 10 mg salt/kg) is initially given to rapidly clear parasitemia and prevent early mortality, followed by a maintenance dose of 0.0125 mg base/kg/min or 0.02 mg salt/kg/min by continuous infusion. Quinidine is known to cause adverse effects including hypotension, hypoglycemia, and cardiotoxicity (QTc and QRS complex prolongation and subsequent ventricular arrhythmias).[2] Therefore, such patients are typically monitored in an intensive care unit. In patients with renal insufficiency, measurement of quinidine levels can aid in dose adjustment. Supratherapeutic levels may lead to an increase in adverse events.

The WHO guidelines recommend intravenous artesunate (not available for commercial use in the United States) as the treatment of choice for severe malaria, which differs from CDC guidelines.[2,4] Artesunate clears circulating parasites faster than other therapies. Randomized clinical trials have shown that adults treated with artesunate have a reduced risk of mortality compared with those treated with quinine (relative risk, 0.61 [95% CI, 0.50-0.75]). Additionally, adverse effects are uncommon with artesunate.[5,6] The current criteria for release of artesunate from the CDC in the United States consists of quinidine intolerance or contraindication, persistent parasitemia greater than 10% after 48 hours of treatment with quinidine, or unavailability of quinidine.[2]

After treatment with a parenteral agent for a minimum of 12 hours with subsequent documentation of reduced parasitemia to less than 1%, subsequent oral treatment should be administered. The best option includes continuation of an artemisinin derivative such as artemether-lumefantrine for 3 days.[4] Alternatives include atovaquone-proguanil or quinine sulfate with doxycycline for 7 days.[2]

Patients with uncomplicated *P falciparum* malaria should preferably be treated with oral agents such as artemether-lumefantrine. Atovaquone-proguanil or chloroquine (if the region in which the patient traveled does not have chloroquine resistance) are alternatives. Other options include quinine sulfate plus doxycycline or clindamycin. Mefloquine is an option if other agents are not available; however, this treatment is often limited by adverse events, mainly neuropsychiatric events.[7] To prevent relapse of *P vivax* or *P ovale* disease, primaquine is added to treat the hypnozoite forms protected within the liver.

Patient Outcome

This patient's thin smear showed *P falciparum* with 28.7% parasitemia. The CDC was contacted for assistance with management, and he was promptly treated with intravenous quinidine and doxycycline. After 24 hours, parasitemia decreased to 1.7%, and parasites were not observed at 72 hours. During hospitalization he developed progressive renal failure and required hemodialysis. His quinidine level was elevated at 14.6 µg/mL after 28 hours of therapy; therefore, after 48 hours of parenteral therapy, he was transitioned to oral quinine and doxycycline. His QRS complex progressively widened with oral quinine (from 84 ms to 130 ms); therefore, only oral doxycycline was maintained, for an additional 7 days. He clinically improved and at discharge had no neurologic deficits. After 1 month, he recovered normal renal function.

ARTICLE INFORMATION

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