A 36-Year-Old Haitian Man With Coma, Acute Kidney Injury, Lactic Acidosis, and Respiratory Failure

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A 36-year-old man was found diaphoretic and unresponsive. Two days of headaches and back pain preceded his presentation. The patient had lived in Haiti all his life, working as an agricultural officer, and arrived in the United States 2 weeks earlier.

Physical Examination

The patient was afebrile but tachycardic (133/min) and tachypneic (40/min). His BP was 119/63 mm Hg, and his arterial oxygen saturation was 93% on 2 L/min of oxygen via nasal cannula. He had no spontaneous eye opening, verbal response, or motor movements, but withdrew from noxious stimuli. His pupils were 3 mm, symmetric, and reactive to light. The results of the remainder of his physical examination were normal.

Laboratory Findings

Serum chemistry profile revealed the following values: sodium 124 mmol/L, bicarbonate <5 mmol/L,

blood urea nitrogen 89 mg/dL, creatinine 6 mg/dL, glucose 93 mg/dL, and lactic acid 20 mmol/L. His measured serum osmolality was 315 mOsm/kg with an estimated osmolar gap of 29 mOsm/kg. His arterial blood gas study revealed a pH of 6.8, PCO₂ of 12, and PO₂ of 185 on 2 L/min of oxygen. His aspartate aminotransferase level was 106 U/L, alanine aminotransferase level was 99 U/L, and bilirubin level was 5 mg/dL. His total WBC count was 24,300/μL with 58% bands and 24% segmented neutrophils. The hematocrit was 32.6%, and the platelet count was 22,000/μL. International normalized ratio was 1.6. Partial thromboplastin time was 93 s. Calcium oxalate crystals were present in the urine. HIV serology was negative.

He was intubated and started on broad-spectrum antimicrobial therapy. Chest radiograph revealed prominent interstitial markings (Fig 1). A CT scan

FIGURE 1. Admission chest radiograph with prominent interstitial markings.

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FIGURE 2. Thin blood film showing numerous burr cells, several schistocytes, and intraerythrocytic parasites (arrow).

of the head without contrast was normal. A lumbar puncture was not done, given coagulopathy and thrombocytopenia. Evaluation for ethanol, salicylates, and acetaminophen returned negative. His blood smear is shown in Figure 2.

What is the diagnosis?

DISCUSSION

Malaria is caused by a protozoan parasite within erythrocytes and is transmitted in endemic areas from person to person by the bite of an infected female *Anopheles* mosquito. The typical incubation period is 9 to 18 days. The majority of the approximately 1,300 cases imported into the United States annually are caused by *Plasmodium falciparum*. Diagnosis of malaria in nonendemic regions is difficult because of low frequency and nonspecific presenting symptoms, which include fever, headache, fatigue, abdominal discomfort, myalgia, arthralgia, chills, anorexia, and vomiting. If untreated, severe malaria (Table 1) can develop rapidly and carries a mortality rate approaching 100%, dropping to 10% to 25% with effective antimalarial therapy and supportive care.

Older children and adults residing in malaria-endemic countries who experience a high rate of malarial inoculations from infected *Anopheles* mosquitoes develop partial immunity after repeated infections and are, thus, at comparatively low risk for severe disease. Haiti has a relatively low malaria transmission rate and, thus, a low level of acquired malaria immunity in the general population, leaving children and adults alike at risk for severe malaria.

Although malaria is routinely considered a febrile illness, up to 40% of patients may not have a fever at presentation. Most patients, however, will have had a history of fevers or subsequently develop fevers (only 2% of patients never develop a fever). Although diagnosis usually requires identification of malaria parasites on Giemsa-stained blood smears, rapid antigen tests and molecular assays are also available. Cerebral malaria is defined by the World Health Organization as severe *P falciparum* infection with cerebral manifestations, usually including coma. Other causes of encephalopathy, such as hypoglycemia, bacterial meningitis, viral encephalitis, intoxicants, and heat stroke, should be excluded.

Table 1—Features of Severe Malaria

Impaired consciousness/coma
Prostration
Seizures
Respiratory distress (acidotic breathing)
Circulatory collapse/shock
Jaundice
Pulmonary edema
Hypoglycemia
Metabolic acidosis
Severe normocytic anemia
Hyperparasitemia
Hyperlactatemia
Acute kidney injury

Metabolic acidosis resulting both from lactic acidosis and acute kidney injury is a major cause of mortality in severe malaria. Acute respiratory failure related to acute lung injury or ARDS, pulmonary edema secondary to severe anemia and volume overload, or superimposed bacterial pneumonia is also associated with significant mortality.

The World Health Organization recommends IV artesunate as first-line therapy for adult severe malaria. Multicenter randomized trials have shown a morbidity and mortality benefit of IV artesunate over quinine in severe malaria. However, quinidine is the most widely available drug for the treatment of severe malaria in the United States, whereas artesunate remains an investigational agent available for use through the Centers for Disease Control and Prevention (CDC) for patients with severe disease, high levels of parasitemia, inability to take oral medication, lack of timely access to intravenous quinidine, quinidine intolerance or contraindications, or quinidine failure. Quinidine, when used, should be administered with a second agent, such as doxycycline, tetracycline, or clindamycin, and is associated with adverse effects, including cardiac conduction abnormalities and hypoglycemia, which require close monitoring.

The CDC recommends consideration of exchange blood transfusion (infected erythrocytes are substituted with uninfected cells) in severe malaria with parasitemia >10%, cerebral malaria, ARDS, or acute kidney injury. Evidence is derived from case series with benefit attributed to reductions in parasite load, microcirculatory sludging, and inflammatory response to parasitic antigens.

Clinical Course

The combination of severe metabolic acidosis, a large osmolal gap, acute kidney injury, and calcium oxalate crystalluria in a comatose patient strongly matched the typical profile of ethylene glycol ingestion. However, the severe hematologic abnormalities—hemolytic anemia and thrombocytopenia—were left unexplained by this diagnosis and mandated an alternative or secondary diagnosis. Accepting the absence of fever on presentation and the unexplained presence of an osmolal gap allowed the clinicians to rapidly examine and address the possibility of malaria. (An osmolal gap in severe malaria has been attributed to sick cell syndrome, which is typically associated with hyponatremia and is ascribed to accumulation of unmeasured osmotically active endogenous solutes in the setting of multiorgan dysfunction.)

Assays for methanol and ethylene glycol sent on admission were negative. IV quinidine and doxycycline were initiated within 7 h of presentation. Following

exchange blood transfusion, the patient's parasite load decreased from 12% to 2%, his mental status improved, and vasopressors were withdrawn. Blood, urine, and respiratory cultures returned negative for bacterial pathogens. Broad-spectrum antimicrobial therapy was discontinued.

The patient's ICU course was complicated by ARDS and ventilator-associated pneumonia requiring 2 weeks of ventilator support and acute kidney injury requiring hemodialysis. He was discharged home 4 weeks after admission with normal cognition no longer requiring dialysis. He returned to Haiti and is back at work.

CLINICAL PEARLS

1. Most patients with malaria develop a fever, but this can be absent at presentation.
2. Severe malaria is typically a disease of the immunologically naive (eg, young children in endemic areas or visitors to those areas) but can develop in individuals from malaria-endemic regions because of low levels of immunity to malaria.
3. Artesunate has a morbidity and mortality benefit in severe malaria and is available through the CDC.
4. Acute lung injury and ARDS can occur days into the course of severe malaria, even after initial response to antimalarial therapy and clearance of parasitemia.

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