Residents' Clinic

27-Year-Old Woman With Fever, Increased Bilirubin Level, and Thrombocytopenia

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A 27-year-old woman came to our emergency department because of a 2-day history of severe headache, retro-orbital pain, fever, chills, rigors, nausea, and vomiting. A native of Montana, in the United States, she had been working in Togo, Africa, for the past 3 years. Four weeks before the onset of symptoms, she had traveled to Burkina Faso, in western Africa, and had stayed in an urban area. Since her return to the continental United States 4 days earlier, she had resided in the area of Amelia Island, Georgia. Her past medical history was remarkable for malaria (type unknown), which had been successfully treated with chloroquine 4 years before the current illness. Because of her prolonged residence in Africa, no antimalarial prophylaxis was administered. She had received vaccinations against cholera, yellow fever, meningitis, typhoid fever, and hepatitis B and prophylactic γ-globulin for hepatitis A. She denied having any recent tick bites or exposure to tuberculosis, and a tuberculin (purified protein derivative) skin test had been negative 3 years previously. She was sexually active with a single partner but had not engaged in sexual intercourse during the previous 2 months. She denied having other specific risk factors for acquiring human immunodeficiency virus (HIV) infection and had a negative HIV-1 serologic result 5 years earlier as part of a blood donor screen.

Physical examination revealed a pulse rate of 88 beats/min, blood pressure of 100/60 mm Hg, respirations of 24/min, and oral temperature of 38.1°C. The patient appeared alert and oriented but had diaphoresis and mild distress. Her pupils were equal and reactive, and ophthalmoscopic findings were normal. The oral mucosa was dry. No sinus tenderness or nuchal rigidity was noted. A grade 1 (on the basis of 1 to 6) systolic ejection murmur was heard over the left upper sternal border. The lungs were clear to auscultation. The abdomen was soft to palpation and nontender, and bowel sounds were normal. No masses or hepatosplenomegaly was detected. Rectal and pelvic examinations were deferred at the patient's request. Neurologic findings were normal.

Initial laboratory studies showed the following results: hemoglobin, 14.2 g/dL; hematocrit, 41.1%; leukocyte count, 6.2 x 10⁹/L; platelet count, 4.1 x 10⁹/L; lactate dehydrogenase, 255 U/L; aspartate transaminase, 34 U/L; total bilirubin, 2.3 mg/dL; and direct bilirubin, 0.4 mg/dL. The results of the rest of the serum chemistry panel and urinalysis were normal.

1. On the basis of the clinical information provided, which one of the following diagnoses is least likely in this patient?
   a. Acute infection by human immunodeficiency virus
   b. Dengue
   c. Babesiosis
   d. Malaria
   e. Ehrlichiosis

   Acute HIV infection can be asymptomatic, or in some patients, an acute mononucleosis-like illness with a truncal rash can develop that sometimes necessitates hospitalization. Even though acute HIV infection or seroconversion illness is clinically indistinguishable from most acute febrile syndromes, it is very unlikely in our patient. She is in a low-prevalence group, and she denied participating in any high-risk activities. Dengue is an acute viral illness, endemic in Africa, Central and South America, the Caribbean, and Asia, that primarily consists of fever, severe myalgias, and a rash. It is caused by a flavivirus and transmitted by mosquitoes (Aedes aegypti). A severe type of dengue, known as hemorrhagic dengue, is characterized by thrombocytopenia, bleeding, and shock. Usually, dengue begins abruptly after an incubation period of 5 to 8 days. Symptoms include fever (temperatures as high as 40°C), weakness, prostration, severe headache, retro-orbital pain, and severe myalgias. Because dengue is highly endemic in western Africa, it should be considered among the possible diagnoses in our patient. Babesiosis is a hemoprotozoan infection of animals characterized by fever, hemolytic anemia, hemoglobinuria, and renal failure. Babesia microti infection usually manifests with a gradual onset of fever, chills, diaphoresis, generalized
myalgia, and fatigue; no periodicity of symptoms has been noted. The incubation period varies from 1 to several days after a tick bite or 6 to 8 weeks after a blood transfusion. On physical examination, the only constant finding is fever. Occasionally, mild hepatosplenomegaly is present. Most patients have a mild to moderately severe hemolytic anemia and a normal or slightly depressed leukocyte count. In approximately half the patients, hepatic enzyme and bilirubin levels are slightly increased. Babesiosis should be considered in a patient with fever and a history of a tick bite or exposure to ticks, even though most patients cannot recall a tick bite. The diagnosis of malaria must be considered in all febrile patients who have traveled to or lived in areas endemic for malaria or those who have received blood transfusions or blood products from persons who have been in such areas. In a person with no prior exposure to the parasite, the classic malarial illness occurs—fever, chills, sweats, and nonspecific symptoms and signs, such as headache, back pain, muscle pain, and malaise. Persons who have had frequent exposure to the parasite have partial immunity and may experience less severe symptoms or may be completely free of symptoms while infected.

Human ehrlichiosis is an infection caused by *Ehrlichia chaffeensis* and should be considered in our patient. Human ehrlichiosis has been reported in 27 states in the United States, including the state of Georgia; in addition, cases have been reported from Europe and Africa. It can manifest as a mild or severe multisystem illness; approximately 40% of affected patients require hospitalization. The incubation period is 7 to 14 days. Symptoms at onset of ehrlichiosis include fever, chills, headache, myalgia, and malaise. Rash is present in almost 40% of patients. Early leukopenia, atypical lymphocytosis, and abnormal results of liver function tests are common.

2. Which one of the following tests is most likely to help in establishing a diagnosis at this point?

- **a. HIV serology (enzyme-linked immunosorbent assay [ELISA])**
- **b. Thin and thick blood smears**
- **c. Buffy coat smear**
- **d. Blood cultures**
- **e. Culture of bone marrow aspirate**

Even if this patient has acquired HIV infection, the serologic findings will be negative in the acute stage if she has HIV seroconversion illness. On the basis of the clinical history and exposure, the most helpful test at this point is thin and thick blood smears for parasites. The results from this examination will help either identify or exclude a potentially lethal disease. Buffy coat smear could help identify ehrlichial morulae in circulating leukocytes, but this test has low sensitivity. The major diagnostic approach to human ehrlichiosis is serologic study by indirect immunofluorescence assay. Blood cultures to rule out a bacterial infection should be performed in most febrile patients who have an acute serious illness and come to the emergency department; however, they are less likely to be of help in making therapeutic decisions in the emergency setting. Culture of bone marrow aspirate is unlikely to be useful in this patient at this time; because of the recent onset of her disease, simpler and less invasive tests should be done first.

On the basis of the initial clinical impression that this patient may have malaria, thin and thick blood smears were obtained (Fig. 1).

3. Which one of the following tests is likely to corroborate the diagnosis indicated by the blood smear shown in Figure 1?

- **a. Erythrocyte sedimentation rate**
- **b. Polymerase chain reaction in blood for *Ehrlichia chaffeensis***
- **c. Indirect immunofluorescence antibody (IFA) titer for *Babesia microti***
- **d. Enzyme-linked immunosorbent assay for *Plasmodium falciparum***
- **e. Thin and thick blood smears repeated every 6 hours for 48 hours**

In this setting, an increased erythrocyte sedimentation rate is likely to be nonspecific and will provide no information about the cause of an acute febrile syndrome. A polymerase chain reaction for *E. chaffeensis* is a test that is not readily available. The diagnosis of human babesiosis necessitates the identification of the characteristic intraerythrocytic parasites on Giemsa-stained thin or thick blood smears. IFA titers may not be detectable during an acute infection. An immunodiagnostic procedure such as ELISA for detection of *P. falciparum* malaria antibodies will provide information about exposure to malaria, but it does not accurately distinguish between present and past infections. The thin and thick blood smears (dehemoglobinized and stained with Giemsa) are the mainstay of diagnosis. Preparation may take 30 to 60 minutes, the process is labor intensive, and interpretation at low levels of parasitemia requires considerable experience. Nonetheless, with a trained microscopist, the sensitivity of a single thick smear can be in the range of 92%. The timing of blood examination in diseases such as malaria is important. Depending on the developmental cycle of the parasite in which the blood sample is obtained, various stages of the parasite will appear on the thin and thick smears. Immediately after a paroxysm, the merozoite-filled erythrocytes rupture, and free merozoites can be found in the bloodstream. These are difficult to locate and virtually impossible to identify by species; however, gametocytes may be present and readily identifiable. If parasites are not found in the first blood films, additional samples for thick
and thin films should be obtained every 6 to 12 hours, for as long as 48 hours if necessary. In our patient, we repeated thin and thick blood smears every 6 hours for 48 hours.

4. Which one of the following organisms is shown in the thick blood smear obtained in our patient (Fig. 2)?
   a. Plasmodium vivax
   b. Babesia microti
   c. Plasmodium falciparum
   d. Plasmodium malariae
   e. Plasmodium ovale

Thick blood smear examination is best used as a screening procedure. Repeated blood smears may need to be assessed because of the low-level parasitemia noted in some patients. In *P. vivax* infections, the erythrocytes in the thin blood smear appear enlarged up to 1.5 to 2 times the normal diameter. In humans, *B. microti* organisms usually appear as a small ring form indistinguishable from young trophozoites of *P. falciparum*. Older stages have more abundant cytoplasm and chromatin. Unlike *Plasmodium* species, no pigment is produced in the erythrocytes infected with *Babesia* parasites. Dividing parasites, consisting of four daughter cells held together by strands of cytoplasm, are rarely seen in human blood films. The identification of the banana-shaped gametocyte (Fig. 2 B) is pathognomonic of *P. falciparum*. Occasionally, the gametocyte forms are difficult to detect in the thick blood smears. Therefore, diagnostic accuracy will rely on the interpretation of the smear by the examiner.

Severe infections, such as in our patient, display the presence of intermediate forms and higher numbers of merozoites (20 to 24 per high-power field); this finding is highly suggestive of falciparum malaria. In *P. malariae* infections, the morphologic features of the erythrocytes may be normal, but high levels of parasitemia are uncommon. In *P. ovale* infections, the erythrocytes appear enlarged and oval.

At this point, the patient was hemodynamically stable, but her platelet count declined to 2.8 x 10^9/L, and the hemoglobin, after infusion of 2 L of fluids intravenously, decreased from 14.2 to 12.5 g/dL. No signs of active bleeding were noted, and the patient remained febrile (temperatures ranging from 38.3°C to 38.7°C). On the basis of the foregoing information, the diagnosis was malaria caused by *P. falciparum*.

5. Which one of the following treatments is least appropriate for this patient?
   a. Mefloquine hydrochloride, 1,250 mg in a single oral dose
   b. Chloroquine, 250 mg intramuscularly every hour until oral therapy can be started and then 500 mg orally at 24 and 48 hours
   c. Quinidine gluconate, 10 mg/kg in isotonic saline intravenously over 1 hour (loading dose) and then 0.02 mg/kg per minute for 3 days or until oral therapy can be initiated
   d. Quinine dihydrochloride, 20 mg/kg in 5% dextrose in water intravenously over 4 hours followed by 10 mg/kg every 8 hours (maximum, 1,800 mg/day) until the patient is able to begin oral therapy
   e. Quinine sulfate, 650 mg orally three times daily for 7 days, plus tetracycline, 250 mg four times daily for 7 days

A single oral dose of mefloquine is an excellent and cost-effective treatment for falciparum malaria. Our patient, however, was unable to swallow because of nausea and vomiting. Thus, oral administration of mefloquine was not attempted because 24 hours earlier she had vomited one full dose of this drug (brought with her to the hospital). Furthermore, it was not immediately available to us. Chloroquine is not indicated if falciparum malaria is suspected because chloroquine-resistant *P. falciparum* accounts for most cases
in western Africa. Intravenously administered quinidine gluconate and quinine dihydrochloride are effective in the treatment of chloroquine-resistant *P. falciparum* malaria, but use of these two drugs necessitates monitoring in a cardiac unit while the loading dose and subsequent doses are administered. Intravenously administered antimalarial drugs should be used only if the oral route is impaired. Quinine sulfate or a combination of drugs should be given orally as soon as the patient's condition allows.

Our patient received quinine sulfate, 650 mg orally three times daily, and tetracycline, 250 mg orally four times daily, through a nasogastric tube that had been previously placed. After the first two doses of medication, the patient was afebrile. Eighteen hours after therapy was begun, the patient remained hemodynamically stable. Serial thin and thick blood smears, obtained 48 hours after therapy, were negative for parasites. The patient remained afebrile, and her hemoglobin concentration was 10.9 g/dL at dismissal, at which time a 7-day oral regimen of quinine sulfate, 650 mg three times daily, and tetracycline, 250 mg three times daily, was prescribed. She was instructed to take antimalarial prophylaxis with mefloquine, 250 mg/wk, on her return to Togo.

**DISCUSSION**

Our patient's initial clinical features were indistinguishable from many acute febrile syndromes. If the epidemiologic history is considered, a higher index of suspicion for certain diseases can be acquired. This approach will affect the diagnostic tests chosen initially and, eventually, the amount of resources spent. In our case, a high index of suspicion for malaria during the initial examination expedited the diagnosis and ensured a cost-effective management. Clinical symptoms and physical findings in patients with malaria are associated with the release of parasites and the destruction of erythrocytes. Cyclic fevers, although not pathognomonic of *P. falciparum* malaria, are not uncommon. Most frequently seen with *P. vivax*, *malariae*, and *ovale* infections, these fevers occur at the time merozoites are released from the infected erythrocytes; however, intermittent and irregular fever spikes are present at the beginning of the infection, before the rhythm of parasitic release is established—especially in nonimmune hosts. Leukopenia and thrombocytopenia are common abnormalities in patients with malaria. The frequent presence of anemia and hyperbilirubinemia reflects the severity of intravascular hemolysis. Hemoglobinemia and hemoglobinuria occur mainly when hemolysis is massive, particularly in *P. falciparum* infection, and renal failure ("blackwater fever") develops in these patients. Thrombocytopenia may be profound (platelet count less than 50 x 10^9/L) but is rarely associated with serious bleeding. Platelet sequestration by the spleen, not decreased production, is the mechanism of this complication.

For appropriate treatment of malaria, the epidemiologic history—and especially the geographic areas where the patient has lived or visited—should be known. This information is important because chloroquine-resistant *P. falciparum* malaria is now widespread throughout the world, a factor that affects the initial choice of antimalarial agents. Parasite resistance to antimalarial drugs was first recognized in South America in 1961 with chloroquine-resistant *P. falciparum*. Subsequently, chloroquine-resistant *P. falciparum* was noted in Southeast Asia (in 1962) and in Africa (in 1978). *P. falciparum* has also become resistant to other 4-aminooquinolines, to pyrimethamine and other antifolate compounds, and to sulfonamide-antifolate combinations. When choosing antimalarial therapy, the clinician should assume that most cases of *P. falciparum* malaria are resistant to chloroquine. This was a key fact to consider in our patient; Togo and Burkina Faso, the places visited by our patient, are located in the western region of the African continent, known for resistant forms of *P. falciparum*.

In Africa, chloroquine resistance has spread from the initial focus in Kenya and Tanzania in 1978 across central, southern, and now western Africa to include most areas where *P. falciparum* is transmitted. Except for some malarious countries in the Middle East, northern Africa, Central America, Haiti, and the Dominican Republic, chloroquine-resistant *P. falciparum* has been identified in all other malarious areas around the world.

**REFERENCES**