39-Year-Old Woman With Headache and Fever

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A 39-year-old woman was transferred to our facility from an outside hospital for neurosurgical management of a right parasellar mass found on computed tomography of the head. Her symptoms had started 2 days before transfer to our facility with a worsening daily headache. The headache was located in the right frontotemporal region and associated with nausea and vomiting. She described the headache as a continuous ache with intermittent throbbing but no associated aura, photophobia, lacrimation, rhinorrhea, or jaw pain. For several days before the onset of symptoms, she had intermittent fever with a maximum temperature of 39.0°C (reference range, 36.0°C-38.0°C), rigors, generalized malaise, light-headedness, and myalgias. She did not have diplopia, blurry vision, dysarthria, paresthesias, productive cough, wheezing, dyspnea, urinary urgency or frequency, dysuria, abdominal pain, loose stools, or any incontinence. A central line had not been placed at the outside facility.

The patient's medical history was notable for untreated hypertension, Bell palsy, and anemia. She was a native of the Ivory Coast and had traveled to Togo and Ghana before arriving in the United States to visit her son 3 months previously. She had no pets, did not consume undercooked meats, and did not take any medications.

On admission, vital signs were notable for a temperature of 37.6°C, a regular pulse rate of 86 beats/min, blood pressure of 152/89 mm Hg, respiratory rate of 16 breaths/min, and normal oxygen saturation while breathing ambient air. Physical examination findings were notable for a mildly erythematous oropharynx and scleral icterus; there was no lymphadenopathy or neck stiffness, and Kernig and Brudzinski signs were absent. Laboratory studies yielded the following notable findings (reference ranges provided parenthetically): white blood cell count of 8.7×10^9/L ($3.5\text{-}10.5 \times 10^9$/L) with a normal differentiation and platelet count of 83×10^9/L ($150\text{-}450 \times 10^9$/L). The total bilirubin level was 1.3 mg/dL (≤1.2 mg/dL) with a conjugated fraction of 0.3 mg/dL (0.0-0.3 mg/dL). Results of an electrolyte panel and liver function studies were otherwise normal. The patient underwent chest radiography, which revealed no consolidations. Urinalysis results were normal. Testing for serum β-human chorionic gonadotropin was negative.

Magnetic resonance imaging of the brain revealed a 6-mm left ophthalmic internal carotid artery aneurysm and a possible cavernous sinus meningioma on the right. On hospital day 2, the patient was scheduled for endovascular treament of the aneurysm, but the development of a fever (temperature, 39.4°C) prompted us to cancel the procedure.

1. Which *one* of the following is the *most likely* explanation for this patient's fever?

a. Lower respiratory tract infection
b. Urinary tract infection
c. Central line–associated infection
d. Tropical illness
e. Liver abscess

Lower respiratory tract infection is unlikely because the patient did not have respiratory symptoms and no abnormalities were noted on chest radiography. She had no signs and symptoms of a urinary tract infection and no history of central line placement. Because the patient is from West Africa, she is at risk of acquiring a tropical illness, which is the most likely diagnosis. Tropical illnesses encountered in West Africa include Ebola, typhoid or enteric fever, yellow fever, dengue fever, malaria, schistosomiasis, and chikungunya. In a patient with liver abscess, fever is typically accompanied by abdominal pain and elevated levels on liver function tests. The patient did not have this presentation.

Further infectious work-up including urine culture, throat culture, rapid *Streptococcus* test, influenza polymerase chain reaction (PCR), QuantiFERON-TB Gold tuberculosis test, and serologies for dengue virus, *Toxoplasma*, *Cryptococcus* antigen, *Histoplasma*, *Coccidioides*, and human immunodeficiency virus yielded negative

See end of article for correct answers to questions.

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results. Blood culture results were also negative. In the hospital, the patient's fever was treated with acetaminophen.

2. At this time, which *one* of the following is the *best* next step?

a. PCR for Ebola
b. Test for yellow fever–specific IgM
c. Thick and thin blood smears for malaria
d. Test for dengue-specific IgM
e. Test for chikungunya-specific IgM

Ebola is included in the differential diagnosis given that the patient is from West Africa. Ebola is a viral illness spread from person to person via contact with contaminated blood or bodily fluids up to 21 days after exposure. Symptoms include fever, headache, myalgias, vomiting, abdominal pain, diarrhea, and, in some cases, hemorrhage.[1] Our patient has been away from home for 3 months. To date, there have been no cases of Ebola in the Ivory Coast, although it shares a border with Guinea and Liberia where there has been an outbreak. Therefore, she is not likely to have Ebola and will not benefit from PCR testing of the blood. There have been outbreaks of yellow fever in the Ivory Coast, and because of this, yellow fever vaccine is recommended for travelers to this country. Illness begins 3 to 6 days after a bite from an infected mosquito. Symptoms include fever, myalgias, headache, photophobia, nausea, and vomiting. Following symptom remission, some patients have progression to a toxic phase that manifests with organ dysfunction and hemorrhage.[2] Our patient has been away from the endemic region for 90 days, much longer than the incubation period for yellow fever, and is unlikely to have this disease. Conversely, malaria can manifest months or even years after initial exposure, especially if one was previously exposed and developed partial immunity or received prophylaxis. Thick and thin blood smear for malaria is the criterion standard for diagnosis and is the most appropriate step at this time.[3] The thick film concentrates the parasites and increases diagnostic sensitivity. Nonimmune individuals may be symptomatic at very low parasite densities that initially may be undetectable by blood smear. In such cases, the smear should be repeated every 12 to 24 hours for 3 sets.

Dengue fever, also known as "break-bone fever," is a mosquito-borne viral illness associated with urban environments and manifests with fever, severe headache with retro-orbital pain, and severe myalgias and arthralgias, The incubation period is several days.[4] Given that the patient has been out of the endemic area for a longer period of time, it is unlikely that she has dengue fever. Chikungunya is another mosquito-borne illness included in the differential diagnosis. Similar to dengue fever, it is associated with urban environments; the incubation period is a few days, and the illness is characterized by sudden onset of fever, rash, and severe joint pain.[5] Our patient is unlikely to have chikungunya because she has been out of the endemic area for longer than just a few days.

A blood parasite smear revealed parasitemia with 0.5% of cells infected with *Plasmodium* that was confirmed by PCR as *Plasmodium falciparum*.

3. Which *one* of the following is the *best* treatment option for a patient who did not take malaria prophylaxis?

a. Chloroquine
b. Atovaquone-proguanil
c. Artesunate
d. Intravenous quinidine gluconate plus doxycycline
e. Exchange transfusion

The treatment choice depends on the malaria species, the clinical status of the patient, and the drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired and the previous use of antimalarial medicines.[6] The initial decision is whether the patient has *P falciparum* malaria or malaria due to *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, or *Plasmodium knowlesi*. *Plasmodium falciparum* and *P knowlesi* infections can cause rapidly progressive severe illness or death, whereas the other species are less likely to have severe manifestations. Also, *P vivax* and *P ovale* infections require treatment for the hypnozoite forms that remain dormant in the liver and can cause relapsing infection.

Subsequent treatment decisions are based on classification of the disease as severe (ie, having end-organ damage) or uncomplicated. Uncomplicated disease is treated with oral antimalarial medications, and severe disease is treated with intravenous antimalarials. Our patient had no evidence of end-organ damage including

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impaired consciousness, hemoglobin level of less than 7 mg/dL, renal failure, acute respiratory distress syndrome, hypotension, acidosis, and/or parasitemia with 5% or more of cells infected. The patient had uncomplicated *P falciparum* malaria. Although she had headache, there was no suspicion for cerebral malaria, which is a manifestation of severe malaria presenting with end-organ damage including alteration in consciousness. Further, the choice of antimalarial is based on the origin of the disease, the susceptibility of the malaria species, and the adverse effects, availability, and cost of the medication.

In general, *P falciparum* malaria acquired anywhere with the exception of the Caribbean, Central America west of the Panama Canal, and most of the Middle East is chloroquine resistant. Non—*P falciparum* malaria is susceptible to chloroquine, but resistance is increasing in Indonesia, Oceania, and Peru. In this patient, *P falciparum* malaria was acquired in West Africa. Chloroquine would not be a good choice because the organism would most likely be resistant to it. Atovaquone-proguanil is the treatment of choice for uncomplicated *P falciparum* malaria in the United States and hence is the most appropriate treatment for this patient.

In most of the world, artemisinin combination therapies are first-line treatment for *P falciparum*, but this is not the case in the United States because of low availability. For cases of severe malaria, intravenous artesunate should be used over intravenous quinine or quinidine because of markedly reduced parasitemia and risk of death when compared head-to-head.[7] In the United States, quinidine is used more often because it is more readily available than artemisinin derivatives. Doxycycline is used only in combination with artesunate or quinine as second-line therapy. The evidence for exchange blood transfusions in severe malaria is anecdotal, and no comparative trials have established efficacy.[8] In 2013, the Centers for Disease Control and Prevention (CDC) performed an analysis of exchange transfusion as an adjunct to antimalarial drugs for treatment of severe malaria and concluded that it did not affect survival.[9] As a result of this analysis, the CDC no longer recommends this treatment.

Our patient was treated with atovaquone-proguanil in the hospital. She tolerated the medication well. Her fever subsided, and her headache and nausea improved. The aneurysm was determined to be stable and did not require immediate intervention.

4. Which *one* of the following tests should be performed *next*?

a. Glucose-6-phosphate dehydrogenase (G6PD) testing
b. Hemoglobin electrophoresis
c. Repeated thick and thin blood smear
d. No additional testing
e. PCR testing for drug resistance

Testing for G6PD is not indicated in this case because patients with G6PD deficiency experience hemolytic anemia from use of primaquine or fluoroquinolones,[10] which our patient has not received. Hemoglobin electrophoresis is helpful in diagnosing sickle cell disease or thalassemia, conditions that are protective against malaria. Thick and thin blood smear remains the criterion standard for diagnosing malaria, but there is no indication to repeat the smear once the diagnosis is established, especially in uncomplicated cases unless the patient has a relapse. In patients with severe malaria, the clinician may consider repeating daily smears to monitor progress with treatment. No additional testing is required for cases of malaria diagnosed outside the United States. The CDC recommends malaria testing including PCR for confirmation of species and identification of drug-resistant mutations because of the growing resistance to antimalarials and because most of the infections are acquired outside the United States. A PCR test is not done in most areas endemic for malaria because of the high cost and the requirement for a specialized laboratory. Rapid diagnostic tests using *Plasmodium* antigens are also available for the diagnosis of malaria, but they are less sensitive in low parasitemia and may not be specific for the species. In that case, the smear is necessary for diagnosis.

The patient was discharged from the hospital with a 3-day regimen of atovaquone-proguanil. She followed up with a neurosurgeon for elective coiling of the aneurysm 1 week after completing treatment of the malaria. She remained afebrile and headache free. Following the neurosurgical procedure, she received dual antiplatelet therapy consisting of aspirin and clopidogrel. The patient planned to return home to the Ivory Coast.

5. **Which *one* of the following is recommended to prevent malaria reinfection when the patient returns home to the Ivory Coast?**
   a. Chloroquine once weekly
   b. Atovaquone-proguanil once daily
   c. Bed nets, spraying the house with insecticide, draining stagnant water
   d. Vaccine
   e. Intermittent presumptive treatment

Chemoprophylaxis for malaria is recommended for travelers to an endemic area, including expatriates who lose their immunity to malaria after approximately 5 years. Chemoprophylaxis consists of chloroquine once weekly in chloroquine-sensitive areas or atovaquone-proguanil once daily when traveling to areas with chloroquine-resistant malaria. Chemoprophylaxis is not recommended for people living in endemic areas. Because our patient lives in the Ivory Coast, an endemic area, chemoprophylaxis is not recommended. Use of insecticide-impregnated bed nets, spraying the house with insecticide, draining stagnant water, using mosquito repellant on exposed skin and clothing, and avoiding the peak mosquito feeding period of dusk to dawn are measures to decrease mosquito bites and risk of infection with malaria. These measures are recommended for travelers as well as for natives of malaria-endemic regions, such as our patient. Another promising preventive therapy is a malaria vaccine, which is not currently available on the market but is in development.[11] Intermittent presumptive treatment can be used in high-risk populations (ie, pregnant women and infants) in endemic areas.[12] Our patient is not in the high-risk group.

DISCUSSION

Malaria is a major global health problem, with an estimated 207 million cases and 627,000 deaths worldwide in 2012. Malaria is endemic in more than 100 countries, and 3.4 billion individuals are at risk worldwide. Although malaria was eliminated from the United States in the early 1950s, approximately 1500 to 2000 cases of malaria are reported each year, almost exclusively in returned international travelers.[13] Malaria is transmitted by the female *Anopheles* mosquito, and infection in humans is caused by 5 protozoan species of the genus *Plasmodium*—*P falciparum*, *P vivax*, *P ovale*, *P malariae*, and *P knowlesi*. Most cases reported in the United States are caused by *P falciparum* (58%) or *P vivax* (17%).[3]

Malaria should be part of the differential diagnosis for all patients who present with fever within 1 year after international travel to an endemic area, even if the patient has had previous exposure and developed partial immunity or has received prophylaxis. More than 90% of cases occur within 30 days of exposure.[14] The differential diagnosis for fever in a returned traveler also includes infections common in nontravelers (urinary tract infection, upper respiratory tract infection, community-acquired pneumonia) as well as typhoidal and nontyphoidal salmonellosis, dengue fever, viral hepatitis, and rickettsial infections. Nearly 95% of patients with malaria in the United States report a history of fever, but only half have a fever the day of presentation. Malaria presents with a "cold" stage in which a patient shakes with rigors, followed by a "hot" stage in which the temperature can exceed 40°C, after which the patient sweats and the temperature returns to normal.[2]

Although the fever is traditionally described as occurring in discrete episodes lasting a few hours every 2 to 3 days, the fever can have an irregular pattern throughout the day. Additional symptoms are generally nonspecific and can include headache, malaise, and myalgias. Patients may also report gastrointestinal symptoms, such as diarrhea or nausea. The most common physical examination abnormality aside from fever is splenomegaly.[2] Laboratory abnormalities are generally mild and may include transaminitis, hyperbilirubinemia, anemia, and/or thrombocytopenia. Patients with *P falciparum* malaria may decompensate rapidly, and infection with this species is a medical emergency that requires immediate treatment, particularly in nonimmune travelers. Complications may include impaired consciousness or coma, seizure, respiratory distress, severe anemia, renal failure, jaundice, or disseminated intravascular coagulation.

The criterion standard for diagnosis of malaria is microscopic identification of malaria parasites on Giemsa-stained thick and thin blood smears. If the initial smear results are negative and malaria is suspected, blood smears should be repeated at 12- to 24-hour intervals for 48 to 72 hours. Other methods of diagnosis include rapid tests and PCR. Patients with malaria should

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be treated immediately. If a patient's presentation is strongly suggestive of severe malaria and there is a compatible travel history, diagnostic testing should not delay treatment. The optimal treatment regimen varies depending on several factors, including severity, the species of malaria, the likelihood of drug resistance (based on where the infection was acquired), patient age, and pregnancy status. Oral treatment options for uncomplicated malaria include chloroquine (in sensitive areas), atovaquone-proguanil, or artemisinin combinations. Severe malaria—characterized by end-organ damage, hemoglobin level less than 7 mg/dL, parasitemia (>5% infected cells), or acidosis—is treated with intravenous artesunate or quinidine. Pregnant women are treated with mefloquine or quinidine and clindamycin for uncomplicated malaria. Detailed treatment guidelines and recommendations are available on the CDC website.[15] A flowchart is available at Ask Mayo Expert.[16]

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CORRECT ANSWERS: 1. d. 2. c. 3. b. 4. e. 5. c