

A Young Woman with Fever and Pancytopenia

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Malaria is one of the most important causes of mortality worldwide, accounting for 1.5 to 2.7 million deaths and 300 to 500 million new cases per year.¹ Although occurrence in the United States is sporadic, the incidence is rising due to international travel and human migration. A diagnosis of malaria can be missed or delayed as presenting signs and symptoms are often nonspecific, thus highlighting the need for a careful travel or migration history in any patient presenting with a febrile illness. We present a case of a young woman infected with *Plasmodium falciparum*, who presented shortly after returning to the United States from western Africa.

CASE REPORT

A 22-year-old woman presented to an outpatient clinic with a chief complaint of fever and chills for 1 week. Associated symptoms included nausea and vomiting, abdominal pain, and myalgias. Routine bacterial blood cultures and a complete blood count were obtained, and the patient was administered 1 gm of ceftriaxone intramuscularly while awaiting results of the laboratory studies. It was later discovered that her peripheral platelet count was 12,000, and she was referred to the emergency department

for further evaluation. There, it was learned that 1 week prior to presentation the patient had returned from West Africa where she had been performing missionary work for several months. A review of her peripheral blood smear revealed the diagnosis of *Plasmodium falciparum* malaria.

The patient's past medical history was unremarkable and her medications included only an unknown herbal agent intended for prophylaxis against malaria. On presentation, her temperature was 102.9°F, heart rate 101 beats/minute, respiratory rate 16 breaths/minute, and blood pressure 103/57 mmHg. She appeared ill and uncomfortable and was notably pale. She was alert and oriented in all spheres. Otherwise, her physical exam revealed mild right upper quadrant tenderness without guarding. There was no splenomegaly or lymphadenopathy. The remainder of the physical exam was unremarkable.

Initial laboratory assessment included a serum sodium of 119mmol/L (135-145mmol/L), potassium of 3.8mmol/L (3.5-5.1mmol/L), chloride of 88mmol/L (96-106mmol/L), bicarbonate of 22mmol/L (22-29mmol/L), creatinine of 1.2mg/dL (0.6-1.2mg/dL), blood urea nitrogen of 17mg/dL (7-18mg/dL), and glucose of 141mg/dL (70-115mg/dL). Total serum bilirubin was 1.8mg/dL (0.2-1.0mg/dL), AST 86u/L (<40u/L), ALT 56u/L (<40u/L),

CME INFORMATION

TARGET AUDIENCE

The July/August Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists, general practitioners, emergency medicine physicians and pathologists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be able to recognize and understand the pathophysiology, clinical presentation, diagnosis, and treatment and prevention of malaria.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

DISCLOSURE

Mr. Hébert has nothing to disclose.
Dr. Huber has nothing to disclose.
Dr. Willis has nothing to disclose.
Dr. Monier has nothing to disclose.

ORIGINAL RELEASE DATE
8/1/2003

EXPIRATION DATE
8/31/2004

Estimated time to complete this activity is 1 hour.

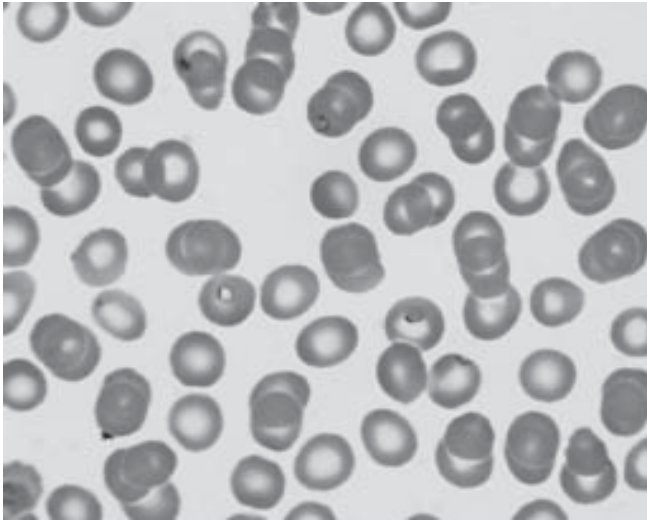


Figure 1. *Plasmodium falciparum*. Normal sized erythrocytes containing small ring forms of trophozoites are seen, classically occupying no more than one-fifth of the total red cell.

and alkaline phosphatase 40u/L (20-120u/L). A complete blood count revealed a hemoglobin of 9.7 gm/dL (12.0-16.0gm/dL), hematocrit of 28.7% (35%-45%), platelet count of 6,000/ μ L (150,000-450,000/ μ L), and white blood cell count of 3,300/ μ L (6,000-11,000/ μ L) with 39% segmented neutrophils, 32% band forms, 19% lymphocytes, and 10% monocytes. A peripheral blood smear demonstrating trophozoite ring forms consistent with a diagnosis of *Plasmodium falciparum* malaria is shown in Figure 1.

The patient was treated successfully with a 7-day course of quinine (650 mg TID) and doxycycline (100 mg twice daily) in addition to supportive care. Despite complications including hyponatremia and hypoglycemia, she was discharged home on the eighth day of hospitalization and at a subsequent follow-up evaluation was noted to be fully recovered.

DISCUSSION

A syndrome of relapsing fever has been described throughout millennia by various civilizations. Ancient Hindu and Chinese writings allude to a strange intermittent fever, and the Greek physician Hippocrates described malaria and some of its complications as far back as the fifth century B.C. When they noticed the association of the sickness with stagnant water, the Greeks and the Romans took steps to control the illness through various methods of drainage. During the 17th century, a successful treatment for the disease was found in the bark of the Peruvian guina-guina (cinchona) tree, which was later discovered to contain the alkaloid quinine. It was the Italians in the 18th century who named the disease *mal aria* meaning "foul air."²

INCIDENCE AND DISTRIBUTION

Malaria is a parasitic infection caused by obligate intracellular protozoa of the genus *Plasmodium*. The four species

that cause disease in humans are *P. vivax*, *P. ovale*, *P. malariae*, and *P. falciparum*. Each of these is typically transmitted by a vector, the female *Anopheles* mosquito, although rare cases of transfusion-related and transplacental transmission have been described. There are approximately 300-500 million cases per year of malaria worldwide with more than 100 million occurring in sub-Saharan Africa. It is estimated that 36% of the world's population resides in areas where malarial transmission occurs.¹ During the early twentieth century, malaria was considered endemic to the United States with an estimated 600,000 cases occurring per year. In 2000, a total of 1,402 cases of malaria among persons in the United States were reported to the CDC, nearly all of which are imported from endemic areas.³ Transmission of malaria within the United States is rare although sporadic cases of suspected local mosquito-transmission continue to occur. Since 1997, four such outbreaks have been described, the most recent involving two cases of *P. vivax* reported in Virginia during the month of August 2002. Neither of the two patients had a recent history of travel, blood transfusions, or organ transplantation.⁴

Malarial transmission occurs mainly in sub-Saharan Africa, Central and South America, areas of the Middle East, Southeast Asia, India, Oceania, and on the Caribbean island of Hispaniola.¹ *P. falciparum* and, to a lesser extent, *P. malariae* are found in Africa, Haiti, and the Dominican Republic. *P. falciparum* and *P. vivax* cause disease in Mexico, Central and South America, Southeast Asia, India, and Oceania. *P. ovale* infection occurs almost exclusively in Africa, while *P. vivax* rarely occurs in Africa because many Africans lack the Duffy blood group antigen essential for *P. vivax* invasion.² Transmission of all species typically occurs in tropical and semitropical environments of endemic areas and is less likely at higher elevations (>1500m) and in arid regions.

LIFECYCLE

The life cycle of malaria parasites in a human host includes transmission, an hepatic stage, and an erythrocytic stage. Transmission occurs when a female *Anopheles* mosquito injects slender malarial sporozoites into the host during the meal. Within one hour, the parasite infects hepatocytes and the hepatic stage begins. Here, sporozoites multiply asexually in a process known as exoerythrocytic schizogony. The infected hepatocyte is then referred to as a schizont, which contains thousands of merozoites. During this stage, the patient remains asymptomatic and liver function studies are typically normal. Approximately 6 to 16 days following infection, the schizont bursts releasing merozoites into the blood stream, often corresponding to the development of fever in the host. The erythrocytic stage begins as merozoites attach to receptors on the red blood cell membrane and invade erythrocytes to form trophozoites. In a process termed erythrocytic schizogony, the trophozoite uses hemoglobin to asexually replicate within infected erythrocytes forming a schizont containing many

merozoites. The schizont bursts releasing merozoites into the bloodstream, the majority of which go on to infect more red blood cells. The patient will experience a typical malarial paroxysm consisting of rigors followed by high spiking fever when this occurs. In order to perpetuate the cycle, a few merozoites develop into micro- and macro-gametocytes, which are then introduced back into a female *Anopheles* mosquito during subsequent feedings. Within the midgut of the mosquito, a sexual form of reproduction called sporogony occurs over a 10-day period in which the microgametocyte fertilizes the macrogametocyte to produce a zygote. From the zygote develops a flagellated ookinete which invades the gut epithelium and develops into an oocyst containing thousands of sporozoites. These migrate to the salivary glands and are injected into the host during the next blood meal.²

An important distinction to note in treating patients with malaria is the existence of a secondary exoerythrocytic form that remains in the liver, the hypnozoite. Both *P. vivax* and *P. ovale* are capable of forming the hypnozoite, which can remain dormant for weeks, months, or even years. This persistent liver stage is the cause of relapse in *P. vivax* and *P. ovale* infections and has important implications in treatment and chemoprophylaxis.

CLINICAL FEATURES AND DIAGNOSIS

Symptoms of malaria correspond to the red-blood-cell stage of infection. A typical malarial paroxysm consists of severe rigors followed by nausea, vomiting, headache, and fever. The presence of periodic fevers is related to the duration of the reproductive cycle for each species (every 48 hours for *P. vivax*, *P. ovale* and *P. falciparum*; every 72 hours for *P. malariae*) and should raise suspicion of malaria; however, daily symptoms often occur in *P. falciparum* infection and in early infection due to any species. High spiking fevers and severe chills are due to cytokines released in response to the release of merozoites by mature schizonts during the erythrocytic stage. Hemolytic anemia due to the destruction of red blood cells by parasites can manifest as pallor, fatigue, and hemodynamic derangement. Splenomegaly may result from the stimulation of the reticuloendothelial system by fragmented erythrocytes; it should be noted that lymphadenopathy is not a feature of malaria, and its presence should prompt investigation into other causes. Jaundice is typically secondary to hemolysis but also occurs as a result of hepatic dysfunction in severe infections. Thrombocytopenia is not uncommon and is either immune-related or, in severe infection, due to disseminated intravascular coagulation. Eosinophilia is not a feature of malaria and suggests either an alternative diagnosis or a concomitant process such as a helminth infection. Other complications can include hypoglycemia due to impaired hepatic gluconeogenesis and hyponatremia.

Malaria due to *P. falciparum* infection has the distinction of being the most devastating of the malarial illnesses and should be assumed as the causative agent in any pa-

tient presenting with severe malarial illness until proven otherwise. Severe disease with multiorgan dysfunction is seen only in *P. falciparum* malaria and is due both to the ability of this organism to achieve a heavy parasite burden and to the intravascular sequestration of parasitized red blood cells leading to impaired oxygen delivery and subsequent end-organ damage. The potential for profound parasitemia in *P. falciparum* infection lies in its ability to invade erythrocytes of all ages, whereas *P. vivax* and *P. ovale* tend to invade only young red blood cells (reticulocytes), and *P. malariae* invades mostly aging erythrocytes. Severe cases of hemolysis due to this marked parasitemia can result in darkening of the urine termed "blackwater fever" (hemoglobinuria). Sequestration of erythrocytes is unique to *P. falciparum*. This species contains large gene sequences of the *var* gene family that express high molecular-weight proteins termed *P. falciparum* erythrocyte membrane protein 1. These proteins act as "sticky knobs" on the surface of erythrocytes, which adhere to other erythrocytes (rosetting) and endothelial adhesion factors (CD36 and PECAM-1). High levels of tumor necrosis factor, a result of infection, up-regulate these endothelial adhesion factors.^{1,5,6} The "sludging" of erythrocytes in the microvasculature of vital organs is hypothesized to result in severe malarial syndromes such as cerebral malaria, acute respiratory distress syndrome, acute renal failure, and multi-system organ failure. Cerebral malaria is manifested as coma or encephalopathic features. Treatment for these syndromes is limited, so the importance of early intervention and prevention of profound parasitemia is of considerable importance.⁷

The most important clue to diagnosing malaria is a history of travel to an endemic area in conjunction with corresponding signs and symptoms of infection. The diagnosis is made by observation of specific malarial forms on a peripheral blood smear. The most widely used method employs simple light microscopy to examine thick and thin peripheral blood smears. The thick smear is a more sensitive study that allows a diagnosis of malaria even when the parasite density is low; however, the ability to determine the species is limited due to the rupture of erythrocytes and alteration of parasite morphology during preparation. The thin smear is more useful in determining which species is responsible for infection. If malarial forms are present on a thin smear, the thick smear becomes unnecessary. The diagnosis of *P. falciparum* malaria is suggested by the presence of only ring forms, banana gametocytes (rarely seen), absence of schizonts, and multi-infected erythrocytes as seen in our patient (Figure 2). Parasite density (estimated by counting the percentage of red blood cells infected under an oil immersion lens on a thin smear) greater than 3% is also suggestive of *P. falciparum* infection. If a high index of suspicion exists for a patient with no parasitic forms seen on thick or thin smears, then these studies should be repeated at 12-24 hour intervals for 3 consecutive days until a diagnosis is established or ruled out. Other diagnostic meth-

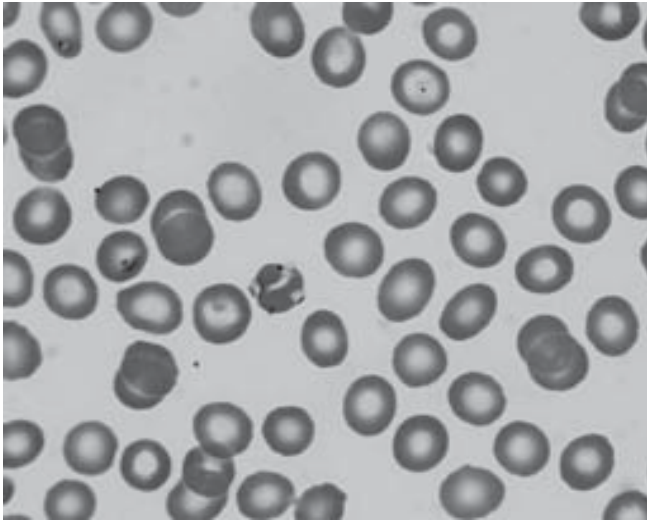


Figure 2. Small ring forms of *Plasmodium falciparum*. Multiple young ring forms seen within individual normocytic erythrocytes are characteristic of *Plasmodium falciparum*. The stuck-on appearance of these forms along the periphery of the cell membrane, the so-called *applied* position, is distinctive to this species.

ods that have been studied include the quantitative-buffy-coat method (QBC™, Becton-Dickinson) using a rapid fluorescent acridine orange stain to visualize centrifuged parasites,⁸ detection of parasitic genetic material using a polymerase-chain reaction technique,⁹ and a convenient dipstick antigen-capture assay based on the presence of the histidine-rich protein 2 of *P. falciparum*.¹⁰

TREATMENT

The emergence of antimalarial drug resistance in *P. falciparum* and *P. vivax* has hindered efforts to contain malarial transmission and has important implications when choosing therapy. Chloroquine is the drug of choice for the treatment of non-falciparum and non-severe falciparum infections acquired in areas of known chloroquine sensitivity.¹

Uncomplicated adult infection with *P. vivax*, *P. ovale*, and *P. malariae* is usually treated as an outpatient with oral chloroquine phosphate. For *P. vivax* and *P. ovale* infection, primaquine is added for prevention of the dormant hypnozoite stage. Chloroquine-resistant strains of *P. vivax* have been reported from the Solomon Islands, Brazil, Papua New Guinea, Indonesia, and Colombia. Treatment with sulfadoxine-pyrimethamine or quinine should be initiated if chloroquine-resistant *P. vivax* is suspected.¹¹ Specific dosing and treatment recommendations are summarized in Table 1.

Treatment of *P. falciparum* should be aggressive and often requires hospitalization. Chloroquine resistance occurs in all regions where this species is transmitted except areas of Central America north of the Panama Canal, Hispaniola, and limited areas of the Middle East and Central Asia. In areas with known chloroquine-resistant *P.*

falciparum, treatment should include oral quinine and sulfadoxine-pyrimethamine. If the organism is resistant to sulfadoxine-pyrimethamine, tetracycline should be substituted. In more severe cases of *P. falciparum* infection, intravenous quinidine gluconate should be considered and is indicated for > 5% parasite density, intolerance of oral medications, and the presence of cerebral malaria. For extreme cases, characterized by > 10% parasitemia, coma, or the most severe symptoms, exchange transfusion can be considered.¹³ If the species of malaria is unknown, it should be assumed to be multi-drug resistant *P. falciparum*.¹

A daily thin smear with parasite counts should be performed during treatment to ensure successful therapy. In patients receiving intravenous therapy quinidine levels should be maintained between 2-6 micrograms/mL. Patients treated with primaquine should have a G6PD level determined prior to initiating therapy.

With appropriate and early intervention, prognosis is excellent and full recovery expected. Even in the setting of cerebral malaria, no residual neurologic phenomena are expected if the patient survives.

PREVENTION IN TRAVELERS

For persons traveling to endemic areas, preventative measures are recommended to reduce the likelihood of illness and include the use of protective clothing and insect repellants containing N,N-diethylmetolamide (DEET), along with chemoprophylaxis. The Centers for Disease Control recommendations for the use of prescription medications to prevent malaria are listed in Table 2.

CONCLUSION

The incidence of malaria in the United States and other industrialized countries will continue to rise as international travel and human migration become more commonplace. What effect global warming will have on the epidemiology of tropical diseases remains to be seen. A diagnosis of malaria should be considered in any person with a febrile illness and recent travel to an endemic area. This case emphasizes the need to obtain a travel history from all patients presenting with febrile illnesses and highlights the importance of counseling and optimal use of chemoprophylaxis against malaria when travel to endemic areas is planned.

REFERENCES

1. Bloland PB. *Drug resistance in malaria*. Chamblee, Ga:Centers for Disease Control and Prevention;2001.
2. Strickland GT. *Hunter's Tropical Medicine and Emerging Infectious Diseases*, 8th edition. Philadelphia, PA: W.B. Saunders Co.; 2000:614-643.
3. Centers for Disease Control and Prevention. Malaria surveillance-United States, 2000. *MMWR CDC Surveill Summ* 2002;51(SS-5):1-23.

Table 1. Recommended Treatment for Malarial Infection

Malarial Species	Recommended Drug	Dosage (Route)
<i>P. falciparum</i> chloroquine-sensitive	chloroquine phosphate <i>or</i> chloroquine sulfate	600 mg base, then 300mg at 6, 24, and 48 hours (PO)
<i>P. falciparum</i> chloroquine-resistant	quinine sulfate <i>plus</i> sulfadoxine-pyrimethamine (S-P)	650 mg TID x 7 days (PO) 500/25 mg, 3 tabs once (PO) day 7
<i>P. falciparum</i> chloroquine-resistant S-P resistant	quinine sulfate <i>plus</i> tetracycline <i>or</i> doxycycline	650 mg TID x 7 days (PO) 250-500 mg QID x 7 days (PO) 100 mg BID x 7 days (PO)
	OR atovaquone/proquanil	250/100 mg BID x 3 days (PO)
	OR mefloquine	750 mg, then 500 mg at 12h (PO)
	OR artesunate <i>plus</i> mefloquine	4 mg/kg/d x 3d (PO) 750 mg, then 500 mg at 12h (PO)
<i>P. falciparum</i> (severe)	quinidine gluconate	10 mg/kg over 1-2 hours, then 1.0-1.5 mg/kg/hr infusion for 72h max (IV)
	OR quinine dihydrochloride <i>plus</i> sulfadoxine-pyrimethamine (S-P)	20 mg/kg over 4 hr, then 10 mg/kg q8-12 hr. (IV) 500/25 mg, 3 tabs once (PO)
<i>P. vivax</i> and <i>P. ovale</i>	chloroquine phosphate <i>followed by</i> primaquine	600 mg base, then 300mg at 6, 24, and 48 hour (PO) 15 mg base QD x 14 days <i>or</i> 45 mg weekly x 8 weeks (PO)
<i>P. vivax</i> chloroquine-resistant	quinine sulfate <i>followed by</i> primaquine	650 mg q8h x 7 days (PO) 2.5 mg base/kg x 3 over 48h (PO)
<i>P. malariae</i>	chloroquine phosphate	600 mg base, then 300mg at 6, 24, and 48 hour (PO)

Table 2. Chemoprophylaxis for Malaria

Drug	Dosage (Route)
chloroquine phosphate (sensitive areas only)	500mg salt/300mg base weekly, 1 week before, during, and 4 weeks after travel (PO)
atovaquone/proquanil	250/100 mg QD 2 days before, during, and 7 days after travel (PO)
doxycycline	100 mg QD 2 days before, during, and 4 weeks after travel (PO)
mefloquine	250 mg weekly, 1 week before, during, and 4 weeks after travel (PO)
primaquine (<i>P. ovale</i> and <i>P. vivax</i> areas)	15 mg base/26.3mg salt QD for 14 days after departing endemic area (PO)

4. Centers for Disease Control and Prevention. Local transmission of plasmodium vivax malaria- Virginia, 2002. *MMWR Weekly* 2002;51:921-922.
5. Berendt AR, Craig AG. Plasmodium Falciparum malaria - sticky jams and PECAM pie. *Nat Med* 1997;3:1315-1316.
6. Turner GD, Morrison H, Jones M. An immunohistochemical study of the pathology of fatal malaria. *Am J Pathol* 1994;145:1057-1067.
7. Steele RW, Baffoe-Bonnie B. Cerebral malaria in children. *Pediatr Infect Dis J* 1995;14:281-285.
8. Rickman LS, Long GW, Obert R, et al. Rapid diagnosis of malaria by acridine orange staining of centrifuged parasites. *Lancet* 1989;1:68-71.
9. Wataya Y, Arai M, Kubochi F, et al. DNA diagnosis of falciparum malaria using a double PCR technique: a field trial in the Solomon Islands. *Mol Biochem Parasit* 1993;58:165-168.
10. Beadle C, Long GW, Weiss WR, et al. Diagnosis of malaria by detection of Plasmodium falciparum HRP-2 antigen with a rapid dipstick antigen-capture assay. *Lancet* 1994;343:564.
11. Drugs for parasitic infections. *The Medical Letter*. New Rochelle, NY: The Medical Letter, Inc; April 2002.
12. Centers for Disease Control and Prevention. Prescription drugs for preventing malaria as of 02/01/01. < <http://www.cdc.gov/travel/malariadrugs2.htm>> (accessed 14 March, 2003).
13. Panosian CB. Exchange blood transfusion in severe falciparum malaria- the debate goes on. *Clin Infect Dis* 1998;26:853-854.

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CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 223. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to August 31, 2004. Participants must attain a minimum score of 75% to receive credit.

For each question, choose the one answer that is most correct.

1. All of the following findings are characteristics of malaria except
 - a) fever and chills
 - b) hemolytic anemia
 - c) generalized lymphadenopathy
 - d) splenomegaly
2. True or False. Peripheral eosinophilia is a common finding in patients with malarial illness.
3. True or False. *Plasmodium falciparum malaria* differs from other causative species in its ability to cause severe illness.
4. For non-immune persons traveling to areas where malaria is endemic, measures to prevent malaria should include
 - a) use of protective clothing
 - b) use of insect repellants containing N,N-diethylmetolamide (DEET)
 - c) chemoprophylactic agents based upon the intended geographic location
 - d) all of the above