A Case of *Plasmodium falciparum* Malaria in a Man 6 Months After Visiting a Malaria-Endemic Region

Jeffrey Jenks, MD, MPH, Shireen Heidari, BA,† Luisa Watts, MD,‡ and Claudia Nader, MD§*

Abstract: Unlike other malaria-causing species of the genus *Plasmodium*, *Plasmodium falciparum* normally manifests symptoms of malaria within weeks of exposure. We report the unusual case of symptomatic malaria in a previously healthy individual 6 months after staying in an endemic region. In addition, potential causes for delayed presentation of *P falciparum* are reviewed. This case shows that *P falciparum* can have a prolonged incubation period and raises questions as to causes of delayed presentation and where parasites reside before symptoms manifest.

Key Words: malaria, *Plasmodium falciparum*, antigenic variation

(*Infect Dis Clin Pract* 2012;20: 173–176)

Mal'aria, Italian for "bad air," has had a significant impact on populations and human history for millennia and continues to exert profound influence today.[1] There were 225 million estimated cases of malaria in 2009, resulting in approximately 781,000 deaths globally. This makes malaria the ninth leading cause of overall mortality in low-income countries, and one of the top 3 leading cause of death from communicable diseases.[2] The significant impact of malaria is evident by the evolutionary selection of certain polymorphisms such as sickle cell trait as protective against malaria, although sickle cell disease can be fatal.[3] Most deaths from malaria occur in sub-Saharan Africa and Southeast Asia, largely owing to *P falciparum*.[2] The Centers for Disease Control and Prevention reported just less than 1300 cases of symptomatic malaria among persons in the United States or one of its territories in 2008, with 2 fatalities.[4]

After inoculation by an *Anopheles* mosquito, *P falciparum* sporozoites mature in the host liver into merozoites, multiplying and causing rupture of the hepatocytes, releasing thousands of merozoites into the bloodstream. After infecting erythrocytes, these merozoites can either differentiate into male or female gametocytes that are subsequently taken up again by an *Anopheles* mosquito or undergo asexual multiplication in erythrocytes, rupturing the host erythrocyte and infecting other red blood cells. It is this cycle of erythrocyte invasion and destruction that causes symptomatic malarial infection.[5]

The normal incubation period of *P falciparum* is 7 to 15 days[6] but can take up to 2 months, only rarely longer.[7,8] According to 2006 data from the Centers for Disease Control and Prevention that examine the interval between date of arrival in the United States and onset of illness by *P falciparum*, 0 of 429 cases had onset of symptoms greater than 6 months after return.[9] In 2007, 6 of 497 cases were presented between 6 months and 1 year, with 3 additional cases presenting after 1 year.[10] In 2008, 0 of 388 cases were presented between 6 months and 1 year, with one case presenting after 1 year.[4] Whereas *P ovale* and *P vivax* are both known to undergo a hibernating stage in the liver where they can lie dormant for months to years in the form of hypnozoites, this dormant liver stage is not known to occur with *P falciparum*.[11]

We describe the case of a man who presented with symptomatic *P falciparum* malaria 6 months after last visiting a malaria-endemic region. Prompted by this unusually long interval, we reviewed other cases with delayed presentation of *P falciparum* and discuss some of the potential reasons for delayed onset of symptoms.

CASE REPORT

Our patient was a 50-year-old man with a history of hypertension, chronic lower back pain secondary to spinal stenosis, and hepatic steatosis who presented to Boston Medical Center in Massachusetts, USA in January 2011. He reported a 3-day history of myalgias and headache, along with recurrent episodes of fever, chills, and sweats that began acutely after shoveling snow. He had been taking acetaminophen for his symptoms, with fevers, chills, and sweats recurring cyclically every 4 hours. He also complained of a dry cough that began 2 days before his admission. He denied photophobia, nausea, vomiting, neck stiffness, sore throat, or other symptoms. He denied a history of intravenous drug use.

Upon presentation to the emergency department, he was noted to have a temperature of 100.5°F, with normal hemodynamic parameters. The remainder of his physical examination was normal, without localizing signs of infection. Blood tests revealed a white blood cell count of 3.5×10^9 cells/L, a hemoglobin level of 12.7 g/L, and a platelet count of 66×10^9 platelets/L. In addition, he had a slightly elevated alanine aminotransferase level of 68 and an aspartate aminotransferase level of 74. Chest radiograph was normal. Serologic test results were negative for both influenza and human immunodeficiency virus. A peripheral blood smear obtained in the emergency department revealed a density of 2.6% parasitized erythrocytes (Fig. 1).

The patient was born in Nigeria and immigrated to the United States some time in 1990. He reported a history of malaria while in his 20s but was unsure how it was treated. He often traveled to Nigeria over the ensuing years to visit family. In 2006, he reported a trip to Nigeria; he remembered taking prophylaxis for malaria but was unsure of details. He did not recall illness during or after that trip. On a subsequent visit the following year, he remembered taking mefloquine for malaria prophylaxis. Most recently, he traveled to Nigeria the previous

From the *Department of Internal Medicine, †Boston University School of Medicine, Departments of ‡Pathology and §Infectious Diseases, Boston University School of Medicine, Boston, MA.
Correspondence to: Jeffrey Jenks, MD, MPH, Boston University School of Medicine, 72 E Concord St, Evans 124, Boston, MA 02118.
E-mail: Jeffrey.Jenks@bmc.org.
The authors have no funding or conflicts of interest to disclose.
This material is original and has not been published elsewhere.
All authors have participated in the study and concur with the submission and subsequent revisions submitted by the corresponding author.

ISSN: 1056-9103

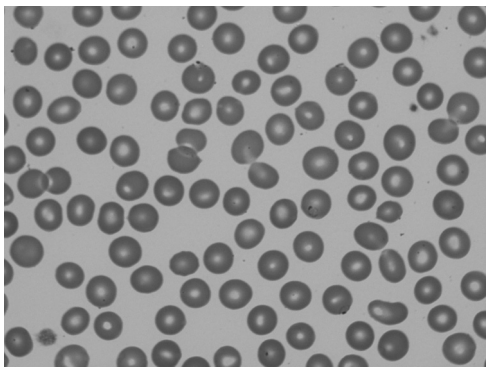

FIGURE 1. Peripheral smear obtained on the patient in the emergency department, revealing a density of 2.6% parasitized erythrocytes.

summer for a 3-week duration, returning in early to mid-July. He did not take prophylaxis at that time, and although he did use repellents, he reported getting mosquito bites. He denied becoming ill during the latest trip. He also reported that his ex-wife and children had recently traveled to Nigeria for approximately 1 month and returned a few days before his presentation to the Boston Medical Center emergency department.

The patient was admitted to the Internal Medicine service, and the Infectious Disease service was consulted. He was started on artemether-lumefantrine (Coartem) for presumptive treatment of *P falciparum* malaria. The total course was 6 doses of 4 tablets each. After the first dose was given, the second dose was administered 8 hours later. The remaining doses were then given every 12 hours. Hospital day number 1 was remarkable for a fever of 102.8°F, along with continued chills and sweats. He continued to have headaches that responded well to acetaminophen. Follow-up peripheral smears on both hospital days 2 and 3 did not identify any parasites. He was discharged on hospital day 3 after completing 4 of 6 doses of artemether-lumefantrine, with instructions to complete therapy at home.

At discharge, there was concern for the possibility of a dual infection with *P falciparum* and either *P ovale* or *P vivax*, which was thought to potentially explain the abnormally long incubation in this case, or recrudescence of an inadequately treated previous infection. Because *P ovale* and *P vivax* would not be adequately treated with artemether-lumefantrine, the patient was discharged on a 14-day course of primaquine, with instructions to take one 30-mg tablet daily. The initial peripheral smear was reviewed by both a microbiologist and a pathologist specializing in microbiology, who identified morphologic characteristics consistent with *P falciparum*. No characteristics of *P vivax* or *P ovale* were identified. He was followed up in the outpatient Infectious Disease clinic, with complete resolution of his symptoms, malaria infection, and resolution of his thrombocytopenia.

DISCUSSION

The normal incubation period for *P falciparum* is 1 to 2 weeks, with more than 95% of patients becoming clinically symptomatic within the first 2 months after exposure to an infected mosquito.[11] The life cycle of the *Plasmodium* parasite in humans consists of 2 stages. During the first stage, known as the liver or exoerythrocytic stage, the parasites invade and multiply in the hepatocytes. In the second stage, known as the blood or erythrocytic stage, the parasites are released into the bloodstream, invading the erythrocytes and causing clinical illness.[11] Both *P ovale* and *P vivax* are known to have prolonged liver stages, in which they can emerge months to years later, causing symptoms of malaria. In contrast to *P ovale* and *P vivax*, neither *P falciparum* nor *P malariae* is known to have a dormant liver stage, although *P malariae* may have a prolonged incubation period of months to years. It is not known where *P malariae* resides during this period.

There is some evidence that persistent *P falciparum* parasitemia can occur in individuals who have developed antimalarial immunity as a result of repeated infections.[9] In our case, the patient recalled a distant malarial infection decades ago, as well as frequent trips to Nigeria during which he could have been exposed. During his 3-week vacation the previous summer, he reported not taking prophylaxis for malaria. Partial immunity is thought to provide protection for a few months but, in the absence of reinfection, typically wanes and results in clinical symptoms.[12] In most cases of delayed presentation due to partial immunity, the parasitemia burden is less than 1%,[12,13] well below our patient's parasitemia burden of 2.6%.

Other factors are thought to predispose toward delayed manifestation of malarial symptoms. Mefloquine prophylaxis is also thought to result in a delayed manifestation of symptoms,[12] but symptoms typically manifest within a few weeks rather than months[14] as in our case. Notably, our patient denied taking mefloquine during his most recent visit to Nigeria. Thus, it is possible that repeated exposure to infected mosquitoes resulted in partial immunity, causing a low parasitemia burden that persisted without clinical symptoms.

In rare cases, individuals either visiting airports or traveling within the vicinity of airports have become infected with malaria. Mosquitoes can be dispersed as far as 4 miles from an airport under favorable wind conditions, and have been known to travel as far as 5 miles in luggage.[15] Infected mosquitoes can survive for extended periods in aircraft cabins, cargo holds that have been sprayed with insecticide, and even in the wheel bays of aircraft.[16] In 1999, a small outbreak of "airport malaria" at the Roissy Charles de Gaulle airport outside of Paris resulted in 4 cases of *P falciparum* malaria. The only commonality noted among the infected individuals was that they lived close to an airport shuttle stop for employees that worked at the airport. Between 1975 and 2000, 75 cases of airport malaria have been reported.[10] Our patient had not been near an airport within weeks of his presentation to our hospital, although his family had recently returned from Nigeria. There is the possibility that a mosquito stowed away in the family baggage, infecting our patient shortly after the return of his family to the states.

Even rarer are documented cases of malaria acquisition through needlestick injuries in hospitals or health centers. A review of the literature in 2005 noted 22 documented reports of "occupational malaria," all from *P falciparum*. The mean incubation time was 12 days, with a range of 4 to 17 days, consistent with incubation periods from direct inoculation by *Anopheles* mosquitoes.[17] More common are the thousands of cases of transfusion-related malaria that have been reported over the past half-century, and this number may be vastly underreported.[18] Transfusion malaria most commonly occurs through contaminated red blood cells but can occur through transfusion of whole blood, cryoprecipitate, platelets, plasma, granulocytes, and even frozen blood. Potential donors who have visited or resided in malaria-endemic regions within a certain time period are excluded from donating blood. Otherwise, there is currently no ideal and sensitive method for screening blood for malaria.[18] From 1963 through 1999, there were 93 cases of

transfusion-transmitted malaria reported in the United States, 35% involving *P falciparum*.[19] Notably, our patient had never received a blood transfusion.

Furthermore, individuals in regions endemic for malaria who are consistently infected with malaria may develop a decrease in disease severity and frequency of malarial episodes. This is likely the result of acquisition of an array of antibodies targeting specific *Plasmodium* antigens.[20] As noted earlier, it seems that this immunity quickly wanes as infections become less frequent. Still, although partial immunity wanes, there is evidence that some residual immunity may persist, protecting against fatal *P falciparum* infection. In one study of Europeans traveling to malarious areas, nonimmune Europeans had significantly higher case fatality rates than non-Europeans (1.7% vs. 0.2%) had. In this study, the source of all fatalities was travelers returning from sub-Saharan Africa, and a large number of the infected non-Europeans were originally from endemic countries.[21] Thus, non-Europeans who had previously lived in malarious regions may have developed residual partial immunity after previous infections, resulting in lower fatality rates from *P falciparum*.

Intriguingly, there is evidence that *Plasmodium* species have the ability to vary surface antigen expression, in effect altering the profile of antigens it exposes to the immune system. Specifically, *P falciparum* expresses the highly variable *P falciparum* erythrocyte membrane protein 1, which belongs to a large gene family called *var*. This protein is expressed on the surface of infected red blood cells, which bind tightly to endothelial cell receptors. As these erythrocytes bind to endothelial cells, they are essentially removed from circulation, resulting in decreased clearance by the immune system and spleen.[22] In addition, there is some evidence that the spleen can remove infected erythrocytes and return the previously infected intact red blood cells back into circulation after antimalarial treatment. In one small study, the spleen was able to clear dead or damaged intraerythrocytic parasites from infected red blood cells and return the intact cells into circulation after artesunate treatment. These findings reinforce the importance of the spleen in combating malaria, especially in conjunction with antimalarial treatment.[23]

It would seem that whereas the host immune system has an array of antibodies available in its arsenal, *Plasmodium* has the capability of evading these defenses by switching the antigens it presents on erythrocytes. These surface antigens seem to play a role in disease virulence, linking "antigenic variation" to pathogenicity.[24] Furthermore, there is evidence that *P falciparum* may even persist in dormant stages, which have been found on histologic examination in the placenta of pregnant women in malaria-endemic regions of Africa.[25] In fact, one variant of *P falciparum* erythrocyte membrane protein 1 specifically binds to receptors in the placenta, which may explain how *P falciparum* is sequestered there.[22] In more than half of these cases, peripheral blood smears were negative for evidence of *Plasmodium* parasites.[25] In addition, there is evidence that a latent form of some species of *Plasmodium* may infect the lymphatic tissue of rodents.[26] Could the same hold true in humans?

CONCLUSIONS

In conclusion, we present the unusual case of a man who presented with symptomatic malaria caused by *P falciparum* 6 months after visiting a malaria-endemic region. The circumstances surrounding his presentation make airport malaria and occupational malaria unlikely. It is likely that he developed partial immunity from an infection obtained after living in Nigeria for many years, or on a previous visit to Nigeria, allowing him to tolerate the level of parasitemia found in his blood.

Lastly, this case raises the intriguing question of whether antigenic variation or prolonged *P falciparum* dormancy may contribute to the delayed onset of symptoms seen in some cases of *P falciparum* infection. Does a sudden alteration in antigen presentation on erythrocytes cause the immune system to react to a previously asymptomatic low-level parasitemia burden? Or, as previous cases have suggested, does *P falciparum* have the ability to sequester itself in tissue outside of the bloodstream? This case demonstrates the need to consider *P falciparum* infection long after potential exposure and raises several questions regarding its biologic characteristics and causes for delayed presentation.

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