Relapsing Malaria Infection Acquired in Kenya

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An American physician-traveler to East Africa presented with manifestations of cerebral
malaria and was treated with intravenous quinidine for chloroquine-resistant falciparum malaria. He
later relapsed with Plasmodium ovale infection, despite previous primaquine therapy. Treatment of
chloroquine-resistant malaria is discussed. The difficulty in diagnosing P. ovale infections and the
predominance of this malaria species over P. vivax in East Africa are reviewed.

CASE PRESENTATION

DR. JAN PATTERSON (Infectious Disease Fellow): A 58-year-old white male physician
from North Haven, Connecticut, was admitted to Yale–New Haven Hospital in July
1985, complaining of chills and fever to 104°F. He had been healthy until ten days
prior to admission when he suddenly developed malaise, chills, and fevers while at
home. He also noted anorexia, nausea without vomiting, and headache associated with
fever. Two days prior to admission, he was noted to be confused and disoriented. He
was treated empirically with oral tetracycline, but fever and malaise continued, and he
presented to Yale–New Haven Hospital.

On physical exam, his skin was flushed and he appeared confused. Systolic blood
pressure was 82 mm Hg and his neck was somewhat stiff. Lungs were clear. Cardiac
exam revealed a regular tachycardia without murmurs. His abdomen was not tender.
Neither hepatomegaly nor splenomegaly were noted. Laboratory examination showed
a white blood count of 4,800 cells/μl with 50 neutrophils, 34 band forms, 5
lymphocytes, 3 monocytes, 7 atypical lymphocytes, and 1 basophil. The hematocrit
was 43 percent, and his platelet count was 96,000/μl. Blood urea nitrogen was 23
mg/dl and serum creatinine was 1.3 mg/dl. His urinalysis showed 2–5 red cells per
HPF, a small amount of hemoglobin, and a few bacteria.

A PHYSICIAN: He lives in North Haven, Connecticut, but has he recently traveled?

DR. PATTERSON: Yes, back in March he traveled from Florida to the coast of South
Carolina. In January he had traveled on safari in Kenya, and to several coastal areas
of East Africa on the Indian Ocean. He took malarial prophylaxis, starting his chloro-

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quine phosphate (Aralen, Winthrop-Breon) two weeks before departure, taking 500 mg weekly during the trip, and continuing for about six weeks after that; however, he did not take pyrimethamine-sulfadoxine (Fansidar, Roche) for prevention of chloroquine-resistant malaria.

A PHYSICIAN: Is it possible he had falciparum malaria that was suppressed by chloroquine but then relapsed?

DR. PATTERSON: He had a peripheral blood smear done by his physician two days prior to admission. It was read as negative for malarial parasites, and he was started on tetracycline for possible Lyme disease at that time.

He had a chest radiograph done on admission here; spleen size was not commented upon but the left hemidiaphragm appeared elevated. Serum LDH was 786 IU/L (normal 110–220). Liver function tests were otherwise normal. So, what would you do at this point?

A PHYSICIAN: I don’t think a single negative malaria smear excludes that diagnosis. I’d get at least three blood smears done. People simply aren’t used to diagnosing it. He appeared quite ill, and you would expect him to have a positive blood smear if he actually had falciparum malaria.

DR. PATTERSON: He had another malaria smear done (Fig. 1) and it was positive. The upper ring form had a double chromatin dot which suggests falciparum malaria. There are two trophozoites shown but the lower one has a more amoeboid appearance. An amoeboid trophozoite is more suggestive of vivax or ovale malaria. Because of his extremely ill appearance and history of travel to an area where about 85 percent of the malaria exposure was to Plasmodium falciparum, we were really concerned about falciparum malaria.

DR. FRANK BIA (Associate Professor of Medicine): Figure 2 shows two ring forms in one red blood cell which is also suggestive of falciparum malaria, but which can occasionally be seen in vivax malaria. Vivax, ovale, and falciparum parasites all prefer to invade reticulocytes; however, falciparum can invade erythrocytes at any stage and cause high levels of parasitemia [1]. A reticulocyte with a ring form may be more noticeable in vivax or ovale malaria, but this finding is nonspecific. Figure 3 shows one of many schizonts containing about 18 merozoites. Falciparum shows a wide range of merozoites (8–32), but schizonts are rarely seen in the peripheral blood smear during
attacks of falciparum malaria unless the parasitemia is quite high. There were no crescent-shaped falciparum gametocytes observed on our patient’s smear.

DR. PATTERSON: In summary, we have a patient with mental confusion, hypotension, and hemoglobinuria who has malarial parasites in his peripheral blood smear. Certainly his clinical appearance is most suggestive of falciparum malaria. His peripheral blood smear has some features suggestive of falciparum, but also of mixed infection with vivax or ovale.

A PHYSICIAN: What about his relapsing this late with falciparum malaria? Wouldn’t that be unusual? It’s not like vivax malaria in which you have a persistent liver stage.

DR. PATTERSON: Relapse and recurrence would suggest our patient had a course of therapy for a primary attack, which he did not; he only received prophylaxis. Relapse is a return of malarial infection due to activation of the exoerythrocytic phase, which only occurs with vivax or ovale. Recurrence or recrudescence can occur with any of the types, when some erythrocytic parasites survive despite treatment [2].

Without prophylaxis, the intrinsic incubation period for falciparum malaria is about 10–14 days and the longest for falciparum malaria is about 25 days. In nonimmune patients, resistant parasites can reappear up to two months after completing therapy.
After prophylaxis, however, the primary falciparum episode can be suppressed for weeks to months, and the relapsing types of malaria can be suppressed for months to years [1].

A PHYSICIAN: Isn’t most of the falciparum malaria in Kenya resistant to chloroquine? Did you decide to use intravenous quinine or quinidine?

DR. PATTERSON: Chloroquine resistance has become much more prevalent. In 1982 an increase in the number of chloroquine-resistant isolates was noted in East Africa [3], and chloroquine-resistant falciparum malaria is a major concern for travelers to Kenya.

DR. BIA: Because falciparum malaria was a serious consideration in this case, it was decided to treat him immediately with intravenous quinidine. This drug is the optical isomer of quinine and is more readily available because it is used as an antiarrhythmic agent. It takes about 8-12 hours to obtain intravenous quinine from the Centers for Disease Control, and this patient was too ill to wait that long. Intravenous quinidine has been used successfully in areas where chloroquine resistance has been a problem, as we will discuss later.

DR. PATTERSON: Because of hypotension the patient was admitted to the Medical Intensive Care Unit for continuous monitoring and for administration of intravenous quinidine. His blood pressure improved with intravenous fluids. He received 1.5 g of quinidine gluconate over four hours as a loading dose (15 mg/kg) followed by 650 mg (7.5 mg/kg) intravenously over four hours every eight hours. This was a fairly high dose of quinidine, but he tolerated it well. The doses were given slowly to avoid hypotension. His cardiogram showed an increased Q-T interval but no dysrhythmias.

He also received chloroquine initially.

He quickly defervesced and his parasitemia began to resolve. By the fourth day after admission, his peripheral smear was negative for malarial parasites, and he was very anxious to leave the hospital. He was treated with oral quinidine sulfate (600 mg by mouth, three times a day) for three more days and also took primaquine phosphate (15 mg base/day primaquine, Winthrop-Breon) for two weeks to prevent a relapse of any possible vivax or ovale malaria.

DISCUSSION

The case brings up several interesting problems. There has been an increase in the incidence of chloroquine-resistant falciparum malaria, particularly in East Africa [4]. Also, this may well have been a mixed infection, and we must return to that issue later. Another important point is the prior administration of tetracycline and any effects that it may have had on diagnosis. Tetracycline is effective against the asexual parasites of chloroquine-resistant falciparum malaria. However, oral quinine is usually given for the first three days until tetracycline can reach its full antimalarial effect. Our patient had received tetracycline prior to admission. This may be the reason his blood smear did not show florid falciparum malaria with high-grade parasitemia.

The worldwide incidence of malaria is still about 300 million cases per year and more than one million deaths per year are attributed to malaria in Africa alone [5]. There were 849 cases of falciparum malaria, acquired abroad by U.S. citizens, which are reported from 1973 through 1983. Thirty-one deaths occurred in this group for a case-fatality ratio of four percent. However, these numbers also reflect a sevenfold
increase in *P. falciparum* infections among U.S. travelers from 1973 to 1983, accounted for largely by a nearly tenfold increase in *P. falciparum* infections acquired in East Africa [6].

The clinical manifestations of malaria are similar to what this patient experienced—malaise, headache, myalgias, and fatigue. High fever, chills, and rigors may occur every 48 hours during attacks of falciparum or vivax malaria, the time it takes to complete asexual reproduction within the red blood cell. Hypotension, related to fever and volume depletion, is common. Hepatosplenomegaly may be present. Although it was not detected by physical exam, our patient did have an elevated left hemidiaphragm, indicating that his spleen may well have been enlarged. Symptoms may appear before the peripheral blood smear is positive; hence, several serial blood smears should be performed.

Cerebral malaria occurs characteristically during attacks of falciparum malaria. Mental status changes can be quite variable, ranging from coma or lethargy to seizures or psychosis. Movement disorders can occur and range from mild tremors to myoclonus and severe tremors [7]. Falciparum-infected erythrocyte membranes eventually form knobs which adhere to vascular endothelium. This condition causes sequestration of the more mature forms and explains why the younger ring forms predominate in the peripheral blood smear. This is the most likely explanation for the obstruction of cerebral vessels leading to cerebral malaria [1]. Early therapy is critical, as this disease left untreated can be fatal within a matter of hours.

His initial hematocrit was 43 percent, but he was quite dehydrated. After hydration, it dropped to 34 percent. Anemia is common in these patients, due to hemolysis of infected erythrocytes [1]. His serum lactic dehydrogenase (LDH) was elevated, and free hemoglobin was detected in his urine, suggesting hemolysis. His initial platelet count was 96,000 per μl and it quickly increased to 150,000. His peripheral smear also showed a left shift and leukopenia. A transient leftward shift can be observed, particularly in the early course of falciparum malaria.

The therapy of chloroquine-resistant falciparum malaria raises some problems. It can be treated orally with a combination of quinine and tetracycline. The indications for parenteral therapy include several complications of falciparum malaria associated with high-grade parasitemia such as severe anemia, renal failure, or cerebral dysfunction. Because of these complications, a parasitemia of greater than 5 percent is considered an indication for parenteral therapy. Our patient had several of these indications for parenteral therapy. He was also given chloroquine initially, because a mixed infection was suspected. Species other than *P. falciparum* are not known to be chloroquine-resistant.

As noted previously, chloroquine-resistant malaria has been on the increase in East Africa since 1982. There are degrees of drug resistance in falciparum malaria. Some organisms have low-level, or R₁ resistance: parasitemia is initially suppressed by chloroquine but returns within weeks. R₂ resistance means there is an initial improvement clinically but then parasitemia rises again. With R₃ resistance, no response to therapy occurs. [1]. Most chloroquine resistance is at the R₁ or R₂ level. Cinchona alkaloids were used to treat malaria prior to the current era of antimicrobial therapy. Quinine has been preferred over quinidine because of less cardiotoxicity [8]. As methodology improved and quinine was purified, other alkaloids, including quinidine, were removed. Earlier studies indicated, however, that quinidine may have been the
more effective of the two; it has been noted to cause more rapid defervescence [9]. Recent studies in areas where multi-drug resistance is a problem showed that *P. falciparum* was more sensitive *in vitro* to quinidine than to quinine [10].

An important study was done in Thailand to evaluate therapy of severe falciparum malaria with intravenous quinidine [11]. Lack of general availability of parenteral quinine, the emergence of both chloroquine and quinine resistance, and favorable experience with oral quinidine dictated the need for such a study. Fourteen patients were treated with intravenous quinidine in doses equivalent to what our patient received. Twelve of the 14 patients so treated survived, and two of the five patients with cerebral malaria died. Two survivors had recurrent parasitemia after return to endemic areas. The drug was given over four hours and was generally well tolerated.

The reluctance to use intravenous quinidine stems from fear of its cardiac toxicity, which is felt to be greater than that of quinine. Although electrocardiographic changes occur, no life-threatening dysrhythmias were observed in the Thailand study or in our patient. If quinidine is administered slowly over four hours, no significant hypotension should occur. In the Thailand study, two of 14 patients developed hypotension during initial drug loading, but it was easily corrected with volume infusion. Some patients completed their course of quinidine with oral therapy, as did ours.

Because of the emergence of chloroquine resistance, CDC had previously recommended using both weekly chloroquine phosphate and Fansidar (pyrimethamine-sulfadoxine) for malarial prophylaxis in East Africa. In April 1985, this recommendation was changed because of cutaneous reactions that were thought to be caused by the sulfa component in Fansidar. There were twenty episodes of severe cutaneous reactions, including Stevens-Johnson syndrome, and six of these reactions reported to CDC were fatal [12]. The risk of Stevens-Johnson syndrome in travelers taking Fansidar is estimated to be 1 in 20,000. The risk of fatal falciparum malaria is 1 in 30,000. Thus, the recommendations for prophylaxis vary according to the length of exposure.

Travelers to areas of high risk for chloroquine resistance for periods of three weeks or less are now advised to carry three tablets of Fansidar to take all at once for a presumed malarial attack when professional medical care is not available. For longer exposure periods, one tablet per week may be taken, in addition to weekly chloroquine, except by those patients who have a history of sulfonamide or pyrimethamine intolerance. Fansidar must be discontinued immediately if mucocutaneous signs or symptoms develop. As far as prophylaxis against *P. ovale, P. malariae*, or *P. vivax* is concerned, chloroquine resistance is not a problem; however, primaquine is needed to prevent recurrent attacks of *P. ovale* or *P. vivax* infection. A normal glucose-6-phosphate dehydrogenase (G-6-PD) level should be documented first, particularly in blacks, Asians, and Mediterranean peoples, because primaquine could cause hemolytic anemia in patients with G-6-PD deficiency.

A PHYSICIAN: How much does the reported resistance to Fansidar represent true resistance versus inadequate response to once-a-week prophylaxis?

DR. BIA: We don't know. Chloroquine maintains adequate suppressive blood levels for a week. Fansidar may not. A Yale faculty member returned from a trip to Tanzania with a blood smear positive for *P. falciparum* while still taking prophylactic chloroquine and Fansidar. CDC pointed out to us that in Tanzania there were problems with
both chloroquine resistance and inadequate blood Fansidar levels to suppress the organism.

People have asked us why we don’t prescribe tetracycline for prophylaxis against malaria. The trouble with tetracycline, particularly doxycycline, is its potential to cause cutaneous photosensitivity reactions. It cannot be given to pregnant women or children less than eight years old because of its effects on dental and bone development.

A PHYSICIAN: Why not simply give patients quinine for malarial prophylaxis?

DR. BIA: Quinine may be cardiotoxic and can prove to be lethal. Unfortunately, Fansidar has also shown itself capable of causing lethal dermatitis. Bird watchers and travelers on safari may get an intense exposure to mosquitoes. Most people aren’t satisfied traveling around with three Fansidar tablets in their back pocket to take as needed for a presumed malarial attack. We try to give them appropriate literature so they understand what a malarial attack is all about. Is this satisfactory? Not really. People are going to get hurt unless better agents are soon available.

Another common malaria problem is posed by people who complete their chloroquine prophylaxis but do not take primaquine. Months later they return with an attack of vivax or ovale malaria. The clinical course in today’s patient emphasized the need to consider this issue more carefully.

FOLLOW-UP

DR. BIA: Despite the therapy this patient received he did not do well after discharge from the hospital in July 1985. He continued to experience episodes of lethargy and headache and was unable to function efficiently. In early December 1985, he noted recurrent fevers and appeared in the emergency room of Yale–New Haven Hospital concerned about a possible relapse of malaria. Blood smears were positive for malarial parasites, subsequently identified as P. ovale by investigators at the Centers for Disease Control. The patient had not been evaluated for a relapse or recurrence of malaria with blood smears until that time. Before it became clear that this was not a case of chloroquine-resistant falciparum malaria he was started on a course of oral quinine and tetracycline. As the diagnostic picture cleared, he subsequently received a standard dose of chloroquine and 14 days of primaquine at double the usual recommended dosage for radical cure of P. ovale infections, for reasons which will be discussed below. Table 1 shows his malarial antibody levels in December. Results indicate a definite response to P. ovale, and the antibodies to P. vivax probably represent cross-reacting antibody.

The December relapse brings up several issues. Did this patient have chloroquine-resistant falciparum malaria in July 1985? How would that have affected our ability to detect concomitant P. ovale infection? Is vivax malaria found in East Africa?

The severity of our patient’s clinical course in July 1985 suggested chloroquine-resistant falciparum which was rapidly advancing to its cerebral phase. The malarial infection was mixed, however, and both falciparum and ovale infections were certainly acquired in Kenya.

P. falciparum is the most common malaria species in Africa, followed by P. malariae. P. ovale is now more prevalent than P. vivax in West Africa, as it has been in East Africa [1]. P. vivax does predominate in North Africa, however. P. ovale
infections are difficult to diagnose for several reasons. Falciparum malaria tends to suppress ovale infections, making them hard to detect [13]. Ovale parasites are not easily distinguished from *P. vivax* on blood smear. The mature ovale trophozoites are compact, rather than amoeboïd like vivax. Infected red cells are oval-shaped in ovale malaria, hence the name. These characteristics are best seen on thin film smears rather than thick smears, which are usually done for diagnosis in these endemic areas [14]. A hurried diagnosis in an overburdened laboratory may overlook ovale malaria during mixed infections [15]. Also, *P. ovale* usually occurs as part of a mixed infection; 50 percent of ovale infections occur with falciparum, 4 percent with *P. malariae*, and 8 percent together with both other forms of malaria [13]. The species-specific sporozoite rates for the four human malaria species are consistent with this clinical observation. They were determined in western Kenya for *Anopheles* mosquitoes and were as follows: *P. falciparum* 5.9 percent, *P. malariae* 1.7 percent, and *P. ovale* 0.2 percent, and 83 percent of those mosquitoes positive for *P. ovale* were co-infected with at least one other *Plasmodium* species [17].

Knowing the geographic area where disease was acquired may be helpful in distinguishing between *P. vivax* and *P. ovale*. Ovale seems to compete with vivax malaria, and they tend toward mutual exclusivity. Vivax is actually rare in sub-Saharan Africa, both based upon this relationship and genetic resistance present in the population there. Sub-Saharan black Africans lack Duffy determinants on erythrocyte surfaces required for invasion by vivax merozoites [15]. This fact makes it unlikely that vivax was a part of our patient's mixed infection, although some vivax occurs in East Africa where there is a European element [13].

Ovale is a relapsing malaria, but some malarialogists have felt that relapses with this organism were rare [14,16]. A study in human volunteers did show that relapses should be anticipated. Five volunteers were infected, and all relapsed at least once [16]. Three relapsed twice, and one three times. Our patient further illustrates the ability of *P. ovale* to relapse, even following the usual recommended dose of primaquine.

Both *P. vivax* and *P. ovale* infections require the administration of primaquine to eliminate the liver phase (hypnozoite) of the organism and prevent relapses. Why did our patient have a relapse of ovale malaria despite a full course of primaquine? The experience using 15 mg of primaquine base per day to eradicate the liver stage of *P. ovale* is limited. It is clear, however, that therapy is not 100 percent effective, and 15 mg/day may not achieve adequate tissue levels, particularly in a patient such as ours, who weighs approximately 100 kg. For this reason 30 mg/day for 14 days was subsequently used to eradicate his infection, and he has had neither clinical relapses
nor positive smears since then. His course emphasizes the difficulties posed when multiple malarial infections are compounded by issues of drug resistance.

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