

# A Woman with a History of a 2-Year Stay in Gabon and Onset of a Cyclical Fever More Than 1 Year Later

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Jean-Luc Benoit

A 23-year-old female medical student presented with fever every other day for 1 week, which she believed was a cyclical fever highly suggestive of malaria. After graduating from college, she spent 1 year as a volunteer in Gabon, West Africa, before starting medical school. She had not traveled to a malaria-endemic area since leaving Gabon 13 months before.

She was healthy until 1 week prior to presentation, when she developed fever up to 102.5 °F, with chills and sweats. The symptoms only occurred every other day. Associated symptoms included myalgia, headache, profuse sweats with defervescence of the fever, and intense fatigue. She denied nasal or sinus congestion, sore throat, odynophagia, cough, chest pain, shortness of breath, abdominal pain, nausea, vomiting, diarrhea, dysuria, urinary frequency, or vaginal discharge. The patient's past medical history was otherwise unremarkable.

During the year spent in Gabon, other than a few episodes of watery diarrhea, she did not develop any illness. She had not swum in freshwater (no risk of exposure to schistosomiasis), and she had taken weekly mefloquine malaria prophylaxis during her stay and until 4 weeks after returning to the United States (US). Since

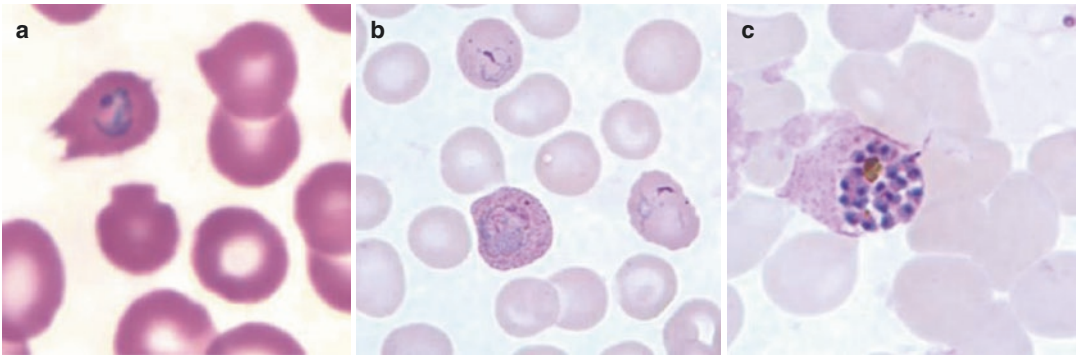
returning to the USA, she had remained in good health with no febrile illnesses. She was very active physically including running a few times a week. She had one sexual partner. She considered that they were in a monogamous relationship and were both at very low risk of HIV or other sexually transmitted infection (STI). She never had an STI herself and was followed regularly by a primary care physician who last did her cervical PAP smear about 3 months prior. She last had a negative HIV screening test 1 year prior to presentation.

She had never had a blood transfusion. She took no prescription drugs and was not taking a contraceptive pill. She had no drug allergies. The patient resided in Illinois and had traveled extensively within the USA including to the Upper Midwest and to New England. She reported never noting any tick bites. She had traveled abroad to the Caribbean, Israel, and Jordan, but she had not been in a malaria-endemic area since her stay in Gabon.

On physical examination, the patient was not in any acute distress. She was afebrile but stated that she had a fever to 102.5 °F the night before. Her blood pressure and pulse and respiratory rate were normal. Her conjunctivae appeared a bit pale but her sclerae were anicteric. She had no rash. The oral exam was normal, and she had no cervical or axillary lymphadenopathy. The heart rhythm was regular, without any murmur or abnormal sound. The lungs were clear to

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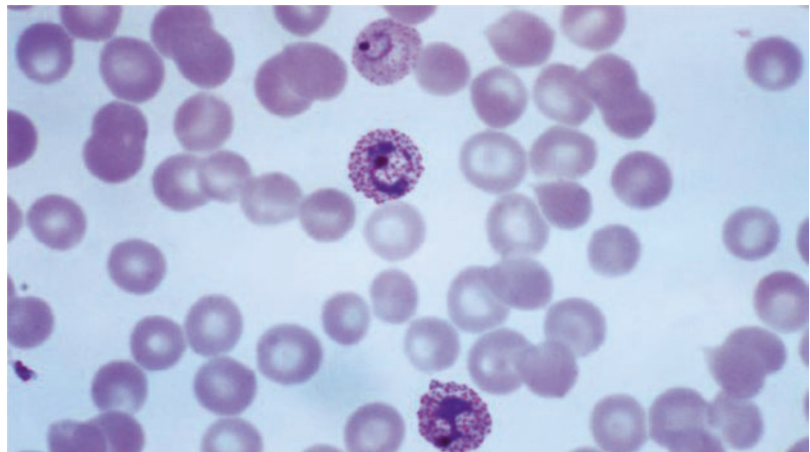
J.-L. Benoit, M.D.  
Section of Infectious Diseases and Global Health,  
Department of Medicine, University of Chicago,  
Chicago, IL, USA  
e-mail: [jbenoit@medicine.bsd.uchicago.edu](mailto:jbenoit@medicine.bsd.uchicago.edu)



**Fig. 46.1** *Plasmodium ovale* on thin blood smear: large ring form with fimbriated red blood cell cytoplasm (a), amoeboid trophozoites (b), and schizont with brown pigment (c). Source: U.S. Centers for Disease Control and

Prevention (CDC), DPDx Laboratory Identification of Parasites of Public Health Concern. [https://www.cdc.gov/dpdx/resources/pdf/benchAids/malaria/Povale\\_benchaidV2.pdf](https://www.cdc.gov/dpdx/resources/pdf/benchAids/malaria/Povale_benchaidV2.pdf) (Accessed June 27, 2017)

**Fig. 46.2** *Plasmodium vivax* on thin blood smear: intracytoplasmic Schüffner's dots; young ring forms are about one third of the diameter of an RBC; amoeboid trophozoites. Source: U.S. Centers for Disease Control and Prevention (CDC), [http://phil.cdc.gov/phil\\_images/20021230/12/PHIL\\_2720\\_lores.jpg](http://phil.cdc.gov/phil_images/20021230/12/PHIL_2720_lores.jpg) (Accessed June 27, 2017)



auscultation. The abdomen was soft and without hepatomegaly or splenomegaly. There was no suprapubic or costovertebral tenderness. A pelvic exam was unremarkable.

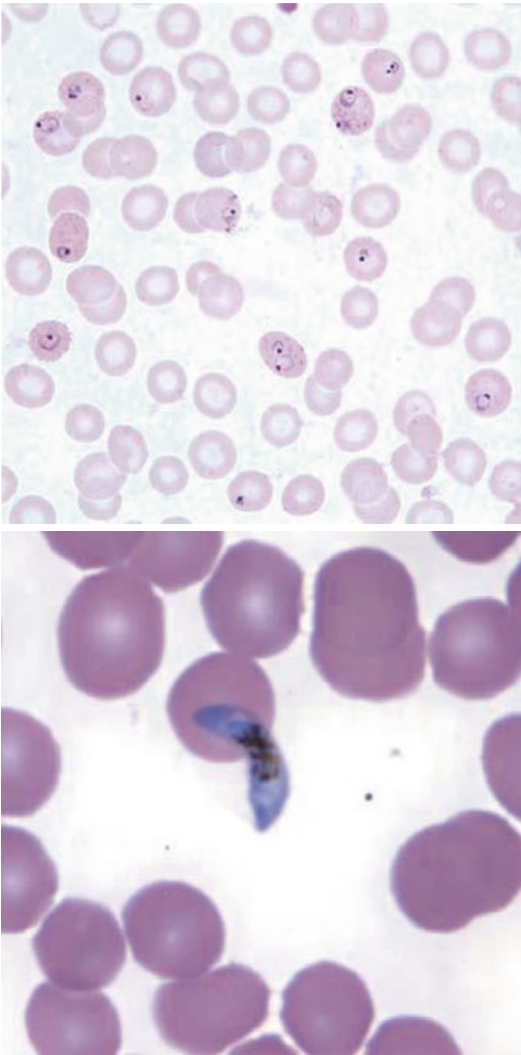
Laboratory tests were notable for hemoglobin 11.0 g/dL, white blood cell count 4000/ $\mu$ L (60% neutrophils, 30% lymphocytes, 8% monocytes, and 2% eosinophils), and platelet count 80,000/ $\mu$ L (normal range, 150,000–450,000/ $\mu$ L). Iron studies, liver enzymes, kidney function tests, and urinalysis were normal. Blood cultures were negative. A chest radiograph was normal.

The differential diagnosis was broad as it included infections acquired in the USA and abroad as well as a few noninfectious etiologies (see Table 1). However, because of the cyclical nature of her febrile illness, malaria

was considered much more likely than other etiologies, although a cyclical fever is not pathognomonic of malaria. Thin and thick blood smears were obtained and reviewed carefully.

Thin blood smears showed intraerythrocytic plasmodia-like protozoa including ring forms, older trophozoites, and schizonts, with a parasitemia of about 2%. Older parasites had brown pigment. Infected red blood cells had intracytoplasmic dots and were enlarged, often with an oval shape. No gametocytes were identified but they may be difficult to recognize.

Babesiosis was ruled out due to the lack of tetrads, polymorphism, or vacuoles and the presence of brown pigment in older protozoa. *Plasmodium falciparum* malaria was also ruled



**Fig. 46.3** *Plasmodium falciparum* on thin blood smear: (top) only delicate, young ring forms with small cytoplasm and 2 chromatin dots; very high parasitemia; multiply infected RBCs; accolé forms; no pigment; (bottom) banana-shaped gametocytes appear only about a week after the onset of illness, but may persist in asymptomatic persons (i.e., the human reservoir). Source: U.S. Centers for Disease Control and Prevention (CDC), DPDx Laboratory Identification of Parasites of Public Health Concern. [https://www.cdc.gov/dpdx/resources/pdf/benchAids/malaria/Pfalciparum\\_benchaidV2.pdf](https://www.cdc.gov/dpdx/resources/pdf/benchAids/malaria/Pfalciparum_benchaidV2.pdf) (Accessed June 27, 2017)

out because in this infection only tiny, young ring forms with two dots of chromatin and a scant cytoplasm are identified on blood smear, with at times a few banana-shaped gametocytes [1]. Maturing *P. falciparum* induces the formation of

**Table 46.1** Differential diagnosis of cyclical fever and abnormal blood smear in a woman with a history of living in Gabon, West Africa

Malaria due to <i>Plasmodium falciparum</i>
Hypnozoite relapse of malaria with either <i>Plasmodium ovale</i> or <i>Plasmodium vivax</i>
Chronic malaria due to <i>Plasmodium malariae</i>
West African trypanosomiasis due to <i>Trypanosoma brucei gambiense</i>
Babesiosis due to <i>Babesia microti</i> acquired in the USA through the bite of <i>Ixodes scapularis</i> or <i>Ixodes pacificus</i> blacklegged deer ticks
Tick-borne relapsing fever acquired in the Western USA through the bite of <i>Ornithodoros</i> species soft ticks
Mononucleosis syndrome due to acute infection by Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), <i>Toxoplasma gondii</i> , or <i>Treponema pallidum</i> (secondary syphilis)
Brucellosis ( <i>Brucella</i> spp.)
Infective endocarditis
Endemic fungal infection
Tuberculosis ( <i>Mycobacterium tuberculosis</i> )
Amoebic liver abscess
Noninfectious etiologies: In a young woman, consider systemic lupus erythematosus, sarcoidosis, and lymphoma

knobs rich in *P. falciparum* erythrocyte membrane protein 1 (PfEMP-1) on the surface of red blood cells (RBC), with binding of PfEMP-1 to endothelial receptors on post-capillary venules, so that older parasites are trapped in the microcirculation [2–4].

Non-falciparum malaria was therefore diagnosed as all *Plasmodium* stages were identified, including young ring forms, older trophozoites, and schizonts. There are three non-falciparum plasmodia to consider. *P. malariae* can cause minimally symptomatic chronic malaria but is not common. In *P. malariae* infection, the parasitemia is very low, infected RBCs are of normal size, and typical trophozoites called band forms are recognized. *P. vivax* and *P. ovale* are quite similar on blood smears. In both of these, infected RBCs are enlarged, with the presence of intracytoplasmic Schüffner's dots; young ring forms are large, about one third of the diameter of an RBC; and ameboid trophozoites are recognized. It is difficult to differentiate between the

**Table 46.2** Morphological comparison of *P. falciparum*, *P. ovale*, *P. vivax*, and *P. malariae* [2–5]

	<i>Plasmodium falciparum</i>	<i>Plasmodium vivax</i>	<i>Plasmodium ovale</i>	<i>Plasmodium malariae</i>
Number of plasmodia per RBC	Multiple	Only one	Only one	Only one
Parasitemia	Often high as all RBCs can be infected	Low to moderate; only young RBCs infected	Low to moderate; only young RBCs infected	Very low; only old RBCs can be infected
Size and shape of infected RBCs	Normal	Enlarged Spherical	Enlarged Oval	Normal
Cytoplasmic Schüffner's dots	None	Present	Present	None
Stages seen on blood smear	Only young trophozoites	Young and older trophozoites, schizonts	Young and older trophozoites, schizonts	Young and older trophozoites, schizonts
Trophozoites: shape, size, and location within RBC	Small rings with two dots of chromatin; scant cytoplasm; at the periphery of RBC	Larger trophozoites, some with filaments in their cytoplasm, called <b>amoeboid trophozoites</b>	Larger trophozoites, some with filaments in their cytoplasm, called <b>amoeboid trophozoites</b>	Trophozoites with <b>band forms</b>
Schizonts	Not seen	Multiple nuclei and brown pigment	Multiple nuclei and brown pigment	Multiple nuclei and brown pigment
Brown pigment	None	Yes	Yes	Yes
Gametocytes	Banana shaped; seen in longer infections	Spherical	Spherical	Spherical

RBC red blood cell

two species, but *P. ovale* tends to cause infected, enlarged RBCs to have an oval shape (see Table 46.2) [1–4].

Both *P. vivax* and *P. ovale* cause late relapses of malaria due to activation of dormant liver forms, called hypnozoites in the US literature. *P. ovale* is not as prevalent as *P. vivax*, except in Western Africa because local populations lack the Duffy blood type that is the major receptor for *P. vivax* entry into RBCs [2–4]. Our patient had therefore acquired *P. ovale* malaria in West Africa despite being on malaria prophylaxis there. She remained asymptomatic for more than a year when a hypnozoite activated and caused a relapse of malaria. The patient was treated for *P. vivax* malaria with chloroquine phosphate 1000 mg once, followed by 500 mg 6 h, 24 h, and 48 h later. Her glucose-6-phosphate dehydrogenase (G6PD) level was normal, allowing her physicians to prescribe safely primaquine 30 mg a day for 14 days to eradicate hypnozoites and to prevent further relapses of malaria [5].

## 46.1 Malaria

Female *Anopheles* mosquitoes transmit malaria at night, injecting sporozoa when they take a blood meal. Plasmodia are Apicomplexa, protozoa that use an apical complex of organelles and microtubules to penetrate into cells. Plasmodia infect hepatocytes (exoerythrocytic schizogony) first, then reach the blood, and infect RBCs (erythrocytic schizogony). There are four species of human plasmodia.

*P. falciparum* is highly lethal, causing about 95% of malaria-related mortality. Because the parasite infects all RBCs regardless of their age, it can cause very high parasitemia. Because it induces RBCs to grow PfEMP-1 knobs on their surface with resulting entrapment of the mature protozoa in the microcirculation, tissue injury is much more severe in falciparum malaria, with manifestations including cerebral malaria, placenta infection with adverse effects on pregnancy, and pulmonary edema or the acute respiratory distress syndrome (ARDS) [2–4]. Uncomplicated



falciparum malaria manifestations include fever (every day initially, especially in travelers without prior semi-immunity; with prior semi-immunity, a fever every other day is often seen) and many associated symptoms (e.g., headache, nausea, vomiting, abdominal pain, and profuse sweats). The complete blood count usually shows anemia, thrombocytopenia, and a normal white blood cell count. Even uncomplicated falciparum malaria can progress rapidly to severe illness. *P. falciparum* can result in a large number of complications (see Table 46.3), and treatment is considered an emergency. Because *P. falciparum* has acquired drug resistance to multiple antimalarial agents, including chloroquine, sulfadoxine/pyrimethamine, mefloquine, quinine, and recently artemisinin derivatives, treatment always includes two different agents, and choice of therapy depends on the severity of illness. Acutely ill patients are best treated in the intensive care unit with rapidly acting intravenous agents, such as quinidine, quinine, or artesunate, plus a second

active drug (doxycycline or clindamycin). Patients who are stable and can take oral therapy usually receive one of three combinations: atovaquone/proguanil, artemether/lumefantrine, or a combination of quinine plus either doxycycline or clindamycin [2–5].

*P. vivax* is highly prevalent, including previously in North America and Europe. It only infects young RBCs, resulting in lower parasitemia (1–2%). It requires the Duffy receptor on the surface of RBCs and therefore is rare in most of sub-Saharan Africa, although common in the horn of Africa and in Madagascar. Liver hypnozoites allow the parasite to survive cold winters. Chloroquine resistance has been described in Papua New Guinea and Indonesia. Patients present initially with daily fever and then get febrile paroxysms every 48 h (benign tertian fever). Splenic rupture is a rare complication.

*P. ovale* causes malaria that is clinically indistinguishable from *P. vivax* malaria and is also associated with late relapses due to the activation of hypnozoites. It is most prevalent in western Africa.

*P. malariae* is a minor species causing chronic malaria of low severity, as it only infects old cells with very low parasitemia. It may cause nephrotic syndrome due to chronic immune complexes [2–4].

*P. knowlesi* causes malaria in long-tailed and pig-tailed, crab-eating macaques found over a wide range of Southeast Asia from Myanmar to Timor. It causes zoonotic human malaria in Malaysia (especially Borneo), with cases reported elsewhere (Thailand, Myanmar, Singapore, and Philippines). Blood smears show tiny ring forms (like *P. falciparum*) and band forms (like *P. malariae*, with which it is confused). It results in a higher mortality than non-falciparum malaria, and chloroquine is an effective therapy [1–5].

**Table 46.3** Complications of *Plasmodium falciparum* malaria [2–4]

Cerebral malaria: seizures, altered mental status, sequelae
Hypoglycemia: due to malaria itself or quinidine release of insulin from islet cells
Severe anemia: hemolysis and splenic clearance; ineffective erythropoiesis
Severe thrombocytopenia
Pulmonary edema and acute respiratory distress syndrome (ARDS)
Hypotension and shock: increase fluids, rule out bleeding, rule out Gram-negative sepsis, avoid epinephrine, and use dopamine
Acute renal failure: prerenal, microvascular injury, intravascular hemolysis (hemoglobinuria), acute tubular necrosis (ATN)
Blackwater fever: macroscopic hemoglobinuria and renal failure due to intravascular hemolysis, may be associated with quinine therapy with or without G6PD deficiency
Bilious remittent fever: abdominal pain, vomiting, diarrhea, and painful hepatomegaly with icterus
Lactic acidosis: major role in death from severe malaria
Bacterial superinfection with sepsis
Symmetrical peripheral gangrene

G6PD glucose-6-phosphate dehydrogenase

**Key Points/Pearls**

- *P. falciparum* smears only show young ring forms, but no mature trophozoites or schizonts because these are entrapped in the microcirculation.
- Banana-shaped gametocytes are pathognomonic of *P. falciparum*, but are not seen in recently infected travelers; gametocytes

appear late and are seen alone in non-ill persons in endemic areas.

- Relapsing malaria only occurs with *P. vivax* and *P. ovale*; the term “relapse” in malaria has a specific meaning: the appearance of blood-stage parasites originating from a dormant liver stage of the parasite, called a hypnozoite.
- Malaria relapses occur in 50% of persons infected with *P. vivax* or *P. ovale*, for up to 1–3 years after infection.
- Only primaquine (30 mg base a day for 14 days) kills hypnozoites, but there is a risk of severe intravascular hemolysis in patients with G6PD deficiency.
- Proper malaria prophylaxis in most areas is mefloquine taken weekly or either atovaquone/proguanil or doxycycline taken daily; malaria prophylaxis is continued after returning to a non-endemic area for 1 week with

atovaquone/proguanil and for 4 weeks with either doxycycline or mefloquine.

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## References

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