Apparent Relapse of Imported Plasmodium ovale Malaria in a Pregnant Woman

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Abstract. A 27 week pregnant woman who had lived in Bangkok, Thailand, for 18 months presented to her obstetrician with a 1-week history of intermittent fever and malaise. Medical history was significant for multiple episodes of malaria during her 10 years of employment in sub-Saharan Africa before her relocation to Thailand. The initial malaria smear was negative. She returned a week later with no resolution of her symptoms, at which time she was found to have Plasmodium ovale by microscopy and polymerase chain reaction. She had an excellent response to chloroquine, which she continued weekly until 36 weeks of gestation. She delivered a healthy term infant and received radical cure with primaquine after cessation of breastfeeding. This case shows challenging issues in detection and management of imported P. ovale malaria.

INTRODUCTION

We report a case of an imported Plasmodium ovale relapse in a pregnant woman at least 18 months after initial infection in sub-Saharan Africa. This case presents many challenges in the diagnosis and management of imported malaria. Little is published on P. ovale infections, particularly in pregnancy. To the best of our knowledge, this is the first case report of a relapse of imported P. ovale in pregnancy. This case illustrates challenging issues in detection and management of imported P. ovale malaria. These issues are discussed. A high index of suspicion for relapse of malaria is increasingly important in this era of globalization.

CASE REPORT

At 27 weeks of gestation, a 36-year-old primigravid Australian woman presented for medical care in Bangkok, Thailand, with a 1-week history of intermittent fever, shaking chills, headache, and nausea. These symptoms would recur approximately every 48 hours, would last for 4–6 hours, and were only partially relieved with acetaminophen and tepid baths. She reported no other constitutional symptoms. Between febrile episodes, she reported malaise, but was otherwise asymptomatic.

At the time of her illness, the patient had resided for 13 months in Bangkok, where malaria is not endemic. However, before residing in Thailand, she had been an aid worker for 10 years in sub-Saharan Africa, including both East and West Africa. While in Africa she was diagnosed with malaria on multiple occasions, including five smear-confirmed cases of Plasmodium falciparum during her final 3 years in Kenya but never with a relapsing species. Her last malaria diagnosis was 18 months before illness onset in Bangkok. This case was microscopically determined to be P. falciparum and she was treated with artemether-lumefantrine. Notably, she received a full course of mefloquine after failing to clear parasites. During her stay in Africa, she declined chemoprophylaxis and did not receive any courses of primaquine for radical cure of potential Plasmodium vivax or P. ovale co-infection, single-dose primaquine for clearing gametocytes of P. falciparum, or presumptive anti-relapse therapy with primaquine (terminal prophylaxis) on leaving Africa. She had no other significant medical history, and her pregnancy was otherwise uncomplicated.

Physical examination was normal for a 27 week gravid woman. A blood sample on initial evaluation showed no malaria parasites by microscopic examination of Giemsa-stained thick and thin blood films, white blood cells (WBC) of 6,800/mm³ (reference range, 4,000–10,000/mm³) with 72% neutrophils and 17% lymphocytes, a hemoglobin of 11.1 g/dL (reference range, 14.1–18.1 g/dL), hematocrit of 32.0% (reference range, 43.5–53.7%), and a platelet count of 216,000/mm³ (reference range, 150,000–450,000/mm³). These parameters were essentially unchanged from her initial obstetrical visit. Urine and stool samples were negative. Fetal ultrasound was normal. Although the diagnosis of dengue fever was considered, the patient was diagnosed with a non-specific viral syndrome, treated symptomatically, and instructed to return in 1 week or sooner if her condition worsened.

When she continued to experience high fever, shaking chills, headache, and nausea, a repeat malaria smear was obtained 7 days later, this time showing P. ovale malaria. This diagnosis was confirmed at the Armed Forces Research Institute of Medical Sciences by expert microscopy (Figure 1) and polymerase chain reaction (PCR) (Figure 2). The remainder of the laboratory diagnostic evaluation, including dengue PCR, was negative. WBC on admission remained normal at 8,300/mm³, with 70% neutrophils and 20% lymphocytes. Hemoglobin had declined somewhat to 10.1 g/dL and hematocrit to 30.0%. Urine and stool exams were negative.

The patient was admitted to the hospital for treatment and observation. On admission, she was treated with chloroquine 600 mg base, followed by 300 mg base in 6 hours and then 300 mg base daily for 2 days. She had a rapid and favorable response; fever and parasitemia resolved within 24 hours. She had no further febrile episodes and was discharged after 72 hours. The patient continued chloroquine suppressive therapy of 300 mg base weekly until 36 weeks of gestation, at which time it was discontinued at her request. She went on to deliver a full-term healthy male infant without complications. Radical curative therapy with primaquine was deferred until breastfeeding was terminated 6 months after delivery. She then took 15 mg base primaquine daily for 14 days after it was determined that she was not glucose-6-phosphate dehydrogenase (G6PD) deficient. As of 15 months after initial evaluation in Bangkok, she has had no further episodes of malaria, and the baby has continued to develop normally. See Table 1 for a timeline summary.
DISCUSSION

This patient presented with a common history of *P. ovale* infection, with fever, chills, headache, and nausea recurring every 48 hours. However, given the initially negative malaria smear, the long latency between presumed initial infection and relapse, lack of a previous diagnosis of *P. ovale*, and the patient’s current residence in an area with a very low incidence of *P. ovale*, a viral illness seemed much more likely. This case underscores the need to obtain a thorough long-term residential and travel history when formulating a differential diagnosis. It also highlights the importance of considering even rare etiologies for febrile illnesses, particularly in pregnant women. These aspects are especially important in the current era of globalization and increasing residential mobility.

Although *P. ovale* is known to be present in East Africa, it is not commonly diagnosed outside West Africa. In fact, it is most often recognized only as a co-infection with *P. falciparum*. Indeed, such co-infection could have been present in this patient during one of her many known episodes of malaria in either West or East Africa. Certainly, this case showed the need to consider even historically distant exposure to *P. ovale*, given the potentially long latency period to relapse. It is also important to note that an initially negative single malaria smear does not rule out *P. ovale* infection, particularly given its typical low parasitemia. Additional smears and closer follow-up may have identified the case in a more timely fashion.

Little information is available regarding the course of *P. ovale* infection in pregnancy, although its occurrence has been reported, with 2.5% of Cameroonian women found by PCR to have *P. ovale* at the time of delivery. Most available information on relapsing malaria in pregnancy relates to *P. vivax* infection, which has been associated with anaemia and reduced birth weight. Chloroquine was selected in this case for its well-documented safety and efficacy against *P. ovale*. Continuance of suppressive therapy after initial clearance of this patient’s *P. ovale* parasitemia was undertaken as the US CDC recommends that pregnant patients with *P. vivax* and *P. ovale* should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The patient elected to receive weekly chloroquine suppressive therapy only until 36 weeks, when the risks of preterm delivery became small. Primaquine is contraindicated in pregnancy and during breastfeeding unless the infant’s G6PD status is known to be normal. For these reasons, radical curative therapy was deferred through the pregnancy and until cessation of breastfeeding.

This case also showed some patient- and provider-specific considerations in the prevention and treatment of malaria. The patient elected to forgo any chemoprophylaxis during her prolonged employment in malaria-endemic regions of Africa and to not receive presumptive anti-relapse therapy with primaquine. She further elected, after being informed of all the risks and benefits of suppressive therapy, to terminate chloroquine suppression of her known *P. ovale* infection at 36 weeks of gestation, not at delivery, based on her personal risk–benefit assessment. Finally, although the US CDC recommends treatment with 30 mg base primaquine per day for 14 days, the patient was treated with the standard therapy in Thailand of 15 mg base primaquine per day for 14 days.
Perhaps the most difficult issue raised by this case relates to the consideration of primaquine for presumptive anti-relapse therapy. In this particular case, the patient had refused anti-malaria prophylaxis during her extended stay in malaria-endemic regions of sub-Saharan Africa. However, she had received multiple courses of antimalarials for microscopically proven *P. falciparum* and *P. vivax,* in which the possibility of co-infection should be considered. The US CDC expert meeting on malaria chemoprophylaxis and the UK malaria treatment guidelines recommend presumptive anti-relapse therapy for those with prolonged exposure to *P. vivax* and *P. ovale,* although this guidance may not often be followed and certainly was not followed in this patient. The US CDC reported 342 cases of relapsing malaria, of which 27 were *P. ovale,* in the United States in 2004, underscoring the importance of providing this therapy in those departing endemic areas. Greater consideration should be given to providing presumptive anti-relapse therapy against these parasites, even when their presence has not been specifically determined, in individuals being treated for malaria or for those departing endemic areas who have had long-term potential exposure to these parasites. A thorough risk-benefit assessment based on the potential for exposure must be made in each case. This may be especially important for those individuals who may later become pregnant, because pregnancy significantly complicates the clinical course and treatment of these infections.

This case showed the importance of obtaining a thorough residential and travel history and of a high index of clinical suspicion for even unusual etiologies for febrile episodes in returning travelers and expatriates. Although the clinical history was strongly suggestive of tertian malaria, the negative initial malaria smear and prolonged time since previous known malaria infection made the diagnosis of *P. ovale* seem unlikely. This case raises issues relating to local standards of care and patient preference in therapeutic decisions. Finally, this case raises the issue of the importance of and compliance with the recommendations for the provision of presumptive antimalarial therapy among those individuals returning from areas endemic for tertian malaria who have prolonged potential exposure. Further research is needed to address these issues, and to document the frequency and time course of recurrent *P. ovale* malaria in pregnant women and others.

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**REFERENCES**