

Plasmodium falciparum malaria recrudescence occurring 2.5 years after leaving an endemic country

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ABSTRACT

Malaria tropica is almost exclusively diagnosed within two months after returning from an endemic country. We present here a male patient with severe *P. falciparum* malaria diagnosed 2.5 years after returning from Burkina-Faso. We speculate that our patient was chronically infected with PF malaria for more than 2 years, with an undetectable parasite index and without symptoms. Because of waning immunity clinically overt PF malaria was able to develop. This case illustrates the importance of malaria suspicion as a cause of illness in immigrants from malaria-endemic countries. Even when these immigrants did not travel for a long time, malaria should be considered in patients with typical symptoms.

KEYWORDS

Plasmodium falciparum, recrudescence, malaria, late-onset

INTRODUCTION

Malaria caused by *Plasmodium falciparum* is an important cause of morbidity and mortality in travellers returning from an endemic country.¹ Ex-pats are at increased risk as they have waning immunity but do not usually comply with prophylaxis.² In contrast to malaria caused by *P. vivax* and *P. ovale*, which can relapse years after infection due to the hypnozoite stage of these species, *P. falciparum* malaria has no hypnozoite stage and is therefore almost exclusively diagnosed within two months after returning from an endemic country.³

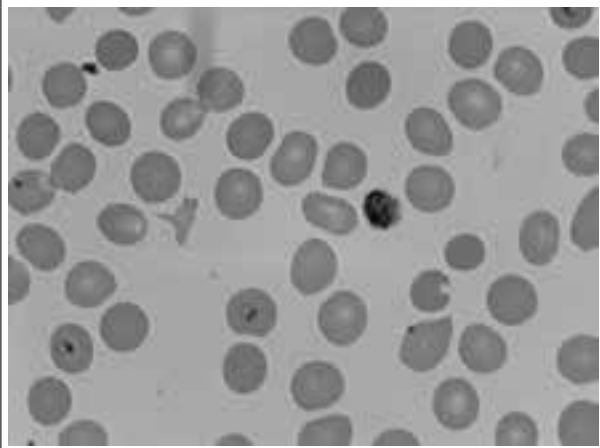
As an exception to this rule, we present here a male patient with severe *P. falciparum* malaria diagnosed 2.5 years after returning from Burkina-Faso.

CASE PRESENTATION

A previously healthy 48-year-old man was admitted to the Canisius-Wilhelmina Hospital in Nijmegen, the Netherlands with a five-day history of general malaise, fever, chills, profuse transpiration and bloody diarrhoea. Originally from Burkina-Faso, he immigrated to the Netherlands eight years before presentation. The patient had not visited his homeland or any other malaria-endemic country in the previous 2.5 years. No recurrent fever episodes were noted during this period. The last time he took malaria prophylaxis was in 1997. There was no history of blood transfusions. No friends or relatives from Burkina Faso had visited him in the last two months.

Physical examination revealed a sick, icteric patient. He was alert and oriented. Body temperature was 36.8°C, blood pressure 135/85 mmHg, and pulse 90 beats/min. Oxygen saturation was 96% with a respiratory rate of 40/min. There was no rash or lymphadenopathy. Cardiac examination revealed normal heart sounds without murmurs. The lungs were clear to auscultation. There were no palpable abdominal masses, nor hepatomegaly or splenomegaly. Neurological examinations were normal. Laboratory results were as follows: C-reactive protein 149 mg/l, haemoglobin 7.8 mmol/l, thrombocytes $14 \times 10^9/l$, leucocytes $9.1 \times 10^9/l$, lactate 4.9 mmol/l, glucose 5.3 mmol/l, creatinine 184 $\mu\text{mol/l}$, bilirubin 218 $\mu\text{mol/l}$, lactate

Figure 1. Erythrocytes with ring-shaped trophozoites and a schizont



dehydrogenase 441 U/l, aspartate aminotransferase 69 U/l, alanine aminotransferase 56 U/l, and alkaline phosphatase 99 U/l. HIV antigen/antibody test was negative. Ultrasound of the abdomen showed an enlarged spleen of 17.5 cm. The chest X-ray was normal. A blood smear was performed and showed ring-shaped trophozoites consistent with *Plasmodium falciparum* (PF) with a parasite density of 3.2% and the presence of schizonts (figure 1). The rapid antigen detection test (Binax Now® ICT Pf/Pv test) was positive.

The diagnosis of PF malaria was confirmed by real-time PCR using species-specific primer sets and probes against the 18S rRNA gene of *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*.^{4,5} No other pathogens were identified.

The patient was admitted to the intensive care unit because of tachypnoea, acute renal failure and lactic acidosis. Treatment with intravenous artemisinin (2.4 mg/kg) was started and he recovered quickly. Parasite density was <0.1% after 24 hours of treatment. By day 3 of treatment, no malarial parasites were seen and treatment was switched to oral atovaquon/proguanil. Follow-up was uneventful. Kidney function recovered completely and splenomegaly disappeared within six months.

DISCUSSION

Malaria is the world's most important parasitic disease and is endemic in more than 105 countries. In 2010 nearly 250 million malaria cases were reported, with an estimated death rate of 655,000 people. Most cases occur in Africa; only 1761 cases of malaria were diagnosed in Europe in 2011.⁶ In the Netherlands the number of imported cases of malaria in 2011 was 276.⁷

The incubation time of PF malaria is typically less than one month; most PF infections occur in the first two months after arrival.³ However, cases of prolonged PF malaria have been described and diagnosed even nine years after living outside an endemic area.⁸⁻¹⁰ In contrast, in other malaria species, including *P. vivax* or *P. ovale* infection, late-onset is more common. In 62.3% of returning travellers with malaria due to *P. vivax* or *P. ovale*, infection developed more than two months after the traveller's return.³ Because most PF malaria patients develop symptoms within two months after the bite of an infected *Anopheles* mosquito, clinicians will initially not suspect the diagnosis of PF malaria, even in patients with typical symptoms. It is important to identify risk factors for the long interval between exposure in a malaria-endemic area and the clinical presentation with a febrile illness.

In *P. vivax* and *P. ovale*, hypnozoites can survive in the liver for many years and finally cause clinical malaria. PF does not have a hypnozoite form, so other causes for late-onset infections have been subject of debate. Ortenzio *et al.*¹¹ performed a case-control study to evaluate risk factors for prolonged PF infection in immigrants. During a ten-year follow-up period, 61 (2.3%) late infections (>59 days after returning from an endemic area) occurred among 2680 diagnosed PF malaria infections. Median diagnosis delay was five months.

Four patients had clinical malaria more than three years after return from a malaria endemic area and all of them were pregnant women. Among immigrant travellers, three groups had a higher risk for prolonged PF infection: first-arrival immigrants, pregnant women and/or those taking mefloquine prophylaxis. The first two factors most likely reflect partial control of parasitaemia by acquired immunity.

Several immunological mechanisms have been suggested to explain late manifestations of PF malaria.

Immunity to malaria evolves relatively slowly and is said to decrease quickly when immune adults leave malaria-endemic countries, suggesting that continued exposure to malarial antigens is essential for maintained immunity. Otherwise, immunity to malaria is temporary. This semi-immunity status does not prevent infection, but seems to protect against severe malaria and clinical symptoms. However, there is no agreement as to which components of immunity to malaria are lost without exposure, and this loss is often identified only by the fact that such people do experience symptomatic infections.¹²

Pregnant women living in malaria endemic countries are vulnerable to develop symptomatic PF malaria even when pre-existing acquired immunity was present to control low parasitaemia.

This loss of immunity is caused by a change in antigens in placenta-dwelling parasites. Primigravidae are fully susceptible to PF malaria because the antigens expressed

on the erythrocyte surface by placental parasites are distinct from those expressed by other PF. New infection with PF is not necessary to initiate placental infection in a woman with low parasitaemia at time of pregnancy as parasites can switch between different surface antigens.^{13,14}

A special risk group for late-onset PF malaria are immigrants from endemic countries who travel to their country of origin to visit friends and relatives (VFR).¹⁵

They have a higher risk for infectious diseases, because they often travel for longer periods of time and do not seek pre-travel advice.² Although the number of infections diagnosed in VFR has declined, it is important to recognise this group because of the possibility of a subclinical and delayed-onset type of PF malaria.

Although PF malaria is usually contracted in the tropics from bites of infected female *Anopheles* mosquitoes, it can also be transmitted via blood transfusion, bone marrow transplants, needle-stick injuries and by the introduction of infected mosquito vectors on aircraft, e.g. suitcase or baggage malaria and airport malaria have been a cause of PF infections.¹⁶⁻²⁰ When these modes of transmission have been excluded, late recrudescence is most the likely cause of disease.

In our case, we found no evidence for any of the above explanations for his PF malaria infection. There was no history of recent travelling or visiting friends from Burkina Faso, nor did our patient import tropical plants which could be a source for the *Anopheles* mosquito.²¹ Another argument for late-onset malaria instead of indigenous malaria is the fact that the patient became ill in winter; at that time it was freezing, a time when proliferation of the vector in the Netherlands should be very difficult.

We considered whether the patient might have withheld anamnestic data on purpose. He was repeatedly asked about his travel history and visiting friends from malaria-endemic countries, but his answer remained the same and seemed to be reliable.

We speculate therefore that our patient was chronically infected with PF malaria for more than two years, with an undetectable parasite index and without symptoms. Because of waning immunity clinically overt PF malaria was able to develop. We found no underlying systemic disease which could have led to decreased immunity.

This case illustrates the importance of malaria suspicion as a cause of illness in immigrants from malaria-endemic countries. Even when these immigrants did not travel for a long time, malaria should be considered in patients with typical symptoms.

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