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Case Report

**Plasmodium falciparum** malaria occurring four years after leaving an endemic area

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We present a case of a 52-year-old woman of Ghanaian origin who developed **Plasmodium falciparum** malaria 4 years after leaving Africa. She had not returned to an endemic area since. We hypothesize several possible scenarios to explain this infection, of which we believe recrudescence of **P. falciparum** is the most plausible. This occurred most likely as a consequence of waning immunity several years after leaving a high-transmission area. She recovered after a 3-day treatment with atovaquone/proguanil.

Keywords: Malaria, **P. falciparum**, Airport malaria, Malaria recrudescence

**Introduction**

Malaria is the most important parasitic disease in humans and is cause of significant morbidity and mortality worldwide. It is caused by Plasmodium parasites that are transmitted by **Anopheles** mosquitoes. There are five known Plasmodium species of which **P. falciparum** is associated with the most severe infections and accounts for nearly 100% of malaria mortality.1 In Europe, malaria was eliminated in the 1970s and is nowadays mostly confined to certain endemic regions. Case reports of malaria that occur within the European Union are collected by the European Centre for Disease Prevention and Control. In most EU countries, reporting is compulsory. The number of cases fluctuates around 1 per 100,000 population per year. Nearly all of the reported cases (>99%) are classified as imported.2 A small percentage of the cases are classified as autochthonous malaria. These are defined as cases of malaria that are acquired locally by a mosquito bite.3 Finally, late recurrences of malaria are also possible.4 As a consequence, when assessing a case of unexplained fever without a recent travel history to an endemic region, malaria still needs to be included in the differential diagnosis. As mortality risk can be significant, the timely diagnosis and treatment of malaria remains a concern, even in developed countries.

**Case Presentation**

A 52-year-old woman of Ghanaian origin was hospitalized in January 2015 with fever and flu-like symptoms. She complained of fever, malaise, headache, a sore throat and a cough. When she presented to the emergency department, there was prominent upper abdominal pain. Her temperature was 39.2°C, the pulse rate and blood pressure were normal. Physical examination was remarkable for diffuse abdominal tenderness. Laboratory values at admission showed leucocytopenia (2.3 × 10^3/μL), trombocytopenia (92 × 10^3/μL), elevated CRP (142 mg/L) and elevated liver enzymes (AST 49 U/L, ALT 61 U/L, alkaline phosphatase 133 U/L, gamma-GT 160 U/L). Chest X-ray, abdominal ultrasonography and gastroscopy were normal. Urine culture was negative. Twenty-four hours after initial admission, the abdominal pain resolved spontaneously. She did, however, continue to develop bouts of fever. Because of the concomitant influenza epidemic, a nasopharyngeal swab was performed to check for respiratory viruses. The PCR for influenza A returned positive. No antibiotics were started at this point and diagnosis of influenza was made. The following days the bouts of fever persisted and CRP rose (266 mg/L). Repetitive blood cultures all remained sterile. HIV serology was negative. After consulting the hospital infectiologist, a treatment
with levofloxacin 500mg daily was started and a blood smear was ordered, which was performed the next day. The blood smear revealed *P. falciparum* trophozoites with a parasitaemia of 22 μL, corresponding to a parasitaemia on thin blood film of < 0.1% affected erythrocytes. In addition, *Plasmodium* LDH Antigen and PCR for *P. falciparum* were positive. Levofloxacin was immediately switched to atovaquone/proguanil 250/100 mg, four tablets daily, of which she received a 3-day course. Retrospectively thin blood film was performed on the earlier blood samples of the same hospitalization period, which showed parasitaemias of up to 2.1% affected erythrocytes. At the end of the hospitalization period, she developed hemolytic anaemia (normocytic anaemia with elevated LDH of 527U/L and lowered haptoglobin of < 10 g/L). Her haemoglobin level dropped to 8.5 g/dL but recovered spontaneously shortly after she was discharged.

The diagnosis of malaria came unexpected as the patient, who originated from Ghana, claimed not to have been in a malaria endemic region during the last 4 years (she moved from Ghana to Belgium in 2011 and did not return since). She did however make a trip to London around the 20th of December 2014 where she came into contact with a friend of her brother who recently suffered a malaria infection and just came back from Ghana. This patient, who originated from Ghana, claimed not to have been in a malaria endemic region during the last 4 years (she moved from Ghana to Belgium in 2011 and did not return since). She did however make a trip to London around the 20th of December 2014 where she came into contact with a friend of her brother who, reportedly, recently suffered a malaria infection and just came back from Ghana.

**Discussion**

The incubation time seen with malaria infections typically is 12–14 days. Moreover, *Plasmodium vivax* and *Plasmodium ovale* are known to cause late recurrences due to their dormant liver stage (hypnozoites). Such a dormant intrahepatic form does not exist for *P. falciparum*. Our patient presented with a case of malaria due to *P. falciparum* 4 years after leaving an endemic area.

First, we considered that the patient could be withholding information voluntarily. While prompted at multiple times and by different doctors about her travel history, during the hospitalization period as well as afterwards, she continued to deny traveling to a malaria endemic area during the last 4 years.

Second, iatrogenic transmission was considered. In this case, however, there was no recent history of hospitalization, blood transfusion or organ transplantation. Nor was there a history of intravenous drug use. During her trip to London, our patient could have come into contact with blood of her brother’s friend who recently suffered a malaria infection, but we consider this possibility highly unlikely.

A more plausible scenario in this case would be autochthonous malaria, which is defined as a case of malaria that is acquired locally by a mosquito bite. In non-endemic areas ‘airport malaria’ is the most frequent cause. In this particular case, the patient could have been infected in one of the international airports she had visited as part of her trip to London one month before. Contracting malaria after visiting international airports distant from endemic regions has been described occasionally. It is caused by indigenous *Plasmodium*-infected *Anopheles* species mosquitoes who have entered a plane coming from the tropics, hiding in luggage or clothes. There have been only 75 described cases in Western-Europe between 1975 and 2000.

The patient could also have been infected by a mosquito that was brought into London in the luggage of her brother’s friend who just came back from Ghana. This form of autochthonous malaria is referred to as ‘Odyssean malaria’ (or ‘suitcase malaria’). We refer to a published case in which a patient contracted malaria after sharing a hostel room with a person who had just arrived from a malaria-endemic country in West-Africa.

Another form of autochthonous malaria exists in which an autochthonous anopheline vector is infected by a gametocyte carrier coming from an endemic country. Theoretically this is possible as *Anopheles plumbeus* and *Anopheles atroparvus* are species that can be found in Belgium. We consider this a highly unlikely hypothesis, however, as this case occurred during the coolest period of the year.

Another scenario, which provides a satisfactory explanation, is malaria recrudescence with an exceptionally long time interval. There are three ways in which malaria recrudescence is theoretically possible: relapse, reinfection and recrudescence. Relapse is defined as the recurrence of asexual parasitaemia derived from dormant liver stages (hypnozoites) and therefore is only seen in *P. vivax* and *P. ovale* infections.7 Recrudescence only occurs in endemic areas, of course. Recrudescence is defined as the recurrence of asexual parasitaemia after treatment of the initial infection and results from incomplete clearance of parasitaemia after inadequate or ineffective treatment.

The duration of *P. falciparum* infections has been a subject of debate since the 1950s. In the early days of malaria research, it was believed that *P. falciparum* infections generally did not last longer than 1 year. More recently, reports of *P. falciparum* persisting in humans for several years have been published. In a recent review by Ashley et al., 29 cases of transfusion- and transplant-transmitted *falciparum* malaria were summarized. The time interval from the last possible exposure to malaria and the accidental transmission of malaria (through transfusion or transplant) ranged from 6 months to 13 years. Thirty-two non-transfusion cases of delayed presentation of *falciparum* malaria were also summarized. The time interval ranged from 7 months up to 15 years. These cases suggest that the parasite’s erythrocytic life cycle is continued at very low densities, adequately suppressed by the host’s immune response: a prolonged asymptomatic infection.

In endemic areas with ‘stable’ malaria transmission people are very frequently and at fairly continuous rates exposed to a high rate of malaria inoculations. In such a setting, malaria morbidity and mortality is primarily seen in young children. By acquired immunity most of
these malaria infections are asymptomatic by adulthood. This applies to a great part of Sub-Saharan Africa.\textsuperscript{1,7} When individuals move out of endemic areas, immunity is often partially lost. This happens gradually and only after several years.\textsuperscript{7} In 13 out of the 29 non-transfusion cases summarized by Ashley et al., the malaria recrudescence occurred simultaneously with some form of reduced immunity (pregnancy, malignancy, diabetes mellitus, HIV). The authors concluded that the occurrence of malaria recrudescence may reflect the waning of host-immunity.\textsuperscript{4}

In conclusion, the above patient history describes an unexpected case of \textit{P. falciparum} malaria in a woman of Ghanaian origin who had not been in an endemic area in the last 4 years. We hypothesize several possible scenarios to explain this infection, of which we believe recrudescence is the most plausible. This occurred most likely as a consequence of waning immunity several years after leaving a high-transmission area. This case report highlights the importance of considering the possibility of malaria in people originating from endemic malarial regions presenting with a febrile illness, regardless of the length of the time interval.

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