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Case Report: Symptomatic Falciparum Malaria after Living in a Nonendemic Area for 10 Years: Recrudescence or Indigenous Transmission?

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Abstract. We report the case of a patient from Mali who, after 10 years of living in Spain, presented with symptomatic *Plasmodium falciparum* malaria without having visited an endemic area during that time. We cannot completely rule out the possibility of indigenous transmission, but this case most likely represents recrudescence of an infection acquired over 10 years earlier.

Plasmodium falciparum malaria is the leading cause of death due to infectious diseases in travelers returning from tropical regions.[1] In most cases, clinical manifestations appear within a few weeks after arriving from the journey,[1] although presentation may be delayed in subjects born and raised in endemic areas and in travelers who have taken chemoprophylaxis against malaria. In immigrants, infection is often asymptomatic, and may require highly sensitive molecular methods for diagnosis.[2] Semi-immune patients may be more likely to develop symptoms with immunosuppression, splenectomy, or pregnancy.[3]

We report the case of a patient from Mali who, after 10 years of living in Spain, presented with symptomatic *P. falciparum* malaria without having visited an endemic area during that time.

The patient is a 38-year-old male immigrant in irregular administrative situation, farm worker, who has lived in Almeria (southeastern Spain) since arriving in our country 10 years earlier. He had no medical history. In August 2016, he consulted in the emergency room of a small hospital referring fever, headache, joint and muscle pain, and mild abdominal discomfort, without vomiting or diarrhea, for the last 24 hours. General condition was good and physical examination was normal. Laboratory tests showed hemoglobin 12.9 g/dL, leukocytes 3,630/uL (neutrophils 73%), platelet count 25,000/uL, and C-reactive protein 8.26 mg/dL (normal range 0.01–0.50).

A diagnosis of possible viral process was made and the patient was discharged under treatment with paracetamol. A blood sample was sent to our hospital for further testing. On account of the presenting features, the patient's sub-Saharan origin and the presence of thrombocytopenia, a rapid diagnostic test (RDT) was performed (SD Bioline malaria Ag Pf/Pan®, Korea), being positive for *P. falciparum* (histidine-rich protein 2) and negative for panmalarial antigen (Plasmodium lactate dehydrogenase), followed by a blood thin smear, which showed the presence of occasional intraerythrocytic parasitic elements consistent with *P. falciparum* (parasitemia < 1/1,000).

The patient was located through his primary care doctor 5 days later and was admitted to our hospital to confirm diagnosis and for further explorations. At the time of admission, the patient reported feeling better, although fever persisted in the evenings. Blood count was normal (hemoglobin 13.4 g/dL, platelet count 253,000/uL) and main biochemistry test results were total bilirubin 0.62 mg/dL (indirect bilirubin 0.47 mg/dL), aspartate aminotransferase 53 IU/L (0–35), alanine aminotransferase 60 IU/L (0–45), gamma-glutamyl transferase 103 IU/L (0–55), lactate dehydrogenase 292 IU/L (0–247), and C-reactive protein 3.87 mg/dL. The patient had no structural hemoglobinopathies by high-performance liquid chromatography (HPLC) method. Malaria RDT showed again exclusive positivity for *P. falciparum* antigen, and in the blood smear, although no parasitic forms were observed, malarial pigment was found in monocytes. Diagnosis was confirmed by polymerase chain reaction (PCR). Serological tests for human immunodeficiency virus (HIV), Hepatitis C virus, syphilis, Epstein–Barr virus-IgM, parvovirus B19-IgM, and cytomegalovirus-IgM were negative, whereas parvovirus B19-IgG and Epstein Barr-IgG were positive. Abdominal ultrasound was normal (spleen diameter: 10 cm). The patient was treated with dihydroartemisin–piperaquine 40/320 mg (4 tablets/day, 3 days). The patient was discharged after 24 hours completely asymptomatic, and remained so in three subsequent outpatient visits.

The patient confirmed that he had not returned to his home country since arriving in Spain nor had lived with people who had recently returned from Africa, at least in the last year and a half, nor had had any contact with the health-care system in the preceding months.

Such late clinical presentation raises the possibility of recent infection due to indigenous transmission or, on the contrary, the occurrence of an unusual case of very late reactivation of submicroscopic falciparum malaria.

Some cases of *P. falciparum* malaria presenting with clinical manifestations after a longer period than usual, sometimes even after a few years, have been described.[3] This is believed to be due to loss of the semi-immunity state that these patients from endemic regions initially have. In other cases, clinical symptoms may appear following splenectomy[4] or during pregnancy.[5] In cases with long intervals between exposure and presentation, the time interval between arrival to the host country and the appearance of symptoms was variable, though usually less than 3–4 years, although one case from 1945 had an interval of

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13 years.[6] Theunissen and others[7] reported a patient from Guinea-Conakry with *P. falciparum* malaria (parasitemia 0.1%) after living in a nonmalaria-endemic area (Belgium) for 9 years. Two weeks before the onset of symptoms, a friend who had just returned from his home country stayed at his home for a week, so it is possible that the malaria vectors were transported in the luggage of the patient's visiting friend. Szmitko and others[8] reported a case of *P. falciparum* malaria in a patient from Angola who presented with fever and had been living in Canada for 8 years without returning to an endemic area. The diagnosis was made by PCR.

The exact mechanism allowing the parasite to persist for years in a subject without causing clinically overt disease is not known. Still, different strategies that *P. falciparum* may use to evade the immune response of the human being have been proposed. One of the best known is called antigenic variation and refers to the capacity of the parasite to modify the surface proteins expressed, which represent targets of the immune response.[9] PfEMP1 protein (*P. falciparum* erythrocyte membrane protein 1), located on the membrane of infected erythrocytes, is essential not only for *P. falciparum* pathogenicity (rosetting, adhesion to endothelium, etc.) but also for its immunogenicity, because it is considered the main target of the humoral immune response. A family of genes called *var* encodes this protein and *P. falciparum* has approximately 60 of these genes in its genome. Through different genetic and epigenetic mechanisms, the parasite has the ability to express at any given time a different PfEMP1 protein to that expressed in the previous generation and against which there is no immunity developed. The successive appearance of phenotypically different populations that may escape the host immune system (immune evasion) could prolong the infection in time.

The fact that the patient was able, all by himself, to limit *P. falciparum* infection, indicates that his semi-immunity played an important role for controlling the disease, even after 10 years of leaving malaria-endemic areas. This point may support the reactivation hypothesis rather than autochthonous infection.

Regarding the possibility of indigenous transmission, the patient's symptoms commenced at the time of year when there is a higher density of mosquitoes and when more cases of imported malaria are diagnosed in our province, specially in patients returning from their home countries in sub-Saharan Africa. Spain was declared country free of malaria in 1964. Since then, autochthonous cases have been reported related to health care[10] and organ transplantation,[11] injecting drug use[12] and airport malaria.[13] Our patient resides in a village 25 km from Almeria airport, where we confirmed that, in the months before the communication of the case, no flight from Africa had landed. Besides that, since 1964, there have been only two cases of true indigenous vector-borne malaria transmission in Spain, both in northern regions of Spain (Aragon and Navarra), and in both cases caused by *P. vivax*.[14,15] *Anopheles atroparvus* is considered as the most effective vector for malaria transmission in Spain. It is widely distributed throughout the national territory and has been shown to be capable of transmitting *P. vivax* Asian strains, although they are refractory to strains of *P. falciparum*.[16] *Anopheles labranchiae* has been the most important vector for *P. falciparum* malaria transmission in Mediterranean Europe. However, since 1973, there is no record of its presence in our country anymore.[17] *Anopheles labranchiae* is indeed very common in Morocco.[18] The province of Almeria is very close to north Africa and hosts a large number of Moroccans working in agriculture; it is also an area of intense vehicle traffic because of many other Moroccans immigrants returning to Europe through the port of Almeria after spending the summer holidays in their home country. The introduction of mosquitoes of this species in cars coming from the Maghreb would also be a possibility. It must be said, though, that studies on *An. labranchiae* specimens from Italy have showed that they are not effective transmitter vectors for African *P. falciparum* strains.[19]

In summary, we report the case of a patient of sub-Saharan origin that presents symptomatic *P. falciparum* malaria without having visited an endemic area in the last 10 years and who does not harbor any condition related to immunosuppression. Although we cannot completely rule out the possibility of indigenous transmission, the most likely cause is a malaria recrudescence because of the loss of acquired semi-immunity over the time. Given the expansion that many vectors are having due to climate change and globalization, the existence of long-term asymptomatic infected individuals may contribute to the resurgence of malaria in eradicated areas.

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