Febrile *Plasmodium falciparum* Malaria 4 Years after Exposure in a Man with Sickle Cell Disease

Tatiana Greenwood,1 Tomas Vikercors,2 Maria Sjöberg,2 Gunnar Skeppner,1 and Anna Färnert3

Departments of 1Pediatrics and 2Infectious Diseases, Örverb University Hospital, Örebro, and 3Infectious Diseases Unit, Department of Medicine Solna, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

We report a case of symptomatic *Plasmodium falciparum* malaria that manifested 4 years after a visit to an area of endemicity in an 18-year-old male patient with sickle cell disease. The exceptionally long incubation time raises the questions of how and where *P. falciparum* parasites can reside for several years before suddenly causing disease.

*Plasmodium falciparum* malaria is an acute and potentially fatal infection that accounts for the main global burden of malaria. After inoculation by the *Anopheles* mosquito, the parasites mature in the liver for at least 1 week before multiplying in the blood to levels that cause fever and a wide variety of symptoms. The incubation time is generally <2 months [1, 2]. Chemoprophylaxis and partial immunity may prolong the prepatent period. However, in contrast to infections caused by the other *Plasmodium* species, delayed onset of *P. falciparum* malaria occurs very rarely [1, 2].

We describe a case of clinical *P. falciparum* malaria that developed 4 years after exposure. This exceptional case raises several issues about the chronicity and activation of *P. falciparum* infection.

**Case report.** The patient was an 18-year-old man who was admitted to Örverb Hospital (Örebro, Sweden) with a 3-day history of chest, stomach, and back pain and recurrent episodes of sweating and fever. He was known to have sickle cell disease with splenomegaly but few other complications. At hospital admission, the patient had a temperature of 39°C, a slight tachycardia, paraesthesia of the lower lip, and splenomegaly. The rest of the findings of the examination were normal, without focal signs of infection. Blood test results revealed a C-reactive protein level of 263 mg/L, an erythrocyte sedimentation rate of 50 mm/h, a hemoglobin level of 118 g/L, a WBC count of 14.2 × 10⁹ cells/L, a platelet count of 110 × 10⁹ platelets/L, slightly elevated liver enzyme levels (lactate dehydrogenase level, 28 µkat/L; alanine aminotransferase level, 2.3 µkat/L; aspartate aminotransferase level, 3.5 µkat/L; alkaline phosphatase level, 4.6 µkat/L), and signs of coagulopathy, with D-dimer >20 mg/L and fibrinogen level of 8.7 g/L. Chest radiograph and electrocardiograph findings were normal.

The patient received a clinical diagnosis of acute chest syndrome (related to his sickle cell disease), with suspected infection. He was treated with intravenous cefotaxime, fluids, analgesics, and oxygen. He improved after 2 days; however, the recurring episodes of fever and sweating persisted. Results of bacterial culture of blood, nasopharynx, urine, and stool specimens were normal, as were the results of serological tests for ongoing Epstein-Barr virus and cytomegalovirus.

The patient was born in Togo, where he lived until he was 4 years of age. During his 14 years in Sweden, he had visited his country of origin on only a few occasions, and his last visit was 4 years before hospital admission. The suspicion of a malarial infection was, therefore, low. However, to exclude the benign forms of malaria, which have longer incubation times (*Plasmodium ovale, Plasmodium vivax, and Plasmodium malariae*), a screening test (MalaQuick; ICT) was performed. Surprisingly, the result of the test was positive for *P. falciparum*. Light microscopic examination of Giemsa-stained blood smears detected *P. falciparum* in <0.01% of erythrocytes, with mainly rings but also with a few trophozoites, schizonts, and gametocytes, as well as crescent-shaped erythrocytes (figure 1). The patient was treated with atovaquone and proguanil (Malarone R) for 3 days and was afebrile after 2 days. The unexpected diagnosis was further confirmed by 2 separate PCR methods: a species-specific PCR [3], which detected only *P. falciparum*, and a *P. falciparum* genotyping method, which identified 1 parasite clone. At follow-up, the patient was fully recovered, and results of another microscopic examination and PCR were negative.

During his visit to Togo, which lasted for 1 month, the patient had taken mefloquine prophylaxis weekly, with uncertain compliance. He recalled having had an episode of fever, which he believed was treated with antimalarial tablets. He denied having any episodes of fever after that. The patient had no history of travel to other areas where malaria is endemic, he had not...
received blood transfusions, he had not visited an airport, and he had not had close contact with a person with malaria. Therefore, it was concluded that he most likely was infected during his last visit to Togo, in June 2002.

Blood smear specimens saved for routine hematological control in May 2002 (i.e., before the visit to Togo) were reanalyzed and found to be parasite-free by microscopic examination. No additional microscopic smear or blood specimens were available for analysis of the presence of parasites during the subpatent period (2002–2006).

Discussion. *P. falciparum* is considered to have an incubation time of 1 week to a few months. In our case, a clinical episode with fever developed 4 years after exposure. In contrast to *P. vivax* and *P. ovale* infections, *P. falciparum* and *P. malariae* infections do not have any dormant liver stages (i.e., hypnozoites that cause relapses after several years). *P. malariae* infection may have a very long incubation period (as long as several decades), but it is not known where the parasites reside. *P. falciparum* infection has a more acute onset, with >95% of infections occurring within 2 months after exposure [1]. Persistent *P. falciparum* parasitemia is, however, often found in individuals in areas of high transmission who have developed antimalarial immunity as a result of repeated infections. This immunity protects from disease but is not considered to be sterilizing (i.e., the parasites are not completely cleared unless antimalarial treatment is received), and the parasites often remains in the blood at low levels. It is, however, not clear how long *P. falciparum* infection can persist without reexposure. At the time when malaria was induced to treat neurosyphilis, *P. falciparum* infection was generally prepatent for up to 4 weeks in patients with primary infection and persisted as asymptomatic parasitemia for a maximum duration of 6–18 months [2].

The incubation time and duration of infection may be extended because of partial immunity. Studies of infection persistence in areas of endemicity are, however, restricted by the risk of new infections. In countries where malaria is not endemic, secondary *P. falciparum* infections have occurred through blood transfusion from asymptomatic semi-immune donors a few years after exposure [4]. Individuals with prior residence in countries of endemicity are, therefore, deferred from blood donation for 3 years in the United States [5]. In semi-immune individuals, infection can persist as low-level parasitemia without symptoms. Here, a *P. falciparum* infection developed into acute malaria after 4 years. Unfortunately, there was no blood sample available to establish how long the parasites were present in the peripheral blood before causing disease.

During his first years of life, our patient was likely to have acquired some immunity against malaria. He had, however, made only occasional visits to Togo after emigrating to Sweden and, thus, had limited exposure and opportunities to stimulate the maintenance of such immunity. At the suspected time of infection, the patient was taking mefloquine prophylaxis and probably received some kind of antimalarial treatment for an undiagnosed febrile episode. These antimalarial drugs were obviously not optimal to prevent or clear the infection, either because of poor efficiency or because of insufficient intake; however, they may have reduced the parasitemia to a level where a partial immunity was able to control the infection.

Moreover, the patient had sickle cell disease. Hemoglobinopathies are well recognized as protective against malaria and are most prevalent in parts of the world where malaria is or has been highly endemic [6]. The sickle cell disease trait, which

Figure 1. Erythrocytes infected with *Plasmodium falciparum* trophozoites (A) and schizonts (B) and crescent-shaped erythrocytes (i.e., sickle cells; C) in Giemsa-stained thin smears of peripheral blood specimens obtained from the patient. Smears are from the time of diagnosis.
is most common in West Africa, results in an equal concentration of hemoglobin S and hemoglobin C, which separately have no significant pathology; however, these forms together cause a clinical syndrome similar to sickle cell anemia. Separately, hemoglobin S and hemoglobin C protect against malaria through the inhibition of parasite growth; however, the effect when combined as sickle cell disease is not as well established [6]. The RBC polymorphism may indeed have contributed to the suppression of parasitemia to a subclinical level. It is unclear whether \textit{P. falciparum} infection triggered a suspected sickle crisis or whether the crisis—maybe triggered by another infection—propagated a chronic subpatent parasitemia to develop into clinical malaria. Sickle cell disease often leads to impaired spleen function, and \textit{P. falciparum} infection has been found to emerge in individuals who have undergone splenectomy [7]. The function of the spleen in our patient may have been of key importance for the control and chronicity of infection.

In partially immune individuals with persistent low-level parasitemia, symptomatic malaria is believed to result from new infections due to antigenically different parasites to which the host is not immune [8]. Here, the absence of reexposure demonstrates that clinical symptoms can develop from a chronic infection. The parasites may have undergone antigenic variation of the polymorphic \textit{P. falciparum} erythrocyte membrane protein 1 and, thus, presented as “new” to the immune system. Such antigenic variation, a mechanism by which the parasite switches the expression of surface antigens and thereby evades clearance in the spleen, may also be triggered by the spleen itself [9]. The finding of trophozoites and schizonts, which are not normally detected in the peripheral blood of patients with \textit{P. falciparum} infection, suggests altered sequestration and reduced clearance of late-stage parasites (figure 1). This supports impaired spleen function as contributing to activation of disease and may contradict the absolute need of an antigenically different parasite for the development of clinical malaria.

Our case leads to an intriguing question: where had the parasites resided for so long? Had they been multiplying in the blood and remained at subpatent levels through continuous immune clearance? Or, as has recently been suggested, does \textit{P. falciparum} infection also have dormant stages [10], perhaps in lymphoid tissue [11], that are perhaps induced by antimalarial drugs [12]?

In addition to demonstrating an interesting clinical situation and the need to consider \textit{P. falciparum} malaria a long time after exposure, our case raises several questions regarding the understanding of the biologic characteristics and the host-parasite interactions of \textit{P. falciparum} infection.

Acknowledgments

We thank Rita Lind, for providing photographs, and Lillemor Karlsson and Berit Schmidt, for parasitological expertise.

Potential conflicts of interest. All authors: no conflicts.

References