Malaria relapse with brain involvement

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Abstract

Malaria is an endemic parasitosis in more than 80 countries, with more than 200 million cases recorded in 2020. Recent literature has shown the economic impact and severity of the disease caused by the *vivax* variant, a species which has been underestimated.

We describe the case of a 19-year-old adult male who was a previously healthy active-duty soldier who had been living in the city of Bogotá for the last six months. He presented with a four-day history of fever coupled with headache, arthralgias and several diarrheal episodes, as well as a three-minute generalized tonic-clonic seizure without sphincter relaxation. He had total amnesia of the event. The only relevant point in the interview was a history of malaria treated seven months prior to admission, while he was in Amazonas Department. A thick blood smear taken during his stay confirmed the presence of *Plasmodium vivax*. The patient was treated with intravenous artesunate and diagnosed with cerebral malaria secondary to a relapse. **(Acta Med Colomb 2022; 48. DOI: https://doi.org/10.36104/amc.2023.2678).**

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Introduction

Malaria is an endemic parasitosis in more than 80 countries, with over 200 million cases reported in 2020. The African continent continues to be the region most affected by the disease. Countries like Angola, the Congo, Uganda, Mozambique, Burkina Faso and Nigeria account for approximately 55% of the overall total recorded, according to WHO data (1). Close to 400,000 people die from the disease every year, representing an important health burden for developing countries (1). *Plasmodium falciparum* is the globally predominant species in up to 94% of the reports and is related to 70% of the recorded mortality. However, in America, up to 71% of the malaria cases are caused by *Plasmodium vivax*. *Colombia, Brazil and the Bolivarian Republic of Venezuela comprise 77% of the statistics (1). In this report, we will describe the case of a malaria vivax relapse with a severe and unusual presentation, highlighting neurological involvement*.

Case report

A 19-year-old male patient was admitted to the emergency room. He was a single, previously healthy, active-duty soldier who had lived in Bogotá for the last six months, and he complained of four days of fever peaks up to 39°C, headaches, arthralgia and several episodes of watery, non-dysenteric diarrhea. Along with this, he had had a three-minute seizure with generalized tonic-clonic movements and eyes rolling back in his head without sphincter relaxation, with drowsiness after the event and complete amnesia of what had occurred. He was admitted accompanied by relatives who witnessed the episode and corroborated the story.

The only relevant medical background he reported was a history of malaria treated six months previously while he was living in Amazonas.

The physical exam on admission showed blood pressure: 115/67 mmHg, temperature: 37°C, oxygen saturation: 99%, Glasgow on admission: 15/15, and heart rate: 98/min. He was in apparently good general condition, with moist mucous membranes, and mildly jaundiced sclera. He had no nuchal rigidity and no enlarged neck lymph nodes. His breath sounds were clear, and he had tachycardic heart sounds with no murmurs. His abdomen was painless with no palpable visceromegaly. There was no extremity edema and distal pulses were present with good capillary refill. The patient responded appropriately to questions with no evidence of a focal neurologic deficit. He had preserved extremity strength, normal reflexes, no Kernig or Brudzinski signs, and the fundoscopic exam by neurology provided no relevant data.

A simple brain tomography was performed with no evidence of collections, bleeding or ischemia. In the paraclinical tests, a complete blood count showed a leukocyte count of 5.3 x 10^9/L, 80% neutrophils, 10.3% lymphocytes, hemoglobin 12.2 gr/dL, hematocrit 36%, platelets 89,000, sodium 137 meq /L, potassium 4.3 meq /L, creatinine 1 mg/dL, CRP 4.07 mg/L, total bilirubin 1.7 mg/dL, normal

transaminases, and a total abdominal ultrasound showing mild splenomegaly. The urinalysis did not suggest infection and a COVID-19 antigen and PCR taken on admission were reported as negative. Neurology performed a lumbar puncture, obtaining crystal clear fluid; the FilmArray for cerebrospinal fluid was negative for bacteria, negative for viruses and negative for fungi (cryptococci). Cytochemistry appeared normal, and latex agglutination for cerebrospinal fluid was negative, with a subsequent fluid culture that was likewise negative; VDRL was negative. The findings of brain magnetic resonance imaging with the epilepsy protocol were within normal limits, and video telemetry showed no epileptogenic foci. With the patient's consent, a sample was taken for HIV testing, which was normal. A chest x-ray was normal. Stool samples were not obtained since the diarrhea disappeared on admission, with no subsequent bowel movements. Blood tests were run for dengue, which were negative, along with a leptospira rapid test (lateral-flow assay), which was positive. A second test was run to corroborate the finding using the ELISA method, which was reported as negative. Given the reported history of malaria, a thick smear was done to look for the blood parasite, which was positive for *Plasmodium vivax*. The count yielded a parasitemia of 10,320/uL (Figure 1). With all this, treatment was begun with intravenous artesunate, considering this to be complicated malaria due to *Plasmodium vivax* with brain involvement secondary to a relapse. This conclusion was reached after ruling out other possible diagnoses. He was switched to oral treatment after 48 hours, as indicated in the treatment protocol. The patient progressed satisfactorily with no more fevers, improved hyperbilirubinemia, no new seizures and a negative thick smear on the third day of treatment. He was discharged in good general condition to continue on outpatient primaquine for 14 days, with an order for outpatient follow up.

Discussion

The relapse phenomenon has been described for more than 100 years. Patrick Mason, with his son as a volunteer, showed that mosquitoes harbored *Plasmodium vivax* as sporozoites. In his description, he mentioned the recurrence of the disease nine months after the bite (2).

It is assumed that two sporozoite forms invade the liver after the mosquito bite. These are known as tachysporozoites and bradysporozoites. These, in turn, have specific transcriptional responses with a unique molecular profile, with bradysporozoites ultimately becoming latent in the form known as hypnozoites (3).

Recent literature has been emphatic in showing more and more the economic impact and severity of the disease caused by *Plasmodium vivax*. This species has been underestimated, probably due to scientific bias in the literature and partly due to the greater lethality known to be associated with *falciparum* (4). Unlike years earlier, the current evidence regarding the capacity of *P. vivax* to cause severe illness is indisputable and robust (5, 6). Between 1998 and 2008, 234 deaths from *P. vivax* were reported in Brazil (7). However, one requirement for speaking of severity due to *P. vivax* or complicated *P.vivax* malaria includes having ruled out, as much as possible, a coinfection with *P. falciparum, ideally using PCR, which is hard to find in the reported studies and was not done with our patient. This search for falciparum is suggested for any form of suspected P. vivax severity, including cerebral malaria. It should be noted that other infectious and noninfectious conditions have also been documented as coexistent conditions in the literature (8, 9). The reported case highlights a late P. vivax relapse in the city of Bogotá, in which there are no native reports of the disease, and therefore it is clearly assumed that the documented infection was related to the history of malaria in Amazonas seven months prior.*

Although the seizure criteria originally described for cerebral malaria require the occurrence of two or more seizures in 24 hours, WHO has highlighted that one seizure episode that cannot be explained by another cause, with the presence of confirmed plasmodium parasitemia, should be assumed to be a "prodrome of cerebral malaria" requiring a consequent treatment strategy. This justified our procedure in this case (10). It should be noted that the criteria for complicated malaria which were previously only valid for *P. falciparum* malaria are currently accepted for *P. vivax*, given the robust evidence of severe disease caused by this species (5, 6, 10).

Finally, we decided not to give credence to the positive rapid test for leptospirosis since the result could not be

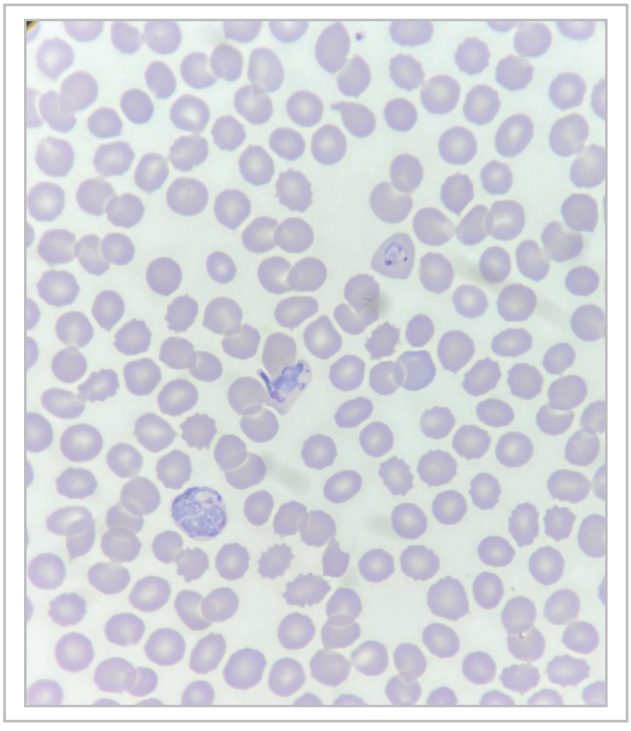

Figure 1. *Plasmodium vivax in various erythrocytic stages in a peripheral blood smear. (With the patient's permission.)*

corroborated with the ELISA method, with which cross-reactions are notably reduced. Furthermore, considering the probabilities and using logical medical reasoning, it was considered highly unlikely that the patient would have both infections simultaneously, and therefore the rapid test was concluded to be a false positive and leptospirosis treatment was not pursued.

In closing, the presented case reminds us that malaria relapse is a diagnostic possibility which, even after a long time has elapsed, should be kept in mind in approaching a patient with febrile syndrome in countries and areas which are endemic for the disease. The parasite's latency period as a hypnozoite ranges from weeks to months. *P. vivax* is a species whose relapse can cause severe disease, including brain involvement, as seen in this case.

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