CASE REPORT

Fever of unknown origin and the role of *Plasmodium vivax* in Sao Paulo

Marcelo Rodrigues Bacci,¹ Janaina Aparecida Boide Santos,² Natalia C P Zing,¹ Felipe Barca Bragatto¹

¹Department of General Practice, Faculdade de Medicina do ABC, Santo André, Sao Paulo, Brazil
²Department of Cardiology, Faculdade de Medicina do ABC, Santo André, Sao Paulo, Brazil

Correspondence to
 Professor Marcelo Rodrigues Bacci, mrbacci@yahoo.com

SUMMARY

Malaria is a disease that hits the northern part of Brazil in an endemic form. Recorded cases outside this region are unusual and, in most cases, limited to travellers. The southeast of Brazil has an extensive wilderness area with a type of vegetation similar to the one found in the equatorial rainforest. We present the case of a patient living in the southeast, with no reported travel history, who evolved to periodic fever, associated with myalgia and chills. With the positive test result for *Plasmodium*, the treatment for malaria was started. This case enabled the study in the Anopheles mosquito affected area, where the patient reported infection, outside the Amazon region.

BACKGROUND

A parasitic disease of major concern owing to its impact on Brazilian and world's health, malaria is caused by a *Plasmodium*—the highlighted species are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*—transmitted through the bite of the female Anopheles mosquito. In Brazil, only the first three species of this parasite can be found, and infections by the *P vivax* are prevalent, followed by the *P falciparum*.

Infections by *P ovale*, occur only in Africa, whereas infections by *P knowlesi* are detected in Southeast Asia; however, imported cases can occasionally be diagnosed in Brazil. Between the years 2009 and 2011, the total number of notified cases of malaria in Brazil was 911 070. The state of Para is the highest incidence area in the country, representing 38.42% of the cases during this period, followed by the state of Amazonas with 25.65%. The state of São Paulo represented 0.07% of the total cases.¹

Thanks to the campaigns conducted by the WHO,² the last decade was granted with a significant financial support focused on disease-control policies, like the implementation of mosquito nets, indoor spraying, insecticides, chemoprophylaxis, diagnostic and treatment tests, causing a steep drop in the average between the cases notified per month and the mortality rate during this period. Owing to their closeness to poverty, countries with the lowest gross national product and/or high mortality rates were the ones which received the highest share of investments, namely Latin America and Africa.

Disease outbreaks mainly occur in rural areas. However, owing to deforestation and the migration

of people to cities, malaria reached urban areas. Rural work, inadequate housing and clothing and closeness to the woods increase the risk of mosquito exposure and thus the mosquito transmission of the *Plasmodium*.

CASE PRESENTATION

A 58-year-old patient of Asian origin with persistent fever presented to the emergency department of São Bernardo do Campo Hospital Complex at Faculdade de Medicina do ABC, Brazil, in the month of January 2013.

After a thorough anamnesis, it was observed that the fever occurred with a regular periodicity of 48 h and it lasted 5 days. As diabetes was an associated comorbidity, the patient made use of NPH insulin and vildagliptin. She complained of intense frontal headaches and palpitations during fever episodes, and she had no nausea or skin rash.

During physical examination, the patient was flushed and her capillary filling time was normal. Her blood pressure was 110/70 mm Hg, axillary temperature 95.9 F and capillary glucose measurement 143 mg/dL. Pulmonary and abdominal physical examinations showed no alterations and the investigation for lymphadenomegaly was negative.

INVESTIGATIONS

First laboratory examinations revealed haemoglobin 13.1 g/dL, haematocrit 38.5%, 7 300 leucocytes with 1% band cells, 53% polymorphonuclears, 37% lymphocytes and 163 000 platelets. The value of C reactive protein was 71.9 mg/dL, alkaline phosphatase 266 U/L, aspartate aminotransferase (AST) 64 U/L, alanine transaminase (ALT) 64 U/L and γ -glutamyl transferase 456 U/L. Results of serology for HIV, cytomegalovirus (CMV), hepatitis B and C were negative.

DIFFERENTIAL DIAGNOSIS

The place where the patient was treated, São Bernardo do Campo, is a municipality in the southeastern part of Brazil surrounded by an extensive area of the Atlantic forest, a Brazilian rainforest subtype. It is an endemic area for Brazilian spotted fever on account of the large amount of ticks of the species Ixodidae. However, the patient had no spots over her body and the fever was intermittent. Infections induced by the CMV cause fever, adynamia and such infections frequently evolve the enlargement of the liver and spleen and mononucleosis. As the patient did not present enlarged nodes, this possibility was ruled out.

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Figure 1 Schizonts of *Plasmodium vivax* in thick blood smear.

Finally, despite the fact she was in a non-endemic region, owing to the fever periodicity on alternate days, material for the investigation of infection by the *Plasmodium* sp was collected. The analysis of a drop of the patient's blood, spread out as a blood smear, confirmed the diagnosis of malaria by *P vivax* (figure 1) and the epidemiological surveillance department certified it as an autochthonous infection once the patient had not travelled to endemic areas in or out of the country.

TREATMENT

Treatment with chloroquine was started and the patient improved, with remission of symptoms.

OUTCOME AND FOLLOW-UP

The patient had full remission of the symptoms with the chloroquine regimen. She returned a month later and there were no schizont forms in her thick blood smear and a full recovery of AST, ALT and ALP levels.

DISCUSSION

The infection by *Plasmodium* triggers a reaction between the host and the parasite which will determine the gravity of the disease. Inhabitants of endemic areas are in general more exposed to the protozoan, thus developing an immune response and presenting milder cases of the disease. On the other hand, primary infections rapidly evolve to severe cases most of the time.³

A study suggests an increase in *Plasmodium* infection in diabetic individuals.⁴ Although the reason is not clear, the hypothesis of these findings lies in the fact that there is an increase of glycaemia in those individuals and, as demonstrated in vitro, the increase of glucose availability may stimulate parasite proliferation. Besides, such individuals may present subtle alterations that affect the olfactory signals that mediate the mosquito

attraction, like alterations in the respiratory pattern; therefore, they would be more susceptible to bites of infected mosquitoes. Immunologically speaking, in individuals with type 2 diabetes mellitus, hyperglycaemia leads to the depression of T lymphocyte-mediated immunity, a fact that also favours the infection.

Given the fact that general symptoms like headache, malaise, fatigue, high fever that may be accompanied by back pain, dizziness, nausea and vomiting are unspecific, it is believed that there are still many undiagnosed cases. The history of visits to endemic areas helps the diagnostic elucidation in such cases.

On account of the presence of the protozoan in cells (red blood cells in particular), several reactions involving especially the cell membrane occur, which lead to cellular lysis, release of interleukins and tumor necrosis factor α , increase in cellular aggregation and adherence and as a result, a significant inflammatory process, anaerobic metabolism and dysfunction of multiple organs related to disseminated intravascular coagulation.⁵

Therefore, early diagnosis is essential for a good prognosis, especially in cases of infection by *P falciparum*, a plasmodium closely related to the more severe forms of the disease. For such, it is necessary to perform the thick blood smear, a test that microscopically identifies the presence of the parasite in a blood sample. The evaluation and treatment of possible organic dysfunctions are also of great importance.

Learning points

- Periodic fever of undetermined origin should be an alert sign for malarial investigation.
- It is important to investigate possible foci of mosquitoes, even out of the endemic areas, whenever malaria is suspected.
- *Plasmodium falciparum* is associated with more severe forms of the disease.

Contributors FBB and NCPZ collected the data and obtained the patient's consent. MRB and JAB conducted the case and wrote the article.

Competing interests None.

Patient consent Obtained.

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