Case report

Imported Case of Malaria by *Plasmodium vivax* in El Salvador. An Epidemiological Approach

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Abstract
Case presentation. Male patient of Guatemalan origin with history of intermittent high fever, myalgia, arthralgia, generalized weakness, dizziness, and vomiting of gastric contents. He was initially treated in a private hospital with a diagnosis of acute febrile illness and referred to a national network hospital with a diagnosis of dengue with warning signs. On the third day of hospital stay a diagnosis of an imported malaria case by Plasmodium vivax was presented. **Treatment.** The patient was given antimalarial treatment consisting of chloroquine and primaquine. **Outcome.** The patient presented clinical improvement, and control laboratory tests were negative for Plasmodium vivax.

Keywords
Malaria, Plasmodium vivax, Vector Borne Diseases, Diagnosis, Case Study.

Resumen
Presentación del caso. Paciente masculino de origen guatemalteco con historia de fiebre alta de tipo intermitente, mialgias, artralgias, debilidad generalizada, mareo y vómito de contenido gástrico. Fue tratado inicialmente en un hospital privado con diagnóstico de síndrome febril agudo y referido a un hospital de la red nacional con diagnóstico de dengue con signos de alarma, al tercer día de estancia hospitalaria se diagnostica como un caso de malaria importado por *Plasmodium vivax*. **Intervención terapéutica.** Se le dio tratamiento antimalárico con cloroquina y primaquina. **Evolución clínica.** Presentó mejoría clínica y las pruebas de laboratorio de control reportaron resultados negativos para *Plasmodium vivax*.

Palabras clave
Malaria, *Plasmodium vivax*, Enfermedades Transmitidas por Vectores, Diagnóstico, Estudio de Caso.

Introduction

Malaria is a potentially fatal infectious disease caused by parasites transmitted to humans by the bite of female mosquitoes of the genus *Anopheles*, infected by obligate intracellular protozoa of the genus *Plasmodium*. Mainly four species cause disease: *P. vivax*, *P. falciparum*, *P. malariae, and P. ovale*.[1,2]

P. vivax has an incubation period of 12 to 17 days after mosquito bite,[3] although cases with incubation periods of more than 90 days have been documented.[4]

Its cycle consists of two main stages. In the schizogonic stage, also called the intrinsic incubation period, which occurs in the vertebrate host, two cycles can be distinguished: one in the liver and the other in the red blood cells. In the hepatic cycle, the parasite reproduces in the liver cells for six to eight days. It then moves to the erythrocyte cycle, where it multiplies inside the red blood cells for two days before they rupture and release new parasites into the bloodstream.[1]

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Caso importado de malaria por *Plasmodium vivax* en El Salvador. Un abordaje epidemiológico

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The sexual or sporogonic stage occurs in the mosquito and lasts eight to ten days. During this period, the sexual parasites fuse in the mosquito's stomach, forming sporozoites that migrate to the salivary glands. When the mosquito feeds on blood, the sporozoites can be transmitted to a new vertebrate host and transmit malaria.[1]

Plasmodium vivax is the most common parasite that causes malaria in humans, found primarily outside Africa.[5] In the Americas, it is responsible for 76 % of malaria cases.[5] For the 21st epidemiological week of the year 2023, Guatemala reported a total of 1276 cases in the country.[6]

Malaria cases worldwide increased in 2021 from 245 million to 247 million.[7] In the Americas during 2021, the World Health Organization (WHO) estimated 597 000 malaria cases and approximately 334 deaths.[5] Paraguay, Argentina, and El Salvador were certified malaria-free by WHO in 2018, 2019, and 2021, respectively.[5]

In 1980, El Salvador contributed 37 % of all reported cases in the region, while today, its contribution is less than 0.1 %.[8] The last recorded case of locally transmitted *Plasmodium falciparum* occurred in 1995, whereas the latest death from *Plasmodium* infection occurred in 1984.[8] In 2017, four cases of *Plasmodium vivax* were registered in the Country; three of them were imported, and the last was a relapse case from the previous year.[8] El Salvador is the first Country in Central America to be certified malaria-free by WHO in 2021.[5] To prevent the recurrence of indigenous malaria transmission, the Country has increased its efforts through a multidisciplinary approach aimed at capturing cases, notifying them, providing timely treatment, and thoroughly investigating each case to carry out the necessary control actions.[9]

The objective of this article is to underline the importance of epidemiological guidance in case management for an accurate and timely diagnosis based on the description of a malaria case in a patient of foreign origin.

Case presentation

This case is about a 23-year-old man from the poqomchí linguistic community in the rural area of Guatemala. He communicated through an interpreter. He entered El Salvador by land to work as a construction assistant in Santa Tecla, municipality of La Libertad. Six days after he arrived in the country, he consulted at the first aid station of his workplace with a history of one day of fever of moderate intensity of intermittent type, quantified at 38.1 °C, accompanied by lumbar pain and myalgias. He had no contributing medical history. Due to his clinical condition, the patient was referred to a private hospital where he was diagnosed with pharyngitis and given outpatient management with acetaminophen 500 mg orally every six hours and amoxicillin 500 mg every eight hours for seven days.

The patient consulted a private hospital after nine days, given that he presented intensified symptoms, such as a high intermittent fever of 39.4 °C, myalgias, arthralgias, generalized weakness, dizziness, and vomiting of gastric content of 500 mL on one occasion. He mentioned that he lives in a house with wooden walls, a tin roof, a dirt floor, only one room, and water obtained from a well and stored in containers with lids; also, he added that there are no health services nearby.

Laboratory tests reported mild anemia, low hematocrit, severe thrombocytopenia, elevated C-reactive protein, and COVID-19 was ruled out (Table 1); he was diagnosed with acute febrile syndrome. The patient was referred to a public network hospital, where he presented blood pressure of 110/60 mmHg, heart rate of 91 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 91 %. Pulmonary, cardiovascular, or hepatic alterations were not identified. Based on the above, dengue with alarm signs was suspected.

Follow-up examinations conducted after two days, reported hyperbilirubinemia and moderate anemia (Table 1). An abdominal ultrasound also reported splenomegaly with a longitudinal axis of 13 cm, with a volume of 480 mL, without solid or cystic focal lesions, with scarce free fluid in the abdominal cavity and right pleural effusion (Figure 1). In addition, the general stool examination reported the presence of *Ascaris lumbricoides*.

By the third day of hospital admission (day 12 of illness), dengue, chikungunya, and zika were excluded through laboratory tests, and *Plasmodium vivax* was identified by gross drop microscopy, with a parasite density of 5467 parasites/µL (Table 1 and Figure 2). A summary of the relevant events is shown in a timeline (Figure 3).

Therapeutic intervention

The patient was isolated with the use of a mosquito net and treatment was started with intravenous saline solution 1 L every eight hours, paracetamol 1 g intravenously every six hours, oxygen by nasal cannula at 3 L per minute, and mebendazole 100 mg orally every 12 hours; the latter was suspended due to the detection of *Plasmodium vivax*. Antimalarial therapy was indicated[10,11] with

Tabla 1. Laboratory tests results

Laboratory tests results	Day 9*	Day 11*	Day 12*
Hemoglobin	10.8 g/dL	-	7.8 g/dL
Hematocrit	31 %	-	22.7 %
Leukocytes	-	-	6390/µL
Neutrophils	68.7 %	-	47.7 %
Lymphocytes	18.6 %	-	39.9 %
Platelets	28 000/mL	-	114 000/mm^3
COVID-19 antigen	Negative	-	-
C-reactive protein	320 mg/dL	-	-
Mean Corpuscular Volumen	-	-	80.8 fL
Mean Corpuscular Hemoglobin	-	-	27.8 fL
General stool test	*Ascaris lumbricoides*	-	-
Total Bilirubin	-	2.14 mg/dL	-
Indirect Bilirubin	-	1.18 mg/dL	-
Aspartate aminotransferase (AST)	-	61.2 UI/L	-
Alanine aminotransferase (ALT)	-	60.7 UI/L	-
Sodium	-	133.3 mEq/L	-
PCR Dengue	-	-	Negative
PCR Zika	-	-	Negative
PCR Chikungunya	-	-	Negative
Thick drop	-	-	*Plasmodium vivax*: Parasitic density 5467 parasite/µL blood

* Sick days.

Source: Data obtained from clinical records.

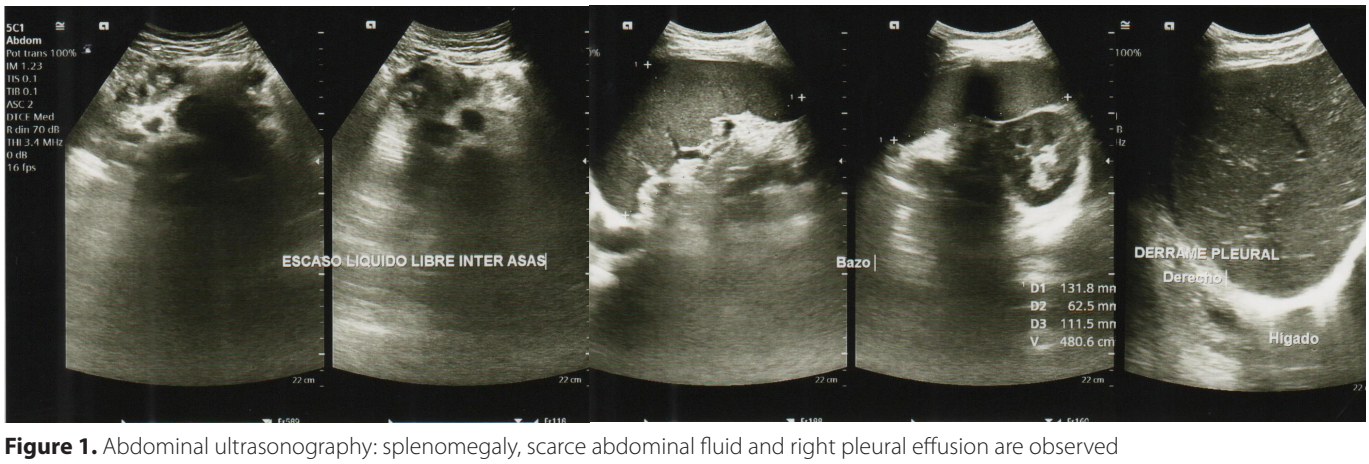

Figure 1. Abdominal ultrasonography: splenomegaly, scarce abdominal fluid and right pleural effusion are observed

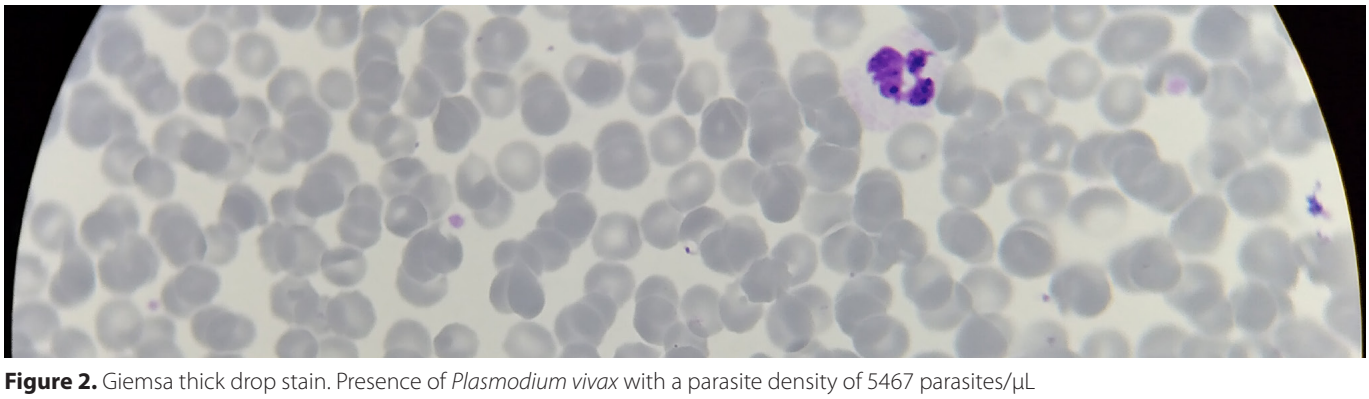

Figure 2. Giemsa thick drop stain. Presence of *Plasmodium vivax* with a parasite density of 5467 parasites/µL

chloroquine 750 mg orally every day (at a dose of 10 mg/Kg) for two days; then, 375 mg orally on the third day (at a dose of 5 mg/Kg), accompanied by primaquine 15 mg orally every day for seven days, and acetaminophen 500 mg orally every six hours, if the body temperature was higher than 37.5 °C; however, fever was not reported again. The case was reported to the epidemiological authorities through the epidemiological surveillance system of El Salvador.

Health authorities received notification as part of the epidemiological management. A sample was sent to the National Public Health Laboratory for quality control and confirmation. Thick blood smear tests collected from workers in contact with the patient, were obtained for analysis. A total of 30 samples were reported among the contacts, all with negative results.

Several vector and entomological surveillance measures, including inspection of the entomological situation within a two-kilometer radius, spraying the area with deltamethrin (adulticide), and application of larvicide with temephos in specific areas to detect possible vectors, were applied. In addition, domiciliary visits to treat water containers with 1 % temephos granules. In addition, water areas were inspected, but no transmitting vector was found.

Clinical evolution

After seven days of treatment, the patient was discharged from the hospital, and during the home visit made two days after discharge, clinical improvement presented; three thick blood smear microscopies were performed as a follow-up control for *Plasmodium vivax*, at 14, 21, and 28 days after the diagnosis of malaria, all with negative results.

Clinical diagnosis

The diagnosis of severe *Plasmodium vivax* malaria was confirmed by thick blood smear microscopy tests, due to the following complications: hyperbilirubinemia, splenomegaly, right pleural effusion, and anemia due to hemolysis.[12]

Discussion

El Salvador has been certified as a malaria-free country since 2021;[4] however, malaria-imported cases are still reported.[8] This situation is also present in China certified during the same year.[9] As a result, the recurrence of indigenous malaria transmission continues to be a potential risk. Therefore, all cases should be detected, reported, treated, and investigated in a timely manner.[9]

In 2015, the United Nations Organization, in partnership with the Bill & Melinda Gates Foundation, published a framework for malaria eradication.[13] Similarly, the WHO published a technical strategy for the eradication of *P. vivax*.[13] However, public health tools for diagnosis, treatment, prevention, and control are sub-optimal in many endemic areas,[13] and a special effort is required in malaria-free countries to strengthen the national response and prevent the recurrence of indigenous malaria transmission.[7,9,14]

In the Americas, Paraguay and Argentina have been certified as malaria-free countries by the WHO since 2018 and 2019, respectively.[5] It gives some cause for optimism, as several endemic countries have shown progress in this regard;[7] malaria control and elimination in endemic areas may assert impacts on the prevalence of imported cases and measures to prevent the return

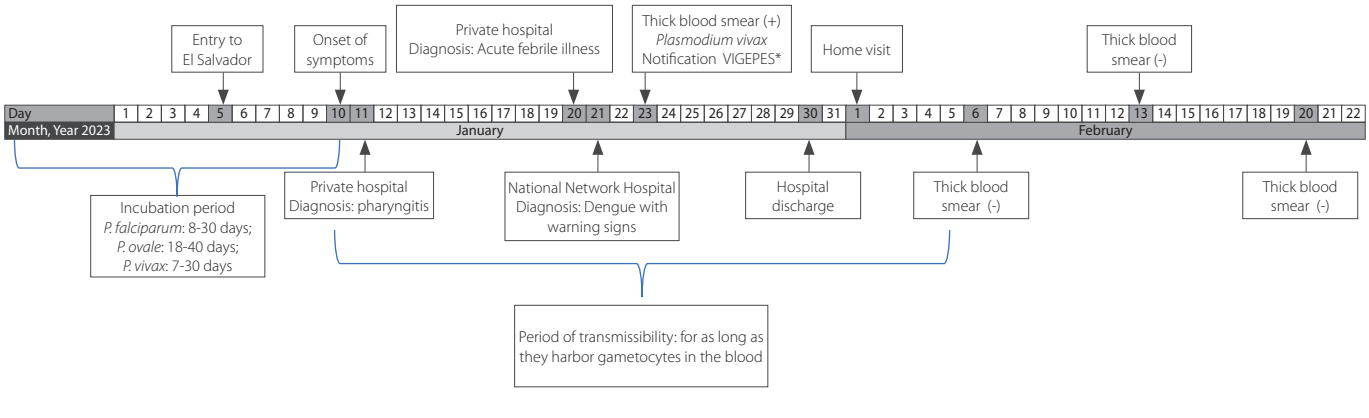

Figure 3. Timeline with key events in the development of the case

*VIGEPES: Epidemiological Surveillance System of El Salvador

of indigenous cases to malaria-free areas.[7] To improve surveillance of *Plasmodium spp.*, contribute to the effective diagnosis of malaria and treatment in both endemic and non-endemic areas.[7]

The increase in total global cases and deaths during 2020 and 2021 is partially traceable to the COVID-19[7] pandemic, as the shutdown and movement restriction of healthcare providers during the pandemic disrupted the continuity of malaria control and elimination programs.[15]

In the case described, symptoms began on the sixth day after the patient entered El Salvador; if considering the minimum incubation period (12 days),[3] the patient became infected outside El Salvador. Therefore, this is an imported case of malaria, given that the patient had been in an endemic country and was in the incubation period at the time of his arrival in El Salvador.

Population movement and international travel lead to tourism and work opportunities in non-endemic areas that increase the risk of case import[1], which, in turn, highlights the need for adequate surveillance and early detection.[9] According to data collected in a systematic review of malaria outbreaks in China from 1990 to 2013, more than half of all outbreaks are traced to population movements.[16] This information is consistent with the findings of this case.

Efforts to control and eliminate *P. vivax* may not present the expected impact due to emerging drug resistance.[17] Endemic countries should regularly evaluate the therapeutic efficacy of antimalarial drugs to adjust their therapeutic guidelines.[17] In this case, the patient responded to conventional treatment, demonstrating the sensitivity of the parasite.

For the initial approach to the patient and a timely diagnosis of febrile infectious diseases in foreigners, it is advisable to guide the diagnosis considering the clinical symptoms, laboratory, and epidemiological criteria according to their country of origin.[14] In this specific case, tests were performed to rule out arbovirosis, due to the prevalence of these diseases in the country. Dengue, Zika, and chikungunya diseases were suggested as presumptive diagnoses; as these were discarded, malaria diagnosis was adopted, based on epidemiological criteria, including the characteristics of the patient's home, which favored the survival and reproduction of the vector,[18] as well as the endemicity and characteristics of the disease in neighboring countries.[14]

In the patient's hematologic findings, thrombocytopenia[19] and anemia stand out. These alterations were the most common in a study published in 2019,[20] in which the authors suggest as diagnostic support criteria for malaria the presence of thrombocytopenia in cases of acute febrile illness, whether or not accompanied by anemia, and recommend taking the management of these abnormalities into account to reduce the associated complications, thus suggesting considering the possibility of malaria in these patients.[20]

Emphasis is placed on the importance of continuous education of health personnel to consider and diagnose malaria promptly, especially in imported cases. In addition, to implement prioritized vector control measures in endemic areas.[7,13]

In this case, the importance of epidemiological surveillance and proper management of malaria, even in non-endemic areas, is highlighted, and emphasis is placed on the need to address the environmental and social risk factors that play a fundamental role in the patient's clinical condition and subsequent recovery.[7,13,14]

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