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Case Report

Misdiagnosis of *Plasmodium vivax* in a Case of Mixed Malaria, Lead to Wrong Anti-Cancer Chemotherapy, Splenectomy, and Partial Hepatectomy Due to Relapse: A Case Report

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Abstract
Malaria is a multilateral parasitic infection, which causes wonderful mortality and morbidity worldwide. It sometimes accompanied a quaint appearance. An Iranian 50-year-old man was admitted to Omid, hospital, a specialized cancer hospital in Isfahan, Iran. Because of a 15-year persisted anemia due to misdiagnose of *vivax* malaria led him to three courses of anticancer chemotherapy and splenectomy. His blood smears were sent to the Department of Parasitology, School of Medicine, Isfahan University of Medical Sciences, Iran. Our findings from his history, file documents, clinical signs and symptoms, and parasitological and molecular assessments revealed an interesting case, which is reported.

Introduction

Malaria has a history longer than humans with surprising mortality and morbidity worldwide. The *Plasmodium vivax, P. falciparum,* and *P. malariae* can be seen in eastern Mediterranean countries as well as in Iran (1). Among them, *P. vivax* has the higher prevalence rate and *P. falciparum* has the medical importance and pathogenicity (2).

Before the past half century, malaria was present all over Iran and one-fourth of all patients were admitted to hospitals and clinics

related to malaria (3). Due to a great deal of effort in the form of malaria eradication programs, it claims that malaria has been eradicated from Iran. In the past 25 years, endogenous malaria was limited to three provinces in the south and southeast of the country, although the imported cases from Afghanistan and Pakistan may be explored all over Iran. About one to two percent of malaria cases are infected with more than one plasmodium species called mixed malaria (2, 3).

Case Presentation

After acceptance and sign of informed consent paper by patient and ethical approvement by the Omid Hospital Ethics Committee, a 50-year-old hypertensive Iranian male was admitted to the Department of Infectious Diseases, OMID Hospital, Isfahan, Iran in December 2019 due to treatment-resistant anemia that had begun 15 years earlier and persisted despite treatment.

The patient also developed malaise, fatigue, night sweating, anorexia, headache, arthralgia, and myalgia. He underwent a splenectomy one year ago because of treatment-resistant hemolytic anemia and splenomegaly (145 cm). He was treated due to malaria *falciparum* fifteen years ago, but he suffered dizziness, headache, anemia, and decreased vision. His hypertension was not well controlled. He took prednisolone 5 mg/bid and captopril 50 mg/day. He had no history of glucose-6-phosphate dehydrogenase deficiency. He was oriented when he was admitted and the Glasgow Coma Scale/GCS was 15/15, but he revealed swelling around the eyes. The heartbeat was regular with tachycardia. Neurological examination revealed normal. Physical examination was remarkable for a pulse rate of 98/ min, blood pressure of 160/90 mmHg, and temperature of 37.3 °C. Laboratory studies revealed a red blood cell count of 5.5×10^{6} /μL, a white blood cell count of 5.9×10^{3} /μL (50% neutrophils), a hemoglobin level of 10 g dL^{-1}, a hematocrit of 28.2 %, a platelet count of 999000 μL^{-1} and reticulocyte count 10.3%, LDH 890 U/L, total bilirubin 0.8, direct bilirubin 0.3 and indirect bilirubin 0.5 mg/dL of serum. Electrolytes were within the normal range.

The patient was sent to our lab as a surgical case for partial hepatectomy due to treatment-resistant anemia with his short illness history and a thin and thick blood smear.

He has lived in Isfahan City, a non-endemic malaria city in central Iran. About 16 years ago, he had taken a trip for an occupational position in Asalluyeh- an Iranian gas company, Bushehr Province in the south of Iran. Bushehr had been an endemic region for *P. falciparum* and *P. vivax* malaria for centuries (4).

After a week, he came back to Isfahan and had no domestic or foreign travel. He has experienced episodes of chilling, fever, and illness after four weeks of his trip. He was referred to a health center and underwent a malaria diagnostic test in Isfahan. They diagnosed *falciparum* malaria and treated him via prescription of a standard dose of chloroquine (25 mg/kg body weight for four meals in three days). According to the patient's status and his file, after ten months of his normal situation, the illness came back and some symptoms such as malaria-like episodes, anemia, splenomegaly, hepatomegaly, and abdomen enlargement have arisen continuously (5, 6).

The unusual and interesting matter, which observed, was the negative replies to several malaria test inquiries. Both governmental and private medical diagnostic laboratories misdiagnosed, caused the patient to undergo splenectomy and three courses of anticancer chemotherapy.

The patient's thick and thin peripheral blood smears were positive for *Plasmodium vivax* (Fig. 1).

Fig.1: Peripheral thin blood smears of the patient show the (Giemsa stain ×1000)
P.v D0: growing trophozoite of *P. vivax* in an enlarged RBC on the first day (arrow) note to many platelets (left). P.v D21: growing trophozoite of *P. vivax* in an enlarged RBC in 21th day after prescription of a standard dose of chloroquine and primaquine indicates the chloroquine-resistant *P. vivax* in this patient

The positive results for *vivax* malaria were reported to his surgeon and not only the patient slave from hepatectomy, but also his anti-malaria treatment began despite some difficulties convincing the malaria managers in the health center of Isfahan Province for giving the anti-malaria drugs.

The patient was treated with a standard course of chloroquine (1500 mg base) over 3 days, followed by primaquine (15 mg daily) for 14 days. Malarial parasites were not cleared from the peripheral blood in 72 h.

Unfortunately, the parasites had been seen up to 21 days after the standard dose of chloroquine and primaquine prescription, although the parasitemia lowered significantly, the parasites were resistant at the R_{II} level. The Coartem™ (artemether 80 mg + lumefantrine 480 mg) was prescribed. Four tablets as a single initial dose, 4 tablets again after 8 hours, and then 4 tablets twice daily (morning and evening) for the following 2 days (total course of 24 tablets). The patient was followed up via physical observation by our tropical diseases specialist co-worker and assessing the parasite by microscopy and nested-PCR methods. The parasite had not been ever presented nor microscopy nor in nested-PCR after day three up to four weeks follow-up. Almost all signs and symptoms started to be corrected and the laboratory measures came to a normal level. Finally, the patient with a normal and good situation returned to his family and occupational activities.

Discussion

Based on adequate experiences with malaria in Iran, we supposed this situation occurred because of a mixed (*P. falciparum* and *P. vivax*) malaria infection. Although the patient's condition was corrected and promoted to normal, he lost his spleen, his normal and welfare life, and his family as well for a long course of about 16 years of illness. Besides, he passed a troublous and expensive three courses of frustrated anticancer chemotherapy.

The patient had spent about 8 months without any malaria paroxysm but thereafter the hypnozoites of *P. vivax* in liver cells underwent tissue schizogony and then entered the bloodstream, multiplication, and established relapse

vivax malaria. All physicians' orders for malaria parasites assessment faced false negative replies by different governmental and non-governmental medical diagnostic laboratories during the 15 years of his illness.

The life cycles of *P. vivax* and *P. ovale* include hypnozoites that can reactivate weeks, months, or years after the initial infection, causing relapse. One study in Papua New Guinea suggested that most episodes of vivax malaria infection reflect relapse from the hypnozoite reservoir rather than a new infection (7). Relapsed infections are also likely to be an important source of ongoing transmission. The life cycles of *P. vivax* and *P. ovale* include hypnozoites, that can reactivate and cause relapse weeks, months, or years after the initial infection (8). The presence of hypnozoites in the liver is not associated with clinical symptoms, and, thus far, diagnostic technology cannot detect these latent parasites. Symptoms of relapse occur when reactivated hypnozoites are released into the systemic circulation. Relapse can also occur in the absence of symptomatic primary infection; this has been observed among individuals who have taken malaria prophylaxis during travel in endemic areas (9).

For malaria strains acquired in tropical areas, the risk of relapse exceeds 80 percent; first relapses typically occur 21 to 30 days after the initial symptomatic illness (10). Four or more relapses may occur at approximately two-month intervals. As many as 10 to 20 relapses within two years have been described (10). In malaria-endemic areas, patients undergoing splenectomy have a high risk of *P. vivax* parasitemia, which is hypothesized to arise from viable parasites accumulated in the spleen being displaced into the peripheral circulation. Hyper-reactive malarial splenomegaly syndrome (HMSS), previously known as tropical splenomegaly syndrome, is a complication of chronic malaria (11). The prevalence is high in Eastern Indonesia and Papuan highlands where *P. vivax* and *P. malariae* are the predominant species, although it can occur in association with any malaria species (10, 11).

The most important issue is the analysis of the factors, which led to such quaint misdiagnosis. It seems that his falciparum malaria attracted all attention due to more importance and severity (12, 13).

We emphasize the more attention of clinical and Para clinical personnel to uncommon infectious diseases like malaria in non-endemic areas. The microscopists used to observe all the smear areas even after finding the first organism; it may present more than a pathogenic agent in the smear. It may confuse and trick the microscopists (14-16). The relapse of malaria may occur in non-endemic areas even 10 years later when the patient left the endemic malaria areas without any travel. Laboratories should apply molecular biology methods (PCR) for the diagnosis of malaria (16). Communicable disease managers should have a scientific and unbiased treatment of such cases and accept the realities (17).

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Conflict of interest

There is not any conflict of interest.

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