Case Report / *Olgu Sunumu*

DOI: 10.5578/ced.201744 • *J Pediatr Inf 2018; 12(1): e35-e38*

A Pediatric Case of Malaria Caused by *Plasmodium vivax*

Plasmodium vivax'ın Etken Olduğu Pediatrik Sıtma Olgusu

Mehmet Kemal Kanık[1], Ayşe Şahin[1], Nazan Dalgıç[1], Zeynep Yıldız Yıldırmak[1], Banu Bayraktar[2], Nurbanu Bilgin[1]

[1] *Clinic of Pediatrics, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey*
[2] *Clinic of Microbiology and Clinical Microbiology, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey*

Abstract

Malaria, caused by the plasmodium species, is a serious disease that is associated with high levels of morbidity and mortality, and is characterized by fever. Here, we present the case of a 10 year-old Syrian-born girl who was admitted to a medical center with fever attacks accompanied by chills, and who was referred to our hospital upon the detection of pancytopenia in an examination and the continuation of complaints in the proposed follow-up. Splenomegaly was detected during a physical examination, and pancytopenia in the laboratory test results. The patient was diagnosed with malaria caused by *Plasmodium vivax* according to a peripheral and thick blood smear. Despite malaria having been all but wiped out in our country following an eradication program, malaria should always be considered in differential diagnoses of foreign patients who admit to medical centers with a fever.

Keywords: Fever, malaria, *Plasmodium vivax*

Özet

Sıtma, *Plasmodium* türlerinin etken olduğu morbidite ve mortaliteye sebep olan ateş ile seyreden ciddi bir hastalıktır. Burada iki haftadır aralıklarla titremenin eşlik ettiği ateş atakları olan bu sebeple dış merkeze başvuran, tetkiklerinde pansitopeni saptanan ve ayaktan izlem önerilen, şikayetlerinin devam etmesi üzerine hastanemize başvuran 10 yaşındaki Suriye doğumlu kız hasta sunulmuştur. Fizik muayenesinde splenomegali saptanan ve laboratuvar incelemelerinde pansitopeni tespit edilen hastaya yapılan periferik yayma ve kalın damla sonucu *Plasmodium vivax*'ın neden olduğu sıtma tanısı konulmuştur. Ülkemizde yerli sıtma olgusu eradikasyon çalışmaları neticesinde görülmüyor olsa da yurtdışı kaynaklı olgular sebebiyle ateşle başvuran hastada ayırıcı tanıda sıtmanın da düşünülmesi gerektiğini vurgulamayı amaçladık.

Anahtar Kelimeler: Ateş, *Plasmodium vivax*, sıtma

Introduction

Malaria is an anopheles mosquito-borne febrile disease caused by *Plasmodium* species, of which *Plasmodium vivax*, *Plasmodium falciparum, Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium knowlesi* are the most common causing disease in humans (1,2).

According to the 2015 World Malaria Report compiled by the World Health Organization (WHO), 262 million cases of malaria were reported in 2000, and despite the number of cases dropping by 18 percent to 214 million in 2015, the disease still resulted in 438.000 deaths. Of the cases resulting in mortality, 91 percent were in Africa, mainly in children below the age of 5 years. Among the causes of death, malaria ranks 10th in the world and second in Africa (2).

The most common species causing infection in Turkey is *P. vivax*, with cases being most common in the Eastern Mediterranean and Southeastern Anatolian regions (3). The number of cases of malaria in Turkey was reported to be 10.224 in 2002, 796 in 2006, 84 in 2009 and 78 in 2010. No new endemic cases of malaria have been reported since 2010, with all reported cases of recurrent infection coming from abroad

Correspondence Address / Yazışma Adresi

Mehmet Kemal Kanık
Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi,
Çocuk Sağlığı ve Hastalıkları Kliniği, İstanbul-Türkiye
E-mail: mkkanik@gmail.com

(2,4). It is observed that cases of malaria traveling to Turkey from abroad increased between 2006 and 2011 (Figure 1). The aim of the present study is to draw attention to the fact that malaria can appear in any part of the world due to travel, immigration and the movement of seasonal workers, although the number of malaria cases has decreased gradually as a result of malaria eradication programs, while emphasizing that a differential diagnosis needs to be carried out for cases presenting fever.

Case Report

A 10-year-old Syria-born girl presented at an external center complaining of fever, abdominal pain and diarrhea, and had been advised follow-up as an outpatient after the detection of pancytopenia and hepatosplenomegaly. Due to lingering symptoms and a fever of 39-40°C, the patient was admitted to the pediatric emergency outpatient clinic of our hospital. Her medical history revealed fever at particular intervals for 2 weeks, accompanied by chills. The patient had travelled to Istanbul from Syria with her family three years previously, and had no later travel history.

Upon a physical examination, the patient's general condition was found to be moderate, she was conscious and cooperative. Her body temperature was 39°C, pulse 120 bpm, blood pressure was 85/50 mm/Hg and respiratory rate was 24 breaths per minute. The patient was moderately dehydrated, her skin turgor was diminished and her skin was pale. There was diffuse tenderness to palpation on an abdominal examination and the liver was 2 cm below the costal margin (hepatomegaly). The spleen was non-palpable, but the Traube's space was closed. Other systems were normal upon examination.

A complete blood count, biochemistry, C-reactive protein (CRP), urine analysis (UA), chest X-Ray and abdominal ultrasonography (USG) were planned. The blood tests revealed hemoglobin, 8.3 g/dL; hematocrit, 22.4 percent; MCV, 75.6 fL; leukocyte, 1870/mm^3; neutrophil, 530/mm^3; lymphocyte, 620/mm^3; platelets, 73.000/mm^3; and CRP, 96.94 mg/L. An abdominal USG revealed hepatosplenomegaly (liver 147 mm, spleen 151 mm), and a chest X-Ray and urine analysis showed normal findings. The patient was admitted to the Pediatric Infectious Diseases ward for follow-up and further investigations. Antipyretics and parenteral fluid therapy were administered as the patient had fever and dehydration. No diarrhea was observed during the clinical follow-up of the patient. On the first day of hospitalization in the ward, the patient's fever reached 40°C, accompanied by chills. A complete blood count obtained upon admission to the pediatric emergency room revealed pancytopenia, and further blood tests and blood smear were performed to identify the etiology of nutritional anemia, revealing: ferritin, 278.4 ng/mL (10.29-55.84); vitamin B12, 126 pg/mL (126.5-505); folic acid, 8.08 ng/mL (3.1-19.9); and 25-hydroxy, vit D: 9.

A blood smear was evaluated with a pediatric hematologist, and revealed signet-ring shaped appearance within the erythrocytes, consistent with *Plasmodium*, for which a thick

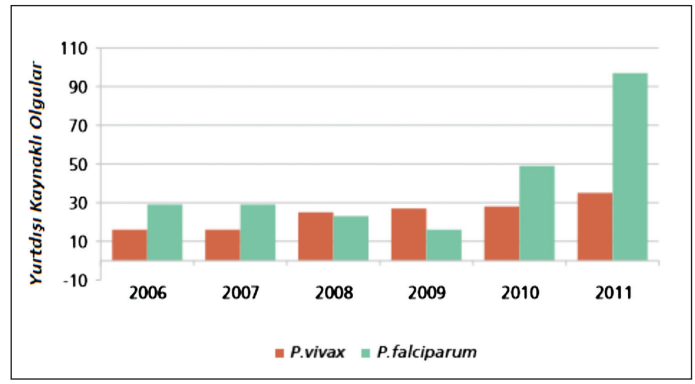

Figure 1. Cases originating from other countries between 2006 and 2011.

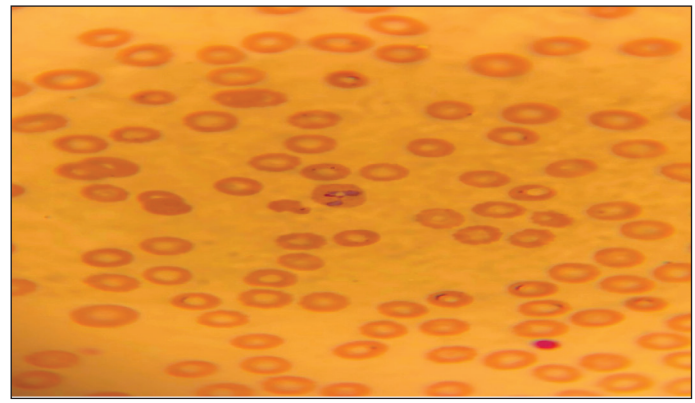

Figure 2. P. Early trophozoite form of vivax (signet-ring).

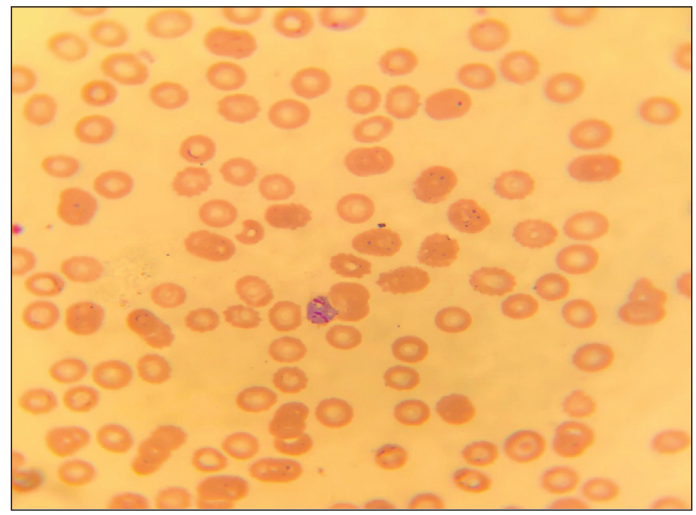

Figure 3. P. Schizont consistent with vivax.

blood smear was planned. *P. vivax* schizonts were observed within the erythrocytes in the thick blood smear (Figures 1 and 2). A peripheral blood smear performed as a first line test due to pancytopenia showed *P. vivax* schizonts, and the diagnosis was established within 24 hours. A venous blood sample was collected in an EDTA tube for a thick blood smear and PCR (Polymerase Chain Reaction) and sent to the National Malaria Reference Laboratory (Public Health Agency of Turkey, Department of Microbiology Reference Laboratories). The Multiplex PCR method was used for the identification of the species, and a PCR analysis performed with 18 rRNAs and circumsporopozite protein genes identified *Plasmodium vivax*.

The patient's general condition was moderate, and she was considered to have an uncomplicated *P. vivax* infection, based on the absence of acidosis, pulmonary edema, severe anemia, disseminated intravascular coagulation and renal failure. Upon the detection of *P. vivax* in the PCR, communication was established with the malaria control dispensary. As per the protocol defined by the Malaria Control Dispensary in Turkey, treatment of the patient was initiated after sourcing arthemeter&lumefantrine and from the public health agency.

Arthemeter&lumefantrine (20/120 mg) was administered as four tablets, twice daily, for three days, and primaquine (7.5 mg) was administered as two tablets, once daily, for 14 days. The patient's body temperature returned to normal 24 hours after therapy. A complete blood count obtained at 72 hours after the initiation of therapy revealed the following results: Hemoglobin, 7 g/dL; hematocrit, 21.1 percent; leukocyte, 3100/mm^3; neutrophil, 1000/mm^3; lymphocyte, 1720/mm^3; and platelets, 135.000/mm^3. The arthemeter&lumefantrine treatment protocol of the Ministry of Health was set to three days and later discontinued. Blood tests at 7 days of the primaquine therapy showed the following results: Hemoglobin, 8.8 g/dL; hematocrit, 27.1 percent; leukocyte, 8230/mm^3; neutrophil, 5360/mm^3; lymphocyte, 2280/mm^3; and platelets, 365.000/mm^3. As the patient's general condition improved and the fever subsided, she was discharged on the ninth day of hospitalization and advised to complete the primaquine therapy for 14 days, to take vitamin B12 tablets once daily for 60 days and vitamin D, and was told to return for a further health-check at the outpatient clinic.

The patient attended underwent a health-check at the Pediatric Infectious Diseases outpatient clinic one week later, when her general condition was found to be good, an abdominal examination revealed no hepatosplenomegaly and other systems were normal. A complete blood count performed as per the recommendation of the Pediatric Hematologist showed the following findings: Hemoglobin, 10.3 g/dL; hematocrit, 38 percent; leukocyte, 6770/mm^3; neutrophil, 3540/mm^3; lymphocyte, 2650/mm^3; and platelets, 300.000/mm^3.

Discussion

As a result of concerted malaria eradication efforts in recent years, the number of cases of malaria declined from 11.384 in 2000 to 78 in 2013 (5). The majority of cases occur in the provinces of Diyarbakır, Şanlıurfa, Batman and southern districts of Mardin. In 2012, there were 218 cases of malaria reported in Mardin among truck drivers travelling to Turkey from endemic regions and due to latency in the recognition of the cases. As a result of the program launched by the Ministry of Health, there were only 34 cases in 2013, five cases in 2014 and three recurrent cases reported in 2015 (6,7). A study by Garnham et al. reported that sporozoites that have completed their maturation phase may be reactivated within a year or over an even longer period due to various factors, and therefore incubation periods could be longer (8). Consistent with literature, the present case had fled from Syria three years previously, showing the importance of cases originating from other countries.

Malaria is typically characterized by episodic fever accompanied by chills. Patients with *P. vivax* and *P. ovale* infestation present with recurring fever every 48 hours, and patients with P. malariae infestation every 72 hours. Although cases with *P. falciparum* infestation have cyclic fever every 48 hours, most patients exhibit irregular and intermittent fever patterns.

Çelikbaş et al. made a retrospective evaluation of 105 cases of malaria who were hospitalized in the Ankara Numune Training and Research Hospital between 1992 and 2006, and reported *P. vivax* in 101 patients and *P. falciparum* in four patients, with the most commonly observed symptoms being chills, fever and thrombocytopenia (9). Consistent with literature, the present case had episodic fever accompanied by chills and pancytopenia.

A large number of Syrian immigrants are admitted to our hospital, and nutritional anemia is significantly common in these patients. Accordingly, folic acid, vitamin B12 and vitamin D levels were ordered in the present case, and the patient was prescribed replacement therapy upon the detection of vitamin B12 and vitamin D deficiencies.

The microscopic examination of peripheral blood smears is still considered the optimum method in the diagnosis of malaria, in that studies in literature report 95 percent sensitivity and 100 percent specificity rates in blood smear for the typing of malaria (10).

In order to investigate for the etiology of pancytopenia and fever, the present patient was screened for such infections such as brucellosis, tularemia, tuberculosis and toxoplasmosis, and malignant diseases such as leukemia, with no further tests made for a differential diagnosis, as the peripheral blood smear performed as the first line test for pancytopenia

revealed *P. vivax* schizonts, and the diagnosis was established within 24 hours.

The incubation period differs among the *Plasmodium* species, and two incubation periods have been described for *P. vivax*. The first incubation period lasts 14 ± 3 days in the first episode, and the second incubation period is related to the hypnozoite form of the parasite in the liver that causes relapses. In a study by Patrícia Brasil et al., of the 80 patients with confirmed malaria diagnosis, 49 (63 percent) were reported to be infected by *P. vivax*, and among these patients, the incubation period was reported to range between 3 and 12 months (11). Commonly used agents in chemoprophylaxis, such as chloroquine, mefloquine and doxycycline, are ineffective against the hypnozoites of *P. vivax* in the liver (12), and so different strategies are used in the treatment and chemoprophylaxis (13). A detailed examination of the patient's medical history suggested that the patient had her first episode, and the treatment was selected accordingly.

WHO recommends chloroquine for the treatment of chloroquine-susceptible *Plasmodium* infections, and primaquine therapy to eradicate hypnozoites in infestations caused by *P. vivax* and *P. ovale*. Quinine, doxycycline, atovaquone/proguanil, mefloquine or artemisinin-based combination therapies are recommended for chloroquine-resistant *P. falciparum* and *P. vivax* infections. In chloroquine-susceptible *P. vivax* infections, WHO recommends chloroquine 5 mg/kg at 6, 24 and 48 hours after a loading dose of 10 mg/kg, and primaquine 0.25-0.50 mg/kg/day in two equal doses for 14 days (9). Antimalarial drugs are supplied by the Ministry of Health Turkish Public Health Agency in Turkey, and as chloroquine cannot be supplied by the Public Health Agency, therapy involving artemeter&lumefantrine for 3 days and primaquine for 14 days is recommended for *P. vivax* infections. This treatment protocol was followed in the current case in collaboration with the Malaria Control Dispensary.

In 2015, 214 million new cases of malaria were identified around the world, killing approximately 438.000 people. Children under the age of five constituting 70 percent of these deaths, and one child dies every 2 minutes due to delays in the diagnosis or administration of an inappropriate therapy (14). The present patient was diagnosed within 24 hours through the collaborative efforts of the clinicians and laboratory staff, and the appropriate therapy was initiated.

Conclusion

In the globalizing world, it must be remembered that malaria can be diagnosed in a patient presenting with fever in a non-endemic region due to travel, immigration and the movement of seasonal workers. Considering its mortality and morbidity, it is important to diagnose and administer appropriate therapies to patients in a timely manner.

Informed Consent: The families of the participating patients were informed of the study and their consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - MKK, ND; Design - MKK, AŞ; Supervision - MKK, AŞ, ND, ZYY; Data Collection and/or Processing - MKK, AŞ, BB; Literature Review - MKK, AŞ, ND, ZYY; Writing - MKK; Critical Review - ND, ZYY, AŞ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authours declared that this study has received no financial support.

References

1. *Alkan MZ, Tamer GS. Plasmodium türleri. In: Topçu AW, Söyletir G, Doğanay M (eds). Enfeksiyon hastalıkları ve mikrobiyolojisi. 3. baskı. İstanbul: Nobel Tıp Kitabevleri, 2008:2486-502.*
2. *World Health Organization. World Malaria Report 2015. Geneva, Switzerland, 2015. Available from: http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158_eng.pdf?ua=1 (Erişim tarihi:18.12.2017).*
3. *Karadağ A, Ünal N, Yanık K, Borucu R, Günaydın M, Hökelek M. Endemik olmayan bir bölgede periferik kan örneği incelemesinde saptanan Plasmodium türlerinin değerlendirilmesi. Turkiye Parazitol Derg 2015;39:5-8.*
4. *T.C. Sağlık Bakanlığı. Sağlık İstatistikleri Yıllığı 2015. Erişim Tarihi: 18.12.2017. Available from: http://www.saglikistatistikleri.gov.tr/dosyalar/SIY_2015.pdf*
5. *Eliminating malaria case study 5. The long road to malaria elimination in Turkey. Geneva: World Health Organization; 2013. Erişim tarihi: 18.12.2017 Available from: http://apps.who.int/iris/bitstream/10665/94961/1/9789241506403_eng.pdf*
6. *Global Malaria Programme. World Malaria Report 2014. Geneva: World Health Organization; 2014.*
7. *World Health Organization. Guidelines for the treatment of malaria. 2010, 2nd ed. Erişim tarihi:18.12.2017 Available from: http://www.who.int/malaria/publications/atoz/9789241549127/en/*
8. *Garnham PCC, Bray RS, Bruce-Chwatt LJ, et al. A strain of Plasmodium vivax characterized by prolonged incubation: morphological and biological characteristic. Bull World Health Organ 1975;52:21-32.*
9. *Celikbaş AK, Ergönül O, Baykam N, Eren S, Güven T, Dokuzoğuz B. Malaria in Turkey and 14 years of clinical experience. Mikrobiyol Bul 2006;40:237-43.*
10. *Iqbal J, Khalid N, Hira PR. Comparison of two commercial assays with expert microscopy for confirmation of symptomatically diagnosed malaria. J Clin Microbiol 2002;40:4675-8.*
11. *Brasil P, Costa AP, Pedro RS, et al. Unexpectedly long incubation period of Plasmodium vivax malaria, in the absence of chemoprophylaxis, in patients diagnosed outside the transmission area in Brazil. Malaria Journal 2011;10:122.*
12. *Pedro RS, Guaraldo L, Campos DP, Costa AP, Daniel-Ribeiro CT, Brasil P. Plasmodium vivax malaria relapses at a travel medicine centre in Rio de Janeiro, a non-endemic area in Brazil. Malar J 2012;11:245.*
13. *Fairhust RM, Wellems TE. Plasmodium species (malaria). Mandell GL, Bennett JE, Dolin R /eds). Mandell, Douglas and Bennett's Principles and Practise of Infectious Diseases. 7th ed. Philaldelphia: Churchill Livingstone, 2010:3437-62.*
14. *World Malaria Report 2016. Erişim tarihi: 18.12.2017. Available from: http://www.who.int/malaria/media/world-malaria-report-2016/en/*