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Clinical and Laboratory Features of Travel-associated Malaria: A University Hospital Experience

Seyahat İlişkili Sıtma Olgularının Klinik ve Laboratuvar Özelliklerinin Değerlendirilmesi: Bir Üniversite Hastanesi Deneyimi

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Abstract

Introduction: Malaria remains an ongoing challenge despite the fact that it seems to have been eradicated in Turkey since 2011. This study aimed to evaluate the status of antimalarial prophylaxis, clinical and laboratory profile of imported malaria cases admitted to a university hospital in a period of 10 years.
Materials and Methods: Patients with malaria hospitalized in a university hospital between the years 2008 and 2017 were evaluated retrospectively. Data were obtained from the hospital database. Thin and thick blood smears were examined for diagnosis. Sociodemographic features, epidemiological, clinical, and laboratory findings as well as response to various treatments were evaluated.
Results: A total of 20 patients (all male) were diagnosed with imported malaria. The median age of the patients was 35 (19-56) years. The median length of travel was 78 (6-545) days. *Plasmodium falciparum* was the most common causative agent (80%). Only one patient had received malaria prophylaxis previously. Fever was the most prominent symptom (95%). C-reactive protein (CRP) levels were higher than 100 mg/dl in 75% (n=15) of patients. Eight cases were re-hospitalized with relapse and/or recrudescence. CRP levels in patients with relapse and/or recrudescence were significantly higher. All the patients received combination regimen. The most commonly used anti-malarial drugs were artemisinin derivatives.
Conclusion: Before visiting malaria-endemic regions it is essential to obtain information about preventive measures and chemoprophylaxis. Sick patients should be monitored until full resolution of symptoms and also peripheral blood smear should be performed due to the high rate of relapses. CRP can be a useful biomarker in follow-up of patients infected with malaria.
Keywords: *Plasmodium vivax*, *Plasmodium malaria*, prophylaxis, atovaquone, artemether

Öz

Giriş: Sıtma Türkiye'de 2011 yılından beri eradike edilmiş gibi gözükmesine rağmen bir sorun olmaya devam etmektedir. Bu çalışmada bir üniversite hastanesine yatırılan import sıtma olgularının antimalaryal profilaksi durumlarının, klinik ve laboratuvar bulgularının değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntem: Bir üniversite hastanesine 2008 ile 2017 yılları arasında yatırılan 20 sıtma hastası retrospektif olarak değerlendirilmiştir. Hastaların verilerine hastane veri kayıt sisteminden ulaşılmıştır. Tanı için ince yayma ve kalın damla preparatlar incelenmiştir. Hastaların sosyo-ekonomik, epidemiyolojik, klinik ve laboratuvar bulguları ile tedaviye yanıt durumları değerlendirilmiştir.
Bulgular: Yirmi import sıtma hastasının hepsi erkekti ve medyan (yaş aralığı) 35 (19-56) yıldı. Seyahat süreleri ortancası 78 (6-545) gündü. En sık etken *Plasmodium falciparum* (%80) idi. Sadece bir hastanın sıtma profilaksisi alma öyküsü vardı. En sık semptom ateşti (%95). Hastaların %75'inin CRP düzeyi 100 mg/dl'nin üzerindeydi. Sekiz hasta relaps ve/veya rekrüdesens nedeniyle tekrar hastaneye yatırıldı. Hastaların hepsi kombinasyon tedavisi aldı. En sık kullanılan antimalaryal ilaçlar artemisin deriveleriydi.
Sonuç: Sıtma için endemik bölgelere seyahat öncesi seyahat sağlığı ile ilgili bilgi almak ve kemoprofilaksi için önerilen ilaçları edinmek zaruridir. Hastalar yüksek relaps oranları nedeniyle semptomları ve periferik yaymaları tam olarak düzelene kadar takip edilmelidir. CRP sıtma ile enfekte hastaların izleminde yararlı bir belirteç olabilir.
Anahtar Kelimeler: *Plasmodium vivax*, *Plasmodium malaria*, profilaksi, atovakuon, artemeter

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Introduction

Malaria is a widespread protozoan disease and globally, an estimated one billion people are at risk of malaria. According to the World Malaria Report 2016, 212 (148-304) million cases of malaria occurred worldwide in 2015 and it is estimated that there were 429.000 (235.000-639.000) malaria-associated deaths globally in 2015[1]. Malaria remains an ongoing challenge in Turkey due to imported malaria cases despite it seems to be eradicated since 2011. According to the World Malaria Report, the number of imported malaria cases was 209 in 2016 in Turkey[2]. Local cases have not been reported since 2011[1,3]. Turkey has made a considerable progress towards malaria eradication and now in the elimination stage (interruption of local transmission and reduction to zero incidence of local cases) of the World Health Organization malaria control programme[4].

Malaria is a transnational problem and without global eradication nobody can be considered safe. Economic factors, lack of antimalarial drugs, increased drug resistance, weak health systems and poor surveillance systems are the main challenges particularly in sub-Saharan countries contrary to opportunities in controlling and eliminating malaria in developed and developing countries[1]. Each year, almost 25-30 million travelers visit malaria-endemic sites. Travel-associated malaria is a serious problem in this population[4]. Fever in the traveler returning from an endemic region is the most common clinical presentation to primary care facilities or emergency service. Malaria should be primarily excluded because of its severe clinical course particularly in non-immune individuals. In this case, biomarkers, such as CRP, are effective in assessing acute malaria infection and also the progression of the disease[5]. This study aimed to evaluate the status of antimalarial prophylaxis, clinical and laboratory profile of imported malaria cases admitted to a university hospital in a period of 10 years.

Materials and Methods

We conducted a retrospective study between 2008 and 2017 in Ondokuz Mayıs University Hospital which is one of the referral centers for malaria cases in the Black Sea region (Northern Anatolia). Malaria patients microscopically confirmed by thin and thick peripheral blood smears were included in the study. The demographic, clinical and laboratory features (complete blood count, biochemistry) of the patients were obtained from hospital health records. We were not able to obtain exact data regarding parasite density. Data on the reasons for travel, destination, duration, history of malaria, and history of receiving malaria prophylaxis were all recorded and evaluated.

Statistical Analysis

SPSS version 21 was used for statistical analysis. The results were presented as mean±standard deviation and median (min-max). A value of less than 0.05 was considered statistically significant.

Results

We identified 20 cases of malaria confirmed by thin and thick blood smear. All the patients were male with a median age of 35 (19-56). All the patients had a history of travel to African countries, such as Sudan (n=4), Guinea (n=4), Ghana (n=4), Mozambique (n=2), Gabon (n=1), Nigeria (n=1), Mali (n=1), Rwanda (n=1), Kenya (n=1) , and Uganda (n=1) for occupational purposes. The median length of travel was 78 (6-545) days. All were Turkish citizens. The median time from onset of symptoms to diagnosis was seven (4-55) days. Patients were commonly hospitalized to investigate the origin of fever. The most common presenting symptom was fever. Seven had additional history of previous visit to malaria-endemic countries and had friends with a history of malaria during their visit. Therefore, there were strong clues for the initial diagnosis of malaria. One had fever, abdominal tenderness and leukopenia, thus, was considered as having typhoid fever. The second case had a history of animal husbandry and consumption of unpasteurized dairy products so hospitalized with the preliminary diagnosis of brucellosis. The remaining 11 had no specific diagnosis on admission and were hospitalized for investigation of the fever etiology. Malaria prophylaxis was recommended for five patients but we learned that four of them did not take prophylaxis. The main diagnostic method was thin and thick blood staining. Records of half of the patients did not include information regarding thick blood films. The others had no trophozoite on thick blood films and two of them were diagnosed only by thin blood smear. Only one patient had a history of receiving malaria prophylaxis. Fever was the most common symptom presenting in 95% of patients, followed by chills (65%), fatigue (60%), and unconsciousness (15%). Diarrhea was present in three (15%) patients. A previous history of malaria was present in 29% of patients.

Hepatomegaly was present in 25%, splenomegaly in 45% of patients. *Plasmodium falciparum* was the most common causative agent (80%). *P. vivax* was present in three patients (15%) and *P. malariae* in one (5%).

Hemoglobin levels on admission were below the reference value (11.9-14.6 g/dl) in 10 (50%) patients. Nineteen patients had a low platelet count. Platelet count on admission was less than 50000/uL in eight of these 19 patients. White blood cell count ranged between 1680/ul and 11400/ul while 40% of patients had leucopenia. The other abnormal laboratory findings were anemia (45%) elevated aspartate transaminase (45%), elevated alanine aminotransferase (50%), and hyperbilirubinemia (40%)

(Table 1). C-reactive protein (CRP) level was higher than 100 mg/dl in 75% of patients. Except two patients, who had pneumonia as a co-existing disease, the control CRP levels got also decreased in whom at least two CRP measurements were performed. In five out of 14 patients, the CRP level became normal within 10 (4-30) days. There was no statistically significant correlation between CRP level and length of hospital stay (r=0.364, p=0.126). The average CRP level in patients with relapse and/or recrudescence was 133 mg/dl (±84).

All the patients were hospitalized for the treatment of malaria and follow-up of the complications with a median length of hospital stay of 5 (3-13) days. All received combination regimen (Table 2). The mean duration of therapy was 5 (±2) days. Two patients received concomitant antibiotic therapy for additional diagnosis of pneumonia. Three out of 20 patients infected with *P. falciparum* were followed up in the intensive care unit until their vital signs became stable.

Eight patients with relapse and/or recrudescence were re-hospitalized and re-treated. A total of six patients with falciparum malaria with recrudescence and two patients with vivax malaria (lack of primaquine in their initial therapy regimen) with relapse were re-hospitalized and re-treated. One out of eight patients with falciparum malaria was admitted to the hospital two months later and the others presented with similar or worse symptoms within a month from their first admission. Before relapse and/or recrudescence, the patients were treated with artemether lumefantrine (2/8), atovaquone-proguanil (2/8), artesunate (2/8). Data on the treatment in two out of eight patients were not available since they were treated in countries where they acquired malaria.

Discussion

This study demonstrated that majority of the patients did not take malaria prophylaxis whereas the general principle of the prophylaxis is taking pills before, during and after the travel to minimize the malaria risk. The goal of malaria prophylaxis is to prevent malaria and its related complications. Obtaining health information for travelers, receiving appropriate prophylaxis regimen and the use of personal protective measures should be combined for effective protection against malaria. Directorate General of Health for Border and Coastal Areas of Turkey provides information for travelers and provides drugs for chemoprophylaxis[6]. Receiving drugs for malaria prophylaxis is a common problem particularly for long-term travelers[7]. Some travelers, who previously experienced malaria, prefer to keep medications until they become infected. However, acquired immunity is lost quickly so they have the same risk with others.

Patients with malaria may present with a wide variety of clinical symptoms[8-10]. The common symptoms in patients in this study were fever (95%), chills (65%) and fatigue (60%). Partial immunity against *Plasmodium* spp. may cause subclinical symptoms or asymptomatic parasitemia in endemic

Table 1. Laboratory characteristics of patients with malaria

Variable	N tested	Mean±standard deviation	Median (min-max)	Normal range
White blood cells on admission (thousand/µL)	20	5±2.8	5 (1.7-11.4)	3.7-9.7
Platelets on admission (thousand/µL)	20	68.4±43.0	64 (20-187)	179-373
Admission hemoglobin(g/dl)	20	12.4±2.8	12.8 (6.2-16.2)	13.3-17.2
Bilirubin (total, mg/dl)	20	2.1±1.7	1.1 (0.7-5.3)	0.1-1.5
Aspartate amino transferase (U/L)	20	58±42	44 (13-168)	8-46
Alanine amino transferase (U/L)	20	45±29	39 (8-112)	0-40
Creatinin (mg/dl)	20	0.9±0.4	0.8 (0.4-2.53)	0.4-1.4
C-reactive protein on admission (mg/dl)	19	151.7±85.8	140 (14-325)	<3.36
Control C-reactive protein (mg/dl)	14	34.9±61.6	9.5 (0-177)	<3.36

Table 2. Malaria species and administered drugs

Malaria species	Treatment
Plasmodium falciparum	- Artemisinin combination therapy (9/20) - Quinine based regimen (2/20) - Mefloquine (3/20) - Atovaquone-proguanil (2/20)
Plasmodium vivax	- Atovaquone-proguanil and chloroquine (1/20) - Quinine based regimen and primaquine (2/20)
Plasmodium malaria	- Quinine based regimen (1/20)

areas. On the other hand, non-immune people tend to have more severe clinical picture[10]. All of our cases lived in non-endemic areas and also all were previously healthy. The risk for a traveler is related to destination, length of stay, destination conditions, and chemoprophylaxis[11]. Other travel-related illnesses may appear with similar symptoms such as Ebola virus disease, chikungunya virus infection, dengue, typhoid fever and yellow fever[12]. Ebola had substantial effect on the number of malaria cases during the recent Ebola outbreak in Western African descent because this epidemic led to ignore the care and treatment of malaria[13]. Cessation of malaria prevention precautions and also inadequate diagnosis and treatment during the epidemic might have caused an increase in the number of malaria cases. Ebola spreads through direct contact with the blood, secretions, organs and other bodily fluids of infected people (through broken skin or mucous membranes). Although it may be rarely seen in severe form of malaria, hemorrhagic symptoms are prominent in Ebola. In the presence of suspicion, immunoassay and nucleic acid tests may be useful for differential diagnosis. We did not encounter any patient infected with Ebola virus in Turkey during the outbreak. However, a Nigerian woman who was travelling on Turkish Airlines and was suspected of having Ebola was approached with expanded precautions and following examinations revealed malaria[14].

A clinician has the responsibility of completely evaluating travelers returning from malaria-endemic zones. A high index of suspicion is required to ensure prompt diagnosis of malaria[5]. We hospitalized most of the patients (65%) with different pre-diagnosis other than malaria in spite of their history of travel to the endemic regions. Rapid identification and treatment of patients with severe and progressive conditions may decrease the risk of mortality and morbidity[11,15-19].

We missed the diagnosis in one patient who had recently returned from Nigeria. He was re-admitted to the infectious diseases clinic when his symptoms deteriorated after 11 days. High number of cases with misdiagnosis has been reported in the literature[8]. False-negative results may lead to delay in starting appropriate therapy[7]. This can be prevented by repetitive Giemsa staining in patients presenting with fever and a history of travel to malaria-endemic areas. The other reason of misdiagnosis may be patients presenting with unusual symptoms[8,9].

CRP has recently started to be investigated in malaria cases. CRP increases in patients infected with *Plasmodium* spp. and decreases under therapy[7]. Its role in assessing malaria severity and also for follow-up has been shown. It has been reported that CRP levels >35 mg/L were highly sensitive in predicting mortality[15]. CRP levels were high in all the patients in this study and they were over 100 mg/dl in 75% of patients. Almost in all patients (13/14) CRP levels decreased under treatment. Furthermore, all the cases with relapse and/or recrudescence presented with elevated CRP levels.

Relapse in patients infected with *P. vivax* is a well known entity but recurrence may occur due to inappropriate or inadequate treatment choices in falciparum malaria. Sometimes recrudescence may be observed because of antigenic variations or infection with different strains[20]. *P. vivax*, *P. ovale*, *P. knowlesi* malaria can be treated either with an artemisinin derivative or chloroquine if susceptible. Primaquine is suggested to prevent relapses. If *P. falciparum* is resistant to chloroquine, artemisinin-based combination therapies are strongly recommended[7]. Infrequent use of these drugs in our series was probably the reason why we encountered relapses in 40% of patients. The other reason for the vivax malaria cases may be the rare appearance of *P. vivax* in endemic areas. The dose of artemisinin derivates particularly artemether lumefantrine has been found to be related to recrudescence[21]. However, in our study, artemether lumefantrine was administered with a total of six oral doses in 3-day treatment schedule. The two cases with falciparum malaria remained unclear because they had been treated in countries where they acquired malaria. We included those cases in the recrudescence group, however, as they may have been re-infected in their second attack. The two relapse cases with vivax malaria had been treated without primaquine which is required for the hypnozoite forms that remain dormant in the liver and can cause a relapse. The main reason is probably the lack of initial primaquine treatment in vivax malaria cases because primaquine is the only antimalarial agent that prevents relapses in vivax malaria[22]. All the patients recovered with no long-term sequelae. One was transferred to another hospital with the consent of his family. The diagnosis and treatment of relapse and/or recrudescence may be delayed until the patient is referred to a experienced specialist. In this case, besides obtaining accurate medical history, the dose, frequency and duration of the drugs should be learned carefully. History of malaria is an important clinical clue for the patients with relapse and/or recrudescence presenting with fever in malaria-free countries[23].

Conclusion

Fever is the most common finding in a traveler returning from malaria endemic areas. However, to prevent misdiagnosis and rule out other diseases, the main step is a high index of clinical suspicion. CRP can be a useful biomarker to follow up patients infected with malaria. Occupational travelers particularly, should be informed to seek medical care in case of fever during or after travel. Additionally, physicians should consider the possibility of

malaria in patients with a history of visiting malaria-endemic countries. Thus, clinicians may avoid lots of redundant tests to differentiate illnesses and time loss to evaluate potentially serious diseases.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: İ.B., Design: İ.B., Data Collection or Processing: M.K., Analysis or Interpretation: İ.B., M.K., Literature Search: İ.B., M.K., Ş.E., Writing: İ.B., M.K., Ş.E.

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