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Case Report Olgu Sunumu

AN UNUSUAL MALARIA CASE: MIXED INFECTION? RESISTANCE? MALADAPTIVE PATIENT?

Alışılmadık bir Sıtma Vakası: Mikst Enfeksiyon mu? Direnç mi? Uyumsuz Hasta mı?

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ABSTRACT

Malaria, a disease known since ancient times and constantly struggled by human beings, still maintains its currency as an important cause of morbidity and mortality today. Although no domestic cases have been observed in Turkey since 2010, around 200-250 malaria cases originating from abroad are observed every year. Resistance to many parasitic drugs has developed over the years since chloroquine resistance emerged in the 1970s. Artemisinin resistance was reported by WHO in Cambodia, Laos, Myanmar, Thailand and Vietnam in 2013 due to P. falciparum malaria, and resistance has been reported also in South Africa and Rwanda recently. It has been shown that resistance development is due to the Kelch 13 mutation detected in parasite and this leads to delayed clearance. According to WHO data, artemether-based combined therapy is still effective in the treatment of patients infected with artemisinin-resistant P. falciparum strains, but possible treatment unresponsiveness is followed meticulously by WHO. Our case is remarkable for its third recurrence despite artemether-based combined therapy twice in 28 days, and its persistent treatment response after quinine and doxycycline treatment.

Keywords: *Malaria, kelch 13 mutation, artemisinin resistance*

ÖZ

Antik çağlardan beri bilinen ve insanoğlunun sürekli mücadele ettiği bir hastalık olan sıtma, günümüzde önemli bir morbidite ve mortalite nedeni olarak güncelliğini korumaktadır. Türkiye'de 2010 yılından bu yana yurtiçinde herhangi bir vaka görülmemekle birlikte, her yıl yaklaşık 200-250 civarında yurt dışından kaynaklanan sıtma vakası görülmektedir. 1970'lerde klorokin direncinin ortaya çıkmasından bu yana yıllar içinde birçok paraziter ilaca karşı direnç gelişmiştir. Artemisinin direnci, DSÖ tarafından 2013 yılında P. falciparum sıtmasına bağlı olarak Kamboçya, Laos, Myanmar, Tayland ve Vietnam'da rapor edilmiş olup, son zamanlarda Güney Afrika ve Ruanda'da da direnç bildirilmiştir. Direnç gelişiminin parazitte tespit edilen Kelch 13 mutasyonuna bağlı olduğu ve bu durumun klirensin gecikmesine yol açtığı gösterilmiştir. DSÖ verilerine göre artemisinin dirençli P. falciparum suşları ile enfekte hastaların tedavisinde artemether-bazlı kombine tedavi halen etkilidir ancak olası tedavi yanıtsızlığı DSÖ tarafından titizlikle takip edilmektedir. Olgumuz, 28 günde iki kez artemether bazlı kombine tedaviye rağmen üçüncü nüksü olması, kinin ve doksisiklin tedavisi sonrasında ise kalıcı tedavi yanıtı ile dikkat çekicidir.

Anahtar Kelimeler: *Sıtma, kelch 13 mutasyonu, artemisin direnci*

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INTRODUCTION

Malaria, a disease known since ancient times and constantly struggled by human beings, still maintains its currency as an important cause of morbidity and mortality today. According to the 2019 World Health Organization (WHO) report, it is known that there are 228 million malaria cases and 409000 of them result in death (1). Although 94% of the cases and deaths are in Africa, malaria is a disease that keeps importance in our country due to the increase in the frequency of travel, irregular migrant movements and our location in the subtropical region (2). There has been no domestic malaria case in our country since 2010, and 200-250 travel-related malaria cases are diagnosed every year (2).

Our case is remarkable for its third recurrence despite artemether-based combined therapy (ABT) twice in 28 days, and its persistent treatment response after quinine and doxycycline treatment.

CASE REPORT

A forty-seven-years-old male patient was admitted to another hospital with complaints of fever, chills, and jaundice one month ago. It was learned that he went to Burkina Faso as a gold mine worker, he stayed there about 3 months, that his complaints started there. The patient, who did not take any medication for prophylaxis before travel, was diagnosed with *Plasmodium falciparum* malaria, and artemether lumefantrine treatment was started. He was discharged after three days of treatment, whose symptoms regressed. He was admitted to our outpatient clinic with fever, headache, nausea and vomiting on the 15th day after discharge. The patient had fever and tachycardia. Other system examinations were normal. Body mass index was 24.3 kg/m^2. Laboratory tests were hemoglobin: 4.9 g/L, platelet: 37000 /mm^3, glucose: 153 mg/dL, Urea: 109 mg/dL, creatinine: 3.46 mg/dL, AST: 80 U/L, ALT: 24 U/L, total bilirubin: 3.96 mg/dL, indirect bilirubin: 3.04 mg/dL. The blood smear showed, banana-shaped gametocytes and young trophozoids compatible with *P. falciparum* were observed (Figure 1, 2).

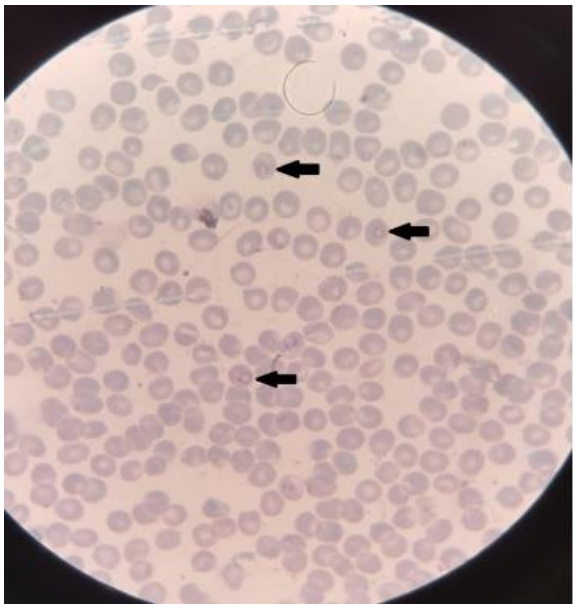

Figure 1: Peripheral blood smear at second malaria attack shows malaria parasites seen as signet ring in erythrocytes

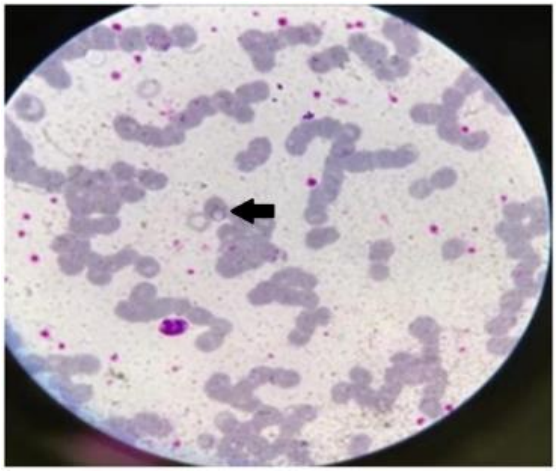

Figure 2: Peripheral blood smear at last malaria attack shows malaria parasites seen as signet ring in erythrocytes

Artemether-lumefantrine was given to the patient for three days for the second time. After artemether-lumefantrine treatment, *P. falciparum* was not observed in the blood smear, laboratory values and his complaints completely recovered.

After 12 days, the patient was admitted to the emergency department again with the complaint of fever, chills, nausea and vomiting. *P. falciparum* trophozoites were observed in the blood smear again. The laboratory test results at all three admissions and after the treatment are shown in Table 1.

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Table 1: Laboratory test results at all three admissions

	First malaria attack		Second malaria attack		Third malaria attack	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Leucocyte (/mm³)	4360	7820	8130	6840	5250	8530
Hemoglobin (g/L)	13.9	13.4	4.9	11.4	7.5	9.4
Platelet (/mm³)	16000	147000	37000	15000	99000	346000
Urea (mg/dL)	113	43	109	32	73	24
Creatinine (mg/dL)	2.89	0.89	3.46	0.99	1.25	0.92
AST (U/L)	78	48	80	27	9	11
ALT (U/L)	57	69	24	19	8	11
Total bilirubin (mg/dL)	8.1	2.4	3.96	0.79	0.96	0.62
Indirect bilirubin (mg/dL)	2.5	0.6	3.04	0.34	0.30	0.31
C-reactive protein (mg/L)	270	29	22	11	70	13

AST: Aspartate aminotransferase, ALT: Alanine transaminase

Upon recurrence with previous artemether-based treatment, the patient was given doxycycline 2x100 mg and quinine 3x10 mg/kg for 7 days. After the treatment, there were no complaints and the laboratory parameters returned to normal, and he was discharged with full recovery. The general condition of the patient, who was invited for follow-up one month later, was good, physical examination was normal, laboratory parameters were in the normal range. *P. falciparum* was not observed in the blood smear.

DISCUSSION

Plasmodium species determination is important for effective treatment and prevention of drug resistance development. In our country, the diagnosis of malaria cases can be made by all institutions (2). Support was also received from the provincial public health laboratory in terms of species determination, since the patient had recurrent malaria cases and mixed cases of foreign origin, mostly caused by *P. falciparum* and *P. vivax* species originating from abroad, were detected in our country. Another method that can be used in the diagnosis of malaria is IFA and ELISA, and their use is not common. Molecular methods are utilized in the diagnosis of malaria, in determining the species, and detecting resistance. Demonstrating the parasite DNA with PCR provides a definitive diagnosis (2-6). We wanted to perform PCR assay, but it could not be performed because the test is unavailable.

It is known that being obese, smoking, and the use of drugs such as rifampicin, efavirenz, and mefloquine reduce the effect of lumefantrine (2). It is known that the patient, who is known to smoke, received three-day treatments in the hospital environment and did not vomit, and it is also mentioned by himself. Our patient weighed 76 kilograms and had a body mass index of 24. Since the absorption of lumefantrine is known to increase with fat intake, the patient's treatment was administered immediately after meals. In the 2019 Malaria Case Management Guideline of the Ministry of

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Health, *P. falciparum* infections occurred four weeks after the first infection of *P. falciparum* are considered as new infections and treated with artemether lumefantrine again, but if fever and parasitemia are observed in the first four weeks, the patient should be re-treated now with regimens containing quinine (2). Same recommendation exists in the WHO malaria guideline (1).

Failure in ABT may be due to reasons such as drug resistance, insufficient dose, insufficient absorption, inadequate compliance, vomiting, pharmacokinetic characteristics of the host, obesity, concomitant drug usage, and it should be kept in mind that mixed infection may occur. It is known that resistance against many antimalarial drugs has developed since the process that started with chloroquine resistance in the 1970s (7,8). Artemisinin resistance was reported by WHO in Cambodia, Laos, Myanmar, Thailand and Vietnam in 2013 due to *P. falciparum* malaria, and also in South Africa and Rwanda recently (9,10). It has been shown that resistance development is due to the Kelch 13 mutation detected in parasite and this leads to delayed clearance (11).

Our case is interesting because the patient presented with similar symptoms within 28 days despite the ABT twice, and the only reason would affect the success of the treatment was smoking. According to the information received from the Centers for Disease Control and Prevention, the resistance of artemisinin has not been determined in Burkina Faso yet (12).

The patient lives in Giresun province in Türkiye. There are no local malaria cases in this province. Since the patient had no history of infected blood transfusion, injury with an infected syringe or contact with malaria cases, domestic transmission was not considered.

In our country, where domestic cases are not observed, the factors affecting the treatment response should be well examined while evaluating the travel-related malaria cases. The agent and resistance profile in the regions where the patient traveled to should be determined, careful attention should be paid not to overlook mixed infections, it should not be forgotten that resistance to antimalarial drugs develops rapidly, and current resistance information should be followed closely.

*Conflict of interest***:** The authors declare no conflicts of interest.

*Informed Volunteer/Consent Form***:** Written informed consent was obtained from the patient for publication of this case report.

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