INTERNAL MEDICINE

□ CASE REPORT □

Falciparum Malaria Incidentally Pretreated with Azithromycin

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Abstract

A 65-year-old man, who recently returned from Liberia, visited a clinic complaining of fever, and azithromycin was prescribed. The patient presented to a general hospital 5 days after the onset of symptoms, however, a blood smear examination failed to detect malaria. Contrary to the blood smear result, a rapid antigen test in our hospital was strongly-positive for falciparum malaria, indicating a high level of malarial antigen in the blood. Moreover, laboratory examinations on admission showed a tendency for improvement. We assumed that the administration of azithromycin partially treated malaria, thus complicating the blood smear diagnosis. We should be careful in prescribing azithromycin, which is widely used in clinics, to travelers returning from malaria-endemic countries.

Key words: Malaria, *Plasmodium falciparum*, azithromycin, returned travelers

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Introduction

Malaria, tuberculosis and human immunodeficiency virus (HIV) infection are known as the top three common infectious diseases in the world. The World Health Organization (WHO) reported that 198 million people suffered from malaria worldwide in 2013 and that malaria infection resulted in 584,000 deaths (1). Japan is categorized as a non-endemic area, thus the malaria patients who are treated in Japan are imported cases from endemic regions (2-4). Patients with malaria develop non-specific symptoms such as fever, headache, and arthralgia, and thus a medical interview that includes questions about the patient's travel history is a key step to diagnosing malaria as well as other tropical diseases.

Azithromycin is widely used in clinics to treat respiratory infections (5). Although monotherapy with azithromycin is insufficient to cure malaria, the drug has been shown to have a weak antimalarial effect (6-9). Thus, physicians should exercise caution in prescribing azithromycin to febrile patients returning from malarial-endemic areas, because insufficient treatment with azithromycin may decrease the number of parasitized erythrocytes, making it difficult to diagnose malaria by blood smear examination. We herein report a case of malaria incidentally pretreated with azithromycin, which resulted in a delayed diagnosis.

Case Report

A 65-year-old Japanese man visited a clinic complaining of a one-day history of low-grade fever and fatigue. He had worked for 10 months in Liberia, where Ebola virus disease (EVD) was epidemic, and had returned to Japan 10 days before he visited the clinic. Although he should have contacted a public healthcare center first because of his travel history to the EVD epidemic area, he visited a primary care physician. He did not take any prophylactic antimalarial drugs

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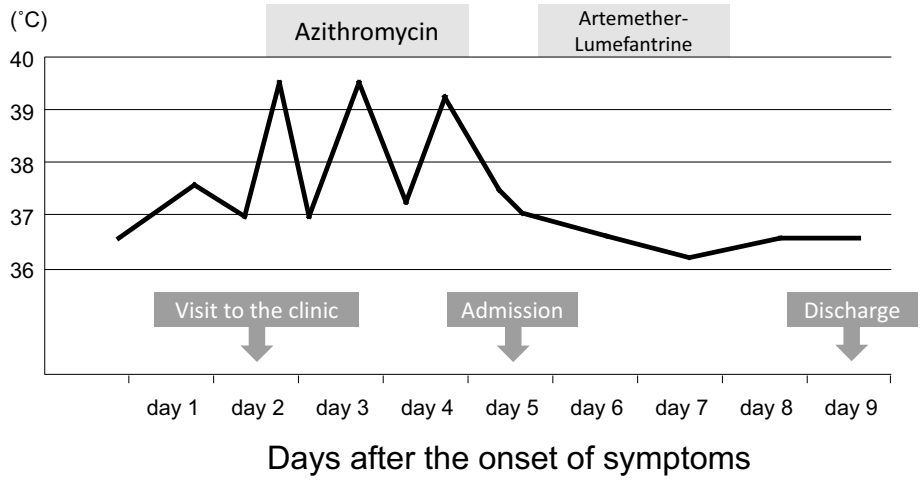

Figure 1. **The clinical course. The patient visited the clinic 2 days after the onset of symptoms and azithromycin (500 mg/day for 3 days) was prescribed. In spite of no authorized antimalarial agent having been administered before admission to our hospital, his body temperature was still as low as 37˚C on day 5. His condition was ameliorated by twice daily administration of artemether-lumefantrine (80 mg/480 mg), and he was discharged on the 5th day of hospitalization.**

Table. **Laboratory Examinations.**

Chemistry	6:30	15:00
T-Bil (mg/dL)	1.7	1.5
AST (U/L)	79	64
ALT (U/L)	95	87
LDH (U/L)	490	372
γGTP (U/L)	144	139
Glu (mg/dL)	148	104
BUN (mg/dL)	24.3	23
Cre (mg/dL)	0.76	0.85
Na (mEq/L)	126	129
K (mEq/L)	4.4	4.2
Cl (mEq/L)	97	99
CRP (mg/dL)	14.9	14.8
CBC & Coagulation		
WBC (/μL)	3,530	3,100
Hb (g/dL)	15.3	14.8
PLT ($\times 10^4$/μL)	3.2	2.5
PT (sec)	13.5	15.2
APTT (sec)	47	41.9
FDP (μg/mL)	109.3	97
Blood gas analysis		
pH	7.5	7.44
PCO_2 (mmHg)	21.9	31
PO_2 (mmHg)	63.2	63.2
HCO_3 (mmol/L)	16.9	21
Respiratory rate (/min)	40	28

T-bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactic dehydrogenase, γ-GTP: gamma glutamyltranseferase, Glu: glucose, BUN: blood urea nitrogen, Cre: creatinine, CRP: C-reactive protein, WBC: white blood cells, Hb: hemoglobin, PLT: platelets, PT: prothrombin time, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products

and had no past medical history of malaria infection. He did not inform his primary care physician of his travel history, and azithromycin (500 mg/day for 3 days) was prescribed without a definite diagnosis. His low-grade fever increased to around 39℃ overnight and 3 days after the visit to the clinic, he presented to an emergency department of a general hospital complaining of headache, chills, and tachypnea with persistent fever (Fig. 1). His vital signs on arrival were as follows: blood pressure, 131/73 mmHg; heart rate, 113 beats/min; body temperature, 37.6℃; and respiratory rate, 40/min. Laboratory examinations revealed thrombocytopenia, liver dysfunction, blood coagulopathy, and metabolic acidosis, as shown in the left column (6:30) of the Table. In addition, hepatosplenomegaly was noted on ultrasonography. Although malaria was highly suspected based on these findings, malaria parasites were not observed on his blood smear. Because of the possibility of EVD, the attending physicians contacted our university hospital about the patient on the same day. We advised them to re-examine the blood smear and to send us the blood sample before the patient was transported. Eventually, a rapid antigen test (Malaria Ag P.f/P.v, Standard Diagnostics, South Korea) performed in our hospital was found to be strongly-positive for *Plasmodium falciparum* and a very small number of ring-form malaria parasites were found in the red blood cells on the blood smear (Fig. 2). Despite the immediate appearance of an obvious band on the rapid antigen test, the proportion of parasitized erythrocytes was less than 0.1%. A re-examination of the blood smear in a general hospital confirmed similar findings to our own.

Eight hours after his visit to the general hospital, the patient was transferred to our hospital. On admission, his body temperature was still as low as 37.0℃ and his respiratory rate had decreased to 28/min without any medication. In addition, our laboratory data indicated the improvement of liver dysfunction, blood coagulopathy, and metabolic acidosis as shown in the Table. We successfully treated the patient with the twice daily administration of artemether-lumefantrine (80 mg/480 mg), and were able to discharge

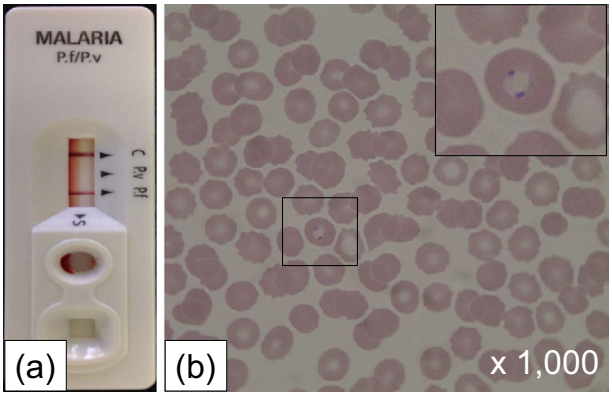

Figure 2. The results of a rapid antigen test and peripheral blood smear (May-Giemsa staining). The rapid antigen test was positive for *Plasmodium falciparum* (C: control, P.v: *P. vivax*, P.f: *P. falciparum*) (a). Ring-form malaria parasites were detected in an erythrocyte of the normal size. The proportion of parasitized erythrocytes was less than 0.1% (b).

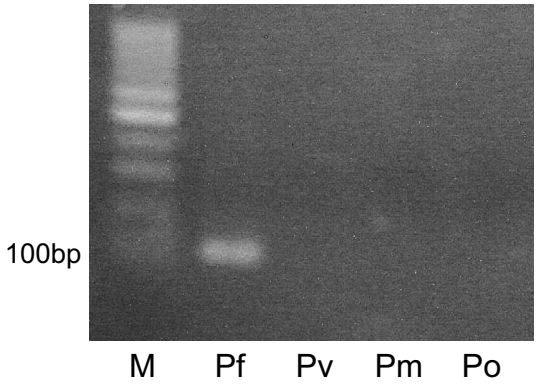

Figure 3. PCR analysis. A PCR analysis showed a single infection of *Plasmodium falciparum*. (M: DNA size marker, Pf: *P. falciparum*, Pv: *P. vivax*, Pm: *P. malariae*, Po: *P. ovale*)

him on the 5th hospital day (Fig. 1). Later, a polymerase chain reaction (PCR) examination of RNA (10) extracted from the patient's blood, confirmed a single infection with *Plasmodium falciparum* (Fig. 3).

Discussion

Malaria is one of the world's top three infectious diseases. Its prevalence is high in tropical and subtropical regions (1). Currently, 5 principal plasmodium species cause human malaria: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi* (11). Because malaria caused by *P. falciparum*, so called tropical malaria, is often life-threatening, prompt diagnosis and treatment is crucial.

The abnormal laboratory findings in the present patient, which included metabolic acidosis, liver dysfunction, and coagulopathy, showed an unexpected trend toward improvement on admission to our hospital, even on the 5th day after the onset of symptoms, as shown in the Table. Since no authorized antimalarial agents were administered before his visit to our hospital, this clinical course could be explained by the use of azithromycin, which was incidentally prescribed by the primary care physician.

The antimalarial effect of azithromycin *in vitro* was first reported in 1992 (12). Azithromycin targets the ribosome of susceptible microorganisms and reversibly inhibits protein synthesis (13). Clindamycin and doxycycline, which have been approved as antimalarial drugs, show the same pharmacological effect on the plasmodial ribosome (14). Although several clinical trials have been performed to investigate the efficacy of azithromycin in the treatment of *P. falciparum* and *P. vivax* infection, there is no evidence to show that azithromycin monotherapy is sufficient to cure malaria (6, 7). On the other hand, recent phase II/III studies demonstrated that a combination therapy of azithromycin and an antimalarial drug against uncomplicated *P. falciparum* malaria was efficacious and well tolerated (9, 15). The prophylactic efficacy of azithromycin against *P. vivax* has been reported; however, the protective effect against *P. falciparum* infection is controversial (16-18).

The rapid antigen test that we used detects the histidine-rich protein II (HRP-II) antigen of *P. falciparum*. It is assumed that azithromycin decreased the number of live parasites in the erythrocytes, and that the antigens derived from dead parasites were strongly detected by the rapid test. Azithromycin is relatively safe and is frequently prescribed in clinics (5), but its administration to a febrile patient with malaria could decrease the number of parasitized erythrocytes and thus make the diagnosis of malaria by the widely used method of blood smear examination, which is the gold standard method for diagnosing malaria, more difficult.

The present case has reminded us of the importance of asking febrile patients about their travel history. EVD is currently epidemic in several countries of West Africa, including Liberia, and has caused serious problems throughout the world (19). Febrile travelers returning from the epidemic area should first contact a local healthcare center; however, this patient visited a nearby clinic and his primary care physician did not seem to recognize his travel history. At the general hospital, he had been routinely treated as a usual patient until a physician asked about his travel history. It is highly possible that a patient suspected of having EVD would visit a local clinic or a general hospital directly like the present case. Healthcare workers should be aware of EVD and ask febrile patients about their travel history when they begin their examination.

In conclusion, we herein report the case of a falciparum malaria patient who was incidentally pretreated with azithromycin. Azithromycin has a weak antimalarial effect, and its inappropriate use might cause delay in the diagnosis of malaria. Furthermore, this case highlights the importance of asking febrile patients about their travel history.

The authors state that they have no Conflict of Interest (COI).

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