J Korean Med Sci. 2024 Jun 10;39(22):e186
https://doi.org/10.3346/jkms.2024.39.e186
eISSN 1598-6357·pISSN 1011-8934

JKMS

Case Report
Infectious Diseases

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Late Parasitological Failure and Subsequent Isolated Gametocytemia of Uncomplicated *Plasmodium falciparum* Malaria in a Returned Traveler From Ghana, 2023

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OPEN ACCESS

Received: May 2, 2024
Accepted: May 15, 2024
Published online: May 29, 2024

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ABSTRACT

Herein, we report a case of uncomplicated falciparum malaria with late parasitological failure in a 45-year-old businessman returning from Ghana. The patient visited the emergency department with high fever, headache, and dizziness. He traveled without antimalarial chemoprophylaxis. Laboratory tests led to the diagnosis of uncomplicated falciparum malaria with an initial density of 37,669 parasites per μL of blood (p/μL). The patient was treated with intravenous artesunate followed by atovaquone/proguanil. He was discharged with improved condition and decreased parasite density of 887 p/μL. However, at follow-up, parasite density increased to 7,630 p/μL despite the absence of any symptoms. Suspecting treatment failure, the patient was administered intravenous artesunate and doxycycline for seven days and then artemether/lumefantrine for three days. Blood smear was negative for asexual parasitemia after re-treatment but positive for gametocytemia until day 101 from the initial diagnosis. Overall, this case highlights the risk of late parasitological failure in patients with imported uncomplicated falciparum malaria.

Keywords: *Plasmodium falciparum*; Malaria; Treatment Failure; Parasitemia; Gametocytemia

INTRODUCTION

Malaria, a mosquito-borne parasitic illness endemic to 84 countries, accounted for approximately 240 million cases and 608,000 deaths worldwide in 2022.[1] Before the coronavirus disease-2019 pandemic, South Korea averaged 76 imported malaria cases annually between 2017 and 2019.[2] After a temporary decline during the pandemic, the number of cases increased to 74 in 2023. Recent imported malaria cases in South Korea have been predominantly attributed to *Plasmodium falciparum* from Africa, a pattern also observed in other countries.[3,4]

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Ethics statement
The patient was informed of the intention to publish a case report, and verbal consent was obtained prior to publication.

Disclosure
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Kim JH. Data curation: Kim S, Huh J. Writing - original draft: Bae J. Writing - review & editing: Bae J, Kim JH, Kim S, Huh J, Choi HJ.

Artemisinin-based combination therapy (ACT) is the recommended treatment for uncomplicated *P. falciparum* malaria by the World Health Organization owing to its high efficacy and safety.[5] However, a recent review reported treatment failure in less than 10% of patients, even with optimal dosage and patient adherence.[6] Treatment failures can be broadly categorized as early or late and require a minimum 28-day follow-up period.[7] Distinguishing between treatment failure and gametocytemia of *P. falciparum* is important for re-treatment decisions in South Korea, where transmission of *P. falciparum* has never been reported except for one nosocomial case.

Herein, we report a case of uncomplicated falciparum malaria in a Ghana-returned traveler with late parasitological failure (LPF) and subsequent isolated gametocytemia after ACT.

CASE DESCRIPTION

A healthy 45-year-old man presented to the emergency department complaining of high fever since three days, headache, and mild dizziness on June 27, 2023. The patient was a businessman who had visited Ghana and Dubai (United Arab Emirates) from June 8 to 18. He did not receive any malarial chemoprophylaxis and recalled being bitten by a mosquito during travel. His initial vital signs were as follows: temperature of 39.7°C, heart rate of 137 beats/min, blood pressure of 160/87 mmHg, and respiration rate of 20 breaths/min. Although the patient appeared acutely ill, physical and neurological examinations did not reveal any abnormalities. However, laboratory tests revealed leukopenia (2.52 × 10^3/μL) and thrombocytopenia (50,000/μL) in the peripheral complete blood count and normal hemoglobin level of 15.3 g/dL. Aspartate transaminase (AST) and alanine transaminase (ALT) levels were elevated to 62 IU/L (normal < 40 IU/L) and 53 IU/L (normal < 40 IU/L), respectively. Plasmodium lactate dehydrogenase was detected, and peripheral blood smear microscopic examination of Giemsa-stained thin blood film (per 200 white blood cells) revealed a high malarial parasite density of 37,669 parasites per μL of blood (p/μL) (**Fig. 1A**). Furthermore, polymerase chain reaction (PCR) confirmed the presence of *P. falciparum*, without any non-falciparum strains. The patient was admitted and immediately administered intravenous artesunate at a dose of 2.4 mg per kg body weight, followed by subsequent doses at 12, 24, and 48 hours. Then, he was administered atovaquone/proguanil at a dose of 1,000/400 mg/day with food. The platelet count reached its lowest level of 42,000/μL on day 3 of admission, followed by gradually recovery. On day 5 of admission, the patient was afebrile. AST and ALT levels peaked at 186 and 188 U/L, respectively, on the same day and then decreased. The number of malarial parasites in the blood initially decreased to 25,956 p/μL at the 24-hour follow-up and then to 887 p/μL on the day before discharge. The patient was discharged on day 7 of admission with improved condition.

At the post-discharge follow-up on July 7, seven days after the completion of artesunate therapy, the malaria parasite density further decreased to 313 p/μL but was not eliminated (**Fig. 1B**). Treatment with atovaquone/proguanil was continued as the patient complained of head pressure. On the second follow-up visit on July 12, his symptoms improved, but blood smear revealed a parasite density of 224 p/μL. Therefore, atovaquone/proguanil treatment was administered for another seven days, leading to a total treatment duration of 19 days.

On July 24, six days after the completion of atovaquone/proguanil treatment, parasite density rose to 4,200 p/μL, but no symptoms were observed. Considering the possibility of LPF due to

https://doi.org/10.3346/jkms.2024.39.e186

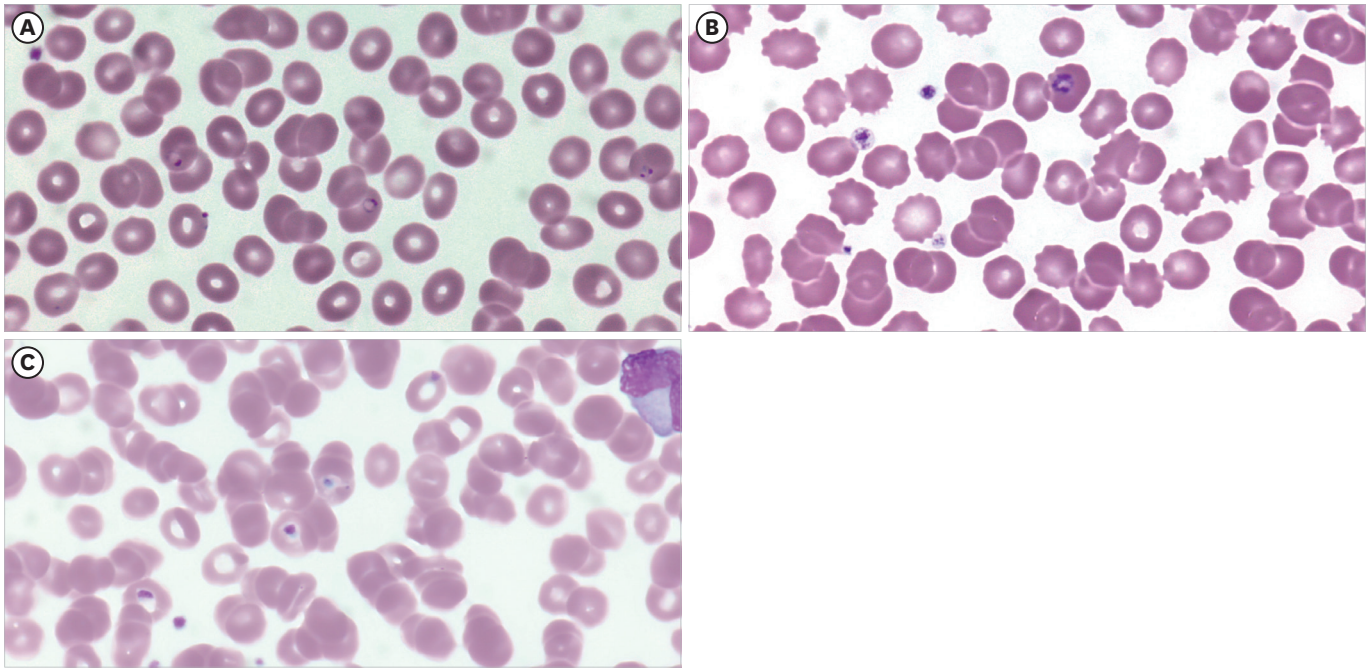


Fig. 1. Peripheral blood smear of the patient. Parasite density significantly decreased from (**A**) to (**B**) after the administration of antimalarial treatment, followed by a resurgence on day 8 after the completion of first treatment. Upon second admission, parasite density increased to 7,630 parasites per μL (**C**). Infected red blood cells with ring forms, trophozoites, and schizonts were detected during the second treatment. Only gametocytemia was observed at the second discharge (figure not shown). Parasite densities on (**A**) day 1 of admission, (**B**) day 7 of admission, and (**C**) day 2 of re-admission (day 31 from diagnosis).

recrudescence and risk of transmission, the attending physician recommended re-admission and re-treatment. Upon re-admission, parasite denisty peaked at 7,630 p/μL (**Fig. 1C**). PCR detected only *P. falciparum*, deeming further differentiation unnecessary. Intravenous artesunate was administered at a dose of 2.4 mg per kg body weight in combination with doxycycline at 200 mg/day for seven days. To accurately distinguish between asexual parasitemia and gametocytemia, the attending physician requested separate reporting of infected red blood cell (RBC) and gametocyte counts to the laboratory medicine department. On day 3 of admission, infected RBC count decreased to 802 cells/μL, and gametocytes were detected for the first time at 126 gametocytes/μL. The gametocyte count gradually increased to 592 gametocytes/μL before discharge. Throughout the second admission, the patient vital signs and laboratory results remained normal, except for mild anemia, indicated by a hemoglobin level range of 12.7–13.6 g/dL. The patient continued treatment with oral artemether/lumefantrine 80/480 mg twice daily for three days post-discharge.

At the initial follow-up appointment, no infected RBCs were detected, but the gametocyte count increased to 1,672 gametocytes/μL. The patient was administered 15 mg of primaquine daily for 14 days. Despite treatment, gametocytemia was observed again on August 23, 36 days after first ACT. Finally, on October 5, the peripheral blood smear tested negative for both infected RBCs and gametocytes.

DISCUSSION

This case report presented LPF in uncomplicated falciparum malaria due to recrudescence after first ACT and subsequent isolated gametocytemia after second ACT.

https://doi.org/10.3346/jkms.2024.39.e186

Early treatment failures indicate a lack of response to treatment, whereas late treatment failures indicate the failure of the antimalarial treatment in eradicating malarial parasitemia or inhibiting recrudescence, regardless of the symptoms.[8] Here, our case can be categorized as LPF due to the resurgence of parasitemia within 28 days of ACT without any reported symptoms.[7]

Increase in malarial parasite density after ACT should lead to a comprehensive examination of various possibilities. First, the likelihood of mixed infections should be tested. In Ghana, approximately 75% of malaria cases are caused by *P. falciparum*, and some are caused by *P. malariae* and *P. ovale*.[9] For our patient, PCR was positive only for *P. falciparum* during both admissions. Clear distinction between isolated gametocytemia and treatment failure is necessary for effective treatment. Persistent parasitemia despite atovaquone/proguanil treatment should suggest the possibility of gametocytemia. Here, although a distinction between infected RBCs and gametocytes was made during re-admission, the gradual increase in gametocyte count was only noted during the second ACT. Our findings suggest that the resurgence of parasitemia could be treatment failure rather than gametocytemia.

When treatment failure is suspected in a patient with malaria, several contributing factors, such as poor patient compliance, pharmacokinetic factors, subtherapeutic drug levels, and antimalarial resistance, should be assessed.[5] Currently, no clinical instances of artemisinin resistance have been reported in Ghana. Here, the observed rapid decline in parasite density after the first and second artesunate treatments indicated no ACT resistance in the patient. However, some genotypes, such as mutations in the Kelch propeller domain on chromosome 13 (*Pfk13*), may be associated with ACT resistance.[10] Analysis of Pfk13 sequences from *P. falciparum* samples in Ghana revealed mutations in 15.7% of cases, of which 11.1% were linked to ACT resistance. Additionally, a case of genetically confirmed atovaquone/proguanil-resistant *P. falciparum* malaria has been documented in a traveler returning from west Africa.[11] A point mutation in cytochrome b gene contributes to subtherapeutic drug levels, leading to the development of resistance. Although specific laboratory tests were not conducted for verification, the patient in this case may have experienced late treatment failure owing to subtherapeutic drug levels or antimalarial resistance. Alternatively, there may be no specific reason as treatment failure only occurs in less than 10% of patients despite optimal dosage and adherence.[6]

In cases of treatment failure within 28 d, an alternative effective ACT is recommended as the second-line treatment, and the 7-day treatment regimen involving artesunate/quinine in combination with tetracycline, doxycycline, and clindamycin is considered to indicate poor response when the treatment is not directly observed.[5] Despite insufficient data for definitive recommendations, prolonged ACT is proposed for cure in regions with artemisinin-resistant *P. falciparum*. Although the regimen administered to the patient in this case deviated from the recommended protocol, atovaquone/proguanil was administered for more than three days to eradicate the residual parasites. Even after the diagnosis of LPF, the patient was responsive to ACT, as evidenced by the substantial reduction in parasite density after the first ACT.[12] A 7-day treatment regimen of artesunate with doxycycline was administered as the optimal second-line therapy. Subsequently, artemether-lumefantrine, an effective long-acting ACT, was used to prevent recurrence, as previously reported.[5,13]

This case emphasizes the importance of patient evaluation and management, including the distinction between treatment failure and isolated gametocytemia and assessment of factors contributing to treatment failure, when the parasite density increases during the follow-up period after ACT.

https://doi.org/10.3346/jkms.2024.39.e186

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