INTRODUCTION

Rapid diagnostic tests (RDTs) for malaria using antibodies against pan-Plasmodium antigen lactate dehydrogenase (pLDH) are commonly used for malaria diagnosis. The level of malaria parasitemia determined by peripheral blood smears (PBS) correlates with the pLDH concentration in most cases. We report a case of malaria recurrence associated with false-negative RDT results. A 22-year-old male patient was admitted to the Armed Forces Capital Hospital with fever and chills, and was diagnosed with malaria infection. Four days after antimalarial treatment, these symptoms recurred. After admitting to our hospital, doxycycline was administered for 4 days. Even after administration of doxycycline, the malaria parasites in blood smears remained positive, but RDT showed negative results. Therefore, for patients receiving doxycycline, serial blood smear testing should be performed to exclude false-negative malaria RDT results.

Key Words: Malaria, Rapid diagnostic test, Peripheral blood smear, Doxycycline, Lactate dehydrogenase

CASE

A 22-year-old man was admitted to the hospital following 4 days of fever and chills. One month prior, the patient, with no remarkable medical history, was admitted to the Armed Forces Capital Hospital and was diagnosed with malaria infection. Four days after antimalarial treatment, these symptoms recurred. After admitting to our hospital, doxycycline was administered for 4 days. Even after administration of doxycycline, the malaria parasites in blood smears remained positive, but RDT showed negative results. Therefore, for patients receiving doxycycline, serial blood smear testing should be performed to exclude false-negative malaria RDT results.

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that caution must be exercised in the diagnosis of malaria when using anti-pLDH antibody.
of malaria reinfection or recurrence, clinicians initiated a course of doxycycline for suspected epidemic hemorrhagic fever (EHF). On the 3rd day of hospitalization, PBS was repeated and yielded a positive result with a titer of 1,131/μL, rising to 1,360/μL on the 5th day. However, RDTs performed on both days remained negative. The patient was administered hydroxychloroquine and primaquine, and PBS results were negative after three days of treatment; he was discharged 10 days after admission (Fig. 1).

To evaluate the inconsistency between the RDT and PBS results on the 3rd and 5th days, the RDT was re-evaluated using internal quality control samples, but the results did not differ. A prozone phenomenon due to a high level of pLDH has been previously described [2], so to investigate this potential explanation, the specimens were diluted 2 and 4 times with normal saline; however, the results of this test were also negative.

**DISCUSSION**

Diagnosis of malaria based only on RDTs is cost-effective and operationally advantageous, since RDTs are easy to perform and provide results rapidly [3]. Most RDTs detect parasite histidine-rich protein 2 (pHRP-2) and pLDH from *Plasmodium falciparum* and *Plasmodium* spp., respectively. While the pHRP-2 antigen can be detected up to 40 days post-antibiotics treatment [4], the pLDH antigen has very short half-life of less than 2 days, and the median time on treatment for this test to become negative was reported as just 2 days [5]. Even though RDTs show good correlation with PBS results and can be used for evaluation of the treatment response and follow-up, low blood levels of pLDH can lead to false-negative results [1, 6]. We were not able to evaluate the pLDH level in this patient’s sample; the parasitemia was much higher than that reported previously with low detectable pLDH (<1,000/μL) [1, 6]. Similarly, Jang et al. [1] reported 7 cases of high parasitemia with low pLDH levels, but did not provide additional detailed data regarding treatment history. pLDH levels reflect the level of viable parasitemia [7], and the World Health Organization guidelines also state that parasitemia is the most important criteria for confident diagnosis [8].

In this case, we suspect that doxycycline administration may have influenced the RDT results. Doxycycline exhibits antimicrobial activity via inhibition of bacterial cell wall synthesis and eliminates malarial parasites in hepatocytes. Due to its effectiveness, doxycycline is administered as a therapeutic and preventive drug for malaria [9]. Despite a lack of studies reporting a direct association between doxycycline treatment and RDT results, Pasricha et al. [10] showed that 50% of patients with malarial infection and negative PBS and RDT results at the time of admission, had a history of treatment with doxycycline. Even though anti-malarial drugs decrease the number of parasites in the blood [11], in our case, the malarial parasite titers were not low. These reports suggest that antibiotics administration lowered the pLDH concentration due to a decreased number of viable parasites, resulting in false-negative RDT results. Therefore, in patients receiving doxycycline, serial PBS testing should be performed to exclude false-negative malarial RDT results. Further studies are required to elucidate the effect of doxycycline administration on RDT results.

**요약**

*pan-Plasmodium* antigen lactate dehydrogenase (pLDH)에 대한 항체를 이용하는 말라리아 신속검사는 말초혈액도말법과 함께 말라리아감염을 진단하는 대표적인 검사 방법이다. 혈청에서의 pLDH의 높도는 말초혈액도말법에서 확인할 수 있는 말라리아 원충수와 상관관계가 있다고 알려져 있다. 우리는 말초혈액도말법에서 말라리아 원충을 관찰할 수 있었지만 신속검사에서 위음성 결과가 보고된 증례를 보고하고자 한다. 22세 남자 환자가 발열과 오
한으로 국군수도병원으로 내원하였고 말라리아 감염으로 진단 후 치료받았다. 치료 종료 후 4일째부터 다시 증상이 재발하여 독시 사이클린을 4일간 투약했다. 독시사이클린 투여 후 발초혈액검사에서 말라리아 원충이 지속적으로 관찰되었지만 신속검사에서 는 위음성으로 일관되게 보고되었다. 신속검사와 독시사이클린 간의 연관성을 배제할 수 없기 때문에 독시사이클린 투여받은 환자들은 발초혈액검사를 통하여 말라리아 신속검사 결과를 확인해야 할 것이다.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

REFERENCES