

## An Atypical Case of *Plasmodium vivax* Malaria after Initiating Adalimumab Therapy

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We report an unusual case of *Plasmodium vivax* malaria that occurred in a 22-year-old ankylosing spondylitis patient after initiating adalimumab therapy. *P. falciparum* malaria was initially included as a possible differential diagnosis due to hyperparasitemia and similar features in

the peripheral blood smear. The patient was successfully treated with conventional therapy for *P. vivax* malaria. **Key Words.** Adalimumab, Malaria vivax, Spondylitis ankylosing

### Introduction

Indigenous malaria was thought to have been eliminated from South Korea until a case reemerged in 1993. Most of the cases have been due to *Plasmodium vivax*; *P. falciparum* malaria has not been reported as an indigenous case. Known endemic areas for *P. vivax* malaria in Korea include some northern regions of Kyunggi province and a sector of the demilitarized zone (DMZ) (1). The diagnosis of malaria is established using a peripheral blood smear and morphological characteristics of individual parasites are often helpful in confirming the diagnosis. We report a case of *P. vivax* malaria in a patient receiving adalimumab that had similar blood smear findings as *P. falciparum* malaria.

### Case Report

A 22-year-old male was admitted because of fever and chills. The patient had been previously diagnosed with ankylosing spondylitis (AS) 1-year previously and adalimumab had been initiated 1-month prior to the current admission. The patient had completed military service 6 months previously in Yeunchun, Kyunggi province, which is an endemic area for *P. vivax* malaria. After military service, the patient moved

back to his hometown, Jeju Island, and did not travel outside the island for the following 6 months. The patient had been in typical health until 7 days prior to the current admission, when subjective fever, chills, fatigue, and malaise developed. Seven days after symptom development, the patient came to the outpatient clinic. He denied cough, sputum, gastrointestinal symptoms, shortness of breath, or night sweats. The patient reported a fluctuating fever over the previous 7 days. On examination, vital signs showed body temperature of 40.0°C, blood pressure 130/80 mmHg, pulse rate 100 beats per minute, and respiratory rate 18 breaths per minute. Lung and heart sounds were clear. Examination of the abdomen revealed no palpable mass or hepatosplenomegaly. Initial laboratory findings were white blood cell count 3,900/mm<sup>3</sup> (neutrophils 48.1%, eosinophils 11.7%), hemoglobin 12.3 g/dL, platelet count 45,000/mm<sup>3</sup>, AST/ALT 30/19 IU/L, creatinine 1.1 mg/dL, erythrocyte sedimentation rate 39 mm/hour, and C-reactive protein 16.27 mg/dL. A peripheral blood smear revealed numerous trophozoites, schizonts, and ring forms in red blood cells (RBC). Hyperparasitemia was also observed (parasites per white blood cell: 180 per 100). Of note, there were multiple ring forms in one RBC and some were located

<Received : July 29, 2011, Revised : (1st: September 28, 2011, 2nd: September 29, 2011), Accepted : September 30, 2011>  
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pISSN: 2093-940X, eISSN: 2233-4718

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peripherally (Figure 1). On the basis of these findings, adalimumab therapy was stopped and chloroquine was begun under the suspicion of malaria. By the second day after treatment the patient became afebrile and parasitemia was improved (parasites per white blood cell: 5 per 100). By the fifth day after treatment, parasitemia disappeared in the peripheral blood smear. Polymerase chain reaction-based molecular analysis showed a positive result for *P. vivax*. Primaquine was administered for 14 days. After being discharged, the patient had no relapse or adverse event during a 2-year follow-up.

### Discussion

We report a case of *P. vivax* malaria that presented with atypical features in a peripheral blood smear after beginning adalimumab therapy. The blood smear showed marked parasitemia and multiple ring forms located peripherally in the RBCs. These features are commonly seen in the blood smear of *P. falciparum* malaria, whereas they are rarely evident in *P. vivax* malaria (2). However, several clues pointed the diagnosis towards *P. vivax* malaria. First, the patient was stationed in a *P. vivax*-endemic area during military service and had not traveled abroad before service. Second, after military service the patient returned to Jeju Island, a non-endemic area for malaria. Thirdly, the patient had never received a blood transfusion. Furthermore, *P. falciparum* malaria has never been reported in South Korea. Therefore, it was reasonable

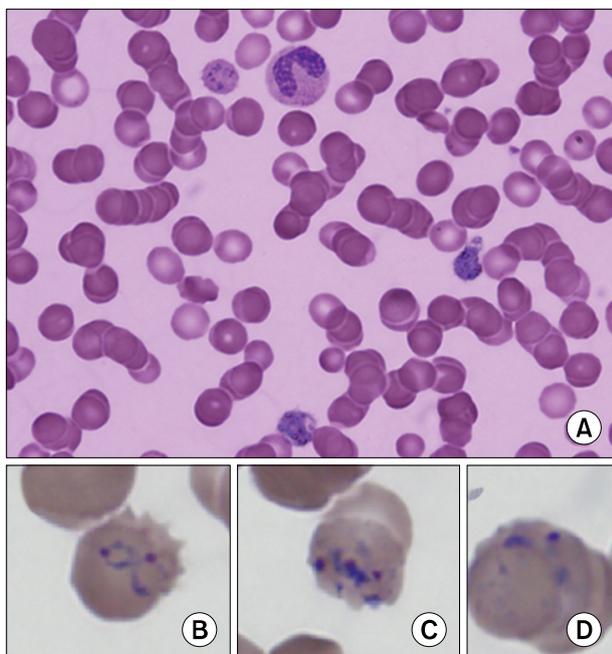
to believe that the *P. vivax* parasites had infected the subject during the military service, remained dormant as hypnozoites in the liver, and reactivated after a latent period of more than 6 months. Interestingly, it was only a month after the subject commenced adalimumab therapy that the symptoms manifested. These two events may have occurred by chance, or the adalimumab treatment may have triggered reactivation of *P. vivax* malaria.

Adalimumab is a tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitor that is now broadly used in patients with autoimmune diseases like rheumatoid arthritis or ankylosing spondylitis. Systematic reviews have reported that TNF- $\alpha$  inhibitors increase the risk of serious infection by 2-4-fold (3). Furthermore, the risk is particularly relevant to intracellular organisms like tuberculosis, histoplasmosis, and listeriosis because of its immunosuppressive effect on cell-mediated immunity (3,4). No clear association has been reported between TNF- $\alpha$  inhibitors and malaria infection, although an anti-malarial effect of TNF- $\alpha$  has been suggested (5). According to an *ex vivo* study on *P. vivax* malaria, TNF- $\alpha$  plays a vital part in aggregating monocytes/macrophages, activating monocytes to secrete reactive nitrogen intermediates, and parasite-killing materials (6). Therefore, TNF- $\alpha$  inhibitors may attenuate the antimalarial effect and increase the risk of malaria infection.

Our case presents a circumstance where a latent infection may have reemerged a month after commencing adalimumab therapy. The agent may have influenced the host immune system to be more susceptible for the multiplication of parasites, resulting in hyperparasitemia and atypical features in the peripheral blood smear.

In contrast, it has been reported that TNF- $\alpha$  inhibitor may help treating cerebral malaria caused by *P. falciparum*. The mechanistic explanation is that TNF- $\alpha$  inhibitor can suppress overwhelming production of TNF- $\alpha$  seen in the infection (7). Excessive production of TNF- $\alpha$  induced by *P. falciparum* infection plays an important role in pathogenesis of severe malaria. The local production of cytokines by activated monocytes and macrophages leads to the activation of endothelial cells, followed by up-regulation of endothelial cell adhesion molecules. This process finally results in sequestration of parasite erythrocytes within small vessels of major organs, one of the major complications of *P. falciparum* malaria (8).

Geraghty et al. reported a case of cerebral malaria in a 45-year-old woman undergoing treatment with infliximab for rheumatoid arthritis (9). Overwhelming parasitemia (estimated to be > 50%) was present in the case even though there appeared to be a lack of severe manifestations, and the patient



**Figure 1.** Peripheral blood smear findings show many trophozoites, schizonts and ring forms ( $\times 1,000$ ) (A). Multiple ring forms are present in a red blood cell (B, C), located peripherally (D).

made a salutary recovery. This seems to be a result of blocking two conflicting actions of TNF- $\alpha$  simultaneously. In other words, although blocking antiplasmodial effects of TNF- $\alpha$  resulted in enhanced multiplication of *P. falciparum* malaria, it also may have restricted excessive TNF- $\alpha$  production, contributing to a comparatively quick recovery without any complication.

In our case, the final diagnosis was *P. vivax* malaria. To our knowledge there has been no report regarding atypical features shown in *P. vivax* infected patients using a TNF- $\alpha$  inhibitor. Within a day of chloroquine treatment, clinical symptoms and signs dramatically improved, as did parasitemia. This suggests that blood features similar to *P. falciparum* in this setting do not always require early antifalciparum treatment, and that conventional treatment is sufficient in treating *P. vivax* malaria. This may be because *P. vivax* malaria is relatively benign and chloroquine-sensitive (10). Ahn et al. reported a case of *P. vivax* malaria in a renal transplant patient after the commencement of immunosuppressant therapy, which showed atypical findings in the peripheral blood smear similar to our case; the patient was treated successfully with conventional antimalarial therapy (11).

### Conclusion

TNF- $\alpha$  inhibitor therapy could result in atypical features of peripheral blood smears in *P. vivax* infection. Therefore, obtaining relevant clinical information is important to make the proper diagnosis. Further research would be needed to better understand the atypical features of malarial infection under anti-TNF- $\alpha$  treatment.

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