



Plasmodium Malaria Combined with Multiple Bacterial and Viral Infections after Travel to Uganda and Rwanda in Africa: A Case Report

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Abstract

A male patient, aged 33, exhibits prolonged fever and is ultimately diagnosed with malaria as well as multiple bacterial and viral infections following a 37-day trip to Uganda, Africa. Despite receiving a regimen of artemisinin, antibiotics, and antiviral therapy, the patient's fever persisted. Consequently, a subsequent round of artemisinin therapy was administered, resulting in the eventual resolution of the fever. This case emphasizes the significance of identifying concurrent bacterial and viral infections in cases of imported malaria, and highlights the efficacy of employing a second course of artemisinin therapy.

Introduction

Malaria, an infectious disease transmitted by mosquitoes and caused by the malaria parasite, primarily affects African regions. However, a significant proportion of the global population remains susceptible to infection [1]. The presence of concurrent bacterial and viral infections contributes to variations in the duration and progression of malaria. Non-typhoidal *Salmonella* and other gram-negative bacteria are isolated from the blood of individuals with malaria [2]. The viruses that are easily contracted include the dengue fever virus, *Chikungunya virus*, viral hepatitis (hepatitis A, B, and C viruses), among others [3]. Some scholars suggest that the susceptibility to bacteremia in malaria patients might be attributed to bacterial translocation from the gut, as malaria infection increases gastrointestinal permeability [4]. Furthermore, it has been suggested that immune suppression and heightened erythrocyte phagocytosis are potential mechanisms contributing to the vulnerability of malaria patients to bacteremia [5]. The precise mechanisms underlying viral infections, on the other hand, remain uncertain and may be associated with compromised immune defenses within the body. The mechanism of viral infection has yet to be fully elucidated, possibly attributable to diminished immune response. Limited information exists regarding the importance of simultaneous bacterial and viral infections in uncomplicated cases of imported malaria. Notably, symptoms of malaria and bacterial/viral infections may manifest similarities. Additionally, immune suppression and increased erythrocyte phagocytosis is also proposed mechanisms for the susceptibility of malaria patients to bacteremia [5]. The mechanisms behind viral infections remain unclear, possibly linked to compromised immune defenses in the body. The mechanism of viral infection is not yet clear, which may be due to low immunity of the body. In uncomplicated cases of imported malaria, little is known about the significance of concurrent bacterial and viral infections. Symptoms of malaria and bacterial/viral infections may exhibit similarities. In this report, we present a case study of a 33-year-old male who contracted with severe malaria, as well as concurrent bacterial and viral infections while traveling in Africa. However, manifestation of symptoms occurred only upon his return to Zunyi, China.

Case Presentation

The patient traveled to Uganda in Africa and, after 37 days, developed unexplained fever (maximum temperature of 40.3°C), headache, fatigue, and sweating on May 11th, 2023. Four days before admission, the patient experienced fever, vomiting, along with symptoms such as dizziness, fatigue, and shortness of breath. Despite the use of ibuprofen suspension, there was no significant reduction in body temperature. Further investigation revealed a positive result for *Plasmodium* on blood thick smear, indicating a possible *Plasmodium* infection. The patient was admitted to our hospital with a diagnosis of 'malaria'. The patient had no previous medical history. No notable personal or family history.

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Table 1: The detected viral DNA.

Viral DNA	The concentration in the specimen	Signal strength
Human Herpesvirus 7	3×10^2 cps/ml	Moderate

Table 2: Detected virus and bacterial signals.

Category	Number of sequences
Parainfluenza Virus Type-3 (PIV-3)	9
<i>Escherichia coli</i>	5
<i>Enterococcus faecalis</i>	14

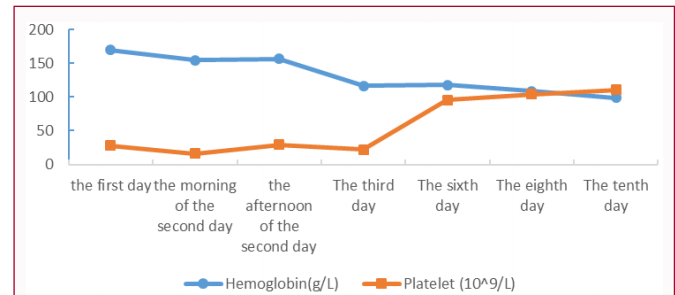
Table 3: Virus testing.

Items	Consequence
EB virus IgM (original titer)	Strong positive
EB virus IgM (1:100)	Positive
Cytomegalovirus IgM (original titer)	Positive
Cytomegalovirus IgM (1:100)	Weak positive
Herpes Simplex Virus IgM (original titer)	Strong positive
Herpes Simplex Virus IgM (1:100)	Positive

The physical examination revealed a blood pressure of 112/71 mmHg, clear consciousness, no petechiae or ecchymosis on the skin. Enlargement of lymph nodes in the neck and axillae was observed, with the largest measuring approximately 2 cm × 1 cm. Examination of the heart, lungs, and abdomen showed no abnormalities. There was no edema in the lower extremities, and pathological signs were negative.

The complete blood count revealed a reduction in red blood cells, a significant decrease in platelets, elevated liver transaminases, increased bilirubin, hyperlipidemia, markedly elevated serum ferritin, and notable increases in calcitonin, interleukin, and high-sensitivity C-reactive protein. Targeted identification of common pathogens (100+ and drug resistance) indicated infections with Human Herpesvirus 7, Parainfluenza Virus 3 (PIV3), *Escherichia coli*, and *Enterococcus* (Table 1, 2). Viral testing showed positive results for Epstein-Barr virus, *Cytomegalovirus*, and Herpes Simplex virus (Table 3). Abdominal ultrasound and abdominal CT indicated fatty liver and splenomegaly. The electrocardiogram showed dextrocardia. Superficial lymph node ultrasound revealed enlarged lymph nodes in bilateral neck, axillary, and inguinal regions. Chest CT revealed mild fibrosis in both lungs, pneumonia, and bilateral pleural thickening. Peripheral blood smear shows malignant *Plasmodium* parasites (Figure 1).

The final diagnosis for the patient is malignant *Plasmodium* malaria along with multiple bacterial and viral infections. We treated

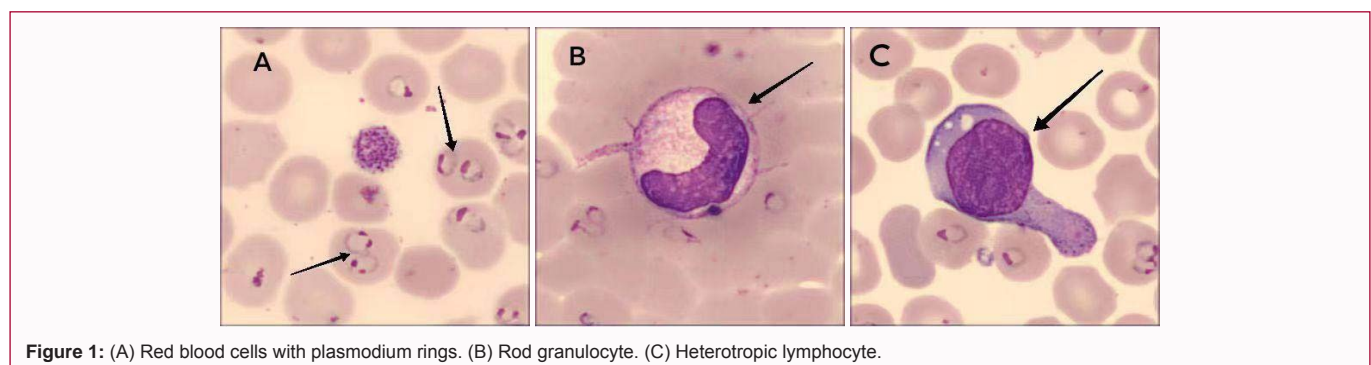
**Figure 2:** Changes in hemoglobin and platelet values during hospitalization.

him with intravenous artesunate at an adult dose of 120 mg (2.4 mg/kg), administered at 0, 12, and 24 h, followed by once daily injections for a total of 6 days. This was switched to a first dose of 2 tablets of dihydroartemisinin-piperazine, followed by 2 tablets orally at 8, 24, and 32 h, continued for 2 days. Due to suspected bacterial and viral co-infections with malaria, we administered intravenous acyclovir (0.25 g qd) and oral doxycycline (0.1 g bid) for 5 consecutive days while treating malaria. Subsequently, as the fever persisted, he was referred to a nearby hospital where he received another course of artesunate treatment. Follow-up showed gradual improvement in clinical symptoms, and the blood smear indicated parasite clearance, leading to his discharge.

Discussion

Malaria is one of the life-threatening diseases, caused by parasites of the *Plasmodium* genus and transmitted by mosquitoes. There are five different species of *Plasmodium* that can infect humans: *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, *Plasmodium falciparum*, and *Plasmodium knowlesi*. Among them, *Plasmodium falciparum* is the most pathogenic [6]. Malaria is primarily transmitted through the bites of infected mosquitoes. In humans, the main clinical manifestations of malaria, in the absence of other complications, include intermittent fever along with possible accompanying symptoms such as nausea, vomiting, headache, and muscle pain [7]. The diagnosis of the disease is primarily based on the patient's medical history, clinical presentation, and relevant auxiliary examinations. However, the clinical manifestations of malaria are similar to other tropical diseases and may also involve co-infections. Therefore, relying solely on the clinical presentation for the diagnosis of malaria lacks accuracy. Currently, the gold standard for diagnosing malaria remains the detection of *Plasmodium* parasites in thick blood smears [8].

Malaria as a cause of concurrent secondary bacterial and viral infections has been uncommon in the past. This may be because previous cases of malaria may be co-infected, but not tested for

**Figure 1:** (A) Red blood cells with plasmodium rings. (B) Rod granulocyte. (C) Heterotropic lymphocyte.

bacteria and viruses, which may be cleared by the body's immune system after the primary disease is treated. A recent study in Myanmar suggested that bacterial infections in adults were higher than in the past [9]. In most cases, the clinical manifestations were non-specific, including nausea and vomiting, convulsions, sensory changes, cough and sputum, urinary system symptoms, shock, acute kidney injury, anemia, etc. [10]. In this case, the patient also had the above symptoms in addition to convulsions and sensory changes. However, malaria combined with a variety of bacterial and viral infections is more common in children than in adults, and co-infection is one of the reasons for the poor prognosis and high mortality in children [11]. Although the patient in this case did not show aggravation of the disease and poor prognosis, we should pay attention to the co-infected adult malaria patients, be alert to the changes of the disease, and prevent life-threatening safety. It is suggested to improve the relevant inspection and take corresponding measures.

In a meta-analysis [12], it was pointed out that *Plasmodium falciparum* was co-infected with gram-negative bacteria, *Salmonella typhi* was the most common cause of bacteremia, *Plasmodium falciparum* was co-infected with Gram-positive bacteria, *Staphylococcus aureus* was the most common infection, while the infected bacteria in this case were *Escherichia coli* and *Enterococcus faecalis*. It may be that the chelation of infected red blood cells blocks the gastrointestinal microvascular system, ultimately leading to the breakdown of the tight and adherent connections that normally serve as a physical barrier to translocated intestinal bacteria [13]. Mast cell activation and translocation to the gastrointestinal tract during malaria exacerbate damage to the physical barrier and weaken the immune barrier by releasing enzymes and factors that alter the host's response to escaping intestinal bacteria [14]. In addition, malaria co-infection with viruses is not uncommon, the most common virus is dengue virus [15], virus infection and malaria I have similar main symptoms, including fever, headache, myalgia, joint pain [16], while the patient in this case mainly combined with human herpesvirus type 7 and Parainfluenza Virus type 3: PIV3 and other infections, like the above symptoms, there are mainly clinical manifestations of fever, the cause of which is not clear.

The blood routine examination of the patient during the hospital after malaria infection indicated that the red egg gradually decreased, which was consistent with the invasion, development and proliferation of the red blood cell in the asexual stage of plasmodium mentioned in the literature [17]. Hyper-plasmodium falciparum parasitemia is negatively correlated with platelet count [18]. The degree of thrombocytopenia is correlated with parasite density, severity of malaria infection, and clinical outcome, possibly because platelets preferentially bind to infected red blood cells rather than to uninfected red blood cells in the blood. Platelets directly bind to and kill the parasites in red blood cells infected with *Plasmodium*, especially in the mature stage [19], so the platelet index of our patient during hospitalization ranged from low to high.

As for the treatment of malaria, artemisinin is the drug of choice, which has the characteristics of the fastest anti-malarial effect and good tolerance [20]. However, the patient in this case still received antibacterial and antiviral treatment during the period after the treatment of anti-malarial treatment and the reexamination of blood smear did not detect malaria parasites. However, the patient's symptoms of high fever remained. The fever symptoms of the patient were relieved only after the second course of anti-malarial

treatment. It is possible that the merozoites had not been released into the blood or the number of parasites was killed by the drug when the early smears were used to find plasmodium, so the number of parasites in the blood was not large. However, it cannot be ruled out that the patient had abnormal blood, respiratory and other systems, which triggered the primary disease after infection with *Plasmodium*. It is also not excluded that the patient's immune system has been compromised, which may make him more susceptible to infections such as bacterial viruses. Infection with more than one pathogen complicates the diagnosis of malaria and changes the clinical course, treatment, and management of the disease. In addition, the clinical manifestations of malaria are similar to viral and bacterial infections, which can lead to underdiagnosis of co-infections. Although there is limited information available to definitively diagnose malaria with bacterial and viral infection, clinicians should be aware that multiple infections prolong the course of malaria, in which case antimicrobial and antiviral treatment may be empirically recommended.

There are few reports of malaria co-infection with multiple bacteria and viruses in China, which may be because there is no routine clinical test for co-infection. However, in the current COVID-19 epidemic, after the suspicious person tested negative for the novel coronavirus, clinicians were alert to other bacterial or disease infections and routinely screened for bacterial and viral infections, and thus found that the patient in this case was infected with *Plasmodium falciparum*. It is associated with a variety of bacterial and viral infections.

Conclusion

In summary, patients should be admitted with fever and have a history of travel to endemic areas, persistent fever in malaria patients should also raise concerns about viral and bacterial co-infection or other systemic diseases, and should be examined. Moreover, after the completion of artemisinin treatment course, the patient's symptoms still did not return to a feasible second artemisinin treatment course. At present, there are no reports on whether a second artemisinin course of malaria treatment will affect the change of the patient's condition, but clinicians should actively treat the disease according to the condition.

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