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Case Report: *Plasmodium knowlesi* Infection with Rhabdomyolysis in a Japanese Traveler to Palawan, the Philippines

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Abstract. Skeletal muscle is known to be damaged by falciparum malaria via sequestration of infected erythrocytes. We present a case of rhabdomyolysis caused by *Plasmodium knowlesi* infection. The patient had fever, myalgia, and muscle weakness 5 days after returning to Japan from Palawan, the Philippines. Blood test revealed thrombocytopenia and an elevated creatine kinase level. Although rhabdomyolysis resolved with fluid therapy, fever of 24-hour cycle continued and thrombocytopenia intensified. On day 7 of illness, Giemsa-stained thin blood smear revealed malaria parasites, with a parasite count of 2,380/μL, which were morphologically indistinguishable between *P. knowlesi* and *Plasmodium malariae*. Rapid diagnostic test showed a negative result. The pathogen was later confirmed to be *P. knowlesi* by nested polymerase chain reaction (PCR). The patient was successfully treated with artemether/lumefantrine. This case suggests that knowlesi malaria might be able to cause skeletal muscle damage.

CASE REPORT

Skeletal muscle is known to be affected by malaria.[1,2] Rhabdomyolysis, a rare complication of malaria, is the most severe form of skeletal muscle damage and can lead to renal failure. Such damage has been reported primarily in severe cases of falciparum malaria.[1,2] Here, we report an uncomplicated *Plasmodium knowlesi* infection with rhabdomyolysis in a 68-year-old Japanese male who had returned from Palawan, the Philippines. This, to the best of our knowledge, is the first case of rhabdomyolysis caused by knowlesi malaria.

The patient had traveled to and worked in Palawan every 3 months for three decades. On the most recent trip, he stayed in a forest cabin in Bacungan for 3 months and taught French cuisine to local cooks at a resort facility. He was healthy with no previous history of malaria and had taken no malaria chemoprophylaxis. Five days after returning to Japan, he awoke, unable to stand because of fever, myalgia, and muscle weakness in his lower extremities, and visited a nearby hospital. Complete blood count and biochemical tests revealed a low platelet count (99,000/μL) and an elevated creatine kinase (CK) level (6,900 IU/L). On day 2 of the illness, his serum CK level elevated further (24,940 IU/L), and his platelet count dropped to 42,000/μL. He was immediately hospitalized and diagnosed with rhabdomyolysis due to viral infection. His general condition was stable, and only intravenous fluid therapy was initiated. His serum CK level peaked on day 3 (13,032 IU/L) and subsequently decreased to a normal range in 3 days. His serum creatinine level was the highest (1.2 mg/dL) on day 2 and returned to within the normal range. His myalgia and muscle weakness improved, however, his fever continued showing a 24-hour cycle (Figure 1) and his fatigue deteriorated. Thrombocytopenia also intensified with a platelet count of 13,000/μL on day 5.

Blood smear test was performed on day 7 and malaria parasites were detected. He was then transferred to our medical center on day 8. He had high fever (38.5°C) and cough, but no myalgia or muscle weakness. The vital signs were stable except for low oxygen saturation (91%, room air). Physical examination revealed pitting edema in both lower extremities. Blood tests showed a low platelet count (28,000/μL), elevated bilirubin (1.6 mg/dL) and aminotransaminase enzyme levels (aspartate aminotransferase 53 U/L, alanine aminotransferase 123 U/L), and normal CK (172 IU/L) and creatinine (0.68 mg/dL) levels. Urine analysis revealed hemoglobinuria. Chest radiographs showed pulmonary edema which was suspected to be due to intravenous fluid therapy. A malaria rapid diagnostic test (RDT) (BinaxNOW® Malaria; Abbott, Lake Bluff, IL) revealed negative results and a Giemsa-stained thin blood film showed malaria parasites. We observed early and mature trophozoites, schizonts, and gametocytes, which were consistent with *Plasmodium malariae/P. knowlesi*. The parasite count was 2,380/μL (0.062%). The malaria species, which was indistinguishable by blood film microscopy alone, was later confirmed as *P. knowlesi* through nested PCR analysis with each specific primer sets targeted for the small subunit rRNA genes of *P. knowlesi* and other human malaria parasite species.[3] Dengue RDT (SD BIOLINE Dengue Duo; Abbott) was also performed on day 8 with negative nonstructural protein 1 (NS1), immunoglobulin G and immunoglobulin M results. Considering that the diagnosis of knowlesi malaria was made on day 8 of illness, the parasite count was very low, and the disease was mild. A 3-day course of artemether/lumefantrine was successfully completed without any adverse events. The patient's fever subsided and parasitemia was cleared on day 9 (Figure 1). The fever and parasite clearance times were 15 and 17 hours, respectively. He was followed-up for 1 month after discharge without any sequela.

DISCUSSION

Plasmodium knowlesi is primarily a simian malaria. It was identified in the 1930s and was believed to rarely infect human beings naturally, until 2004 when a large focus was discovered in Malaysian Borneo.[4] It is now known to be more widely distributed than first assumed, and its cases have been reported throughout Southeast Asia.[5] It is transmitted from its reservoir hosts, long-tailed and pig-tailed macaques, to humans via infected mosquitoes.[5] Its clinical manifestation, as

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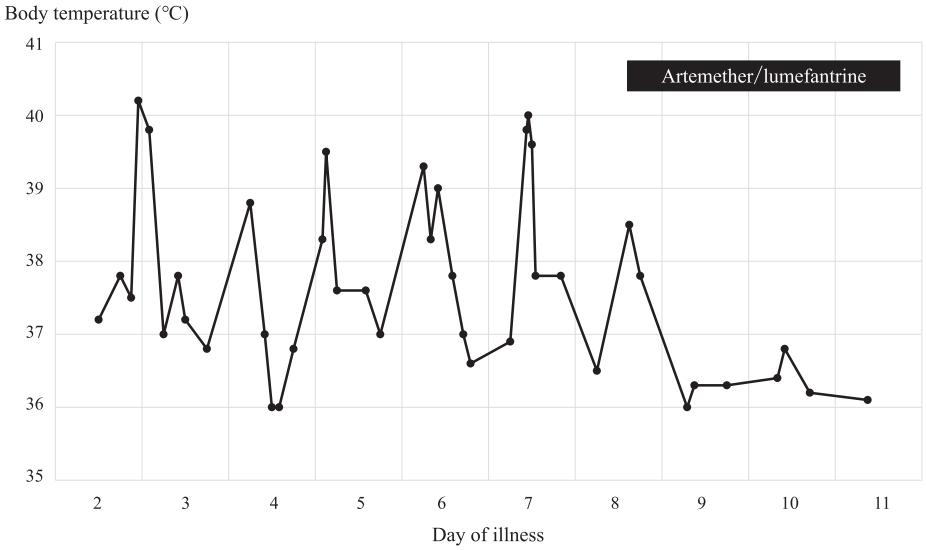

FIGURE 1. Fever chart from day 2 to 11 of illness.

nonspecific febrile illness, is similar to that of the four malaria species more commonly causing human infection.[5] The disease progresses rapidly because of the 24-hour erythrocytic life cycle of the parasite, and it is known that the severity of the disease can vary from uncomplicated to fatal disease.[5] The diagnosis of knowlesi malaria is challenging. It is not possible to distinguish *P. knowlesi* from *P. malariae* by microscopy because of their morphological similarities. The performance of RDTs for detecting knowlesi malaria has not been thoroughly investigated, but their sensitivity is known to be suboptimal.[5,6] In a recent systematic review, although the accumulated evidence is not sufficient, the overall sensitivity varied between 2% and 48% depending on the RDT kit used.[6] The RDT kit which we used for this patient targets histidine-rich protein 2, specific to *Plasmodium falciparum*, and aldolase, a panmalarial antigen. This RDT showed a sensitivity of 24% in detecting *P. knowlesi*. It was also suggested that the sensitivity could be lower in patients with low parasitemia.

The skeletal muscle is the largest organ of the human body to be damaged by malaria.[1,2] Skeletal muscle damage has been reported in cases of *P. falciparum* infection. Only one case of rhabdomyolysis has been reported due to *Plasmodium vivax* infection during antimalarial therapy with chloroquine.[7] The underlying mechanisms are not fully understood, but they are thought to be a combination of detrimental effects from both the parasites and the host, with the damage, at least partly, caused by the sequestration of infected erythrocytes. *Plasmodium falciparum* causes microvascular ischemia in skeletal muscle tissue[8] through the sequestration of infected erythrocytes, which bind to the endothelium via human endothelial receptors such as intracellular adhesion molecule 1 (ICAM-1),[9] vascular cell adhesion molecule 1 (VCAM-1), and cluster of differentiation 36 (CD36).[10] Considering the large size of the muscle mass in the human body, skeletal muscles might harbor a significant volume of sequestration in severe malaria.[1] Malaria is also known to damage the microvasculature and increase oxygen consumption in host muscles in the same manner as other pathogens causing sepsis.[11] Clinically significant skeletal muscle damage occurs with severe malaria, and its intensity is proportional to the severity of the disease and parasite burden.[12] Rhabdomyolysis, the most severe form of skeletal muscle damage, therefore, accompanies severe falciparum malaria with high parasite counts.

To the best of our knowledge, rhabdomyolysis due to *P. knowlesi* infection has not previously been reported. *Plasmodium knowlesi* is the dominant malaria species in Malaysia and might become the most common malaria species in the Southeast Asia region, because many of those countries are heading toward elimination of human malaria.[13] It is, therefore, of great importance to understand the pathophysiology of this zoonotic malaria. The pathogenesis of knowlesi malaria, especially when severe, is not well known, but it is suggested that severe infections of *P. knowlesi* and *P. falciparum* share pathological similarities.[14,15] A postmortem study of a fatal case of knowlesi malaria revealed sequestration of infected erythrocytes in the cerebrum, cerebellum, kidney, and heart.[14] According to an ex vivo study of five patients from Malaysia, erythrocytes infected by *P. knowlesi* bind to ICAM-1 and VCAM, but not to CD36.[15] The parasite might be able to cause sequestration of infected erythrocytes and, therefore, result in skeletal muscle damage like *P. falciparum*.

Regarding this case, however, even if knowlesi malaria can cause skeletal muscle damage, there are still two unresolved questions. The first is that rhabdomyolysis occurred in the early phase of the patient's illness and resolved without antimalarial therapy. The second is that the rhabdomyolysis occurred in an uncomplicated malaria with a very low parasite count.

This case suggests that knowlesi malaria might cause sequestration of infected erythrocytes and result in rhabdomyolysis in a fashion similar to falciparum malaria. Further research is necessary to understand the pathophysiology of *P. knowlesi* infection.

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