Case Report: Severe Rhabdomyolysis Caused by *Plasmodium vivax* Malaria in the Brazilian Amazon

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Abstract. Severe rhabdomyolysis (creatinine phosphokinase = 29,400 U/L) developed in a 16-year-old boy from Manaus, Brazil, after he started treatment with chloroquine for infection with *Plasmodium vivax*. Treatment led to myoglobinuria and acute renal failure. After hemodialysis, the patient improved and a muscle biopsy specimen showed no myophosphorylase or deaminase deficiency. This case of rhabdomyolysis associated with *P. vivax* infection showed no comorbidities. The pathogenesis is still unclear.

Although rhabdomyolysis is generally reported as a complication of *Plasmodium falciparum* malaria, leading to metabolic and renal complications,¹ it has been reported in a patient with *P. vivax* infection with myoadenylate deaminase deficiency.² We report a case in a patient without typical muscle enzyme deficiencies in which severe rhabdomyolysis developed while the patient was being treated with chloroquine for a confirmed *P. vivax* infection.

CASE REPORT

A 16-year-old boy from Manaus (Amazonas State), Brazil had high fever, headache, chills, myalgias, and arthralgias. Because of severe myalgia, the patient was given intramuscular sodium diclofenac. On the fifth day of the disease, he sought treatment at the Tropical Medicine Foundation of Amazonas and was diagnosed (for the first time in his life) as having a *Plasmodium vivax* infection (1,520 asexual parasites/mm³). He was treated with chloroquine (10 mg/kg/day on the first day, followed by 7.5 mg/kg/day on the second and third days) plus primaquine (0.5 mg/kg/day for 7 days), according to Brazilian Antimalarial Therapy Guidelines. Soon after the first dose of chloroquine and primaquine, the myalgias became worse and weakness, rigors, and functional disability developed, mainly in the lower limbs. He was admitted to the Tropical Medicine Foundation of Amazonas with severe muscle pain and dark urine. Vital signs were normal. Biochemical analysis identified severe rhabdomyolysis (creatinine kinase [CK] = 29,400 U/L, aspartate aminotransferase = 5,792 U/L, lactate dehydrogenase = 2,125 U/L), as shown in Table 1. Plasma myoglobin concentration was not determined. Urinalysis showed myoglobinuria.

Treatment with chloroquine was stopped and he was treated with artesunate (1 mg/kg intravenously two times a day for three days), followed by clindamycin (10 mg/kg intravenously two times a day for five days), vigorous intravenous hydration with saline and intravenous sodium bicarbonate for urine alkalization. On day 2 in the hospital, urine output nearly ceased and on day 3, a substantial increase in blood urea nitrogen, creatinine and potassium levels was observed (Table 1). He underwent five sessions of hemodialysis on alternate days.

A thick blood smear was negative on day 3 after starting anti-malarial treatment, and he had no fever. However, muscle pain continued, and a month passed before he started to walk again. The patient completely recovered after two months, and he was discharged for the follow-up in the Outpatient Clinic.

The patient had no history of chronic diseases, drug or alcohol abuse, contact with heavy metals, trauma, severe exercise, seizures, use of medications, snakebite, or other recent infectious diseases. His thyroid stimulating hormone level was in the reference range. None of his family had experienced a similar problem. Dengue fever and leptospirosis were ruled out by serologic tests (negative enzyme-linked immunosorbent assay IgM result at the time of admission and 15 days later). Blood culture for aerobic bacteria was negative. Tropical pyomyositis was ruled by a normal result for soft tissue ultrasound of the lower limbs. The kidneys were not subjected to biopsy because of satisfactory clinical recovery after hemodialysis, a syndrome compatible with acute tubular necrosis. A nested polymerase chain reaction (PCR) performed as described elsewhere³ on a peripheral blood sample obtained on day 1 confirmed only a *P. vivax* infection.

Five months after the acute malarial attack (CK and aspartate aminotransferase levels were in the reference range), a biopsy specimen of brachial biceps muscle was obtained. A 0.4 × 0.8 cm sample was frozen for histochemical analyses and fixed in glutaraldehyde for ultrastructural study. Specimens were stained with hematoxylin and eosin; modified Gomori trichrome; periodic acid-Schiff; and oil red O. Samples were also stained for ATPase 4.3, 4.6, and 9.4, NADH, sorbitol dehydrogenase, and cyclooxygenase activities; alkaline and acid phosphatases; myophosphorylase; and deaminase. Microscopic analysis showed polygonal muscular fibers without morphologic alterations or any cytoskeletal damage after oxidative reactions. There was no endomysium or perimysium soft tissue proliferation, or inflammatory cell infiltration. There were no alterations in phosphatases reactions, and ATPase reactions showed preservation of muscle fiber type distribution. To study the integrity of the muscular membrane, immunohistochemical analysis for spectrin was performed; results were normal. Results of staining for myophosphorylase and deaminase were also normal. Ultrastructural alterations were not detected by electron microscopy.

The patient was seen at the outpatient clinic one and two years after the acute malarial attack and he never experienced a rhabdomyolysis relapse or any sequelae from the acute event. He had no additional malarial attacks.

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TABLE 1
Hematologic and biochemical analysis of the patient, Manaus, Brazil*

Characteristic	Day 1	Day 2	Day 3	Day 5	Day 7	Day 12	Day 19	Day 23	Day 75
Leukocytes ($\times 10^3/\mu\text{L}$)	9.4	13.0	12.3	10.2	9.7	20.7	9.7	6.9	5.3
Hemoglobin (g/dL)	16.5	16.1	10.0	10.2	9.4	8.5	8.5	11.9	12.7
Platelets ($\times 10^3/\mu\text{L}$)	12.0	21.0	97.0	146.0	225.0	274.0	292.0	303.0	259.0
BUN (mg/dL)	34	—	91	118	145	159	50	65	12
Creatinine (mg/dL)	1.2	—	5.3	6.6	7.9	7.2	4.2	2.2	0.8
Total bilirubin (mg/dL)	1.3	0.9	0.8	0.8	0.7	—	—	—	—
AST (U/L)	2,513	5,792	2,036	9,072	3,113	391	78	88	21
ALT (U/L)	412	1,150	1,348	2,198	1,291	402	157	124	30
ALP (U/L)	136	130	88	107	68	—	—	—	—
LDH (U/L)	—	2,125	—	—	856	392	216	215	—
Potassium (mmol/L)	5.2	6.8	7.4	5.6	4.8	4.1	4.3	4.6	4.1
Magnesium (mg/dL)	—	—	2.3	—	—	—	—	—	—
CK (U/L)	29,400	—	—	—	12,400	—	—	—	84
CK-MB (U/L)	—	—	—	—	280	—	—	—	—
Parasitemia (asexual parasites/mm ³)	1,520	20	0	0	0	0	0	0	0

* BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; CK = creatine phosphokinase; MB = muscle-brain.

DISCUSSION

Myoglobin levels are often increased in patients with severe *P. falciparum* malaria.¹ However, development of myonecrosis in these patients is rare.⁴ The clinical spectrum of rhabdomyolysis is broad, as shown by the report of a patient in whom muscle pain, loss of exercise tolerance, and an exercise-related increase in the CK level was the principal manifestation of malaria.⁵

The most serious complication of rhabdomyolysis is acute renal failure caused by the nephrotoxic potential of myoglobin released from muscles. Together with hypovolemia, hypotension, concomitant use of nonsteroidal antiinflammatory drugs, fever, and acidosis, it can potentiate kidney damage. Conversely, there is little information available on the incidence of asymptomatic rhabdomyolysis in non-severely ill patients because no population-based studies have been performed.

Severe *P. vivax* malaria is usually considered a rare event, but evidence in the past few years suggests that its occurrence is increasing.⁶ Rhabdomyolysis is rare in patients infected with *P. vivax*. To our knowledge, there is only one case in the literature of myonecrosis related to *P. vivax* infection in a patient who was deficient for myoadenylate deaminase.² In our patient, an extensive search for muscular enzyme deficiencies showed normal muscles. In inflammatory myopathies, even after clinical recovery and normalization of CK levels, morphologic alterations persist and can be seen in all muscle groups. The absence of these findings suggests a direct effect of the *P. vivax* infection upon the muscle tissue of our patient. *Plasmodium vivax* infection was confirmed by PCR, which has the highest sensitivity for ruling out mixed infections.

Because muscle damage in the patient became clinically more severe after treatment with chloroquine, there are two potential mechanisms of pathogenesis. The first mechanism is vacuolar myopathy induced by chloroquine, as described.⁷ However, if one considers that our patient ingested only one dose of chloroquine (600 mg) and that the induction of vacuolar myopathy is related to a cumulative effect of the drug, it is highly improbable that chloroquine contributed to the severe rhabdomyolysis. The second mechanism involves the fact that most, but not all, *P. vivax*-associated acute respiratory distress syndrome develops after the start of antimalarial chemotherapy, which is consistent with exacerbation of the inflammatory response associated with parasite killing by the drug.⁸ A similar reaction may have occurred in our patient because this

reaction has been shown to be a mechanism of muscle damage during treatment of patients infected with *P. falciparum*.⁹ Severe rhabdomyolysis can trigger acute renal failure, but use of nonsteroidal antiinflammatory drugs, such as diclofenac sodium, substantially contributes to renal hypoperfusion and worsens renal function. Rhabdomyolysis could also have been induced by the diclofenac administered prior to arrival at the hospital, as previously reported.^{10,11} However, these reported cases are related to cumulative doses of diclofenac, which is not the case for our patient. Although less likely and not reported, primaquine used on the first day of the antimalarial treatment cannot be ruled out as an additional contributing cause of the muscle damage.

The mechanisms of the rhabdomyolysis in our patient are speculative, but additional cases should be investigated for muscular cytokine production, endothelial activation, and cytoadherence of *P. vivax*-infected erythrocytes.⁸ Diagnosis of *P. vivax* malaria is based only on a thick blood smear. Thus, any patient with signs of severe disease should be treated as having a mixed infection. Thick blood smears have a low sensitivity for diagnosis of mixed infections, and PCR is usually not readily available to guide treatment.

In conclusion, in all cases of acute renal failure related to malaria, the possibility of muscle damage should be considered.¹ Likewise, because aminotransferases, especially serum aspartate aminotransferase, are also present in muscle tissue, increases in levels of these enzymes are not necessarily related to hepatic involvement in malaria. Therefore, in all cases where malarial hepatitis is suspected, the CK level should be routinely measured.

In 2007, Brazil reported 457,659 cases of malaria, mostly in the Brazilian Amazon, with 85% caused by *P. vivax* infection.¹² Unusual clinical cases related to *P. vivax* infection have been increasingly reported in Latin America.¹³ This finding underscores the need for systematic clinical surveillance and reporting of these cases to define the clinical spectrum of severe *P. vivax* infection. Key concerns in this effort are to rule out mixed infections with *P. falciparum* and other potential comorbidities, which may be augmented by the parasite–host interaction.

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