

Case Report

Myoglobin Cast Nephropathy Diagnosed on Renal Biopsy in a Patient Treated for Malarial Infection

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Received 10 August 2023; Revised 12 December 2023; Accepted 8 January 2024; Published 12 February 2024

Academic Editor: Bernard G. Jaar

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Myoglobin cast nephropathy occurs in cases of acute renal injury in which large amounts of myoglobin accumulate in the renal tubules, presenting as muscle pain, reddish-brown urine, and elevated creatine kinase levels. Our case describes a 60-year-old male who came to the emergency department with fevers, mild abdominal pain, and constitutional symptoms one day after returning to the United States from a trip to Nigeria. Initial workup demonstrated an acute kidney injury and elevated aminotransferase levels and the patient was started on atovaquone-proguanil for possible malaria given a recent diagnosis in Nigeria. Two days later, the patient was found to have rhabdomyolysis, resulting in a renal biopsy that showed myoglobin cast nephropathy. Previous literature has suggested mechanisms for the development of rhabdomyolysis in malarial infection, including inflammatory processes, direct effect of parasite accumulation, and drug-induced toxicity. Our case further implicates antimalarial therapy as a cause of rhabdomyolysis and increases awareness of myoglobin cast nephropathy as a potential complication of malaria.

1. Introduction

Rhabdomyolysis is a rare complication of malarial infection that results from skeletal muscle injury and the release of intracellular muscle contents into systemic circulation. Causes of rhabdomyolysis include trauma, substance abuse, infections, and medications [1]. Rhabdomyolysis may cause acute renal injury, a feature of which is the presence of myoglobin casts [2] formed from large amounts of myoglobin accumulating in the renal tubules and precipitating with Tamm-Horsfall protein [3]. In one retrospective study, 6% of the myoglobin cast nephropathy cases were due to infection [4], and malarial infection has been associated with rhabdomyolysis-induced acute renal failure in an even smaller subset of cases reported in the literature. Herein, we present a unique case of myoglobin cast nephropathy which occurred during treatment for malarial infection and in which renal biopsy played a significant role in diagnosis.

2. Case Presentation

A 60-year-old man with a past medical history of asthma, rheumatoid arthritis being treated with methotrexate, hypertension, and no known history of chronic renal disease presented to the emergency department with generalized weakness, intermittent fevers, nausea, vomiting, and mild abdominal pain one day after returning to the United States from a trip to Nigeria. Two days prior to leaving Nigeria, he noted the onset of intermittent fevers, was diagnosed with malarial infection, and was subsequently started on artemether-lumefantrine 80 mg/480 mg without any symptomatic improvement. The patient discontinued his artemether-lumefantrine course within the first two days of symptom onset. There was no known concurrent use of herbal supplements or plant extracts. Upon presentation to our emergency department three days after the initial symptom onset, the patient was hemodynamically stable and had an unremarkable physical

exam. Complete blood counts, *Plasmodium* species antigen blood tests, *Plasmodium falciparum* antigen blood tests, light microscopy of thick and thin blood smears, respiratory infection PCR panel, and hepatitis viral antigen and antibody panel were all unremarkable. These results indicated possible but unconfirmed suppression of malarial infection by the time of testing. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes were elevated at 1,331 U/L and 259 U/L, respectively (AST: normal range = 10–50 U/L; ALT: normal range = 5–50 U/L). Serum creatinine was elevated at 2.57 mg/dL and blood urea nitrogen was elevated at 29 mg/dL (normal range = 8–23 mg/dL), indicating intrinsic acute kidney injury (AKI). He had an elevated protein/creatinine ratio of 74 mg/g (normal range = 0–30 mg/g). Abdominal ultrasound and computed tomography (CT) were unremarkable for abdominal pathology, but both abdominal CT and chest X-ray revealed focal interstitial thickening and ground-glass infiltrates consistent with pneumonia in the left lower lung lobe.

The patient was admitted and immediately started on atovaquone-proguanil for possible malaria, and the following day, he was initiated on azithromycin and ceftriaxone for suspected pulmonary infection and intravenous fluids for acute kidney injury. On the third day of the admission (two days after initiation of treatment and six days since symptom onset), the patient was found to have rhabdomyolysis with creatine kinase (CK) level above 19,000 U/L and worsening liver function tests, prompting aggressive hydration with an increase in 5% dextrose, 0.45% sodium chloride intravenous fluid infusion rate from 75 mL/hr to 150–175 mL/hr.

In light of worsening acute kidney function and proteinuria, a percutaneous renal needle biopsy was done. The biopsy showed 20 glomeruli, one of which was obsolescent. Glomerular tufts were slightly enlarged and were without increased cellularity, segmental sclerosis, subepithelial spikes on Jones silver stain, thrombi, or necrosis. No significant interstitial inflammatory infiltrates or edema were present. Blood vessels showed mild arteriosclerosis and were without vasculitis. There was evidence of acute tubular injury consisting of tubular epithelial attenuation and flattening with marked tubular cell proliferation, and Mib-1 immunohistochemical stain showed increased proliferative activity of tubular cell nuclei. There were many tubular granular eosinophilic casts (Figures 1(A) and 1(B)) which stained positively for myoglobin on immunohistochemistry (Figure 1(C)). Immunofluorescence was weakly positive for immunoglobulin M (IgM) and complement component 3 (C3) in glomeruli (1+ segmental mesangial staining each) and negative for immunoglobulin G (IgG), immunoglobulin A (IgA), complement component 4 (C4), complement component 1a (C1q), Kappa light chain, and Lambda light chain. Electron microscopy was essentially unremarkable in glomeruli and did not show podocyte foot process effacement, electron-dense deposits, or glomerular basement membrane reduplication. There was nodular hyaline deposition in one small artery. Clumps of very dark acellular material were seen filling tubules, corresponding to the myoglobin casts seen on light microscopy (Figure 1(D)).

Over his seven-day hospital course, the patient's acute kidney injury began to resolve without the need for dialysis and he completed the standard course of atovaquone-proguanil. Prior to discharge, most laboratory values had improved. Creatinine was 3.68 mg/dL from a peak of 4.45 mg/dL, blood urea nitrogen (BUN) was 43 mg/dL from a peak of 61 mg/dL, AST was 667 U/L from a peak of 2,638 U/L, and ALT was 398 U/L from a peak of 697 U/L. CK remained >19,000 U/L. He was discharged after a nine-day hospital stay with a seven-day course of oral levofloxacin to cover for the initially suspected infectious pneumonia.

3. Discussion

The first reported case of acute rhabdomyolysis associated with malarial infection was by De Silva et al. in 1988 [5]. Several patients since then were reported to develop rhabdomyolysis in association with malarial infection, with [6–18] or without [19–21] the development of renal impairment. Infectious malarial species in this setting included *Plasmodium falciparum* [7–9, 11–15, 18, 20, 21], *Plasmodium knowlesi* [19], and *Plasmodium vivax* [10, 17]. Figure 2 summarizes the previously reported cases of rhabdomyolysis in malarial infection.

There are several possible mechanisms by which rhabdomyolysis may occur in malarial infection. A direct cause of muscle injury may be the accumulation of malarial parasites in skeletal muscle. This hypothesis is supported by the findings that increasing levels of malarial parasitemia correlated with serum myoglobin and CPK levels in a study of 58 Gambian children with malaria [22] and by a study confirming the presence of malarial parasites in skeletal muscle tissue in 36 patients with cerebral falciparum malaria [23]. The patient's elevated ALT and acute kidney injury present on admission support the hypothesis that rhabdomyolysis was a result of the malarial infection itself.

The inflammatory response in malarial infection may also cause or contribute to the development of rhabdomyolysis. Muscle biopsy in a patient with malarial infection showed increased numbers of CD4-positive T-lymphocytes, which are known to produce tumor necrosis factor alpha (TNF- α), interferon, and cytokines [13]. High-grade fever in malaria may also lead to the release of TNF- α , a known myotoxin [24]. The subsequent development of renal failure secondary to myoglobinemia and deposition of myoglobin in the kidney may be exacerbated by an inflammatory response in the kidney, as was seen on renal biopsy in one case [13]. Interestingly, in our case, no significant interstitial inflammation was seen on renal biopsy, thus showing that renal impairment may still follow rhabdomyolysis without a significant inflammatory response in the kidney itself.

Our patient was found to have rhabdomyolysis after antimalarial therapy and no detectable malarial infection on admission, raising the possibility that rhabdomyolysis could have occurred as an effect of antimalarial therapy. *Plasmodium* species antigen blood tests, *Plasmodium falciparum* antigen blood tests, and thick and thin blood smears were used to screen the patient for malarial infection on admission and were all negative for active parasitemia. Light

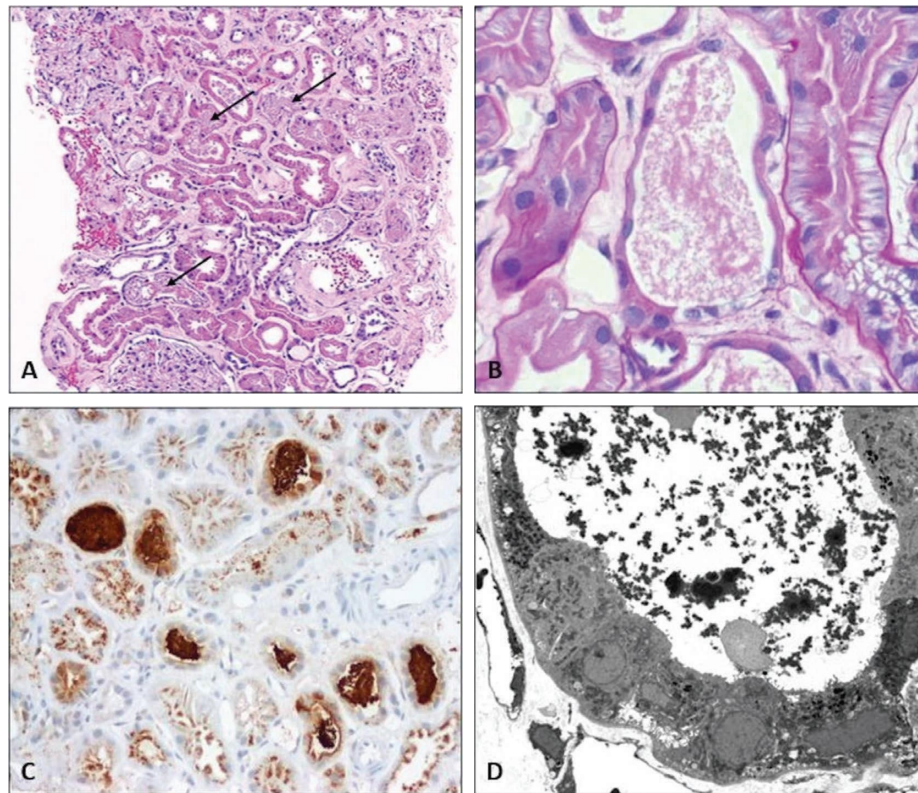


FIGURE 1: (A) Kidney biopsy showing acute tubular injury with numerous granular casts (arrows) (H&E stain, 100x). (B) PAS-stained section showing a tubule containing granular cast material (PAS, 600x). (C) Multiple myoglobin casts staining positively by immunohistochemistry (IHC-stained section, 200x). (D) Very dark acellular material within tubules corresponding to myoglobin casts (electron microscopy photomicrograph, 3000x).

microscopy of thick and thin blood smears is considered the gold standard for diagnosis, with thick smears able to detect a parasite load as low as 10–50 trophozoites/ μ L, while the sensitivity of antigen testing is limited for parasite loads below 100 parasites/ μ L [25]. Previous case reports suggest treatment with antimalarial drugs as a potential cause of rhabdomyolysis, including a case of a 36-year-old man who started antimalarial prophylaxis with mefloquine prior to a trip to Nigeria [6]. After several weeks of taking this medication, he developed malaise and fatigue, and a workup revealed elevated creatine kinase at 2,978 U/L and elevated creatinine at 1.24 mg/dL [6]. Medical management with fluid resuscitation lowered his creatine kinase levels and normalized creatinine [6]. Another antimalarial drug, chloroquine, is also hypothesized to cause muscle damage by two mechanisms. Chloroquine accumulation over time can lead to vacuolar myopathy, a condition in which autophagic vacuoles develop in muscle tissue on the ultrastructural level [26]. In addition, parasite killing by the drug can exacerbate inflammatory response, resulting in six documented cases of toxic myopathy and neuropathy after long-term administration of chloroquine over several years [17]. Our patient took artemether-lumefantrine and atovaquone-proguanil, which have not previously been implicated as a cause of rhabdomyolysis occurring in the setting of malarial infection. In addition, some antimalarial plant extracts (*Sida acuta* (PSA), *Malvaceae*, and *Enantia polycarpa*) used in

conjunction with the antimalarial drugs artesunate-amodiaquine and artemether-lumefantrine have been noted to cause renal, hepatic, and neurological damage [27] though the use of these supplements was not noted in our patient.

Another explanation of rhabdomyolysis occurring following the resolution of detectable parasitemia is that myoglobin can influence renal function by precipitating in the loop of Henle [23]. Myoglobin is not detectable in the urine until serum concentrations are greater than 15,000 U/L, allowing for an insidious onset and late presentation of renal symptoms [23]. This emphasizes the importance of recognizing the possibility of rhabdomyolysis and renal impairment in patients even after the resolution of malarial infection.

Secondary factors in specific cases may also contribute to the development of rhabdomyolysis and renal injury in malaria. A case was reported of a football player who traveled to Nigeria, reported noncompliance with malarial prophylaxis, and developed rhabdomyolysis and renal failure in the setting of *Plasmodium falciparum* malarial infection. The authors of this report concluded that rhabdomyolysis and renal failure in this patient were a consequence of a combination of malarial infection with exertional effects [7]. Other secondary factors that may contribute to the development of renal failure in malarial infection are hypovolemia, excessive hemolysis,

Ref #	Publication (year)	Age/ Sex	Presenting symptoms	Lab Values	Species of malaria	Treatment	Rhabdo myolysis	Renal injury/ dialysis needed?	Renal/muscle biopsy done?	Complications	Exacerbating Factors	Other notes
[6]	Cornelli (2016)	36/ M	Malaise, fever/ chills	Cr: 1.24 mg/dL CK: 2,978 U/L AST: normal ALT: normal	No malaria	IV hydration	Y	Y/N	N/N		Mefloquine prophylaxis	
[7]	Lutz (2019)	18/ M	Malaise, fever/ chills, myalgias, dark urine	Cr: 1.7 mg/dL BUN: 11 mg/dL CK: 43,102 U/L AST: 1063 U/L ALT: 196 U/L	<i>Plasmodium falciparum</i>	Atovaquone-proguanil	Y	Y/N	N/N		Exercise	
[8]	Prabakar (2014)	22/ M	Fever/ chills, myalgias, nausea/ vomiting, oliguria/ anuria	Cr: 10.6 mg/dL CPK: 9,170 U/L Mb: 375 mg/dL	<i>Plasmodium falciparum</i>	Antimalarial drugs	Y	Y/Y (HD)	N/N			
[9]	Yang (2012)	49/ M	Fever/ chills, myalgias	CK: 99 U/L Mb: 17.5 U/L AST: 84.4 U/L ALT: 113.4 U/L	<i>Plasmodium falciparum</i>	IV fluids IM sodium diclofenac for dengue fever < 7 days	Y	Y/Y (CRRT)	N/N	Myoglobinuria		Blood film findings: Plasmodium falciparum (in 40% of erythrocytes)
[10]	Siqueira (2010)	16/ M	Fever/ chills, myalgias	CK: 29,400 U/L AST: 9,072 U/L ALT: 2,198 U/L LDH: 2,125 U/L	<i>Plasmodium vivax</i> **	IV fluids IM sodium diclofenac Chloroquine → Artesunate + Primaquine Clindamycin	Y	Y/Y (HD)	N/Y	Myoglobinuria	Chloroquine and primaquine (myalgias worsened after 1 dose)	
[11]	Mishra (2010)	N = 12	Malaise, fever/ chills, myalgias, dark urine; seizures (N = 3)	Cr: 2.4 mg/dL CK: elevated	<i>Plasmodium falciparum</i>	IV fluids Quinine dihydrochloride injections	Y	Y/N	N/N			
[12]	Reynaud (2005)	20/ F	Fever/ chills, myalgias, nausea/ vomiting, oliguria/ anuria	CK: 71,940 U/L AST: elevated ALT: elevated Mb: >20K U/L	<i>Plasmodium falciparum</i>	IV chloroquine (24 mg/kg/day) IV hydration	Y	Y/N	N/N	Vision loss	Recent travel to Madagascar, no ppx	
[13]	Srinath (2000)	17/ M	Malaise, fever/ chills, myalgias, nausea/ vomiting, dark urine, oliguria/ anuria	Cr: elevated BUN: elevated CK: 10,254 U/L	<i>Plasmodium falciparum</i> ***	Fansidar Chloroquine Quinine Aggressive hydration & alkalization	Y	Y/Y (HD)	Y/Y	Hematuria Myoglobinuria		Renal biopsy IHC: Luminal material and casts positive for myoglobin. Muscle biopsies: Patchy inflammation in perimuscle. Inflammation predominantly around blood vessels.
	First author (year)	Age/ Sex	Presenting symptoms	Reported lab values	Species of malaria	Treatment	Rhabdo myolysis	Renal injury/ dialysis needed?	Renal/muscle bx done?	Complications	Exacerbating Factors	Notes
[14]	Jacobs (1997)	25/ X	Mental confusion, worsening vision, oliguria	—	<i>Plasmodium falciparum</i>	Plasma exchange Anti-malarial therapy	Y	Y/Y	N/N	Edema Impending gangrene Vision loss Hypotension Advanced DIC		
[15]	Allo (1997)	32/ F	Fever/ chills	Cr: elevated CK: 127,800 U/L UA: tubulopathy, heme pigment	<i>Plasmodium falciparum</i>	IV quinine	Y	Y/N	N/Y	Neurological deterioration Diffuse cerebral edema on CT	After returning from Ivory Coast (48 hrs); no ppx	Muscle biopsy: nonspecific myonecrosis.
[16]	Meier (1995)	N = 12	—	CK: >1000 U/L	unspecified	Quinine HCl Doxycycline (57%) Clindamycin (25%) Deferoxamine (25%)	4/12	Y/Y (HD: 6/12)	N/N	Coma (16%) DIC (33%) Acidosis (8%) Respiratory distress (42%)	No ppx	Mortality: 42%
[17]	Poels (1993)	32/ M	Malaise, fever/ chills	CK: 85,500 U/L AST: 10,052 U/L ALT: 446 U/L LDH: 4,228 U/L	<i>Plasmodium vivax</i>	Chloroquine sulfate 1500 mg base total in 3 days. IV Mannitol	Y	Y/Y (HD)	N/Y	Proteinuria Myoglobinuria Hypotension Respiratory failure Cardiomyopathy Metabolic acidosis		Muscle biopsy: Extensive muscle necrosis. Second muscle bx (4 weeks after attack) showed myoadenylate deaminase deficiency.
[18]	Taylor (1992)	18/ M	Malaise, myalgias	Cr: high BUN: high CK: 73,000 U/L	<i>Plasmodium falciparum</i>	Quinine sulfate PYR-sulfadoxine	Y	Y/Y (PD)	N/N	Proteinuria, Increased free hemoglobin	Recent travel to Gambia, no ppx	
[19]	Takaya (2018)	68/ M	Fever/ chills, myalgias, dark urine	Cr: 1.2 mg/dL CK: 24,940 U/L	<i>Plasmodium knowlesi</i>	IV fluids AM-LUM x 3 days	Y	N/N	N/N		Travel to Japan from Philippines	Blood film findings: malarial parasites (low count)
[20]	O'Donnell (2006)	N = 100	Dark urine	Unknown	<i>Plasmodium falciparum</i>	Unknown	N	N/N	N/N	Myoglobinuria		- 1 median plasma myoglobin in children with hematuria 1 median plasma myoglobin concentration in children with cerebral malaria, hyperlactatemia, mortality
[21]	Knochel (1993)	32/ M	Fever/ chills, myalgias, nausea/ vomiting, syncope	Cr: 1.0 mg/dL BUN: CK: 32,000 U/L	<i>Plasmodium falciparum</i>	IV quinine, PO quinine Mannitol, IV hydration PYR-sulfadoxine Tetracycline	Y	N/N	N/N	Hematuria Psychosis	Recent travel to Nigeria	

FIGURE 2: Summary of cases of rhabdomyolysis associated with malarial infection noted in previous literature. *Bx: biopsy, M: male, F: female, Cr: creatinine, BUN: blood urea nitrogen, CK: creatine kinase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Mb: myoglobin, Y: yes, N: no, IV: intravenous, PO: per os (oral), CRRT: continuous renal replacement therapy, HD: hemodialysis, PD: peritoneal dialysis, CT: computed tomography, DIC: disseminated intravascular coagulation, AM-LUM: artemether-lumefantrine, PYR: pyrimethamine, IHC: immunohistochemistry, ICU: intensive care unit, RBC: red blood cells, Ppx: prophylaxis, ** thick blood smear negative for *Plasmodium* species on day 3 of antimalarial treatment, and *** in 250 of 1000 erythrocytes.

disseminated intravascular coagulopathy, and impaired microcirculation due to high levels of parasitized erythrocytes [28].

Of all the reports of rhabdomyolysis in malarial infection in the literature, only another one to our knowledge reported on findings of a renal biopsy [13]. In our case, a renal biopsy confirmed myoglobin-induced injury as the cause of acute renal failure. This is especially important when one considers the many other causes and factors that may lead to renal failure in malarial infection [29]. Renal biopsy may also rule out other causes of acute kidney injury that may be unrelated to malarial infection, including glomerulonephritis after immune complex deposition, which was also ruled out in our case given negative findings on immunofluorescence microscopy.

In conclusion, we present a rare case of myoglobin cast nephropathy in malarial infection. Our case highlights the important contribution of renal biopsy in reaching the diagnosis, possibly implicating antimalarial therapy as the cause of rhabdomyolysis, and focuses on awareness of myoglobin-induced renal failure as a complication of malaria [30].

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this case review.

Disclosure

We confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere. The manuscript was already published as an abstract based on the link <https://meridian.allenpress.com/aplm/article/144/9s1/e2/443992/Abstracts-and-Case-Studies-for-the-College-of>.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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