Acute tubulointerstitial nephritis due to severe malaria

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Abstract

Malaria is a common tropical disease in America, with the ability to affect multiple organs; this includes acute kidney injury, mostly related to acute tubular necrosis. However, other kidney disease processes secondary to the infection have been reported. We present the case of an adult male from an endemic area who was admitted for severe *Plasmodium vivax* malaria with severe kidney involvement requiring renal replacement therapy. On kidney biopsy, he was found to have acute tubulointerstitial nephritis, which improved after glucocorticoid treatment. (Acta Med Colomb 2024; 49. DOI: https://doi.org/10.36104/amc.2024.3055).

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Introduction

Malaria is a public health problem in endemic countries like Colombia and is associated with significant morbidity and mortality (1). Kidney involvement is recorded in approximately 30% of cases, and its mortality may reach 15-45% in adult patients with no prior immunity (2). This phenomenon is reported more often in *Plasmodium falciparum* (65%) malaria infections than in *Plasmodium vivax* (30%) infections. Although chronic glomerular signs and symptoms are described, its most common clinical presentation is kidney injury secondary to acute tubular necrosis (3). We present the case of a patient with severe *Plasmodium vivax malaria who developed acute kidney injury secondary to tubulointerstitial nephritis (TIN), with a good response to glucocorticoids, an unusual presentation of malaria with kidney involvement*.

Case report

This was a male patient in his 30s who was a carpenter, residing in a rural area of Colombia, with no significant medical history. He complained of four days of fever, chills, nausea, myalgia and arthralgia which left him bedridden, in addition to generalized jaundice. He was admitted in poor general condition, with hypotension, a fever, dehydration, jaundice, palpable splenomegaly, no neurological abnormalities and no evidence of active bleeding.

His initial laboratory exams were notable for a complete blood count without leukocytosis, mild normocytic anemia (hemoglobin: 10.6 g/dL), severe thrombocytopenia (platelets: 14,000 mm^3), abnormal kidney function (creatinine: 3.17 mg/dL, urea nitrogen: 48 mg/dL), elevated acute phase reactants (erythrocyte sedimentation rate: 120 mm/hora – C-reactive protein: 34 mg/L) and hyperbilirubinemia (total bilirubin: 23 mg/dL – direct bilirubin: 16 mg/dL). Since he reported living in an area endemic for malaria, a thick smear was taken which reported *Plasmodium vivax* schizonts, trophozoites and gametocytes (10,731 parasites/uL of blood), with dengue coinfection documented through positive IgM serology. Hepatitis B, hepatitis C, HIV and leptospira coinfections were ruled out. A liver and bile duct ultrasound reported hepatosplenomegaly.

The patient was admitted to the intensive care unit with a diagnosis of severe malaria and was treated with crystalloids, with hemodynamic improvement and resolved hypotension. He did not require vasopressor support, and antimalaria treatment was given as established in the national guidelines (4), with 180 mg of intravenous artesunate at 0, 12, and 24 hours. Since he was able to take things by mouth, on his second day in the hospital he was started on artemether/lumefantrine at 80 mg/480 mg per dose at 0, 8, 24, 36, 48 and 60 hours, along with primaquine 20 mg/day for 14 days.

Although the follow up thick smear at 72 hours was negative for hemoparasites, the patient had elevated nitrogen again on the third day, which did not respond to medical treatment. This led to signs of pulmonary fluid overload, metabolic acidosis and elevated blood urea nitrogen with an indication for hemodialysis on day four of hospitalization. The urinalysis showed no urinary sediment, and a kidney and urinary tract ultrasound reported normal-sized kidneys with no evident structural abnormalities. Therefore, the initial diagnostic impression was acute tubular necrosis secondary to severe malaria.

Without having recovered kidney function, he devel-

oped anemization with no clear cause between hospitalization day 6 and 8. A simple abdominal tomography showed a subcapsular hematoma in the spleen without active bleeding, and therefore the general surgery service adopted a "wait and see" strategy. Its etiology was associated with the severe thrombocytopenia with which the patient was admitted and which resolved on approximately day 7 of hospitalization, with no recurrence of bleeding phenomena or anemization.

During the second week of hospitalization, he continued to have nonoliguric kidney failure requiring hemodialysis (Figure 1). Further studies documented antinuclear antibodies with 1:160 titers and a homogenous pattern (AC-1), negative antineutrophil cytoplasmic antibodies (ANCAs), negative total extractable nuclear antigen antibodies (ENAs), a C3 fraction of complement at 120 mg/dL and C4 at 19.2 mg/dL and 24-hour proteinuria of 1.1 gr/dL. Since there was no clear diagnosis, a kidney biopsy was performed which showed mixed acute TIN and acute tubular necrosis (Figure 2) changes. He was started on glucocorticoid treatment, receiving 500 mg of intravenous methylprednisolone every 24 hours for three days and then continuing with prednisolone at 1 mg/kg/day (60 mg). He had a good clinical response and did not require new hemodialysis sessions after day 22 of his hospital stay, with steadily decreasing nitrogen levels. The patient was discharged with a gradual steroid taper plan and outpatient follow up by nephrology.

Discussion

Acute kidney injury is a common complication of severe malaria, with repercussions in terms of mortality and chronic kidney disease sequelae. Despite these clinical implications, its pathophysiology is not fully understood. The most widespread hypothesis is renal hypoperfusion secondary to cytoadherence and sequestration processes caused by the parasite in the kidney microcirculation, added to hypovolemia secondary to increased insensible losses, poor oral intake or vomiting. Ultimately, the hemodynamic outcome will lead to acute tubular necrosis, the most frequent cause of malaria-induced acute kidney injury (5).

In the case we have presented, it is important to highlight the role of the immune system, which is thought to have an exaggerated proinflammatory response that contributes to the pathology of the disease. The evaluated hypothesis explains that the characteristic hemolysis in malaria releases molecules from the host (like the heme group) and the parasite which activate the immune system and inflammatory response, triggering kidney damage through both humoral and cellular pathways (6).

In this same vein of dysregulated inflammation, it is consistent to think of the pathological association of TIN with malaria, as this has already been documented in other infectious diseases, including protozoans close to *Plasmodium spp, like Babesia spp* (7,8). As far as malaria is concerned, TIN has already been documented in murine (9) and primate (10) models, but very few cases have been reported in humans.

In the literature review, there were two reports of TIN in severe malaria (11,12), both associated with glomerular involvement (minimal change and focal segmental glomerulosclerosis) caused by *Plasmodium falciparum* in Africa, which were sufficiently severe to require hemodialysis. From a therapeutic perspective, one of the patients

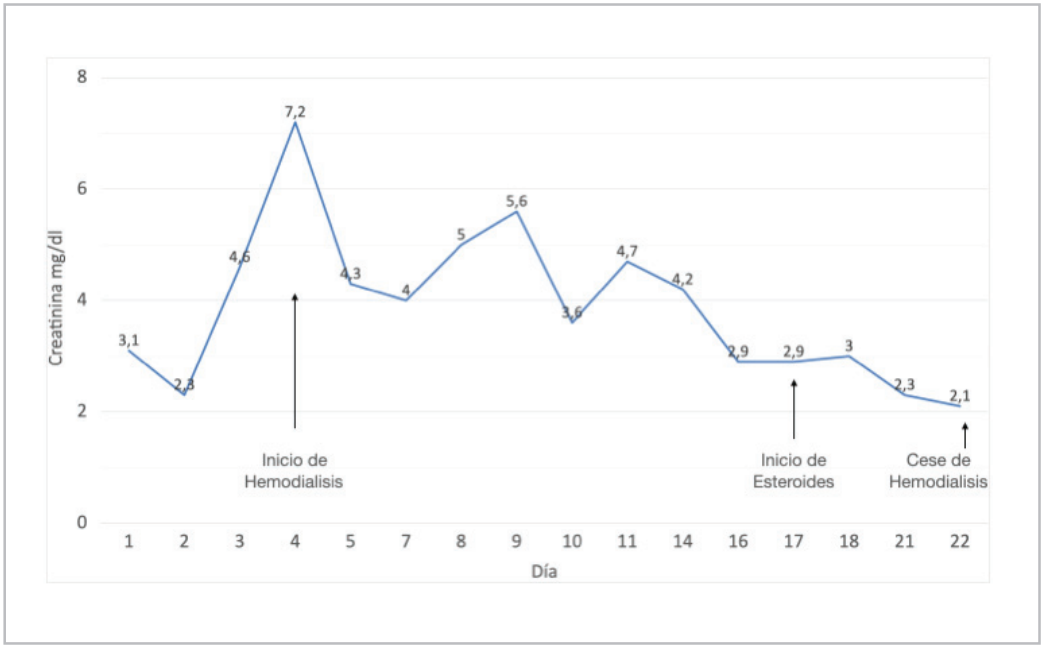

Figure 1. *Creatinine behavior over time during the hospital stay.*

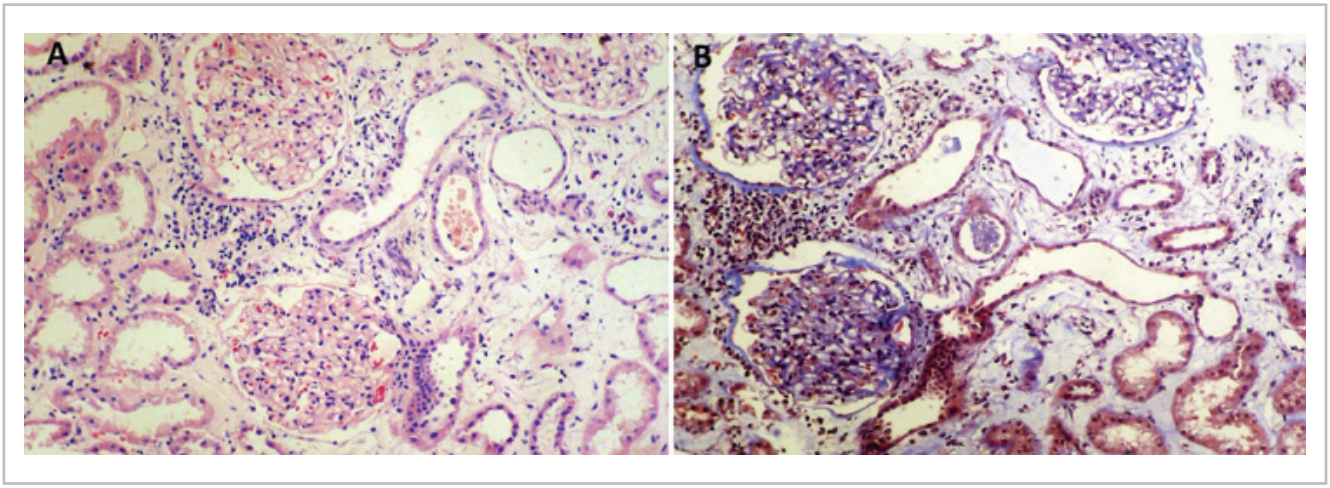

Figure 2. *Kidney biopsy: Hematoxylin-eosin staining at 200x (A) and Masson's trichrome staining at 200x (B). Renal interstitium showing edema and multiple foci of mononuclear inflammatory infiltrate with diffuse eosinophils, without fibrosis or tubular atrophy (acute tubulointerstitial nephritis changes), as well as dilated tubules with cellular desquamation, basement membrane denudation and hyaline and granular casts (acute tubular necrosis changes).*

improved early with antiparasitic treatment (11), and was able to discontinue renal replacement therapy. In the second case, despite adding a three-month cycle of steroids, the patient was unable to recover kidney function (12).

As far as we know, the case we present is the first report of TIN associated with severe *Plasmodium vivax* malaria, the main pathogen found in Colombia. After ruling out other potential causes of TIN like medications, infections and autoimmunity, and knowing that pathophysiological plausibility has already been shown in animal models, we can report a probable association between TIN and severe *Plasmodium vivax* malaria.

Transferring the experience obtained with drug-induced TIN (13), due to the severity of the kidney involvement shown by the persistent need for hemodialysis even with completed antiparasitic treatment, the patient was started on glucocorticoid treatment. Our patient progressed favorably, tolerating the discontinuation of hemodialysis and showing a persistent nitrogen reduction to what was recorded during hospitalization. This contribution to medical literature provides not only a potential diagnosis of acute kidney injury in malaria, but also a treatment to consider.

Conclusions

Within the spectrum of acute kidney involvement in *Plasmodium vivax* malaria, it is important to consider TIN as a cause. In addition to antiparasitic treatment, steroids will probably contribute to improving the prognosis of patients with TIN. In the future, more biopsies in malaria-induced acute kidney injury could have an impact on clarifying the pathophysiology, as well as providing earlier treatment to modify the morbid course of a severe complication of malaria.

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