Malaria Journal

CASE REPORT

Open Access

Kidney involvement in *Plasmodium falciparum* infection in a pregnant patient

Octavio René García-Flores[1], Mayra Eugenia Avilés-Ramírez[1], Sabrina Vianey Castillo-Paniagua[1], Edgar Misael Pérez-Jiménez[1], José Carlos Gasca-Aldama[2], María Virgilia Soto-Abraham[3], Juan Carlos Bravata-Alcántara[4], Juan Manuel Bello-López[5], Giorgina Barbara Piccoli[6] and Enzo Vásquez-Jiménez[1*]

Abstract

Background The course of kidney function and outcomes of severe malaria infection in pregnant women is poorly understood. The indications for renal replacement therapy in pregnant patients with AKI are similar to the general population. This is the case of a pregnant patient with severe *Plasmodium falciparum* infection that caused cerebral malaria, acute kidney injury (AKI) who required renal replacement therapy and kidney biopsy during her hospitalization.

Case presentation A 29-year-old pregnant woman from Equatorial Guinea was admitted to the hospital with haemolytic anaemia, hyperbilirubinaemia and thrombocytopenia. During hospitalization, a thick blood smear was performed where parasitaemia by *P. falciparum* were observed and confirmed by real-time PCR assay. The patient developed cerebral malaria secondary to an ischaemic-type cerebral vascular event, hypotension and severe. After confirming diagnosis of *P. falciparum* infection, artesunate, artemether/lumefantrine and primaquine were started. Kidney biopsy revealed an active tubulointerstitial nephritis with acute tubular lesion and pigment tubulopathy with negative immunofluorescence. After CVVHDF, the patient received intermittent haemodialysis until the recovery of kidney function. After discharge, follow-up was carried until the successful resolution of the pregnancy by cesarean delivery and not shown deterioration in kidney function or proteinuria.

Conclusion In this case, intensive dialysis was started and dialysis intensity progressively reduced when kidney function improved. Due to the evolution of kidney function, a kidney biopsy was performed which showed tubulointerstitial nephritis as a manifestation of the infection. While the kidney biopsy was of interest for discriminating between tubular and glomerular involvement, the availability of placental biomarkers (sflt1-PlGF) would have been of help for ruling out preeclampsia and placental damage. The multidisciplinary approach to AKI during pregnancy should be the rule, with diligent care of maternal–fetal well-being during pregnancy and monitoring of kidney function after delivery.

Keywords Kidney biopsy, Pregnancy, Acute kidney injury, Hemodialysis

*Correspondence:
Enzo Vásquez-Jiménez
enzo.vas.ji@gmail.com
Full list of author information is available at the end of the article

Background

Malaria is an infectious disease caused by *Plasmodium* spp. that is transmitted by the *Anopheles* mosquito [1]. The clinical presentation spams from non-specific symptoms, such as fever, headache, muscle pain, to life-threatening pictures [2]. In Mexico, the endemic species is *Plasmodium vivax,* which usually causes a mild illness. The number of autochthonous cases has decreased; however, imported cases of malaria are becoming more frequent due to the effects of global warming and migratory flows [3]. *Plasmodium falciparum* infections are infrequent, but may cause severe disease.

Acute kidney injury (AKI) is a rare and serious manifestation of *P. falciparum* infection. In fact, the presence of AKI is an independent predictor of mortality and the development of chronic kidney disease. Various mechanisms can cause AKI in patients with *P. falciparum* infection, including haemodynamic effects associated with parasitaemia, parasite sequestration, endothelial dysfunction, intravascular haemolysis, oxidative stress and immunological damage. Malaria-associated AKI is usually oliguric. All kidney structures may be involved, with more frequently acute tubular necrosis (ATN) and less commonly interstitial nephritis and glomerulonephritis [4, 5].

Pregnancy increases susceptibility to malaria and its complications and *P. falciparum* infection, with sequestration in the placental vessels, is associated with miscarriages, placental insufficiency, pre-term delivery, and stillbirth, with fetal loss occurring in up to 15% of the cases [6].

This is the case of a pregnant patient with severe *P. falciparum* infection that caused cerebral malaria, AKI who required renal replacement therapy secondary to interstitial nephritis confirmed by kidney biopsy.

Case report

A 29-year-old pregnant woman from Equatorial Guinea was admitted, during the 17th gestational week of her first pregnancy, to the Hospital Juárez de México because of constant and intense abdominal pain, nausea, vomiting, jaundice, fever, chills, myalgia, arthralgia and cough that began two weeks earlier. The patient arrived in Mexico from her country of origin one week prior to admission. She reported previous vaccination for SARS-CoV-2, influenza and yellow fever.

At admission, she reported no previous complication in her pregnancy (17 weeks and 5 days). The tests performed showed anaemia (hemoglobin 8.9 g/dL, platelets 10×10^9 /L, white blood cells 10×10^9/L), high total bilirubin (21 mg/dL, direct: 15 mg/dL). Alanine aminotransaminase (64 UI/L), aspartate aminotransaminase (27 UI/L), blood urea nitrogen (BUN 21 mg/dL) and creatinine (0.7 mg/dL) were in the usual ranges. No evidence of SARS-CoV-2 infection was found. Urinalysis showed isomorphic erythrocytes, granular and pigmented casts. Complement C3 was normal and C4 was low (3 mg/dL), antinuclear antibodies and reactivity against extractable nuclear antigens were negative and there was no sign of present or previous infection from HIV, Hepatitis B and C. Haemolytic anaemia was confirmed by Coombs test. Considering the area of origin and the haemolytic anaemia, a thick blood smear was performed and *P. falciparum* parasitaemia was observed (Fig. 1). A real-time PCR assay was performed for confirmation and identification of the specific *Plasmodium* (*P. falciparum, P. vivax, Plasmodium ovale* and *Plasmodium malariae*) (Fig. S1). After confirming *P. falciparum* infection, artesunate, artemether/lumefantrine and primaquine were started.

Two days after admission the patient needed admission to the ICU due to neurological deterioration,

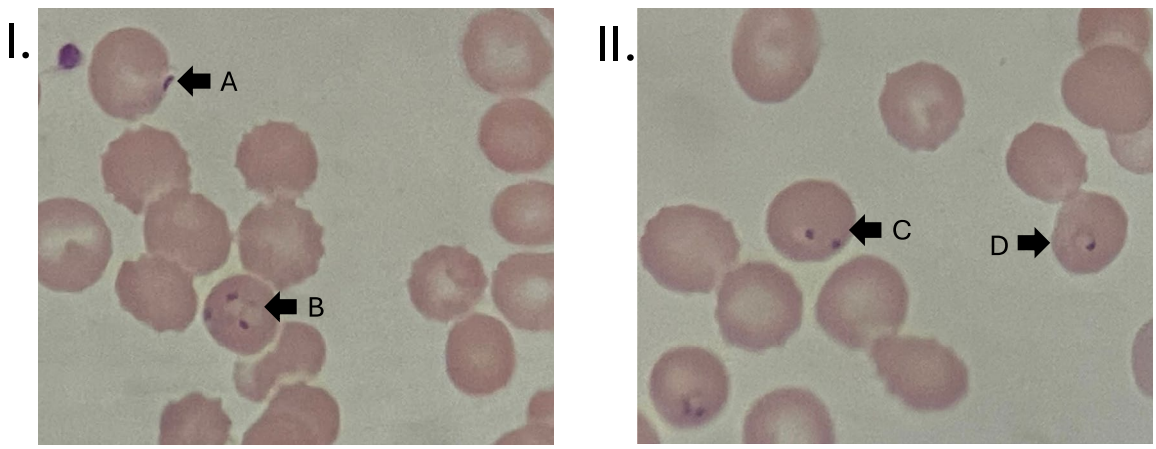

Fig. 1 Detection of *Plasmodium falciparum* by observation of parasites states on thick blood smears of immigrant pregnant patient. I) **A** Marginal form and **B** Triple dotted rings. II) **C** Double dotted rings, and **D** Ring form

hypotension and severe AKI (creatinine 3.7 mg/dL and anuria); nephrotic level proteinuria was observed when she regained some kidney function. Mechanical ventilation, norepinephrine and continuous renal replacement therapy were started. Brain magnetic resonance imaging showed an ischaemic lesion in the corpus callosum. A kidney biopsy revealed an active tubulointerstitial nephritis with tubular epithelial cytoplasm showing brown-colored pigment (Fig. 2).

Twelve days after admission to the ICU, the patient improved and was extubated. Continuous venovenous haemodiafiltration (CVVHDF) was performed for three days in the ICU (Table S1), followed by eight intermittent haemodialysis after ICU discharge, until kidney function recovered (Table S2). The main laboratory data are shown in Fig. S2. During hospitalization, she received blood transfusions and was treated for hypertension with alpha methyldopa 1 g every 8 h and nifedipine 60 mg every 12 h. No signs of placental damage were observed and fetal well-being was confirmed by Doppler ultrasounds and regular growth. The patient was discharged 24 days after admission. After discharge, follow-up was carried out by obstetric and nephrology teams until at 37 weeks of gestation plus one day elective cesarean section allowed for successful delivery of a healthy male baby weighting 2.5 kg (Intergrowth < 1 centile). At the last follow up, the patient had no neurological alteration, her serum creatinine was 0.67 mg/dL without hypertension or proteinuria.

Discussion

Our patient was in her second trimester of pregnancy when she acquired *P. falciparum* infection; prompt AKI treatment was probably the key for the overall favorable

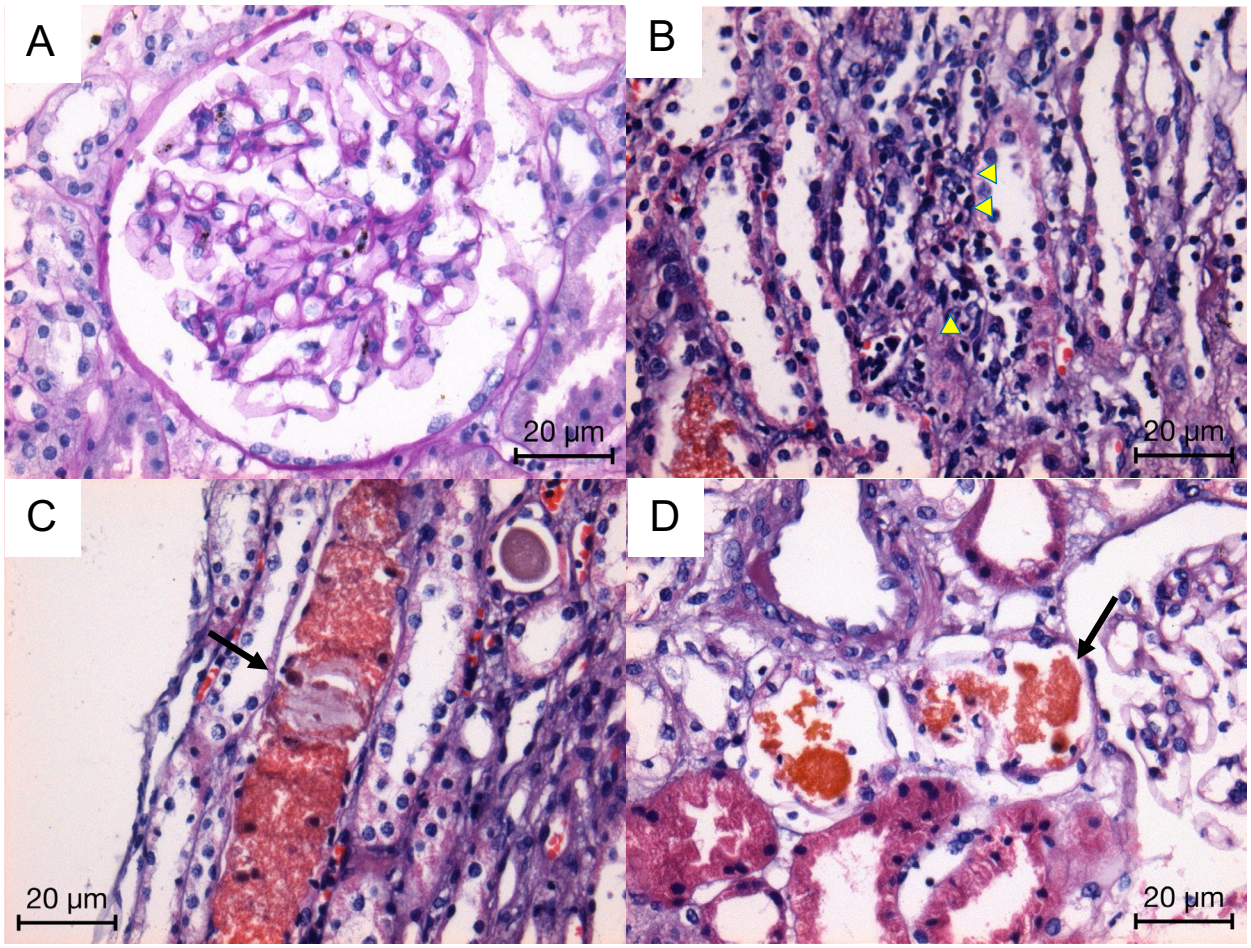

Fig. 2 Kidney biopsy. I. Periodic Acid-Schiff. **A** intact glomerulus without sclerosing lesions, mesangial, endocapillary and extracapillary proliferation. II. Haematoxylin & eosin stain. **B** Interstitial inflammatory infiltrate with eosinophils (arrowheads). **C, D** Tubular dilation with loss of tubular epithelium and multifocal flattening of epithelial cells. There are intratubular pigmented casts with blood cell fragments and proteinaceous and cellular debris (arrows)

outcome. The indications for renal replacement therapy in pregnant patients with AKI are similar to the general population, but the BUN thresholds are presumably lower, as extensively described in patients on chronic haemodialysis [7]. On this account, intensive dialysis was started and dialysis intensity progressively reduced when kidney function improved.

Performing a kidney biopsy is not an easy choice in a pregnant woman [8]. We however felt that characterizing the kidney involvement was important for the clinical management, also considering the high-level proteinuria and hypertension, at a gestational age in which differential diagnosis with preeclampsia was needed. In our case, we found tubulo-interstitial abnormalities, as previously described in malaria (Fig. 2). Ruling out preeclampsia and glomerular disease led to a kidney supportive policy, and anti-malarial treatment ultimately resulted in complete kidney function recovery. Treatment in these cases requires combinations of an artemisinin derivative and a quinine derivative [2]. Artesunate is recommended for severe malaria and can be used during pregnancy when the benefit outweighs the risk. Artesunate has high efficacy greater even in patients with neurological impairment. Both drugs are not cleared by haemodialysis [4].

Cerebral involvement, a severe complication of malaria, is due to microvascular obstruction secondary to sequestration of parasitized erythrocytes in the microvascular bed, impairing blood flow, and leading to inflammation. While not necessarily associated with severe hypertension, in pregnancy these manifestations may call for a differential diagnosis with eclampsia [9].

This is the first reported case of a pregnant patient with severe *P. falciparum* infection with cerebral malaria, proteinuria and AKI requiring renal replacement therapy, whose treatment led to a successful pregnancy outcome. In spite of the success obtained with our multidisciplinary approach, with periodic checks of maternal–fetal well-being during pregnancy and monitoring of kidney function after delivery, this case may also plead for a wider availability of all available tests in high risk pregnancy. While the kidney biopsy was of interest for discriminating between tubular and glomerular involvement, the availability of placental biomarkers (sflt1-PlGF) would have been of help for ruling out preeclampsia and placental damage. Reducing inequalities in care, especially in young and fragile individuals, such as pregnant women, should be always underlined as a priority.

Due to the ease of travels and exchanges in our globalized society, we felt that discussing this case should raise awareness of this infrequent cause of AKI, and of its difficult differential diagnosis in pregnancy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12936-024-05182-9.

Additional file 1.

Acknowledgements
Dr. Vasquez Jiménez & Dr. Bello López are currently supported by "Sistema Nacional de Investigadoras e Investigadores (SNII)" from Consejo Nacional de Ciencias Humanidades y Tecnologías (CONAHCyT), Mexico.

Author contributions
ORGF, EVJ, MEAR, SVCP, EMPJ & JCGA were involved in the design, conduct of the manuscript, interpretation of results and writing of the manuscript. MVSA interpreted the results of the kidney biopsy, JCBA & JMBL were involved with the PCR sequentiation, VHGM performed the microscopic following of parasitemia by thick blood smears across the days/doses of treatment. EVJ, GBP & JMBL review and editing the manuscript. Authors' approval: All authors have read and approved the manuscript in its current state.

Funding
This study was not supported by any sponsor or funder.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The authors declare that they have obtained consent from the patient/relatives discussed in the report.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Nephrology, Hospital Juárez de México, Av Instituto Politécnico Nacional 5160, 07760 Mexico City, Mexico. [2]Intensive Care Unit, Hospital Juárez de México, Mexico City, Mexico. [3]Pathology Department, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico. [4]Molecular Diagnostic Laboratory, Hospital Juárez de México, Mexico City, Mexico. [5]Research Division, Hospital Juárez de México, Mexico City, Mexico. [6]Nephrology, Centre Hospitalier Le Mans, Le Mans, France.

Received: 4 September 2024 Accepted: 8 November 2024
Published online: 18 November 2024

References

1. Coban C, Lee MSJ, Ishii KJ. Tissue-specific immunopathology during malaria infection. Nat Rev Immunol. 2018;18:266–78.
2. Phillips MA, Burrows JN, Manyando C, van Huijsduijnen RH, Van Voorhis WC, Wells TNC. Malaria. Nat Rev Dis Primers. 2017;3:17050.
3. Informe quinquenal de vigilancia epidemiologica de paludismo. Available at: https://www.gob.mx/cms/uploads/attachment/file/886925/PUBLICACION_PALUDISMO_SE_03_2024.pdf. Accessed May 2024.
4. Silva GBD Jr, Pinto JR, Barros EJG, Farias GMN, Daher EF. Kidney involvement in malaria: an update. Rev Inst Med Trop Sao Paulo. 2017;59:e53.
5. Katsoulis O, Georgiadou A, Cunnington AJ. Immunopathology of acute kidney injury in severe malaria. Front Immunol. 2021;12: 651739.
6. Afrifa J, Essien-Baidoo S, Baffour Gyau A, Ephraim RK. Evaluation of renal function in pregnant women with malaria: a case-control study in a mesoendemic area. Obstet Gynecol Int. 2017;2017:6030943.

7. Asamiya Y, Asamiya Y, Otsubo S, Matsuda Y, Kimata N, Kikuchi KA, et al. The importance of low blood urea nitrogen levels in pregnant patients undergoing hemodialysis to optimize birth weight and gestational age. Kidney Int. 2009;75:1217–22.
8. Taber-Hight E, Shah S. Acute kidney injury in pregnancy. Adv Chronic Kidney Dis. 2020;27:455–60.
9. Pesonen A, Ben-Hamouda N, Schneider A. Acute kidney injury after brain injury: does it exist? Minerva Anestesiol. 2021;87:823–7.

Publisher's Note