CASE STUDY

ACUTE KIDNEY DAMAGE AS A COMPLICATION OF MALARIA CAUSED BY PL. MALARIA AND PL. FALCIPARUM: CLINICAL CASES

DOI: 10.36740/WLek202208218

Vadym A. Bodnar, Tetiana M. Kotelevska, Tetiana I. Koval, Serhii L. Ponimatchenko
POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE

ABSTRACT

We have described two clinical cases of severe malaria caused by different pathogens: Pl. falciparum and Pl. malaria, common to which there was a severe course, complicated by acute renal failure and hemolytic anemia.

In a detailed analysis of both clinical cases, Patient 1 had acute kidney damage arose after the increase of anemia and thrombocytopenia, in combination with hemoglobinuria. This shows that the leading mechanism of kidney injure in this case is acute tubular necrosis, due to the toxic effects of free hemoglobin and sequestration in the capillaries of the glomerulus. A Patient 2 had a significant increase of anemia after appears of acute kidney damage; there was no hemoglobinuria, however, significant leukocytosis was observed. It seems, that the leading mechanism in this case is immune-mediated kidney injure or due to hypoperfusion of kidney tubules with the development of acute interstitial nephritis or immune complex glomerular injure with the development of glomerulonephritis, or a combination of them.

A detailed analysis of the described two clinical cases of severe malaria caused by Pl. falciparum and Pl. malaria, respectively, and complicated by acute renal failure and hemolytic anemia, suggests that the pathogenetic mechanisms and severity of kidney damage depend on the type of malaria.

KEY WORDS: malaria, acute renal failure, hemolytic anemia

Wiad Lek. 2022;75(8 p2):2041-2044

INTRODUCTION

Malaria is a transmissible anthroponotic natural focal disease caused by the simplest genus of Plasmodium, which is transmitted through mosquito bites of the genus Anopheles. The disease is followed by paroxysmal fever, hepatosplenomegaly, hemolytic anemia and others manifestations, and also has a tendency to recurrence [1].

Malaria remains a relevant problem in modern infectology taken into account high accrues not only in endemic areas but also worldwide, significant proportion of severe and complicated manifestation as well as the difficulties of early diagnosis and the choice of effective specific therapy [2-4].

According the WHO data, in 2019 229 million cases of malaria where registered and 409 thousand deaths [2]. Acute kidney damage in malaria is characterized for 1.0-4.8% cases in endemic countries, 20-30% in European region, and 20-50% of hospitalized patients [3, 5, 6]. However, one interesting fact is that the population of endemic areas is less prone to complications including kidney damage. In contrast, people from nonendemic areas and those who have lived in nonendemic areas for a long time, have more frequent complications. It may be explain by the weakening or lack of immunity [1].

In this regard, it is desirable to conduct further research with a detailed acquaintance of practitioners with individual clinical cases of malaria.

CASE STUDIES

CLINICAL CASE 1

Patient D, a citizen of Ukraine, 41 years old, engineer, fell ill in September 2019 with the onset of febrile fever, which was accompanied by weakness; jaundice, myalgia, arthralgia, darkening of urine, nausea, vomiting appeared after 2 days; hemogram parameters remained essentially in the normal range (Hb-129, RBC-4,03, PLT-130, WBC-10,2). The patient received symptomatic and pathogenetic therapy in local hospital. Over time, the patient's condition progressively worsened, the amount of urine decreased significantly; periodic eclipses of consciousness appeared, the patient answered questions with a long delay; the intensity of jaundice increased; nausea intensified; episodes of vomiting became more frequent, body temperature reached 40 C with periods of profuse sweating; myalgias and arthralgias become more severe (severe); respiratory rate 26/min; pain in the right hypochondrium and hepatosplenomegaly appeared.

The patient was admitted to a university hospital in serious condition with suspected malaria.

It is known from the history that the patient was on a business trip in Equatorial Guinea from March to September. Immediately before the trip, the patient took a course of prophylactic drugs against malaria. Also, in April, he was admitted to a local hospital in Equatorial Guinea with a

diagnosis of malaria-falciparum, where he received treatment for 3 days and was discharged with improvement.

In complete blood count on Day 1 of the current hospitalization, we observed signs of anemia (RBC-2,44, Hb-83), thrombocytopenia (PLT-74) and normal level of leucocytes (WBC-5,11); in a biochemical analysis – hypoproteinemia (Total protein-50,6), abnormal kidney test (Creatinine-177,1, Urea-42,7), bilirubin metabolism disorder (Total bilirubin-804,4 (conjugated-230,8; nonconjugated-573,6)), signs of mild cytolytic syndrome (ALT – 48.2 U/l, AST – 113.1 U/l), normal amount of glucose (Glucose-3,4 mmol/l). On ultrasound, we observed reactive changes in the liver against the background of hepatosplenomegaly and bilateral nephritis. In parasitological examination (thick-blood film) we observed a hight level of parasitaemia (more than 10 parasites in the field of view); in erythrocytes, Plasmodium falciparum trophozoites in the ring stage were detected. Based on a comprehensive examination the patient was diagnosed with the following: severe malaria-falciparum complicated by acute kidney damage (KDIGO 3), hepatolienal syndrome, metabolic encephalopathy. The patient began to receive etiotropic treatment with the combination of Artemether 80 mg/Lumefantrine 480 mg, 1 tablet 2 times a day.

In addition, in order to correct the indications of nitrogen metabolism, the decision to conduct daily hemodialysis was made (hemodialysis sessions were subsequently carried out for 22 days every 24 hours). On Day 2 of hospitalization, taking into account the patient's serious condition and the increasing signs of anemia and thrombocytopenia (RBS-1,69, Hb-53, PLT-19), it was decided to conduct blood transfusion (blood transfusion sessions were subsequently repeated three more times during the hospitalization period). During treatment, a gradual decrease in parasitemia was found; on Day 8 Pl. falciparum was no longer detectable in blood samples. Starting on Day 9, the patient's condition began to improve with a gradual restoration of urine output.

However, on Day 22 of the current hospitalization the patient condition suddenly got worse (increased body temperature to 39 C, jaundice, hepatosplenomegaly, high parasitaemia (more than 10 parasites in field of view), anemia (RBS-2,08, Hb-54), and signs of acute kidney damage (Creatinine-712). Perhaps these symptoms were indicative of a late recurrence of malaria.

The patient resumed the etiotropic treatment: Artesunate 120 mg. intravenously 1 per day during of 3 days. He received hemodialysis sessions every 24 hours for 5 days, as well as erythrocyte mass (twice). The very next day we determined a decrease in the patient's level of parasitemia; two days later Pl. falciparum was not detected in blood. Over time, the patient's condition improved and at the time of discharge was considered satisfactory.

CLINICAL CASE 2

The patient, a citizen of Mali, 20 years old, a professional sportsman, fall sick in the end of September 2019, when a febrile fever and general weakness appeared. The patient was hospitalized in the university clinic of infection disease in begin October 2019 with the following symptoms: weakness, nausea, vomiting, diarrhea (up to 5 times a day), darkening urine.

According to the medical history it is known that he went home to Mali in September 2019 (he has been living in Ukraine for the last 3 years). General condition is moderate severity, light jaundice, t-36,6 C, breath rate – 20 per minute, slight hepatomegaly and increased bowels peristalsis. The next day the patient's condition worsened; thirst and decreased urine output were determined. The preliminary diagnosis was as follows: "Acute intestinal infection. Viral hepatitis?". Observations in dynamics, examination according to the protocol for the management of patients with intestinal infections, jaundice of unknown origin, as well as microscopy of thick-blood film were recommended.

Additional examination revealed the following changes: in the complete blood count – mild anemia (Hb-118; RBC-3,94), normal amount of platelets (PLT-182), severe leukocytosis (WBC-19,15); in biochemical analysis of blood: Total Protein – 58 g/l, kidney test parameters (Urea-35,7; Creatinine-610), moderate hyperbilirubinemia (Total Bilirubin-123,5 (conjugated-83,2; nonconjugated-40,3), moderate cytolitic syndrome (ALT-55,1; AST-151), Glucose-4,2. Serological markers of viral hepatitis were negative. Parasitological examination (thick-blood film): ring-shaped trophozoitess and shizonts of Pl. malarie (1-10 parasites in the field of view). On ultrasound, we detected hepatomegaly and bilateral nephritis. Final diagnosis: Severe malaria caused by Pl. malarie, complicated by acute kidney damage (KDIGO 3), malarial hepatitis.

Etiotropic treatment was made with Artesunate 120 mg, intravenously once a day during for 3 days. Hemodialysis was prescribed every 48 hours during a week. Feather anemia and thrombocytopenia parameters sequentially increased (RBC-2,63; Hb-74; PLT-46). Subsequently, the patient's condition improved and at the time of discharge was assessed as satisfactory.

DISCUSSION

Thus, above we have described two clinical cases of severe malaria caused by different pathogens: Pl. falciparum and Pl. Malaria, common to which there was a severe course, complicated by acute renal failure and hemolytic anemia.

The pathogenesis of acute kidney injure in malaria has not been fully, however, it is believed that it covers a wide range of mechanisms: hemodynamic (mechanical), immune-mediated and metabolic, which form a complex combination of factors leading to acute renal failure [7-11].

The hemodynamic mechanism, which is predominantly characteristic of Plasmodium falciparum, consists in cytoadhesion and sequestration of the affected erythrocytes both among themselves and with platelets, lymphocytes and endothelial cells of the vessels of the microvasculature (in particular, postcapillary venules) with the formation of rosettes and, as a result, the cessation of blood flow the subsequent development of tissue hypoxia [9,12-14]. The adhesive ligands on the parasitic membranes of red blood

cells are called "knobs" and are composed of abnormal proteins of parasitic origin. The main factor determining adhesion of erythrocytes is Plasmodium falciparum erythrocyte membrane proteins (PfEMP-1) [15]. Other types of adhesive protein have also been identified: rifines, rosettins and Plasmodium falciparum histidine-rich protein 2 (PfHRP-2) [16-18].

In addition, negative affect of erythrocyte sequestration intensified by hypovolemia which develops due to vomiting, insufficient oral hydration, tachypnea and other factors. There is a decrease in the total oxygen-binding capacity of the blood due to anemia [2,7].

Black water fever is complication of malaria characterized by massive immune-mediated hemolysis, which lids to a significant accumulation of extraerythrocytic (free) hemoglobin in the blood plasma and filtration by the kidneys from the urine [19]. Free hemoglobin is the cause of oxidative stress [20]. Another mechanic factor of kidney injure is myoglobin, which enters the bloodstream due to rhabdomyolysis caused by malarial sequestration [11]. In additional probable mechanical factor of the damage is thrombotic microangiopathy of kidneys as consequents of systemic coagulopathy or hemolytic-uremic syndrome. This is confirmed by the presence of thrombin in microvascular system of glomerulus at autopsy [2,3]. The combination of these pathogenetic mechanisms results in the development of acute tubular necrosis [7,10].

Impaired immune regulation with subsequent development of inflammation is a possible mechanism of acute kidney injure in malaria due to deposition of immune complexes [21]. Surfaces antigens of affected erythrocytes and plasmodium antigens induce a monocyte-mediated immune response. These monocytes produce TNF-a, interleukins (IL) 1, 6 ,8 and interferon γ. IL production leads to the proliferation of killer T cells (Th1 and Th2) and the release of lysosomal enzymes such as neutrophil elastase. Th1 proliferation with the relies of appropriate anti-inflammatory cytokines enhances kidney hipoperfusion, which leads to the development of acute interstitial nephritis. Stimulation of Th2 causes the activation of complement with subsequent deposition of immune complexes and development of glomerulonephritis [3, 11]. Histopathological samples showed proliferation of mesangial cells, which leads to glomerular edema. Immunofluorescence and radioimmune analysis data detected the presence of immune complexes of malarial antigens and IgG and IgM, compounds of complement, deposited in the mesangial and capillary wall [11]. Anticardiolipin and antiphospholipid antibodies are also likely to play a role in immune mediated vascular pathology associated with malarial infection [11].

The mechanism is associated with metabolic disorders and competitive capture by the parasite of nutrients and cofactors of the hosts blood (glucose), leading to energy deficiency. Thiamine intake increases, which is associated with the utilization of glucose by the parasite and inhibits the aerobic glycolysis of the host, that promotes the accumulation of lactic acid [11]. Significant hyperbilirubinemia may influence an acute kidney damage.

In a detailed analysis of both clinical cases, Patient 1 had acute kidney damage arose after the increase of anemia and thrombocytopenia, in combination with hemoglobinuria. This shows that the leading mechanism of kidney injure in this case is acute tubular necrosis, due to the toxic effects of free hemoglobin and sequestration in the capillaries of the glomerulus. A Patient 2 had a significant increase of anemia after appears of acute kidney damage; there was no hemoglobinuria, however, significant leukocytosis was observed. It seems, that the leading mechanism in this case is immune-mediated kidney injure or due to hypoperfusion of kidney tubules with the development of acute interstitial nephritis or immune complex glomerular injure with the development of glomerulonephritis, or a combination of them.

Both cases were characterized by elevated bilirubin levels, which could also increase the severity of kidney damage. Also it is interesting that in both patients the glucose level was within the normal range upon admission to the hospital and during the entire period of hospitalization. This shows a secondary role of the metabolic link in the pathogenesis of kidney damage in the described cases.

At the same time we can not completely rule out the cumulative effect of all the factors that coast kidney damage in both cases.

However, there is reason to believe that the pathogenetic mechanisms and severity of kidney damage depend on the type of malaria.

CONCLUSIONS

A detailed analysis of the described two clinical cases of severe malaria caused by Pl. falciparum and Pl. malaria, respectively, and complicated by acute renal failure and hemolytic anemia, suggests that the pathogenetic mechanisms and severity of kidney damage depend on the type of malaria. The obtained data substantiate the need for further scientific research of this disease with an adequate characterization of the leading mechanisms of the development of complications in order to optimize diagnostic and treatment management.

REFERENCES

1. Gholubovskaja O.A., Shkurba A.V., Kolos L.A. K. VSY «Medycyna». 2015, 288p.
2. World malaria report 2020: 20 years of global progress and challenges. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
3. Da Silva Junior G.B., Pinto J.R., Barros E.J.G. et al. Kidney involvement in malaria: an update. Rev Inst Med Trop Sao Paulo. 2017. doi: 10.1590/S1678-9946201759053.
4. World Health Organization. Guidelines for the treatment of malaria, 3rd ed. World Health Organization. 2015.
5. Plewes K., Royakkers A.A., Hanson J. et al. Correlation of biomarkers for parasite burden and immune activation with acute kidney injury in severe falciparum malaria. Malar J. 2014;13:91. doi: 10.1186/1475-2875-13-91.
6. Tangpukdee N., Elshiekh S.B., Phumratanaprapin W. et al. Factors associated with acute renal failure in falciparum malaria infected patients. Southeast Asian J Trop Med Public Health. 2011;42:1305-1312.

7. Brown D.D., Solomon S., Lerner D. et al. Malaria and acute kidney injury. Pediatr Nephrol. 2020; 35:603-08. doi: 10.1007/s00467-018-4191-0.
8. Eiam-Ong S., Sitprija V. Falciparum malaria and the kidney: a model of inflammation. Am J Kidney Dis. 1998;32:361–375. doi: 10.1053/ajkd.1998.v32.pm9740151.
9. Pongponratn E., Riganti M., Punpoowong B. et al. Microvascular sequestration of parasitized erythrocytes in human falciparum malaria: a pathological study. Am J Trop Med Hyg. 1991;44:168-175 doi: 10.4269/ajtmh.1991.44.168.
10. Bodnar V.A., Koval T.I., Pryimenko N.O. et al. Some clinical and epidemiological features of influenza-associated pneumonia depending on the etiological agent. Wiad. Lek. 2020;73(7):1410-1414.
11. Barsoum R.S. Malarial acute renal failure. J Am Soc Nephrol. 2000;11:2147-2154. doi: 10.1681/ASN.V11112147.
12. David H., Handunnetti M., Leech J.H. et al. Rosetting: A new cytoadherence property of malaria-infected erythrocytes. Am J Trop Med Hyg. 1988;38:289-297. doi: 10.4269/ajtmh.1988.38.289.
13. Berendt A.R. Sequestration and its discontents: Infected erythrocyte-endothelial cell interactions in Plasmodium falciparum malaria. Res Immunol. 1993;144:740-745. doi: 10.1016/s0923-2494(93)80059-8.
14. Sitprija V. Nephropathy in falciparum malaria. Kidney Int. 1988;34:867–877. doi: 10.1038/ki.1988.262.
15. Baruch D.I., Pasloske B.L., Singh H.B. et al. Cloning the P. falciparum gene encoding PfEMP1, a malarial variant antigen and adherence receptor on the surface of parasitized human erythrocytes. Cell. 1995;82:77-87. doi: 10.1016/0092-8674(95)90054-3.
16. Kyes S.A., Rowe J.A., Kriek N. et al. Rifins: a second family of clonally variant proteins expressed on the surface of red cells infected with Plasmodium falciparum. Pro Natl Acad Sci U S A. 1999;96:9333-9338.
17. Helmby H., Calerier L., Pettersson U. et al. Rosetting Plasmodium falciparum-infected erythrocytes express unique strain-specific antigens on their surface. Infect Immun. 1993;61(1):284-288.
18. Parra M.E., Evans C.B., Taylor D.W. Identification of Plasmodium falciparum histidine-rich protein 2 in the plasma of humans with malaria. J Clin Microbiol. 1991;29:1629-1634. doi: 10.1128/jcm.29.8.1629-1634.1991.
19. Plewes K., Turner G.D.H.., Dondorp A.M. Pathophysiology, clinical presentation, and treatment of coma and acute kidney injury complicating falciparum malaria. Curr Opin Infect Dis. 2018;31:69-77. doi: 10.1097/QCO.0000000000000419.
20. Plewes K., Kingston H.W.F., Ghose A. et al. Cell-free hemoglobin mediated oxidative stress is associated with acute kidney injury and renal replacement therapy in severe falciparum malaria: an observational study. BMC Infect Dis. 2017;17:313. doi: 10.1186/s12879-017-2373-1.
21. Kotelevska T.M., Pryimenko N.O., Dubynska H.M. et al. A first clinical case report of West Nile Viral encephalitis in Poltava region of Ukraine. Wiad. Lek. 2020; 73(4): 831—4.

The article is a fragment of the research topic: "Optimization of medical and diagnostic tactics for infectious diseases of viral, bacterial, parasitic etiology and their mixed forms based on the study of clinical and pathogenetic features" (№ state registration 0119U102923).

ORCID and contributionship:
Vadym A. Bodnar: 0000-0002-1277-9344 [A,B,D]
Tetiana M. Kotelevska: 0000-0001-7508-4876 [B]
Tetiana I. Koval: 0000-0003-2685-8665 [E,F]
Serhii L.Ponimatchenko: 0000-0001-6490-6280 [B,D]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Vadym A. Bodnar
Poltava State Medical University
23 Shevchenka st., 36011 Poltava, Ukraine
tel:+38 067 78 79 510
e-mail:bodnar.vadym@gmail.com

Received: 16.09.2021
Accepted: 19.04.2022

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article