Collapsing glomerulopathy and hemolytic uremic syndrome associated with *falciparum* malaria: completely reversible acute kidney injury

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Abstract Acute kidney injury (AKI) is one of the most dreaded complications of severe malaria. Herein, we report a case of spontaneous resolution of AKI due to collapsing glomerulopathy (CG) and hemolytic-uremic syndrome (HUS) associated with *P. falciparum* malaria. Our case report highlights the fact that early intervention on the triggering cause of CG without a long course of steroids may obtain a remission of this severe subset of CG and may obtain a remission of HUS without therapeutic plasmapheresis. The etiologic treatment of CG and HUS may avoid progression to end-stage renal disease.

Keywords Acute kidney injury · *Plasmodium falciparum* · Collapsing glomerulopathy · Hemolytic-uremic syndrome

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Introduction

Malaria is a major public health problem in tropical countries (Mishra and Das 2008; Eiam-Ong and Sitprija 1998; Das 2008; Prakash et al. 2003; Jha and Chugh 2008; Eiam-Ong 2003). About 500 million people suffer from malaria, leading to death in one to three million cases. Acute kidney injury (AKI) is one of the most dreaded complications of severe malaria (Mishra and Das 2008). AKI occurs commonly in *Plasmodium falciparum* (PF) malaria and rarely in *Plasmodium vivax* malaria. Prompt and accurate diagnosis of malaria is needed for implementation of appropriate treatment to reduce associated morbidity and mortality. The management of malaria-induced AKI includes appropriate antimalarials (parenteral artesunate or quinine), fluid electrolyte management, supportive therapy, avoidance of nephrotoxic drugs, and Hemodialysis (HD) at the earliest (Mishra and Das 2008; Das 2008; Prakash et al. 2003; Elsheikha 2007). Collapsing glomerulopathy (CG) and hemolytic-uremic syndrome (HUS) associated with malaria has been reported (Niang et al. 2008; Adonis-koffy 2004; Sharma et al. 1993). Herein, we report a case of spontaneous resolution of AKI due to CG and HUS associated with *falciparum* malaria.

Case report

A 12-year-old boy was admitted with fever with chills/rigor, shortness of breath, and decrease urine output of 12 days duration. On examination, he was breathless with blood pressure of 190/110 mmHg, temperature 40 °C, respiratory rate of 35 breaths per minute, heart rate of 112 bpm. Laboratory investigations revealed hemoglobin, 65 g/L; total white cell count, $7.45 \times 10^9/L$ (differential

count: 50 % neutrophils, 45 % lymphocytes, 3 % monocytes, and 2 % eosinophils); platelet count, $79 \times 10^9/L$; pack cell volume, 20 %; peripheral blood smear was positive for hemolysis; serum creatinine (SCr), 503.88 $\mu\text{mol/L}$ [Modification of Diet in Renal Disease Study glomerular filtration rate value, 13 mL/min (1.73 m^2)]; sodium, 127 mmol/L; potassium, 5.3 mmol/L; blood urea, 199 mg/dL, alanine aminotransferase, 23 U/L (normal range, 0–40); aspartate aminotransferase, 49 U/L (normal range, 5–40); serum bilirubin, 11.97 $\mu\text{mol/L}$; serum albumin, 30 g/L; lactate dehydrogenase, 1150 U/L (normal range, 100–190); and blood glucose, 3.99 mmol/L. The diagnosis of *PF* malaria was confirmed by direct visualization of the parasite in giemsa stained blood smear. Ultrasonographies of the abdomen, and initial chest radiograph were normal. The initial blood, urine, and sputum cultures were sterile. The serological tests for leptospirosis, dengue, and viral hepatitis were negative. Urine examination revealed +3 albumin, red cell casts with 50–60 dysmorphic red cells and 3–5 white cells/hpf, while tests for antinuclear antibody, anti-double-stranded deoxyribonucleic acid, anti-neutrophil cytoplasmic antibody (c-ANCA/p-ANCA), anti-glomerular basement membrane antibody, Coombs' test, cryoglobulins and C-reactive protein were all negative and complement components (C3 and C4) were normal. Enzyme-linked immunosorbent assays (ELISA) test for human immunodeficiency virus (HIV), hepatitis B surface antigen and hepatitis C virus were negative.

The patient was managed using anti-malarial drugs (artesunate and doxycycline), fluid replacement and HD. IV ceftriaxone 1g BD was given initially until a bacterial infection (notably *Salmonella*) was excluded. Supportive measures were instituted as needed. Intermittent HD was initiated 2–3 times per week through temporary jugular dialysis catheter for 4 h. He remained oliguric and required HD for a total of 28 times. Six packed red blood cells were transfused during HD sessions. He developed seizure due to uncontrolled blood pressure and required maximum doses of six types of anti-hypertensive drugs to control blood pressure and started on anticonvulsant drugs. Computerized tomography showed bilateral symmetrical white matter hypodensity in posterior parietal and occipital area confirming diagnosis of posterior reversible encephalopathy syndrome (PRES). Renal vessel Doppler was normal.

Renal biopsy (Figs. 1, 2, 3) revealed single fragment of renal tissue containing 14 glomeruli with associated tubules and vessels. Capillary lumina were fairly open, mainly congested and lined by duplicated membranes. About three glomeruli shrunken tufts surrounded by swollen visceral epithelial cells forming pseudo crescents (Fig. 1). Tubules were moderately degenerated. Interstitium was moderately prominent for focal fibrosis and

overlying scattered leucocyte infiltration. Most of the glomeruli show moderate mesangial prominence with mesangiolysis (Fig. 2). Immunofluorescence (IF) microscopy (Fig. 3) revealed fine granular fluorescence (+2) across 70–80 % of the capillaries on staining with anti-human sera tested (IgG, IgM, C3). No fluorescence revealed on staining with anti-human IgA, C1q, fibrinogen, kappa and lambda light chain). Renal biopsy concluded diagnosis of HUS with CG and was attributed to malaria. During hospital course, patient developed left lower zone pneumonia so therapeutic plasma exchange (TPE) could not be done for HUS.

The serology for HIV, parvovirus B19, pulmonary tuberculosis, cytomegalovirus infection was negative. After 7 weeks and a total of 28 HD sessions, urine volume was 1.1 L/day and SCr was 79.56 $\mu\text{mol/L}$. There was complete recovery of renal function. On clinical improvement; he was discharged. He was followed up for 3 months. At that time, blood pressure was 120/80 mmHg, proteinuria was negative, SCr was 79.56 $\mu\text{mol/L}$ and the blood count was normal.

Discussion

This case was puzzling. It was characterized by an attack of *falciparum* malaria complicated by oligoanuric AKI, which is not surprising in this setting. However, the case was unusual in that HUS with CG were the consequence of *falciparum* malaria and still more unusual by the fact that the patient developed a seizure due to uncontrolled blood pressure/PRES. Finally, in contrast to the dismal prognosis of HUS and CG, especially in absence of TPE and glucocorticoids, antimalarial treatment was credited with a complete and stable remission of the renal involvement. Each of these features deserves discussion.

HUS complicating malaria

Secondary HUS may complicate bacterial, viral, parasitic or fungal infections, haemopathic malignancy, autoimmune diseases and various medications (Tostivint et al. 2002; Ruggerenti et al. 2001). Our patient was free from bacterial or viral infections. There was no laboratory evidence for a systemic disease and no responsible medication. The only valid cause for the HUS was *falciparum* malaria. In fact, a few cases of HUS complicating malaria have so far been published (Adonis-koffy 2004; Sharma et al. 1993). The mechanism of HUS in malaria is not known, but high serum levels of cytokines have been reported in patients suffering from these associated conditions (Schwartz et al. 1999). The cascade of inflammatory cytokine activation leading specifically to renal

Fig. 1 Renal biopsy showing collapsing glomerulopathy JSM, $\times 200$ and PAS, $\times 200$. The glomeruli showed shrunken tufts surrounded by swollen visceral epithelial cells forming pseudo crescents. Tubules were moderately degenerated. Interstitium was moderately prominent for focal fibrosis and overlying scattered leucocyte infiltration

Fig. 2 Renal biopsy showing mucointimal proliferation of vessel suggesting hemolytic uremic syndrome JSM, $\times 400$. The glomeruli showed moderate mesangial prominence with mesangiolysis

Fig. 3 Renal biopsy showing IgG and C3 positive on IF $\times 400$

damage remains enigmatic (Jha and Chugh 2008). Anti-malarial treatment was administered with clearing of blood-borne parasitic infection and complete and stable remission of the renal involvement, suggesting that malaria associated HUS recovered completely without need of TPE after the parasite has been eradicated.

Collapsing glomerulopathy complicating malaria

CG has been reported in association with infections (HIV, parvovirus B19, pulmonary tuberculosis, cytomegalovirus infection, and leishmaniasis), autoimmune disorders, malignancy, renal transplant and certain drugs, particularly bisphosphonates/anabolic steroids (Schwimmer et al. 2003).

Our patient was free from infections. There was no laboratory evidence for a systemic disease and no responsible medication. The only valid cause for the CG was *falciparum* malaria. Whether these are truly etiologic associations is not well understood. In fact, a few cases of CG complicating malaria have so far been published (Niang et al. 2008). In most previous reports, the prognosis of CG not associated with HIV infection was poor. Combination treatment with glucocorticoids and immunosuppressive agents are recommended for CG with efficacy based on anecdotal evidence only. Our patient had complete renal recovery despite advanced renal insufficiency especially in absence of the glucocorticoids therapy. CG, as highly cellular forms of focal segmental glomerulosclerosis (FSGS), especially in patients of black African ancestry (Barri et al. 2004), usually follows a rapid course to end-stage renal disease (ESRD) despite treatment. Albaqumi et al. (2006) analysed 97 cases of the literature and showed that idiopathic FSGS does not respond to corticosteroid treatment in 72 % of the cases. In fact, suppressing the cause of secondary FSGS, such as a toxic agent (Pascual et al. 2007), or treating HIV-associated nephropathy with highly active antiretroviral therapy may halt the progression of the nephrotic syndrome to ESRD (Herlitz et al. 2010).

Our case confirms that early intervention on the triggering cause of CG without a long course of steroids may obtain a remission of this severe subset of FSGS. The etiologic treatment of CG and HUS without corticosteroid therapy may avoid progression to ESRD. Further studies are needed to determine this less known entity.

PRES was originally used to describe a reversible, predominantly posterior leukoencephalopathy in patients who had renal insufficiency, hypertension, or who received immunosuppressive therapy. Since PRES is prevalent in children with kidney diseases, awareness and understanding of it is important for practicing pediatric nephrologists. Timely control of predisposing factors, malaria/hyper-

tension leads to clinical resolution of PRES (Ishikura et al. 2012).

Conclusion

Plasmodium falciparum can lead to serious, potentially life-threatening complications, such as CG and HUS. To the best of our knowledge this is the first report of spontaneous resolution of AKI due to CG and HUS associated with *P. falciparum* malaria. The etiologic treatment of CG and HUS without corticosteroid therapy or TPE may avoid progression to ESRD.

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