Collapsing glomerulopathy and haemophagocytic syndrome related to malaria: a case report

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Abstract

Authors report a 37-year-old Senegalese woman with no known history of nephropathy who was admitted for fever related to malaria, severe acute renal failure requiring dialysis with nephrotic syndrome. Biological examinations and bone marrow aspiration showed haemophagocytic syndrome. A kidney biopsy found a ‘collapsing glomerulopathy’ (CG). A protracted course of steroids yielded a complete, unexpected remission of the nephrotic syndrome and renal function was normal at 18 months.

Keywords: collapsing glomerulopathy; haemophagocytic syndrome; nephrotic syndrome

Haemophagocytic syndrome (HPS) is characterized by a bone marrow infiltration with histiocytes expressing a phagocytic activity for the blood cell precursors. This non-malignant proliferation is accompanied by the release of pro-inflammatory cytokines [1,2]. HPS may be primary as observed in genetic diseases affecting the immune system in children [3]. More often it is secondary to a malignancy, an autoimmune disease or a severe infection [3]. Since its initial description in 1939 [4], few data related to its renal complications have been published. The most frequent is acute renal failure (ARF) as part of a multi-organ involvement [5–7]. Nephrotic syndrome complicating HPS was more recently described, and amongst the patients in five cases, kidney biopsy found a ‘collapsing glomerulopathy’ (CG) [7,8]. We report a new case of HPS that complicated malaria and was accompanied by nephrotic syndrome. Following a period of oliguria requiring dialysis, diuresis resumed with significant proteinuria. A kidney biopsy showed a CG. A protracted course of steroids yielded a complete, unexpected remission of the nephrotic syndrome and renal function was normal at 18 months.

Case

A 37-year-old Senegalese woman was referred to our unit with a 4-day episode of fever (38°C), shivers, diffuse pain and vomiting. She appeared acutely ill. She had a lifelong history of asthma but no known history of nephropathy. A blood smear found trophozoites of Plasmodium falciparum. She was thrombocytopenic (41 000/mm³). Haemoglobin (Hb) was 13.9 g/dl and white blood cell count was 10700/mm³. The erythrocyte sedimentation rate was 22 mm/h and the C-reactive protein 601 mg/l. She was treated with quinine intravenously for 3 days, and with acetaminophen and metopimazine. On Day 5, she was anuric and had nosebleed. Serum creatinine was 880 µmol/l. At that time, blood counts disclosed a bicytopenia with anaemia (Hb 9.8 g/dl), thrombocytopenia (39 000/mm³) and 13 000 leukocytes/mm³. She was treated with saline infusion and furosemide. She remained oliguric and with acetaminophen and metopimazine. On Day 5, she was acutely ill. She had a life-long history of asthma but no known history of nephropathy. A blood smear found trophozoites of Plasmodium falciparum. She was thrombocytopenic (41 000/mm³). Haemoglobin (Hb) was 13.9 g/dl and white blood cell count was 10700/mm³. The erythrocyte sedimentation rate was 22 mm/h and the C-reactive protein 601 mg/l. She was treated with quinine intravenously for 3 days, and with acetaminophen and metopimazine. On Day 5, she was anuric and had nosebleed. Serum creatinine was 880 µmol/l. At that time, blood counts disclosed a bicytopenia with anaemia (Hb 9.8 g/dl), thrombocytopenia (39 000/mm³) and 13 000 leukocytes/mm³. She was treated with saline infusion and furosemide. She remained oliguric and haemodialysis was commenced when the serum creatinine reached 1330 µmol/l. On Day 7, Hb was 3.7 g/dl, and reticulocytes were 127 000/mm³ with schistocytes, low haptoglobin (<0.20 g/l) and hyperleukocytosis (18 500/mm³). A direct Coombs test was negative. The blood smear no longer disclosed trophozoites. The lactate dehydrogenase was 2379 U/l (11 N), the creatine-phospho-kinase was 6005 ng/ml (40 N), and glycosylated ferritin was 1525 µg/l (22 N) with the percentage of glycosylation at 33% (N < 50%). Bone marrow aspiration showed erythroid hyperplasia and infiltration by macrophages with medullary haemophagocytosis. Other laboratory data were as follows: fibrinogen 3.23 g/l, d-dimers 28.38 µg FEU/ml and fibrin degradation products 160 µg/ml. Antinuclear antibodies were positive (>1/640) but anti-DNA antibodies were negative and total serum complement was >140%. Serology was negative for HIV1, HIV2, HBV, HCV, Herpes virus, EBV and CMV. Diuresis resumed and the presence of proteinuria (1.45 g/day) suggested that she suffered from some kind of glomerular lesions. A kidney biopsy was performed. Light microscopy found a typical picture of CG (Figure 1) along with tubulointerstitial lesions, tubular necrosis, interstitial oedema, infiltration by inflammatory cells and no vascular thrombosis. Immunofluorescence was...
negative. She was treated by haemodialysis and pulses of methylprednisolone 10 mg/kg/day for 3 days, followed by prednisone 1 mg/kg/day. After 4 weeks and five haemodialysis sessions, urine volume was 1.5 l/day. Hb rose from 3.7 to 7.9 g/dl, platelets to 395 000/mm$^3$ and serum creatinine was 167 µmol/l. Corticosteroids were tapered progressively after 3 months and discontinued after 6 months of treatment. She was followed up for 18 months. At that time, blood pressure was 120/80 mmHg, proteinuria was negative, serum creatinine was 98 µmol/l and the blood count was normal.

**Discussion**

This case was puzzling. It was characterized in short succession by an attack of *P. falciparum* malaria complicated by oligaunuric acute renal failure, which is not surprising in this setting. However, the case was unusual in that hematologic disturbances were the consequence of a HPS and still more unusual by the fact that the patient developed a nephrotic syndrome with lesions of CG. Finally, in contrast to the dismal prognosis of CG, especially in black Africans, corticosteroid treatment was credited with a complete and stable remission of the nephrotic syndrome. Each of these features deserves discussion.

**HPS complicating malaria**

Secondary HPS may complicate bacterial, viral, parasitic or fungal infections, haemopathic malignancy, autoimmune diseases and various medications [7–10]. 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 HPS was *P. falciparum* malaria. In fact, a few cases of HPS complicating malaria have so far been published [11]. The mechanism of HPS in malaria is not known, but high serum levels of cytokines have been reported in patients suffering from these associated conditions [12]. Antimalarial treatment was administered with clearing of blood-borne parasitic infection but no effect on the HSP, suggesting that once the cytokine cascade is triggered, HPS may continue after the parasite has been eradicated [11].
Collapsing glomerulopathy complicating the HPS

Renal involvement during HPS is less well documented. Clinical features were described as acute renal failure [5,8] and nephrotic syndrome [7,8]. Acute tubular necrosis (ATN) in the context of multiorgan failure, with tubulointerstitial toxicity of HPS via TNF-α release or following a nephrotoxic treatment, has been described [7]. Glomerular involvement has rarely been reported. Nephrotic syndrome appears at the time of HPS or shortly after its onset. It is characterized by profuse proteinuria and is often associated with ARF. Thaunat et al. [7] reported nine cases of nephrotic syndrome and ARF associated with HPS, the aetiology of which was predominantly haematological. Six out of nine patients were black and in five of them, all five HIV negative, the pathological finding was a CG. The authors hypothesized that the renal complications resulted from a systemic cytokine burst, as already documented for other clinical manifestations of HPS. Recent research has shown that HPS is characterized by a primary uncontrolled T-cell activation followed by a cytokine burst involving IFN-γ, TNFα, IL-6, IL-1b and other proinflammatory cytokines [7]. The treatment of HPS comprised steroids in all cases. The prognosis of HPS-related nephrotic syndrome is poor, as 64% of the patients in the series described by Shimazaki et al. [8] died.

Suppressing the cause of CG may halt its progression to end-stage renal disease

CG, as highly cellular forms of focal segmental glomerulosclerosis (FSGS), especially in patients of black African ancestry [12], usually follows a rapid course to end-stage renal disease (ESRD) despite treatment. Albaqumi et al. [13] analysed 97 cases of the literature and showed that idiopathic CG does not respond to corticosteroid treatment in 72% of the cases. In fact, suppressing the cause of secondary FSGS, such as a toxic agent [14], or treating HIVAN with HAART [15] may halt the progression of the nephrotic syndrome to ESRD. Our case confirms that early intervention on the triggering cause of CG along with a long course of steroids may obtain a remission of this severe subset of FSGS.

Conclusion

HPS, a consequence of non-malignant macrophage activation, may be complicated by renal involvement. The lesions can affect the glomeruli and assume the features of CG, especially in black patients. The aetiological treatment of HSP followed by long-term corticosteroid therapy may avoid progression to ESRD.

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References


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