Exceptional Case

Histiocytic glomerulopathy associated with macrophage activation syndrome

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Abstract

We present an interesting case of a 37-year old man with acute renal failure following a febrile illness. Laboratory results showed features of macrophage activation syndrome (MAS) with anemia, thrombocytopenia, hypoﬁbrinogenemia and elevated ferritin levels. Renal biopsy was then done to determine the cause of renal failure and showed unique glomerular ﬁndings with massive histiocytic inﬁltration (‘histiocytic glomerulopathy’) and evidence of endothelial injury. Recognizing that the histiocytic inﬁltrate and endothelial injury is a part of MAS is important because early recognition and treatment is of utmost importance since the disease can be fatal.

Keywords: hemophagocytic syndrome; histiocytosis; macrophage; macrophage activation syndrome; thrombotic microangiopathy

Introduction

Macrophage activation syndrome (MAS) is a severe condition due to a hyperinﬂammatory response resulting from exaggerated activation and proliferation of non-malignant macrophages [1]. MAS falls under the umbrella group of diseases known as of hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome (HPS) [2]. HLH is classiﬁed into two forms: primary HLH and secondary HLH [2, 3]. Primary forms of HLH include familial hemophagocytic lymphohistiocytosis (FHL), Chediak–Higashi syndrome and Griscelli syndrome [2]. FHL is autosomal recessive and affects mostly infants and young children and less often adults. Disease-causing mutations have been reported that code for proteins crucial for lymphocyte/macrophage cytotoxicity in primary HLH [4–6]. These mutations lead to impaired production and generation of cytolytic enzymes, granzyme and perforin, which are required to induce apoptosis of the target cell. On the other hand, secondary HLH can be triggered by infections, rheumatologic diseases and malignancies, especially lymphomas. The term MAS is often used as a synonym for secondary or acquired HLH/HPS in adults regardless of the underlying condition and without speciﬁc reference to rheumatologic disease [2, 7].

Acute renal failure is often present in HLH/MAS and correlates with a poor prognosis [8]. Nephrotic syndrome also occurs in HLH and kidney biopsy ﬁndings in this setting have been recently described [9]. However, there are only few reports of kidney biopsy ﬁndings in the setting of acute renal failure. Acute tubular necrosis is the most common renal manifestation in HLH/MAS [10], but little has been reported about glomerular involvement in acute renal failure. Here, we present unique kidney biopsy ﬁndings that were primarily limited to the glomeruli in a patient with MAS.

Case report

Clinical history and initial laboratory data

A previously healthy 37-year-old African American man, who recently traveled to Africa, presented to the emergency department of a hospital with a 6–8 week history of febrile illness accompanied by night sweats, weight loss, diarrhea, abdominal pain, fatigue, dyspnea, nausea and anorexia. The patient denied any skin rashes, cough, headaches, arthralgias or myalgias. On physical examination, he was febrile (39°C), tachycardic (heart rate 109 beats/min and regular), and the respiratory rate was 16 breaths/min. Lung ﬁelds were clear to auscultation and extremities showed mild pitting edema. Palpation of the left axillary contents revealed enlarged axillary lymph nodes. Blood pressure was 118/63 mmHg.

The patient had a penile blood clot requiring surgery 1 year previously. He otherwise denied any previous medical history. Family history was positive for diabetes and hypertension, but negative for infectious diseases, connective tissue diseases or blood disorders.

Laboratory studies at presentation are listed in Table 1. He had signiﬁcant leukocytosis, anemia and thrombocytopenia. Liver transaminases, bilirubin, lactid dehydrogenase
developed a progressive renal dysfunction with serum creatinine that gradually increased from 1.8 to 3.3 mg/dL requiring dialysis. A percutaneous renal biopsy was performed to aid in diagnosis.

Kidney biopsy

Four cores containing both renal cortex and medulla were received for light microscopy. Twelve glomeruli were present, none of which were globally sclerosed. The glomeruli were enlarged and the glomerular capillary loops were filled with foam cells/macrophages. The endothelial cells were swollen and some of the loops showed a subendothelial expansion by fluffy granular material, cellular elements and new basement membrane formation, resulting in segments of double contours. Neutrophils were conspicuous by their absence. Crescent or necrotizing lesions were not present. Basement membrane spikes or pinholes were not present along the capillary walls. Significant interstitial inflammation was not present and ~5% of the sample showed tubular atrophy and interstitial fibrosis. Arteries and arterioles were unremarkable. The cells within the capillary loops were CD3 and CD20 negative. Immunofluorescence studies were negative for immune deposits in glomeruli. On ultrastructural examination some of the glomerular capillary loops showed subendothelial expansion with granular material and new basement membrane formation, resulting in double contours. Most of the loops were plugged with macrophages containing numerous phagocytic vacuoles. Immune-type electron dense deposits were not present along the capillary walls or in the mesangium. Representative light and electron microscopy findings are shown in Figure 2.

Diagnosis

Kidney, needle biopsy: ‘histiocytic glomerulopathy’ associated with MAS.

Clinical follow-up

The patient was placed on prednisone 60 mg/day and hemodialysis was initiated. Serum creatinine was 5.06 mg/dL and blood urea nitrogen (BUN) was 79 mg/dL. He developed progressive shortness of breath and required oxygen therapy. Chest X-ray showed bilateral pleural effusions,
atelectasis and infiltrates suggestive of volume overload. The patient continued to have significant leukocytosis, anemia and thrombocytopenia. Ferritin levels also remained elevated (1349 μg/L). A provisional diagnosis of viral-induced MAS/HPS was made. Considering the life-threatening implications of this diagnosis, the patient was referred to our institution to initiate therapies to target activated macrophages/histiocytes (prednisone 60 mg/day, etoposide and cyclosporine 75 mg/day) and responded well (Figure 1). Hemoglobin increased to 12.8 mg/dL; white blood cell and platelet count also normalized (8.1 and 276 x 10^3/μL, respectively). His serum creatinine went down to 1.7 mg/dL with an eGFR of 55 mL/min/1.73 m^2 and the patient went off dialysis. The inflammatory response did not completely resolve at the time of discharge and the CRP levels were still elevated at 45.7 mg/L although much lower than at presentation. Natural killer (NK) cell population was within normal range and both granzyme and perforin were adequately expressed in those cells ruling out a primary HLH. Unequivocal evidence of hemophagocytosis was not present on his bone marrow biopsy.

Although the pathogenesis of MAS is poorly understood, a defect in NK and cytotoxic T cells has been described [17, 18]. In addition, higher levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 have been reported [19, 20]. In patients with MAS, activated macrophages are typically seen in bone marrow and lymph nodes. Renal involvement is uncommon and usually seen in the sickest patients [21]. Acute tubular necrosis and tubulointerstitial lesions have been described in MAS in the setting of acute renal failure, and glomerular involvement has been described in the setting of nephrotic syndrome [9, 22]. Thaunat et al. reported the

Discussion

We describe unique kidney biopsy findings in a patient who presented with a systemic inflammatory response syndrome known as MAS. MAS represents an exaggerated immune response with activation and proliferation of well-differentiated macrophages secondary to infections, malignancies, drugs and rheumatologic diseases particularly systemic juvenile arthritis [11, 12]. This potentially life-threatening syndrome was first described in patients with systemic juvenile idiopathic arthritis and has an incidence of ~7% in juvenile idiopathic arthritis [11]. Clinically, MAS is characterized by the combination of fever, pancytopenia, lymphadenopathy, hepatosplenomegaly, hyperferritinemia, hypofibrinogenemia, low sodium levels, and elevated triglycerides, liver enzymes and LDH levels [13, 14]. The exact diagnostic criteria for this syndrome are still not validated but in order of frequency include thrombocytopenia, elevated ferritin levels, hemophagocytosis, increased liver enzymes, leukocytopenia, fever, falling erythrocyte sedimentation rate, splenomegaly, hypofibrinogenemia and hypertriglyceridemia [15, 16]. Our patient met many criteria for MAS (e.g. fever, cytopenia, hypofibrinogenemia, elevated ferritin levels and hepatomegaly) but did not have splenomegaly and his lipid profile was normal. Unequivocal evidence of hemophagocytosis was not present on his bone marrow biopsy.
renal histology findings of 11 patients with HPS and concomitant nephritic syndrome [9]. Renal lesions in patients with nephrotic syndrome and HPS include minimal change disease, collapsing glomerulopathy and thrombotic microangiopathy. By CD68+ staining, interstitial intrarenal hemor- rhage was seen in one patient associated with mild interstitial inflammation and vascular changes. These findings are listed in Table 2.

Our case showed unique glomerular findings which consisted of massive infiltration of the glomerular capillaries by macrophages. The cells were CD68+ and CD3-CD20−. This resulted in complete occlusion of the capillary lumen. In addition, there was evidence of endothelial injury characterized by swelling, loss of fenestrations and subendothelial accumulation of cellular debris and lipid-like granular material. However, there were no fibrin thrombi present, and both small and large arteries were unremarkable. The endothelial injury is likely due to release of (TNF-α), interleukin (IL)-1β and IL-6 from the activated macrophages. We use the term ‘histiocytic glomerulopathy’ to describe this entity, and the glomerular findings are not completely unsurprising given that MAS is a condition of activated/proliferating macrophages.

Considering the rapidly fatal course of this disease, treatment should be initiated immediately after clinical suspicion. The underlying cause should also be treated as soon as it is identified. Therapeutic strategies include high-dose steroids, cyclosporine A and etoposide [2, 23, 24]. In our patient, administration of these three drugs resulted in improvement of his symptoms and laboratory parameters.

In conclusion, we describe the kidney biopsy findings in a patient with MAS. The biopsy showed a ‘histiocytic glomerulopathy’ with numerous endocapillary macrophages and features of endothelial injury. It is important to recognize these features in the setting of MAS because early diagnosis and prompt treatment is of the utmost importance.

Conflict of interest statement. None declared.

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Table 2. Renal lesions in MAS

| Renal lesion | Description |
|-------------|-------------|
| Glomerular | Minimal change disease, Collapsing glomerulopathy, Thrombotic microangiopathy, ‘Histiocytic glomerulopathy’ |
| Tubulointerstitial | Acute tubular necrosis, Microcystic tubular dilatation, Interstitial nephritis, with polymorphic T lymphocytes and CD68+ macrophages, Tubular atrophy and interstitial fibrosis |
| Vascular | Thrombotic microangiopathy |