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Kidney Biopsy Teaching Case

Hemophagocytic Syndrome With Histiocytic Glomerulopathy and Intraglomerular Hemophagocytosis

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Hemophagocytic syndrome (HPS), a rare and life-threatening disease, is characterized by hyperactivation of the immune system that causes hypercytokinemia and potential multiorgan failure. Acute kidney injury is the most common kidney manifestation of HPS and is generally considered a poor prognostic factor. Glomerular involvement is uncommon and usually manifests as either podocytopathy with collapsing glomerulopathy or thrombotic microangiopathy. We report a rare case of severe histiocytic glomerulopathy in a patient with HPS who presented with acute kidney injury and proteinuria. Kidney biopsy revealed massive glomerular infiltration by macrophages resembling proliferative glomerulonephritis accompanied by intraglomerular hemophagocytosis and mild features of glomerular thrombotic microangiopathy. The patient's kidney failure and proteinuria responded rapidly to high-dose pulse methylprednisolone followed by a tapering course of oral prednisone. Our case expands the renal pathologic spectrum of HPS to include histiocyte-rich glomerular infiltration and intraglomerular hemophagocytosis. Greater awareness of this entity is needed to ensure prompt recognition and appropriate therapy.

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INDEX WORDS: Histiocytic glomerulopathy; hemophagocytosis; hemophagocytic syndrome; macrophage activation syndrome; acute kidney injury (AKI); proteinuria; kidney biopsy.

INTRODUCTION

Hemophagocytic syndrome (HPS) is an acute aggressive disease characterized by hyperactivation of the immune system leading to marked cytokine release into the circulation (hypercytokinemia) and multiorgan failure.[1] Acute kidney injury (AKI) is the most common kidney manifestation of HPS and is generally considered a poor prognostic factor.[2] Glomerular disease is rare and usually manifests as a podocytopathy with features of collapsing glomerulopathy or glomerular thrombotic microangiopathy (TMA).[3] We present the case of a young woman with HPS who presented with AKI, proteinuria, and microscopic hematuria. Kidney biopsy revealed massive and diffuse glomerular macrophage infiltration accompanied by intraglomerular hemophagocytosis and mild features of glomerular TMA. Kidney function recovered fully following prompt institution of immunosuppressive therapy with glucocorticoids. Greater awareness of this rare kidney manifestation of HPS is needed to ensure swift recognition and appropriate therapy of this potentially life-threatening condition.

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CASE REPORT

Clinical History and Initial Laboratory Data

A 20-year-old white woman with a medical history of obesity and gastroesophageal reflux disease was admitted for evaluation of anemia and thrombocytopenia. She had initially presented 2 weeks earlier with fever, left-sided flank pain, nausea, and vomiting and was treated with intravenous antibiotics for suspected pyelonephritis. Computed tomography of the abdomen and pelvis revealed retroperitoneal lymphadenopathy. Urine dipstick showed protein (1+) and undetectable heme, and urine culture gave negative results. Serum creatinine (Scr) level on discharge was 1.0 mg/dL (corresponding to estimated glomerular filtration rate [eGFR] of 75 mL/min/1.73 m^2, as calculated using the MDRD [Modification of Diet in Renal Disease] Study equation). Outpatient magnetic resonance imaging of the abdomen performed the week after discharge showed hepatomegaly and splenomegaly with persistent mild retroperitoneal lymphadenopathy, and she was readmitted for further workup.

On readmission, physical examination findings were notable for blood pressure of 141/93 mm Hg and temperature of 100.2°F. Laboratory evaluation (Table 1) showed AKI with Scr level of 1.9 mg/dL (eGFR, 36 mL/min/1.73 m^2), anemia (hemoglobin, 8.7 g/dL), and thrombocytopenia (platelet count, 39 $\times 10^3/\mu L$). Urinalysis revealed protein (3+) by dipstick, with a spot urine protein-creatinine ratio of 1.76 g/g. Urinary microscopy showed 25 to 60 red blood cells per high-power field. Serologic evaluation was notable for serum antinuclear antibody titer of 1:320 in a homogeneous pattern. An abdominal ultrasound showed a right kidney that measured 11.9 cm and a left kidney that measured 10.3 cm. Over the next 5 days, Scr level continued to increase, peaking at 3.8 mg/dL (eGFR, 16 mL/min/1.73 m^2). The patient also experienced worsening thrombocytopenia (platelet count, 20 $\times 10^3/\mu L$) and anemia requiring transfusion. A diagnostic kidney biopsy was performed on day 10 of admission.

Table 1. Laboratory Findings

Parameter	Value (Reference Range)
Scr, mg/dL	1.9 (0.6-1.2)
eGFR, mL/min/1.73 m^2	36 (>90)
SUN, mg/dL	35 (8-20)
Serum albumin, g/dL	2.0 (3.5-5.1)
AST, U/L	21 (12-38)
ALT, U/L	28 (7-41)
Hemoglobin, g/dL	8.7 (12.0-16.0)
WBC count, $\times 10^3/\mu L$	7.7 (4.5-13.5)
Differential blood count, %	
Neutrophils	71 (40-70)
Monocytes	10 (0-10)
Lymphocytes	18 (20-50)
Eosinophils	0.3 (0-6)
Platelets, $\times 10^3/\mu L$	39 (150-400)
PT, s	14.9 (11.6-14.6)
PTT, s	30.2 (24.2-34.5)
LDH, U/L	217 (115-221)
Haptoglobin, mg/dL	350 (41-165)
Urine dipstick protein	3+
Urine RBC/HPF	25-60
Urine WBC/HPF	10-25 (0-2)
Spot urine PCR, g/g	1.76 (<0.3)
Urine culture	No growth
Blood cultures	No growth
CH50, mg/dL	24 (<30)
C3, mg/dL	151 (83-177)
C4, mg/dL	30 (16-47)
ANA	1:320 titer; homogeneous
Anti-dsDNA antibody	Negative
MPO-ANCA	<1:20 (<1:20)
PR3-ANCA	<1:20 (<1:20)
Rheumatoid factor	Negative
ADAMTS13 level, %	76 (50-160)
Anticardiolipid antibody (IgG & IgM)	Negative
HIV	Negative
HCV antibody	Negative
HBV core antibody	Negative
HBV core antigen	Negative
Soluble CD25/IL-2Rα, pg/mL	2,341 (<1,033)
Ferritin, IU/L	580 (13-150)
Triglycerides, mg/dL	277 (25-150)

Note: Conversion factors for units: Scr in mg/dL to μmol/L, ×88.4; SUN in mg/dL to mmol/L, ×0.357; triglycerides in mg/dL to mmol/L, ×0.01129.

Abbreviations and definitions: ADAMTS13, von Willebrand factor protease; ALT, alanine aminotransferase; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; AST, aspartate aminotransferase; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPF, high-power field; IgG, immunoglobulin G; IL-2Rα, interleukin 2 receptor α; LDH, lactate dehydrogenase; MPO, myeloperoxidase; PCR, protein-creatinine ratio; PR3, proteinase 3; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; Scr, serum creatinine; SUN, serum urea nitrogen; WBC, white blood cell.

Kidney Biopsy

Twenty-six glomeruli were sampled for light microscopy, none of which was globally sclerotic. Glomeruli appeared diffusely enlarged and hypercellular. Glomerular capillary lumina were narrowed or occluded by diffuse and global endothelial cell swelling and marked glomerular macrophage infiltration, including focal endocapillary foam cells (Fig 1A). Immunohistochemical stains for monocytes/macrophages confirmed the presence of abundant intracapillary macrophage infiltration (Fig 1B-D). Periodic acid–Schiff and Jones methenamine silver stains delineated loosening of the mesangial matrix of engorged hypercellular capillaries, consistent with mesangiolysis, but with only rare duplications of glomerular basement membrane and no intracapillary fibrin thrombi (Fig 1E). Many glomeruli contained intrahistiocytic erythrocytes consistent with intraglomerular hemophagocytosis by the infiltrating macrophages (Fig 1F). A mild patchy inflammatory infiltrate of macrophages accompanied by mild focal interstitial edema involved ~5% of the cortex. There was no significant tubular atrophy or interstitial fibrosis. Vessels were unremarkable. Immunofluorescence showed only weak glomerular tuft staining for fibrin/fibrinogen (1+) and sparse granular mesangial positivity for immunoglobulin M (trace). Electron microscopy showed glomerular luminal obliteration by numerous infiltrating macrophages, some of which contained intracytoplasmic erythrocytes, consistent with intraglomerular hemophagocytosis (Fig 2). Additionally, there were focal ultrastructural features of TMA, including endothelial cell swelling, loss of fenestrations, rare widening of the subendothelial zone by relatively electron-lucent material, and mesangiolysis (Fig 2). Foot-process effacement was evident in 60% of the glomerular capillary surface area. There were no immune-type electron-dense deposits, fibrin thrombi, or endothelial tubuloreticular inclusions identified.

The major kidney biopsy finding was prominent glomerular macrophage infiltration, confirmed by immunohistochemical staining for CD68 (using PG-M1 and KP1 monoclonal antibodies), consistent with a diagnosis of histiocytic glomerulopathy. There were minor features of glomerular TMA in the form of endothelial swelling and mesangiolysis. The unique finding of intraglomerular erythrocyte phagocytosis seen at both the light microscopic and ultrastructural levels provided tissue documentation of hemophagocytosis. In the clinical setting of febrile hepatosplenomegaly, anemia, and thrombocytopenia, the possibility of underlying HPS was proposed.

Diagnosis

Severe histiocytic glomerulopathy associated with glomerular features of thrombotic microangiopathy in a patient with hemophagocytic syndrome.

Clinical Follow-up

Additional laboratory tests revealed an elevated soluble CD25/interleukin 2 receptor α (IL-2Rα) level of 2,341 (upper limit of reference range, 1,033) pg/mL, hyperferritinemia with ferritin level of 580 (reference range, 13-150) IU/L, and fasting hypertriglyceridemia with triglyceride level of 277 (reference range, 25-150) mg/dL. Bone marrow biopsy showed normocellular marrow with trilineage differentiation, mild megakaryocytic dysplasia, and increased reticulin fibrosis, without evidence of hemophagocytosis. Two sets of blood cultures yielded no organisms. Serologic studies for cytomegalovirus, Epstein-Barr virus, parvovirus, HIV-1 (human immunodeficiency virus type 1), *Borrelia burgdorferi*, and toxoplasmosis gave negative results.

Treatment was initiated with intravenous pulse methylprednisolone (1 g/d for 3 days) followed by a course of oral prednisone (80 mg/d) tapered over the course of the next month. Laboratory results from 12 days after the kidney biopsy included Scr level of 0.97 mg/dL (eGFR, 78 mL/min/1.73 m^2), platelet count of 59 $\times 10^3/\mu L$, serum soluble IL-2Rα level of 659 pg/mL, and serum ferritin level of 361 IU/L. Two weeks after discontinuation of immunosuppression, Scr level had improved to 0.67 mg/dL (eGFR, 119 mL/min/1.73 m^2), urine protein-creatinine ratio had