Histiocytic Glomerulopathy Associated With Hemophagocytic Lymphohistiocytosis

Pouneh Dokouhaki, Da-elene Van der Merwe, Karan Vats, Samar M. Said, Vivette D. D'Agati, and Samih H. Nasr

Hemophagocytic lymphohistiocytosis (HLH) is a systemic inflammatory syndrome characterized by heightened activation and proliferation of nonmalignant macrophages and excessive cytokine release. Whereas acute kidney injury is common in this syndrome, direct glomerular involvement by activated histiocytes is very rare. We present the case of a man in his 20s who presented with fevers, malaise, flank pain, anemia, thrombocytopenia, severe acute kidney injury, and proteinuria. A kidney biopsy revealed histiocytic glomerulopathy and subacute thrombotic microangiopathy, and he was diagnosed with HLH. Recovery of kidney function occurred following steroid therapy. A review of kidney involvement by HLH is provided.

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INTRODUCTION

Glomerular infiltration by abundant histiocytes (macrophages, with or without intracytoplasmic lipid inclusions (foam cells), is rare and can be seen in a variety of conditions, including cryoglobulinemic glomerulonephritis, crystal-storing histiocytosis, cellular focal segmental glomerulosclerosis, Alagille syndrome, lecithin-cholesterol acyltransferase deficiency, and apolipoprotein E2 homozygote glomerulopathy (Table S1). Recently, glomerular infiltration by macrophages with endothelial cell injury has been reported in hemophagocytic lymphohistiocytosis (HLH), and this lesion is termed histiocytic glomerulopathy. Here, we describe a rare case of HLH-associated histiocytic glomerulopathy.

CASE REPORT

A man in his 20s of Middle Eastern descent with no prior medical history presented with a 3-week history of malaise, fatigue, nausea, and flank pain, which had been treated empirically with antibiotics for a suspected urinary tract infection. Ten days after the first presentation, he presented to the emergency department with acute kidney injury (AKI) with a serum creatinine (Scr) level of 2.4 mg/dL. He was given intravenous fluid and sent home on oral Ibuprofen at 400 mg every 6 hours. He was admitted to the hospital 2 days later with similar symptoms and non-resolving AKI, with an Scr level of 2.8 mg/dL. After 3 days of hydration, he was discharged on oral antibiotics for presumed urinary tract infection with an Scr level of 1.7 mg/dL.

On readmission 3 days later, notable physical findings included pallor, a temperature of 100.4 °F, blood pressure of 155/80 mmHg, peripheral edema, and ascites. Laboratory findings (Table 1) indicated AKI with an Scr level of 2.1 mg/dL, anemia, and thrombocytopenia. Urinalysis showed 2+ proteins, 3-5 red blood cells/high-power field, 3-5 white blood cells/high-power field, and granular casts. The urine albumin-creatinine ratio was 0.028 g/g, with a 24-hour urine protein value of 0.45 g. An abdominal ultrasound revealed hepatomegaly (19.6 cm) with significant ascites but no splenomegaly. Over the next 10 days, the patient’s clinical course worsened. He had a persistent fever of 102.0 °F, hypotension with a blood pressure of 90/60 mm Hg, and hypoxic respiratory failure (O2 saturation on Room Air 87%), requiring supplemental oxygen through a non-rebreather mask (FiO2 50%) in an observation unit. He developed nephrotic range proteinuria (24-hour urine protein 4.5 g). Kidney replacement therapy was initiated for oligoanuric AKI (Scr level of 4.4 mg/dL with volume overload). His anemia and thrombocytopenia worsened (platelet count 15 × 10^3/μL, hemoglobin 6 g/dL, lactate dehydrogenase 18 U/L, haptoglobin 0.55 g/dL) with no schistocytes on peripheral blood smear, with hyperferritinemia of 1,642 ng/mL. A bone marrow aspirate was performed 5 days after admission for suspected HLH, which showed reactive left-shifted erythropoiesis, increased megakaryopoiesis, and no evidence of hemophagocytosis. Pulse steroids, plasmapheresis, and empiric intravenous immunoglobulin (IVIG), in addition to platelets and blood transfusion, were administered. The patient’s clinical status and thrombocytopenia improved 10 to 14 days after the initiation of high-dose steroids, at which point a kidney biopsy was deemed safe. The AKI with nephrotic range proteinuria of an unclear etiology made a kidney biopsy crucial to establish a tissue diagnosis, as well as to differentiate between an infectious etiology and a condition requiring further immunosuppression.

Thirty-six glomeruli were sampled, none of which were globally or segmentally sclerotic. The glomeruli were hypercellular and showed diffuse occlusion of capillaries by numerous infiltrating histiocytes (confirmed by CD68 immunostaining) and endothelial cell swelling (Fig 1). Some glomeruli exhibited intracapillary foam cells and segmental thickening and duplication of the glomerular basement membranes. No crescents, fibrinoid necrosis, or
Hematologic tests

Other

Microbiology

Virology

Table 1. Laboratory Findings

| Parameter                          | Value (Reference Range) |
|------------------------------------|-------------------------|
| Biochemical tests                  |                         |
| Scr, mg/dL                         | 2.28 (0.68-1.2)         |
| eGFR, mL/min/1.73 m²               | 30 (>90)                |
| Serum albumin, g/dL                | 1.1 (3.5-5.2)           |
| AST, U/L                           | 66 (10-40)              |
| ALT, U/L                           | 83 (8-60)               |
| ALP, U/L                           | 242 (30-110)            |
| LDH, U/L                           | 318 (130-230)           |
| Ferritin, µg/L                     | 1,642 (20-250)          |
| Triglycerides, mg/dL               | 297 (53-204)            |
| Urine tests                        |                         |
| Urine dipstick protein             | 2+                      |
| Urine RBC/HPF                      | 3-5 (0-2)               |
| Urine WBC/HPF                      | 3-5 (0-2)               |
| Urine albumin-creatinine ratio, g/g| 0.028 (<0.07)           |
| Urine protein (24 hour), g/day     | 4.5 (<0.15)             |
| Hematologic tests                  |                         |
| Hemoglobin, g/dL                   | 6.4 (13.5-18.0)         |
| WBC count, 10⁹/µL                  | 14 (4.00-11.00)         |
| Platelets, 10⁹/µL                  | 15 (150-400)            |
| INR                                | 1.5 (0.8-1.2)           |
| PTT, s                             | 30 (27-39)              |
| Haptoglobin, g/dL                  | 0.5 (0.015-0.2)         |
| Fibrinogen, g/dL                   | 0.8 (0.15-0.45)         |
| Immunologic tests                  |                         |
| CRP, mg/dL                         | >30 (0.0-0.7)           |
| C3, g/dL                           | (0.09-0.2)              |
| C4, g/dL                           | 0.029 (0.015-0.045)     |
| ANA                                | <1.80 (<1.80)           |
| MPO-ANCA                           | <1.20 (<1.20)           |
| PR3-ANCA                           | <1.20 (<1.20)           |
| Anti-GBM level                     | <20 (<20)               |
| Anti-mitochondrial antibody        | <1.40 (<1.40)           |
| Anti-smooth muscle antibody        | <1.40 (<1.40)           |
| Virology                           |                         |
| HIV                                | Negative                |
| HCV antibody                       | Negative                |
| HBV core antibody                  | Negative                |
| HBV core antigen                   | Negative                |
| CMV                                | Negative                |
| EBV                                | Negative                |
| Parvo virus                        | Negative                |
| Microbiology                       |                         |
| Urine cultures                     | No growth               |
| Blood cultures                     | No growth               |
| Other                              |                         |
| ADAMTS13 activity, %              | 38 (>70)                |
| Soluble CD25/IL-2Ra, U/mL          | 2152 (45-1105)          |

Note: Conversion factors for units: serum creatinine in mg/dL to umol/L, x88.4; urine albumin-creatinine ratio in g/g to g/m, x860.113; triglycerides, mg/dL to mmol/L, x0.01129.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibody; AST, aspartate aminotransferase; C3, complement component 3; C4, complement component 4; CMV, cytomegalovirus; CRP, C-reactive protein; EBV, Epstein-Barr virus; eGFR, estimated glomerular filtration rate; GBM, glomerular basement membranes; HBV, hepatitis B virus; HCV, hepatitis C virus; HPF, high-power field; IL-2Ra, interleukin 2 receptor α; INR, international normalized ratio; LDH, lactate dehydrogenase; MPO, myeloperoxidase; PR3, proteinase 3; PTT, partial thromboplastin time; RBC, red blood cell; Scr, serum creatinine; WBC, white blood cell.

Thrombosis were identified. The tubules exhibited mild acute injury. There was no significant tubular atrophy or interstitial fibrosis. A CD68 immunostain highlighted scattered macrophages within the interstitium. The vessels were unremarkable. Immunofluorescence was negative.

On electron microscopy, glomerular capillaries were occluded by intracapillary infiltrating macrophages and swollen endothelial cells (Fig 1). Entrapped erythrocytes were seen in the markedly narrowed capillary lumina, but no intrahistiocytic erythropoiesis was seen. There was segmental multilamellation of the internal aspect of glomerular basement membranes, with an associated widening of the subendothelial zone by electronlucent fluffy material (Fig 2). No immune complex–type electron-dense deposits were seen. Podocytes displayed segmental foot process effacement.

The diagnosis was histiocytic glomerulopathy with features of subacute glomerular thrombotic microangiopathy.

Additional laboratory findings including blood and urine cultures, and serologic testing for cytomegalovirus, Epstein-Barr virus, Parvovirus, HIV, and hepatitis A and B were all negative. Rheumatologic and vasculitic screening tests (Table 1) were unremarkable. ADAMTS-13 activity was reduced at 38% (normal, >70%). An atypical hemolytic uremic complement panel was normal. Fasting triglyceride was elevated at 297 mg/dL. Soluble CD25/interleukin 2 receptor α was increased at 2,152 U/mL (45-1,105). Genetics testing for HLH revealed heterozygosity c.1360T>C in the LYST (lysosomal trafficking regulator) gene, which is predicted to result in the amino acid substitution p.Trp454Arg. This variant has not been reported and is of unknown clinical significance.

Two weeks after initiation of the above-mentioned treatments, anemia and thrombocytopenia improved, with a sustained hemoglobin level over 10 g/dL and platelet count of 150 × 10⁹/µL. Kidney replacement therapy was discontinued 3 weeks after initiation of therapy. The patient was treated with 60 mg of dexamethasone tapered over 4 months. His kidney function recovered to an Scr level of 1.0 mg/dL with an albumin-creatinine ratio of 0.133 g/g after 1 month of treatment. His hemoglobin level was 14.9 g/dL, and his platelet count was 324 × 10⁹/µL. Two years after hospital admission, he remains in full kidney and systemic remission, with an Scr level of 0.97 mg/dL and minimal albumin-creatinine ratio of 0.034 g/g with no further treatment.

DISCUSSION

Hemophagocytic lymphohistiocytosis, also called hemophagocytic syndrome, is a severe and potentially fatal systemic inflammatory syndrome characterized by heightened activation and proliferation of nonmalignant macrophages and excessive cytokine release, leading to cytopenias, organomegaly, and systemic immunologic and metabolic perturbations. It is classified into 2 major subtypes: primary and secondary HLH. The primary or
familial form occurs in children or young adults and is mainly due to germline mutations in the genes associated with immune cell cytotoxicity, while the secondary forms are acquired and occur in response to a wide spectrum of diseases, including infections, malignancies, autoimmune disease, bone marrow or solid organ transplant, and drug hypersensitivity. Commonly, HLH is triggered by a combination of genetic susceptibility and exposure to acquired conditions. Despite the divergent etiologies in HLH, there is a rather well-defined common downstream pathway of unregulated cytokine release from disharmonious innate immune cells. This phenomenon, referred to as a “cytokine storm,” is caused by uncontrolled activation of cytotoxic T lymphocytes and natural killer cells in response to infections or other direct or indirect stimulators of the innate immune system.

The diagnosis of HLH, as established by the Histiocyte Society (in 2004), requires 5 of 8 criteria, namely, fever, splenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis in bone marrow spleen or lymph nodes, elevated ferritin, and soluble CD25. Despite its name, the finding of hemophagocytosis is neither sensitive nor specific for a diagnosis of HLH. As many as 30% of confirmed HLH cases are negative for hemophagocytosis on initial investigation. The number of hemophagocytic cells at the initial bone marrow aspiration is often variable and as low as 1/500 cells, necessitating a repeat bone marrow biopsy in many cases. Our patient had 5 of the 8 criteria, namely, fever, anemia, thrombocytopenia, hyperferritinemia, hypertriglyceridemia, and a high soluble CD25/interleukin 2 receptor α measurement. Although splenomegaly was absent, he had significant hepatomegaly.

Kidney involvement in the form of AKI is a relatively common clinical manifestation of HLH, especially in critically ill patients, and is associated with increased mortality. AKI in HLH is likely multifactorial, related to hemodynamic changes, coagulation disorders, nephrotoxic levels of tumor necrosis factor α or other cytokines, nephrotoxic drugs, and the underlying disease. The histology of HLH-associated AKI is typically acute tubular injury but, rarely, marked interstitial infiltration by activated macrophages and lymphocytes is seen. The concurrence of AKI and HLH has adversely affected survival rates in patients with secondary

Figure 1. (A) The glomerulus appears hypercellular because of abundant intracapillary infiltrating histiocytes and some lymphocytes (hematoxylin & eosin; Original magnification, ×400). (B) Periodic acid-Schiff highlights occlusion of peripheral capillaries by infiltrating histiocytes and endothelial cell swelling and through widening of the subendothelial cell zone, with associated segmental duplication of the glomerular basement membrane (Original magnification, ×600). (C) The CD68 immunohistochemical stain highlights granular cytoplasmic staining of the abundant intracapillary infiltrating histiocytes and fewer interstitial histiocytes (Original magnification, ×400). (D) An electron microscopy image showing occlusion of the peripheral capillaries by many intracapillary infiltrating histiocytes and endothelial cell swelling. There is also widening of the subendothelial zone with segmental duplication of the glomerular basement membrane (lower left; Original magnification, ×1,200). Arrows in panels A and D indicate lipid-laden macrophages (foam cells).
HLH (36% vs 57% in non-AKI patients).12,15 Most patients with AKI required dialysis and, more importantly, one-third of HLH patients with AKI were diagnosed with chronic kidney disease at 6 months.12

HLH-induced nephrotic syndrome is less well characterized and, in most patients, is associated with AKI and significant podocyte injury.16 Reported HLH-associated glomerulopathies include, in descending order of frequency, collapsing glomerulopathy, minimal change disease, and thrombotic microangiopathy, and are more frequent in patients of African descent.16-18 The pathogenesis of HLH-associated podocytopathy likely involves cytokine-induced podocyte injury.12,13 The higher incidence in individuals of African descent suggests underlying genetic factors, such as the presence of nephropathic apolipoprotein L1 variants, as recently documented in a patient with HLH and collapsing lupus podocytopathy.19 Close to two-thirds of reported patients with HLH-associated nephrotic syndrome died of HLH-associated multiorgan failure.16 The outcomes of the few surviving patients were variable; some had remission of nephrotic syndrome, while others developed chronic kidney disease.18

Direct glomerular involvement by activated histiocytes in the form of histiocytic glomerulopathy is an extremely rare histopathologic manifestation of HLH, with many histologic mimickers (Table S1). HLH glomerulopathy has been reported in only 3 previous case reports.1-3 Table 2 summarizes the clinicopathologic characteristics and outcomes of these cases and our case. A trigger for HLH was documented in 2 cases: cytomegalovirus in 1 and ovarian carcinoma in the other. Patients presented with fever, anemia, thrombocytopenia, AKI, proteinuria (range, 0.4–10.5 g/day), and hematuria. None of the patients had evidence of hemophagocytosis in the bone marrow, and only 1 had intraglomerular hemophagocytosis by the infiltrating histiocytes.3 All cases showed histiocytic glomerulopathy with features of subacute thrombotic microangiopathy characterized by numerous intracapillary infiltrating histiocytes, endothelial cell injury, and widening of the subendothelial zone. No case showed glomerular fibrin thrombosis or vascular involvement. The absence of vascular involvement favors glomerular endothelial cell injury because of the local release of cytokines (such as tumor necrosis factor α and interleukin 1β) from activated intraglomerular macrophages.

Given the nonspecific presentation of HLH, a high clinical index of suspicion is required for the prompt diagnosis of this life-threatening condition. Treatment is focused on suppression of hyperinflammation (with corticosteroids, IVIG, anticytokine agents), elimination of activated immune cells (with corticosteroids, etoposide, T-cell antibodies, rituximab), elimination of an infectious trigger with antimicrobial therapy, and eventually replacement of a defective immune system in the form of stem cell transplant for those patients with primary HLH. Appropriate use of antibiotics and supportive measures are critically important. A short course of steroids and IVIG are indicated to control hypercytokinemia in the presence of multiorgan failure; however, steroids and cytotoxic drugs should be avoided in the later stages of sepsis. Not all patients with HLH require etoposide, and less severe cases can be managed with steroids and IVIG alone.

In the 4 reported patients with histiocytic glomerulopathy, treatment included cancer-directed chemotherapy; steroids alone; a combination of steroids, plasmapheresis, and IVIG; and steroids and HLH-specific agents (Table 2). All patients recovered kidney function on follow-up. Thus, HLH-associated histiocytic glomerulopathy appears to be highly responsive to therapy, leading to sustained kidney remission and favorable long-term outcomes.

SUPPLEMENTARY MATERIAL
Supplementary File (PDF)
Table S1: Histologic differential diagnoses of histiocytic glomerulopathy.

ARTICLE INFORMATION
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### Table 2. Reported Cases of HLH-Associated Histiocytic Glomerulopathy

| Characteristics                      | Eirin et al<sup>1</sup> | Santoriello et al<sup>2</sup> | Hiser et al<sup>3</sup> | Present Case |
|--------------------------------------|-------------------------|-------------------------------|------------------------|--------------|
| Age/sex/race                         | 37/M/AA                 | 20/F/W                        | 45/F/NR                | 26/M/Asian   |
| HLH trigger                          | CMV                     | Unknown                       | Ovarian cancer         | Unknown      |
| Fever                                | Yes                     | Yes                           | NR                     | Yes          |
| Anemia                               | Yes                     | Yes                           | Yes                    | Yes          |
| Thrombocytopenia                     | Yes                     | Yes                           | NR                     | Yes          |
| Hypertriglyceridemia                 | No                      | Yes                           | No                     | Yes          |
| Hyperferritinemia                    | Yes                     | Yes                           | Yes                    | Yes          |
| Splenomegaly                         | No                      | Yes                           | NR                     | No           |
| Hemophagocytosis in bone marrow      | No                      | No                            | NR                     | No           |
| Peak Scr, mg/dl                      | 5.1                     | 3.8                           | 1.9                    | 4.4          |
| Peak proteinuria                     | 0.4 g/day               | PCR (mg/dL)                   | PCR (mg/dL)            | 4.5 g/day    |
| Serum albumin, g/dl                  | 3.2                     | 2                             | 3.1                    | 2.6          |
| Hematuria                            | Yes                     | Yes                           | NR                     | Yes          |
| Glomerular pathology                 | Histiocytic glomerulopathy + subacute TMA | Histiocytic glomerulopathy + subacute TMA | Histiocytic glomerulopathy + subacute TMA | Histiocytic glomerulopathy + subacute TMA |
| Intraglomerular hemophagocytosis     | No                      | Yes                           | No                     | No           |
| Treatment                            | HD, steroids, etoposide, cyclosporine | Steroids                      | Cancer-directed Chemotherapy | HD, steroids, plasmapheresis, IVIG |
| Follow-up in months                  | 12                      | 8                             | NR                     | 12           |
| Kidney recovery                      | Yes (Scr 1.6)           | Yes (Scr 0.7 mg/dL, no proteinuria) | Yes                    | Yes (Scr 1.0 mg/dL, no proteinuria) |

Abbreviations: AA, African American; CMV, cytomegalovirus; F, female; HD, hemodialysis; HLH, hemophagocytic lymphohistiocytosis; IVIG, intravenous immunoglobulin; M, male; NR, not reported; PCR, urine protein to creatinine ratio; Scr, serum creatinine; TMA, thrombotic microangiopathy; W, White.

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