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Direct Reversible Kidney Injury in Familial Hemophagocytic Lymphohistiocytosis Type 3

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**ABSTRACT**

Hemophagocytic lymphohistiocytosis is a hyperinflammatory disorder resulting from primary or secondary immune dysfunction. AKI is frequent in severe hemophagocytic lymphohistiocytosis and has been attributed to multiorgan failure or the use of nephrotoxic drugs, but AKI is rarely considered a direct consequence of the disease process. We describe a child with familial hemophagocytic lymphohistiocytosis type 3 who developed AKI requiring prolonged renal replacement therapy because of severe renal inflammation. There was massive infiltration of the renal parenchyma by activated macrophages and cytotoxic T cells, and acute tubular injury. The patient responded to high-dose intravenous methylprednisolone, which resulted in improvement of renal function and discontinuation of renal replacement therapy. This case confirms the occurrence of reversible AKI due to hemophagocytic lymphohistiocytosis-induced activated macrophage infiltration of the renal parenchyma and inflammation.


Hemophagocytic lymphohistiocytosis (HLH) is a rare disease that causes severe systemic inflammation in a wide range of target organs including the kidney. The precise etiology of AKI in patients with HLH has not been adequately defined. We describe a child with familial hemophagocytic lymphohistiocytosis (FHLH) in whom we confirmed direct inflammatory injury to the kidney. The patient responded well to high-dose intravenous corticosteroids and continuous hemofiltration. Although HLH is an uncommon condition, it is important to consider this diagnosis and treat patients promptly because the disease-mediated AKI is responsive to therapy.

**CASE REPORT**

An 11-year-old boy, born to nonconsanguineous Honduran parents, presented with a 1-week history of fatigue, body aches, vomiting, and high fever after visiting family in rural Honduras. His past medical history included Kawasaki disease at 3 years of age, and acute disseminated encephalomyelitis 3 months prior to the current illness. The patient had a brother who died 7 years ago from a disease at 3 years of age, and acute disseminated encephalomyelitis 3 months prior to the current illness. The patient had a brother who died 7 years ago from HLH, and a genetic test for Munc 13–4 mutation identified Munc 13–4 variants.

At presentation, the patient’s blood pressure was 97/51 mmHg. On examination, he was found to have a 3/6 systolic murmur and splenomegaly. His neurologic examination was normal and he did not have edema or a rash. Urine microscopy showed specific gravity 1.018, pH 7, small ketones, moderate proteinuria, 0−2 red blood cells/high power field (hpf), and 11 white blood cells/hpf. The patient had Na 125 mEq/L, albumin 2.6 g/dL, triglycerides 317 mg/dL, and lactate dehydrogenase 1128 U/L. There was pancytopenia with hemoglobin 9.3 g/dL, white blood cells 1.1×10^9/L, and platelet count 65×10^9/L. His serum creatinine level was 1.4 mg/dL (baseline of 0.4 mg/dL 4 months prior) with an eGFR3 of 43 mL/min/1.73 m². The initial fractional excretion of sodium was 0.15% suggesting prerenal azotemia. A broad infectious work-up, including blood and urine cultures, was negative. A bone marrow biopsy was performed and showed a hypocellular marrow with increased histiocytes, loose stromal fibrosis, and serous atrophy. Given his significant family history, specific serological studies for HLH were obtained, and these revealed elevated ferritin and soluble IL-2 receptor α (sIL2Rα, also termed soluble CD25) levels, significantly above age-adjusted normal ranges, as well as decreased to absent natural killer (NK) cell activity. Genetic testing for Munc 13–4 was carried out, and this showed a splice donor site mutation and confirmed FHLH type 3.

Despite prompt initiation of treatment with the Histioocyte Society HLH-2004 immunochemotherapy protocol, which includes chemotherapy (dexamethasone, etoposide, intrathecal methotrexate) in conjunction with immunotherapy (cyclosporine A), the patient’s mental status, and renal function deteriorated over a period of 48 hours, and RRT was initiated with continuous veno-venous hemodiafiltration to treat

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severe fluid overload and worsening azotemia. The serum creatinine concentration was 5.8 mg/dL at the start of treatment. The patient did not receive any drugs that are known to be associated with acute interstitial nephritis (AIN) in temporal relationship to the worsening of kidney function. The patient underwent a renal biopsy 4 weeks after initiation of RRT to determine the cause and prognosis of the AKI.

**RENAI#L BIOPSY**

The renal biopsy specimen was studied at multiple levels of section and stained with hematoxylin and eosin, periodic acid–Schiff, trichrome, and silver. The renal biopsy specimen contained 40 glomeruli, none of which was globally sclerotic. All glomeruli had normal cellularity without mesangial, endocapillary, or extravascular proliferation. There was diffuse, mild interstitial edema and diffuse severe interstitial inflammatory cell infiltrate (Figure 1A). The inflammatory cells were predominantly small lymphocytes. Blood vessels were unremarkable without perivascular inflammation. There was no evidence of hemophagocytosis by light microscopy.

Immunohistochemistry staining was performed and the majority of the lymphocytes were positive for CD3 (T-cell specific marker) (Figure 1B). Few lymphocytes were positive for CD20 (B-cell specific marker) (Figure 1C). Scattered plasma cells were present. There was a diffuse and marked increase in interstitial CD163 positive macrophages (Figure 1D). It is important to note that the CD163 antibody used in the immunohistochemistry analysis stains activated macrophages.

Frozen tissue contained four glomeruli and was stained with antisera for IgG, IgA, IgM, C3, C4, C1q, kappa and lambda, albumin, and fibrinogen. There was no positive glomerular, tubular, or vessel staining.

Two glomeruli were cut for ultrastructural study. There was segmental lamina rara interna expansion. There were no subepithelial, subendothelial, or mesangial electron-density deposits. Visceral epithelial cells were prominent and 50% of the foot processes were effaced. Segmental microvillus transformation and cytoplasmic vacuolization of podocytes were noted. There was no hemophagocytosis identified in the tubulo-interstitium.

The pathology diagnosis was infiltration in the renal interstitium by inflammatory cells associated with FHLH.

Four cases of AIN of comparable clinical severity (mean serum creatinine at the time of the diagnostic kidney biopsy, 4.9±1.9 mg/dL) were selected and renal sections were stained with CD163. There were 137±87 (mean±SD) macrophages/hpf in these four cases, compared with 422/hpf in our patient.

**CLINICAL COURSE**

After the biopsy, the patient was treated with high-dose intravenous methylprednisolone, 30 mg/kg per dose for three consecutive doses on alternate days. This resulted in an improvement in his renal function, with onset of diuresis in the first 24 hours after the initial methylprednisolone dose. Renal function steadily improved over the next 4 weeks leading to discontinuation of RRT 3 weeks after the methylprednisolone therapy. Five days after dialysis was discontinued, the patient experienced a disease relapse, including AKI. Salvage chemotherapy with antithymocyte globulin was initiated, and three doses of intravenous methylprednisolone were administered, with good response. After this second episode of AKI, his serum creatinine declined to a nadir of 0.9 mg/dL, corresponding to an eGFR of 67 ml/min/m². He developed transient hypertension that was successfully managed with amlodipine and propranolol. He was referred for an allogeneic hematopoietic stem cell transplantation as curative therapy for the HLH. Unfortunately, he died from complications of myeloablative therapy.

**DISCUSSION**

HLH is a rare and severe immunologic disorder characterized by multiorgan system involvement, fever, rash, hepatosplenomegaly, cytopenias, and a range of neurologic manifestations. The incidence is estimated...
to be 1.2 cases per million per year. It is classified as primary (familial, underlying genetic abnormality) or secondary to an underlying condition such as infection, autoimmune/rheumatologic disease, malignancy, or metabolic disorder. Regardless of cause, HLH results from excessive release of IFN-γ from activated T cells, which leads to continual expansion and activation of the cytotoxic CD8+ T cell, histiocyte, and macrophage population. Activated CD8+ T lymphocytes and macrophages infiltrate multiple organs, including the bone marrow, lymph nodes, spleen, liver, brain, and kidney, and secrete high levels of inflammatory cytokines including IL-1, IL-6, IL-18, and TNF-α, chemokines, and other substances (“cytokine storm”), leading to tissue damage and multiple organ failure. The diagnosis of any form of HLH is based on a number of clinical signs and laboratory findings that often overlap with other illnesses resulting in delayed diagnosis.

The patient had Munc 13–4 deficiency, caused by mutations in UNC13D. This variant accounts for 30% to 35% of FHLH. Munc 13–4 is essential for lytic granule fusion with other structures related to the cytoplasmic membrane, and the disease-causing mutations result in defective degranulation. The exocytosis of cytotoxic granules from Munc 13–4-deficient T and NK lymphocytes is impaired. Renal involvement, particularly AKI, is seen in up to 50% of patients with HLH. Clinical manifestations include oliguria, azotemia, and nephrotic syndrome. The spectrum of AKI is similar in patients with secondary HLH. It is considered a strong predictor of poor outcomes. Acute tubular necrosis associated with interstitial inflammation is the most frequent renal histopathologic finding seen in 45% of patients with HLH. Glomerular involvement has also been observed in patients with HLH, and the abnormalities range from collapsing glomerulopathy, FSGS with marked podocytosis, minimal change disease, and thrombotic microangiopathy in children and adults. The presence of hemophagocytosis has been documented in the kidney but it is not required for the diagnosis of HLH or AKI. The acute change in kidney function has been attributed to vasoactive instability and ischemia, inflammatory mediators, disseminated intravascular coagulation, or exposure to nephrotoxic drugs. Infiltration of the kidneys by activated cytotoxic T cells and macrophages has been suggested as a potential underlying mechanism of AKI and has been supported by findings or enlarged kidneys on ultrasound. However, it has never before been confirmed on renal biopsy and in the review by Karras it is considered rare and an inadequate explanation for AKI.

AIN, as seen in our patient, is characterized by infiltration of the tubulointerstitium with a wide variety of immunoeffector cells. Hemophagocytosis or histiocytosis are not always present in injured tissue in patients with HLH. However, in an effort to define an AIN cellular profile that distinguishes FHLH-induced AIN from other causes, we focused on the presence of macrophages because they are the central cell in HLH. The density of activated macrophages was more than three-fold higher in our case compared with four cases of AIN of comparable clinical severity. We think that this verifies the pivotal role of the macrophage in our case of HLH-induced AIN, a feature that has not been emphasized in prior reports of kidney injury in patients with this disease. To the best of our knowledge, this is the first case in which AKI in a patient with HLH has been shown to be a direct consequence of disease-specific renal parenchymal involvement by HLH with infiltration of activated macrophages, the cardinal cell type involved in the hyperinflammatory state.

With regard to management, because most reports involve single patients or a small case series, it is hard to define an optimal treatment for FHLH. Overall,
patient survival is 55% at 3 years of follow-up.\(^9\) The patient was initially treated in accordance with the Histiocyte Society HLH-2004 protocol. The steroid dose in this protocol is much lower than the amount that is usually administered to treat patients with severe AIN. We suggest that the high-dose intravenous administration of methylprednisolone contributed to the reversal of the renal injury caused by the HLH.

Hemofiltration has been reported to improve clinical outcomes in patients with sepsis-related AKI.\(^20\) Although we cannot prove that continuous veno-venous hemofiltration normalized the elevated levels of cytokines that have been implicated in the severe tissue damage in HLH, our patient’s condition stabilized after he was started on RRT. In addition, when dialysis was discontinued, he experienced an overall disease relapse, including AKI, which again responded well to three doses of intravenous methylprednisolone. However, it is important to note that he only started to diurese after he received the methylprednisolone infusions.

In conclusion, this case demonstrates that patients with HLH can have severe AKI secondary to dysregulated immune responses and direct overwhelming inflammation mediated by activated macrophages within the kidney. Early diagnosis is critical, because irreversible kidney damage can be prevented with aggressive pulse steroid therapy and RRT (Figure 2).

**DISCLOSURES**

None

**REFERENCES**