Hemopagocytic Lymphohistiocytosis Associated With Nephrotic Syndrome and Multi-organ Failure

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Hemophagocytic lymphohistiocytosis (HLH) is still an important elusive and misdiagnosed condition despite of improved knowledge. Nephrotic syndrome associated with HLH is not a common feature and has been rarely reported in hemophagocytic syndrome. We report a 27-year-old man with HLH who progressed to multi-organ failure as well as nephrotic-range proteinuria, generalized edema, and hypoalbuminemia.

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INTRODUCTION

Hemopagocytic lymphohistiocytosis (HLH) nomination, etiology, pathogenesis, diagnosis and treatment have been developing, since 1939, when a case of histiocytic medullary reticulocytosis was introduced.[1] Despite of improved knowledge, HLH is an important elusive and misdiagnosed condition. Two major entities of familial and secondary or reactive HLH (the presence of an underlying genetic disorder and HLH due to malignancies, infections, and autoimmune disorders, respectively) are well known.[2-6] The most important pathologic feature in HLH is activated macrophages engulfing erythrocytes, leukocytes, platelets, and their precursor cells.

In 2004, Henter and colleagues introduced a revised diagnostic guideline for HLH, the most common protocol used worldwide.[2] They proposed a molecular diagnosis consistent with HLH or diagnostic criteria including fever, splenomegaly, cytopenia (affecting 2 of 3 lineages in the peripheral blood, including hemoglobin < 9 mg/dL, platelet count < 100 × 10^9/L, neutrophils < 1.0 × 10^9/L), hypertriglyceridemia or hypofibrinogenemia (fasting triglycerides > 3.0 mmol/L and fibrinogen < 1.5 g/L), hemophagocytosis in bone marrow, spleen or lymph nodes, low or absent natural killer cell activity, and elevated serum ferritin and soluble CD25.[7]

Hemopagocytic lymphohistiocytosis may result in very severe and life-threatening condition and multi-organ failure. Renal involvement, particularly acute kidney failure due to acute tubular necrosis is seen frequently, but nephropathy and nephrotic syndrome associated with HLH is not a common feature and has been rarely reported in hemophagocytic syndrome.[8,9] We report an HLH case with progressive and critical condition led to multi-organ failure that also fulfilled all nephrotic syndrome criteria.

CASE REPORT

A 27-year-old man was admitted due to respiratory distress, abdominal distension, and lower extremities edema. His symptoms had been developed since 1 month earlier and progressed in the recent week. On examination, he was toxic, cachectic, pale, and icteric. Vital signs revealed critical condition (blood pressure, 70/60 mm Hg; heart rate, 120/min; respiratory rate, 36/min; axillary body temperature, 37.2°C; and oxygen saturation with ambient air, 80%). Decreased respiratory sounds in the basilar zones of both lungs, in addition to tachypnea and coarse crackles in other fields, were dominant respiratory findings. A III/VI systolic murmur in the left sternal border, abdominal ascites, mild left upper quadrant tenderness, huge splenomegaly and hepatomegaly without lymphadenopathy, pitting edema in the lower extremities, and scattered

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purpuric lesions were remarkable.

He was a tailor and without remarkable medical and familial history. He had been healthy since 7 months earlier when malaise, low-grade fever, weight loss, hepatosplenomegaly, and pancytopenia developed.

Several diagnostic procedures performed in hematology and gastroenterology departments, consisted of bone marrow aspiration and biopsy, microbiology investigations, rheumatologic tests, and endoscopy, have had no definite results. Laboratory analysis is shown in the Table. Chest radiography revealed alveolar patchy infiltration and pleural effusion in both lungs. Serum and urine protein electrophoresis were unremarkable. Other laboratory data also revealed low plasma fibrinogen-derived proteins (15 µg/mL) and fibrinogen (39 mg/dL) and high D-Dimer (1000 ng/mL) and ferritin (>1000 ng/mL). A 24-hour urine sample showed nephrotic-range proteinuria (3.6 g/d). The other evaluations (rheumatologic tests and infective causes) had no abnormal findings. Bone marrow aspiration and biopsy and also a fresh touch of biopsy revealed hypocellular marrow with marked macrophages infiltration and hemophagocytic activity, dyserythropoiesis, and shift to the left of myeloids line. Large activated macrophage that contained phagocytosed eryhrocytes and granulocytes was prominent.

The bone marrow histopathology, hepatosplenomegaly, low fibrinogen level, and elevated serum ferritin led to the diagnosis of HLH; thus promptly, intravenous immunoglobin, cyclosporine, granulocyte colony stimulating factor, and corticosteroid were initiated. However, kidney function and glomerular filtration rate were decreased on the following days and despite intensive care, his condition progressively deteriorated. The patient died due to extreme critical condition before a proper dose of aforementioned regimen and kidney biopsy.

DISCUSSION

Hemophagocytic lymphohistiocytosis, formerly known as hemophagocytic syndrome, has been described in recent decades, but due to difficulties in clinical description, diagnostic aspects, and its mimicking features, HLH has remained as an important pitfall in clinical practice. Renal involvement is not a diagnostic criterion for HLH, but frequently has been reported. Edema, hypoalbuminemia, and hyponatremia are the most

Laboratory Data 7 Months Before and During Admission

Blood Parameter	Measurement			Reference Range
	7 Months Before	On Admission	5th day of Admission	
Hemoglobin, g/dL	10.8	7.9	4.6	…
Platelet count, × 10^9/L	114	17	12	…
Leukocyte count, × 10^9/L	2.1	2.6	1.0	…
Polymorphonuclear cells, %	40	72	…	…
Lymphocytes, %	20	10	…	…
Reticolocytes, %	1.6	…	…	…
Urea nitrogen, mg/dL	52	64	191	7 to 20
Creatinine, mg/dL	1.0	1.0	1.6	0.6 to 1.2
Aspartate transaminase, U/L	47	220	194	12 to 38
Alanine transaminase, U/L	106	66	43	7 to 41
Bilirubin (total), mg/dL	0.6	7.0	19.6	0.3 to 1.3
Bilirubin (direct), mg/dL	0.4	3.1	14.0	0.1 to 0.4
Alkaline phosphatase, U/L	813	1291	…	33 to 96
Lactate dehydrogenase, mg/dL	594	…	2100	115 to 220
Triglyceride, mg/dL	…	…	410	40 to 200
Sodium, mEq/L	140	130	151	136 to 146
Potassium, mEq/L	4.4	4.5	5.0	3.5 to 5.0
Partial thromboplastin time, sec	20	100	> 100	26 to 39
International Normalized Ratio	1.01	2.99	4.90	1
Erythrocyte sedimentation rate, mm/h	6	2	2	…
Human immune deficiency virus antibody	Negative	…	Negative	…
Hepatitis C virus antibody	Negative	…	Negative	…
Hepatitis B surface antigen	Negative	…	Negative	…

clinical manifestations due to kidney injury, but as mentioned above, all of them can be developed in association with other organ failures, including liver failure and circulation impairment, and also it can be due to underlying causes of HLH.[10]

Recently, reviews of renal involvement in HLH have shown that despite of frequently reports of renal manifestations in patients with HLH, there is not a concise description for it. The most frequent renal manifestation is usually acute renal failure and it can be considered as a predictor of poor prognosis.[9] Nephrotic-range proteinuria and nephrotic syndrome induced by HLH in patients without a history of previous nephropathy has been rarely found in hemophagocytic syndrome. Over 20 years, the most cases of nephrotic syndrome (11 patients) have been reported from four nephrology centers.[9] All of them were biopsy-proven nephropathies and the pathologic features showed collapsing glomerulopathy, minimal change nephrotic syndrome and thrombotic microangiopathy, respectively. It is important that all of collapsing glomerulopathies had negative human immunodeficiency virus serology.

It seems that cytokine release in HLH including interleukin-1, interleukin-6, interferon-γ, and tumor necrosis factor-α result in histiocytes proliferation and overproduction of other cytokines which is the backbone of the pathogenesis of nephropathy in these patients.[7,9-11]

The cure rate in HLH, particularly associated with multi organ failure, is very poor; the reports revealed 50% mortality rate.[12] In the aforementioned multicenter study, 7 of 11 patients (63%) with HLH-induced nephrotic syndrome died, one of them were still nephrotic and another patient remained with chronic kidney failure. Only 2 patients were completely cured.[9,10]

Unfortunately, because of the patient's condition and fulminant clinical deterioration, kidney pathology was not available, but he fulfilled all nephrotic syndrome criteria. He did not have a previous history of nephropathy, and laboratory analysis few months before admission revealed normal kidney function. It means nephrotic syndrome in this case has developed after HLH without demonstrated underlying cause.

Delay in diagnosis and treatment of this case explains a diagnostic pitfall and mimicking characteristics of HLH. Furthermore, these misdiagnoses and pitfalls imply on underestimation of its incidence. It seems that high clinical suspicion and repeating diagnostic procedure including bone marrow aspiration and biopsy and microbiologic analysis can be helpful for early diagnosis and intensive treatments.

CONFLICT OF INTEREST

None declared.

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