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CASE REPORT

A Hemophagocytic Lymphohistiocytosis Patient Initiated with Prominent Liver Dysfunction: a Case Report

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HEMOPHAGOCYTIC lymphohistiocytosis (HLH) is an aggressive and potentially fatal syndrome that results from inappropriate activation of lymphocytes and macrophages. It is characterized by fever, hepatosplenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, and pathologic findings of hemophagocytosis in the bone marrow or other tissues. We report an adult HLH case admitted to hepatology department.

CASE DESCRIPTION

A previously healthy 49-year-old man was admitted to hepatology department due to remarkable liver dysfunction. Two weeks ago, he developed high spiking fever (up to 39°C), along with enlargement of cervical lymph nodes and sore throat. He attended the local county hospital, and significantly elevated aminophenase and bilirubin were found (given no exact details). He was treated with cephalosporins and antiviral medicines for about 3 days. Symptoms of pharyngalgia and neck swelling were relieved, but he still remained hyperpyretic. So he was transferred to local municipal hospital. Tests were shown as follows: white blood cell $2.78 \times 10^9/L$ (normal

range $4-10 \times 10^9/L$), platelet $82 \times 10^9/L$ (normal range $100-300 \times 10^9/L$), alanine aminotransferase (ALT) 756 (normal range 0-40) U/L, glutamic-oxalacetic transaminase (AST) 1075 (normal range 0-40) U/L, total bilirubin 165.5 (normal range 1.7-25.7) $\mu\text{mol/L}$, and direct bilirubin 105.7 (normal range 1.7-6.8) $\mu\text{mol/L}$. Hemophagocytes and atypical lymphocytes were found in bone marrow smear, but proportions were not reported. Serological tests of human immunodeficiency virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, herpes simplex virus (HSV), rubella virus, and cytomegalovirus (CMV) were negative. He received treatments including liver protection, plasma transfusion, albumin transfusion, and anti-infection (Cefepime and Ganciclovir) for 8 days. Then ALT and AST levels were going down while bilirubin level kept climbing.

So he was admitted to our hospital with confusion of the past 2-week history of fever and liver dysfunction. He was notably jaundiced. There were several enlarged lymph nodes in the cervical, axillary and inguinal regions which were soft and without tenderness. Abdominal examination was dissatisfactory because of his strong abdominal muscles. Laboratory tests revealed: white blood cell $1.12 \times 10^9/L$, hemoglobin 119 (normal range 110-150) g/L, platelet $35 \times 10^9/L$, ALT 249 U/L, AST 249 U/L, total bilirubin 207.9 $\mu\text{mol/L}$, direct bilirubin 150.2 $\mu\text{mol/L}$, albumin 25.2 (normal range 35-55) g/L, fibrinogen 1.22 (normal range 2-4) g/L, serum ferritin 16 568 (normal range 13-400)

ng/ml, soluble CD25 19 059.7 (normal range <6400) pg/ml, and natural killer cell activity 7.21% (normal range 31.54%-41.58%). Blood smear showed no atypical lymphocyte. A 24-hour urine sample showed nephrotic-range proteinuria (4.41 g/d). Bone marrow smear and biopsy revealed 7% hematophages and showed no malignant sign. Abdominal ultrasound indicated splenomegaly. Other evaluations of autoimmune disorders and infections, including PCR of CMV, Epstein-Barr virus (EBV), HSV1, HSV2, varicella zoster virus, human herpes virus (HPV) 6, HPV 7 and HPV 8, had no positive findings. The diagnosis of HLH was made.

We treated him with prednisone 50 mg once a day for 4 days, 40 mg twice a day for 3 days, 30 mg twice a day for 6 days, 20 mg twice a day for 7 days, and planned to reduce the dosage gradually. He also received transfusion of plasma, albumin, and fibrinogen to improve coagulation function and the state of hypoproteinemia. Besides, human immunoglobulin was used as an important adjunctive therapy. We also gave him some treatments for improving liver function, eliminating jaundice, preventing infection, and dropping the urine protein. His condition was improved remarkably after 16-day hospitalization. During the first month after discharge, he was taking prednisone with tapering dose. And then, he had remained asymptomatic without any treatments on 8-month follow-up visit.

DISCUSSION

Hemophagocytic syndrome is characterized by uncontrolled nonmalignant proliferation of histiocytes and macrophages in the bone marrow, lymphoid tissues or other organs. The incidence is estimated to be approximately 1.2 cases per million individuals per year, which is obviously underrated.¹ Diagnosis of HLH is challenging because there is no specific findings of HLH.² Guidelines for the diagnosis of HLH require the presence of 5 out of 8 findings of fever, splenomegaly, cytopenia, hypertriglyceridemia or hypofibrinogenemia, hemophagocytosis in the bone marrow, spleen or lymph nodes, low or absent natural killer cell activity, and elevated serum ferritin and soluble CD25.² The syndrome was first described as uncontrolled histiocyte proliferation in 1939, and a set of diagnostic and therapeutic guidelines was first presented by the Histiocyte Society in 1991 and was revised in 2004. The condition is classified into primary and secondary forms, which are difficult to be distinguished from one another.

The primary form, also called familial hemophagocytic lymphohistiocytosis (FHL), usually happens in infants or younger children. Several genes have been reported to be

associated with FHL, such as PRF1, UNC13-D, STXBP-2, Syntaxin-11 and so on.³ Survival time of patients with active FHL is less than 2 months after diagnosis if untreated. The onset of FHL can be triggered by infections. Appropriate treatments including corticosteroids, cyclosporine, etoposide and anti-thymocyte globulin, can control the condition temporarily. Hematopoietic stem cell transplantation is the only available treatment with potential for cure.

The secondary HLH is a result of excessive immunological activation of the immune system, and may occur in patients with malignancy, autoimmune disease, drug hypersensitivity reaction, and infection. Infection-associated HLH has been reported from time to time. Common infectious pathogens causing HLH include EBV, CMV, human immunodeficiency virus, hepatitis A virus, bacteria, parasites, mycobacterium, and fungus. EBV is the most frequent infection associated with HLH, both familial and acquired.⁴

Early diagnosis is the key step to survival. The full clinical picture of HLH is quite characteristic, but the initial presentation is non-specific and misleading. HLH may be misdiagnosed as hepatitis, nephropathy, infection, and other diseases. Late diagnosis is associated with high mortality. Despite recent gains in knowledge, the diagnosis of HLH remains challenging. Initial treatment is based on dexamethasone, cyclosporin A, and etoposide, by inhibiting the activation of lymphocytes. For most patients with secondary HLH or less severe forms of HLH, the use of corticosteroids and high-dose immunoglobulin may be sufficient. Etoposide is not recommended in mild cases, because of the potential risk of secondary malignancies. For patients with genetic HLH and with severe symptoms, combination therapy of dexamethasone, cyclosporin A, and etoposide is recommended.⁵ During the therapy, patients should be closely followed up for signs of improvement as well as possible complications.

The patient was admitted to hepatology department because of prominent liver dysfunction. Liver involvement is not a diagnostic criterion for HLH, but as we have observed, patients with HLH almost always have evidence of liver inflammation, ranging from very mild elevations of transaminases to liver failure.⁶ The case meets all 8 diagnostic criteria of HLH-2004. Soluble CD25 may be one of the most significant inflammatory markers, and it correlates with current disease activity better than other indices.¹ However, soluble CD25 assays are not available at all institutions. Ferritin is also a sensitive and specific marker, especially when levels >1000 g/L.

There are some noteworthy issues existing in this case. First, the form and trigger of HLH remain unclear.

Patients in the primary form often have clear familial inheritance, and are usually infants or younger children. Besides, those patients are at high risk of recurrence and usually hardly get long-term survival without hematopoietic cell transplantation. The patient is 49 years old, and so far remains symptom-free since discharge. So the diagnosis of secondary HLH is more possible than FHL. Combined of fever, sore throat, enlarged lymph nodes and atypical lymphocytes in bone marrow smear at the onset of the course, we consider EBV infection as the most suspicious. As we mentioned above, EBV is the most common known infectious trigger of both hereditary and nonhereditary HLH. In local hospital, the patient had some virus tests including HSV, rubella virus and CMV, but EBV was not included. Considering of that EBV infection may resolve spontaneously and the patient received antiviral therapy for about 10 days, we cannot rule out EBV infection, though negative result of PCR was shown in our hospital. Usually, patients with HLH due to infections have lower mortality than those with noninfectious causes.⁷ The patient showed excellent progress in recovery and good situation in follow-up visit, which supports our suspicion to some extent.

Second, kidney was involved in the procession of disease. By searching literature, we found that renal involvement has frequently been reported, particularly acute kidney failure. Our patient showed normal renal function, but presented nephrotic-range proteinuria and severe hypoproteinemia. Nephrotic syndrome associated with HLH is not a common feature and has been rarely reported. Alavi Darazam *et al*⁸ reported an HLH case who ultimately progressed to multi-organ failure and also fulfilled all nephrotic syndrome criteria recently, but it is a pity that the patient deteriorated rapidly and died soon before kidney biopsy. Cao *et al*⁹ revealed the presence of hemophagocytic macrophages in the glomerulus of an HLH patient in 2011. We may likely find erythrophagocytosis in renal biopsy sample if the renal puncture was done.

HLH is a hematologic disease, but not all HLH patients come to hematologic department at the beginning of the progress. As it is a complex syndrome which infects many other systems, doctors of other specialty should also be aware of the syndrome.

After all, HLH is a potentially life-threatening multi-system hyperinflammatory disorder, which is difficult to

diagnose and treat. Advances have been made during the past 20 years in the diagnosis and treatment of HLH, and the survival rate of HLH patients has improved much.¹⁰ There still remains much to explore about HLH.

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