

Case Report

Early Recognition and Treatment of Hemophagocytic Lymphohistocytosis in A Child with the Early Symptom of DIC

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Abstract

Background: Hemophagocytic lymphohistocytosis (HLH) is a potentially fatal multiple organ inflammatory response syndrome that is characterized by proliferation of histiocytes and inflammatory factor storm. The disease progress varies fast and has a high death rate. Disseminated intravascular coagulation (DIC) is one of the leading causes of death in HLH. Here, we reported a child suffered from secondary HLH with the early symptom of DIC.

Case Description: A 2.5 year-old boy was hospitalized in our ward of the Second Affiliated Hospital of Dalian Medical University due to persistent high fever. The patient had the early manifestation of DIC, which was different from sepsis, and also had progressive pancytopenia, high serum ferritin level, hepatic dysfunction, hypertriglyceridemia, elevated soluble IL-2 receptor level, and hemophagocytosis in the bone marrow. With early treatment of HLH, the patient recovered rapidly without recurrence.

Conclusion: DIC can appear in the early phase of HLH, and also note that it should be distinguished with sepsis. Early diagnosis and reasonable therapy are very important to improve the prognosis of HLH.

Keywords: Hemophagocytic lymphohistocytosis; Disseminated intravascular coagulation; Children; Sepsis

1. Introduction

Hemophagocytic lymphohistocytosis (HLH) is not a single disease, but rather a hyperinflammatory syndrome caused by excessive activation of lymphocytes and macrophages that produce high levels of cytokines. The main symptoms of HLH are prolonged high fever, hepatosplenomegaly, and cytopenias. Characteristic laboratory abnormalities include elevated ferritin, triglycerides, transaminases, lactate dehydrogenase (LDH) and low

fibrinogen [1]. Here, we reported a child HLH with the early symptom of DIC and provided clinical experience for its early diagnosis and treatment.

2. Clinical Information

A 2.5 year-old boy was hospitalized in January 2020 due to persistent high fever 3 days. The highest body temperature was 40°C. He was given oral azithromycin and oseltamivir for 2 days, but the effect was not satisfactory. Physical examination: T 38.6 °C, P 136/min, R 26/min, Bp 92/61 mmHg, BW: 13.5 kg. He was conscious but tended to sleep. The pharyngeal mucous membrane was congested. The liver and spleen were not touched under the ribs. Endings of limbs were warm, and capillary filling time was normal. Laboratory testing on admission: Blood routine test: WBC $6.08 \times 10^9/L$, Neutrophil count $2.22 \times 10^9/L$, Hb 101 g/L, PLT $114 \times 10^9/L$, CRP 3.26 mg/L; DIC test: D-dimer 25.13 ug/ml, FDP > 150 ug/ml, PT 16.8 s, APTT 53.1 s, TT 24.6 s, Fbg 1.18 g/L. Pancytopenia and coagulation disorders were aggravated progressively while hospitalized (Table 1). Other laboratory examinations: Liver biochemistry: ALT 42.1 U/L, AST 289.5 U/L, LDH 1931.6 U/L, TB 30.4 umol/L; Myocardial enzyme: α -HBDH 1275.42 U/L, CK 489.69 U/L, CK-MB 53.08 U/L; Serum ferritin (SF) > 1650.0 ng/mL; Soluble IL-2 receptor level: 1317.00 U/ml; Triglyceride (TG): 3.2 mmol/L; NK%: 9.2%; Bone marrow examination showed evidence of hemophagocytosis. The boy was diagnosed as HLH. Although the common pathogens such as epstein-barr virus (EBV) and cytomegalovirus (CMV) were negative during hospitalization, we considered he was secondary HLH because the gene variation about primary HLH had not been detected by genetic testing. The boy had a cefathiamidine for anti-infection and a nadroparin calcium as anticoagulant therapy. In order to inhibit inflammation reaction, he was given IVIG (500 mg/d) for 4 days, combined with a intravenous injection of dexamethasone (5 mg/d) for 6 days, and then changed to oral. The symptoms recovered gradually. Laboratory parameters returned to normal 10 days later. After being discharged, oral dexamethasone treatment was continued. The dosage was reduced by 50% every 2 weeks and discontinued at the end of 8 weeks. At the time of follow-up, the boy was fine without relapse.

Laboratory parameter	Day 1	Day 2	Day 4	Day 6
Neutrophil count ($\times 10^9/L$)	2.22	1.62	0.95	1.22
Hemoglobin (g/L)	101	96	88	101
Blood platelet count ($\times 10^9/L$)	114	105	61	236
D-dimer (ug/ml)	25.13	Negative	17.09	0.57
PT (s)	16.8	Negative	18	12.2
APTT (s)	53.1	Negative	35.3	31.7
TT (s)	24.6	Negative	34.2	19
Fibrinogen (g/L)	1.18	Negative	0.6	1.32

Table 1: The change in blood routine and coagulation function test.

3. Discussion

HLH is related to abnormal immune activation and inflammation. It can occur in people of all ages, however, early childhood is the high-risk period [2]. It is classified as genetic (primary) and acquired (secondary) forms of HLH due to different pathogenesis. Primary HLH (pHLH) is caused by genetic defects involved in cytotoxic granule exocytosis or function. Secondary HLH (sHLH) is related to infection, autoimmune diseases, malignant tumor, immunosuppression, metabolic diseases and even drugs [3-4]. The diagnostic criteria of HLH include fever, hepatosplenomegaly, hypocytosis, high serum ferritin level, decreased natural killer cell activity, elevated soluble IL-2 receptor level, hypertriglyceridemia or hypofibrinogenemia, and hemophagocytosis in the bone marrow, spleen, or lymph nodes. At least 5 of the 8 criteria above must be met for diagnosis [5-6]. In addition, elevated transaminase, LDH, bilirubin, low albumin, hyponatremia and abnormal symptoms of central nervous system (CNS) are considered as evidences supporting diagnosis [7].

This case is characterized by beginning with DIC as an early symptom. The severe abnormal DIC parameter had already appeared on admission, including the high level of D-dimer, FDP, prolonged APTT, PT and decreased fibrinogen. According to the International Society on Thrombosis and Haemostasis (ISTH) DIC scoring system [8], the score of this patient was 6 as DIC. Sepsis is one of the main reasons that can lead to DIC, and also has the similar characters with HLH, such as cytopenia, prolonged prothrombin time, activated partial thromboplastin time, hypofibrinogenemia, and elevated liver enzymes. Therefore it is important to distinguish HLH from sepsis for treatment. In this patient, DIC was an early symptom of HLH, whereas it often occurs in the terminal stage of sepsis, and always accompanied by multiple organ dysfunction syndrome (MODS).

Current guidelines recommend application of the HLH-94/2004 protocol, including use of etoposide, in patients with primary HLH and severe secondary HLH [9]. Corticosteroid and intravenous immunoglobulin (IVIG) can control the hyperactivated immune system, which are often selected for initial treatment [10]. Although the onset was acute and progress fast, our patient received good therapeutic effect with early combined treatment of dexamethasone and IVIG. So the early recognition and treatment may contribute to improve the prognosis of HLH.

In conclusion, DIC can be an initial symptom of HLH, which might be confused with sepsis. It is important for pediatricians to know the clinical characteristics of HLH for early treatment.

Conflict of Interest

Authors declare to have no conflict of interest.

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