A Case of Hemophagocytic Lymphohistiocytosis following Refractory Kawasaki Disease

Ein Fall von hämophagozytischer Lymphohistiozytose nach refraktärer Kawasaki-Krankheit

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a systemic inflammatory disorder characterized by uncontrolled histiocytic proliferation, hemophagocytosis, macrophage activation, and up-regulation of inflammatory cytokines (Grom AA., Current opinion in rheumatology 2003; 15: 587–590). HLH is usually divided into two types: primary (familial) HLH and secondary (reactive) HLH. Primary HLH is associated with primary immune deficiencies in which specific gene mutations play an important role, such as perforin defects. Secondary HLH has been associated with systemic diseases such as infections, malignancy, autoimmune disease, and immune-suppression. HLH can be secondary to systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis (JIA) (Al-Samkari H et al., Annual review of pathology 2018; 13: 27–49). Kawasaki disease (KD), which is also known as mucocutaneous lymph node syndrome (MCLS), causes panarteritis in infants and young children, especially from six months to five years old (Wang W et al., Seminars in arthritis and rheumatism 2015; 44: 405–410). KD has also been reported to be associated with secondary HLH in a few cases (Palazzi DL et al., The Pediatric infectious disease journal 2003; 22: 663–666), (Titze U et al., Pediatric blood & cancer 2009; 53: 493–495).

HLH and KD both have complicated immunological pathogenic processes. Activation of immune cells, especially T cells, is known as the initiation of immune injury in KD. Abnormal activation of immune cells releases large amounts of cytokines and inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (INF-γ), interleukin (IL-1, IL-6, IL-8, IL-10), endothelin, platelet growth factor, soluble adhesion molecules, and p-selectin (Kobayashi T et al., Clinical and experimental immunology 2007; 148: 112–118). These high concentrations of inflammatory cytokines are responsible for the acute phase of KD fever. Excessive activation and proliferation of immune cells leads to excessive release of inflammatory cytokines such as INF-γ, IL-1, IL-6, IL-18 and TNF-α,causing multisystem immune injury in HLH patients (Al-Samkari H et al., Annual review of pathology 2018; 13: 27–49). In this condition, the body fails to control infection and clear infected cells, leading to the persistence of antigenic stimuli. These persistent antigens stimulate an increased release of cytokines, ultimately leading to activation and proliferation of T cells. Collectively, the above findings indicate partial overlap of HLH and KD in terms of immunological mechanisms, as they share similar pathogenic processes involving cytokine patterns and immune imbalance. In the present study, we report a case report of hemophagocytic lymphohistiocytosis following refractory Kawasaki disease.

Case Presentation

A two-year-old boy presented at the Children's Medical Center of the Second Hospital of Shandong University after nine days of intermittent fever without chills or rigors. The patient was commenced on cephalosporin for nine days before his hospitalization. Coughing and marginal hepatomegaly appeared after initial presentation. The fever lasted for 30 days, with the highest temperature being 41.0 °C during the hospitalization. The occurrence of a scarlatiniform skin rash, which was a red, diffuse, and non-specific skin eruption that progressively presented on his face and had descended to his chest and back, led to suspicion of incomplete KD. Cervical lymphadenectasis existed continuously during the disease process. The patient was sometimes irritable. On the 12th day after initial presentation, the child had a convulsive seizure that lasted for 10 min and had an accompanying high fever above 40 °C. Additionally, desquamation of the fingertips eventually appeared. No redness of the eyes, petechia or polyarthritis was observed.

At admittance, the total leucocyte count (TLC) was 23.97 × 10^9/L, the differential counts consisted of 78.4 % neutrophils and 17.3 % lymphocytes, the hemoglobin level was 12.1 g/dl, the platelet count was 130 × 10^9/L, and the level of C-reactive protein (CRP) was 78.07 mg/L. Alanine transaminase (ALT) was 81 IU/L and aspartate transaminase (AST) 86 IU/L, and procalcitonin (PCT) was 8.25 ng/ml (markedly elevated). In contrast, on the 18th day after admittance, the TLC decreased to 5.07 × 10^9/L and the differential counts of neutrophils were reduced to 28.2 % and lymphocytes were raised to 61.2 %, respectively. Additionally, on the 18th day after admittance, the hemoglobin level was 7.4 g/dl, the platelet count was 52 × 10^9/L, the erythrocyte count was 2.52 × 10^{12}/L, and the CRP level was 18.13 mg/L; the ALT level rose to 115.2 IU/L (markedly elevated) and the AST level rose to 248.4 IU/L (markedly elevated). The PCT level was 5.001 ng/ml and the D-dimmer level was 4,666 ng/ml. The serum ferritin (SF) level was 59,718 mg/L (strikingly elevated), and triglyceride (TG) levels were 5.71 mmol/L (elevated; ►**Table 1**). A positive anti-nuclear antibody (ANA) revealed negative results eventually. Anti-double-stranded DNA (anti-dsDNA) was also invariably negative. The child exhibited coughing and crackles that were heard in the chest upon examination, additionally, chest X-ray image revealed bronchopneumonia with bronchial wall thickening and focal opacity. Blood culture testing once displayed Staphylococcus hominis (S. hominis) and urine cultures were sterile. Renal function tests were normal. Cerebrospinal fluid (CSF) analysis showed that two leukocytes and protein (1099 mg/L) while glucose and lactate were both normal. Microbiological examinations and hemophagocytosis of CSF were negative. Bone marrow aspiration demonstrated an infected marrow image with no evidence of malignancy or hemophagocytosis. Ultrasound of the abdomen demonstrated no splenomegaly. Echocardiography (ECHO) on admission (day 10 of illness) showed a marked dilatation of the bifurcation of the left coronary arteries (2.6 mm), normal ventricular function, and no pericardial effusion. Coronary artery dilatation was defined as the internal

▶ **Table 1** Laboratory investigations of the patient on admission and at the time of diagnosis of HLH.

Laboratory parameter	Normal value	Admission	At the time of diagnosis of HLH
Hb (g/dL)	12–14	12.90	7.40
TLC (x10^9/L)	8–12	23.97	5.07
N/L (%)	N = 30–50 % L = 50–70 %	78/17	28/61
Platelet count (×10^9/L)	100–400	130	52
CRP (mg/L)	0–10	78.07	18.13
ALT (U/L)	21–72	81	115.20
AST (U/L)	17–59	86	248.40
Serum triglycerides (mmol/L)	0–2.26	ND	5.71
Serum ferritin (mg/L)	30–400	ND	59,718
Serum fibrinogen (mg/dL)	2–4	ND	2.33
Procalcitonin (ng/mL)	0.04–0.25	8.25	5.00

Note. TLC = total leucocyte count, ND = not done.

lumen diameter > 2.5 mm in children < 3 years of age. Cervical lymph nodes demonstrated to be enlarged in ultrasound (the largest was about 1.9 cm × 0.7 cm). HSV, EBV, coxsackievirus, echovirus, and adenovirus were all negative. The function of NK cell was assayed at the Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College. This assay revealed that the activity of NK cells was normal. The positive rates of perforin and granzyme B expressions were 98.92 and 98.72 %, respectively, which were both within the normal range. Perforin and degranulation assays have been suggested to be preferentially performed to screen patients for primary HLH diseases (Rubin TS et al., Blood 2017; 129: 2993–2999). Soluble CD25 level was 14 196.34 pg/ml.

The diagnosis of classic KD is based on the presence of ≥ 5 days of fever and the presence of ≥ 4 of the 5 following principal clinical features: (1) erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; (2) bilateral bulbar conjunctival injection without exudate; (3) maculopapular, diffuse erythroderma, or erythema multiforme-like rashes; (4) erythema and edema of the hands and feet in the acute phase and/or periungual desquamation in subacute phase; (5) cervical lymphadenopathy (≥ 1.5 cm diameter), which is usually unilateral (Ayusawa M et al., Pediatrics international : official journal of the Japan Pediatric Society 2005; 47: 232–234). This child only met three of the five principal clinical symptoms (the third, fourth and fifth in the list above, ▶ **Table 2**); hence, classic KD could not be diagnosed. However, a diagnosis of incomplete KD was considered in this child since he had a prolonged unexplained fever, fewer than four of the principal clinical findings, and compatible laboratory and echocardiographic findings. According to a scientific statement for health professionals from the American Heart Association (AHA) (McCrindle BW et al., Circulation 2017; 135: e927-e999), other clinical, laboratory, and echocardiographic findings can support the diagnosis of incomplete KD in a patient whose clinical presentation suggests KD but whose clinical features do not meet the epidemiological case definition. As ▶ **Table 1** shows, this child with a fever ≥ 5 days and with three compatible clinical criteria on admission—anemia, elevated ALT level, and a white blood cell (WBC) count of ≥ 15 000/mm^3 (15x10^9/L))—should be diagnosed with suspected incomplete KD (McCrindle BW et al., Circulation 2017; 135: e927-e999). It is noteworthy that the presence of coronary artery abnormalities is considered a specific criterion supportive of the diagnosis of incomplete KD, particularly for those patients who do not meet the full clinical criteria for a diagnosis of complete KD. However, in the absence of a "gold standard" for diagnosis, the informed opinion of the expert committee of AHA cannot be evidence-based but, rather, represents an evaluation of suspected incomplete KD (McCrindle BW et al., Circulation 2017; 135: e927-e999). In accordance with the diagnostic criteria proposed by the HLH-2009 protocol (Filipovich AH., Hematology American Society of Hematology Education Program 2009, 2009.1 (127): 127–131), a diagnosis of HLH was made in which five of the following eight criteria were met: (1) fever; (2) splenomegaly; (3) cytopenia in two or more cell lines (hemoglobin < 9 g/dL, platelets < 100 × 10^9/L, and neutrophils < 1 × 10^9/L); (4) hypertriglyceridemia (> 3 mmol/L) or hypofibrinogenemia (≤ 150 mg/dL); (5) the presence of hemophgocytosis in the bone marrow, spleen, and lymph node; (6) elevated ferritin (≥ 500 ng/mL); (7) an impaired function of NK cells or an absence of NK cells; and (8) an increased concentration of serum soluble CD 25 (soluble interlukin-2 receptor, ≥ 2,400 IU/mL). Specifically, this patient met five of the eight criteria (the first, third, fourth, sixth, and eighth criteria in the list above).

After intravenous immunoglobulin (IVIG) levels reached 2 g/kg with aspirin in addition to empirical antibiotics (cefoxitin), intermittent fever still existed. Then, the patient received a multiple course of IVIG with a different antibiotic (linezolid) , which did not yield any improvements. In accordance with the ineffective results of these courses of treatments, refractory KD was diagnosed. Since the patient had a refractory fever, mer-

▶ **Table 2** Diagnostic Scoring in Hemophagocytic Lymphohistiocytosis (HLH) and Kawasaki Disease (KD) and Our Patient.

Clinical and laboratory features	KD	HLH	Patient
Fever	+	+	+
Conjunctivitis	+	–	–
Lymphadenopathy	+	–	+
Skin rash	+	–	+
Edema/desquamation	+	–	–
Splenomegaly	–	+	–
Cytopenia a	–	+	+
Hypertriglyceridemia/hypofibrinogenemia	–	+	+
sCD25 elevation	–	+	+
Hyperferritinemia	–	+	+
Absent NK function b	–	+	–
Hemophagocytosis	–	+	–

Note. sCD25 = soluble CD25. [a] Cytopenia in 2 or more cell lines (hemoglobin < 9 g/dL, platelets < 100×10^9/L, and neutrophils < 1×10^9/L). [b] The NK cell function test includes perforin and degranulation assays related to CD107a testing.

openem combined with vancomycin was used based on the drug sensitivity test of the blood culture results for the sake of caution. Meropenem was used for 21 days and vancomycin was used for 16 days. Subsequently, the patient was also treated with dexamethasone and methylprednisolone after the onset of HLH. Supportive treatment included blood transfusion (packed red cells at 15 ml/kg given once) and administration of an expectorant. After a refractory fever of 30 days, the patient recovered with consistently normal temperatures. The fever persisted for 17days after completion of IVIG infusion. Inflammatory markers also declined consecutively to be nearly normal ultimately. ECHO that was repeated 20 days after admission showed dilatation of the left main coronary artery (3.4 mm) and no thrombotic obliteration.

Discussion

In the present case, the patient had rash, desquamation, and cervical lymphadenopathy with a fever for ≥ 5 days. The successive ECHO analyses demonstrated persistent vascular ectasia. In addition, the patient presented no response to IVIG. Hence, this patient was diagnosed with refractory KD. Additionally, the patient exhibited a fever, cytopenias in two cell lines, hypertriglyceridemia, elevated ferritin and an increased concentration of serum soluble CD 25 (▶**Table 1**). Secondary HLH induced by KD manifested itself late after a prolonged and recurrent course of KD. The present findings from this case report suggest that when a KD patient exhibits elevated ALT and SF levels with a prolonged resistant fever and cytopenias, a suspicion of a progression from KD to HLH should be considered.

In all published cases of HLH accompanying KD, KD patients have had a prolonged or recurrent course, and the symptoms of HLH became apparent long after treatment initiation for KD (Palazzi DL et al., The Pediatric infectious disease journal 2003; 22: 663–666). Hence, both diseases should be considered in young children with concurrent KD-like and HLH-like manifestations. Notably, the finding of S. hominis in the blood culture might be not reflecting the true invasive bacterial infection but rather contributed to contamination as the particular blood culture finding of S. hominis is well known the issue of contamination remains. After meropenem combined with vancomycin was used, the fever still lasted for two weeks and the positive result was also followed by a negative rechecked blood culture. Hence, there was the very possibility that the finding of S. hominis in the blood might be contributed to contamination. Nevertheless, considering the complexity of the disease and the persistent fever, meropenem combined with vancomycin was used as blood culture remains the most accepted standard for the detection of bacteremia (Pai S et al., Expert review of anti-infective therapy 2015; 13: 1073–1088). Since the patient once developed a seizure, encephalitis and whether central nervous system (CNS) was involved should be suspected. The child was sometimes irritable but was otherwise in a good mental state during the course. Examinations of CSF appeared without definitive abnormalities or hemophagocytosis. Although the patient had a long period of a fever, his general condition and appetite were not significantly influenced. Considering HLH can occur secondary to autoimmune diseases-such as systemic onset juvenile idiopathic arthritis (SoJIA) and coronary artery dilatation has been recently recognized as one of the cardiac manifestations of patients with SoJIA (Al-Samkari H et al., Annual review of pathology 2018; 13: 27–49), the possibility of an evolving SoJIA should also not be ignored. In spite of the positive result of ANA initially, the patient showed no manifestation of arthritis.

HLH, a life-threatening disease, is reported to have a mortality rate of 8–22 % (Sawhney S et al., Archives of disease in childhood 2001; 85: 421–426). By contrast, the outcome of this child was promising without using immu-

nosuppressants (e. g. Cyclosporin A) other than steroids or cytotoxic drugs (e. g. etoposide - VP16). The child is currently on follow-up with a good health condition despite residual coronary artery dilatation. Collectively, our case report corroborates earlier reports that KD may lead to secondary HLH.

HLH can be classified and graded in detail according to symptoms and bone marrow aspiration results, as well as via other factors in order to better understand and treat this disease. Also, whether repeated bone marrow biopsy is imperative or not should be discussed further in future studies. If early diagnosis of the mild progression of HLH can be established, high-dose IVIG may be not indispensable in HLH-KD patients, which would avoid unnecessary hospitalization and financial burden. However, there is still a considerable lack of understanding of HLH-KD. Hence, some unknown common triggering mechanisms throughout HLH-KD or by which KD progresses to HLH are expected to be revealed in future studies.

Patient Consent

This report does not contain any personal information that could lead to the identification of the patient.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Bibliography

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