Hemophagocytic Lymphohistiocytosis (HLH) with History of Kawasaki Disease (KD)

Omar E. Alalawi MBBS* Salman M. Al-Khalifa MD, FAAP**

Hemophagocytic Lymphohistiocytosis (HLH) is an aggressive inflammatory systemic disease characterized by hyperinflammation and dysregulation of the immune system. HLH can be secondary to infections, such as Epstein-Barr virus (EBV), malignancy, immunodeficiency and Kawasaki Disease (KD) or primary due to familial mutations. Clinical manifestations are not specific, such as fever, skin rash, lymphadenopathy.

KD is a form of vasculitis affecting the medium-sized vessels; it is diagnosed by clinical criteria as there is no laboratory test to confirm the diagnosis. Clinical manifestations include fever, skin rash and lymphadenopathy. There is overlap of clinical manifestations of HLH and KD.

We report a three-year-old female who presented with clinical features of KD, but further investigations revealed the diagnosis of HLH. HLH is a rare disease and presents with non-specific clinical manifestations which overlap with other diseases. The diagnosis is often challenging and delayed.

Bahrain Med Bull 2020; 42 (1): 76 - 78

Childhood histiocytosis is a vast group of disorders characterized by their severity in clinical expression[1]. The reason for grouping these disorders together is the proliferation or accumulation of cells derived from monocytes-macrophages system of bone marrow origin[1]. The diagnosis of these disorders is often challenging[1].

Hemophagocytic lymphohistiocytosis (HLH) is a rare and aggressive disease due to hyperinflammation and dysregulation of the immune system in which inflammatory cytokines are up-regulated and histiocyte proliferation results in hemophagocytosis[1, 2]. This is a result of lack of downregulation, which normally activated by macrophages and lymphocytes; therefore, the end result of hyperinflammation is tissue destruction which leads to multiple organ dysfunction[2]. Hemophagocytosis is the engulfment of red blood cells, platelets, white blood cells or fragments of these cells by macrophages[2].

The terminology has been a cause of confusion. If the disease was caused by a familial gene mutation, the term primary HLH was used[2]. However, the term secondary HLH, also known as sporadic or acquired, was used in patients with no known familial mutation. However, both primary and secondary HLH have a genetic defect[2]. Hence, the term primary HLH, also known as familial hemophagocytic lymphohistiocytosis (FHLH) may cause confusion.

In addition, both primary and secondary HLH can be triggered by infections or immune activating events; however, when there is a typical known trigger identified for acute HLH, the patient is then described to have secondary HLH[2].

The main clinical finding of HLH is fever. Typical laboratory findings of cytopenia, high ferritin level, liver function abnormalities including coagulopathy and hypertriglyceridemia.

The diagnostic criteria are as follow: molecular diagnosis of HLH or 5 of the following 8 features: fever, splenomegaly, cytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, low or absent natural killer cell cytotoxicity, hyperferritinemia, elevated soluble CD25[1].

Treatment of HLH aims to suppress the triggers as well as to manage the hyperactivity of the immune system[3]. Chemotherapeutic agent Etoposide, Dexamethasone and hematopoietic stem cell transplantations (HSCT) are the mainstay of treatment[3]. Even with the use of chemotherapy, the fatality rate is high in FHLH. Allogeneic stem cell transplantation has shown high success rates in the treatment of FHLH[1].

KD is a form of vasculitis affecting the pediatric population, specifically infants and children below the age of 5 years[4]. The etiology of KD is not known and the disease is described as an acute febrile illness which leads to the formation of coronary artery aneurysms in approximately 25% of untreated cases[5]. In developed countries, KD is considered as a leading cause of acquired heart disease[5].

The diagnosis of KD is based on clinical criteria. Signs and symptoms typically include fever for more than five days, non-exudative conjunctival injections, cervical lymphadenopathy, polymorphic exanthem, such as maculopapular rash, erythema of the oropharynx or strawberry tongue and swelling of the hands and feet[5].

* Resident
** Consultant Pediatrician and Pulmonologist
Department of Pediatrics
Bahrain Defence Force Hospital - Royal Medical Services
Kingdom of Bahrain
E-mail: omar-1993alalawi@outlook.com

The treatment of KD includes intravenous immunoglobulin (IVIG) which decreases the incidence of coronary dilatation as well as the duration of febrile illness if given early[5].

The aim of this case presentation is to report a case of Kawasaki's disease, which might be associated with HLH.

THE CASE

A three-year-old female presented with history of fever and skin rash for three weeks. The patient developed redness in both eyes and cracked lips. The patient received multiple antibiotics without clinical improvement. The fever was responding to paracetamol which was given every six hours. Skin rash started to appear in the trunk and lower limb then all over the body. There was no joint pain or swelling. The parents denied any cough, harsh breathing, runny nose, diarrhea and constipation. There was no history of recent travel or sick contacts. Past medical history included similar episode of symptoms a year before and was diagnosed with Kawasaki disease, for which the patient received IVIG with significant improvement.

The patient was conscious and alert, vital signs were as follow: temperature 38.6 ○C (measured axillary), heart rate 135 beat/minute, respiratory rate 23 breath/minute, blood pressure 96/62 mmHg and oxygen saturation: 98% on room air.

The patient was well hydrated and showed no signs of respiratory distress or jaundice. However, cracked lips with strawberry tongue was noted along with redness in the oral cavity. Cervical lymphadenopathy was present mainly in the anterior cervical triangle with the largest lymph node measuring 2x1.5cm. Chest examination was clear with normal bilateral airway entry and no added sounds. Cardiovascular examination was not significant and normal S1 and S2 sounds were heard with no added sounds or murmurs. The abdomen was soft and lax without tenderness. A maculopapular skin rash was covering the whole body including the groin, face, back, trunk and extremities.

Laboratory investigation revealed anemia with low mean corpuscular volume and normal platelets and white blood cells. The liver function test and kidney function test were normal. Blood culture report showed no evidence of growth. C-reactive protein was elevated.

The patient was initially diagnosed as KD and did not improve following administration of IVIG with persistence of fever that was responding to paracetamol and ibuprofen. Due to lack of response to treatment, suspicion was raised about the diagnosis.

Labs and radiology revealed hypertriglyceridemia, hyperferritinemia, anemia and ultrasound showed splenomegaly. Antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA) and cytomegalovirus (CMV) IgM were negative. Urine analysis showed sterile pyuria.

Skeletal survey was normal. Echocardiography revealed normal heart structure and function without ectasia, dilatation or aneurysm in the coronary vessels.

Moreover, a bone marrow aspiration revealed significant hemophagocytosis and the diagnostic guidelines for HLH were met.

DISCUSSION

Our patient had typical signs and symptoms of KD and met the criteria of fever for more than five days associated with changes of the oral cavity and lips, polymorphous rash, bilateral non-purulent conjunctivitis and cervical lymphadenopathy more than 1.5 cm in diameter. The patient received a single dose of IVIG as part of management of KD, but no response. IVIG introduction as a part of management of KD to modulate the acute inflammatory process showed positive results[6].

The diagnosis of HLH was made because the diagnostic criteria of HLH were met: fever, splenomegaly, hyperferritinemia, hypertriglyceridemia and hemophagocytosis in the bone marrow.

The most common cause of secondary HLH is the Epstein-Barr virus (EBV)[7]. Our patient's blood test was positive for anti-EBV IgG, which could confirm that the patient had secondary HLH triggered by EBV.

KD and HLH are well known to cause prolonged fever and the clinical symptoms of HLH and KD overlap, as seen in our patient[8]. It is reported that there is a co-existence of HLH and KD and the mechanism is not known; however, hypercytokinemia is proposed to contribute in the pathogenesis of both HLH and KD[8].

The co-existence of HLH and KD was reported in a 4-month-old girl; the findings were similar to our case, in presenting with prolonged fever and a polymorphic skin rash[8]. In addition, another case was reported with recurrent KD and development of secondary HLH in a 6-year-old boy who presented with fever[9].

CONCLUSION

HLH is a rare disease entity which is not usually considered during presentation of a child with fever and skin rash. It is important to consider that HLH could trigger Kawasaki disease and should be considered in the differential of Kawasaki disease not responding to treatment.

Author Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None.

Competing Interest: None.

Sponsor Ship: None.

Acceptance Date: 16 November 2019.

Ethical Approval: Approved by the Research Ethics Committee of the Royal Medical Services at Bahrain Defence Force Hospital. Informed written consent was obtained from the patient's guardian.

REFERENCES

1. Histiocytosis Syndromes of Childhood. In: Kliegman R, Stanton B, St. Geme J, eds. Nelson Textbook of Pediatrics. 20th Edition. Philadelphia, PA: Elsevier Saunders; 2016: 2484-2488.
2. UpToDate. McClain KL, Eckstein O. Clinical Features and Diagnosis of Hemophagocytic Lymphohistiocytosis. https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis Accessed on 04 April 2019.
3. Schram AM, Berliner N. How I Treat Hemophagocytic Lymphohistiocytosis in the Adult Patient. Blood Journal 2015; 125: 2908-2914.
4. Hassan B, Kalis NN. Early Compared to Late Presentation of Kawasaki Disease. Bahrain Medical Bulletin 2010; 32(1).
5. Engorn B, Flerlage J, eds. The Harriet Lane Handbook. 20th edition. Philadelphia, PA: Elsevier Saunders; 2015: 166-168.
6. Burns JC, Franco A. The Immunomodulatory Effects of Intravenous Immunoglobulin Therapy in Kawasaki Disease. Expert Rev Clin Immunol 2015; 11(7): 819–825.
7. Kang HR, Kwon YH, Yoo ES, et al. Clinical Characteristics of Hemophagocytic Lymphohistiocytosis following Kawasaki Disease: Differentiation from Recurrent Kawasaki Disease. Blood Res 2013; 48(4): 254–257.
8. Doğan V, Karaaslan E, Özer S, et al. Hemophagocytosis in the Acute Phase of Fatal Kawasaki Disease in a 4 Month-Old Girl. Balkan Med J 2016; 33(4): 470–472.
9. Al-Eid W, Al-Jefri A, Bahabri S, et al. Hemophagocytosis Complicating Kawasaki Disease. Pediatr Hematol Oncol 2000; 17:323–9.