## Case report

# Hemophagocytic lymphohistiocytosis (HLH)

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**Abstract**

Hemophagocytic lymphohistiocytosis (HLH This aggressive and potentially life-threatening disease most often affects infants from birth to 18 months of age, but cases in older children and adults have been reported. We describe a 14-year-old boy whom (HLH) developed. He suffered from fever with disturbed level of conciseness. Physical examination revealed drowsy but easily arousal, pallor, no cyanosis, no jaundice, faint macular rash, soft distended abdomen, and hepatomegaly. Laboratory findings were abnormal liver function, coagulopathies, hypertriglyceridemia, high renal indices, urinalysis show hematuria and proteinuria, anemia, thrombocytopenia, high serum ferritin level and abnormal bone marrow findings.

**Key words:** Hemophagocytic lymphohistiocytosis

## Introduction

Hemophagocytic lymphohistiocytosis (HLH) is also known as autosomal recessive familial hemophagocytic lymphohistiocytosis (FHL), familial erythrophagocytic lymphohistiocytosis (FEL), and viral-associated hemophagocytic syndrome (VAHS) (1-5). Use of the term "primary HLH" to denote the presence of an underlying genetic disorder and "secondary HLH" to denote presence of the HLH phenomenon occurring secondary to another condition (eg, viral illness, autoimmune disease, lymphoma) has caused a great deal of confusion among clinicians. This reflects the fact that in patients with inherited mutations predisposing to HLH, clinical symptoms are often triggered by viral infections. The pathway implicated in most instances of HLH, the lack of perforin-dependent cytotoxicity, is an essential function of natural killer (NK) and cytotoxic T lymphocytes (6, 7), These cells normally store perforin and granzyme proteins in specialized secretory lysosomes that are secreted when they encounter a virally-infected or tumor-derived target cell, leading to apoptosis., Here we describe a 14-year-old boy whom HLH developed secondary to overwhelming sepsis.

The diagnosis of HLH requires the presence of five of the following criteria. If a patient meets only four criteria and the clinical suspicion for HLH is high, one must initiate appropriate treatment, as delays may be fatal.

Diagnostic criteria— the diagnosis of HLH is dependent on a defined set of presenting major signs and symptoms, including the following (1):

1-Fever: peak temperature >38.5°C for seven or more days

2-Splenomegaly: spleen palpated >3 cm below the left costal margin

3-Cytopenia involving two or more cell lines (hemoglobin <9.0 g/dL, or platelets <100,000/µL, or absolute neutrophil count <1000/µL)

4-Hypertriglyceridemia or hypofibrino-genemia

5-Hemophagocytosis: demonstrated in bone marrow, spleen, or lymph node; no evidence for malignancy

6-Hepatitis

7-Low or absent natural killer cell activity

8-Serum ferritin level >500 µg/L (although >3000 µg/L is a more realistic cut off to

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exclude infections and autoimmune diseases
9-Soluble CD25 (sIL-2 receptor) >2400 U/mL

## Case report

a 14-year-old boy presented with history of high grade fever and drowsiness for one week duration The condition started 3 weeks ago as increase in body temperature, joint pain and headache, the patient admitted to the hospital for two weeks duration, investigations were done for him, ESR = 107 mm/hr, S. ferritin =25.000 µg/L, CBC show leukocytosis mostly neutrophils, CRP titer was high>8mg/dl and L.P. done and it was normal.
The patient managed with double antibiotics (ceftriaxone and vancomycin) after that the patient discharged home on his family responsibility.
They visit a rheumatologist who treated him by nonsteroidal anti-inflammatory drugs as an outpatient basis for four days duration, but with no benefit.
The patient condition deteriorated more regarding his conscious and decreasing urine output and the family visit a consultant pediatrician, who did other investigations which shows increase in renal indices, he advised to consult a pediatric nephrologist who admitted the patient to the hospital for urgent peritoneal dialysis as blood urea was 215.46 mg/dl and serum creatinine 4.94 mg/dl subsequently a four sessions of hemodialysis done (each session last for two hour duration)

On examination: temperature was 40 centigrade axillary corrected , heart rate 138 beat per minute, respiratory rate 21 breath per minute, blood pressure = 75/35 mm Hg, delayed capillary refill time

The patient looks pale, drowsy, no jaundice or cyanosis, macular rash in the face, non-itchy and fade on pressure.
Chest examination reveals good air –entry with no added sounds, heart normal 1st and 2nd heart sounds with no murmur or pericardial rub.
Soft distended abdomen, hepatomegaly, and 6cm below costal margin, rounded edge, smooth surface, non-tender with clinical evidence of ascites (positive shifting dullness and transmuted thrill). Fundoscopy was normal.

## On Admission

Initial **CBP** showed Hb 9.9 gm /dl, WBC-14000 /cmm, platelets 158000/cmm. **Blood film**: mild hypochromic anemia with left shift leukocytosis.
After five days of admition the **CBP** showed Hb 4.2 gm /dl, WBC- 7040 /cmm, platelets 67000/cmm.
**Liver function test :** SGPT 708.66 U/L, SGOT 670 U/L, alkaline phosphatase 105 unit /ml , total serum bilirubin 2.13 mg/dl, S. albumin 2.83 g/dl, total S. protein 5.69 g/dl, S. glucose 156.13 mg/dl.
Prothrombin time 26.6 (sec), APTT 39.2 (sec), bleeding time 2.72 minute.
**Serology for hepatitis** negative
**Urinalysis**: RBC+++, protein+
**CRP** 1.04 mg/dl
$S.Na^{+}$142 mg/dl, $S.K^{+}$4.7 mg/dl, $S.CL^{-}$111 mg/dl, $S.Ca^{++}$6.5 mg/dl
Complement C3 level 84.4 mg/dl, Complement C4 level 45.6 mg/dl, ANA 0.43 IU/dl, Anti-DS.A 18.2 IU/dl
**Echocardiography:** moderate pulmonary hypertension, mean 40mmHg, systolic 80mmHg, dilated pulmonary arteries.
**ECG:** normal, apart from tachycardia
**Bone marrow (B.M) examination**, which was performed as a further work up of hematologic abnormalities as shown in figure 1 hypocelluler marrow in fragment and trials.
Megakaryocytes look well representative with different stage of maturation.
Erythropoiesis: look hypocelluler with normoplastic maturation.
Granulopoiesis: look active with different stage of maturation to segmented forms. There is no excess in blast cells.
Reticuloendothelial cells activity: prominent histiocytic activity and some showing hemophagocytic features.

**Conclusion**: Hypocellular marrow to patient age with prominent histiocytic activity.

He was diagnosed a HLH secondary to overwhelming sepsis, treated with:

Dialysis in form of: (peritoneal dialysis and hemodialysis)

Dopamine as inotropic to support blood pressure

Meropenem 60mg/kg/day

Methyl prednisolone (pulse therapy) 500mg/$m^2$

Loop diuretics and captopril for pulmonary hypertension

Cryo ppt for the coagulopathy

Blood transfusion four pints for the anemia

## Discussion

Many children with HLH are probably not diagnosed, so its incidence may be higher, as suggested by the following observation:

1. The difficulty in making the diagnosis is illustrated by the results of one series in which the diagnosis of HLH was made antemortem in only 11 of 32 patients with HLH (8)

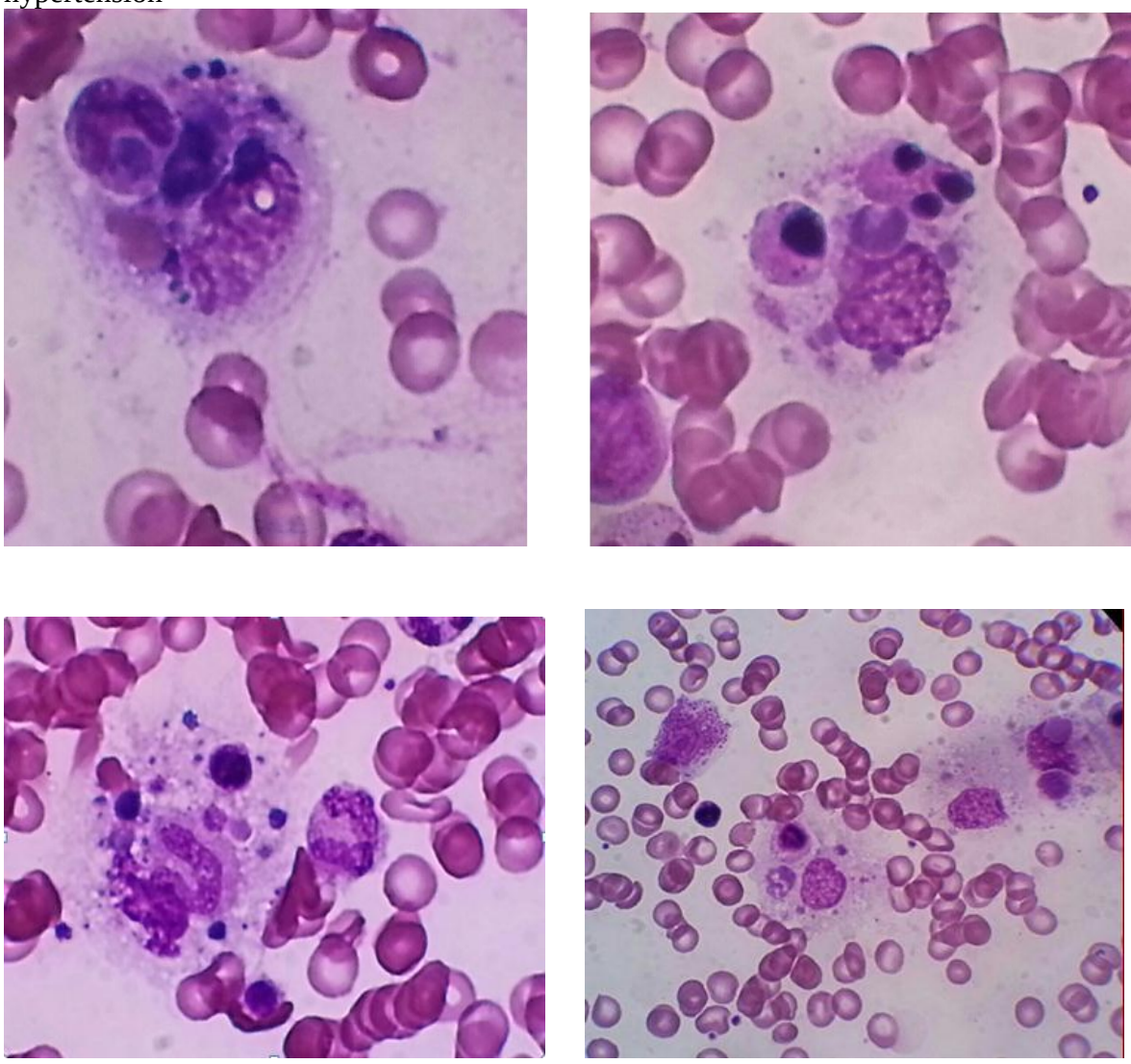

**Figure** 1. Bone marrow slides

2. Initial signs and symptoms of HLH are the same as, or mimic, common infections, fever of unknown origin, hepatitis, multiple organ failure syndrome, encephalitis, and even child abuse.

Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal disorder of children and adults due to cytokine dysfunction, resulting in uncontrolled accumulation of activated T-lymphocytes and activated histiocytes (macrophages) in many organs (9-10). HLH may be familial, associated with a number of different infections, autoimmune disorders, or coincident with a number of malignancies.

When to suspect and diagnose HLH — Initial signs and symptoms of HLH are the same as, or mimic, common infections, fever of unknown origin, or hepatitis. HLH should be suspected in those with fever, splenomegaly, cytopenias, elevated triglyceride and ferritin levels, and hemophagocytosis demonstrated in bone marrow, spleen, or lymph nodes.

Differential diagnosis — HLH may simulate a number of conditions, such as infectious fever, hepatitis, encephalitis, multiple organ failure syndrome, and acute respiratory distress syndrome. A similar condition, macrophage activation syndrome (MAS) may be seen in patients with systemic juvenile idiopathic arthritis or systemic lupus erythematosus.

The patient described here showed typical clinical and laboratory feature of HLH, Triggering episodes like infection, among the infections associated with HLH are Epstein-Barr virus, cytomegalovirus, parvovirus, herpes simplex, varicella-zoster, measles (11), as well as human herpes virus-8 and HIV infection, alone or in combination ( 12-13 ). HLH may coincide with various bacterial infections (Brucella, gram negative bacteria, and tuberculosis), parasites (Leishmaniasis), and fungal infections (14).

The diagnosis of HLH is dependent on a defined set of presenting major signs and symptoms, requires the presence of five of the previous described criteria

The patient described here showed typical six criteria: fever for 14days duration, dicytopenia, hypertriglyceridemia, hemophagocytosis demonstrated in bone marrow, hepatitis like picture and high serum ferritin level.

PCV dropping in second, third, fourth and fifth days consequently as follow (27%,18%,15%,10%).

Four blood transfusions alternate with fresh frozen plasma and cryo ptt and three doses of vitamin k were given.

Meanwhile start urgent peritoneal dialysis followed by uncuffed nontunneled dialysis catheter, inserted in the femoral vein (which is the second choice in patients with acute kidney injury according to KDIGO clinical practice guideline for acute kidney injury),and four sessions of heparin free heamodialysis performed , intra peritoneal bleeding stopped (checked by intra peritoneal tapping) after ten days from admission, fever subsided with marked improvement of general condition and patient discharged with oral prednisolone 1mg/kg for one month then tappering slowly for another one month.

In summary, we report a case of HLH triggered by severe infection in 14-year- old boy, which could be the 1st case described in Iraq.

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