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## WHAT'S YOUR DIAGNOSIS?

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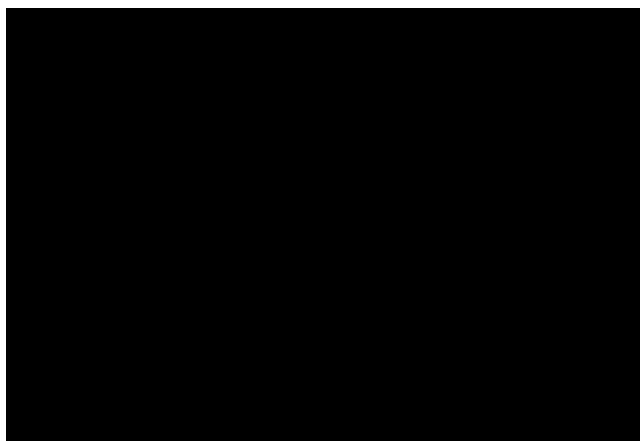


FIGURE 1.

### History

A 15-month-old boy presented with high-grade fever, abdominal distention and pallor of two weeks' duration. The past medical history, review of systems, and family history were unremarkable. The child had not received blood transfusions prior to the onset of this illness. He traveled to Taif, in the Western part of Saudi Arabia, one week prior to the onset of his symptoms. On physical examination, he was pale and sick-looking. His temperature was 39°C; vital signs were normal. He had hepatomegaly and marked splenomegaly, but the rest of the examination was within normal limits. Laboratory findings were as follows: white blood cell count  $5.7 \times 10^9/L$  (20% polymorphonuclear cells, 13% bands and 55% lymphocytes); hemoglobin 66 g/L; platelet count  $20 \times 10^9/L$ ; blood smears for malaria were negative; alanine

serum transferase 71 IU/L (normal: 10-45 IU/L), alanine aminotransferase 108 IU/L (normal: 10-50 IU/L), alkaline phosphatase 846 IU/L (normal: 60-350 IU/L); prothrombin time 15.3 second (normal: 10-13.3 sec.) and partial thromboplastin time 38.1 sec. (normal: 25-34 sec.); serum triglycerides 5.8 mmol/L (normal: 0.4-1.8 mmol/L); serum ferritin 955 (normal: 22-322  $\mu\text{g/L}$ ); serology for cytomegalovirus, Epstein-Barr virus, hepatitis B and C viruses, human immunodeficiency virus, toxoplasma, leishmania, and schistosoma were negative; quantitative immunoglobulins were normal. Culture of the blood, bone marrow, and urine did not reveal any pathogens. Bone marrow aspirate was performed and the smear is shown in the above picture.

1. What abnormality can be seen?
2. What is the differential diagnosis?
3. How is the diagnosis confirmed?

ANSWER TO WHAT'S YOUR DIAGNOSIS? (PREVIOUS PAGE)

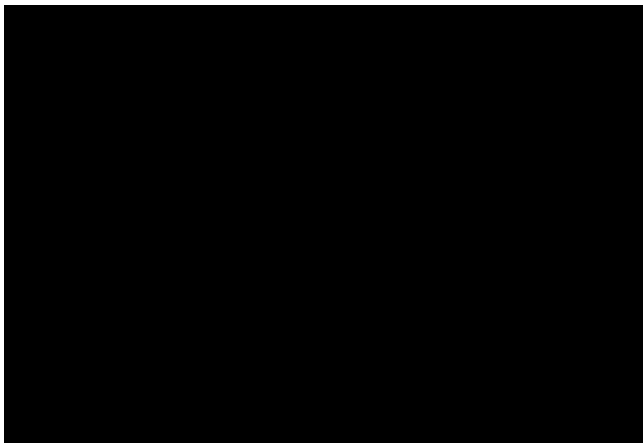


FIGURE 1. The smear shows a normocellular bone marrow with hemophagocytosis, where the scattered histiocytes engulf erythrocytes, platelets and leukocytes.

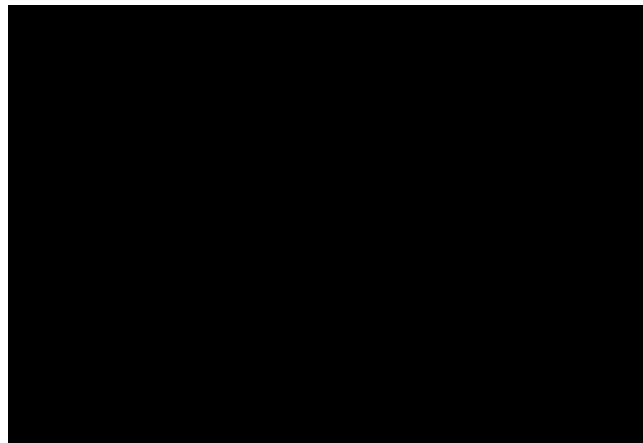


FIGURE 2. Splenic puncture from a patient with hemophagocytic syndrome showing increased histiocytes and hemophagocytosis.

**Diagnosis:** Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome.

**Differential diagnosis:** The differential diagnosis includes infection, e.g., leishmania, Epstein-Barr virus, cytomegalovirus, and malaria. Hematopoietic malignancies, especially leukemia and lymphoma, are major considerations as well. Hemophagocytic syndrome is an important differential in a child with such a clinical presentation.

**Discussion:** Hemophagocytic lymphohistiocytosis (HLH) embraces a group of disorders, including familial and sporadic hemophagocytic syndrome, and viral (or other infections) associated hemophagocytic syndrome. The condition may occur in association with underlying hematopoietic malignancies, and congenital or acquired immunodeficiency. It is an important differential diagnosis in infants presenting with fever and hepatosplenomegaly. The clinical presentation may mimic infectious mononucleosis, septicemia, malignancy, encephalitis and autoimmune disorders. Eighty percent of familial hemophagocytic syndromes present before two

years of age. The criteria for diagnosis of HLH are listed in Table 1. It is associated with a high mortality rate.

In HLH, there is infiltration of the bone marrow, spleen, lymph nodes, liver, meninges and other tissues by ordinary, but activated, histiocytes. Hemophagocytosis is the hallmark of the disease and is seen principally in spleen, bone marrow, lymph nodes and the central nervous system. The diagnosis of this disease is confirmed by bone marrow aspiration and biopsy; however, the bone marrow may be negative initially, and repeated bone marrow specimens may be necessary to confirm the diagnosis. Material obtained by splenic puncture may confirm the disease much earlier in the disease process than the bone marrow. Lymph node biopsy or liver biopsy may also show evidence of hemophagocytosis.

Familial HLH is uniformly fatal. Prognosis of HLH that is associated with other diseases depends on the underlying etiology. Infection-associated HLH carries 30%-50% mortality.

Treatment with steroid and VP-16 controls the disease in most cases; however, the recurrence rate is very high. Results of bone marrow transplantation for this condition are promising.

TABLE 1. *Clinicopathological criteria for the diagnosis of hemophagocytic lymphohistiocytosis.<sup>1</sup>*

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Fever: $\geq 38.5^{\circ}\text{C}$ for seven or more days
Splenomegaly: 3 cm or more below the costal margin
Two of the following hematological abnormalities:
Anemia: less than 90 g/L hemoglobin
Thrombocytopenia: less than 100 platelets/ $10^9$ /L
Neutropenia: less than 1.0 neutrophils/ $10^9$ /L
Hypertriglyceridemia: greater than 2.0 mmol/L or 3 SD over the normal value for the patient's age; OR:
Hypofibrinogenemia: fibrinogen less than 1.5 g/L or 3 SD below the normal value for the patient's age
Hemophagocytosis in bone marrow, spleen or lymph node
No evidence of hypoplastic bone marrow* or malignancy neoplasia*

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\*These criteria do not apply to a secondary hemophagocytic syndrome.

### Acknowledgements

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### References

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