Hemophagocytic syndrome

Melissa Hovanetz, MD

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Case Study

- 9 y/o male with 2-week history of fevers, cough, dyspnea, vomiting
- Lymphadenopathy, pancytopenia
- Viral pneumonia-like picture
Peripheral blood
Bone marrow aspirate
Bone marrow aspirate
Bone marrow biopsy
Bone marrow biopsy
Lymph node biopsy
Case Study - Diagnosis

- **Lymph node:** Hemophagocytic lymphohistiocytosis, etiology undetermined
  - Negative for CMV, EBV, Parvovirus

- **Bone marrow:** Extensive hemophagocytosis
  - No leukemia or lymphoma

- **Viral-associated hemophagocytic syndrome (VAHS)**
  - HHV-6 serology = 3.56 (>1.11)

- Transferred to MDACC
Syndrome Definition

“Hemophagocytosis” – Process by which macrophages engulf RBCs, WBCs, platelets and their precursors

Hemophagocytic syndrome = Hemophagocytic lymphohistiocytosis (HLH)
  – Two main groups: Genetic and acquired
  – Highly active yet ineffective immune response that is life-threatening
HLH – Clinical Criteria

- **Cardinal sx:** Fever, cytopenias, SM (LAD, skin rash, CNS)

- **Laboratory findings**
  - Elevated triglycerides, ferritin, transaminases, bilirubin, sCD25 (alpha chain of soluble IL-2 receptor)
  - Decreased fibrinogen

- **Histopathology:**
  Hemophagocytosis seen in spleen, BM, LN, CNS, skin, liver (but not always present)

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**Table 3. Diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH).**

1. Familial disease/known genetic defect
2. Clinical and laboratory criteria (5/8 criteria)
   - **Fever**
   - **Splenomegaly**
   - **Cytopenia ≥ 2 cell lines**
     - Hemoglobin < 90 g/L (below 4 weeks < 120 g/L)
     - Neutrophils < 1 x 10^9 /L
   - **Hypertriglyceridemia and/or hypofibrinogenemia**
     - Fasting triglycerides ≥ 3 mmol/L
     - Fibrinogen < 1.5 g/L
   - **Ferritin ≥ 500 µg/L**
   - **sCD25 ≥ 2400 U/mL** §
   - Decreased or absent NK-cell activity
   - Hemophagocytosis in bone marrow, CSF or lymph nodes

Supportive evidence are cerebral symptoms with moderate pleocytosis and/or elevated protein, elevated transaminases and bilirubin, LDH > 1000 U/L
HLH - Pathophysiology

- Proliferation of activated macrophages/histiocytes that phagocytose RBCs, WBCs, platelets

- Nonmalignant, but fatal without treatment

- Not clonal
  - Contrast with Langerhans cell histiocytosis
HLH - Pathophysiology

- **Theory:** Inappropriate immune reaction caused by proliferating, active T cells and macrophages with inadequate apoptosis of immunogenic cells

- **Impaired cytotoxic function of NK cells and CTLs**
  - Decreased NK activity with persistent T-cell activation

- **Cytokine hypersecretion, inflammatory response**
  - IFN-gamma, TNF-alpha, IL-6, IL-10, M-CSF
  - Responsible for clinical signs, cytopenias, coagulopathy, high triglycerides
  - Infiltrate tissues and lead to necrosis and organ failure
Table 1. Classification and underlying conditions of hemophagocytic lymphohistiocytosis (HLH).

**Genetic HLH**

- Familial HLH (Farquhar disease*)
  - Known gene defects (perforin, munc 13-4, syntaxin 11)
  - Unknown gene defects
- Immune deficiency syndromes
  - Chédiak-Higashi syndrome (CHS)
  - Griscelli syndrome (GS)
  - X-linked lymphoproliferative syndrome (XLP)

**Acquired HLH**

- Exogenous agents (infectious organisms, toxins)
  - Infection-associated hemophagocytic syndrome (IAHS)
- Endogenous products (tissue damage, metabolic products)
- Rheumatic diseases
  - Macrophage activation syndrome (MAS)
- Malignant diseases

* Familial HLH was first described by Farquhar and Claireaux in 1952
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- AR inheritance
- Present as young children
- Poor prognosis
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- AR inheritance
- Chronic pyogenic infections
- Oculocutaneous albinism
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- Very rare
- AR inheritance
- Silver hair
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- Predilection for fatal EBV-induced mononucleosis
- Hypogammaglobulinemia
- Risk for lymphoma
Mechanisms of Genetic HLH: Defective cytotoxic function

Table 2. Genetic defects in hemophagocytic lymphohistiocytosis.

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<tr>
<th>Disease</th>
<th>Chromosome Location</th>
<th>Associated Gene</th>
<th>Gene Function</th>
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<tr>
<td>FHLH-1</td>
<td>9q21.3-22</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>FHLH-2</td>
<td>10q21-22</td>
<td>PRF1</td>
<td>Induction of apoptosis</td>
</tr>
<tr>
<td>FHLH-3</td>
<td>17q25</td>
<td>UNC13D</td>
<td>Vesicle priming</td>
</tr>
<tr>
<td>FHLH-4</td>
<td>6q24</td>
<td>STX11</td>
<td>Vesicle transport; t-SNARE</td>
</tr>
<tr>
<td>GS-2</td>
<td>15q21</td>
<td>RAB27A</td>
<td>Vesicle transport; small GTPase</td>
</tr>
<tr>
<td>CHS-1</td>
<td>1q42.1-q42.2</td>
<td>LYST</td>
<td>Vesicle transport; not further defined</td>
</tr>
<tr>
<td>XLP</td>
<td>Xq25</td>
<td>SH2D1A</td>
<td>Signal transduction and activation of lymphocytes</td>
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Abbreviations: FHLH, familial hemophagocytic lymphohistiocytosis; GS, Griscelli syndrome; CHS, Chédiak-Higashi syndrome; XLP, X-linked lymphoproliferative syndrome.
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- After strong immune activation
- Little incidence data
Mechanisms of Infection-associated HLH

- EBV infection with monoclonal T-lymphocyte expansion
- Apoptosis and end-organ damage
- Fever
- IL-1, TNF-α
- TNF-α
- IL-1, IL-6, IL-18
- ?
- Sepsis or infection with intracellular organisms
- Hemophagocytosis with pancytopenia
HLH and Infection

- Viruses, bacteria, parasites, spirochetes, mycobacteria, fungi

- Difficulty distinguishing acquired from familial
  - Familial cases may be precipitated by infection
  - May mimic an infectious illness
HLH and Infection

- Impractical to exclude all possible infectious causes
- If HLH criteria are met, then screen for EBV, CMV, parvovirus B19, HIV
- History should guide testing
  - Animal exposure: Brucella, Rickettsia
  - Travel exposure: Leishmania, malaria
HLH and other Associations

- Malignancy
  - T-cell lymphoma

- Autoimmune diseases
  - Macrophage activation syndrome
  - Juvenile RA, Still’s disease, SLE
HLH - Laboratory

- CBC, AST/ALT, bilirubin, TG, ferritin, coags (fibrinogen)
- Bone marrow: Insensitive
  - May be negative in 2/3 of initial aspirates
  - Dysplastic RBCs → myelodysplasia
- sCD25 >2400 U/ml
  - Highly specific serum parameter
- NK cell perforin expression by flow cytometry
- Genetic testing
  - PRF1, Munc13-4 available at Cincinnati Children's Hospital
HLH - Treatment

- Immediate goal: Immune suppression
  - Corticosteroids
  - Dexamethasone: Preferred, Xs BBB > prednisolone
  - Cyclosporin A: prevents T cell activation
  - Etoposide: Critical for EBV-infected pts, inhibits EBNA synthesis in EBV-infected cells

- Genetic HLH: Bone marrow transplant
More Information

- The Histiocyte Society
- www.histio.org
References

- Dr. Uthman

- Fisman, DN. Hemophagocytic syndromes and infection. *Emerging Infectious Diseases* (6), Nov-Dec 2000.

