Widening the Differential: a Case of Hemophagocytic Lymphohistiocytosis Disguised as a Fever of Unknown Origin

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**Introduction:**

Hemophagocytic Lymphohistiocytosis (HLH) is an under recognized, aggressive inflammatory disease characterized by excessive activity of histiocytes and lymphocytes. The HLH-2004 guidelines, which were designed for a pediatric population, require 5 of 8 criteria to diagnose HLH.

**HLH-2004 Guidelines (5 of 8 criteria):**

- Cytopenias affecting ≥ two cell lines
- Splenomegaly
- Fever > 38.5
- Evidence of Hemophagocytosis in bone marrow, spleen or lymph nodes
- Hypertriglyceridemia or Hypofibrinogenemia
- Hyperferritinemia
- High Levels of Soluble CD25
- Low NK Cell Activity

Once HLH is established, investigations into the etiology must be pursued. The most common etiologies of HLH are:

- Infectious (EBV, CMV, HIV, Tuberculosis, Histoplasmosis)
- Malignant (Lymphoma, Leukemia)
- Autoimmune (Systemic JIA, SLE)

**References:**


Case:

A 38 year old man with no significant past medical history presented four times:

1. He originally presented with diffuse abdominal pain and a fever, and subsequently had an appendectomy that revealed mild inflammation.
2. He returned with continued fever, night sweats and abdominal pain, but a definitive diagnosis was not made.
3. He returned again with continued fever and was found to have hepatosplenomegaly and lymphadenopathy. He was diagnosed with atypical mononucleosis secondary to EBV.
4. Finally, he presented with recurrent fevers and respiratory distress.

Exam: Significant for bilateral rhonchi, hepatosplenomegaly and a new truncal rash

Diagnosis: 5 of 8 HLH Criteria were met, including:

- Fever
- Splenomegaly
- Anemia with Thrombocytopenia
- Hypertriglyceridemia
- Elevated Ferritin

The patient was ultimately diagnosed with HLH secondary to ALK-positive Anaplastic Large Cell Lymphoma via lymph node and bone marrow biopsies and underwent CHOP-E chemotherapy.

**Discussion:**

- HLH is a rare condition that is challenging to diagnose because it presents with common clinical signs and symptoms; a high index of suspicion is required to diagnose HLH.
- The 2016 Bone Marrow (BM) score, can assist in early detection of HLH in an adult population.
- Consider HLH when identifying etiologies of FUO.

**2016 Bone Marrow (BM) Score:**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
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<tbody>
<tr>
<td>Fever &gt; 38.5</td>
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<tr>
<td>Splenomegaly</td>
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<tr>
<td>Cytopenias affecting ≥ two cell lines</td>
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<tr>
<td>Evidence of Hemophagocytosis in bone marrow, spleen or lymph nodes</td>
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<tr>
<td>Hemoglobin &lt;10 gm/dL</td>
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<td>Platelets &lt; 100x10^9/L</td>
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<td>Leukocytosis</td>
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<td>Hyperbilirubinemia</td>
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<td>Hyperferritinemia</td>
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<tr>
<td>Splenomegaly</td>
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</tbody>
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**Image 1:** Non-blanching, erythematous, macular truncal rash in our patient