Secondary HLH in A 25-Year-Old Female on Adalimumab

Mohit Chandi, Alexander Hoffman, Andrew V. Stern DO, Sohail Sarwar MD

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening disease that usually affects young adults and children. Its incidence is estimated to be approximately 1.2 cases per 1,000,000 individuals per year. It is characterized by an overactivation of lymphocytes and macrophages which secrete cytokines leading to an uncontrolled immune response. It can be caused by gene mutations or in association with malignancy, infection, autoimmune disease or immunodeficiency (secondary).

CASE HISTORY

A 25-year-old African American female with past medical history significant for seronegative rheumatoid arthritis and childhood Behcet disease, who was recently starting a new biologic agent with severely elevated inflammatory markers. Fourteen days after receiving her first dose of adalimumab she presented to emergency department with a four-day history of fevers, nausea, vomiting, watery diarrhea, headache, and cough. Physical exam was significant for a sick appearing female but otherwise was a reassuring exam. Vitals BP 106/54 Temperature 39.5 C Pulse 115 Respiration rate 20. Concerns were raised for HLH vs Macrophage Activation Syndrome in the setting of her rheumatoid arthritis and starting a new biologic agent with severely elevated inflammatory markers.

LAB VALUES

<table>
<thead>
<tr>
<th>FERRITIN</th>
<th>&gt;40,000 mg/L</th>
<th>IL2 Receptor, Soluble</th>
<th>4245.6</th>
<th>125</th>
<th>94</th>
<th>13</th>
<th>88</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRON</td>
<td>33</td>
<td>Triglyceride</td>
<td>283</td>
<td>3.7</td>
<td>20</td>
<td>0.96</td>
<td>7.5 g/dL</td>
</tr>
<tr>
<td>TRANSFERRIN</td>
<td>95</td>
<td>Lactate Dehydrogenase (LD)</td>
<td>1928</td>
<td>445</td>
<td>445</td>
<td>112k/uL</td>
<td></td>
</tr>
<tr>
<td>SATURATION</td>
<td>28</td>
<td>AST</td>
<td>94</td>
<td>25.1%</td>
<td>25.1%</td>
<td>112k/uL</td>
<td></td>
</tr>
<tr>
<td>IRON BINDING CAPACITY</td>
<td>119</td>
<td>ALT</td>
<td>94</td>
<td>7.5 g/dL</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

THERAPEAUTIC INTERVENTION

The patient met 4/8 of the diagnostic criteria for HLH (fever, bicytopenia, elevated ferritin, hypertriglyceridemia, elevated IL-2 receptor), had supporting lab data including hyponatremia, elevated liver function tests, elevated LDH and there was a high clinical suspicion from consulting specialists. Hematology/oncology was consulted and recommended starting high dose steroid treatment for suspected HLH. The patient’s hematologist was contacted and recommended holding Humira until she could be seen in the office later that week. During her clinical course, she improved rapidly and was able to be discharged two days later on high dose and a long taper of dexamethasone. She was also switched to tocilizumab to treat her rheumatoid arthritis.

REFERENCE


DISCUSSION

• HLH is a rare, severe hyperinflammatory syndrome that may be genetic (primary) or acquired (secondary). Acquired or secondary HLH is much more common in adults, however, little is known about management.

• HLH 2004-diagnostic criteria was developed for children and is commonly applied to adults even though it has not been validated for adults.

• Therefore, the diagnosis of HLH in adults should be based on the HLH-2004 diagnostic criteria in conjunction with clinical judgment and the patient’s history.

• The temporality of initiation of immunotherapy (Adalimumab) with development of a phenotype consistent with HLH suggests that immunotherapy may cause secondary HLH.

• Mortality is high for patient’s with HLH making early detection and treatment critical.

• HLH should be on the differential diagnosis for any patient presenting with hyperferritinemia, unexplained cytopenias and fever.

HLH DIAGNOSTIC CRITERIA USED IN THE HLH-2004 TRIAL

A. Molecular diagnosis consistent with HLH: pathologic mutations of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4 or

B. Five of the 8 criteria listed below are fulfilled:

1. Fever ≥38.5°C
2. Splenomegaly
3. Cytopenia (afflicting at least 2 of 3 lineages in the peripheral blood)
   - Hemoglobin <9 g/dL (infants <4 weeks: hemoglobin <10 g/dL)
   - Platelets <100 × 10^9/L
   - Neutrophils <1 × 10^9/L
4. Hypertriglyceridemia (fasting, >265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin >500 ng/mL
8. Elevated sCD25 (α-chain of IL-2 receptor)

Table adapted from Jordan et al.

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