CASE REPORT

Hemophagocytic Lymphohistiocytosis: A Rare Complication of Acute Hepatitis E Infection

Nihar Desai1*, Darpan Vetal2, Abhishek Kulkarni3, Niteen Karnik4, Trupti Trivedi5

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive hematological disorder caused by uncontrolled activation of cytotoxic T-cells (CTL), natural killer (NK) cells, and macrophages leading to hyperinflammation and cytokine storm. The clinical course is characterized by high-grade fever, cytopenia, and multiorgan dysfunction. HLH is classified as either primary/familial or secondary, the latter being most often triggered by infections, malignancies, and autoimmune disorders. Viral infections are commonly known to cause HLH with Epstein–Barr virus (EBV), cytomegalovirus (CMV), influenza virus, adenovirus, and parvovirus being most often implicated. Hepatitis E virus (HEV) has infrequently been reported to cause HLH with less than five cases being reported in the literature. We report a case of a young man who presented with hepatitis E–associated HLH.

CASE DESCRIPTION

A previously healthy, 26-year-old gentleman presented with complaints of high-grade fever for 4 days accompanied by yellowish discoloration of eyes for 2 days. He also complained of generalized abdominal pain and three episodes of vomiting on the day of admission. He denied a history of alcohol intake and the use of complementary medication. On general physical examination, his temperature was 101°F, pulse rate 114/minute, and blood pressure 98/68 mm Hg. Other significant findings included conjunctival pallor, scleral icterus, liver, and spleen palpable 2 and 4 cm below the costal margin, respectively.

Laboratory investigations were significant for pancytopenia, hyperbilirubinemia, elevated lactate dehydrogenase (LDH), aspartate and alanine aminotransferase, serum triglycerides, and serum ferritin (Table 1).

In view of the abdominal pain, vomiting, icterus, and fever, a diagnosis of viral hepatitis was considered and serological tests for hepatitis A, B, C, and, E were ordered and he tested positive for immunoglobulin M (lgM) anti-hepatitis E virus (HEV) antibodies, 1,232 IU/mL (normal <0.417 IU/mL). As no cause of pancytopenia was apparent, a bone marrow examination was performed and it showed significantly increased hemophagocytic activity (Fig. 1). The patient’s history, physical examination, and laboratory tests were consistent with a diagnosis of hemophagocytic lymphohistiocytosis (HLH) as per the HLH-2004 criteria of the histiocyte society.1 In addition, his HScore was 198 points which is 80–88% predictive of HLH.2 Serological tests for cytomegalovirus (CMV), Epstein–Barr virus (EBV), parvovirus B19, human immunodeficiency virus 1 and 2, COVID-19, dengue, and malaria were all negative. Blood and bone marrow cultures for bacteria and fungi, and serum procalcitonin were also negative. Cross-sectional imaging of his chest, abdomen, and pelvis did not reveal any abnormalities.

Given the temporal association with HLH and no alternate explanation for his clinical findings, acute hepatitis E infection was identified as the most probable triggering event. The patient received supportive care in the intensive care unit and corticosteroids (dexamethasone, 10 mg/m2/day) were added once the diagnosis of HLH was confirmed. This led to a resolution of fever on day 2 of therapy. The serum ferritin reduced to 1,369 mcg/L (from 21,926 mcg/L) and there was an improvement in his blood counts and liver function by day 3 of therapy. He made a full recovery and was discharged from the hospital on day 12 of admission.

DISCUSSION

The HLH is a life-threatening disorder caused by the inability of the immune system to restrict the stimulatory effects of an immune trigger. There is an uncontrolled, pathological activation of cytotoxic T-cells (CTL), natural killer (NK) cells, and macrophages that causes uninhibited cytokine production leading to multiorgan dysfunction and if untreated, death.1

In adults, malignancies, autoimmune disorders, and infections are the most

Table 1: Laboratory investigations

<table>
<thead>
<tr>
<th></th>
<th>At presentation</th>
<th>At discharge</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>101 gm/L</td>
<td>131 gm/L</td>
<td>120–150 gm/L</td>
</tr>
<tr>
<td>White blood count</td>
<td>1.8 × 109/L</td>
<td>4.5 × 109/L</td>
<td>4–10 × 109/L</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>0.4 × 109/L</td>
<td>1.6 × 109/L</td>
<td>2.5–6 × 109/L</td>
</tr>
<tr>
<td>Platelet count</td>
<td>106 × 109/L</td>
<td>201 × 109/L</td>
<td>150–300 × 109/L</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>9.7 mg/dL</td>
<td>1.6 mg/dL</td>
<td>0.6–1 mg/dL</td>
</tr>
<tr>
<td>Conjugated bilirubin</td>
<td>6.8 mg/dL</td>
<td>0.9 mg/dL</td>
<td>&lt;0.3 mg/dL</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>460 U/L</td>
<td>82 U/L</td>
<td>&lt;40 U/L</td>
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<tr>
<td>Alanine aminotransferase</td>
<td>198 U/L</td>
<td>38 U/L</td>
<td>&lt;40 U/L</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>1.1 mg/dL</td>
<td>0.9 mg/dL</td>
<td>0.7–1.3 mg/dL</td>
</tr>
<tr>
<td>LDH</td>
<td>676 U/L</td>
<td>350 U/L</td>
<td>&lt;250 U/L</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>21,926 mcg/L</td>
<td>1,369 mcg/L</td>
<td>30–300 mcg/L</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>630 mg/dL</td>
<td>188 mg/dL</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>16 seconds</td>
<td>13 seconds</td>
<td>10–13.6 seconds</td>
</tr>
<tr>
<td>Activated partial prothrombin time (aPTT)</td>
<td>44 seconds</td>
<td>27 seconds</td>
<td>26–32 seconds</td>
</tr>
<tr>
<td>Serum fibrinogen</td>
<td>2.1 gm/L</td>
<td>2.8 gm/L</td>
<td>1.5–3.5 gm/L</td>
</tr>
</tbody>
</table>

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common triggers of HLH. DNA viruses like EBV, CMV, herpes simplex virus, adenoavirus, and intracellular organisms like leishmania and tuberculosis are most often implicated. The diagnosis is usually established by the detection of HEV RNA by reverse transcription polymerase chain reaction (RT-PCR) or detection of anti-HEV antibodies using commercially available kits which are highly sensitive and specific (99.6%) for the virus. Despite causing >20 million infections each year, hepatitis E has rarely been associated with HLH with only five cases having been reported in the literature (Table 2).6-10

The diagnosis of HLH in adults is difficult to establish due to the overlap of symptoms with more common disorders like sepsis and disseminated intravascular coagulation. There is also no standard diagnostic test for HLH. A combination of the HLH-2004 diagnostic criteria and the patient’s clinical history is often used to establish the diagnosis. The criteria suggested by the histiocyte society include fever, splenomegaly, cytopenias affecting >2 cell lines (hemoglobin ≤90 gm/L, neutrophil count ≤ 0.1 × 10⁹/L, platelets ≤ 100 × 10⁹/L), hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (≤1.5 gm/L), hyperferritinemia (≥500 mcg/L), hemophagocytosis in the bone marrow, spleen, or lymph nodes, low/absent NK cell activity, and soluble CD25 level ≥2400 IU/L. In the absence of such specialized tests, serum ferritin, a widely available test can be used to support a diagnosis of HLH. Extreme hyperferritinemia (≥25,000 mcg/mL) is frequently associated with HLH, infections, and cytokine release syndrome. Fauter et al. found that a serum ferritin level ≥13,405 mcg/L is associated with a 76.4% sensitivity and 94% specificity for the diagnosis of HLH. Another study found serum ferritin levels ≥10,000 mcg/L to be characteristic of HLH with >90% sensitivity and specificity.5 Our patient also had a significantly raised serum ferritin level (21,926 mcg/L). Though not a part of any diagnostic criteria, serum LDH has also been associated with an increased likelihood of HLH, albeit with a lower specificity than serum ferritin (57%).7

The treatment of HLH is three-pronged, the rapid institution of supportive care, identification, and treatment of the underlying trigger, and suppression of the cytokine storm. There is no consensus regarding the optimal treatment of adults and therapy is tailored as per the HLH-triggering factor. Since the mean age of HLH in adults is close to 50 years, the HLH-2004 protocol which has dramatically improved survival in primary HLH may lead to increased toxicity in this population.8 It is recommended that infection-triggered HLH be usually treated with a short course of corticosteroids with or without intravenous Ig (IVig) and etoposide to be reserved for severe HLH with imminent organ dysfunction.6 Our patient was treated with single-agent dexamethasone and made a full recovery within 2 weeks. The corticosteroid dose was gradually tapered and stopped over the next 2 weeks. IVlg could not be administered because of financial constraints.

Our case underscores the need to consider hepatitis E as a possible cause of secondary HLH. The diagnosis must be suspected in patients who present with or develop cytopenia during the course of their illness. Maintaining a high index of suspicion is critical as delays in diagnosis and institution of therapy can prove to be detrimental.

### Declaration of Patient Consent

Yes.

### References


ANNOUNCEMENT

Nominations are invited from members of API for the posts of Editor-in-Chief “Journal of the Association of Physicians of India” (JAPI) and Editor-in-Chief “API Textbook of Medicine” 14th edition.

The nomination should be proposed and seconded by two members along with seven copies of the Biodata in sealed envelope and should reach by 31st July 2024, to the Hon. General Secretary of API, Dr. Agam Vora, Unit No. 6 & 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E. Moses Road, Near Mahalaxmi Station West, Mumbai – 400011.

Dr. Agam Vora
Hon. General Secretary