Enterovirus-associated hemophagocytic lymphohistiocytosis with multiorgan failure

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ABSTRACT

Hemophagocytic lymphohistiocytosis is a highly fatal hyperinflammatory syndrome that is increasingly being recognized in adults. It can be primary or secondary in the setting of malignancy, autoimmune disorders, infections, or acquired immune deficiencies. We present a case of a 50-year-old man with enterovirus-associated multiorgan system dysfunction and hemophagocytic lymphohistiocytosis.

KEYWORDS Cytokine storm; enterovirus; ferritin; hemophagocytic lymphohistiocytosis; soluble interleukin-2 receptor

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome caused by aberrant activation of macrophages and cytotoxic T cells resulting in a potentially fatal cytokine storm. While primary genetic HLH generally occurs in children, secondary HLH, triggered by infections, malignancies, autoimmune disorders, and acquired immune deficiencies, is more frequently encountered in adults.¹ We present an adult patient with multiorgan failure related to HLH triggered by enterovirus viremia.

CASE PRESENTATION

A 50-year-old man with known mantle cell lymphoma who had had an autologous bone marrow transplant 6 years earlier followed by yearly maintenance rituximab presented with fever, chills, nausea, and vomiting. Three months prior to this admission, he was admitted for elevated liver enzymes (aspartate aminotransferase 323 IU/L, alanine aminotransferase 443 IU/L, alkaline phosphatase 783 IU/L). Tests for hepatitis, Epstein-Barr virus, cytomegalovirus, acetaminophen level, anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, human immunodeficiency virus, ceruloplasmin, and alpha-1-antitrypsin were negative. A liver biopsy showed marked portal and lobular inflammation, concerning for drug-induced liver injury. Prednisone 20 mg daily was initiated, and

the patient saw improvement in liver enzymes. After completion of the prescribed prednisone, the patient again saw a spike in his liver enzymes. A repeat course of 15 mg prednisone daily and 50 mg azathioprine daily was initiated.

His symptoms persisted, and follow-up laboratory tests revealed worsening liver enzymes, which prompted repeat hospitalization. At the time of admission, his aspartate aminotransferase was 5451 IU/L; alanine aminotransferase, 3818 IU/L; alkaline phosphatase, 701 IU/L; and total bilirubin, 10.9 mg/dL. Upon admission, prednisone was continued and the patient was started on antibiotics empirically. An extensive infectious workup was negative, including blood cultures, cryptococcal antigen, *Histoplasma* urine and serum antigen, *Leptospira* antibody, and *Coccidioides* serum antibody by enzyme-linked immunosorbent assay. Stool polymerase chain reaction (PCR) and cultures were negative for *Salmonella*, *Shigella*, *Escherichia coli*, *Campylobacter*, *Vibrio*, and *Yersinia*. Stool smear and PCR for *Cryptosporidium*, *Cyclospora*, and *Isospora* was also negative. Serum PCR was negative for herpes simplex, varicella zoster, cytomegalovirus, adenovirus, and influenza. Treponema pallidum particle agglutination assay was negative for syphilis. Enterovirus was detected in the plasma and respiratory panel by PCR.

Laboratory tests revealed elevated ferritin and triglycerides, low fibrinogen, and thrombocytopenia, raising concern

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Figure 1. (a, b) Immunohistochemical studies for CD68 demonstrating markedly increased histiocytes in spinal marrow and spleen, respectively. (c) Spinal aspirate smear demonstrating hemophagocytes. (d) Spleen showing prominent sinusoidal histiocytes.

for hemophagocytic lymphohistiocytosis. Subsequent bone marrow biopsy revealed histiocytes with hemophagocytosis. Dexamethasone was initiated at this time along with one dose of intravenous immunoglobulin with minimal clinical improvement. By day 8, the patient continued to decompensate with worsening shock, lactic acidosis, and multiorgan failure. He subsequently died after his family decided to withdraw care early on day 10 of hospitalization. Soluble interleukin-2 receptor (sIL-2r) sent early in admission was found to be elevated at 8980 U/mL.

Enterovirus RNA (Coxsackievirus A9) by PCR was detected in autopsy specimen from the bowel, kidney, liver, and lung with subsequent PCR subtyping by the Centers for Disease Control and Prevention. Autopsy revealed a systemic inflammatory response with multiorgan dysfunction in the setting of disseminated Coxsackievirus A9, acute hepatitis with multifocal necrosis, pancreatitis, and hemophagocytic lymphohistiocytosis (*Figure 1*). There was no evidence of residual or recurrent lymphoma.

DISCUSSION

Primary and secondary HLH are aberrant hyperinflammatory hyperferritinemic immune syndromes that mimic a sepsis-like syndrome, leading to delay in diagnosis and poor prognosis.^{1,2} *Table 1* describes common causes of HLH. To our knowledge, this is the first reported case of hemophagocytic syndrome associated with an enterovirus in an adult.

Enterovirus as a trigger for HLH is rare. Several case reports have reported enterovirus-associated HLH in neonates who were treated with a combination of intravenous immunoglobulin, corticosteroids, and etoposide. The addition of anakinra to intravenous immunoglobulin and corticosteroids

Table 1. Common causes of hemophagocytic lymphohistiocytosis

Type	Cause
Primary	<ul style="list-style-type: none"> Genetic alterations causing defects in cytotoxic T cells and NK cells or defects in inflammatory regulation
Secondary	<ul style="list-style-type: none"> Infection (Ebstein-Barr virus, herpes simplex virus, cytomegalovirus, adenovirus, human immunodeficiency virus; also bacteria, fungi, and parasites) Malignancy (mainly lymphoma) Autoimmune disorders (systemic idiopathic juvenile arthritis, systemic lupus erythematosus, other autoimmune and inflammatory disorders) Other causes (organ or stem cell transplant, vaccination, immunosuppression, hemodialysis, pregnancy)

Table 2. HLH-2004 diagnostic criteria for hemophagocytic lymphohistiocytosis*

Five of the eight criteria below:

1. Fever
2. Splenomegaly
3. Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood):
Hemoglobin < 90 g/L (hemoglobin < 100 g/L in infants < 4 wk)
Platelets $< 100 \times 10^9/L$
Neutrophils $< 1.0 \times 10^9/L$
4. Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥ 265 mg/dL)
Fibrinogen ≤ 1.5 g/L
5. Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy.
6. Low or no NK cell activity (according to local laboratory reference)
7. Ferritin ≥ 500 mg/L
8. sCD25 (i.e., soluble IL-2 receptor) ≥ 2400 U/mL

*From Henter et al, 2007⁶

was reported to lead to marked clinical improvement in a 13-month-old boy with enterovirus-associated HLH.³

In terms of pathogenesis, primary and secondary HLH share a common terminal pathway with elevated inflammatory markers driven by T cells leading to a cytokine storm. HLH is driven by a defect in natural killer cells and cytotoxic T lymphocytes, which is permanent in primary HLH and transient in secondary HLH.⁴ This defect leads to elevated inflammatory cytokines, including interleukin-2, interleukin-6, tumor necrosis factor- α , and interferon- γ , which subsequently lead to overactivation of histiocytes, macrophages, and CD8+ T cells. The uninhibited cytokine storm causing cytotoxic T lymphocyte activation and T-helper cell migration leads to end-organ damage.^{2,5}

The diagnostic criteria for HLH were revised in 2004, and individuals need to meet five or more of the eight

criteria listed in [Table 2](#).⁶ The HLH-2004 was developed for pediatric populations and is not validated for adults; its use is based on expert opinion.¹ While ferritin levels >10,000 µg/L are 90% sensitive and 96% specific in pediatric populations, hyperferritinemia has been found to be less specific in adults.⁷ Schram et al identified 113 adult patients with serum ferritin levels >50,000 µg/L, and 17% were diagnosed with HLH; other observed conditions included renal failure, hepatocellular injury, infections, and hematologic malignancies.⁸ On the other hand, sIL-2r appears to be a good to excellent diagnostic tool for HLH in adults, with an area under the curve of 0.90 (95% confidence interval, 0.83–0.97) compared with an area under the curve of 0.78 (95% confidence interval, 0.67–0.88) for ferritin. An sIL-2r of >2515 U/mL had a 100% sensitivity and 72.5% specificity.⁹

The treatment of HLH is targeted toward suppressing the immune system, treating the unregulated hyperinflammation, and identifying the underlying trigger. The HLH-94 treatment protocol consists of dexamethasone, cyclosporine A, intrathecal therapy, and etoposide. Corticosteroid is usually the first-line treatment.^{1,2,5} In Epstein-Barr virus-triggered HLH, addition of rituximab to target viral replication in B cells has been effective. In primary HLH, allogeneic hematopoietic stem cell transplant has been shown to improve outcomes dramatically.¹ Along with meeting diagnostic criteria, a high clinical suspicion and expert guidance are required to treat HLH.¹ In conclusion, HLH is a highly morbid condition that requires early recognition and treatment. If left untreated, it leads to progressive multiorgan failure, with mortality rates ranging from 40% to 75%.¹⁰

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