# Hemophagocytic Lymphohistiocytosis Syndrome in a Crohn's Patient with Subacute EBV Infection

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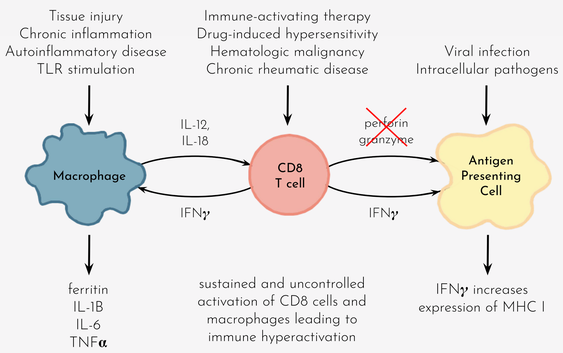
## INTRODUCTION

- Hemophagocytic lymphohistiocytosis (HLH) syndrome is a rare, life-threatening hyperinflammatory condition of pathologic immune activation involving impaired cytotoxic T and NK cell function.[1,2]
- Here we outline a case of Hemophagocytic lymphohistiocytosis syndrome in the setting of Crohn's disease and subacute Epstein Barr Virus (EBV) infection.

## BACKGROUND

- In HLH syndrome, cytotoxic T and NK cells' ability to eliminate activated macrophages is impaired, leading to excessive cytokine secretion with resultant tissue damage and multi-organ failure. [1,2]




- Impaired cell function can be due to genetic or environmental causes, or specific underlying disease states, including infection, malignancy, rheumatologic disorders, and primary immunodeficiencies.[3,4]
- In young adults, HLH is most commonly associated with infection.[7]
- Patients can present with a febrile illness with multiple organ involvement. A few cases have reported gastrointestinal symptoms.[5]
- Early in the disease course, some patients may not meet the strict diagnostic criteria for HLH, thus representing potentially preventable delays in diagnosis and treatment.[8]

Table 1

**Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis**

Five of the following eight findings:
- Fever ≥ 38.5ºC
- Splenomegaly
- Peripheral blood cytopenia, with ≥ 2 of the following:
  - hemoglobin < 9 g/dL
  - platelets < 100,000/uL
  - absolute neutrophil count < 1000/ul
- Hypertriglyceridemia (fasting > 265 mg/dL) and/or hypofibrinogenemia (fibrinogen < 150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent NK cell activity
- Ferritin > 500 ng/mL
- Elevated soluble CD25 (alpha chain of the soluble IL-2 receptor) > 2400 U/mL

## INITIAL PRESENTATION

- **HPI** 22 year old male with Crohn's disease on Vedolizumab presents for nausea, vomiting, and left-sided abdominal pain that began 10 days prior. He visited an emergency department 5 days earlier for similar symptoms and was discharged home with prednisone for likely Crohn's flare. Patient returned to the ED because symptoms failed to improve. History reveals sore throat 1 month prior, negative for strep throat.
- **Vital Signs** T 101.3ºF, HR 29, RR 17, BP 101/63, 97% on room air.
- **Physical Exam** Alert and oriented. Mucous membranes moist. Abdomen soft, diffusely tender to palpation without guarding, rigidity, or rebound tenderness. No hepatosplenomegaly. Bowel sounds normoactive. Palpation of neck and groin reveals no swelling or tenderness of groin nodes.
- **Labs**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 13.2 | | 141 | 109 | 10 | | CRP 1.00 | AST 22 |
| 2.84 | | 151 | | | | 97 | lactic acid 1.9 | ALT 21 |
| | 38.7 | | 4.0 | 28 | 0.88 | | | Alk Phos 59 |
| | | | | | | | | TBili 0.5 |

- **Imaging** CT abdomen/pelvis with contrast: wall thickening in transverse, descending, and sigmoid colon.

## HOSPITAL COURSE

- **Hospital day 1** Patient started on Methylprednisolone for acute Crohn's flare
  Consulted Gastroenterology; colonoscopy showed colitis with moderate disease activity.
- **Hospital day 2** Patient became febrile.
  Labs: downtrending leukopenia and thrombocytopenia, microcytic anemia, and uptrending CRP.
  Consulted Infectious Diseases; extensive infectious and autoimmune workup initiated.
  Patient was started empirically on Vancomycin and Cefepime given high suspicion for infectious etiology.
- **Hospital day 3** Oncology consulted for worsening leukopenia and thrombocytopenia, CD4 count 204.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 12.2 | | 135 | 106 | 11 | | CRP 13.20 | AST 496 |
| 1.62 | | 43 | | | | 98 | lactic acid 2.4 | ALT 241 |
| | 34.9 | | 4.1 | 23 | 0.81 | | ferritin > 40,000 | Alk Phos 116 |
| | | | | | | | transferrin 36 | TBili 1.1 |

  Abdominal ultrasound and acute hepatitis panel to evaluate for transaminitis were unremarkable.
- **Hospital day 9** EBV IgM resulted positive, but no heterophile antibodies detected. HIV negative.
  CBC with manual diff showed uptrending reactive lymphocytes.
  CT abd/pelvis: markedly increased spleen length; unilateral hilar adenopathy, likely reactive lymph node.
- **Hospital day 10** CT-guided bone marrow biopsy revealed active megakaryopoiesis and histiocytes with hemophagocytosis. Lab findings include:

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 10.6 | | 137 | 108 | 8 | | ferritin 24,214 | AST 661 |
| 2.71 | | 49 | | | | 108 | fibrinogen 118 | ALT 531 |
| | 31.3 | | 3.6 | 25 | 0.55 | | ANC 890 | Alk Phos 485 |
| | | | | | | | CD4 39 | TBili 7.5 |

- Patient was transferred to a tertiary care center for chemotherapy induction and adjuvant therapy with Rituximab and Acyclovir for underlying EBV infection.



**Figure 1**
Wright stained bone marrow aspirate smear showing macrophages (histiocytes) containing ingested cells, namely erythrocytes (2 left arrows).[9]




**Figure 2**
Patient's CT abdomen/pelvis showing marked splenomegaly, greater than 16cm.

## DISCUSSION

- The etiology of the patient's rapidly increasing transaminitis was initially unclear, as it was significantly more elevated than could be attributed to Vedolizumab-induced hepatotoxicity. The pattern of transaminitis followed by hyperbilirubinemia appears to be consistent with ischemic hepatopathy, likely related to sepsis; it is also consistent with EBV-associated HLH.[3]
- Distinguishing between a primary EBV infection, such as infectious mononucleosis, and EBV-associated HLH is necessary to guide treatment. In contrast to a primary EBV infection, EBV complicated by HLH presents significantly more toxic-appearing and is associated with persistent life-threatening bicytopenias, more severe and persistent hepatitis and coagulopathy, and worsening splenomegaly.
- HLH was considered in the differential diagnosis after anemia workup revealed significantly elevated ferritin with less than 45% transferrin saturation. Ferritin > 10,000 alone is 90 percent sensitive and 96 percent specific for the diagnosis of HLH.[7]
- While there have been case reports of EBV-associated HLH in patients with Crohn's disease, IBD is not commonly associated with HLH. The patient's history of Crohn's disease and chronic immunosuppression may have made the patient more susceptible to contracting and developing a primary EBV infection as well as the subsequent immune system derangement.
- Treatment of EBV-associated HLH requires addressing the underlying cause as well as the HLH. The patient was treated with adjuvant Rituximab and, later, Acyclovir to reduce the EBV viral load, which studies have shown to correlate with overall survival. [3,4,5]

## CONCLUSION

- Due to its variable clinical presentation, association with other conditions, and low incidence, HLH is often underdiagnosed.[3,4]
- The prognosis for HLH is significantly improved with prompt diagnosis and treatment,[1,3] especially for patients with EBV-associated HLH, given a 1 year mortality rate of 78%.[4,7]
- Maintaining clinical suspicion for HLH in patients not traditionally identified as high risk for HLH, such as those with IBD, is critical.

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