

## INTRODUCTION

- Viral infections such as Epstein Barr Virus (EBV) have been associated with secondary hemophagocytic lymphohistiocytosis (HLH) with some recent studies alluding to an association between severe COVID-19 and HLH.
- Herein, we report a case of a patient with an earlier mild case of COVID, followed by EBV infection, that precipitated HLH.

## CASE DESCRIPTION

- A 36-year-old man with a history of mild COVID-19 infection a month prior presented to an outside hospital with nausea, fatigue, and jaundice.
- Patient had total bilirubin (tibili) 7.1, ALT 2714, AST 1273 and an elevated EBV viral capsid antigen.
- Liver US was negative; CT abdomen showed significant portal hepatitis and peri-pancreatic head lymphadenopathy.
- Lymph node biopsy was unrevealing.
- Patient was diagnosed with mononucleosis and discharged.
- Patient presented to multiple institutions and discharged with mononucleosis associated liver injury. With worsening jaundice, patient ultimately presented to Cleveland Clinic with tibili 23.8, conjugated bilirubin 19.8, ALT 1400, AST 1145, Alkaline phosphatase 461, with repeat EBV titers negative.
- CT revealed upper abdominal lymphadenopathy in peri-portal and periceliac regions. MRCP confirmed lymphadenopathy, borderline splenomegaly with no biliary dilation.
- Acute liver injury workup was negative.
- Liver biopsy showed marked lobular hepatitis, areas of dropout with hemorrhage and increased cellularity within the sinusoids and evidence of hemophagocytosis.
- The portal areas were expanded by inflammatory cell infiltrates including plasma cells, lymphocytes, histiocytes, and granulocytes.
- Patient was diagnosed with HLH, using the criteria in Table 1.
- H-score was 184 points with 70-80% probability of HLH.
- Patient was discharged with close follow-up with hepatology and hematology for treatment initiation.

HLH-2004 Criteria *		H-Score Criteria	
Fever	<input checked="" type="checkbox"/>	Temperature, °F (°C)	101.1–102.9 (38.4-39.4) (+33)
Splenomegaly	<input checked="" type="checkbox"/>	Organomegaly	Hepatomegaly or splenomegaly (+33)
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood) • Hemoglobin <90 g/L • Platelets <100 x 10 <sup>9</sup> /L • Neutrophils <1.0 x 10 <sup>9</sup> /L	<input checked="" type="checkbox"/>	Number of cytopenias Defined as hemoglobin ≤9.2 g/dL (≤5.71 mmol/L) and/or WBC ≤5,000/mm <sup>3</sup> and/or platelets ≤110,000/mm <sup>3</sup>	1 lineage (0)
Hypertriglyceridemia and/or hypofibrinogenemia: • Fasting triglycerides ≥ 3.0 mmol/L (i.e. ≥265 mg/dl) • Fibrinogen ≤1.5 g/L	<input checked="" type="checkbox"/>	Triglyceride, mg/dL (mmol/L)	132.7-354 (1.5–4) (+44)
		Fibrinogen, mg/dL (g/L)	≤250 (≤2.5) (+30)
Hemophagocytosis in bone marrow/spleen/lymph nodes	<input checked="" type="checkbox"/>	Hemophagocytosis features on bone marrow aspirate	No
Ferritin ≥ 500 µg/L	<input checked="" type="checkbox"/>	Ferritin, ng/mL (or µg/L)	2,000–6,000 (+35)
Low or absent NK-cell activity	<input checked="" type="checkbox"/>	AST, U/L	≥30 (+19)
Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2,400 U/ml	<input checked="" type="checkbox"/>	Known underlying immunosuppression	No (0)

\*The diagnosis of HLH can be established if one of either 1 or 2 below is fulfilled 1) A molecular diagnosis consistent with HLH, 2) Diagnostic criteria for HLH fulfilled (5 out of 8 criteria below)

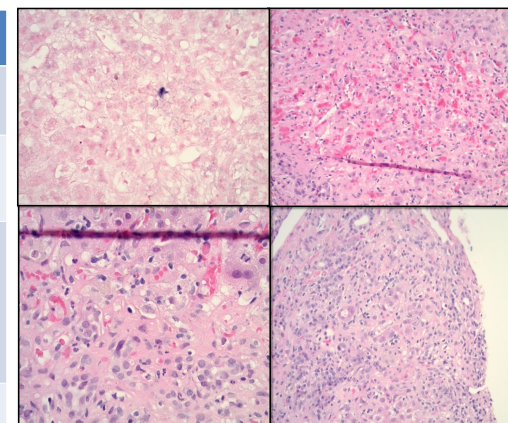


Figure 1a. Rare EBV positive cell. 1b. Hemophagocytosis. 3. Centrilobular hepatitis with collapse. 4. Portal tract expanded by mixed inflammatory infiltrate

## DISCUSSION

- HLH carries a grim prognosis and requires earlier detection and treatment.
- Acute phase COVID-19 has been associated with HLH, though post-COVID 19 cases associated with HLH are rare.
- It is thought that post-COVID19 causes immune dysregulation and activation of macrophages which can cause HLH.
- Though asymptomatic, our patient subsequently tested positive for EBV, which was cleared by the time repeat testing was done.
- This raises the question for concurrent or subsequent infections as precipitating factors for HLH.
- Our case report highlights the importance of exploring HLH in patient where no obvious signs of acute liver injury are present, particularly in patients with COVID-19 infection.