Epstein-Barr Virus Induced Hemophagocytic Lymphohistiocytosis: a Rare Cause of Acute Liver Failure

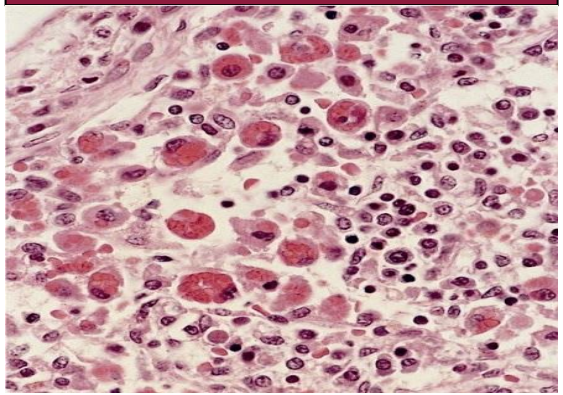
Andreas Bub MD, Jonathan Kandiah MD, Shehrose Chaudry MD, Henry Beecher MD

Stamford Hospital Department of Medicine, Norwalk Hospital Section of Gastroenterology

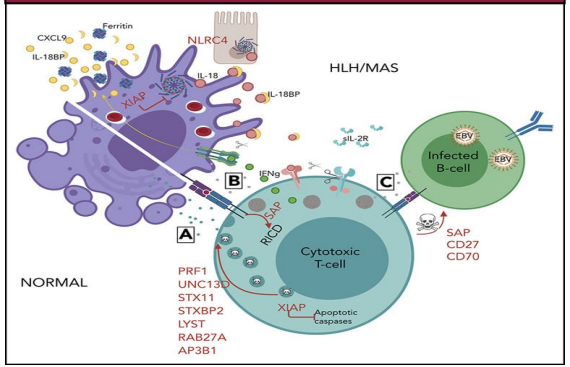
Hemophagocytic Lymphohistiocytosis

- Hemophagocytic lymphohistiocytosis (HLH) is caused by unregulated immune-mediated inflammation
  -Commonly causing failure of affected organs.
- It is most common in children but may occur at any age.
-HLH may be seen in genetic syndromes, autoimmune disorders, malignancy, and viral infections such as Epstein-Barr Virus (EBV).
- Findings: Fever, cytopenia in two lines, hepatosplenomegaly, hypertriglyceridemia, hemophagocytosis on bone marrow or liver biopsy, low natural killer T-cell (NK) activity, hyperferritinemia, and elevated soluble IL-2 receptor (sIL2r).
  -Diagnosis is made when 5 of the 8 criteria are met.
- Survival for HLH 50% after 6 years even if treated.
- Treatment: IV Dexamethasone (mild), Etoposide (severe), Intrathecal Methotrexate and Hydrocortisone (CNS involvement)

Pathology



Biochemistry



Case Presentation

Patient: 57-year old woman with selective IgA-deficiency.
CC: Malaise, jaundice, and right upper quadrant tenderness.
Exam: Jaundice, Hepatomegaly, Abdominal Tenderness in RUQ.
Labs: Pancytopenia, cholestasis, elevated sIL2r, hyperferritinemia, decreased liver synthetic function.
Serologies: Positive for acute EBV infection.
Ultrasound: Dilated common bile duct, no identified stones.
MRCP: Hepatosplenomegaly and numerous hepatic cysts.
Diagnosis: ALF secondary to EBV was made. HLH was considered after the patient developed encephalopathy and the sIL2r resulted, confirming the diagnosis.
Treatment: IV Corticosteroids.
Disposition: The patient improved the same day as initiation of corticosteroids. Her encephalopathy and other symptoms resolved. She had an uncomplicated discharge remains relapse free.

Shi, Jinjin et al. (2021)

Group	CD3+ (×10⁹/L)	CD4+ (×10⁹/L)	CD8+ (×10⁹/L)	NK (×10⁹/L)	CD3-CD19+ (×10⁹/L)	CD4+/CD8+ (×10⁹/L)	IgA (g/L)	IgG (g/L)	IgM (g/L)
EBV-IM group	8.21 (4.98,11.63)	1.87 (1.19,3.00)	4.36 (3.00,6.77)	0.89 (0.62,1.92)	0.85 (0.43,1.29)	0.40 (0.30,0.60)	1.30 (0.92,1.92)	10.32 (8.63,12.52)	1.72 (1.31,2.08)
EBV-HLH group	0.93 (0.53,2.67)	0.43 (0.19,1.00)	0.55 (0.20,1.26)	0.10 (0.02,0.22)	0.15 (0.07,0.43)	0.90 (0.40,1.65)	0.48 (0.17,0.90)	6.97 (4.13,14.08)	0.57 (0.28,0.94)
Z value	−6.411	−5.763	−6.290	−6.468	−5.401	3.856	−5.496	−1.677	−5.562
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.094	< 0.001

Discussion

HLH may occur as a result of an infection, amongst other etiologies, but it is possible that our patient's IgA deficiency is relevant. In a study of 92 pediatric patients who developed either Infectious Mononucleosis (IM) or HLH, from acute EBV infection, IgA levels were significantly lower in patients who developed HLH (3). Of note, our patient's serum IgA level was 10 times lower than those in this study. The function of serum IgA is not understood but it does inhibit macrophages through an IgA-specific receptor, Fc-a-RI (4). Lack of macrophage inhibition in an IgA deficient patient combined with the abnormal signaling from abnormal lymphocytes that are produced by acute EBV infection may explain why these patients were predisposed to developing HLH.

Selective IgA deficiency is the most common human immunodeficiency with a prevalence of 1 in 500. Most patients are asymptomatic though IgA deficient patients have higher prevalence of autoimmune disorders, allergic disorders, transfusion reactions, and mucosal infections. More research is required into HLH as it remains a complex syndrome that needs to be identified before catastrophic tissue destruction occurs.