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CASE REPORT | LIVER

Hemophagocytic Lymphohistiocytosis Associated With Hepatitis B and HIV Coinfection With Resultant Liver Failure

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ABSTRACT

Hemophagocytic lymphohistiocytosis is a syndrome of excessive immune activation frequently attributed to infection. We report a case of hemophagocytic lymphohistiocytosis secondary to hepatitis B in a patient with human immunodeficiency virus coinfection and subsequent liver failure.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare clinical syndrome of immune dysregulation and macrophage activation resulting in a hyperinflammatory state associated with high mortality. It is characterized by pyrexia, cytopenias, hepatosplenomegaly, hypertriglyceridemia, hypofibrinogenemia, elevated interleukin (IL)-2, low natural killer (NK) activity, and evidence of hemophagocytosis. HLH is frequently attributed to viral infections, most commonly Epstein-Barr and cytomegalovirus.[1,2] The following is an unusual case of HLH diagnosed in a patient with active hepatitis B virus (HBV) and human immunodeficiency virus (HIV), ultimately resulting in liver failure and death.

CASE REPORT

A 33-year-old man presented with complaints of fever, nausea, and productive cough and was admitted for severe septic shock. He was recently diagnosed with chronic HBV (anti-HBc and HBsAg positive, IgM anti-HBc negative) and HIV. He was started on bictegravir, emtricitabine, and tenofovir a month before his admission. Of note, the patient had several recent hospitalizations for pancytopenia and sepsis without a clear cause. On arrival, his vital signs were as follows: temperature 103.1°F, heart rate 152 beats per minute, blood pressure 133/63 mm Hg, and SpO_2 97% on 2 L nasal cannula with respiratory rate 60 breaths per minute. Shortly after arrival, he became hypoxic (SpO_2 85%) and hypotensive (90s/40s mm Hg), requiring intubation and vasopressor support. His admission laboratory test results were notable for hemoglobin 6.5 g/dL, white blood cells 3.1 10×9/L, platelet count 30 10×9/L, Cr 1.34 mg/dL, albumin 2 g/dL, bilirubin 0.9 mg/dL, aminotransferase aminotransferase (AST)/alanine aminotransferase 72/38 IU/L, and international normalized ratio 1.7. HBV viral load on admission was 511,000 copies, with CD4 count of 15 and HIV viral load 10,500 copies. Thoracic X-ray and computed tomography were concerning for pneumonia. Abdominal and pelvic computed tomography demonstrated hepatosplenomegaly without cirrhotic morphology, with spleen and liver measuring 16 cm and 24 cm, respectively, with small abdominal ascites. He received a blood transfusion and was treated with broad-spectrum antibiotics (meropenem and vancomycin) as well as empiric treatment for *Pneumocystis jiroveci* pneumonia and corticosteroids for septic shock. He received renally dosed dolutegravir, tenofovir, and emtricitabine for his HIV.

Despite these measures, the patient continued fever and require frequent blood transfusions. He underwent an extensive infectious and autoimmune disease evaluation including negative blood, acid-fast Bacilli blood, urine, and bronchial alveolar lavage cultures,

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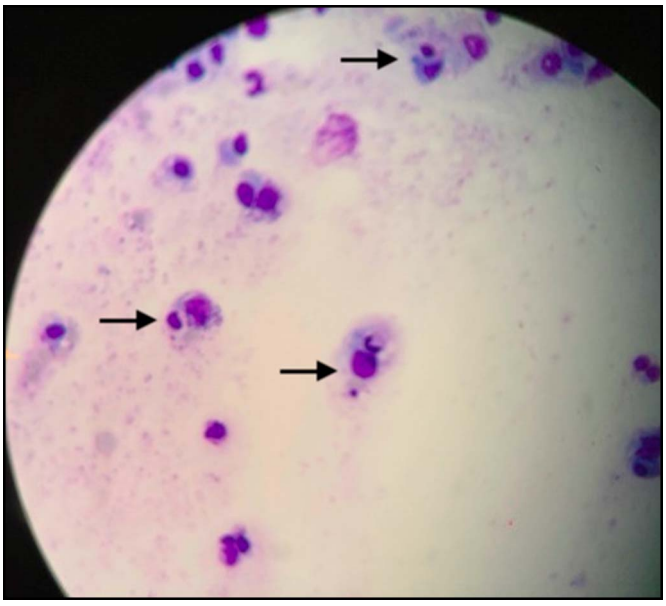

Figure 1. Hematoxylin and eosin stain of bone marrow biopsy with hemophagocytosis. Arrows demonstrate hemophagocytosis of red blood cells.

respiratory virus and pneumonia panels, fungal and parasitic serologies, herpes virus and cytomegalovirus polymerase chain reactions, with evidence of previous Epstein-Barr virus and parvovirus infections. He also had negative leukemia and lymphoma panel. The patient was noted to have increasing bilirubin (5.6) and AST (120), with scleral icterus on examination. His HBV viral load was redrawn, increasing to 12,500,000. Entecavir was started in addition to tenofovir and emtricitabine, with subsequent decrease in his viral load to 5,600 over 4 weeks. HBV genotype revealed no resistance. HIV viral load became undetectable. Immune reconstitution inflammatory syndrome was considered, although this diagnosis could not explain his increasing HBV viral load. Given his persistent pyrexia and elevated ferritin, HLH was suspected. Further evaluation revealed ferritin of 17,918 ng/mL, triglyceride 434 mm/dL, fibrinogen 151 mg/dL, and soluble IL-2 receptor 27,900 pg/mL (high), with low NK activity. Our pathologists reviewed a bone marrow biopsy previously performed at an outside hospital with scant hemophagocytosis findings (Figure 1).

The diagnosis of HLH was made, and the patient was treated with a dexamethasone taper initially resulting in reduced transfusion requirements as well as decreased pyrexia. However, transfusion requirements and pyrexia returned. The decision was made to begin treatment with renally dosed etoposide per HLH-94 protocol resulting in significant clinical improvement.[3] His hospital course was complicated by acute renal failure requiring temporary dialysis, a gastrointestinal bleed secondary to a duodenal ulcer requiring endoscopic intervention, encephalopathy with subarachnoid hemorrhages, and 2 episodes of acute hypoxic respiratory failure requiring intubation and ventilatory support. He eventually recovered enough to be discharged home on a steroid taper. Unfortunately, patient was unable to obtain his HBV and HIV medications on discharge and presented 5 days later with acute hypoxic respiratory failure again requiring intubation. He continued to decompensate, with ferritin above assay limits of 40,000, bilirubin peaking at 26, international normalized ratio 2.5, AST 358, and alanine aminotransferase 180, with persistent fevers and a high daily blood product requirement. The family decided to move to comfort measures, and he succumbed to his illness.

DISCUSSION

HLH is a rare immune-mediated life-threatening syndrome that can involve multiple organ systems. HLH is classified into primary (genetic) and secondary (reactive), which is further subclassified into infectious and autoimmune, although about a third of adult cases are multifactorial.[1] HLH overlaps clinically with many more common conditions frequently leading to a delay in diagnosis.

Our patient met 8/8 criteria for HLH, with hyperferritenemia, hypofibrinogenemia, hypertriglyceridemia, pancytopenia, hepatosplenomegaly, low NK activity, elevated IL-2, and evidence of hemophagocytosis on bone marrow biopsy. Liver injury is very common in HLH, with up to 85% of patients with secondary HLH having abnormal liver function.[4] The liver injury is possibly secondary to cytokine storm and infiltration of the parenchyma by activated hemophagocytic histiocytes.[5] Liver transplantation is frequently contraindicated in these patients secondary to severe systemic illness.

Our patient's HLH was most likely secondary to his active HBV infection, as his viral load increased 25-fold, likely inciting the aberrant immune response. The reason for his rapid increase in HBV viral load is unclear, since genotype revealed no mutations and he was on 2 active antivirals. Extensive evaluation for additional infectious causes or malignancy was unremarkable. Although HLH has been associated with HIV infection, his HIV was less likely contributory, as his viral load became undetectable on treatment over his hospital course.[2] The brief period without antiviral medications after discharge could have resulted in acute HBV hepatitis and subsequent worsening of HLH because laboratory markers for HLH dramatically worsened on his second admission.

On literature review, HLH was attributed to HBV in 13 cases.[6–10] Two detailed case reports treated the patient with etoposide and dexamethasone per HLH-94 protocol.[8,9] To the best of our knowledge, this is the first reported case of HLH attributed to HBV with HIV coinfection. As about 10% of patients with HIV have HBV coinfection, HLH should be considered in coinfected febrile patients with cytopenias.[11] Early recognition and treatment of HLH is essential for survival.

DISCLOSURES

Author contributions: H. Blaney wrote the manuscript. D. Thotakura reviewed the literature. L. Sisco edited the manuscript and reviewed the literature and is the author guarantor.

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