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Case Report

Epstein-Barr Virus (EBV) Induced Hemophagocytic Lymphohistiocytosis (HLH) with Granulomatous Hepatitis

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of immune hyperactivation that can result in severe multiorgan failure and death. This disease has classically been described in the pediatric setting but over the past decade has garnered more notoriety in adult populations. The true incidence rate in adults is unclear and suspected to be underdiagnosed.[1] A retrospective cohort study conducted from 2006 to 2019 in the United States found over 16,000 non-elective admissions for HLH and observed an increasing rate of HLH diagnoses during this time period which could be attributed to increased awareness.[2] In clinical practice, early recognition and diagnosis of HLH is critical, as mortality is high without timely intervention to control the immune response. Making the diagnosis of HLH can be difficult as its presentation can mimic other disease processes in the presence of confounders such as sepsis.[3]

In this case report, we discuss an adult patient who initially presented with jaundice and acute liver injury, requiring hospitalization with extensive multidisciplinary workup before revealing a diagnosis of HLH secondary to acute Epstein Barr Virus (EBV) infection. Acute liver injury has a broad differential diagnosis, and this case illustrates the exceptional difficulty providers encounter in making the diagnosis of HLH.

CASE REPORT

A 34-year-old male with no significant medical history presented to his primary care physician with sore throat, malaise, intermittent fever, nausea, vomiting, and jaundice. A positive MonoSpot™ test raised suspicion for a viral illness. Abdominal ultrasound revealed marked hepatosplenomegaly, with a spleen measuring 17.6 cm (normal range: 12-14 cm in adult males).[4] He was referred to the hospital for further evaluation.

On admission to the emergency department, he was afebrile but tachycardic, with palpable hepatosplenomegaly. Laboratory tests showed leukocytosis (WBC 13.4 K/µL, 85% neutrophils), anemia (Hb 7.5 g/dL), elevated liver enzymes (ALT/AST 258/249 U/L), hyperferritinemia (3,926 ng/mL), and marked hyperbilirubinemia (total bilirubin 39.4 mg/dL). Serum creatinine and platelet counts were within normal limits. A computed tomography (CT) scan of the abdomen and pelvis confirmed hepatosplenomegaly with punctate calcified granulomas in the spleen.

After transfer to our tertiary care hospital, repeat labs showed a further hemoglobin (Hb) decline to 6.3 g/dL. He received a transfusion of packed red blood cells and N-acetylcysteine for suspected EBV-induced acute liver injury. Minutes after starting the transfusion, he developed fever, tachycardia, and dyspnea, necessitating a rapid response activation and intensive care unit (ICU) transfer. The transfusion was stopped, and his symptoms resolved, but his Hb dropped further to 5.0 g/dL, with worsening hyperbilirubinemia (total bilirubin 47.7 mg/dL, direct bilirubin 26.4 mg/dL) and acute kidney injury (creatinine 2.57 mg/dL, up from 0.8 mg/dL baseline). Additional labs showed hypertriglyceridemia (538 mg/dL), hypofibrinogenemia (71 mg/dL), and elevated LDH (725 U/L). Hematology initiated high-dose steroids (methlyprednisolone 1 mg/kg divided twice daily) and plasmapheresis for suspected autoimmune hemolytic anemia (AIHA), leading to Hb stabilization at 7.5 g/dL.

Infectious diseases and gastroenterology were consulted. Empiric ceftriaxone (2 g IV daily) and doxycycline (100 mg PO twice daily) were started for suspected tick-borne illness. EBV serologies revealed positive capsid IgG, capsid IgM, and early antigen antibodies, with negative nuclear antigen antibody and an EBV PCR of 16,300 copies, confirming acute EBV infection. Tests for viral hepatitis, syphilis, HIV, parvovirus B19, and tick-borne illnesses were negative. A direct Coombs test was positive for C3, suggesting cold agglutinin syndrome, which was corroborated by an elevated cold agglutinin titer (1:128, normal <1:32). However, hemolysis markers (haptoglobin and indirect bilirubin) were normal.

A bone marrow biopsy and repeat peripheral smear showed trilineage hematopoiesis with 1% blasts, and hemophagocytosis in neutrophils and monocytes on the smear, though not in the marrow biopsy. A liver biopsy revealed granulomatous hepatitis with fibrin-ring granulomas, cholestasis, scattered EBV-positive lymphoid cells (Figure 1), and sinusoidal hemophagocytosis, supporting a diagnosis of EBV-induced HLH. IL-2 receptor was markedly elevated at 7,611 pg/mL (RR 175-852 pg/mL).

The patient remained on high-dose steroids with clinical improvement, allowing discontinuation of antibiotics. Etoposide and rituximab were considered but deferred as his condition improved on steroids alone. He required only two plasmapheresis treatments, and his hemoglobin stabilized without further transfusions. He was discharged on hospital day seven with an eight-week dexamethasone taper and prophylactic trimethoprim-sulfamethoxazole (80/400 mg PO daily).

At discharge, his hemoglobin was 8.4 g/dL, total bilirubin had decreased to 4.4 mg/dL, and ferritin was 745 ng/mL. Two months post-discharge, EBV PCR was negative, and liver and renal function had normalized. By the end of his steroid taper, ferritin had declined to 355 ng/mL. Follow-up positron emission tomography (PET)/CT imaging at 10 weeks showed significant improvement in hepatosplenomegaly, and he had returned to his baseline health.

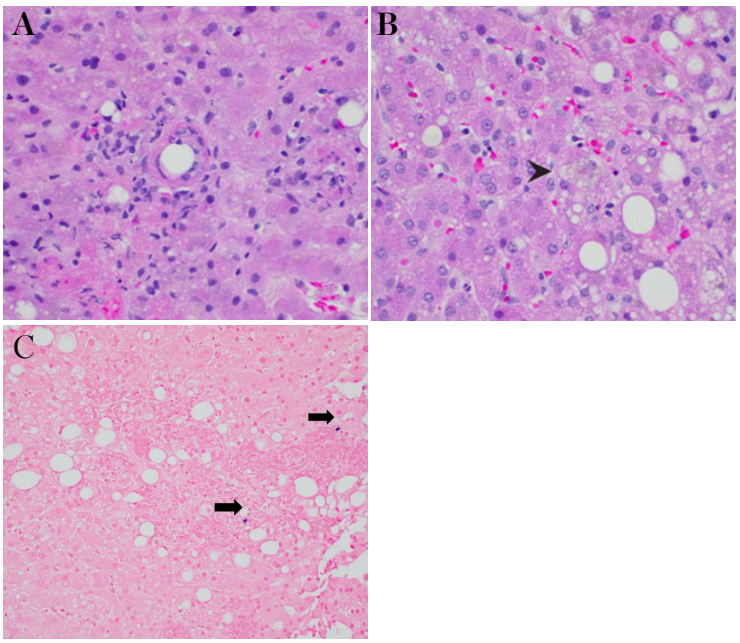

Figure 1. Liver core biopsy histopathology. A) Fibrin ring granuloma characterized by a central fat droplet surrounded by a ring of fibrin and epithelioid histiocytes (400X magnification, hematoxylin and eosin (H&E) stain). B) Hepatocellular cholestasis (arrowhead) and hemophagocytosis within sinusoids (400X magnification, H&E stain). C) In situ hybridization for Epstein-Barr virus (EBV) shows scattered positive lymphoid cells (200X magnification).

DISCUSSION

HLH is a syndrome of immune hyperactivation caused by various triggers depending on the patient population. It is characterized by dysregulated activation of T cells and macrophages, leading to a cytokine storm, systemic inflammation, multiorgan dysfunction, and cytopenias. Clinically, HLH often mimics sepsis, most triggered by infections or hematologic malignancies. Previously considered primarily a pediatric disease, increasing literature has highlighted its occurrence in adults. Adult HLH carries a high mortality rate, potentially greater than in pediatric cases, with estimates ranging from 20% to 40%. Given its severity, early diagnosis and treatment are critical.[5-8]

Diagnosing HLH in adults is challenging due to its overlap with other conditions. While pediatric HLH often is linked to genetic mutations (familial/primary HLH), adult HLH typically arises from an underlying disease (secondary/reactive HLH).[5,7] Common triggers include infections, malignancies, and autoimmune disorders, with immune checkpoint inhibitors and chemotherapy also implicated.[5,9] A 2014 study of 2,197 adult HLH cases found infections responsible for 50.4% of cases, with hematologic malignancies accounting for 44.6%.[6] Among infections, viruses were the most frequent triggers (34.6%), with EBV being the most common (15%).[6]

EBV-related HLH occurs when the virus infects B cells, requiring cytotoxic immunity for viral clearance. Failure of this mechanism can lead to uncontrolled viremia and excessive cytokine activation.[10] Patients with underlying immune deficiencies, such as X-linked lymphoproliferative disease types 1 and 2, are at higher risk for EBV-induced HLH.[10,11]

The most widely used diagnostic criteria come from the *HLH-2004* study, which requires either a molecular diagnosis or at least five of the following eight criteria: fever, splenomegaly, cytopenias (affecting ≥2 lineages), hypertriglyceridemia, hemophagocytosis on bone marrow histology, decreased NK cell activity, hyperferritinemia, and elevated soluble IL-2 receptor levels.[12,13] However, these criteria were originally developed in pediatric populations, raising concerns about their applicability to adults, who are more likely to develop HLH from secondary causes. Comorbid conditions such as diabetes and hyperlipidemia also may affect laboratory markers, reducing diagnostic specificity.[14] Consequently, HLH in adults often is considered a diagnosis of exclusion, leading to delays in care and worse outcomes.

In this case, the patient met five *HLH-2004* criteria (splenomegaly, fever, hypertriglyceridemia/hypofibrinogenemia, hyperferritinemia, and elevated soluble IL-2). Although bone marrow biopsy did not confirm HLH, hemophagocytosis was present in both the peripheral blood smear and liver biopsy, alongside fibrin-ring granulomas and EBV-positive lymphoid cells, findings consistent with active EBV infection, a known HLH trigger.[15]

Given the limitations of *HLH-2004* criteria in adults, alternative diagnostic tools have been proposed.[2,14] The HScore, developed in *Arthritis & Rheumatology*, assesses nine clinical and laboratory parameters to estimate the probability of HLH. Our patient had an HScore of 219, corresponding to a 96% likelihood of HLH.[16]

Additionally, a retrospective study at MD Anderson reviewed 61 cases of confirmed adult HLH and found that only 21% met *HLH-2004* criteria, though many had incomplete workups.[17] To improve diagnostic accuracy, researchers expanded the *HLH-2004* criteria from 8 to 18 variables while maintaining the requirement that at least five be met for diagnosis.[17] New criteria included renal failure, elevated liver enzymes, coagulopathy, hypoalbuminemia, and increased LDH. Applying this expanded system, our patient met 10 of 18 criteria.

Current HLH treatment strategies are largely derived from pediatric studies (*HLH-94*[12] and *HLH-2004*[13]), which emphasize etoposide and steroid therapy, with hematopoietic stem cell transplantation (HSCT) for refractory cases. Cyclosporine was initially included in induction therapy, but subsequent studies failed to show additional benefit.[13] No major clinical trials specifically guide adult HLH treatment, leading to therapeutic uncertainty.

In this case, the patient responded rapidly to steroids and plasmapheresis, which were initiated for suspected autoimmune hemolytic anemia rather than HLH.[18] By the time HLH was confirmed, etoposide was deferred. Although rituximab is sometimes used for EBV-HLH in cases of high viremia, it was unnecessary here.

Despite increasing recognition, adult HLH remains difficult to diagnose due to its nonspecific presentation and overlap with other conditions. The *HLH-2004* criteria lack specificity in adults, and some diagnostic tests (e.g., soluble IL-2 receptor) are costly and time-consuming. Although alternative markers like glycosylated ferritin and IL-18 have been explored, no large-scale trials have validated their utility. Refining diagnostic strategies, especially for adult and EBV-associated HLH, remains a critical need.

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