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Case Report

The Mononucleosis Masquerade'' — A Cautionary Tale in The Diagnosis of Pediatric Hemophagocytic Lymphohistiocytosis

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Abstract:

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome that may occur secondary to infections, most commonly Epstein-Barr virus (EBV). Delayed diagnosis can result in multiorgan failure, including acute liver failure. We report a 7-year-old girl who presented with fever, lethargy, headache, cervical lymphadenopathy, and neck pain and subsequently developed progressive jaundice, hepatosplenomegaly, coagulopathy, and acute liver dysfunction. EBV infection was confirmed by polymerase chain reaction, while an extensive infectious evaluation was otherwise negative. Markedly elevated ferritin, hypertriglyceridemia, hypofibrinogenemia, elevated soluble interleukin-2 receptor levels, and hepatosplenomegaly fulfilled six of the seven updated HLH-2024 diagnostic criteria, confirming secondary EBV-associated HLH. Prompt treatment with dexamethasone, anakinra, etoposide, and intravenous immunoglobulin resulted in significant clinical and biochemical improvement. This case highlights the importance of early recognition of HLH in children with EBV infection and progressive liver dysfunction, emphasizing timely diagnosis and initiation of immunomodulatory therapy to improve outcomes.

Key words: hemophagocytic lymphohistiocytosis; epstein-barr virus; acute liver failure; secondary hlh; pediatric; hyperferritinemia

Abbreviations: HLH - Hemophagocytic Lymphohistiocytosis, EBV- Ebstein Barr Virus, ALF -Acute liver failure.

1.Introduction

Hemophagocytic lymphohistiocytosis (HLH) can simply be described as a hyperinflammatory syndrome due to excessive activation of the macrophages, natural killer (NK) cells and cytotoxic lymphocytes leading to excessive cytokine production [1]. Ideally, natural killer cells and cytotoxic lymphocytes should lyse/eliminate activated macrophages. However, in HLH, there is a failure of normal feedback system, and an increased number of activated macrophages continues to trigger cytokine production [1,2]. HLH can be primary (familial or genetic) or secondary which is induced by multiple triggers that include autoimmune diseases, infections, and immunodeficiency syndromes. The most common infectious trigger is a viral infection, especially EBV infection [3]. Studies have shown that EBV can trigger HLH in individuals with a genetic defect in perforin-dependent cytotoxicity but also can induce HLH in those without any known predisposition [1,4]. EBV can induce liver failure via multiple mechanisms. The cytokine storm which leads to excessive inflammatory damage to the hepatocytes causes hepatic dysfunction and apoptosis [5,8]. EBV also has direct viral effects by viral replication within the hepatocytes. Disseminated intravascular coagulation (DIC) and endothelial damage can impair hepatic perfusion leading to ischemia, synthetic failure and coagulopathy [1,5]. Another mechanism is hemophagocytosis, where the macrophages engulf hepatocytes and blood cells [5]. The endpoint of the above-mentioned mechanisms is an eventual liver failure.

Case presentation

The patient is a 7-year-old female with a past medical history of attention-deficit hyperactivity disorder (ADHD) who presented to the Emergency Department (ED) with 3 days of high-grade fever, 2 days of lethargy, and headache associated with neck pain. Given concerns for meningitis, ceftriaxone and vancomycin were initiated in the ED after sending an infectious workup, including blood, urine, and cerebrospinal fluid (CSF) cultures. The patient was noted to have cervical lymphadenopathy and a

strawberry-like tongue. She was diagnosed with infectious mononucleosis confirmed by serological testing showing positivity for Epstein-Barr virus (EBV) IgM and EBV IgG viral capsid antigen. The EBV DNA PCR level was elevated (746,375 copies/mL). The CSF analysis was unremarkable. During hospitalization, the patient developed worsening jaundice and persistent fever and was subsequently transferred to the pediatric intensive care unit. Laboratory tests revealed transaminitis and rising bilirubin levels. She was found to have mild coagulopathy with hypofibrinogenemia and prolonged prothrombin time (PT). Vitamin K and fresh frozen plasma (FFP) were administered as supportive therapy for coagulopathy [6]. An ultrasound revealed gallbladder inflammation and mild hepatosplenomegaly. A neck CT showed cervical adenopathy without abscess. Due to concerns for hemophagocytic lymphohistiocytosis (HLH), a ferritin level was obtained and found to be elevated at 24,680 ng/mL. Hematology/Oncology was consulted, and per their recommendation, anakinra and corticosteroids were initiated. In view of HLH, perforin/granzyme B expression, CD107a, and soluble IL-2 receptor levels were sent out. Laboratory results included a platelet count of 38,000/μL, normal white blood cell (WBC) counts and hemoglobin levels 9.8 g/dL,aspartate transaminase [AST] 507 IU/L, alanine transaminase [ALT] 230 IU/L, lactate dehydrogenase [LDH] 1,812 IU/L, alkaline phosphatase 324 IU/L, and total bilirubin 4 mg/dL, fibrinogen 100 mg/dL, ferritin (24,680 ng/mL), soluble interleukin-2 receptor [sIL2R] 3,391 U/mL, PT 20.3 seconds. CD107a level was unexpectedly elevated. Evaluation for autoimmune hepatitis, including liver kidney microsomal type 1 (LKM-1) antibody immunoglobulin G (IgG) and F-actin smooth muscle antibody, was negative, as was serologic testing for viral hepatitis. Respiratory and CSF multiplex polymerase chain reaction panels were also negative. All bacterial cultures remained negative.

Diagnosis

Based on these findings, HLH triggered by EBV infection (EBV-HLH) was suspected, with acute liver failure considered a complication of the underlying hyperinflammatory syndrome [2,5]. The patient met six of the seven updated HLH-2024 diagnostic criteria, including fever, splenomegaly, bicytopenia, hypertriglyceridemia/hypofibrinogenemia, hyperferritinemia, and elevated soluble interleukin-2 receptor (sIL2R), thereby establishing the diagnosis of secondary EBV-associated HLH [1].

Management

The patient was initially treated with corticosteroids, anakinra, and ursodiol [1,2,9]. She remained clinically stable on this regimen. The genetic HLH panel was negative except for a GATA2 mutation, which was classified as a variant of uncertain significance in this context. A review of the literature shows that there have been only a handful of cases describing an underlying GATA2 deficiency in patients with acute secondary HLH [10]. Therapy as per HLH-1994 protocol was subsequently considered. Dexamethasone was continued [12]. Etoposide was initially withheld due to elevated direct hyperbilirubinemia. Following improvement in liver enzymes and total bilirubin levels, etoposide was initiated at 50% of the standard dose twice weekly, consistent with recommendations for dose modification in patients with hepatic dysfunction [1,5,9]. Monthly intravenous immunoglobulin (IVIG) was also initiated, along with Pneumocystis jirovecii pneumonia (PJP) prophylaxis using pentamidine and antifungal prophylaxis with fluconazole as supportive care during immunosuppressive therapy [9,12]. Later, she was transferred to a pediatric liver center due to concerns of progressive liver failure. She remained stable and avoided the need for liver transplantation. She was transferred back to our facility for continuation of care. The patient received HLH therapy for 16 days and was eventually discharged with a short course of tapering steroids. She continues to follow up with various specialists as an outpatient and remains in remission.

Figure 1: Schematic diagram of the pathogenesis of hemophagocytic lymphohistiocytosis (HLH). Cited in Wu et al. (2024). Hemophagocytic lymphohistiocytosis: current treatment advances, emerging targeted therapy and underlying mechanisms. J Hematol Oncol 17, 106.

HLH-2024 criteria — Diagnosis is based on fulfilling ≥5 of the following
●**Fever** – ≥38.5° C
●**Splenomegaly** – ≥2 cm below the costal margin
●**Cytopenias** – ≥2 of the following
•Hemoglobin <90 g/L (<100 g/L in neonates)
•Platelets <100 x 109/L
•Neutrophils <109/L
●**Hypofibrinogenemia or hypertriglyceridemia** – ≥1 of the following:
•Fibrinogen ≤1.5 g/L
•Triglycerides ≥3.0 mmol/L
●**Hyperferritinemia** – ≥500 microg/L
●**Hemophagocytosis** – In bone marrow or other tissues
●**Elevated soluble CD25** (also called soluble interleukin 2 receptor alpha) – ≥2400 units/mL

Table 1: Adapted from Henter JI. (2025). Hemophagocytic lymphohistiocytosis. N Engl J Med; 392(6):584–598.

Discussion

This case emphasizes the importance of recognizing HLH as a possible cause of acute liver failure in the pediatric population [4,5]. Although uncommon, EBV-associated HLH can lead to severe hepatic injury and acute liver failure, resulting in significant morbidity and mortality if not recognized and treated promptly [1,4,5,9]. Viral infection is a common trigger for secondary HLH, with EBV representing the most frequent infectious etiology worldwide [1,3,4,7]. In the United States, EBV has been reported to account for approximately one-third of pediatric HLH cases [7]. Excessive cytokine release causes inflammatory hepatocyte injury and apoptosis, while viral replication within hepatocytes, endothelial injury, disseminated intravascular coagulation (DIC),

impaired hepatic perfusion, and hemophagocytosis further contribute to progressive hepatic dysfunction and acute liver failure [2,5]. Following HLH–2024 criteria is necessary in making the diagnosis of HLH [1]. HLH treatment involves three key steps: providing life-saving supportive care, addressing triggers like infections or malignancies, and controlling excessive inflammatory response and cell proliferation with immunosuppressive and cytotoxic drugs such as glucocorticoids, anakinra, and etoposide amongst others [5]. Management of HLH in patients with severe liver dysfunction remains particularly challenging because etoposide undergoes partial hepatic metabolism [1,5,13]. Nevertheless, etoposide remains a cornerstone of HLH-directed therapy and should not be unnecessarily delayed, as postponement has been associated with worse clinical outcomes [1,12,13]. In patients with significant hepatic impairment, initiating treatment with a reduced dose (e.g., 75 mg/m²) followed by dose escalation as liver function improves is a reasonable strategy that balances efficacy with safety [1,9,13]. Our patient demonstrated marked clinical and biochemical improvement following early immunomodulatory therapy and ultimately avoided liver transplantation, underscoring the importance of timely diagnosis and multidisciplinary management.

Conclusion

EBV induced HLH is a rare but severe etiology of liver failure in the pediatric population [1,2,5]. It requires early diagnosis and aggressive management to prevent multiorgan complications such as liver failure and subsequent need for a liver transplant [1,2,6,9]. Management is based on multidisciplinary approach and adherence to the established HLH protocol.

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Drs Chimeremeze Ndubuoke, Laxman Aryal, Kathryn Williams, Hamayun Imran and Nita Davies identified the case, performed literature review, drafted the initial manuscript, and critically reviewed and revised the manuscript.

Dr David Gremse contributed to clinical data interpretation, critically reviewed and revised the manuscript and will provide funding support for Open access, if manuscript is accepted for publication.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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