IDCases 30 (2022) e01616

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

A mild, self-resolving case of Epstein-Barr virus-induced hemophagocytic lymphohistiocytosis

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ARTICLE INFO

Keywords:
Epstein-Barr Virus
EBV
Hemophagocytic lymphohistiocytosis
HLH

ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a multisystem disease caused by an excessive activation of the immune system. In most instances, HLH can be fatal without treatment; a life-threatening syndrome driven by a dysregulated immune system and activation of macrophages resulting in cytokine release and consequent cellular damage. HLH can occur as a consequence of multiple genetic abnormalities or environmental triggers. We present an interesting case of mild, self-resolving, HLH due to Epstein-Barr Virus (EBV) infection in a young woman. The best-known diagnostic criteria are based on the HLH-2004 trial, incorporating either the presence of known mutations or five of eight clinical and laboratory findings. Prompt initiation of etoposide-containing therapy is associated with improved survival. Rituximab, an anti-CD20 antibody, can also remove EBV-harboring B-cells and improve outcomes. In a rare subset of patients, the disease can spontaneously resolve without any therapeutic interventions thus sparing the patients from toxic therapies.

Background

Hemophagocytic lymphohistiocytosis (HLH) is a multisystem disease caused by an excessive activation of the immune system [1]. Often a life-threatening syndrome, it results from a prolonged activation of antigen presenting cells (APC) and cytotoxic T cells [2]. Critical regulatory pathways involved in the termination of inflammatory responses are overwhelmed or disrupted in HLH [1].

HLH can occur as a consequence of multiple genetic abnormalities or environmental triggers. The activation of the immune system can occur in patients with or without genetic predisposition. Epstein-Barr virus (EBV), a ubiquitous and predominantly B-lymphotropic human herpesvirus, is the most commonly implicated trigger for secondary HLH (sHLH) [3]. EBV-associated HLH (EBV-HLH) is often associated with fatal disease. We present an interesting case of mild, self-resolving, EBV-HLH in a young woman.

Case presentation

A 20-year-old college female with no significant past medical history presented to an urgent care center in the context of fever, chills, body aches and ongoing fatigue for 5 days. She had adjunctive symptoms of rhinorrhea but denied sore throat. She was febrile to 38.5 °C, with otherwise stable vital signs. She was fully vaccinated against COVID-19 along with a booster. Physical examination at that time had demonstrated mild pharyngeal erythema, but no evidence of oropharyngeal exudates, sinus tenderness, trismus, or cervical adenopathy. COVID-19 and rapid strep testing was negative. Monospot testing, however, was notably positive and she was diagnosed with infectious mononucleosis (IM). She was ultimately prescribed acyclovir and ondansetron, with continued recommendation for conservative management of fever and rhinorrhea.

Two days later, the patient subsequently presented to our hospital facility in the context of ongoing nausea (without emesis), poor oral intake, and upper abdominal discomfort. She endorsed non-compliance with acyclovir but was taking acetaminophen for conservative management, as well as aspirin/paracetamol/caffeine and ibuprofen for migraines. She described her abdominal pain as band-like across the upper abdomen, waxing and waning, without any specific exacerbating or alleviating factors. She denied easy bruisability, but endorsed some neck discomfort, mild adenopathy, and continued intermittent fevers. She was unclear regarding how she contracted IM, noting that her boyfriend lived in another state, but that she shared an apartment with two fellow college students, locally.

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https://doi.org/10.1016/j.idcr.2022.e01616
Received 10 July 2022; Received in revised form 20 August 2022; Accepted 3 September 2022
Available online 6 September 2022

On presentation to the emergency room, she was afebrile but mildly tachycardic (102 beats per minute), with otherwise normal vital signs. Physical examination was remarkable for a dry, non-erythematous oropharynx without palatal petechiae, mild right upper quadrant abdominal tenderness, no noted left upper quadrant tenderness, negative Carnett's sign, and no costovertebral angle tenderness. Initial laboratory diagnostics demonstrated mild hypokalemia to 3.4 mmol/L (reference range: 3.5–5.1 mmol/L), elevated aspartate transaminase (AST) at 165 units/L (reference range: 0–33 units/L), elevated alanine transaminase (ALT) at 116 units/L (reference range: 10–49 units/L), elevated total bilirubin at 3.7 mg/dL (reference range: 0.3–1.2 mg/dL), and adjunctive elevation in alkaline phosphatase to 280 units/L (reference range: 46–116 units/L). Complete blood count demonstrated a normal leukocyte count of 4.6 k/uL (reference range: 4.0–10.8 k/uL), hemoglobin at her baseline of 12.6 g/dL (reference range: 11.0–14.5 g/dL), and thrombocytopenia to 67 k/uL (reference range: 145–400 k/uL) with an inappropriately low immature platelet fraction of 5.6 %. Elevated monocytes (15 %; reference range: 3–12 %) were also noted. Testing for COVID-19, influenza, and respiratory syncytial virus was once again negative.

A contrast-enhanced CT scan of the abdomen and pelvis demonstrated hepatomegaly with subtle heterogeneous enhancement and moderate periportal edema and moderate gallbladder wall thickening without evidence of gallstones, inflammatory changes, or biliary ductal dilatation (Fig. 1). There was moderate splenomegaly (measuring 11.5 cm in the greatest width) and the spleen was noted to have a rounded configuration with heterogeneous enhancement with mottled lucency, but no evidence of wedge-shaped infarction. The remainder of the intra-abdominal organs including the pancreas, adrenals, kidneys, reproductive tract organs, and gastrointestinal tract were unremarkable. A small amount of free fluid was noted in the pelvis, likely reactive in nature. Mildly enlarged retroperitoneal lymph nodes, as well as enlarged inguinal lymph nodes were identified, without overt evidence of bulky adenopathy. A subsequent right upper quadrant ultrasound demonstrated gallbladder wall thickening/edema without evidence of biliary ductal dilatation. The surgical service was consulted given the splenic imaging findings with recommendations for continued conservative management given no indication for acute surgical intervention. The patient was admitted to the hospital for further management.

Additional laboratory diagnostic testing revealed elevated ferritin level of 1486.2 ng/mL (reference range: 7.3–270.7 ng/mL) and an elevated triglyceride level of 526 mg/dL (reference range: 0–149 mg/dL), prompting concern for HLH. Further laboratory testing for EBV DNA, soluble interleukin-2 receptor (sCD25) and work-up for fever of unknown origin, hepatitis, and thrombocytopenia was sent. Testing for acute viral hepatitis, cytomegalovirus, HIV, syphilis, *B. henselae, B. quintana*, *E. chaffeensis*, *C. burnetii*, *Leptospira,* and tuberculosis was negative. The patient's thrombocytopenia and elevated ferritin level gradually decreased with conservative management and her clinical symptoms improved. Ultimately, EBV DNA returned elevated at 113,149 copies/mL (reference range: $\leq$ 200 copies/mL), along with elevated EBV IgM at $>$ 160.0 units/mL. Furthermore, sCD25 returned elevated at 5387.5 pg/mL, effectively fulfilling five criteria for HLH (Table 1). Given the patient's overall clinical improvement, resolution of thrombocytopenia and down-trending ferritin level, she was discharged with recommendations to continue conservative management, and planned outpatient follow up with her primary care provider.

Discussion

We describe a rare case of EBV-HLH that resolved without treatment. In most instances, HLH can be fatal without treatment; a life-threatening syndrome driven by a dysregulated immune system and activation of macrophages resulting in cytokine release and consequent cellular damage [4]. Clinically, the hypercytokinemia can manifest as fever, cytopenias, and splenomegaly [5]. While previously thought to be a pediatric disease secondary to underlying genetic mutations, recent studies have suggested that multiple genetic and environmental triggers

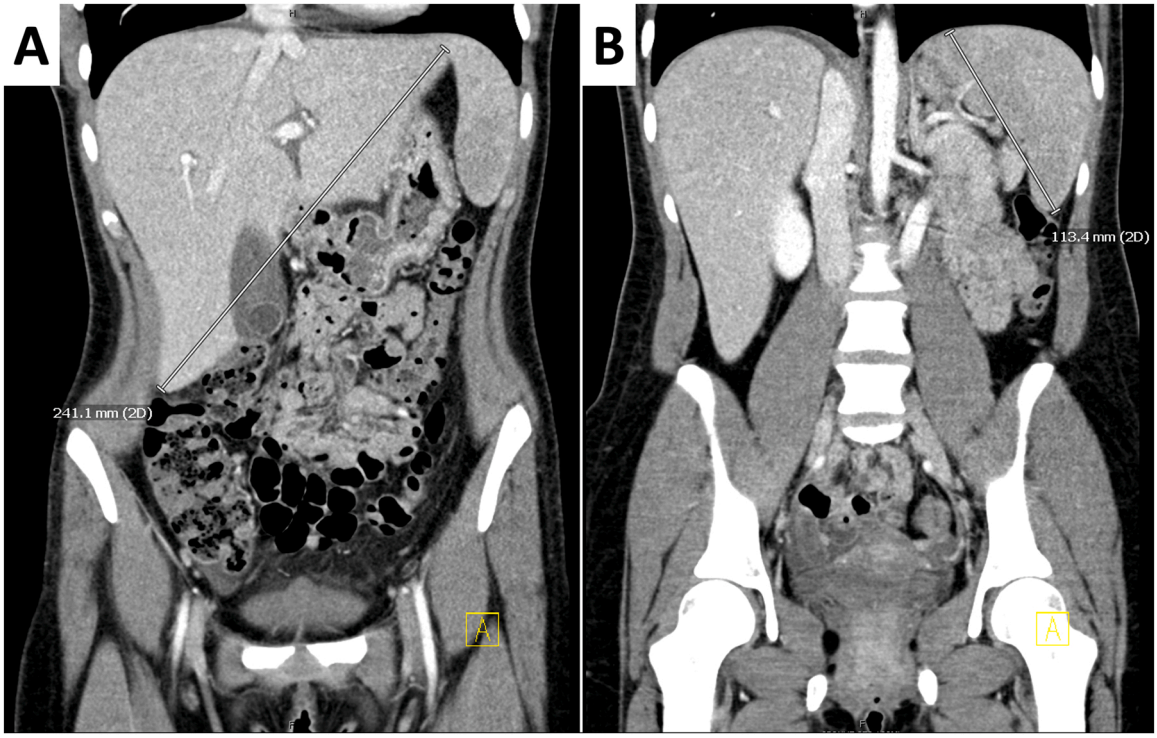

Fig. 1. Contrast enhanced CT scan of the abdomen and pelvis. **(A)** Hepatomegaly with subtle heterogeneous enhancement and moderate periportal edema, moderate gallbladder wall thickening without evidence of gallstones or inflammatory changes and no biliary ductal dilatation. **(B)** Moderate splenomegaly with rounded configuration of the spleen with heterogeneous enhancement with mottled lucency.

Table 1
Diagnostic criteria for HLH. Shaded rows indicate diagnostic criteria met by our patient.

Criterion	Diagnostic Range	Our Patient
Fever	≥ 38.5°C	38.5°C
Splenomegaly	Present	Present
Peripheral blood cytopenia (at least 2 present)	Hgb < 9 g/dL Plt < 100,000/microL ANC < 1000/microL	Hgb 9.9 g/dL Plt 69/microL ANC 2.2/microL
Hypertriglyceridemia and/or hypofibrinogenemia	Triglycerides > 265 mg/dL Fibrinogen < 150 mg/dL	Triglycerides 526 mg/dL
Hemophagocytosis in bone marrow, spleen, lymph node, or liver	Present	Unknown
Natural killer cell activity	Low or absent	Unknown
Elevated ferritin level	> 500 ng/mL	1,486.2 ng/mL
Elevated soluble CD25 (soluble interleukin-2 receptor alpha)	> 2,400 pg/mL	5,387.5 pg/mL

Hgb: Hemoglobin; **Plt:** Platelets; **ANC:** Absolute Neutrophil Count.

can lead to HLH [1]. Defects in the *PRF1* gene (encoding Perforin) was the first discovered underlying genetic basis for inherited HLH [6]. Since then, various other mutations have been discovered, commonly occurring in the *UNC13D, STXBP2, Rab27a, STX11, SH2D1A,* and *XIAP* genes [7]. However, HLH can also occur in people without any underlying genetic defects secondary to extrinsic triggers, which is referred to as secondary HLH (sHLH).

Dysregulated immune system activation from an infection is the most common trigger for sHLH; viral infections remain the most common inciting factor, with EBV and Cytomegalovirus as the most common viruses [3]. There are also case reports of SARS-CoV-2 triggering HLH in the setting of post-acute COVID-19 syndrome [8]. Mycobacteria are the most commonly associated bacterial pathogens [9]. sHLH can also occur with vasculitides like Kawasaki disease, malignancies (most commonly lymphomas), rheumatologic disorders, immune deficiencies (chronic granulomatous disease), or HIV infection. It has also been linked to the use of checkpoint inhibitors like nivolumab and ipilimumab [10].

HLH often presents a diagnostic dilemma and can often be difficult to differentiate from severe infection especially as infection can itself be the trigger for sHLH. In a case series of 10 patients who had fever, cytopenia, and elevated CRP, all received broad spectrum antibiotics. The median time to diagnose HLH in this population was 20 days [11]. HLH is diagnosed in the context of a compatible clinical picture and elevated inflammatory markers. The best-known diagnostic criteria are based on the HLH-2004 trial [12], incorporating either the presence of known mutations (as described above) or five of the eight clinical and laboratory findings. Our patient fulfilled five criteria and had positive EBV PCR and IgM thus diagnosing her with EBV-HLH (Table 1).

EBV-HLH occurs in greater frequencies in pediatric patients but has been seen in all age groups [13]. EBV-HLH can range from spontaneously resolving inflammation to refractory disease requiring hematopoietic stem cell transplantation (HSCT) [14]. The virus can trigger HLH in any patient regardless of underlying genetic predisposition. Male patients with *SH2D1A* gene mutation, suggestive of X-Linked proliferative syndrome (XLPS) are at particularly high risk of developing EBV-HLH, with up to sixty percent of patients with XLPS developing EBV-HLH, thus requiring frequent screening [15].

Prompt initiation of etoposide-containing therapy is associated with improved survival in EBV-HLH [16,17]. Rituximab, an anti-CD20 antibody, can remove EBV-harboring B-cells and improve outcomes. The use of rituximab was associated with significant reductions in ferritin and EBV load levels in a retrospective multi-center study [18]. Other agents used infrequently to treat EBV-HLH include anti-interleukin-1 agents like anakinra and canakinumab or anti-tumor necrosis factor alpha therapies like etanercept and infliximab. A subset of patients with spontaneously resolving EBV-HLH might go on to develop recurrent and unrelenting HLH that requires immunotherapy and HSCT. Notably this may occur even in patients without XLPS [14].

Conclusion

HLH is a difficult to diagnose and often life-threatening disease that may be caused by multiple extrinsic etiologies. One of the most implicated causes of sHLH is EBV. In a rare subset of patients with sHLH, the disease can spontaneously resolve without any therapeutic interventions thus sparing the patients from toxic therapies. However, these subsets of patients may develop recurrent sHLH.

CRediT authorship contribution statement

Biplov Adhikari: Writing – original draft, Data Collections. **Shiavax J. Rao:** Writing – original draft, Data, Collections, Writing – review & editing. **Christopher J. Haas:** Writing – review & editing.

Sources of funding

None.

Ethical approval

N/A.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflicts of interest

None.

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