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Not another case of mono: Epstein-Barr virus (EBV) associate hemophagocytic lymphohistiocytosis (HLH)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 30
Final Diagnosis: Hemophagocytic lymphohistiocytosis (LHL)
Symptoms: Abdominal pain • fever • hypotension • pancytopenia
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare disease
Background: Hemophagocytic lymphohistiocytosis (HLH) is a result of dysregulated cellular response system. Primary HLH is an autosomal recessive disorder of childhood, with defects in cellular cytotoxicity. Secondary HLH is an acquired syndrome that presents in young adulthood secondary to a variety of inflammatory conditions: viral infections, rheumatologic conditions, or malignant processes. The inflammatory nature of certain conditions triggers a cytokine release in individuals who have abnormal T cell activation.

Case Report: A 30-year-old Hispanic male presented with worsening abdominal pain for 5 months and was found to have fever, pancytopenia, and hypotension. Serial CT scans of the abdomen/ pelvis showed splenomegaly but no abscesses, areas of infection, or masses. Infectious causes were considered but results of all cultures and tests were negative except for a high Epstein-Barr viral load. The patient deteriorated and required intubation on hospital day 28. Repeat bone marrow biopsy on day 32 suggested a diagnosis of hemophagocytic lymphohistiocytosis, although there was no evidence of hemophagocytosis within the bone marrow. The patient continued to deteriorate and was too unstable to receive treatment with chemotherapy. He died on hospital day 34.

Conclusions: This case highlights the importance of early consideration and treatment of secondary HLH in an individual presenting with progressive fever, hepatomegaly, and cytopenias.

Key words: EBV • EBV associated with hemophagocytic lymphohistiocytosis • hemophagocytic lymphohistiocytosis

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Background

Hemophagocytic lymphohistiocytosis (HLH) is a rare disorder, with both primary (familial) and secondary (acquired) forms [1]. Secondary HLH most typically presents with fever, hepatosplenomegaly, and cytopenias. Other common manifestations include hepatitis or acute liver failure, coagulopathies, bone marrow failure (including anemia or thrombocytopenia), skin rashes (maculopapular rashes, petechiae, purpura), or evidence of pulmonary dysfunction [2]. HLH is commonly associated with Epstein-Barr virus (EBV), which most commonly occurs in immunocompetent individuals [2]. In a recent study, EBV was the leading viral cause of secondary HLH [3].

Case Report

A healthy 30-year-old Hispanic male was admitted to the hospital in April with complaints of right lower quadrant abdominal pain with guarding and rebound tenderness associated with a few days of fevers and chills. On admission, the patient was found to be febrile (39.2°C), hypotensive (95/55 mm Hg), and tachycardic (124 bpm). An abdominal/pelvis CT showed a ruptured appendix with pericecal abscess and splenomegaly (19.7 cm) (Figure 1). A complete blood cell count demonstrated mild pancytopenia and coagulopathy: white blood cell count, 4100/μL; hemoglobin level 12 g/dL; platelet count 126,000/μL; INR 2.3; prothrombin time 24.0; partial thromboplastin time 48.3. The patient was admitted and treated with intravenous antibiotics, after which he began to improve clinically and was discharged home on oral antibiotics.

Over the next 4 months, the patient was admitted 3 additional times with similar complaints of subjective fever and abdominal pain. During each admission, the patient was febrile, hypotensive, tachycardic, pancytopenic, and coagulopathic. The patient was repeatedly treated with intravenous antibiotics. Due to his persistent splenomegaly, fevers, and pancytopenia, a hematology/oncology specialist was consulted, who recommended a bone marrow biopsy, which showed normochromic normocytic anemia, normocellular marrow, and no neoplasia. The pancytopenia was thought to be infection-induced.

One month later, the patient was re-admitted to the hospital because of abdominal pain, nausea, vomiting, subjective fever, and decrease oral intake for 5 days. An abdominal/pelvis CT scan showed a focal small bowel ileus in the right lower quadrant, and no abscess at this time. As part of the follow-up work-up, a right upper quadrant ultrasound was ordered, which showed cholelithiasis. Due to the patient's history of working on a farm in Mexico, a number of lab tests were ordered to rule infection, but results on PPD, cocci, histoplasmosis, and *Cryptococcus* were negative.

Figure 1. Patient's CT of abdomen and pelvis showing an enlarged spleen.

On hospital day 9, the patient became more tachycardic, hypotensive, febrile, pancytopenic, and coagulopathic; therefore, he was transferred to the intensive care unit for sepsis. A complete blood cell count demonstrated: white blood cell count 1900/μL; absolute neutrophil count of 2,000; hemoglobin level 7.8 g/dL; platelet count 89,000/μL; peripheral smear showed pancytopenia without blast cells; INR 1.6; prothrombin time 19.1; and partial thromboplastin time 43.2. He was transfused with packed red blood cells and multiple units of fresh frozen plasma, and was put on broad-spectrum intravenous antibiotics. Blood cultures were sent (all negative) and tested for: CMV, HSV, HIV, and hepatitis panel were all negative, but EBV PCR came back positive, with 54843copies.

The following day, he began complaining of right upper quadrant pain. An ultrasound showed a thickening of the gallbladder wall, but HIDA scan was negative. In addition, the liver function test result began to become markedly abnormal, with ALT 121 U/L; AST 274 U/L; AP 374 U/L; total bilirubin 4.1 mg/dL; total protein: 4.6 g/dL; and albumin 1.8 g/dL. On physical exam, the patient became progressively more jaundiced and edematous. CT abdomen/pelvis, however, continued to show worsening of the small bowel loop dilation, with air fluid levels (small bowel thickening vs. walled-off abscess). Gastroenterology was consulted and a colonoscopy with mucosal wall biopsies was done, which came back negative.

Over the next few days, the patient began to deteriorate and became more hypotensive and requiring vasopressors. As the patient became further pancytopenic and coagulopathic, he received multiple transfusions of fresh frozen plasma, platelets, and packed red blood cells. At this point, another bone

marrow biopsy was done. The peripheral aspirate showed normochromic normocytic anemia, rare nucleated red blood cells, marked leucopenia, and thrombocytopenia. Bone marrow showed hypercellular bone marrow with erythroid hyperplasia and decreased granulopoiesis, with no leukemic process identified.

The patient died the night before chemotherapy was to be initiated.

Discussion

The diagnosis of secondary HLH has been detailed in the HLH 2004 protocol. According to the protocol, 1 of the following criteria should be satisfied [2]:

1. A molecular diagnosis consistent with HLH is made (Mutation of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, BIRC4) OR.
2. 5 of the 8 criteria shown below: fever >38.5 ; splenomegaly, cytopenias (Hgb <9 , Platelets $<100 \times 10^9$, neutrophils $<1 \times 10^9$); hypertriglyceridemia or hypofibrinogenemia; hemophagocytosis in bone marrow, spleen or lymph nodes; low or absent NK cell activity; ferritin $>500 \mu\text{g/L}$; elevated soluble CD25 (a component of the IL2 receptor found on T-cells and that has been shown to be indicative of inflammatory states in individuals with HLH) [3].

Although the criteria above are a vital component of diagnosis, analyzing peripheral blood smears and bone marrow biopsies should also show certain common features. It is important to analyze lymphocyte morphology. Individuals with HLH will typically exhibit proliferation of large granular lymphocytes. Familial and EBV HLH variants will usually show proliferation of mature or blastic-LGL, whereas HSV and adenovirus-HLH will typically show promonocytic cell proliferation [4].

References:

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Conclusions

Our patient fulfilled criteria for secondary HLH, including fever, splenomegaly, cytopenias and hypofibrinogenemia. His initial bone marrow biopsy, done on his first admission in April, revealed no evidence of malignancy or bone marrow pathology; however, a repeat bone marrow biopsy done on day 32 of admission showed common findings of HLH. However, by the time he had developed the necessary clinical manifestations for diagnosis, his condition had deteriorated immensely. Therefore, early consideration of HLH, despite initial noncontributory bone marrow biopsies and limited clinical symptoms, is vital.

The treatment options for HLH are quite diverse. Recent literature strongly advocates treatment of the underlying inflammatory condition. The most widely accepted treatment regimen includes etoposide and dexamethasone. The HLH 94 protocol states etoposide, dexamethasone, and Cyclosporine A are most effective. Recent studies have shown that the doses and frequency of this regimen may need to be adjusted based on disease severity and responsiveness. If no response is noted within 2–3 weeks, salvage therapy is recommended. In addition, adjunct therapy includes controlling the inflammation. Rituximab has shown promise in controlling the underlying EBV. Similarly, alemtuzumab has been shown to be successful with suppressing T-cell activation. According to Freeman et al, survival is highest if started within 4 weeks of diagnosis. However, even relapse rate was approximately 30% after 8 weeks [4]. Hematopoietic stem cell transplant has been shown to be useful in individuals with familial HLH, progressive disease, or brain involvement [3]. In individuals who received hematopoietic stem cell transplant, there was a 50% complete resolution rate and 30% of individuals had a partial resolution [3].

Although Epstein-Barr virus (EBV) is best known for causing infectious mononucleosis, it is also commonly associated with secondary HLH. Early diagnosis can lead to increased survival – one study described an overall survival rate of 43.9% among adult patients who received treatment with chemotherapy [5].