Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in a postpartum patient with preeclampsia: a case report

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Hemophagocytic lymphohystiocytosis is an extremely life-threatening immune deregulatory syndrome. It is characterized by pathologic activation of immune cells, leading to excessive cytokine production, multiorgan failure, and potentially, death. A 28-year-old primigravida at 32 weeks and 3 days of gestation presented with newly-diagnosed preeclampsia with severe features, fever, and fetal tachycardia. She was delivered by cesarean delivery. After delivery, she had a fever of unknown origin, with evidence of a hyperinflammatory state. Extensive infectious work-up was significant for positive Epstein-Barr Virus. A bone marrow biopsy demonstrated hemophagocytosis. She was diagnosed with Epstein-Barr-Virus-associated hemophagocytic lymphohystiocytosis and was treated with immunosuppression and chemotherapy. Hemophagocytic lymphohistiocytosis is a rare, life-threatening immune dysregulatory syndrome with both genetic and extragenic triggers that can occur in the postpartum period. Rituximab is an effective add-on therapy to conventional treatment.

Key words: Epstein-Barr virus, fever of unknown origin, hemophagocytic lymphohistiocytosis, postpartum preeclampsia

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a very rare and potentially fatal syndrome characterized by a dysregulated immune system and hyperinflammatory state. Persistent activation of cytotoxic lymphocytes ultimately leads to a cytokine storm, multiorgan failure, and potential death.[1] In 1994, the Histiocytic Society first proposed the diagnostic criteria for HLH that were later revised in the HLH-2004 trial (Table).[2]

A large systematic review of 2197 cases of adult HLH from 1974 to 2011 identified only 50−149 cases occurring in the United States.[2] Interestingly, the incidence of HLH is the highest in Japan, where upto 50% of cases are found.[3] Currently, there are various clinical guidelines for management in adults, and treatment is often on the basis of expert opinion aimed to address the underlying cause.[1,4] In a review of 1109 adult patients, the mortality rate was 41%.[5] Larger treatment studies have demonstrated a varied mortality rate of 20% to 88%.[2]

HLH has traditionally been classified as primary (familial) or secondary (reactive). The secondary causes include infection, autoimmune diseases, malignancy, pregnancy, and drugs. Increasing genetic complexities and diverse environmental factors make diagnosing HLH and providing appropriate directed therapies a challenge for clinicians.[2,4] Pregnancy-related HLH is a rare clinical scenario with sparse case reports.[5−7]

We present a case of Epstein-Barr virus (EBV)-associated HLH diagnosed in a postpartum patient with a fever of unknown origin.

Case report

A 28-year-old primigravida at 32 weeks and 3 days gestation was transferred from an outside hospital after a diagnosis of preeclampsia with severe features for higher-level neonatal intensive care unit care. She had no significant past medical or surgical history. She was born in Mexico and immigrated to the United States 16 years ago. She currently works on a dairy farm. Family history was notable for a sister who had prolonged fevers after delivery several years ago.

The patient had received magnesium sulfate and betamethasone before arrival. On admission, she reported a mild headache and 1 episode of a subjective fever 2 weeks ago. Her vital signs were as follows: body temperature 36.8° C, blood pressure 131/67, heart rate 117 beats per minute, respiratory rate 16 breaths per minute. The physical exam was unremarkable.

She was initially diagnosed with severe preeclampsia on the basis of elevated transaminases >2 × the upper limit of normal on admission. There was concern for evolving atypical hemolysis with elevated liver enzymes and low platelets owing to increases in both transaminases and lactate dehydrogenase (LDH). The admission labs were remarkable for

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TABLE
Revised diagnostic guidelines for hemophagocytic lymphohistiocytosis[2]

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled.
(1) A molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
(A) Initial diagnostic criteria (*to be evaluated in all patients with HLHL*)
Fever
Splenomegaly
Cytopenias (affecting ≥ 2 of 3 linages in the peripheral blood):
Hemoglobin < 90 g/L (in infants < 4 weeks: hemoglobin < 100 g/L)
Platelets $< 100 \times 10^9$ /L
Neutrophils $< 1.0 \times 10^9$ /L
Hypertriglyceridemia and/or hypofibrinogenemia:
Fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥ 265 mg/dl)
Fibrinogen ≤ 1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
(B) New diagnostic criteria
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin ≥ 500 μg/L
Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2,400 U/ml

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hemoglobin 10.9 g/dL (normal, 12−16 g/dL), platelets 288×10^3 /uL (normal, 150 -450×10^3 /uL), aspartate transaminase/alanine transaminase 78/114 U/L (normal, 7−37 U/L and 10−49 U/L respectively), LDH 264 U/L (normal, 120−246 U/L), urine protein/creatinine 1111 mg/g (normal, 0−100 mg/g), and fibrinogen 786 mg/dL (normal, 173−454 mg/dL). Creatinine, total bilirubin, and haptoglobin were normal. The peripheral blood smear was negative for hemolysis. During triage evaluation, she developed a fever of 38.1°C and maternal and fetal tachycardia. Given the concern of worsening maternal and fetal status, she underwent an uncomplicated primary cesarean delivery with the delivery of a viable 2032 g infant with an Apgar score of 6/8. The estimated blood loss was 355 mL. Amniotic fluid cultures were obtained owing to a high suspicion of chorioamnionitis.

Her postpartum course was complicated by a fever of unknown origin (FUO), with high-grade quotidian fevers of upto 40.5°C Figure 1. While febrile, the patient experienced chills, night sweats, and rigors but appeared clinically well in-between the fevers.

The initial work-up included the following: an unremarkable chest X-ray, computed tomography chest negative for pulmonary embolism, a right upper quadrant ultrasound demonstrating hepatomegaly secondary to hepatic steatosis, and a normal transthoracic echocardiogram. Consultations with maternal-fetal medicine, general medicine, infectious disease, rheumatology, gastroenterology, and hematology were obtained.

The labs were significant for a positive EBV DNA quantification of 280 IU/mL (log 2.4) with a negative monospot test and negative EBV early antigen, indicating a reactivation of a chronic infection. Elevated C-reactive protein 104.5 mg/L (normal, 0−10 mg/L) and erythrocyte sedimentation rate 78 mm/h (normal, 0−20 mm/h). The iron studies were as follows: Fe 48 ug/dL (normal, 50−170 ug/dL), 15% saturation, total iron binding capacity 311 ug/dL (250−450 ug/dL), and ferritin 12,667 ng/mL (normal range 10 −291 ng/mL). The serial blood cultures were negative. The amniotic fluid cultures at the time of cesarean delivery were negative. Urine culture was negative. Extensive virology, fungal, parasitic, and rheumatologic work-up was negative.

She was empirically treated with broad-spectrum antibiotics on postpartum day one with intravenous ampicillin, gentamycin, and clindamycin and was subsequently transitioned to intravenous piperacillin-tazobactam and doxycycline for a total of 9 days for presumed chorioamnionitis and potential Q fever (given farm work). In addition, therapeutic heparin was initiated for 48 hours for suspected deep septic thrombophlebitis. Despite using board-spectrum antibiotics and anticoagulation there was no improvement of the fevers.

Hematology was consulted on hospital day 12 owing to findings of hyperferritinemia of 12,669 ng/dL (normal range, 10−291 ng/mL). HLH was suspected because of significantly elevated ferritin, FUO, and hepatic dysfunction. Further

FIGURE 1
Patient fever curve

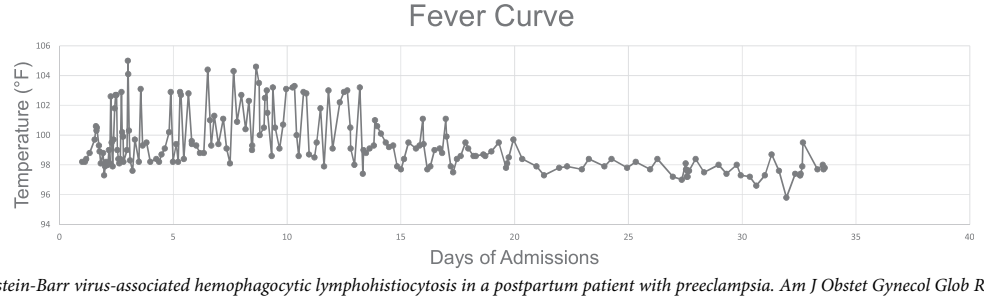

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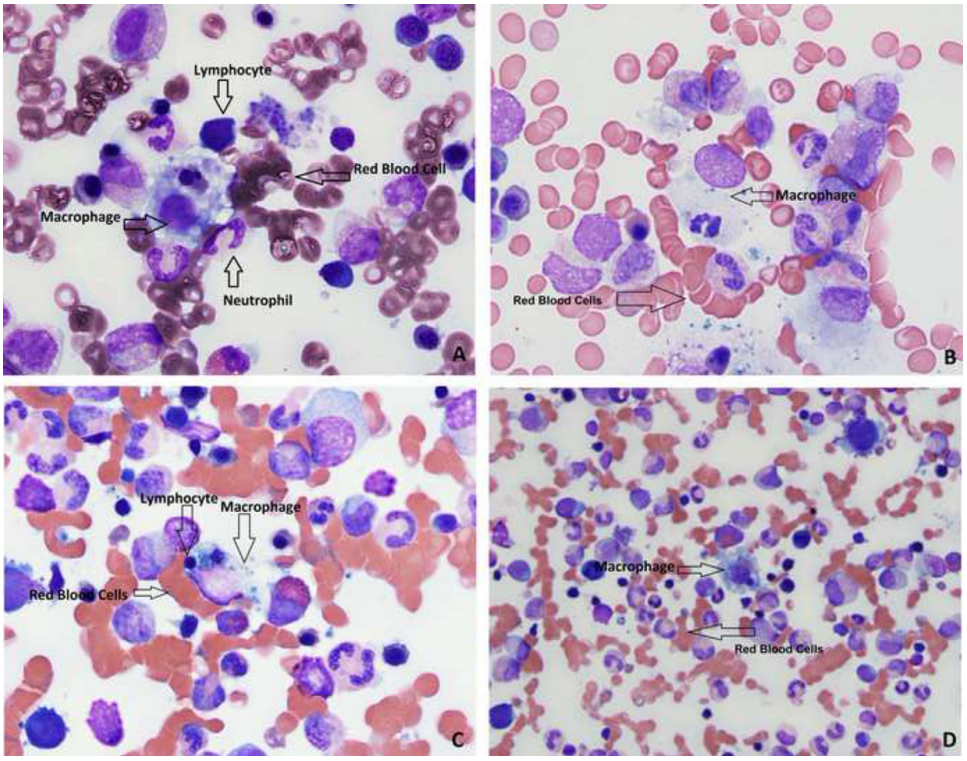
FIGURE 2
Bone marrow biopsy showing phagocytosis of hematopoietic cells by macrophages



Giemsa stain at 100 × magnification (**A**, **B**, **C**) and 50 × (**D**) of activated macrophages phagocytosing hematopoietic cells on bone marrow biopsy in our postpartum patient with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis.

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laboratory testing showed soluble interleukin-2 receptor at 21,950.3 pg/mL (normal range, 175.3−858.2 pg/mL) and triglycerides at 822 mg/dL (normal range, 30−150 mg/dL). She subsequently underwent a bone marrow biopsy confirming hemophagocytosis Figure 2. She met the full diagnostic criteria for HLH (following 5 of 8): fevers, hyperferritinemia, hypertriglyceridemia, hemophagocytosis on bone marrow biopsy, and elevated soluble interleukin-2 receptor. The
bone marrow biopsy was negative for bacterial, viral, fungal, parasitic, and malignant causes. Genetic testing showed the following 2 genetic variants of uncertain significance (VUS) in the PRF1 gene: c.1106C>T (p.Thr369Met) and c.796A>C (p.Ile266Val).

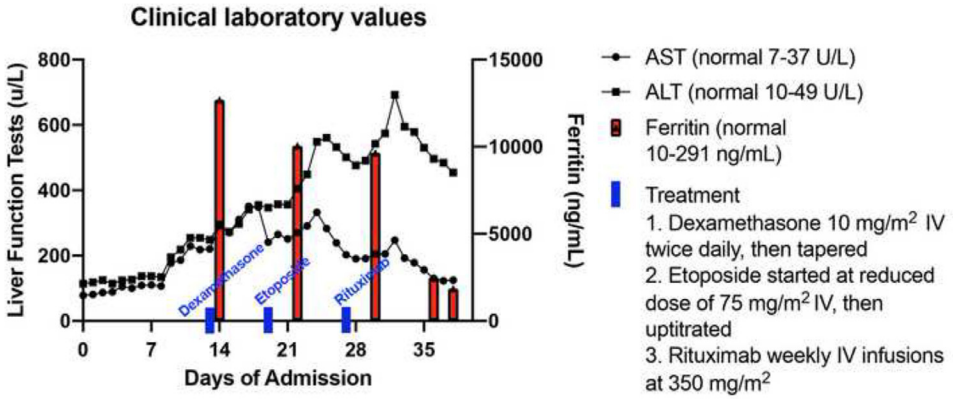
The HLH-94 treatment protocol was used to guide treatment. Treatment consisted of intravenous dexamethasone (10 mg/m^2) and etoposide (twice weekly for 2 weeks, then weekly for weeks 3−8) at a 50% reduced dosage owing to hepatic dysfunction starting at 75 mg/m^2). Fevers resolved on hospital day 13 after initiating steroids. Given the further elevation in her EBV titer to a log value of 3.0 (previously log 2.4), she was subsequently started on weekly rituximab infusions for 4 weeks at 375 mg/m^2 and received 2 infusions before discharge. The EBV titers were trended during her admission and were unquantifiable on the day of discharge. She was discharged on hospital day 39 after decreasing the ferritin and transaminases to complete the outpatient treatment course with hematology Figure 3.

Comment

HLH is an extremely rare and complex dysregulated hyperinflammatory syndrome with both genetic and environmental causes that can lead to a cytokine storm, multiorgan failure, and death.[1] The diagnosis of HLH is challenging in the postpartum cesarean delivery patient who presents with an FUO in the setting of preeclampsia, as the symptoms are nonspecific with several overlapping laboratory abnormalities.

The American College of Rheumatology developed the H-score in 2014 to estimate an individual's risk of HLH; it is characterized by 9 variables (3 clinical, 5 biologic, and 1 cytologic).[8] Her H-score was 240, with a 98% to 99% probability of HLH. This remains a clinically useful tool as waiting for the full diagnostic criteria before initiating HLH-directed therapy can prove to be fatal. Our patient met the following 5 out of the 8 criteria for HLH: fevers, hyperferritinemia, hypertriglyceridemia, hemophagocytosis on bone marrow biopsy, and a markedly elevated sL-IL2R (21,950.3 pg/mL). The

FIGURE 3
Clinical course showing changes in liver function tests and ferritin levels



Dexamethasone was initiated on HD#13, etoposide on HD#19, and rituximab on HD#27.
ALT, alanine aminotransferase; *AST*, aspartate transaminase; *HD*, hospital day; *IV*, intravenous.

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diagnosis was further supported by her transaminitis, hyperbilirubinemia, and elevated LDH. Importantly, there was no evidence of malignancy on computed tomography imaging and bone marrow biopsy.

The pathophysiology of HLH is complex, with both genetic and secondary causes (EBV, pregnancy and postpartum period, and severe preeclampsia). In the only case series of postpartum HLH, the infections implicated included the following: EBV, cytomegalovirus, herpes simplex virus, adenovirus, *Staphylococcus schieferi*, and *Leishmania*.[7] Like in our case, all patients had abnormal liver enzymes. In addition, the recent literature shows a possible immunologic link with a similar secretion of proinflammatory cytokines, changes in T-cell subsets (shift toward TH-1 response), and suppression of natural killer cell cytotoxicity in the postpartum period.[7] Genetic testing in our patient showed 2 genetic VUS in the PRF1 gene. The PRF1 gene is 1 of the several genes involved in cytotoxic granule formation and release pathways. It encodes for the perforin enzyme, a glycoprotein that is contained in the secretory granules of cytotoxic lymphocytes and facilitates the entry of granules into specific target cells, leading to apoptosis.[9,10] Although these variants are not pathologic, they likely served as permissive mutations, predisposing her and likely her sister to HLH. Her risk of relapse or recurrence remains unknown.

The HLH-94 treatment protocol is the current standard of care, with a combination of dexamethasone and etoposide with the subsequent addition of weekly rituximab infusions. Rituximab is a B-cell-targeting monoclonal antibody that can reduce EBV-infected B lymphocytes. In 2013, a retrospective study of 42 patients with EBV-associated HLH showed that rituximab in combination with conventional HLH-directed therapies improved symptoms, decreased viral load, diminished inflammation, and reduced transaminitis.[12] In our case, there was a 7-day delay in administering etoposide as her symptoms were stable. However, as her liver enzymes continued rising, etoposide was initiated. As rapid clinical deterioration is common in treatment-naïve EBV-infected patients, earlier treatment should be initiated without delay as it is associated with improved survival.[1,11–13]

Our patient responded well to treatment with 8 weeks of weekly etoposide and dexamethasone, with a 5-fold decrease in transaminases and a decrease in ferritin to 550 ng/mL to date. However, the risk of clinical deterioration with a possible need for allogenic hematopoietic stem cell transplant remains. The risk of recurrence in pregnancy is unknown but possible, given her family history and VUS in the PRF1 gene. Future case reports may elucidate the development of HLH in this specific gene mutation during the postpartum period.

In conclusion the differential diagnosis in the postpartum patient with high-grade quotidian fevers, hepatic dysfunction, and hyperferritinemia should be broad and should include HLH. A potential delay in the diagnosis of a rapidly progressing disease course may prove fatal for patients. HLH treatment consists of immunosuppression and etoposide. The treatment is highly individualized, and rituximab can be an effective add-on therapy in EBV-associated HLH. ■

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