CLINICAL VIGNETTE

Postpartum Hemophagocytic Lymphohistiocytosis

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Case Report

A 27-year-old primiparous female who was one month post-partum presented to a local emergency department with diffuse abdominal pain, unrelenting fevers to 102.3F and jaundice. Initial evaluation revealed a grade II transaminitis, coagulo-pathy and pancytopenia. CT imaging revealed mild hepatomegaly but no nidus of infection or malignancy. Drug toxicities were ruled out. She was evaluated by ID, rheumatolo-gy and gastroenterology and started on empiric antibiotics, evaluated for underlying connective tissue disorders and underwent imaging. Despite broad antibiotic coverage and multispecialty evaluations, the fevers persisted and liver synthetic function worsened. She also developed worsening pancytopenia requiring both platelet and red cell transfusions. At her nadir the ferritin was >16500, total bilirubin 6.0 (direct bilirubin 5.0), fibrinogen 60, INR 3.0, WBC 2.5 with an ANC of 0.5, platelets 80,000 and hemoglobin was 7.5g/dl (MCV 92fL). Her Triglyceride level was elevated at 456 mg/dL.

Bone marrow biopsy revealed a slightly hypocellular bone mar-row with trilineage hematopoiesis and progressive maturation. Normal storage iron was present. No ringed sideroblasts were seen. There was no evidence of fibrosis on reticulin stain. CT-guided core biopsy of liver revealed severe macro and microvesicular steatosis, moderate chronic portal and lobular inflammation and perisinusoidal fibrosis.

Given her rapid clinical deterioration, and no other overt etiolo-gy, she was started on empiric therapy for hemophagocytic lymphohistiocytosis (HLH) with high dose of dexamethasone. Typically, the use of the chemotherapeutic agent etoposide is also included, but the patient was reluctant to receive it. Over the subsequent 5 days, the fevers resolved, liver enzymes corrected and hepatic synthetic function improved.

Discussion

HLH is a rare and potentially fatal clinical syndrome involving uncontrolled activation of histiocytes with phagocytosis of normal hematopoietic cells and impaired cytolytic function of both natural killer and cytotoxic T cells[1] leading to fulminant cytokine storm. It can be classified as either primary (familial), or secondary (acquired) if it develops in response to an inciting event such as infection, autoimmune disease, pregnancy or malignancy. There are a few reported cases of pregnancy related HLH and the most of them occurred in the second and third trimester.[2] Song et al published the first case series of 8 patients with postpartum HLH all involving young females in their third decade of life presenting with fever, liver enzyme abnormalities, and with onset of HLH during the first few days after giving birth.[3] Fever in the postpartum period is common and often due to infectious etiology. In the case series, cyto-penia was less prominent, which could hinder timely diagnosis of HLH.[3] Our case of HLH presented 4 weeks postpartum with fever, liver enzyme elevation, hepatomegaly, cytopenia, hypo-fibrinogenemia, hyperferritinemia meeting five of the eight criteria per HLH-2004 diagnostic guideline.[4]

The possible mechanisms contributing to development of postpartum HLH is likely due to do prolonged physiological immunomodulation of T cells and suppression of NK cell cytotoxicity during pregnancy which persisted into the post-partum period. NKG2A is an inhibitor of NK cytotoxicity which has been shown to rise during postpartum. HLH associated immune dysregulation can be similar to pre-eclampsia with a shift in T cell subpopulations leading to overwhelming inflammatory cytokine release. Most of the patients in Song's case series had no underlying etiology for their HLH which further supports the theory of a disarrayed immunological system relating to the pregnancy event. Our patient did not present with her cytokine surge until a month after she delivered which differs from other cases which all took place shortly after delivery.

Prompt recognition and diagnosis of HLH may timely management according to the published HLH-2004 protocol.[4] Therapy aims to suppress the disordered immune response and treat any underlying disease. Primary treatment involves high dose of steroid and possible cytotoxic agents such as etopside. Postpartum HLH is fortunately, not limited by fetal safety concerns if chemotherapy is necessary. Our patient responded immediately to high dose of dexamethasone and there was no need for cytotoxic chemotherapy as seen in most cases of HLH in pregnancy.[5] This differs from the 2019 review by Song *et al* where etoposide was necessary to achieve remission of HLH in most cases.[6]

In summary, increased awareness to the possibility of HLH during pregnancy as well as the postpartum period is vital for early diagnosis of this rare entity in order to deliver timely therapy. When formulating the differential diagnosis of a pregnant/postpartum patient presenting with fever, hepatic dysfunction, cytopenia, and elevated ferritin, it is important to

consider HLH. We need more studies to understand the pathophysiology of this unique clinical syndrome. Additional observational data will further define unique clinical characteristics of this rare disease. In order to improve the prognosis of HLH, one needs early suspicious and diagnosis with prompt treatment.

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