CLINICAL VIGNETTE

Peripartum Hemophagocytic Lymphohistiocytosis (HLH)

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Introduction

Hemophagocytic Lymphohistiocytosis (HLH) is a life-threatening disorder of immune homeostasis that, when unidentified and/or untreated, results in near certain mortality. The disorder is more common in children less than 18 months of age, but can also occur in adults. HLH can be familial or sporadic, typically requiring an inflammatory trigger of which broad categories include infection, malignancy (usually lymphoproliferative or hematological), and autoimmune.[1] There have been a handful of published HLH cases that involve peripartum states.[2] Emerging trends include females in their late second or third decade of life presenting with unexplained fever and transaminitis.[2] We present a 31-year-old female who fits this clinical picture, was treated per the HLH 94 protocol[3,4] and is now recovering well at six-month follow up.

Case Report

A 31-year-old female with no significant past medical history and two uncomplicated vaginal deliveries (G3P2) presented to an outside hospital's emergency room at 30 weeks gestation with 3 weeks of fever, daily drenching night sweats, and transaminitis. At the time, physical exam was negative for lymphadenopathy and was overall not remarkable. Infectious evaluation was unrevealing. Although she denied abdominal pain, given her abnormal liver tests, she eventually underwent a diagnostic laparoscopy due to concern for gallbladder disease which did not find a source of her symptoms. Post-operatively, she went into early labor at 34 weeks gestation and vaginally delivered a healthy baby. She defervesced for two days after delivery and was discharged. Unfortunately, on day 4 after delivery, her daily fevers resumed, with highest temperature of 103°F and she was subsequently admitted to our hospital.

In addition to transaminitis, labs revealed low fibrinogen, elevated triglycerides, markedly elevated ferritin (>40,000 ng/ml), and pancytopenia (white blood cells 2.4 K/cumm, hemoglobin 9.3 g/dL, platelet count 133 K/cumm). Other tests included haptoglobin of 67 mg/dL, LDH 2175 U/L, total bilirubin 1.2 mg/dL, direct bilirubin 0.9 mg/dL, PT 15, PTT 44, and elevated D-dimer 14.4 mcg/ml FEU. Peripheral smear revealed no schistocytes. Her right upper quadrant abdominal ultrasound revealed mild, irregular gallbladder thickening. CT chest/abdomen/pelvis with contrast revealed a subcapsular hepatic collection measuring up to 10cm and splenomegaly, with no enlarged lymph nodes or masses noted. Unilateral bone marrow biopsy revealed hypercellular trilineage hematopoiesis with scattered hemophagocytes and left-shifted maturation; no blasts; no overt evidence of lymphoma. Flow cytometry on bone marrow sample also confirms only left-shifted maturation. Infectious disease and rheumatology were consulted. Blood, urine, and hepatic collection cultures were all negative for infection and rheumatologic serologies returned unrevealing.

The subhepatic collection was thought to be a hepatic abscess, and the patient was placed on broad spectrum antibiotics. A hepatic drain was placed, that drained largely sanguineous fluid, without clinical improvement.

Prior to delivery, key differential diagnoses for the patient's presentation included cholestasis of pregnancy and HELLP syndrome. Typically, in cholestasis of pregnancy, patients can also present with fever and transaminitis. However, transaminitis in cholestasis is associated with pronounced elevation in total bilirubin, and patients usually also have abdominal pain and pruritus. Our patient did not have significant bilirubinemia nor abdominal pain or pruritus. Additionally, her exploratory laparoscopy did not reveal changes consistent with cholestasis of pregnancy. In HELLP syndrome, patients may have transaminitis and thrombocytopenia as seen in our patient. Peripartum patients with HELLP typically present with abdominal pain, nausea/vomiting and general malaise. Hypertension and proteinuria are also characteristic of this disorder but not necessary for diagnosis. Additionally, HELLP syndrome can present with hepatic hematomas. Although our patient did have a hepatic hematoma, she did not have any abdominal pain, nausea or vomiting, hypertension, nor proteinuria. Furthermore, peripheral smear and blood-work did not reveal evidence of intravascular hemolysis.

After the patient delivered, the differential diagnosis included infectious and rheumatologic disorders. However, evaluation for these were negative and the patient did not improve with antibiotics or after hepatic drain placement. There was low concern that a clot or other obstetric etiology would have caused the patient's cyclic fevers. Thus, a diagnosis of HLH was made

based on the fact that the patient met five of the nine criteria (Table 1).

She was started on dexamethasone 20 mg intravenous push daily and showed improvement in her symptoms within 24 hours, with resolution of fevers, night sweats, and fatigue. Her laboratory studies also improved with resolution of transaminitis, hypertriglyceridemia, hypofibrinogenemia, and cytopenias. Ferritin also improved. She was discharged six days after starting steroids with a long taper, per HLH 94 protocol.[4] HLH genetic panel was sent and was negative for pre-disposing genetic alternations.

After discharge she continued to show improvement on steroids alone and thus, etoposide was initially omitted. However, during week 6 of her steroid taper, she missed two days of steroids and presented again with fevers, chills, and fatigue. Laboratory studies were notable for pancytopenia (including neutropenia with absolute neutrophil count of 700), elevated LFTs, and hypokalemia, suggesting recurrence of HLH. She was readmitted and restarted on high dose dexamethasone along with etoposide as per HLH 94 protocol. She completed 8 doses of weekly etoposide and a prolonged steroid taper. At follow up off treatment for 8 weeks, she was feeling well with resolved inflammatory markers and cytopenias.

Discussion

Hemophagocytic Lymphohistiocytosis (HLH) is an uncommon, aggressive disorder of immune hyperactivation that requires prompt recognition and appropriate therapy. In secondary HLH, therapy is directed against the underlying disease process. In primary HLH or HLH without an identified underlying cause, immunosuppressive therapy and sometimes chemotherapy can suppress the overactive and dysregulated immune response. A definitive diagnosis of HLH can be made in two ways: (1) HLH-verified genetic mutations along with clinical signs/symptoms of HLH; and/or (2) meeting at least five of the nine criteria as described in the HLH-2004 trial.[5] These criteria are described in Table 1.

Table 1.

Criteria for HLH	Patient Evaluation
1) Fever ≥38.5°C	MET
2) Splenomegaly	MET
3) Peripheral blood cytopenia, with at least two of the following: hemoglobin <9 g/dL; platelets <100,000/microL; absolute neutrophil count <1000/microL	NOT MET
4) Fasting triglycerides >265 mg/dL and/or fibrinogen <150 mg/dl	MET
5) Hemophagocytosis in bone marrow, spleen, lymph node, or liver	MET
6) Low or absent NK cell activity	MET
7) Ferritin >500 ng/mL (with a level >3000 ng/mL as more indicative)	MET (Ferritin >40,000 ng/mL)
8) Elevated soluble CD25 (soluble IL-2 receptor alpha [sIL-2R]) two standard deviations above age-adjusted laboratory-specific norms	MET
9) Elevated CXCL9	NOT TESTED

Our approach to this case includes having a broad differential and keeping HLH as part of our differential diagnosis, so steroid therapy was initiated. We initially omitted etoposide from the patient's treatment regimen based on how well the patient was doing on steroids alone. Unfortunately, she recurred after some missed days of treatment, which attests to the effectiveness of the HLH 94 protocol.

A thorough review of published literature reveals only a handful of cases describing HLH associated with peripartum state (Table 2). Of these, delivery of the newborn typically did not resolve patients' systemic symptoms. In many cases, delivery of the newborn resulted in worsening of systemic inflammatory response and served an additional trigger for the disease process. Some patients presented with concomitant abdominal pain, vomiting and hemolysis - making differential diagnoses even more difficult. Nearly all of the cases describe significant transaminitis and even fulminant liver failure as part of the disease course. This is especially interesting as transaminitis is not one of the criteria for diagnosis of HLH. In at least two cases, pathologic review of liver morphology revealed hemophagocytes, suggesting that peripartum HLH may have a predilection for the liver.[6]

Teaching Points

Our case details a peripartum female who eventually met seven out of the nine criteria for diagnosis of HLH with features of liver involvement given transaminitis that resolved with HLH-directed therapy, including etoposide treatment. The patient's clinical picture fits well with what is described to date in the body of literature suggesting that peripartum HLH may frequently involve the liver. This pattern should be further studied and characterized. As early diagnosis and therapy for HLH is paramount to divert disastrous results, this case study calls for a higher index suspicion for HLH in setting of pregnancy.

Table 2.

Case Study	Patient Age, Parity	Criteria Met	Other Relevant Clinical Features	Treatment	Outcome
Sarkissian S, et. al. [7]	30, G1P0	Elevated ferritin, Trig, IL-2R, fever	Transaminitis EBV/CMV +	Dexamethasone & Etoposide	Maternal death from secondary infections
Jha N, et. al. [8]	26, G2P1	Cytopenias elevated ferritin and trig Splenomegaly Low fibrinogen	Transaminitis Cough Nausea/vomiting	Dexamethasone & oral Augmentin	Clinically improved
Simard C, et. al. [9]	34, -	Cytopenias, fever, elevated ferritin	Fulminant hepatitis	Dexamethasone & Etoposide, then Anakinra^	-
Parrott J, et. al. [6]	28, G2P1	BM + HMP, elevated ferritin, cytopenias	Acute hypoxic respiratory failure, transaminitis, massive CVA	Steroids & Etoposide	Fetal and maternal death
Parrott J, et. al. [6]	37, G4P3	Elevated ferritin, cytopenias, liver bx +HMP	Acute liver failure, Fetal CMV+	Steroids & Etoposide	Clinically improved
Chmait RH, et. al. [2]	24, G2P1	Fever, cytopenias, HMPs on autopsy	DIC, transaminitis, ARDS	High dose IVIG, acyclovir	Maternal death from ARDS

^Transitioned to anakinra to allow for breastfeeding. Not documented to have failure of HLH 94 protocol.
- = information not available
HMP = hemophagocytes
Trig = triglycerides
Bx = biopsy

LIST OF ABBREVIATIONS
dl = deciliter
G3P2 = Gravida 3 Para 2
HLH = Hemophagocytic Lymphohistiocytosis
ng = nanogram
NK = natural killer
mg = milligram(s)
ml = milliliter(s)

REFERENCES

1. **Janka GE, Lehmberg K**. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. *Hematology Am Soc Hematol Educ Program*. 2013;2013:605-11. doi: 10.1182/asheducation-2013.1.605. PMID: 24319239.
2. **Chmait RH, Meimin DL, Koo CH, Huffaker J**. Hemophagocytic syndrome in pregnancy. *Obstet Gynecol*. 2000 Jun;95(6 Pt 2):1022-4. doi: 10.1016/s0029-7844(00)00834-6. PMID: 10808012.
3. **Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL**. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011 Oct 13;118(15):4041-52. doi: 10.1182/blood-2011-03-278127. Epub 2011 Aug 9. PMID: 21828139; PMCID: PMC3204727.
4. **Henter JI, Aricò M, Egeler RM, Elinder G, Favara BE, Filipovich AH, Gadner H, Imashuku S, Janka-Schaub G, Komp D, Ladisch S, Webb D**. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. HLH study Group of the Histiocyte Society. *Med Pediatr Oncol*. 1997 May;28(5):342-7. doi: 10.1002/(sici)1096-911x(199705)28:5<342::aid-mpo3>3.0.co;2-h. PMID: 9121398.
5. **Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G**. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007 Feb;48(2):124-31. doi: 10.1002/pbc.21039. PMID: 16937360.
6. **Parrott J, Shilling A, Male HJ, Holland M, Clark-Ganheart CA**. Hemophagocytic Lymphohistiocytosis in Pregnancy: A Case Series and Review of the Current Literature. *Case Rep Obstet Gynecol*. 2019 Feb 12;2019:9695367. doi: 10.1155/2019/9695367. PMID: 30891322; PMCID: PMC6390238.
7. **Sarkissian S, Khan Y, Farrell D, Constable D, Brem E**. Hemophagocytic lymphohistiocytosis in the setting of HELLP Syndrome. *Clin Case Rep*. 2018 Nov 5;6(12):2466-2470. doi: 10.1002/ccr3.1828. PMID: 30564350; PMCID: PMC6293182.
8. **Jha N, Balachandran DM, Jha AK**. Fever, cough and gastrointestinal symptoms in a pregnant woman. *Clin Med (Lond)*. 2021 Sep;21(5):e526-e528. doi: 10.7861/clinmed.2021-0443. PMID: 34507938; PMCID: PMC8439520.
9. **Simard C, Tardif M-L**. Hemophagocytic lymphohistiocytosis in pregnancy evolving towards fulminant hepatitis. *Obstetric Medicine*. March 2021. doi:10.1177/1753495X21999914