Idiopathic hemophagocytic lymphohistiocytosis during pregnancy treated with steroids

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare and severe clinical syndrome characterized by a dysregulated hyperinflammatory immune response. The diagnosis of HLH during pregnancy is especially challenging due to the rarity of this condition. The highly variable clinical presentation, laboratory findings, and associated diagnoses accompanying this syndrome further complicate the problem. A pronounced hyperferritinemia in the setting of systemic signs and symptoms along with a negative infectious and rheumatological workup should raise suspicions for HLH. While treatment ideally consists of immunosuppressive chemotherapy and hematopoietic stem cell transplant, the potential toxicity to both the pregnant woman and the fetus poses a challenging decision. We report the first case of idiopathic HLH presenting as fever of unknown origin in a pregnant woman successfully treated with steroids.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and severe clinical syndrome characterized by a dysregulated hyperinflammatory immune response. The syndrome includes familial (primary) HLH, acquired (secondary) HLH, and macrophage-activation syndrome (MAS), which is seen primarily in juvenile idiopathic arthritis and other rheumatological diseases. Common features of HLH include fever, pancytopenia, splenomegaly, and decreased function of T-lymphocytic and natural killer cells, along with an upsurge in macrophages that leads to hemophagocytosis. Untreated, HLH can result in end-organ damage and death. While HLH is mainly considered to be an entity within the pediatric population, it has been reported among adults of different age groups. In adults, HLH usually occurs secondary to underlying infections, malignancies, or rheumatologic diseases that elicit a severe activation of the phagocytic system.

Case Report

A healthy 36-year-old African-American woman presented at 16 weeks gestation with a dry cough and high-grade fever. On admission, she reported that her fevers date back to 1 month prior to presentation, manifesting intermittently not improving after antibiotics. In the emergency room, her temperature was 40.3°C and her pulse rate was 165 beats per minute. Physical examination did not reveal any rash, arthritis, lymphadenopathy or organomegaly. Laboratory studies demonstrated pancytopenia: normocytic anemia (hemoglobin 9.9 g/dL), leukopenia (white blood count 1300 cells/µL), and thrombocytopenia (125,000 cells/µL). Peripheral blood smear showed slight hypochromia and anisocytosis. Preliminary infectious workup including blood culture, urine culture, and chest X-ray failed to identify the source of her fever. Further testing showed an erythrocyte sedimentation rate (ESR) of 85 mm/h, LDH of 1096 U/L (without further evidence of hemolysis), and an elevated ferritin level of 4000 ng/mL. During the first three days, the patient’s temperature was persistently elevated prompting a more thorough infectious workup for FUO. This included testing for human immunodeficiency virus (HIV), viral hepatitis, Epstein-Barr virus (EBV), cytomegalovirus, parvovirus B19, herpes simplex viruses (HSV), quantiferon, legionella, ehrlichia, bartonella, Lyme, and leptospriosis. As the patient’s high-grade fevers failed to subside, she was maintained on broad-spectrum antibiotics empirically while further imaging studies and rheumatologic workup were pursued. Abdominal ultrasound revealed hepatosplenomegaly. Computed tomography (CT) of the chest and abdomen showed no evidence of a mass or lymphadenopathy. Antinuclear antibody (ANA), rheumatoid factor, complement levels, and lupus/antiphospholipid syndrome antibodies were all within normal range. Furthermore, serum and immune-electrophoresis failed to show any suspicious clon-
al patterns. Additional testing conducted by the oncolo

gy. However, the diagnosis of HLH remained
test the potential teratogenicity of chemotherapy

tuberculosis (TB), alcoholic cirrhosis, or pancreatitis

documented cases, the underlying associated diagnoses were viral

in the treatment of HLH during pregnancy. Hence, the deci-

for diagnostic and prognostic purposes.

manifesting during pregnancy continues to be a

mre. In 2007, Perard et al. published the only available literature on the subject in a

HLH cases described in pregnant women. In the previously published documented cases, the

using in treating a pregnant patient

stereos-resistant cases with positive outcomes reported in some cases. Both Gill and Perard et al. have reported suc-

cessful results with IVIG in the treatment of HLH during pregnancy. Hence, the deci-

cases in pregnant women. In the previously reported cases, patients either

HLH was made based on 5 out of 8 criteria according to

ferred, but is present in other cases.12,13 Moreover, one of the mothers died as a conse-

pregnancy that was successfully treated with

adverse obstetric outcome. Furthermore, other similar cases received

the patient's pancytopenia gradually improved.

Our patient did not experience an adverse obstetric outcome. Therefore, our case is the first described

in the HLH-2004 trial (fever, pancytopenia, hyper-

in the HLH-2004 guidelines: dexamethasone, etoposide (VP-

cases in pregnant women. In the previously reported cases, patients either

related to pregnancy. Of these, three cases achieved

Heusiner-Beck et al. described a case of par-

cases previously outlined by Perard et al. in addition to six new

cases. We present in Table 2 an updated list of

cases described in pregnant women. In the previously published documented cases, the underlying associated diagnoses were viral

in the treatment of HLH during pregnancy. Hence, the deci-

cases with positive outcomes reported in some cases. Both Gill and Perard et al. have reported suc-

Table 1. Revised diagnostic guidelines for hemophagocytic lymphohistiocytosis (HLH)

HLH 1994 and 2004 protocols and have been used in the treatment of HLH regardless of the precipi-

moglobin (<9 g/dL in infants <4 weeks: <10 g/dL), platelets <100,000/µL, absolute neutrophils count <1000 µL

hypertriglyceridemia and/or hypofibrinogenemia: fasting triglycerides at least 3.0 mmol/L

hemophagocytosis in bone marrow or spleen or lymph nodes with no evidence of malignancy


cases. We present in Table 2 an updated list of

the patient's fever sub-

IVIG and cyclosporine were mostly used in steroids-resistant cases with positive outcomes reported in some cases. Both Gill and Perard et al. have reported suc-

HLH-2004 trial. The diagnosis of HLH can be made if either A) or B) below is fulfilled.

A) A genetic mutation associated with HLH (PRF1, UNC13D, STXBP1, RAB27A, STX11)

B) Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)

- Fever >38.5°C

- Splenomegaly

- Bi or pan-cytopenia: hemoglobin <9 g/dL (in infants <4 weeks: <10 g/dL), platelets <100,000/µL, absolute neutrophils count <1000 µL

- Hypertriglyceridemia and/or hypofibrinogenemia: fasting triglycerides at least 3.0 mmol/L (i.e., >265 mg/dL); fibrinogen less than 150 mg/dL

- Hemophagocytosis in bone marrow or spleen or lymph nodes with no evidence of malignancy

- Low or absent NK cell activity

- Ferritin at least 500 mg/L

- Soluble CD25 (i.e., soluble IL-2 receptor) at least 2400 U/mL

The remaining three cases had complete remission following delivery of the fetus. These cases seem to imply that pregnancy itself is a major contributor to the development of HLH. Such assumption may be weak due to the rarity of HLH in pregnancy. However, the evidence of positive outcome reported in some cases after termination of pregnancy may lead us to suspect a link or association between pregnancy and the dysregulated immune sys-

vovirus B19 (Parvovirus B19, HIV, EBV, HSV), systemic lupus erythematosus (SLE), autoimmune hemolytic anemia, Still's disease, or lympho-

in the literature contained remis-

In the majority of previously reported cases, steroids were used as first line therapy. However, the evidence of positive outcome reported in some
cases after termination of pregnancy may lead us to suspect a link or association between pregnancy and the dysregulated immune sys-

ferritinemia, splenomegaly and decreased NK

Additionally, six new cases with a diagnosis of HLH that was reported in the English literature

Hemophagocytic lymphohistiocytosis mani-

fetal death. Fortunately, our patient did not expe-

Robertson et al. had surveyed a total of eleven cases of


due to its rarity), remains subject to specula-

in situ hybridization or karyotyping. The diagnosis of HLH requires a combination of clinical

the patient's fever sub-

Finally, our case is the first described

Therefore, our case is the first described


due to its rarity), remains subject to specula-

resulted in a favorable outcome. It is perhaps


thoracic imaging. Therefore, our case is the first described

in the inflammatory response. Therefore, corticosteroids


to the patient's condition. Due to the

by Perard et al.10 In 2007, Mayama et al. described a case of par-

steroids.13 Again, full remission was attained after fetal delivery. The only fatal case was

underlying etiology causing hemophagocyto-

In our patient, the diagnosis of idiopathic HLH was estab-


diagnosis of HLH. In other reported cases, patients either


diagnostic and prognostic purposes.

Hemophagocytic lymphohistiocytosis mani-

in the English literature. The diagnosis of HLH can be made if either A) or B) below is fulfilled.

A) A genetic mutation associated with HLH (PRF1, UNC13D, STXBP1, RAB27A, STX11)

B) Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)

- Fever >38.5°C

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- Bi or pan-cytopenia: hemoglobin <9 g/dL (in infants <4 weeks: <10 g/dL), platelets <100,000/µL, absolute neutrophils count <1000 µL

- Hypertriglyceridemia and/or hypofibrinogenemia: fasting triglycerides at least 3.0 mmol/L (i.e., >265 mg/dL); fibrinogen less than 150 mg/dL

- Hemophagocytosis in bone marrow or spleen or lymph nodes with no evidence of malignancy

- Low or absent NK cell activity

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The remaining three cases had complete remission following delivery of the fetus. These cases seem to imply that pregnancy itself is a major contributor to the development of HLH. Such assumption may be weak due to the rarity of HLH in pregnancy. However, the evidence of positive outcome reported in some cases after termination of pregnancy may lead us to suspect a link or association between pregnancy and the dysregulated immune system. In the future, a case-control study could determine the specific potential factors implicated in pregnancy-related HLH. In another case, Yamaguchi et al. showed a utility for cyclosporine A in treating a pregnant patient with HLH after failing initial therapy with steroids.13 Again, full remission was attained after fetal delivery. The only fatal case was
Table 2. Reported cases of hemophagocytic lymphohistiocytosis during pregnancy and their characteristics.

| Publication | Underlying disease/associated infection | Gestational age (wks) | Pertinent labs | Presenting symptom or sign | Treatment | Outcome |
|-------------|----------------------------------------|-----------------------|----------------|----------------------------|-----------|---------|
| Chmait et al.12 | History of necrotizing lymphadenitis; EBV (discovered postmortem) | 29 | Ferritin; Na; TG; Na; Hb; 9; WBC: 2600; Plt: 70,000; DIC: NA | Routine checkup; pancytopenia | Delivery at 30 weeks | Course complicated by DIC, multi organ failure and death |
| Yamaguchi et al.13 | HSV 2, genital herpes infection | Mid gestation | Ferritin: 865.8; TG: 180; Hb: 8; WBC: 2600; Plt: 123,000; DIC: - | High grade fever, pancytopenia, hepatosplenomegaly, high-grade fever at 23 wks gestation | Corticosteroids; Cyclosporin A | Failed corticosteroids (Remission with Cyclosporin A; Successful delivery) |
| Hanaoka et al.14 | B-cell lymphoma | 23 | Ferritin: 587.6; TG: 222; Hb: 9.5; WBC: 5810; Plt: 104,000; DIC: + | Pancytopenia, high grade fever | Emergent C-section (fetal distress); R-CHOP chemotherapy | Remission; successful C-section |
| Perard et al.18 | Systemic lupus erythematosus | 22 | Ferritin: 15,000; TG: 9.7; Hb: 9.2; WBC: 3500; Plt: 80,000; DIC: - | High grade fever | Corticosteroids; IVIG 3 doses | No improvement with steroids; premature delivery; successful remission after third IVIG dose (and/or delivery) |
| Chien et al.15 | Unclear etiology | 23 | Ferritin: 1.36; TG: 386; Hb: 7.4; WBC: 8900; Plt: 11,000; DIC: - | High grade fever, pancytopenia | Cesarean delivery | Preterm labor; successful C-section delivery; complete remission |
| Teng et al.16 | Autoimmune hemolytic anemia at 23 weeks of gestation | 23 | Ferritin: 8926; TG: 386; Hb: 7.4; WBC: 8800; Plt: 109,000; DIC: - | High grade fever, pancytopenia | Corticosteroids | Failed corticosteroids; remission post termination of pregnancy |
| Arewa et al.17 | HIV | 21 | Ferritin: NA; TG: NA; Hb: 6; WBC: 4200; Plt: 125,000; DIC: NA | Jaundice, fever, abdominal pain | HAART; delivery | Complete remission |
| Dunn et al.11 | Still’s disease | 19 | Ferritin: 3745; TG: 355; Hb: 9.8; ANC: 400; Plt: 343,000;DIC: - | Rash, fever, and headache | High-dose corticosteroids | Stable blood counts; successful delivery |
| Shukla et al.18 | Unclear etiology | 10 | Ferritin: 2200; TG: 588; Hb: 6.3; WBC: 1880; Plt: 18,000; DIC: - | Moderate grade fever for 2 wks | Corticosteroids; spontaneous abortion | Failed steroids; remission after abortion |
| Mayama et al.19 | Parvovirus B19 | 21 | Ferritin: 1289.2; TG: NA; Hb: 4.2; WBC: 600; Plt: 83,000; DIC: - | Fever and pancytopenia | Corticosteroids | Remission with steroids |
| Our patient | Unclear etiology | | Ferritin: 4000; TG: 110; Hb: 9.9; WBC: 1300; Plt: 125,000; DIC: - | Fever and pancytopenia | Corticosteroids | Remission with steroids |

NA: Non-available; Hb: hemoglobin (g/dL); WBC, white blood cell count (/mL); Plt, platelet count (mm³); TG, triglycerides (mg/dL); DIC, disseminated intravascular coagulopathy; ANC, absolute neutrophil count (/mL).

reported in the year 2000. Post-mortem bone marrow biopsy confirmed the diagnosis of EBV-associated HLH.12

**Conclusions**

The diagnosis of HLH during pregnancy is especially challenging due to the rarity of this condition. The highly variable clinical presentation, laboratory findings, and associated diagnoses accompanying this syndrome further complicate the problem. Difficulties in establishing a diagnosis would inevitably result in effective treatment delay. A pronounced hyperferritinemia in the setting of systemic signs and symptoms along with a negative infectious and rheumatological workup should raise suspicions for HLH. Initiating treatment before the pregnancy is advanced can be critical to the survival of both the mother and her fetus.

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