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.[1] 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.[2] Common features of HLH include fever, pancytopenia, splenomegaly, and decreased function of T-cytotoxic and natural killer cells, along with an upsurge in macrophages that leads to hemophagocytosis.[3] Untreated, HLH can result in end-organ damage and death.[4] While HLH is mainly considered to be an entity within the pediatric population, it has been reported among adults of different age groups.[5] In adults, HLH usually occurs secondary to underlying infections, malignancies, or rheumatologic diseases that elicit a severe activation of the phagocytic system.[6,7]

The diagnosis of HLH has been particularly challenging to both clinicians and researchers over the years. Ferritin is an iron storage protein and an acute phase reactant, which can be used as a non-specific marker of inflammation (hemochromatosis, malignancies, rheumatologic and autoimmune disease). HLH is characterized by hyperferritinemia (as high as 5000 ng/mL or more) and the presence of activated macrophages in hemopoietic organs. A combined picture of cytopenia, hyperferritinemia, and liver profile abnormalities should raise the suspicion for HLH in the correct clinical setting. However, none of the above laboratory findings are solely sufficient for the diagnosis of HLH. Furthermore, a bone marrow biopsy, which may fail to demonstrate HLH initially, should be repeated during the disease course.[8] Based on the HLH-94 study,[9] the specificity of a serum ferritin level >500 ng/mL was only 80 percent sensitive towards a diagnosis of HLH. In 2004, the Histiocyte Society updated the set of diagnostic guidelines that were initially introduced in 1991 (Table 1).[2,9] The more recent guidelines take into account clinical, laboratory and histopathological features. The diagnosis of HLH requires the presence of a genetic mutation associated with primary HLH (*PFR1*, *UNC13D*, and *STX11*) or the fulfillment of 5 from 8 criteria for the diagnosis of secondary HLH. These include: fever, splenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, low serum natural killer (NK) cell activity, and elevated serum soluble interleukin 2 receptor.

Hemophagocytic lymphohistiocytosis is poorly described during pregnancy and clinical management appears inconsistent across the eleven scattered published cases. While treatment ideally consists of immunosuppressive chemotherapy and hematopoietic stem cell transplant,[9] 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 (FUO) in a pregnant woman successfully treated with steroids.

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 105 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 leptospirosis. 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-

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Key words: Hemophagocytic syndrome; hemophagocytic lymphohistiocytosis; pregnancy; fever of unknown origin; steroids.

Contributions: BS, drafted the manuscript, MY, SA and JA critically reviewed, corrected and significantly contributed in writing the final version of the submitted case report.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 6 July 2015.
Revision received: 7 September 2015.
Accepted for publication: 7 September 2015.

Hematology Reports 2015; 7:6100
doi:10.4081/hr.2015.6100

al patterns. Additional testing conducted by the oncology team ascertained a natural killer (NK) cell lytic activity of 0.8% (normal range >2.6%). This was followed by a bone marrow biopsy, which did not reveal any hematological or oncological abnormalities (including normal cytogenetics/fluorescent *in situ* hybridization). However, the diagnosis of HLH remained highly suspected and the treatment options were discussed with the patient. Due to the potential teratogenicity of chemotherapy (etoposide), the patient decided to be treated with steroids only. High dose solumedrol (1 g intravenous daily for three days) was initiated four days after admission, followed by oral dexamethasone 20 g daily. The patient's fever subsequently resolved. The diagnosis of HLH was made based on 5 out of 8 criteria according to the HLH-2004 trial (fever, pancytopenia, hyperferritinemia, splenomegaly and decreased NK cells activity). After two weeks of treatment, the patient's pancytopenia gradually improved.

Therefore, our case is the first described idiopathic HLH case occurring during pregnancy that was successfully treated with steroids only. No underlying disease or associated infection was found and the patient continued her pregnancy safely without undergoing abortion or C-section.

Discussion

The evaluation of a patient presenting with HLH is often extensive in order to uncover the underlying etiology causing hemophagocytosis. In our patient, the diagnosis of idiopathic HLH was established after meeting five criteria according to the HLH-2004 trial with a negative infectious, rheumatologic, and malignancy workup. As evident in our case, a multidisciplinary infectious, oncologic, and rheumatologic workup was conducted for diagnostic and prognostic purposes.

Hemophagocytic lymphohistiocytosis manifesting during pregnancy continues to be a rare entity. In 2007, Perard *et al*. published the only available literature on the subject in a series of five available cases.[10] All cases were treated with intravenous immunoglobulins (IVIG), while three out of five received corticosteroids. The article highlighted the adverse outcomes that HLH can pose to the fetus and the mother, especially if uncontrolled in the third trimester. In the previously reported cases, two mothers suffered obstetric complications giving birth to premature children. Moreover, one of the mothers died as a consequence of multi-organ failure. By 2012, Dunn *et al*. had surveyed a total of eleven cases of HLH during pregnancy.[11] The data provided by Dunn *et al.* included the five cases previously outlined by Perard *et al.* in addition to six new cases. We present in Table 2 an updated list of all cases published in the English literature only.[10-19] Fevers with or without pancytopenia were the presenting symptoms in all HLH cases described in pregnant women. In the previously published documented cases, the underlying associated diagnoses were viral (Parvovirus B19, HIV, EBV, HSV), systemic lupus erythematosus (SLE), autoimmune hemolytic anemia, Still's disease, or lymphoma. In contrast with the pathogenesis of genetic HLH, which has been well described in pediatric literature, the process of acquired HLH in adults, and pregnancy in particular (due to its rarity), remains subject to speculation. We can only assume at this stage that our case is idiopathic in etiology based on the negative workup that was done to rule out the known triggers or diseases associated with HLH. In other reported cases, patients either suffered adverse outcomes or required urgent delivery. Fortunately, our patient did not experience an adverse obstetric outcome. Furthermore, other similar cases received alternate therapies including chemotherapy or cyclosporine. The standard treatment of HLH consists of supportive (for infection and bleeding) and immunochemotherapy as proposed by the pediatric Histiocyte Society (HLH-2004) guidelines: dexamethasone, etoposide (VP-16), and cyclosporine while the addition of intrathecal therapy with methotrexate plus hydrocortisone is reserved for high-risk patients.[2] Less aggressive immunosuppressive therapy with high dose IVIG has been proposed for severe infection or immunologic disorder. Steroids constituted an integral part of the HLH 1994 and 2004 protocols and have been used in the treatment of HLH regardless of the precipitating cause. Corticosteroids are anti-inflammatory medications that decrease the immune system activity and are classified as category C by the Food and Drug Administration. In the majority of previously reported cases, steroids were used as first line therapy.[14,16,17,19,20] 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 successful results with IVIG in the treatment of HLH during pregnancy.[10,20] Hence, the decision was made to treat our patient with steroids first. Of the ten cases of HLH summarized in Table 2, only two had remission after corticosteroid therapy. However, the first case was associated with Still's disease and the second case with parvovirus B19 infection. In 2014, Mayama *et al*. described a case of parvovirus B19 infection associated with HLH during pregnancy that responded to prednisolone.[19] Similarly, Dunn *et al.* presented the case of a 41-year-old pregnant woman with Still's disease who consequently developed HLH that was treated with corticosteroids resulting in a favorable outcome.[11] It is perhaps noteworthy to mention that the six reported cases in the literature attained remission after cessation of pregnancy (whether preterm labor, emergent C-section or terminated pregnancy). Of these, three cases achieved remission with a treatment that targeted their underlying disease (R-CHOP for B-cell Lymphoma, IVIG for SLE and HAART for HIV respectively) followed by fetal delivery.[10,14,17] The remaining three cases had complete remission following delivery of the fetus.[15,16,18] 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 1. Revised diagnostic guidelines for hemophagocytic lymphohistiocytosis (HLH) used in the HLH-2004 trial.[9] 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

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: 2620; Plt: 123,000; DIC: -	High grade fever, cytopenia	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, hepatosplenomegaly, high-grade fever at 23 wks gestation	Emergent C-section (fetal distress); R-CHOP chemotherapy	Remission; successful C-section
Perard *et al.*[10]	Systemic lupus erythematosus	22	Ferritin: 15,000; TG: 9.7; Hb: 9.2; WBC: 3500; Plt: 80,000, DIC: -	High grade fevers	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, cytopenia	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: 8900; Plt: 109,000; DIC: -	High grade fever, cytopenia	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: 358; 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: 1269.2; 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 (mm^3); TG, triglycerides (mg/dL); DIC, disseminated intravascular coagulopathy; ANC, absolute neutrophile 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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