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Case Report

Pregnancy-related hemophagocytic lymphohistiocytosis associated with cytomegalovirus infection: A diagnostic and therapeutic challenge

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ABSTRACT

Objective: Hemophagocytic lymphohistiocytosis (HLH) is a disorder characterized by uncontrolled mature histiocyte proliferation, hemophagocytosis, and hypercytokinemia. We describe a previously healthy pregnant patient who presented in the third trimester of pregnancy with HLH.

Case Report: A 35-year-old woman presented at 38 weeks' gestation with pyrexia, jaundice, severe anemia, elevated liver enzymes, and lactate dehydrogenase suggestive of HELLP (hemolysis, elevated liver enzyme, low platelet) syndrome. Unfortunately, her condition deteriorated and she was ventilated in the intensive care unit despite delivery of the baby and administration of dexamethasone. She developed microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment suggestive of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. However, she was refractory to plasma exchange, intravenous immunoglobulin, and broad-spectrum antibiotics. HLH was eventually diagnosed from biochemical and bone marrow findings. An extensive search for possible causes yielded negative results. She improved significantly with intravenous dexamethasone and cyclosporine A and was transferred out of the intensive care unit. Unfortunately, she developed cytomegalovirus disease 2 weeks later, which improved transiently with intravenous ganciclovir; later, however, she succumbed to multidrug-resistant nosocomial infections, rapidly progressive cytomegalovirus disease, and multiorgan failure.

Conclusion: This case highlights the challenges and difficulties involved in the diagnosis and management of pregnancy-related HLH. Immunosuppressive treatment for HLH can precipitate life-threatening opportunistic infections, which need to be promptly diagnosed and treated.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare yet potentially fatal clinicopathological entity because of uncontrolled immune system activation. It results in histiocytic proliferation with significant hemophagocytic activity in the bone marrow and massive release of inflammatory cytokines [1]. Its diagnosis is based on the HLH-2004 criteria, which requires at least five of the following manifestations: fever $\geq$ 38°C, splenomegaly, cytopenia affecting at least two lineages in the peripheral blood, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in the bone marrow, spleen, lymph nodes or liver, low or absent natural killer cell activity, ferritin $\geq$ 500 ng/mL, and elevated sCD25 [2]. Its incidence worldwide is not known. According to Ishii et al [3], the annual incidence of HLH in Japan is approximately one in 800,000.

HLH can be classified as either primary or secondary. Primary HLH is an autosomal recessive disorder, also termed familial HLH. It commonly occurs in infancy and childhood, but can also present later and is often fatal when untreated [4]. Defects in a number of genes have been linked to familial HLH: Perforin (PRF1), Munc 13-4 (UNC13D), Syntaxin 11 (STX11), and Munc 19-2 (STXBP2) [2]. Secondary HLH can be triggered by a variety of diseases such as infections, immunodeficiency syndromes, hematological malignancies, and autoimmune diseases. This classification is not always

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straightforward because primary HLH can present at any age. An underlying genetic mutation is found in only 40% of all primary HLH patients, and both types could be triggered by a variety of infections [4]. However, it is useful in long-term management, as mortality is generally higher in primary HLH unless it is treated by hematopoietic stem cell transplant.

To date, there are few reported cases of pregnancy-related HLH that are associated with significant morbidity and mortality [5–18]. The majority of cases occurred during the second trimester of pregnancy (Table 1). The diagnosis of HLH in pregnancy can be extremely challenging as some of the clinicopathological features may mimic the presentation of other common conditions exclusive to pregnancy such as HELLP (hemolysis, elevated liver enzyme, low platelet) syndrome and acute fatty liver of pregnancy. There are no established guidelines for the management of pregnancy-related HLH.

We report our experience in managing a previously healthy pregnant patient who presented in the third trimester of pregnancy with HLH. This case highlights the complexity of pregnancy-related HLH and identifies some key areas in the management of this disease that should be addressed in order to improve survival in this potentially fatal disease.

Case Report

A 35-year-old woman presented with a 2-day history of vomiting, jaundice, pruritus, and dark-colored urine at 38 weeks' gestation. Antenatally, she was diagnosed with gestational diabetes, which was diet-controlled. During her first pregnancy, she had an emergency cesarean section for severe preeclampsia at 32 weeks' gestation. She denied any abdominal pain, diarrhea, joint pain, alopecia, malar rash, or bleeding tendency. There was no history of recent travels, and she was not on any medication. On examination, she looked pale and jaundiced. She was apyrexial with a blood pressure of 125/72 mmHg and a heart rate of 100 beats/min. An abdominal examination revealed a gravid uterus without organomegaly. Examination of other systems yielded unremarkable results, and there was no evidence of lymphadenopathy.

Table 1
Summary of reported cases of pregnancy-related HLH.

No.	Age (y)	Period of gestation (wk)	Cause/associated factor	Treatment	Outcome of pregnancy		Study
					Maternal	Fetal	
1	28	23	Autoimmune hemolytic anemia (AIHA)	Steroids—no response, Termination of pregnancy	Alive	Delivered at 29 wk of gestation—died from pulmonary distress	Teng et al [5]
2	32	16	EBV	Methylprednisolone 1 g/d for 3 d + IV immunoglobulin 20 g/d for 3 d + acyclovir 750 mg/d + gabexate mesilate 2 g/d Maintenance: oral prednisolone 5 mg/d + camostat mesilate 600 mg/d	Alive	Delivered at 35 wk of gestation—alive	Mihara et al [6]
3	33	23	B cell lymphoma	Steroids—no response Six cycles of R-CHOP, then autologous peripheral blood stem cell transplantation	Alive	Delivered at 28 wk of gestation - alive	Hanaoka et al [7]
4	[a]	2nd trimester	HSV-2	Acyclovir (750 mg/d) & prednisolone (30 mg/d) → transient reduction in fever IV pulse methylprednisolone followed by full-dose prednisolone & later cyclosporine A	Alive	Delivered at 37 wk of gestation—alive	Yamaguchi et al [8]
5	24	29	Necrotizing lymphadenitis—EBV	IV immunoglobulin 60 g/d for 3 d & IV acyclovir 750 mg every 12 h	Death	Delivered at 30 wk gestation—alive	Chmait et al [9]
6	41	19	Twin pregnancy, history of Still's disease	High-dose corticosteroids	Alive	Delivered at 30 wk of gestation—alive	Dunn et al [10]
7	28	22	SLE	IV immunoglobulin 1 g/kg/d for 2 d then IV methylprednisolone 1 g/d for 3 d followed by oral prednisone 0.5 mg/kg/d Another 2 doses of IVIg given at 28 wk & 30 wk of gestation, respectively	Alive	Delivered at 30 wk of gestation—alive	Perard et al [11]
8	31	21	HIV & malaria	Antimalaria treatment (amodiaquine) & HAART	Alive	Delivered at term—alive	Arewa & Ajadi [12]
9	[a]	21	Preeclampsia	Antibiotics + immunoglobulin given but failed Antithrombin concentrates	Alive	Alive	Nakabayashi et al [13]
10	30	9 d after delivery	Human parvovirus B19	[a]	[a]	[a]	Tsuda et al [14]
11	29	21	Systemic lupus erythematosus	[a]	[a]	[a]	Hannebicque-Montaigne et al [15]
12	36	38 d after delivery	Primary Sjogren's syndrome	Oral prednisolone 1 mg/kg/d	Alive	Alive	Komaru et al [16]
13	33	After delivery	SLE	Oral prednisolone 55 mg/d	Alive	Alive	Yoshida et al [17]
14	[a]	Second trimester	—	High-dose IV Ig	Alive	[a]	Gill et al [18]

EBV = Epstein-Barr virus; HAART = highly active antiretroviral therapy; HLH = hemophagocytic lymphohistiocytosis; HSV-2 = herpes simplex virus 2; IVIg = intravenous immunoglobulin; R–CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone chemotherapy regimen; SLE = systemic lupus erythematosus.
[a] Information not available.