CASE REPORT

Pregnancy-Induced Hemophagocytic Lymphohistiocytosis: A Case Report and Literature Review

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Abstract Hemophagocytic lymphohistiocytosis (HLH) is a rare but devastating disease characterized by dysregulated immune response and hyperinflammation. To our knowledge, pregnancy-induced HLH has been rarely reported in the literature. A 30-year-old pregnant woman presented persistent fever for 21 days since 17 weeks of pregnancy. The possible etiologies such as infection, autoimmune disorder, and malignancy had been ruled out based on a series of exhaustive examinations. The disease progressed despite the use of broad-spectrum antibiotics and dexamethasone. The patient was diagnosed as pregnancy-induced HLH, and finally recovered completely after termination of pregnancy by caesarean and the continuous use of glucocorticoid which played a crucial part in controlling hyperinflammation. Pregnancy-induced HLH could be fatal if effective treatment was not initiated timely. Further studies are needed to improve early diagnosis and etiology identification of HLH.

HEMOPHAGOCYTIC (HLH) is a rare but fatal disease in clinical practice, of which the pathophysiological feature centers on the dysregulated immune activation.^[1] Patients generally present unspecific symptoms such as fever, lymphadenopathy, liver dysfunction, cytopenia,

hyperferritinemia, etc.^[2] Most of HLH are secondary to infection, autoimmune diseases, and malignancy. Pregnancy-induced HLH has been rarely reported. In this paper, we introduce a case of pregnant woman with persisted fever until the termination of pregnancy. The challenges in diagnosis and treatment are discussed.

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CASE DISCUSSION

A 30-year-old woman at 17 weeks of pregnancy (gravida 1 para 0) suffered from fever for 21 days with

highest body temperature of 41.2°C and intermittent productive cough and vomit. Seven days later, she went to a local hospital and underwent a series of tests. Laboratory tests showed leukocytopenia, hypertriglyceridemia, elevations of serum ferritin, lactate dehydrogenase (LDH), D-dimer, C-reactive protein (CRP), and procalcitonin (PCT). Bone marrow aspiration revealed pancytopenia and active phagocytosis of hematopoietic cells. She was diagnosed as pneumonia and suspicious for HLH. Subsequently, she received treatment with sequential moxifloxacin, meropenem, ganciclovir and immunoglobulin. However, the fever persisted. The patient's medical and family history were unremarkable.

The patient was transmitted to our hospital. Her vital signs were stable except high body temperature of 38.3°C, and the physical examination upon admission only found oral ulcer, with no rash, arthralgia, organomegaly, or cardiopulmonary abnormalities. The laboratory tests upon admission indicated that white blood cell and hemoglobin were low, while CRP, procalcitonin, LDH, triglyceride and ferritin were high (**Table 1**). Besides, the infection-related examinations, including blood culture, sputum culture, urine culture, T-SPOT.TB test, Xpert Mtb/RIF, G test and GM test, nucleic acids tests for influenza A virus, influenza B virus, H1N1, H7N9, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and respiratory syncytial virus (RSV), were all negative; viral serology tests for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV), TORCH syndrome (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex virus) were not significant, neither were the series of autoimmune antibodies examinations. In light of suspicion of HLH and in case of infection, she was put on the treatment of methylprednisolone (0.04g, po, qd), moxifloxacin (0.4g, ivgtt, qd) and Ganciclovir (0.3g, ivgtt, bid) with supportive medical care.

However, the symptoms progressed with body temperature up to 40°C. The laboratory results worsened rapidly. Vaginal secretion culture revealed *Enterococcus faecalis* group D which was sensitive to Vancomycin, teicoplanin, linazolidine. PET-CT scan reported increased metabolic activity of spleen and bone marrow, with no splenomegaly. The bone marrow biopsy revealed proliferative myelogram, but no feature of hemophagocytosis. Based on disease progress and the examination results, the diagnosis of pregnant-induced HLH was established. The therapy formula then shifted to dexamethasone (10mg, po, qd), Cefoperazone/

Sulbactam (3g, iv, q12h), vancomycin (1g, iv, q12h), supported with transfusion of erythrocyte, platelet and albumin. Caesarean section was conducted on 22 weeks and 6 days of the pregnancy.

The temperature dropped to normal post-operatively, but rose up again the next day after operation. Meanwhile, the cytopenia gradually recovered, and serum D-dimer, triglyceride, ferritin came down to normal. Inflammatory indexes such as PCT and CRP were still high. Sonography indicated local hematoma or inflammatory effusion subcutaneously around cesarean incision site. The bacterial culture was pathogen-negative. Thus the postoperative fever was attributed to the infection instead of recurrence of HLH. Consequently, we adjusted antibiotic therapy to Meropenem (0.5g, iv, q8h), vancomycin (1g, iv, q8h), with dexamethasone as before.

Since the 7th day after the adjustment of antibiotics, patient's body temperature dropped to normal. The laboratory test results related to HLH went to normal as well. De-escalation strategy of dexamethasone therapy was administrated subsequently. The patient recovered well at the 10th month follow-up.

DISCUSSION

We reviewed about 19 cases of HLH during pregnancy reported in literature (**Table 2**). One of them was primary HLH with UNC13D gene mutation, but the disease was triggered by pregnancy.^[3] Most of them were secondary to infection such as EBV, rheumatic disease such as lupus, malignancy such as lymphoma, and some had unclear etiology.^[4] The diagnosis of secondary HLH is fulfilled if manifests meet at least 5 out of 8 criteria:^[5] fever (>38.5°C); at least two cytopenia; hypertriglyceridemia (>3.0 mmol/L) and/or hypofibrinogenemia (<150 mg/dL); hyperferritinemia (>500 ng/mL); splenomegaly; hemophagocytosis in bone marrow; decreasing activity of NK cell; soluble CD25>2400 U/mL. From literature review, the symptoms and signs of pregnancy related HLH were unspecific,^[6] fever and cytopenia were the most common symptoms. So it's important to consider a diagnosis of HLH when a maternal patient complains about fever.^[7]

In this case, the extensive infection-related work-up was negative, making it unreasonable to attribute the etiology to infections. However, given the elevated CRP and PCT levels, antibiotics were still given. Rheumatic diseases were not considered since the patient didn't have any suggestive sign such as rash,

Table 1. Laboratory test results of the reported patient during disease development

Laboratory test indexes	Admission (2018-9-26)	Rapid progression (2018-10-16)	Recovery (2018-11-6)	Normal range
White blood cell ($\times 10^9/L$)	2.6	3.9	10.0	4-10
Hemoglobin (g/L)	91	85	90	110-150
Platelet ($\times 10^9/L$)	169	49	253	100-300
C-reaction protein (mg/dL)	7.1	17.1	1.4	<0.8
Procalcitonin (ng/mL)	0.72	0.78	<0.05	<0.05
Sodium (mmol/L)	129.6	131.1	137.6	135-148
Lactate dehydrogenase (U/L)	663	1109	189	109-245
Triglyceride (mmol/L)	3.8	4.5	1.8	<1.7
Ferritin (ng/mL)	4378.8	12445.2	453.8	4.63-204
Activity of NK cell (%)	16.4	15.2	/	>15.11
Soluble CD25 (pg/mL)	5267	13170	7137	<64000
D-dimer (ng/mL)	8314	52309	1927	<1000

arthralgia or elevated autoimmune antibodies. Besides, PET-CT showed no evidence of malignancy. These negative work-up results and dramatic improvement after the termination of pregnancy suggested the pregnancy was the inciting factor for her HLH.

The pathophysiology of HLH associated with pregnancy has not been clearly elucidated. Several theories have been proposed. The placenta plays a role of immunologically privileged barrier during pregnancy. Teng *et al.*^[11] hypothesized that defective placenta may release fetal-originated components, such as soluble RNA, DNA and trophoblast debris, into the maternal circulation. The maternal T-lymphocytes fail to recognize fetomaternal human lymphocyte antigens and embark the rejection to genetically foreign fetus, which creates strong systemic inflammatory response.^[26] Besides, the IFN- γ stimulated macrophages are believed to elevate production of TNF- α , subsequently activating the inflammatory effector pathway.^[20] Yamaguchi *et al.*^[27] suggested that the low ratio of Th1/Th2 (to adapt to the genetically foreign fetus) led to weakness of cell-mediated immunity, which resulted in macrophage overactivation and increased risk for infection. The uncontrolled inflammation cascade explained the manifestation of fever, cytopenia, hyperferritinemia and other symptoms.^[28]

The treatment for HLH should target on the potential etiology and hyperinflammation,^[24] meanwhile provide supportive care. In a cohort study, etoposide was considered to play a role in part in T-cell deletion and cytokines suppression, and set as standard therapy,^[22] but the safety of chemotherapeutics in pregnant

women has not been confirmed. Corticosteroids mediate anti-inflammatory effect by suppressing T lymphocytes and NK cells and releasing tumor necrosis factor (TNF), interleukin-6 (IL-6), etc.^[29] Considering that glucocorticoids may trigger infection outbreak, in this case, we applied low dose of it to control the hyperinflammation. However, the fever went down until termination of pregnancy, which confirmed the speculated link between pregnancy and HLH. Shukla *et al.*^[13] reported complete remission of a HLH patient after delivery of fetus, which seemed to imply that pregnancy was one of the contributor to HLH. In this case, termination of pregnancy proved to be of great significance in the disease control along with the continuous use of low dose glucocorticoid.

The diagnosis of HLH is challenging due to the unspecific clinical symptoms and laboratory tests. Whether to continue or terminate the pregnancy requires carefully balance the effects and the risks by multidisciplinary professionals. The current case enriches experiences in the treatment of HLH.

Conflict of interests disclosed

None.

Compliance with ethics

Written informed consent was obtained from the reported patient.

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Table 2. Cases of HLH during pregnancy reported in the literature

No.	Reference	Maternal age (years)	Gestation (weeks)	Associated disease	Treatment	Maternal outcome	Fetal outcome
1	Nakabayashi <i>et al.</i> , 1999 ^[8]	30	21	Preeclampsia	Antithrombin	survive	survive
2	Chmait <i>et al.</i> , 2000 ^[9]	24	29	Necrotizing lymphadenitis, EBV	Ampicillin, acyclovir Betamethasone, IgG	death	survive
3	Hanaoka <i>et al.</i> , 2007 ^[10]	33	21	B-cell lymphoma	Emergent caesarean section ; R-CHOP chemotherapy	survive	survive
4	Teng <i>et al.</i> , 2009 ^[11]	28	23	Autoimmune haemolytic anaemia	No response to corticosteroid; caesarean section	survive	death
5	Arewa <i>et al.</i> , 2011 ^[12]	31	21	HIV	HAART	survive	survive
6	Shukla <i>et al.</i> , 2013 ^[13]	23	10	NS	No response to prednisolone; spontaneous abortion	survive	death
7	Goulding <i>et al.</i> , 2014 ^[14]	27	23	HSV-2	Acyclovir	survive	death
8	Mayama <i>et al.</i> , 2014 ^[15]	28	20	Parvovirus B19	Prednisolone	survive	survive
9	Klein <i>et al.</i> , 2014 ^[16]	39	30	EBV	Corticosteroid, cyclosporine A, etoposide, Rituximab	death	survive
10	Tumian <i>et al.</i> , 2015 ^[17]	35	38	CMV	Dexamethasone	death	survive
11	Giard <i>et al.</i> , 2016 ^[18]	35	13	Streptococcal pharyngitis, KF lymphadenitis	No response to corticosteroids; dexamethasone and etoposide; abortion	death	death
12	Rousselin <i>et al.</i> , 2017 ^[19]	44	30	Raynaud syndrome, thrombocytopenia	Antimicrobial therapy, glucocorticosteroids	survive	survive
13	He <i>et al.</i> , 2017 ^[20]	27	30	NK/T cells lymphoma	Dexamethasone, rituximab and etoposide	death	survive
14	Ikeda <i>et al.</i> , 2017 ^[21]	36	11	EBV	Dexamethasone, cyclosporine, Etoposide	survive	survive
15	Yildiz <i>et al.</i> , 2018 ^[22]	36	NS	Acute hepatitis, HIV	Metronidazole, ceftriaxone, methylprednisolone, antibiotherapy	survive	survive
16	Wang <i>et al.</i> , 2018 ^[23]	40	NS	UNC13D gene mutation	Etoposide, dexamethasone	survive	death
17	Nasser <i>et al.</i> , 2018 ^[7]	36	31	HSV-2	Acyclovir	survive	death
18	Neistadt <i>et al.</i> , 2018 ^[24]	NS	27	NK/T-cell lymphoma	Corticosteroids, etoposide, pembrolizumab	death	death
19	Parrott <i>et al.</i> , 2019 ^[25]	28	18	Lupus	No response to etoposide and corticosteroid	death	death

EBV, Epstein-Barr Virus; R-CHOP, chemotherapy of Rituximab-Cyclophosphamide, Doxorubicin Hydrochloride (Hydroxydaunomycin), Vincristine Sulfate (Oncovin), and Prednisone; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; HSV-2, herpes simplex virus 2; CMV, cytomegalovirus; NS, not stated.

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