Pregnancy-induced Hemophagocytic Lymphohistiocytosis Combined with Autoimmune Hemolytic Anemia

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Hemophagocytic lymphohistiocytosis (HLH), presenting with fever, cytopenia, liver dysfunction, hepatosplenomegaly, hypertriglyceridemia, and hyperferritinemia, is associated with various etiologies, including infections, collagen vascular diseases, and malignancies. The present report describes a 28-year-old woman who developed HLH combined with autoimmune hemolytic anemia (AIHA) at 23 weeks of gestation. Without response to corticosteroid, the patient completely recovered from both HLH and AIHA after termination of the pregnancy. Pregnancy-induced immune dysregulation and cytokine overproduction in genetically susceptible women may play critical roles in HLH. The differential diagnosis of pregnant women with fever and cytopenia should include HLH. Pregnancy termination should be considered when pregnancy-induced HLH is refractory to medical treatment. [*J Chin Med Assoc* 2009;72(3):156–159]

Key Words: hemolysis, hemophagocytosis, pregnancy

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, fatal disorder, presenting with fever, cytopenia, liver dysfunction, hepatosplenomegaly, hypertriglyceridemia, and hyperferritinemia.[1] Accumulation in the reticuloendothelial system of activated macrophages showing phagocytosis of hematopoietic cells is the characteristic histologic finding. HLH may be primary, as observed in familial HLH, X-linked lymphoproliferative syndrome, and Chediak-Higashi syndrome,[2] or it may be secondary to malignancies, infections, autoimmune diseases, or drugs.[3] Malignancy, particularly lymphoma, and Epstein-Barr virus (EBV) infection are the leading causes of adult HLH.[3] Pregnancy-induced HLH has only been reported in a few cases.[4] Here, we report a case of pregnancy-induced HLH combined with autoimmune hemolytic anemia (AIHA). Both the HLH and AIHA did not respond to steroid treatment, but spontaneously recovered after pregnancy termination.

Case Report

A 28-year-old woman was admitted to the hospital at 23 weeks of gestation in her first pregnancy after fever up to 39°C of 2 weeks' duration. She had been healthy prior to this fever. Her complete blood count was within normal range at the 10th week of gestation. Her blood pressure on admission was 118/64 mmHg, with regular heart beat. Physical examination revealed no skin rash, no arthritis, but palpable liver and spleen, which were 3 cm and 4 cm below the right and left subcostal regions, respectively. Infection surveys including blood culture, urine culture, chest X-ray, and abdominal magnetic resonance imaging were made. Hepatosplenomegaly and mild right-side hydronephrosis were the noted abnormalities. Serial laboratory examinations were done. The patient's white blood cell count was 8.9×10^9/L, with 92% neutrophils and 7% lymphocytes. Her red blood cell count, hemoglobin, and mean corpuscular volume were 2.63×10^{12}/L, 7.4 g/dL, and 84 fL, respectively. She also had

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thrombocytopenia. Her platelet count was 109×10^9/L. Serum aspartate transaminase and alanine transaminase for liver function were 92 IU/L and 18 IU/L, respectively. Blood urea nitrogen and serum creatinine for renal function were 9 mg/dL and 0.7 mg/dL. Her lactate dehydrogenase (LDH) was extremely high, at 1,760 IU/L (normal, 120–240 IU/L). In hemostasis tests, prothrombin time and activated partial thromboplastin time were 13.4 seconds (control, 11.5 seconds) and 31.4 seconds (control, 30.0 seconds), respectively. Tests for autoimmune disease, including antinuclear and anticardiolipin antibodies, were negative. Serum triglyceride level (386 mg/dL; normal, 20–200 mg/dL), ferritin (8,926 ng/mL; normal, 6–81 ng/mL), and soluble interleukin-2 receptor (2,892 pg/mL; normal, < 880 pg/mL) were elevated. Bone marrow examination revealed marked hemophagocytosis (Figure 1). Peripheral blood smear showed no prominent schizocytes. Microangiopathic hemolytic anemia was excluded because there were no impaired renal function and no peripheral blood fragmented red blood cells, and the patient's disseminated intravascular coagulopathy profiles were negative. In addition, without arthritis and skin rash, adult-onset Still's disease was less likely. Diagnosis of HLH was by fulfillment of the criteria of fever, cytopenia, elevated LDH, hyperferritinemia, hepatosplenomegaly, and hemophagocytosis in bone marrow.[1] Viral serology tests for EBV, herpes simplex virus, and hepatitis B were negative. Real-time quantitative polymerase chain reaction also did not detect EBV DNA. Fever subsided after treatment with intravenous methasone 5 mg every 6 hours per day for 2 days, but anemia and thrombocytopenia persisted. Repeated bone marrow examination continued to reveal profound hemophagocytosis. Because the fever had subsided, the patient only accepted follow-up without any medication. During this period of time, she still had anemia, with hemoglobin of around 8 g/dL.

At 28 weeks of gestation, the patient suffered from a sudden onset of dyspnea on exertion, plus icteric sclera and tea-colored urine. Her hemoglobin dropped from 7.8 g/dL to 4.9 g/dL, with relatively stable platelet count (245×10^9/L). Positive direct and indirect antiglobulin tests, decreased haptoglobulin (< 5.8 mg/dL; normal, 20–200 mg/dL), and elevated reticulocyte count (13.73%; normal, 0.5–1.5%) indicated AIHA. Serum alloantibody screening test was negative. Her tea-colored urine and anemia persisted despite treatment with methasone. For the safety of the fetus, only packed red blood cell transfusion and adequate hydration were given.

At 29 weeks of gestation, because of decreasing fetal movement, the patient delivered a 740-g girl by cesarean section. The baby died at 3 days of age from pulmonary distress. Three days after delivery, the patient's serum ferritin, LDH, and complete blood count improved. Four weeks after delivery, repeated bone marrow examination revealed no hemophagocytosis. Blood tests revealed no anemia, no thrombocytopenia, normal LDH, and a negative antiglobulin test. Two years after this episode, the patient delivered a healthy girl without any complications.

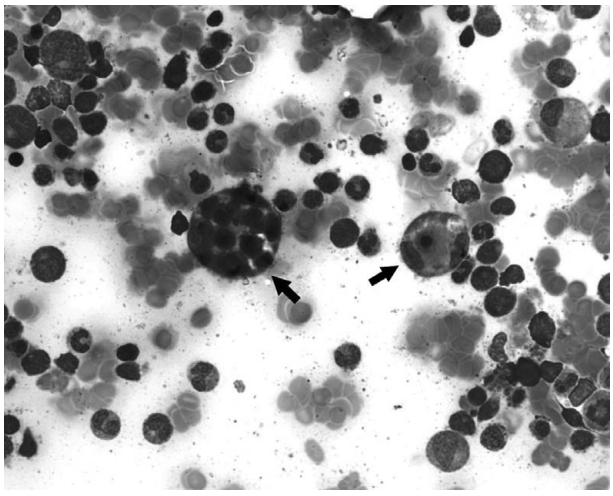

Figure 1. Bone marrow aspiration smear reveals activated macrophages with phagocytosis of hematopoietic cells, including mature red blood cells, nucleated red blood cells, lymphocytes, and neutrophils (arrows). (Wright and Giemsa stain, 400×.)

Discussion

HLH is associated with a variety of viral, bacterial, fungal, and parasitic infections, as well as with collagen vascular diseases and malignancies, especially lymphoma.[3,5] For patients with HLH, it is important to survey every possible etiology because the underlying diseases strongly affect the treatment and outcome of HLH. Due to the rarity of HLH and it having similar clinical presentations to microangiopathic hemolytic anemia and adult-onset Still's disease, such as fever of unknown origin, cytopenia and extremely elevated serum ferritin, HLH is easily missed during pregnancy. There are only a few cases of pregnancy-related HLH in the reviewed literature.[4] In these published cases, however, it was unclear as to whether it was the pregnancy itself, EBV infection, or even both, that were responsible for the HLH. Pregnancy-induced HLH without evidence of EBV infection and other identified etiologies, combined with AIHA, has rarely been reported previously.

The pathophysiology of HLH is not completely understood, not to mention its relation to pregnancy.

A cytokine storm is believed to be responsible for HLH. Osugi et al[6] hypothesized that activated Th1 lymphocytes secrete interferon-γ, stimulating macrophages. Stimulated and uncontrolled macrophages result in phagocytosis of hematopoietic cells and rapid production of tissue necrosis factor-α, initiating the inflammatory effector pathway, resulting in fever, hyperferritinemia, and other associated symptoms.[7] According to these proposed mechanisms, different T-cell regulations adapted to pregnancy must play important roles in pregnancy-induced HLH. During normal pregnancy, T helper lymphocytes typically shift from Th1 to Th2 dominance because of immune adaptation to the genetically foreign fetus and antigenicity.[8] Elevated Th1/Th2 ratio in pregnancy induces recurrent pregnancy losses, failure of implantation, and preeclampsia.[9]

In this patient, we hypothesized that fetomaternal trafficking was the key element in pregnancy-induced HLH and its cytokine storm. The evidence came from preeclampsia. Preeclampsia is a form of maternal immune rejection of the genetically foreign fetus due to unsuccessful maternal T-lymphocyte recognition of fetomaternal human lymphocyte antigens.[10] Immature placenta releases trophoblast debris, including syncytiotrophoblast components, soluble RNA and DNA of fetal origin, and even cytotrophoblast cells, into the maternal circulation. This fetomaternal trafficking induces a profound systemic inflammatory response, mimicking pregnancy-induced HLH.[11]

AIHA is also uncommon during pregnancy. Increased red blood cell autoantibody production during pregnancy has been reported, but rarely causes clinically significant symptoms.[12] In addition, the clinical spectra among general patients with red blood cell autoantibodies vary from no signs to severe hemolysis. It is believed that profound inflammatory cytokines produced by the mononuclear phagocytic system participate in the destruction of opsonized erythrocytes.[13] Further study demonstrated that monocyte monolayer assay activity and *in vitro* cytokine production may reflect the *in vivo* activity of autoantibodies and sequential AIHA.[14] According to these studies, we believe that an activated phagocyte system and cytokine overproduction in HLH were responsible for the severe AIHA in this patient.

Treatment guidelines for pregnancy-induced HLH and AIHA have not been established. Steroids are generally the first treatment option for both HLH and AIHA.[15,16] Our patient, however, was not responsive to steroid treatment. Prognosis of secondary HLH is usually poor and largely depends on the underlying diseases. Etoposide-based chemotherapy is almost always required for aggressive HLH.[15] The use of chemotherapy in pregnant women, however, is a big challenge because of its toxicities and potential teratogenic effects. Even though successful delivery has been reported for women who had received chemotherapeutic agents during pregnancy,[17] in this case, etoposide was not used for aggressive HLH because of the risks to both the mother and fetus. In addition to conventional therapies, novel treatments such as rituximab have been increasingly applied to autoimmune hematologic diseases.[18] For patients with lymphoma-associated HLH, rituximab might be helpful as well.[19] It remains unclear, however, if rituximab is effective for pregnancy-induced HLH.

The baby eventually died of complications arising from its retarded growth and immaturity. The mother completely recovered within 3 days after the termination of pregnancy. In this case, for both the mother and fetus, early termination of pregnancy appeared to be of greater benefit than treatment with steroid and chemotherapeutic agents. The patient had a normal pregnancy and delivery 2 years after this event, which indicated that pregnancy-induced HLH might be accidental.

In conclusion, we have reported a rare case of pregnancy-induced HLH combined with AIHA. Fetomaternal trafficking probably induced the cytokine storm in this genetically susceptible pregnant woman that may have caused the disease. Termination of pregnancy might be a distinct therapeutic option for such a situation. The differential diagnosis of pregnant women with fever and cytopenia should include HLH.

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