Hemophagocytic Syndrome Secondary to Tuberculosis at 24-week Gestation

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Abstract

Hemophagocytic syndrome is a life-threatening disease characterized by the uncontrolled activation of macrophages, resulting in hemophagocytosis of blood cells in the bone marrow. A 20-year-old gravida at 23-week and 5-day gestation was admitted to hospital to evaluate fever up to 104°F of unknown origin, moderate cytopenia, and elevated levels of liver enzymes. Bone marrow biopsy confirmed hemophagocytic syndrome, and polymerase chain reaction came back positive for Mycobacterium tuberculosis. Supportive care and tuberculosis treatment resulted in clinical improvement. At 27 weeks and 5 days, premature rupture of the membranes occurred, and because of the high probability of reactivating the hemophagocytic syndrome, a cesarean section was performed at 29-week and 2-day gestation. Hemophagocytic syndrome is an uncommon disease which rarely appears during pregnancy. Early diagnosis and treatment can save both maternal and fetal lives.

Keywords: Congenital, hemophagocytic syndrome, neonatal, pregnant, tuberculosis disease

INTRODUCTION

Hemophagocytic syndrome is a disorder characterized by the proliferation of macrophages with increased phagocytic capacity on hematopoietic cells. The etiology may be infectious, tumoral or autoimmune. Non-specific clinical presentation characterized by fever, severe cytopenia, coagulation disorders, hepatosplenomegaly and lymphadenopathy may lead to multiple organ failure, and its complexity increases during pregnancy.

CASE REPORT

A 20-year-old healthy Spanish woman living in a rural area, gravida 1, 23 weeks and 5 days, with a normal course of pregnancy, came to the emergency department with abdominal pain in the right hypochondrium and hypogastric region associated with a high fever of up to 104°F and 6 days of cold symptoms with a dry cough, sometimes with hemoptysis. Complementary laboratory studies showed her hemoglobin to be 9.7 g/dl, platelet count of 94,000, leukocytes of 4600 (6% immature forms), aspartate aminotransferase of 131, alanine aminotransferase of 69, lactate dehydrogenase of 929, total bilirubin of 1.5, C-reactive protein (CRP) >90, and an abdominal ultrasound revealed mild splenomegaly [Figure 1].

The patient was hospitalized to evaluate the fever, without a clear focus and analytical disorder. Empirc antibiotic treatment began with 1 g of ampicillin for every 6 h, 240 mg of gentamicin for every 24 h, and 600 mg of clindamycin for every 8 h intravenously. Fetal lung maturation was initiated with 12 mg of betamethasone administered intramuscularly and repeated after 24 h without the need for tocolytics because of electronic fetal monitoring with uterine irritability and a stable cervical length of 18 mm.

The patient remained hemodynamically and clinically stable for the first 48 h of hospitalization. During the 2nd day, she presented analytical worsening with hypertransaminasemia and platelet count lowered to 17,000 [Figure 1].

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Subsequently, the patient presented with epistaxis and deteriorated respiratory function with tachypnea and desaturation to 85%, and she also cited decreased perception of fetal movements. The endotracheal tube and electrocardiogram were normal, and a chest radiograph showed bilateral cottony diffuse infiltrates. Due to the clinical state and laboratory results, one pool of platelets was dispensed, and blood and bone marrow samples were taken. The patient was moved to the Intensive Care Unit.

The bone marrow showed intense hematopoietic hemophagocytosis of the three series. The initial diagnosis was hemophagocytic syndrome of unknown cause and this was treated with immunoglobulin (1 dose of 1 g/kg), high-dose corticosteroids, cyclosporine (4 mg/kg/day), and etoposide (150 mg/m² intravenously twice a week), and administration of a broad-spectrum antibiotic with piperacillin-tazobactam began. Because of the rapid evolution to severe respiratory failure, invasive mechanical ventilation was required.

Due to the critical state of the patient and the state of her pregnancy, a multidisciplinary committee was established comprising gynecology, pediatrics, intensive medicine, internal medicine, hematology, and pharmacy. Considering the need for treatment with unknown effects on the fetus, elective cesarean section was proposed. Because of the extreme prematurity and high surgical risk, it was decided to maintain the treatment and defer the delivery as much as possible. The family was informed and it was agreed only to perform a cesarean section in the case of a peri-mortem situation.

After 72 h, the patient had stabilized, the mechanical intubation was removed, and the analytical parameters improved [Figure 1]. The patient still had a low fever, so the antibiotic therapy was escalated to meropenem.

An investigation of the etiology of hemophagocytic syndrome showed the following results: Urine and blood cultures were negative, and serology tests for Brucella, Legionella pneumophila, Leishmania, Treponema pallidum, Toxoplasma, HIV, herpes simplex virus, hepatitis C virus, hepatitis B virus, zoster virus, influenza virus, cytomegalovirus (CMV), rubella, parvovirus B19, Coxiella burnetii, and Rickettsia conorii were all negative. IgM and IgG Chlamydia pneumoniae were positive. Bone marrow studies were negative for tumoral cells and autoimmune markers.

The presence of a granuloma in the bone marrow biopsy with subsequent bone marrow polymerase chain reaction positive for Mycobacterium tuberculosis complex was determined. With the diagnosis of hemophagocytic syndrome secondary to M. tuberculosis, tuberculosis standard treatment with isoniazid, pyrazinamide, ethambutol, and rifampicin was initiated. None of these drugs have been reported as teratogenic. Azithromycin treatment was also began for C. pneumoniae.

The patient showed a marked improvement both clinically and analytically with hemodynamic and respiratory stability, being afebrile, and not needing mechanical intubation after 6 days. The patient was discharged from the Intensive Care Unit after 9 days. Obstetrically, the fetal Doppler was normal, and the patient actively perceived fetal movements.

During her recovery outside the Intensive Care Unit, cyclosporine treatment was maintained and the glucocorticoid dose was progressively decreased. Electronic fetal heart rate monitoring was carried out daily, with good variability, and no uterine contractions were detected. The patient continued to be hospitalized for observation and to finish the course of intravenously administered drugs.

At 27 weeks and 5 days, preterm rupture of the membranes occurred. There were signs of chorioamnionitis, which was excluded with a hemogram, CRP, urine culture, and cervical and rectal-vaginal exudate. Because of the correct analytical parameters and the absence of uterine contractions, it was decided to wait before further action was taken. Broad-spectrum treatment with amoxicillin 500 mg for every 8 h and erythromycin 500 mg for every 8 h was administered intravenously over a 48-h period. At 28 weeks, an obstetric ultrasound was performed that showed an amniotic fluid index (AFI) of 6 and a normal fetal Doppler, with no signs of fetal anemia or abnormal middle cerebral artery-peak systolic velocity values.

At 29 weeks, an estimated fetal weight in the 6th percentile was detected with evidence of oligohydramnios of unknown cause; the most common reason for this percentile and AFI is maternal organic stress in previous weeks or the drugs administered although previously all ultrasounds were normal. The patient then presented febrile episodes for 2 days despite tuberculosis treatment. Due to the possibility of reactivating the hemophagocytic syndrome, or chorioamnionitis, it was decided to perform the delivery at 29 weeks.

As the presentation was breech, at 29 weeks and 2 days, a cesarean section was performed. A 1140 g male was delivered without complications. He was moved to the neonatal unit because of his prematurity. Apart from a spermatic cord torsion that required surgery, no pathology related to the drugs used on the mother has been detected up to the time of this report (2 months). At present, the child receives tuberculosis treatment because of positive cultures in the gastric fluid and placenta. The patient continued being treated for tuberculosis and is asymptomatic, showing normal analytical parameters.

**Discussion**

We present a case of hemophagocytic syndrome in association with TBC in a pregnant woman who came to our emergency...
department reporting a history of 6 days of fever, diffuse abdominal pain, and a dry cough accompanied by occasional hemoptysis. Finding analytical disorders such as severe cytopenia, coagulation disorders, and elevated levels of liver enzymes in the absence of hypertension and schistocytes was decisive in the search for an alternative diagnosis to HELLP syndrome,[1,2] in conjunction with the fact that it is unusual to develop HELLP syndrome before the third trimester. In this case, a bone marrow analysis was essential for the initial clinical diagnosis and the subsequent etiological diagnosis.

Almost any pathology may precipitate hemophagocytic syndrome. Classically, Epstein–Barr virus and CMV have been cited as two of the main triggers. A wide variety of infections, neoplasia, and autoimmune diseases can also lead to this syndrome.[3,4] We have found another 41 cases of M. tuberculosis-associated hemophagocytic syndrome in literature and only two cases of hemophagocytic syndrome in pregnant women, both secondary to Epstein–Barr virus.

In our case, the pregnancy was an added complication. It is known that pregnancy involves greater hemodynamic needs. The possible teratogenic effects of any drug used and the possibility of fetal death in the case of the mother’s death were the added difficulties.

The most common course of this disease is rapid multi-organ failure that leads to death in 20% of the cases.[4] A survival rate of 56% has been described after 5 years of follow-up.[4] In our case, a rapid worsening of the clinical situation made us fear a fatal outcome. Considering the dramatically high surgical risk and the extreme prematurity of the fetus, the inter-departmental group decided to delay the delivery and maintain aggressive medical treatment. Early diagnosis and multi-disciplinary intervention contributed to crucially extending the time until a cesarean delivery became the most feasible option.

Common treatment for hemophagocytic syndrome described in literature combines chemotherapy and immunotherapy, with the hemophagocytic lymphohistiocytosis-94[5,6] protocol being the most common pathway. This treatment begins with 8 weeks of etoposide (150 mg/m² twice a week for 2 weeks and then weekly) and dexamethasone (10 mg/m² for 2 weeks and then decreasing doses). The addition of cyclosporine-A (6 mg/kg) is controversial.[4] Resilient cases may be candidates for salvage therapy using alemtuzumab because of the key intervention of T-cells in the pathogenesis of the disease.[7] The efficacy and adverse effects of these therapies on mother and fetus are mostly unknown.

We hope that our report on this clinical case may be helpful in similar settings in the future although further studies will enable us to better understand the evolution of the disease, as well as test the effectiveness of the various treatments described in literature.

**CONCLUSION**

- Early diagnosis of hemophagocytic syndrome and treatment of its cause may lead to an improved outcome for both the fetus and the mother
- Despite the potentially harmful drugs used in this case, no adverse effects have been reported yet in the child.

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**Conflicts of interest**
There are no conflicts of interest.

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