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Contents Thrice Monthly Volume 11 Number 26 September 16, 2023

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 26 September 16, 2023

Contents

SCIENTOMETRICS

CASE REPORT

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 26 September 16, 2023

Contents

Contents

Thrice Monthly Volume 11 Number 26 September 16, 2023

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CASE REPORT

Postpartum hemophagocytic lymphohistiocytosis: A case report

Ju Ho An, Jung Hwan Ahn

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Abstract

BACKGROUND

Postpartum hemophagocytic lymphohistiocytosis (HLH) is a rare disease with unclear pathophysiology. It is a secondary HLH diagnosed using the pediatric diagnostic criteria; however, the clinical diagnosis of postpartum HLH remains challenging. Hence, HLH may remain undiagnosed, leading to poor patient prognosis. Therefore, improvements in the accuracy of postpartum HLH diagnoses and treatments are necessary.

CASE SUMMARY

We report the case of a 40-year-old female with postpartum HLH. The patient attended the postpartum care center for 3 wk after giving birth and underwent needle aspiration due to thyroid gland enlargement 11 d before an emergency department visit precipitated by fever and abdominal pain. Since no abnormal emergency room findings were noted, the patient was discharged with a prescription for broad-spectrum antibiotics. Three days later, she returned to the emergency room in a hemodynamically unstable state and was admitted to the intensive care unit with suspected sepsis or hematologic disease. The patient was treated, without effect, for sepsis using broad-spectrum antibiotics, and for suspected hematologic disease with steroid therapy. However, she died due to rapidly worsening symptoms.

CONCLUSION

Rapid recognition and appropriate treatment of postpartum HLH are needed to improve the prognosis.

Key Words: Bone marrow; Pregnancy; Lymphohistiocytosis; Infection; Steroids; Case report

Core Tip: Postpartum hemophagocytic lymphohistiocytosis (HLH) is a rare disease that is not often considered clinically and is difficult to diagnose because of its rarity and varied clinical presentations. Its clinical features are similar to those of sepsis or some pregnancy-related diseases, but the treatment is different. Therefore, an accurate diagnosis is necessary, and early recognition and treatment are needed, to improve patient prognoses. Although clinicians are unfamiliar with postpartum HLH, awareness of the disease is necessary to improve the prognoses of patients with postpartum HLH.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and potentially life-threatening condition that develops concurrently with various conditions, including infection, immunodeficiency syndrome, hematologic malignancy, autoimmune disease, and pregnancy[1-3]. Postpartum HLH is often overlooked due to its low incidence rate[4]; currently, only 11 cases have been reported in English literature[3,5-8]. Therefore, patient symptoms may not prompt this disease to be considered in a differential diagnosis, which may delay accurate diagnosis and lead to adverse outcomes. To prevent this, awareness of this disease should be increased.

This case report aims to augment the existing body of medical evidence regarding postpartum HLH and enhance its awareness among healthcare professionals. Additionally, the 11 reported cases of postpartum HLH, including 8 patients in a case series[3] and 3 case reports[6-8], have been reviewed in this report. We compared the diagnostic criteria used in these cases, focusing on initial treatment and mortality, to help increase the awareness of this disease.

CASE PRESENTATION

Chief complaints

A 40-year-old female patient visited the emergency department (ED) with a 3 d history of fever, minor headache, and abdominal pain.

History of present illness

The patient had been living in a postpartum care center after giving birth by cesarean section 3 wk prior to her ED visit. Eleven days prior, the front of her neck was swollen, and a needle aspiration was performed at a private surgical hospital; however, her thyroid gland showed no specific findings.

History of past illness

The patient had no relevant medical history, apart from a cesarean section performed 3 wk before presentation.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

During physical examination in the ED, the patient's vital signs were measured: Body temperature (40.6 °C), blood pressure (100/48 mmHg), heart rate (100 bpm), and respiratory rate (18 breaths/min). No specific findings were observed in the thyroid gland. Moreover, no notable clinical findings such as neck stiffness, tonsil hypertrophy, abdominal tenderness, abnormal breath sounds, or costal spine angle tenderness were observed. Additionally, the patient exhibited no signs of infection at the site of abdominal surgery (cesarean section) or thyroid fine-needle aspiration. Colposcopy was performed to preclude endometritis; however, no specific findings were observed.

Laboratory examinations

The patient's laboratory test results revealed bicytopenia (hemoglobin: 14.0 g/dL; platelets: 133000/μL; absolute neutrophil count: 2512/μL). However, other laboratory tests including total bilirubin level measurement (0.3 mg/dL), liver enzyme level measurement [aspartate transaminase (AST): 65 U/L; alanine transaminase (ALT): 35 U/L], thyroid function test (T3: 65.1 ng/dL; free T4: 0.88 ng/dL), and urinalysis (one white blood cell/high-powered field), showed no significant abnormalities. The C-reactive protein (CRP) level was elevated at 4.46 mg/dL.

Imaging examinations

The patient's chest radiograph was normal. Abdominal computed tomography (CT) was performed due to elevated CRP

levels and intermittent post-delivery abdominal pain. However, a prominent infectious focus was not observed.

Further diagnostic work-up

After administration of an antipyretic drug, the patient's fever subsided, and vital signs remained stable during long-term follow-up in the ED. Four days later, the patient was discharged with a prescription for broad-spectrum antibiotics and a referral to the infectious disease outpatient department to evaluate her fever of unknown etiology. However, 4 d after discharge, the patient returned to the ED with a fever of 38 ℃ and decreased blood pressure of 60/30 mmHg. Laboratory test results revealed thrombocytopenia (platelets: 94000/μL), and other test results [total bilirubin level: 3.1 mg/dL; liver enzyme levels (AST: 202 U/L; ALT: 444 U/L)] and renal function indicators (blood urea nitrogen: 42.1 mg/dL; creatinine: 3.35 mg/dL) indicated multiorgan failure. The patient's ferritin and triglyceride levels were 3429.0 μg/L (normal range: 13.0-150.0 μg/L) and 957 mg/dL (normal range: 10.0-150.0 mg/dL), respectively.

FINAL DIAGNOSIS

Postpartum HLH.

TREATMENT

Given the possibility of septic shock and hematologic disease, the patient was admitted to the Department of Infectious Disease Intensive Care Unit (ICU) and treated with broad-spectrum antibiotics and steroids; however, a high-dose steroid regimen (HLH-2004, recommended for HLH) was not administered. This was because the results of the patient's bone marrow biopsy had not been confirmed. Furthermore, the immune system might be weakened after childbirth, leaving her vulnerable to infection.

OUTCOME AND FOLLOW-UP

During the ICU admission, the patient's thrombocytopenia had worsened, and serum ferritin levels had increased. The patient's condition rapidly deteriorated, and she died with a large amount of hematochezia due to disseminated intravascular coagulation. HLH diagnosis was confirmed following a bone marrow examination; however, its etiology was unclear.

DISCUSSION

HLH, a rare disease associated with uncontrolled inflammatory response[9], is characterized by dysregulated hyperinflammatory immune response resulting in histiocytic proliferation, significant bone marrow hemophagocytic activity, and massive release of inflammatory cytokines[1,2]. The disease may be classified as primary or secondary[2,10], with underlying causes of secondary HLH including infections, malignancies, and autoimmune diseases. Pregnancy-related HLH is a type of secondary HLH, with postpartum HLH being the less well-known subtype. To date, only a few cases of the latter have been reported[3,5]. Yildiz *et al*[5] described 21 cases of pregnancy-related HLH, only three of which were postpartum. Additionally, Song *et al*[3] described a case series of eight patients with postpartum HLH. Despite the paucity of published information, understanding this disease is important to minimize diagnostic delays leading to poor patient prognoses.

HLH is characterized by tissue cell proliferation, hyperinflammation, bone marrow hemophagocytic activity, and release of large amounts of inflammatory cytokines produced by lymphocytes. These characteristics are similar to those observed during pregnancy[4,11-15]. However, unlike pregnancy-related HLH, postpartum HLH is characterized by disease onset after childbirth. Here, HLH may have been induced by an infection and the resultant inappropriate immune response where the pathophysiology of pregnancy/childbirth was similar to that of HLH. Since the pathogenic factors associated with pregnancy and childbirth have been eliminated, they cannot be part of the etiology of postpartum HLH. However, even after childbirth, the altered immune system may have been confounded by infection, leading to postpartum HLH[16].

Since no diagnostic criteria exist for postpartum HLH, pediatric HLH diagnostic criteria have been used (Table 1)[4,17]. In this case, when the patient returned to the ED, the diagnostic criteria for HLH were not met, except fever and elevated ferritin levels. Cytopenia, hypertriglyceridemia, and bone marrow hemophagocytosis were not confirmed until after ICU admission. In clinical practice, all tests necessary to meet the HLH diagnostic criteria cannot be conducted in the ED. Blood test results may not meet diagnostic criteria during the early stages of the disease, which are characterized by rapid disease progression. As in our case, if a postpartum patient visits the ED with fever, but the symptoms are nonspecific and ferritin levels are high, the patient should be advised to undergo a bone marrow biopsy under the outpatient setting.

Table 1 Diagnostic criteria of hemophagocytic lymphohistiocytosis: Hemophagocytic lymphohistiocytosis-2004

Criteria	Diagnosis will be established if one of either 1 or 2 below is fulfilled	
A	A molecular diagnosis consistent with HLH: Pathogenic mutations of PRF-1, UNC13D, STXBP2, Rab27a, STX11, SH2D1A, or XIAP	
B	Diagnostic criteria for HLH fulfilled (5 of 8 criteria below)	
	1	Fever ≥ 38.5 C for ≥ 7 d
	2	Splenomegaly ≥ 3 finger breadth below left subcostal margin
	3	Cytopenia affecting ≥ 2 of 3 lineages in peripheral blood: Hemoglobin < 9 g/L; platelets < 100 × 10^9/L; absolute neutrophil count < 1.0 × 10^9/L
	4	Hypertriglyceridemia (> 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL)
	5	Hemophagocytosis in bone marrow or spleen or lymph nodes or liver
	6	Low or absent natural killer cell activity
	7	Ferritin > 500 ng/mL
	8	Elevated soluble CD25 (sIL-2 receptor) ≥ 2400 U/mL

CD25: Cluster of differentiation 25; HLH: Hemophagocytic lymphohistiocytosis; PRF-1: Perforin 1; SH2D1A: SH2 domain-containing 1A; sIL-2: Soluble interleukin 2; STXBP2: Syntaxin binding protein 2; STX11: Syntaxin 11; UNC13D: Unc-13 homolog D; XIAP: X-linked inhibitor of apoptosis protein.

The first case series of patients with postpartum HLH was described by Song *et al*[3]. In addition, three more cases reported in English were identified[6-8]. Eleven patients were compared in Table 2, which shows the number of diagnostic criteria met by each patient, as well as initial treatments and patient outcomes. Nine patients survived; however, the two patients who died met five or seven of the diagnostic criteria described in Table 1. The time from disease onset to diagnosis is not described for each patient. However, considering the rarity of the disease in the postpartum setting, the relationship between treatment regimen and survival described for the eight patients is important. In our case, although five of the diagnostic criteria were met, the prognosis was poor due to diagnostic treatment delays. Based on the criteria reported by Song *et al*[3], fever was reported in 11 patients, splenomegaly in 9, cytopenia in 7, hypertriglyceridemia and/or hypofibrinogenemia in 11, hemophagocytosis in 9, low natural killer cell activity in 6, ferritin level elevation in 11, and soluble cluster of differentiation 25 level elevation in 7. Where a differential diagnosis is required based on clinical symptoms and results, conducting a ferritin test is important after confirming cytopenia, hypertriglyceridemia, and/or hypofibrinogenemia. In addition, a bone marrow biopsy should be performed to confirm hemophagocytosis, as this provides clinicians with more information than other nonspecific symptoms and test results.

Because HLH diagnosis is made according to diagnostic criteria, accurate diagnosis of the disease remains difficult. In our study, we faced similar challenges. Although the diagnostic criteria for HLH were met, they were not differentiated from those for other diseases. However, no particular reaction was observed upon administration of antibiotics; therefore, the possibility of infection-related diagnosis seemed low. A final consensus on HLH diagnosis was reached when experts discussed the diagnosis after the patient's death.

Currently, no standard therapeutic regimen exists for postpartum HLH treatment[4,18]. Based on previous studies, the standard post-abortion HLH-94/04 treatment seems to be the most efficient and safe option[19]. In this regimen, etoposide and dexamethasone, with or without cyclosporine A, are used to treat active HLH. A recent review estimates the mortality rate for secondary HLH as approximately 41%[14]. Additionally, doxorubicin, etoposide, and high-dose methylprednisolone[20], as well as fludarabine with prednisolone, can be used to treat refractory HLH in adults[21].

During the postpartum period, the effects of cytotoxic drugs on the fetus are negligible. However, the patient's general condition deteriorates markedly after childbirth, and use of high-dose steroids may increase risk of infection. In addition, most postpartum HLH cases are confused with sepsis, metabolic disorders, or hemolysis, elevated liver enzymes, and low platelets syndrome (characterized by hemolytic anemia, elevated liver enzyme levels, and thrombocytopenia)[22,23]. These factors delay postpartum HLH diagnosis, and may contribute to the high mortality rate.

Early diagnosis and prompt immunosuppressant administration are required to improve the prognoses of patients with postpartum HLH[24,25]. However, complications may occur if a severe infection is mistaken for HLH and immunosuppressants are administered[26]. Nevertheless, it is necessary to consider treatment methods, including high-dose steroids, that improve prognosis. Unfortunately, the paucity of reported studies dealing with postpartum HLH prognosis makes determining the optimal treatment regimen challenging; therefore, more research is needed on methods to improve prognosis.

CONCLUSION

Postpartum HLH is a type of secondary HLH that is difficult to diagnose and that can be fatal if treatment is delayed. As

Table 2 Number of diagnostic criteria met, treatments, and outcomes

Case No	Diagnostic criteria met	Primary therapy	Outcome
1	1,2,3,4,5,7,8	HLH-04	Died
2	1,2,3,4,5,6,7	HLH-04	Survived
3	1,3,4,5,7,8	HLH-04	Survived
4	1,2,4,5,6,7,8	HLH-94	Survived
5	1,2,4,5,6,7,8	HLH-94	Survived
6	1,3,4,5,7	HLH-94	Died
7	1,2,4,6,7,8	FD	Survived
8	1,2,4,5,6,7,8	DEP	Survived
9	1,2,3,4,5,6,7,8	HLH-94 with anakinra	Survived
10	1,2,3,4,5,7	HLH-04	Survived
11	1,2,3,4,7	Methylprednisolone	Survived

Diagnostic criteria met, 1: Fever; 2: Splenomegaly; 3: Cytopenia affecting ≥ 2 of 3; 4: Hypertriglyceridemia and/or hypofibrinogenemia; 5: Hemophagocytosis in bone marrow or spleen or lymph nodes or liver; 6: Low or absent natural killer cell activity; 7: Ferritin elevation; 8: Elevated soluble cluster of differentiation 25. DEP: Doxorubicin + etoposide + methylprednisolone; FD: Fludarabine + prednisolone; HLH: Hemophagocytic lymphohistiocytosis.

patients usually visit the ED with postpartum fever, emergency medicine physicians should consider other postpartum diseases in differential diagnoses. Absent established diagnostic criteria, conscious efforts are needed to identify postpartum HLH through blood tests included in the HLH diagnostic criteria and clinical symptoms in the ED. Furthermore, if necessary, invasive tests such as bone marrow biopsy should be conducted.

FOOTNOTES

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