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CASE REPORT

A Case Report of Pregnancy Complicated with Primary Hemophagocytic Lymphohistiocytosis

Yan Chen*, Xiaohuan Huang*, Hongfei Chen, Junru Tong, Lingling Huang, Junyou Su, Li Deng

Department of Obstetrics, The Second Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, 530007, People's Republic of China

*These authors contributed equally to this work

Correspondence: Li Deng; Junyou Su, Email dengli@gxmu.edu.cn; sujunyou@sr.gxmu.edu.cn

Background: Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome characterized by excessive activation of NK cells and cytotoxic T lymphocytes, subsequently leading to macrophage activation and increased cytokine production. Misdiagnosis due to nonspecific clinical presentations and inadequate understanding of the disease can significantly jeopardize the safety of both the mother and the infant. We report a case of pregnancy combined with HLH and conduct a literature review to provide insights into the diagnosis and treatment of pregnancy-related HLH.

Case Presentation: We discussed a case of a pregnant woman with persistent postpartum fever, serum ferritin, and elevated liver function, who failed to respond to repeated anti-infective therapy and was diagnosed with HLH after multidisciplinary diagnostic treatment. We gave dexamethasone treatment, and the patient's temperature and blood cells quickly returned to normal. Finally, exome sequencing revealed heterozygous variation in *UNC13D* gene, so we considered this case as pregnancy combined with primary HLH (pHLH).

Conclusion: We report the case of HLH diagnosed during pregnancy and show that early diagnosis and timely intervention can prevent rapid disease progression, reduce maternal mortality rates, and improve survival rates. Additionally, molecular genetic testing can confirm pathogenic gene mutations, providing essential genetic counseling for patients with pHLH who plan to conceive a healthy child.

Keywords: hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, pregnancy, case report

Introduction

Hemophagocytic lymphohistiocytosis (HLH), also known as hemophagocytic syndrome (HPS), is a severe hyperinflammatory syndrome characterized by excessive activation of NK cells and cytotoxic T lymphocytes, subsequently leading to macrophage activation and increased cytokine production. While there are two types of HLH—primary and secondary—based on whether a specific genetic abnormality linked to HLH exists, growing research characterizes HLH as a more complicated condition that arises from particular immune challenges in patients with a susceptible genetic background.[1] Primary (pHLH), which includes familial HLH (FHL), immune deficiency syndrome-associated HLH, and Epstein-Barr virus (EBV)-driven HLH, is an autosomal or sex chromosomal recessive disorder that often occurs in childhood.[2] Secondary (sHLH) is often induced by infections (viral, bacterial, fungal, or other), autoimmune diseases, malignancies, drugs and other risk factors, and there is usually no known genetic defect causing HLH and no family history of it.[3] However, the complicated reality of genetic causality in HLH is oversimplified by this dichotom.[4] For instance, the distinction between sHLH and pHLH has become obscure due to the ongoing advancements in the detection and comprehension of gene mutations, and it is also thought that sHLH has a specific genetic background.[5] Moreover, placing nearly all non-FHL patients under sHLH suggests an unjustified similarity in etiology and therapy, which could result in ineffective or inappropriate care.[6] With the deepening of molecular genetics research, some primary immunodeficiency disorders (PID) and inborn metabolic defects are susceptible to HLH, and new candidate genes for pHLH are gradually expanding.[3] In addition, after suffering from external triggers (such as viral infection, etc.) after the "second blow" showed HLH onset. HLH has a worldwide annual incidence of 1 in 800,000, with a high mortality rate of up to 40%. Untreated HLH has a median survival time of no more than two months.[6,7] Currently, the majority of reported cases

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of pregnancy-associated HLH both in China and internationally are sHLH, whereas research on pregnancy-associated pHLH remains limited. Misdiagnosis due to nonspecific clinical presentations and inadequate understanding of the disease can significantly jeopardize the safety of both the mother and the infant. This report presents a case of pregnancy-associated pHLH, which was successfully treated at the Second Affiliated Hospital of Guangxi Medical University. In addition, we conducted literature review to provide insights into the diagnosis and treatment of pregnancy-associated HLH. This case report has been approved by the Medical Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University [Approval number: 2023-KY (0626)].

Case Presentation

A 35-year-old primiparous woman was admitted to the hospital at 29 weeks gestation, with a history of abdominal pain for 2 hours, and vaginal discharge for 1 hour. She had regular prenatal check-ups during pregnancy, with a diagnosis of gestational diabetes and G-6-PD deficiency. The patient had no history of chronic diseases such as hypertension, diabetes, or hepatitis before pregnancy and denied any family history of hereditary diseases. Before admission, her serum ferritin level was measured at 1910.84 ng/mL by routinely prenatal test. Upon admission, the patient's vital signs were recorded as follows: Temperature (T) - 36.4°C, Pulse rate (P) - 92 beats/minute, Respiratory rate (R) - 20 breaths/minute, Blood Pressure (BP) - 130/74 mmHg. No palpable enlargement of superficial lymph nodes was detected. On pelvic examination, the cervix was fully dilated at 10 cm, the amniotic membrane had ruptured, and the fetal presented as cephalic with a station of 2cm below the ischiatic spine. Laboratory tests showed a white blood cell count (WBC) of 8.69×10^9/L, hemoglobin (HGB) of 102 g/L, platelet count (PLT) of 259×10^9/L, alanine aminotransferase (ALT) of 50 U/L, aspartate aminotransferase (AST) of 101 U/L, and fibrinogen (FIB) of 4.94 g/L. Following admission, dexamethasone was given via intramuscular injection to promote fetal lung maturation and cefazolin sodium pentahydrate was administrated for anti-infective treatment. The patient delivered a baby girl weighing 1300 g, with Apgar scores of 8-9-9. However, several hours later, the patient started experiencing recurrent chills and fever, with a maximum temperature of 40.0°C. Although we upgraded antibiotics to strengthen anti-infection and antiviral treatment, the patient continued to have a fever for 8 days. The patient had no other clinical manifestations of systemic infection except for fever. Due to the unclear cause of the fever, a multidisciplinary team (MDT) composed of experts in obstetrics, hematology, rheumatology, respiratory medicine, endocrinology, critical care medicine, and genetic and genomic medicine was consulted to analyze the patient's condition. Improved examinations were provided based on the MDT consultation (Table 1). With recurrent fever (temperature ≥38.5°C for over 7 days), leukopenia, decreased hemoglobin, elevated triglycerides, decreased fibrinogen, elevated ferritin, decreased NK cell count, and reduced NK cell activity, along with increased soluble CD25 levels, and NK cell CD107a degranulation assay suggesting impaired NK cell function (Figure 1), a diagnosis of HLH was considered. Accordingly, the patient was admitted to Hematology Department for bone marrow aspiration and biopsy. The examination revealed the tissue hemophagocytosis (Figure 2). The patient had elevated levels of sCD25 (2170.72 U/mL), and the NK cell CD107a

Table 1 HLH-2004 Diagnostic Criteria and Patient's Examination Results

HLH-2004 Diagnostic Criteria	Patient
The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled	
1. A molecular diagnosis consistent with HLH	UNC13D
1. Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)	
(A) Initial diagnostic criteria (to be evaluated in all patients with HLH)	
Fever (T >38.5°C, last >7 days)	T_{max} 40.0°C, last >7 days
Splenomegaly	No splenomegaly
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):	
Hemoglobin <90 g/L	81 g/L
Platelets $<100\times10^9$/L	193×10^9/L
Neutrophils $<1.0\times10^9$/L	1.35×10^9/L

(*Continued*)

Table 1 (Continued).

HLH-2004 Diagnostic Criteria	Patient
Hypertriglyceridemia and/or hypofibrinogenemia	
Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL)	4.35 mmol/L
Fibrinogen ≤1.5 g/L	1.41 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes	Hemophagocytosis in bone marrow
No evidence of malignancy	No evidence of malignancy
(B) New diagnostic criteria	
Low or absent NK-cell activity (according to local laboratory reference)	CD3-CD16+CD56+%: 6.62%, CD3-CD16+CD56+Abs: 53/μL, indicating a decrease in NK cell count
Ferritin ≥500 microgram/L	25766.52 ng/mL
Soluble CD25 (ie, soluble IL-2 receptor) ≥2400 U/mL	2170.72 U/mL
The results of NK cell CD107a activation test decreased (New test, supplement of HLH-2004 Diagnostic Criteria)	Degranulation of NK cells is a functional defect

Abbreviations: HLH, hemophagocytic lymphohistiocytosis; T_{max}, maximum temperature; NK, natural killer.

degranulation assay showed functional impairment of NK cell degranulation, which supported the diagnosis of HLH. Two days after MDT consultation, the patient received dexamethasone (16 mg, once daily), and then twenty-four hours later, the patient's temperature returned to normal. The dose of dexamethasone was adjusted according to the patient's condition (Table 2). At the same time of treatment, the etiology of the patient's HLH was examined. The pathogen screening tests showed that influenza A and B viruses, human parvovirus DNA (B19-DNA), CMV-DNA, and EBV-DNA were negative, so viral infection was not supported; fungal β-D glucan assay (G test), GM test and fungal culture showed no abnormality, hence no obvious fungal infection; Autoantibody spectrum (including ANA, anti-dsDNA, ACA, nRNP/Sm, Sm, SSA, R0-52, SSB, ScI-70, Jo-1, CENP) B, anti-dsDNA, Nucleosome, Histone, Rib.P-Prot.pANCA, cANCA, MPO-ANCA, PR3-

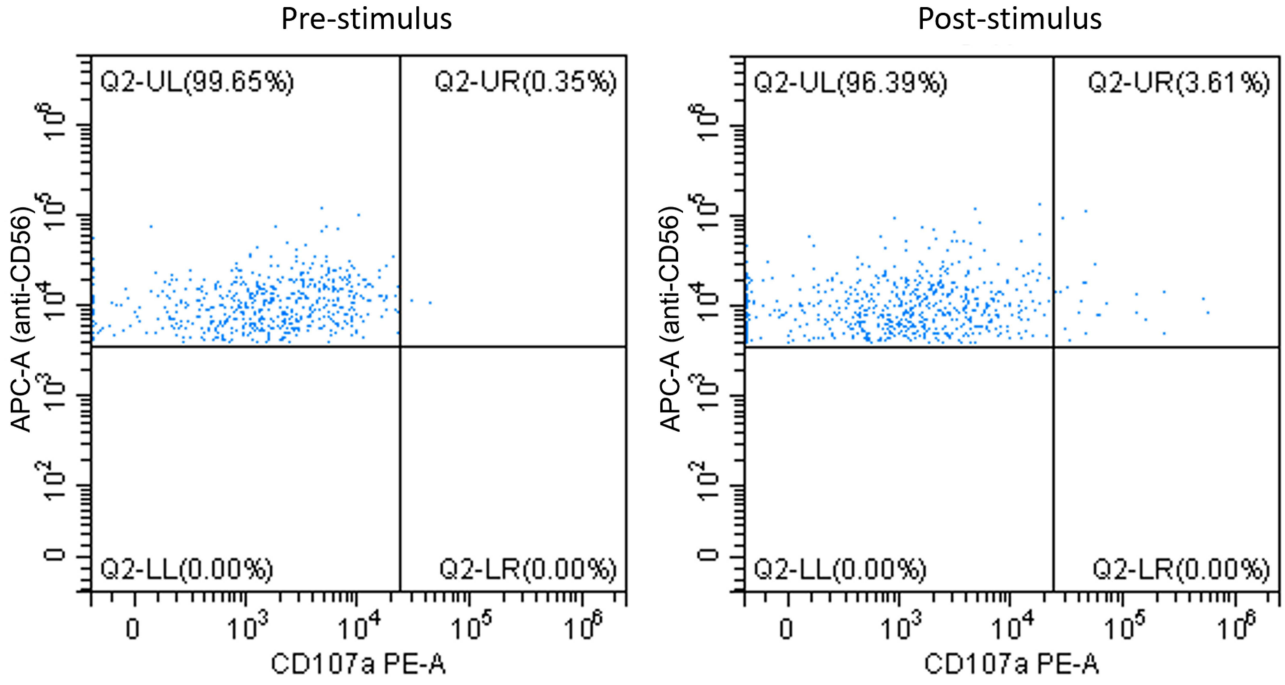

Figure 1 NK cell degranulation assay. PBMCs were isolated and co-incubated with a specific proportion of K562 cells for stimulation or incubated with medium alone (control group). Flow cytometry was then performed with anti-CD3 (FITC), anti-CD56 (APC) and anti-CD107a-PE labeled samples. CD3-CD56+NK cells were gated to assess their expression in response to K562 stimulation and non-stimulation by measuring amplitude changes in CD107a (NK-ΔCD107a) surface expression. The reference intervals were defined as <5% being deficient, >5% and <10% being abnormal, and >10% being normal.

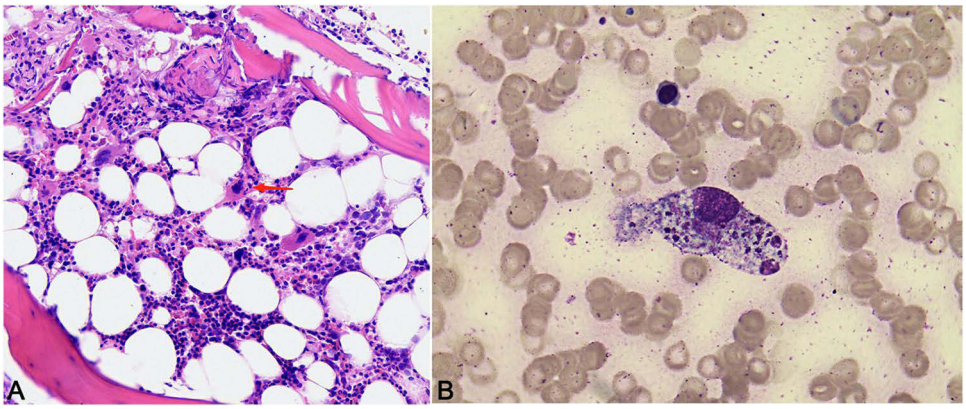

Figure 2 Bone marrow examination: active bone marrow hyperplasia, normal granulocyte lines with reactivity changes, elevated red blood cell lines, normal megakaryocyte lines, and observed tissue hemophagocytosis. (**A**) Bone marrow pathology (HE staining, ×80): bone marrow cells phagocytosis of nucleated red cells (as shown by arrow). (**B**) Bone marrow cytology (Reye's staining, ×100 oil mirror): bone marrow cells phagocytosis of granulocytes and nucleated red cells.

ANCA, etc.), complement C3 and C4, immunoglobulin G4 was not abnormal. In addition, tumor markers and superficial lymph node ultrasound showed no significant abnormalities. Positron emission tomography and computed tomography (PET/CT) indicated diffuse inflammatory lesions in the liver, while liver biopsy suggested non-alcoholic fatty liver disease (NAFLD). Exome sequencing showed NM_199242.3 (UNC13D): c.1280G >A p.(Arg427Gln), suggesting heterozygous variation in *UNC13D* gene (Figure 3). This patient was considered for possible concomitant pHLH. Therefore, a complete exome sequencing in the patient's family members was suggested, which was rejected by the patient and her family. After discharge, the patient continued to receive oral dexamethasone hormone therapy and gradually tapered off the medication on a weekly basis, with follow-ups showing good recovery and no relapse.

Discussion

We retrieved all information from PubMed and Google Scholar to support our findings. Search items included pregnancy-induced/related HLH, HLH during pregnancy, familial HLH, and mutation genes, and excluded search items included pregnancy-related secondary HLH. HLH can occur during pregnancy and the postpartum period, with approximately 20% of cases developing in the postpartum period. Notably, HLH during the postpartum period has a higher mortality rate compared to HLH during pregnancy.[8] The occurrence of HLH during pregnancy is primarily reported as individual cases. The most significant risk factor for pregnancy HLH is infection, accounting for 30% of all causative factors, among which EBV infection is the most common trigger.[9,10] FHL is a rare autosomal recessive genetic disease, characterized by cellular cytotoxic T-cell dysfunction or alterations due to gene mutations, leading to the

Table 2 Patient's Treatment Options and Temperature Changes

Date	T_{max} (°C)	Treatment
8.31	39.5	Cefazolin Sodium 2g Bid ivgtt
9.1	40.0	Cefazolin Sodium 2g Bid+ Oseltamivir Phosphate 75mg Bid ivgtt
9.2	38.4	Cefoperazone Sodium and Sulbactam Sodium 2g Q8h ivgtt
9.3–9.4	39.6	Cefoperazone Sodium and Sulbactam Sodium 2g Q8h+ Ornidazole 0.5mg Q12h ivgtt
9.5–9.9	40	Ceftriaxone sodium 4g qd+ moxifloxacin 0.4g qd ivgtt
9.10–9.22	36.8	Dexamethasone 16mg qd intravenous ivgtt
9.23–9.29	36.7	Dexamethasone 8.25mg, Qd, profess to convinced (Discharge)
9.30–10.6	36.6	Dexamethasone 3.75mg, Qd, po
10.7–10.13	36.5	Dexamethasone 1.5mg, Qd, po
10.14–11.3	36.6	Dexamethasone 0.75mg, Qd, po
11.4	36.8	Dexamethasone 0.375mg, Qd, po

Notes: T_{max}, maximum temperature; Bid, bis in die; ivgtt, intravenous drip; Q8h, quaque 8 hours; Qd, quaque day; po, peros.

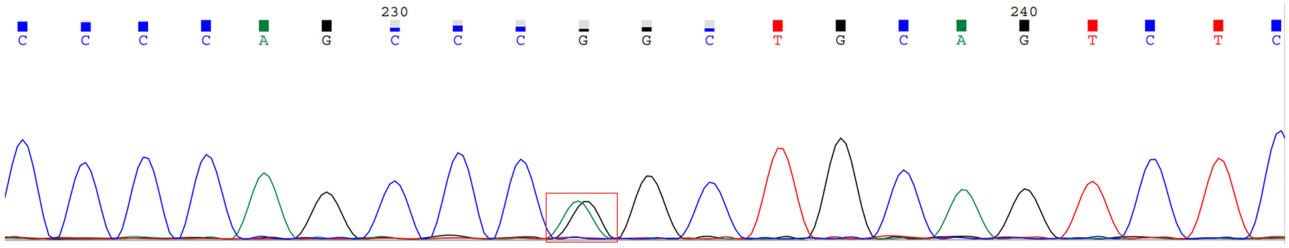

Figure 3 Exome sequencing revealed heterozygous mutations in *UNC13D* gene.

pathogenesis. FHL can be divided into five subtypes (FHL-1, 2, 3, 4, 5). Although the causative genes for FHL-1 are not yet clear, the abnormal genes associated with FHL-2 to FHL-5 subtypes are *PRF1, UNC13D, STX11*, and *STXBP2*, respectively.[11] Upon occurrence, HLH can cause multiple organ failure, miscarriage, and intrauterine distress in pregnant women, leading to adverse outcomes for the fetus, such as restricted growth, stillbirth, neonatal or pediatric HLH. Take neonatal rheumatic disease-related HLH as an example, mothers with rheumatic immune diseases may trigger pathogenic effects in their fetuses that can cause macrophage activation syndrome (MAS).[12] Furthermore, the mother-child exchange between the two enables inflammatory mediators in the mother to enter the fetus through the placenta, resulting in similar abnormal immune states in the child and ultimately triggering the occurrence of MAS. In addition, whether the mother takes drugs during pregnancy and whether there are clinical symptoms may affect the onset time and severity of neonatal HLH/MAS. The mortality rates for pregnant women and fetuses are reported to be 22% and 40%, respectively.[13] Of note, a study by Parrott et al[14] suggested that pregnancy-induced HLH may occur due to the placenta releasing fragments of the nutrient layer containing fetal RNA and DNA into the maternal circulation, leading to a systemic inflammatory response between the fetus and the mother.

During pregnancy, HLH may present with non-specific clinical features, commonly characterized by the triad of fever, cytopenia, and hepatosplenomegaly, which can be easily confused with other pregnancy-related liver diseases or infectious conditions such as intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy, HELLP syndrome, autoimmune liver diseases, and sepsis.[8] The similarities and differences between them are shown in Supplementary Table 1. The internationally recognized diagnostic criteria for HLH are outlined in HLH-2004[11] (Table 1). In this particular case, the serum ferritin level was already elevated to 1910.84 ng/mL before the onset of fever. After admission, the patient showed abnormal liver function. As the condition progressed and fever developed, infection was initially considered as the cause. Despite aggressive anti-infection treatment, the patient had a persistent fever and the results of pathogen screening were negative. Thus, infections were fully excluded as a potential trigger for HLH. Consequently, a multidisciplinary team (MDT) approach was employed to analyze the patient's condition. Further examinations revealed leukopenia, decreased hemoglobin, elevated triglycerides, decreased fibrinogen, elevated ferritin, reduced and hypofunctional NK cell count, increased soluble CD25, and functional deficiency of NK cell degranulation as evidenced by the NK cell CD107a degranulation assay. Additionally, bone marrow biopsy revealed hemophagocytosis, leading to a definitive diagnosis of HLH. Malignancy-associated HLH and rheumatic autoimmune-related HLH were ruled out through tests for rheumatologic factors, tumor markers, PET/CT, and liver biopsy. In this case, the patient was found to have heterozygous variations in the *UNC13D* gene through whole-exome sequencing. Generally speaking, pHLH is caused by identifiable genetic mutations, such as *UNC13D*, an abnormal gene associated with the FHL-3, which belongs to autosomal recessive genetic disease. pHLH is primarily found in infancy and early childhood, however late-onset pHLH can also occur in patients triggered by pregnancy.[13] However, more studies[15] have indicated that this is an oversimplification of a complex condition, and rather than classifying HLH as a dichotomous condition, it should rather be perceived and treated as a spectrum in which milder conditions are linked to later onset and more severe environmental triggers, while the most severe ones inevitably result in HLH at a young age (mutation as risk factor). Therefore, we highly suspect that this patient's HLH is pHLH. According to Mendelian inheritance laws, HLH can only occur if both alleles of the related gene have mutations. It is notable that clinical observations have shown cases where single allele gene mutations result in the disease, possibly due to dominant negative

mutations leading to loss of protein function.[16] However, the patient's family declined to undergo familial whole-exome sequencing. Therefore, the exact source of the gene mutation remains uncertain.

HLH involves multiple disciplines and presents with non-specific clinical manifestations, making early diagnosis extremely challenging. The recommended clinical diagnostic strategy for adult HLH is as follows.[3] First, identify the suspect HLH - Consider the possibility of HLH when a patient presents with unexplained persistent fever, cytopenia, and splenomegaly or abnormal liver function. Differential diagnosis between HLH and sepsis is crucial since misdiagnosis as sepsis might lead to a missed opportunity for timely immune therapy. Moreover, sepsis and HLH can occur as complications of each other, emphasizing the need for clinicians to be vigilant in recognizing HLH.[17] Second, advance the initial diagnostic - Serum ferritin, which is an acute-phase reactant and an important diagnostic and prognostic marker for HLH, has been used as a biomarker for diagnosis and prognosis of HLH. Specifically, a ferritin level above 10,000 μg/L can increase sensitivity and accuracy to 90%, providing strong indications for the HLH diagnosis.[18] Third, confirm the diagnosis – The diagnosis should be based on the HLH-2004 diagnostic criteria, combined with clinical judgment and medical history.[6] Although the HLH-2004 guidelines are currently the most commonly used diagnostic criteria for HLH, these criteria were developed in children with familial HLH and have not been prospectively validated in adult HLH patients at this time, and some of these criteria remain diagnostic deficiencies. For example, according to HLH-2004 diagnostic criteria, serum ferritin ≥500μg/L meets the criteria for hyperferritinemia.[11] However, in adult HLH patients, serum ferritin levels are significantly elevated.[19] In addition, for patients with mild initial symptoms, the use of this set of criteria may delay diagnosis. Therefore, the diagnosis of HLH should be combined with other diagnostic criteria and clinical expertise. Song et al[20] observed elevated ferritin, decreased NK cell activity, and elevated soluble CD25 in 8 cases of pregnancy-related HLH, with a 100% diagnostic coincidence rate. This study suggested that these three positive indicators have significant diagnostic value for pregnancy-related HLH. In most cases, bone marrow hemophagocytosis can confirm the diagnosis of HLH. Compared to biopsies of other sites, bone marrow biopsy is easy to perform, the results are readily available, and the risks are minimal. However, hemophagocytosis may not be detected by bone marrow biopsy in the early stages of HLH and may not appear until later in the course of the disease.[21] As reported by Carter et al[22] and Thompson et al[23] repeated bone marrow biopsies may be required for confirmation. It is important to note that bone marrow hemophagocytosis may not be specific to HLH, but may be a physiological manifestation after blood transfusion or surgery, or may occur in infections, malignancies, and other acute diseases.[24,25] Finally, determine the underlying cause - Once HLH is diagnosed, early cytotoxic function tests, protein expression detection of HLH-related genes, pathogen screening, and screening for neoplastic or rheumatic diseases should be conducted. Of note, the use of cytokines as diagnostic markers for HLH is still under investigation.[26] With the continuous advancement of molecular genetics, gene sequencing has become the gold standard for diagnosing pHLH. In cases with rapid case progression and unrecognized causes, early gene sequencing examination is recommended.

The treatment principles for HLH involve controlling the progression of HLH, addressing the underlying cause, correcting potential immune defects, managing the primary disease, and preventing HLH recurrence. The HLH-1994 protocol is currently recognized as the first-line treatment, utilizing drugs such as dexamethasone, immunoglobulins, and etoposide to suppress excessive inflammatory responses and organ failure.[27] In cases of HLH during pregnancy, obstetricians can systematically manage pregnant women with HLH, which is not an absolute indication for pregnancy termination. Patients with HLH during early pregnancy may face challenges in continuing the pregnancy. For pregnant patients with HLH, dexamethasone monotherapy is commonly adopted, with generally successful outcomes and no significant adverse effects on the mother and fetus, allowing for efforts to extend the gestational period whenever possible. Although hemophagocytic lymphohistiocytosis during pregnancy is uncommon, it frequently goes undiagnosed, which raises the risk of death for both the mother and the fetus.[28] Furthermore, for patients with HLH during pregnancy, treatment with the HLH-1994/04 regimen after termination of pregnancy appears to be the safest and most effective.[29] However, in fact, many study[8,30,31] reports that HLH patients with pregnancy onset often show signs of remission after termination of pregnancy, and show a good long-term prognosis without recurrence. In cases where medical treatment for HLH during pregnancy proves ineffective, pregnancy termination may be an effective treatment.[32] It is noteworthy that there is no unified consensus on the optimal termination method, and decisions should be based on the gestational age and cervical evaluation of the mother. As an example, Wang et al[13] reported a case of a 40-year-old patient diagnosed

with pHLH during pregnancy with a UNC13D heterozygous mutation. The patient underwent successful treatment with the HLH-1994 protocol after a natural miscarriage and eventually received a bone marrow transplant, resulting in a favorable prognosis. Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) currently stands as the only means to achieve long-term cure for pHLH.[33] In the case of this patient, other triggering factors were ruled out, leading to a diagnosis of FHL. The use of dexamethasone monotherapy yielded favorable results, with rapid normalization of relevant indicators. We recommended that this patient undergo familial genetic testing, which would require allo-HSCT if pHLH was diagnosed, but the patient and her family did not undergo genetic testing.

Conclusion

In conclusion, pregnancy-associated HLH is a rare, life-threatening, and often misdiagnosed condition with nonspecific clinical presentations. Obstetricians should be vigilant about HLH during pregnancy and consider the possibility of HLH when faced with continuous fever, leukopenia, splenomegaly, abnormal liver function, or elevated serum ferritin levels. Patients who meet the diagnostic criteria for HLH should undergo early etiological screening. Early diagnosis and timely intervention can prevent rapid disease progression, reduce maternal and fetal mortality rates, and improve survival rates. Additionally, molecular genetic testing can confirm pathogenic gene mutations, providing essential genetic counseling for patients with pHLH who plan to conceive a healthy child.

Data Sharing Statement

All supporting documents have been submitted along with the case report.

Ethics Approval and Informed Consent

This case report has been approved by the Medical Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University [Approval number: 2023-KY (0626)] and the patient has provided written informed consent.

Consent for Publication

Written informed consent was obtained from the patient for publishing this report.

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Author Contributions

Yan Chen and Xiaohuan Huang drafted the manuscript; Hongfei Chen, Junru Tong and Lingling Huang performed the data processing and statistical analyses; Junyou Su and Li Deng made critical revisions related to relevant intellectual content of the manuscript. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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