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CASE REPORT

Familial Hemophagocytic Lymphohistiocytosis in a Premature Low Birth Weight Infant: a Rare Case Report

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SUMMARY

Background: **Familial hemophagocytic lymphohistiocytosis (FHL) onset in the fetal and neonatal periods is sporadic, and infants are susceptible to intrauterine death. Early and accurate diagnosis and treatment are the keys to preventing complications and death in FHL patients due to the complex and diverse clinical manifestations of the disease.**
Methods: **We report a rare case of a preterm infant with a low birth weight of 2,010 g and a gestational age of 32 + 4 weeks who presented with a leaky syndrome similar to sepsis after birth. Anti-infective, other support, and symptomatic treatments were not effective. Bone marrow examination results on day 13 suggested hemophagocytosis.**
Results: **Various compound heterozygous UNC13D genes were found by exome sequencing, which confirmed the diagnosis of FHL type 3. Genetic variants of this locus have never been reported in the literature.**
Conclusions: **Neonatal onset FHL is challenging to diagnose, especially in premature infants. It is necessary to complete exome sequencing if the patient has no apparent pathogen infection or effective treatment.**
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KEYWORDS

familial hemophagocytic lymphohistiocytosis, premature infant, whole exome sequencing, UNC13D gene

INTRODUCTION

Familial hemophagocytic lymphohistiocytosis (FHL) is a rare autosomal recessive disease. The disease is often accompanied by clinical symptoms, including fever, hepatosplenomegaly, cytopenias, elevated triglycerides, lower fibrinogen, and elevated serum ferritin. Hemophagocytosis can be found in the biopsy of PRF1, UNC-13D, STX11, and STXBP2, whose mutations cause the occurrence of FHL-2, FHL-3, FHL-4, and FHL-5 [1-3]. This disease mainly occurs in infants, primarily in those that are two months to two years old [4]. FHL onset in the fetal and neonatal periods is sporadic, accounting for 4% of all cases; fetuses and neonates are susceptible to intrauterine death [5]. The clinical signs in these patients are still unclear, and the onset FHL in premature

infants has not been reported. Here, we report a rare case of a preterm infant with a low birth weight of 2,010 g and a gestational age of 32 + 4 weeks who presented with a leaky syndrome similar to sepsis after birth. Genetic analysis of the infant and her parents confirmed that the baby had a compound heterozygous variant of the UNC13D gene, which confirmed the diagnosis of FHL type 3.

CASE PRESENTATION

This case was a female preterm newborn whose gestational age was only 32 + 4 weeks, and the infant's birth weight was 2,010 grams. This study protocol was approved by the Medical Ethics Committee. Written informed consent was obtained from the parents of this baby for publication of this case report. This low birth weight infant (LBWI) was born by emergency cesarean section because of intrauterine asphyxia with normal Apgar scores, edema of the umbilical cord, and contaminated amniotic fluid. She was the product of the second pregnancy of nonconsanguineous parents. The first pregnancy ended at 40 days of pregnancy as a spontaneous abortion (Figure 1). There were no infections or other medical disorders during the pregnancy. However, abdominal effusion and pericardial effusion were found by ultrasound on the day before the cesarean section. The infant was admitted to the Neonatal Intensive Care Unit (NICU) for severe dyspnea and abdominal distension fifteen minutes after delivery. We found that the baby had shortness of breath, groaning, pale face, and anemia, and there were many bleeding points on her skin. The child also had significant abdominal distension with hepatosplenomegaly and systemic edema accompanied by hypothermia.

Routine blood tests showed an increase in white blood cells (30.6 x 10^3 mm/L with neutrophils - 21%), anemia (hemoglobin - 9.3 g/dL), and thrombocytopenia (platelets - 29 x 10^3 mm/L). However, the level of C-reactive protein was normal (4.5 mg/dL). There were also abnormalities in the blood coagulation function. The liver function results included hypoalbuminemia (serum albumin - 2.5 g/dL) and hyperlipemia (triglyceride - 0.45 mmol/L). The renal function was normal, and a blood gas analysis showed lactic acidosis. The patient's serum ferritin was very high at 1,500 ng/mL (reference range: 11 - 306.8 ng/mL). The blood and cerebrospinal fluid cultures were both negative. The routine biochemical tests of cerebrospinal fluid were normal, and screening tests for TORCH, human immunodeficiency virus (HIV), hepatitis B, and hepatitis C were negative. A bedside ultrasound showed pleural effusion, abdominal effusion, and hepatosplenomegaly.

The infant was treated by mechanical ventilation and surfactant replacement because of neonatal respiratory distress syndrome. Because the infant developed clinical manifestations of systemic edema, anemia, thrombocytopenia, hepatosplenomegaly, and increased lactic acid-like septic leakage syndrome on day 1, intravenous antibiotics were also administered. We administered multiple infusions of red cell suspension, plasma, and platelets, but this did not effectively correct the baby's anemia, blood coagulation abnormalities, and thrombocytopenia. Anti-infective treatments were also not effective. Therefore, we suspected that the infant had hemophilia syndrome. We performed a bone marrow examination on day 13, which suggested hemophagocytosis (Figure 2). Thus, we administered glucocorticoid immunosuppressive therapy from day 16. However, the parents gave up the treatment on day 18. The baby died on day 32 and automatically discharged.

Various compound heterozygous UNC13D genes, including c.2773C>T (p. Q925X) and c.2560dupG (p. E854Gfs * 7), were found by Whole-Exome Sequencing (WES) and Sanger sequencing, which confirmed the diagnosis of FHL-3. The c.2773C>T nonsense variant changed the amino acid at position 925 of the protein from glutamine to a stop codon (p. Q925X), resulting in premature termination of protein synthesis. The variant was inherited from the infant's father. The c.2560dupG frameshift variant changed the amino acid at position 854 of the protein from glutamate to a stop codon (p. E854Gfs * 7), resulting in premature termination of protein synthesis; this was inherited from the infant's mother (Figure 3).

DISCUSSION AND CONCLUSION

FHL is characterized by uncontrolled inflammation of multiple systems. Therefore, the clinical manifestations are complex and diverse. Due to its extreme rarity, the clinical aspects of neonatal FHL are still not well described. A study from the United States shows that hydrops fetalis and multi organ failure were common presentation in neonatal FLH [6]. In a case report and literature review by Yang et al. [7], most cases have atypical presentation, non-immune hydrops or fetal distress may be the only clinical symptom. The onset of FHL is often due to the activation of immune cells induced by infection, which leads to the outbreak of inflammation. Recently Hon et al. reported a neonate who recovered from COVID-19 infection, but the infant developed hemophagocytic lymphohistiocytosis a few weeks later. It was confirmed that the infant and his father have mutations of UNC13D [8].

Most newborns without a positive family history are diagnosed late in the course of the disease or after death. The rare case we reported was a LBWI, with fetal manifestations including pleural effusion, respiratory distress, systemic edema, hypoproteinemia, hepatosplenomegaly, thrombocytopenia, systemic hemorrhage, and abnormal coagulation. The clinical symptoms were similar to sepsis leakage syndrome, but infection and symptomatic treatment were ineffective. Finally, genetic analysis confirmed the presence of a compound heterozygous variant in the UNC13D gene. The baby was di-

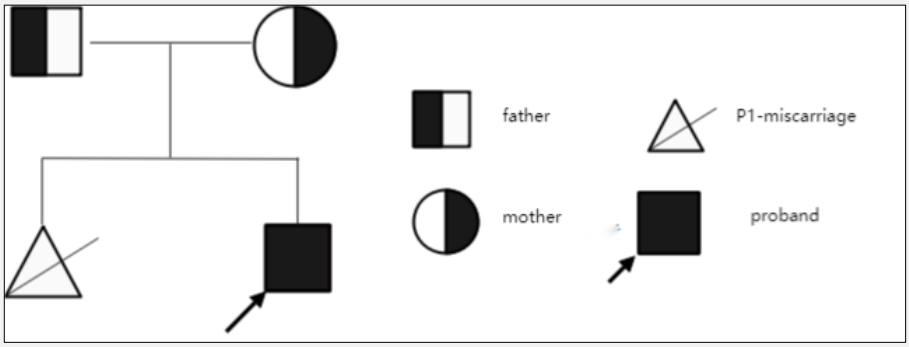

Figure 1. Pedigree from the FHL families.

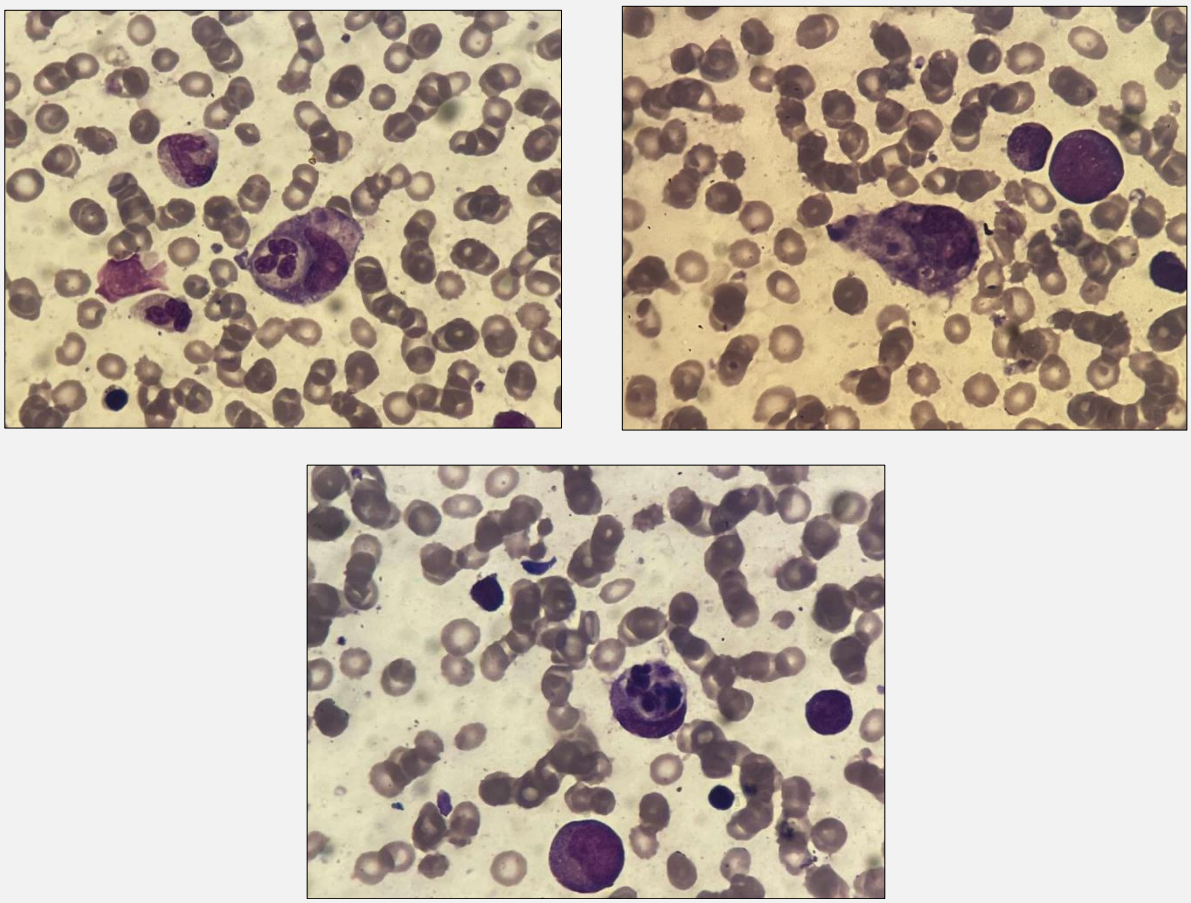

Figure 2. Bone marrow smear.

Phagocytosis could be clearly observed.
Oil mirror: 10 x 100.

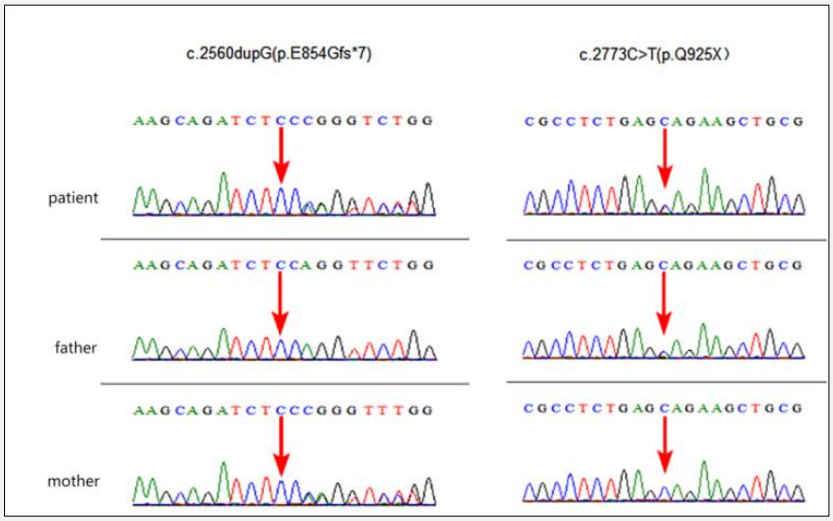

Figure 3. The UNC13D gene c.2773C>T (p. Q925X) and c.2560dupG (p. E854Gfs * 7) for compound heterozygous variants.

agnosed with FHL type 3.

FHL type 3 is associated with the genetic variation of the UNC13D gene [9]. The UNC13D gene encodes the protein Munc13-4, which plays a crucial role in the fusion process of cytotoxic particles and the target cell membrane [10]. Approximately 30 - 40% of FHL cases are FHL type 3, caused by UNC13D mutation. Sequencing the UNC13D gene is a very valuable diagnostic method [11]. In a recent study in China, 87 (32.83%) of 265 FLH patients had genetic variants. Thirty-six (13.58%) patients had UBC13D gene mutations, suggesting that UNC13D gene mutations were the most common [12]. To date, more than 100 mutations have been identified in the UNC13D gene, occurring in 32 exons of the gene, with the mutations commonly affecting mRNA splicing [9]. It was confirmed that the rare case we reported had heterozygous compound variants of the TUNC13D gene c.2773C>T (p. Q925X) and c.2560dupG (p. E854Gfs * 7), obtained from the parents of the infant. The c.2773C> T and c.2560dupG variants have not been reported or included in the database. Whether this genotype is associated with the clinical phenotype is still unknown.

Neonatal-onset FHL is difficult to diagnose early. The clinical presentations are often similar to sepsis. Due to low lipid metabolism levels, atypical biochemical enzymatic changes, and significant differences in coagulation function, it can easily be misdiagnosed, especially in premature infants without fever or even hypothermia. Therefore, to diagnose and treat FHL early, it is necessary to complete exome sequencing if the patient has no apparent pathogenic infection. The rare case we reported was a premature LBWI. Her genetic variant locus has never been reported in the literature. However, whether there is a correlation between the genotype and clinical phenotype requires further clinical case analyses to confirm.

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Declaration of Interest:

The authors declare that they have no competing interests.

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