CASE REPORT

Haemophagocytic lymphohistiocytosis in a preterm infant: A case report

Na Mi Lee,[1] Dae Yong Yi,[2] Shin Weon Yoon,[3] Soo Ahn Chae,[4] In Seok Lim,[5] Yong-Sung Choi[6]

Abstract

Haemophagocytic lymphohistiocytosis (HLH) is a rare disease with a sepsis-like progression that leads to multiple organ dysfunction syndrome, especially in preterm infants. We present herein a case of HLH in a premature infant presenting with disseminated intravascular coagulopathy (DIC) and liver failure. A male infant, with weight 810g and delivered at the gestational age of 25 weeks and 2 days, was misdiagnosed with tyrosinaemia for several weeks. He presented with anaemia, thrombocytopaenia, persistent DIC, and elevated liver enzymes despite continuous transfusion and broad-spectrum antibiotics. A bone marrow puncture biopsy revealed haemophagocytosis, leading to HLH diagnosis. It is important for paediatricians to consider the possibility of HLH when liver function test results are abnormal in such patients.

Keywords: Hemophagocytic lymphohistiocytosis, Liver failure, Premature infant.

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a rare disease, especially in premature infants. Although HLH can occur in all age groups, neonatal onset is rare, accounting for only 4% of all HLH cases.[1] The disease is characterised by a widespread accumulation of lymphocytes and mature macrophages due to uncontrolled hyper-inflammation caused by unremitting activation of antigen-presenting cells and CD8+ T cells, in addition to excessive levels of cytokines.[2,3] The signs and symptoms of HLH are nonspecific; therefore, an accurate diagnosis is very difficult in most cases. The overall 3-year disease-free survival rate is 55%,[4] and the survival rate may increase with early diagnosis and appropriate treatment.[5,6] Herein we report a case of a premature infant misdiagnosed with tyrosinaemia for several weeks before HLH was diagnosed.

Case Report

A male infant weighing 810g was born at gestational age of 25 weeks and 2 days by emergency Caesarean section on June 4, 2014 as the mother was diagnosed with perforated appendicitis. She was a 36-year-old woman with a birth history of one previous spontaneous abortion. Laboratory findings associated with disseminated intravascular coagulopathy (DIC) were positive from the 14th postnatal day. Sepsis-associated DIC was suspected, however, bacterial cultures of blood, cerebrospinal fluid (CSF), ascitic fluid, urine, and stool were all negative. Viral serological tests for rotavirus, cytomegalovirus, enterovirus, and hepatitis A, B, and C viruses were also negative.

Table: Diagnostic criteria of haemophagocytic lymphohistiocytosis seen in our patient.

Diagnostic criteria	Present in our patient
Fever	Absent
Splenomegaly	Present
Cytopenia (in at least two of the three cell lineages)	
Haemoglobin level < 9 g/dL	Present
Platelet count < 100 x10^9/L	Present
Neutrophil count < 1.0 x 10^9/L	Present
Hypertriglyceridaemia and/or hypofibrinogenaemia	Present, hypofibrinogenaemia
Low or absent natural killer cell activity	Not checked
Haemophagocytosis in bone marrow, spleen, or lymph nodes	Present, in bone marrow
Ferritin level $\geq$ 500 ug/L	Present
Soluble CD25 level $\geq$ 2400 U/mL	Not checked

On the 36th postnatal day, the infant's direct bilirubin level gradually increased to 4 mg/dL. Ultrasonography did not show biliary tree dilatation. Parenteral nutrition-associated cholestasis (PNAC) was diagnosed at this time and ursodeoxycholic acid was administered. The treatment allowed feeding to progress satisfactorily. However, even as full feeding (120 ml/kg/day) was achieved on the 84th postnatal day, the infant's direct bilirubin level increased to 12.3 mg/dL and his liver enzymes (aspartate aminotransferase and alanine transaminase) were elevated at 106 and 202 IU/L, respectively. His lactate dehydrogenase level was increased at 235 IU/L, and ferritin level was also elevated at 2758.7 ng/mL. He subsequently developed increasing respiratory difficulties due to a grossly distended abdomen. Abdominal ultrasonography revealed hepatomegaly and splenomegaly, with the

[1-5]Department of Pediatrics, Chung-Ang University Hospital, College of Medicine, Chung-Ang University, [6]Department of Pediatrics, Kyung Hee University School of Medicine, Seoul, Korea.

Correspondence: Shin Weon Yoon. Email: yswmd@cau.ac.kr

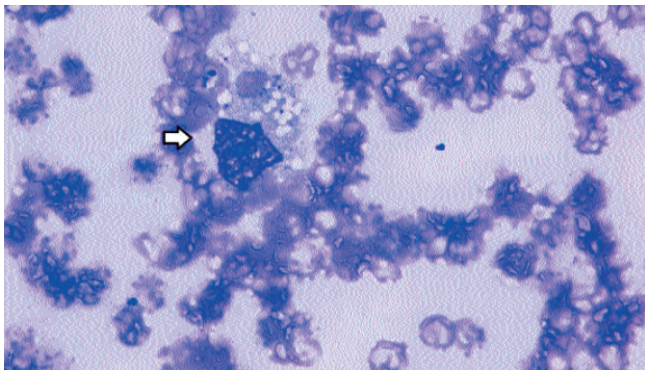

Figure: Histological features of the bone marrow aspiration specimen in a patient with haemophagocytic histiocytes.

spleen measuring 7.43 cm, and he developed ascites on the 135th postnatal day. Liver biopsy could not be performed as he was susceptible to excessive bleeding due to DIC.

Laboratory tests for inborn errors of metabolism were performed. A tandem mass spectrometry was negative when he received nothing by mouth, but was positive for tyrosinaemia after full feeding. His serum and urine tyrosine level were elevated at 942 nmol/mL and 26082.7 nmol/mL, respectively; however, succinylacetone was not detected in the urine. Fumarylacetoacetate hydrolase gene mutation testing was performed to rule out tyrosinaemia type I and yielded a normal result.

Anaemia and thrombocytopenia did not improve. Leukopaenia was present from the 46th postnatal day and neutropaenia developed on the 125th postnatal day. A bone marrow aspiration at the right anterior iliac crest was performed on the 127th postnatal day. A histological analysis of the aspirate revealed histiocytes associated with erythrophagocytosis. Further, haemophagocytic histiocytes were observed with a decrease in erythropoietic and granulopoietic cells, while megakaryocytes were rarely observed (Figure). CSF and ascites examination did not exhibit evidence of haemophagocytosis. Based on these findings, we diagnosed our patient with HLH; however, familial HLH-related mutations in the perforin 1 and UNC13D genes were not detected. Although treatment was initiated according to the HLH-2004 protocol (dexamethasone, etoposide, and cyclosporine A), his clinical condition deteriorated. He developed multiple organ dysfunction syndrome and died of a cardiorespiratory failure and sustained DIC. Written informed consent was taken from the parents for prior to writing of this case report.

Discussion

Extremely premature infants admitted to the neonatal intensive care unit often suffer from DIC, sepsis, and PNAC. Sepsis is frequently accompanied by DIC, rendering the condition more difficult to treat as DIC is not easily reversible despite multiple platelet transfusions. Most of these infants require total parenteral nutrition for extended periods of time. As a result, their direct bilirubin level is often increased due to PNAC. Our patient experienced DIC from 14th postnatal day. We believe that his increased direct bilirubin level was initially the result of PNAC as he started feeding on the 36th postnatal day and reached full feeding on 76th day. However, his direct bilirubin level did not improve; ascites appeared and thrombocytopenia persisted despite full feeding. We also suspected inborn errors of metabolism as his liver function worsened with the appearance of hyperammonaemia and tyrosinaemia. However, tyrosinaemia was transient due to worsening liver function.

Neonatal HLH with an onset within 4 weeks after birth is rare. HLH in premature infants is especially difficult to diagnose, and the diagnosis is typically made during autopsy or is missed entirely. Cases of premature infants with HLH have been reported and most such cases have a poor prognosis.[5] According to a report from Japan, eight of the twenty neonates diagnosed with HLH were premature infants, and only two among them survived.[7]

A diagnosis of HLH requires either a molecular diagnosis consistent with HLH or the fulfillment of five of the following eight clinical, laboratory, and histopathological criteria: fever; splenomegaly; cytopaenia affecting at least two of three cell lineages in the peripheral blood; hypertriglyceridaemia and/or hypofibrinogenaemia; haemophagocytosis in the bone marrow, spleen, or lymph nodes; low or absent natural killer cell activity; hyperferritinaemia; and high levels of soluble-IL-2 receptor (Table).[3,6] However, the clinical symptoms exhibited by premature infants with HLH are nonspecific and, therefore, difficult to diagnose.[7]

Fever is not easy to detect as the temperature of the premature infants is controlled in the incubator. In previous reported cases of HLH in premature infants, fever was detected in only two of the eight cases.[8] Further, anaemia in premature infants is often a consequence of blood loss due to frequent blood sampling. Thrombocytopenia and coagulopathy caused by DIC, and hyperferritinaemia caused by frequent transfusions, are also common in premature infants. However, hepatosplenomegaly, which is not often seen in

premature infants, has been reported in seven of the eight HLH cases.[9]

Therapeutic guidelines for HLH are available (HLH-2004 protocol) for all age groups, including neonates. Treatment includes a combination of etoposide and a corticosteroid with cyclosporine A, and this chemoimmunotherapy lasts for 8 weeks for all HLH cases. Thereafter, familial HLH and persistent or reactivated acquired HLH cases require continuation of therapy until haematopoietic stem cell transplantation may be performed. In cases of acquired HLH, treatment may be stopped if a complete recovery has been made.[3] Thrombocytopenia and anaemia should be managed with frequent blood transfusions. For premature infants, empirical antibiotics should also be considered as neutropaenia can lead to severe infections.[8]

A study from Sweden reported a case of an extremely premature infant who was diagnosed early with severe bacteria-associated HLH. The infant was treated according to the HLH-2004 protocol, following which, there was no signs of HLH reactivation until 19 months.[10]

Conclusion

It is very difficult to diagnose HLH by signs and symptoms alone due to a high likelihood of misdiagnosing the condition as an infection or a metabolic disease, therefore delaying diagnosis.[6] In premature infants exhibiting cytopaenia affecting at least two of three cell lineage in the peripheral blood and hepatosplenomegaly, neonatologists should suspect HLH and perform bone marrow aspiration and biopsy. As neonatal HLH can rapidly lead to death without specific intervention, it is recommended that treatment be started whenever a high clinical suspicion exists, even if confirmatory test results are awaited.[7]

Disclaimer: None to declare.

Conflict of Interest: None to declare.

Funding Disclosure: None to declare.

References

1. Isaacs H Jr. Fetal and neonatal histiocytoses. Pediatr Blood Cancer. 2006; 47: 123-9.
2. Roganovic J, Kvenic B, Jonjic N, Seili-Bekafigo I, Kardum-Skelin I. Neonatal hemophagocytic lymphohistiocytosis-case report. Coll Antropol. 2010; 34: 285-90.
3. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007; 48: 124-31.
4. Filipovich AH. Hemophagocytic lymphohistiocytosis and other hemophagocytic disorders. Immunol Allergy Clin North Am. 2008; 28: 293-313.
5. Woods AG, Woods CW. Hemophagocytic lymphohistiocytosis in the premature neonate: a case study. Adv Neonatal Care .2009; 9: 274-8.
6. Woods CW, Bradshaw WT, Woods AG. Hemophagocytic lymphohistiocytosis in the premature neonate. Adv Neonatal Care. 2009; 9: 265-73.
7. Suzuki N, Morimoto A, Ohga S, Kudo K, Ishida Y, Ishii E, et al. Characteristics of hemophagocytic lymphohistiocytosis in neonates: a nationwide survey in Japan. J Pediatr. 2009; 155: 235-8.
8. Lipton JM, Westra S, Haverty CE, Roberts D, Harris NL. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 28-2004. Newborn twins with thrombocytopenia, coagulation defects, and hepatosplenomegaly. N Engl J Med. 2004; 351: 1120-30.
9. Rugolotto S, Marradi PL, Balter R, Maccario R, Padovani EM, Locatelli F. Familial haemophagocytic lymphohistiocytosis: survival of a premature twin with immuno-chemotherapy and bone marrow transplantation from an HLA-identical unrelated donor. Acta Paediatr. 2005; 94: 971-4.
10. Edner J, Rudd E, Zheng C, Dahlander A, Eksborg S, Schneider EM, et al. Severe bacteria-associated hemophagocytic lymphohistiocytosis in an extremely premature infant. Acta Paediatr. 2007; 96: 1703-6.