Case Report

Hemophagocytic Lymphohistiocytosis in A Newborn Infant Presenting with Nonimmune Hydrops Fetalis: A Case Report

Badr Hasan Sobaih[1], Shihab Ahmed Almashhadani[2]
[1]King Saud University, College of Medicine, Department of Pediatrics, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia
[2]King Saud University, College of Medicine, Pathology Department, Hematology Division, King Khalid University Hospital, Riyadh, Saudi Arabia

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ABSTRACT

Nonimmune hydrops fetalis is a condition that may result as a cause of many underlying conditions and in around 15% of cases no cause could be identified. Hemophagocytic lymphohistiocytosis had been identified as a rare cause of nonimmune hydrops fetalis in the newborn period in few cases around the world. Here, we reported one case of nonimmune hydrops fetalis born for Saudi parents associated with Hemophagocytic lymphohistiocytosis presented at birth and was born at 32 weeks of gestation. Diagnosis was confirmed by bone marrow aspiration. She was treated with chemotherapy but did not respond to therapy and died. We suggest that Hemophagocytic lymphohistiocytosis should be seriously considered as a cause of nonimmune hydrops fetalis, if the later condition is associated with unexplained cytopenias, high ferritin level, and splenomegaly.

KEY WORDS: cytopenias, hemophagocytic lymphohistiocytosis, high ferritin, nonimmune hydrops fetalis

INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a rare hematologic disorder which affects the immune system characterized by abnormal proliferation of macrophages in various tissues and organs causing multi organ failure and often results in death[1]. HLH encompasses several entities, including a primary form that may be familial HLH, with an estimated incidence of one in 50,000 births[2], and a secondary form associated with infections, malignancies, and rheumatologic disorders[3].

Hydrops fetalis is a condition with many underlying causes. Despite advances in ante-natal and post-mortem diagnostic techniques, the cause remains unknown in up to 15% of cases[4].

Hemophagocytic lymphohistiocytosis had been reported as one of the rare causes of non immune hydrops fetalis in few case reports [5-10]. To our knowledge, this is the first reported case in Saudi Arabia.

CASE REPORT

A newborn girl was admitted to our Neonatal Intensive Care Unit (NICU) as a case of non-immune hydrops fetalis which was diagnosed by ante-natal ultrasound. She was delivered by emergency cesarean section at 32 weeks of gestation for a healthy 25 years old, booked Saudi primigravida due to fetal distress. Apgar score was 2, 5, and 7 at 1, 5, and 10 minutes respectively, with birth weight of 2.8 kg. Delivery was attended by three senior neonatologists who conducted full resuscitation for this hydropic baby. Pleural effusion was drained through bilateral thoracocentesis, while normal saline boluses were infused *via* an emergency umbilical venous catheter (UVC). She needed high frequency oscillatory ventilation (HFOV). She developed pneumothorax which was drained *via*

Address correspondence to:
Badr Hasan Sobaih, MBBS, ABP®, Department of Pediatrics, King Saud University, College of Medicine, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia, Mobile: 966505453580, Fax: 96614672395, PO Box 2925, Riyadh, 11461, Email: badrhasansobaih@gmail.com, drbsobaih@yahoo.com, bsobaih@ksu.edu.sa;

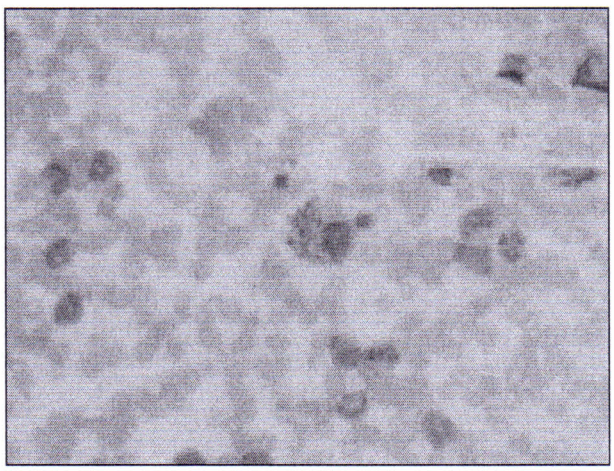

Fig. 1: Bone marrow slide showing single hemophagocytic histiocyte containing depris in its cytoplasm.

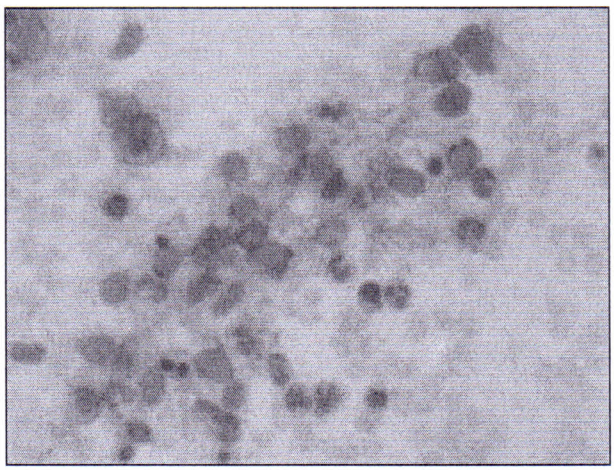

Fig. 2: Bone marrow slide showing many hemophagocytic histiocytes in clusters containing cellular depris in their cytoplasm.

chest tube. Her pleural effusion and pnuemothorax eventually resolved within four days. Echocardiogram was done as part of evaluation for hydrops fetalis and showed partial atrio-ventricular septal defect, large atrial septal defect (ASD) secundum, small muscular ventricular septal defect (VSD), and large patent ductus arteriosus (PDA). She also developed severe supra systemic persistent pulmonary hypertension (PPHN). The impression of our cardiologist is that these findings cannot explain the etiology of hydrops fetalis for this baby. Renal ultrasound was normal. Generalized edema resolved gradually with the use of diuretics and fluid management. Physical examination revealed Splenomegaly which was persistent throughout her hospital course.

Initial CBC showed WBC count of 35.65 × 10^9/l, Hemoglobin was 124 g/l, and low platelet count of 19 ×10^9/l. Subsequent CBC results showed persistent anemia with marked thrombocytopenia for which multiple transfusions of platelets and packed red cells were given, but failed to show acceptable improvement. Intravenous immunoglobulin and dexamethasone also failed to improve the condition. She was empirically covered with broad spectrum antibiotics after obtaining blood culture. Hemoglobin level remained below 90 g/l and platelets count never exceeds 30 × 10^9/l.

Other investigations for the etiology of hydrops fetalis such as TORCH screen, Parvovirus antibodies, Hepatitis markers, and HIV antibodies all came to be negative. Pediatrics hematology/oncology service was involved in the investigation and management of this case. Serum Ferritin level was 1926.00 µg/L then increased to 6844.00 µg/L two weeks later. Peripheral blood film demonstrated leuko-erythroblastic blood picture. Neutrophilia with left shift and some toxic changes were evident. RBC morphology reveals some degree of anisopoikilocytosis and polychromasia. Severe thrombocytopenia was confirmed. B and T lymphocytes subsets were low. Bone marrow aspiration was done and revealed hypercellular particles with hypercellular trails that show adequate megakaryocytes with occasional coarse basophilic granulations. Erythropoiesis looks essentially normoblastic and shows progressive maturational sequences. Granulopoiesis looks adequate and reveals slight left shift. M: E ratio 3.9:1. Blasts account for 3% of all nucleated cells. Macrophages were prominent with obvious hemophagocytosis involving mostly erythroid cells and platelets. Some hemophagocytic cells were in clusters and some in single form all over the marrow aspirate smears (Fig. 1, 2). Iron stain: Stainable iron stores. Iron was markedly increased with adequate erythron iron and no ring sideroblasts. With these findings, it was concluded that this hypercellular bone marrow aspirate showed adequate lineage hematopoietic elements with prominent phagocytic activity. These findings were compatible with the diagnoses of hemophagocytic Lymphohistiocytosis (HLH).

Henceforth, she was started on triple drug regimen Cyclosporin, IV Immunoglobulin and Dexamethasone and showed progressive but transient response. Baby's general condition progressively deteriorated despite full and aggressive management until she had fulminant gram negative septicemia which eventually led to her death at the age of 44 days.

DISCUSSION

We described a newborn baby who presented to us as a case of non-immune hydrops fetalis and was treated accordingly. This is the first time in our practice to see unusual course for such neonates as she persistently had bicytopenia despite our aggressive

intervention, although there was great improvement in pleural effusion and ascitis as well as generalized edema. The presence of persistent bicytopenia raised our suspicion of dealing with a rare cause of hydrops fetalis that could be related to a disease affecting cell proliferation. After seeing the results of bone marrow aspiration we searched the literature to find if there is association between hydrops fetalis and hemophagocytic Lymphohistiocytosis and we found few reported cases [5-10].

According to HLH-2004 protocol for diagnostic guidelines [11], diagnosis of HLH can be established after fulfillment of either one or two of the following criteria: A molecular diagnosis consistent with HLH, and or Fulfillment of five out of eight of the following diagnostic criteria [Fever, Splenomegaly, Cytopenias affecting ≥ 2 of 3 lineages in the peripheral blood Hypertriglyceridemia and/ or hypofibrinogenemia, Hemophagocytosis in bone marrow or spleen or lymph nodes, Low or absent NK-cell activity, High ferritin, High CD 25 (soluble IL-2 receptor)].

Our patient fulfilled the criteria for the diagnosis of HLH as she presented with cytopenias, splenomegaly, low B and T lymphocytes subsets, high ferritin level, and hemophagocytosis in bone marrow.

Around 10% of cases with HLH present within the first month of life, often after a symptom-free period. However, presentation in the first day of life seems to be rare [12]. Natural killer cell activity, T-lymphocyte mitogen response, antibody-dependent cellular cytotoxicity, and interleukin-1 and interferon production are all diminished [13]. The lymphoproliferative disorder of HLH can be divided into two categories: primary (familial) hemophagocytic lymphohistiocytosis (FHL) with an incidence of 1:50,000 births and equal gender distribution, and secondary HLH which may affect any age and may resolve spontaneously. FHL is seen primarily in children and is fatal if untreated, with most cases diagnosed before two years of age, and the disease may present in the newborn period [14]. HLH may be due to an immunoregulatory defect that predisposes to an uncontrolled production of activated histiocytes in response to a stimulus such as a viral infection [15]. The aim of current treatment protocols is to achieve remission with immune-chemotherapy, followed by a cure with bone marrow transplantation [16].

CONCLUSION

We conclude from this case that hemophagocytic lymphohistiocytosis (HLH) should be considered as a possible cause of nonimmune hydrops fetalis in hydropic newborns presenting with persistent unexplained bicytopenia, splenomegaly, and high serum ferritin especially when no metabolic or infectious cause is found. Diagnosis of HLH purely by clinical presentation in newborn period is difficult. Establishment of the diagnosis by appropriate investigation tools such as bone marrow aspiration is mandatory for parent's counseling and initiation of therapy.

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