Case Report

Familial hemophagocytic lymphohistiocytosis in two Saudi siblings

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ABSTRACT

Primary familial hemophagocytic lymphohistiocytosis (HLH; or familial erythrophagocytic lymphohistiocytosis [FEL]) is a heterogeneous autosomal recessive disorder more prevalent with parental consanguinity. There is aggressive proliferation of activated macrophages and histiocytes, which phagocytose red blood cells (RBCs), white blood cells (WBCs), and platelets, leading to anemia, neutropenia and thrombocytopenia. The exaggerated response of immune system in familial HLH can occur in the absence of infection. We report on two Saudi siblings with familial hemophagocytic lymphohistiocytosis. The first case was diagnosed and started on treatment but died after ten days of treatment while the second one was referred to a higher centre for treatment but died before commencing chemotherapy treatment. This rare inherited aggressive disease needs high index of suspicion and early treatment. Anti-inflammatory therapy consisting of steroids, etoposide or antithymocyte globulin (ATG), should be instituted promptly, followed by curative hematopoietic cell transplantation to get a better outcome. Without treatment, most patients with familial hemophagocytic lymphohistiocytosis survive only a few months.

Keywords:

Hemophagocytic lymphohistiocytosis; Antithymocyte globulin; Bone marrow; Paracentesis; Child; Saudi Arabia.

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INTRODUCTION

The pathology in hemophagocytic lymphohistiocytosis (HLH) is characterized by multi-system inflammation due to uncontrolled aggressive proliferation of activated macrophages and histiocytes, which phagocytose RBCs, WBCs, and platelets [1,2]. Familial hemophagocytic lymphohistiocytosis (HLH) is uniformly fatal if not treated; the median survival time reported in various studies is 2-6 months after diagnosis [2,3]. Even with treatment, only 21-26% can be expected to survive 5 years [2]. Bone marrow transplant is the only hope for cure [2].

Herein, we report these two Saudi siblings with lethal familial HLH which did not respond to treatment.

CASE REPORTS

Case 1

A full term female baby was born vaginally at King Fahad Hospital (KFH) in Al Baha after uneventful pregnancy. Apgar scoreS were 7 and 9 at 1 and 5 minutes, respectively. Her birth weight was 2.2 kg. She developed respiratory distress with stridor so admitted to the neonatal intensive care unit (NICU) for further management. The mother was a 26-year-old Gravida 2 Para 2 and was not suffering from any acute or chronic illness during pregnancy. Parents are first-degree cousins.

The baby was intubated because of respiratory distress. On examination, she was found to be small for gestational age (SGA) and dysmorphic features in form of low set ears, depressed nasal bridge, and clenched hands with overlapping fingers. She was persistently febrile, had ascites, hepatosplenomegaly and skin rash (Figure 1A). The initial and repeat septic screenings were negative, complete blood count (CBC) showed pancytopenia. She had normal serum electrolytes and kidney profile. The results of other investigations were as follows: TORCH screening was negative, chromosomal analysis was normal (46XX), metabolic screen was unremarkable and echocardiography showed ASD and PDA. In addition, ultrasound scan (USS) of the head was normal and CT-brain was normal but abdominal USS showed ascites with hepatosplenomegaly. The baby developed cholestasis; serum bilirubin (SBR): 170µmol/l, direct: 116µmol/l with deranged liver function tests (LFTs) [AST: 352, ALT: 103, LDH: 1023, GGT: 112]. Serum ammonia was 96 µmol/l, coagulation profile was prolonged and she received fresh frozen plasma (FFP). Because of severe ascites (Figure 1B), paracentesis was done several times but ascetic fluid accumulated again fast and aggravated respiratory distress, so we could not extubate the baby. The patient was referred to King Fahad Medical City where bone marrow aspiration and biopsy was done showing increased number of histiocytes with hemophagocytic activity. Hence, baby was diagnosed as HLH and started on HLH chemotherapy protocol. The baby developed pseudomonas sepsis and she died, while on treatment, after two weeks of initiation of therapy.

Case 2

This is the second baby for the same family, born at 36 weeks gestational age. Apgar scores were 6 and 8 at 1 and 5 minutes, respectively. The baby was found to have hepatosplenomegaly and respiratory distress with stridor; so he was intubated and admitted to NICU for further management. The pregnancy was uneventful. His growth parameters showed birth weight of 2.2 kg, head circumference 32 cm, length 50 cm (SGA). He was stabilized on ventilator. On examination, there was no dysmorphism; chest was clear, no cardiac murmur and abdomen was distended with massive ascites. Liver was 4 cm below the right costal margin while the spleen was 6 cm below the left costal margin and there was normal male genitalia and bilateral hydrocele. Neurological examination was unremarkable. His initial CBC

showed thrombocytopenia (37000/ mm3), and later on he developed pancytopenia (Hb 8.2gm/dl, ANC 600 µ/l, platelets 18,000/mm3). In addition, he had normal electrolytes and renal profile. TORCH and HIV screening were negative. He showed deranged LFTs and coagulation profile (prolonged aPTT), and albumin was 18gm/l. His chest X-RAY was normal and CT-brain was also normal with no calcifications. However, abdominal X-ray showed ascites. The metabolic and septic screenings were negative and the patient had normal echocardiographic study. Immunoglobulin assay showed low IgG of 5.6 gm/l (N=6.8 – 16.5) and low IgM of 0.2gm/l (N= 0.5 – 3.1). A peripheral smear showed normocytic normochromic anaemia with neutropenia and thrombocytopenia. Bone marrow biopsy and aspirate showed numerous hemophagocytic histiocytes with hemophagocytic activity. His triglycerides were 2.3 mmol/L and serum ferritin level was elevated at 1327 ng/ml. The patient developed generalized purpuric rashes all over his body and cholestasis (SBR: 280 µmol/l) with direct bilirubin level of 225 µmol/l. He developed massive ascites requiring frequent paracentesis. The patient was diagnosed as familial HLH and it was planned to transfer him to paediatric haematology/oncology centre for further treatment but, unfortunately, he died before then.

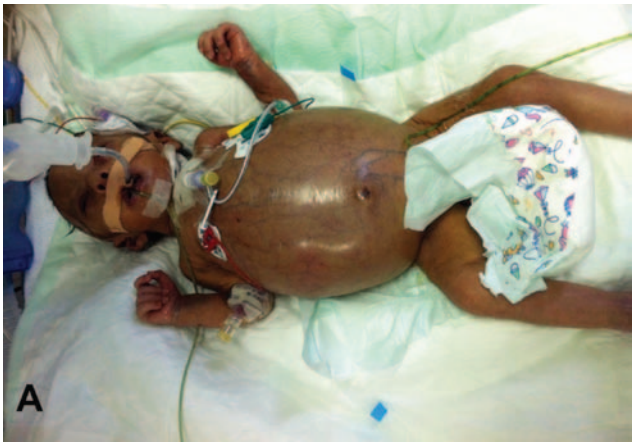

Figure 1A - Case 1 ventilated with cholestasis and ascites

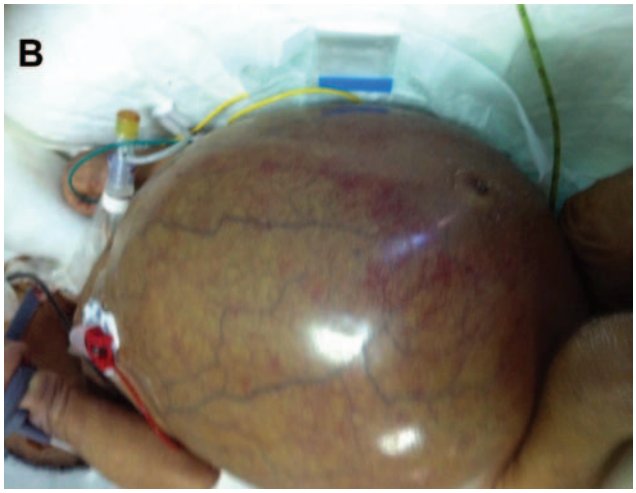

Figure 1B - Case 1 with massive ascites, cholestasis and abdominal wall erythema

DISCUSSION

The familial form of HLH is a rare autosomal recessive disorder (1 in 50,000 individuals worldwide) that has been classified into 6 different types based on genetic linkage analysis and chromosomal localization. Five specific genetic defects have been identified, which account for approximately 90% of all patients. Type 1 is due to a gene defect on chromosome 9, type 2 is due to mutations in the perforin gene, type 3 is due to mutations in the Munc-13-4 (UNC13D) gene, type 4 is due to mutations in the syntaxin 11 (STX11) gene, and type 5 is due to mutations in the gene encoding syntaxin-binding protein 2 (STXBP-2). The mutations in STX11 are said to be responsible for much of the familial HLH in the Middle East [1, 3-5]. Perforin mutations account for approximately 20% of cases of FEL, with a somewhat higher prevalence (30%) in children of Turkish descent [3]. Familial form of the disease frequently affects infants from birth but can rarely affect older children as well [5].

Our patients fulfilled the 5 diagnostic criteria, which must be met to establish a diagnosis of HLH. These are:

- Fever - > 7 days with temperature as high as 38.5°C (101.3°F)
- Splenomegaly - A palpable spleen greater than 3 cm below the costal margin
- Cytopenia - Counts below the specified range in at least 2 of the following cell lineages:
  - Absolute neutrophil count (ANC) < 1000/µL
  - Platelets < 100,000/µL
  - Haemoglobin < 9.0 g/dL
- Hypofibrinogenemia or hypertriglyceridemia: -
  1. Fibrinogen < 1.5 g/L or levels >3 SDs below the age adjusted reference value or
  2. Fasting triglyceride > 2 mmol/L or levels > 3 SDs above the age-adjusted reference range value
- Hemophagocytosis - Must have tissue demonstration from lymph node, spleen or bone marrow without evidence of malignancy.

Other physical findings include: Skin rashes on the scalp and behind the ear, swollen or haemorrhagic gums that can result in tooth loss; feeding problems; abdominal pain, vomiting, diarrhoea, and weight loss [6]. Ferritin has been observed as a marker for hemophagocytic lymphohistiocytosis, as has been found in Case 2. This patient had pancytopenia secondary to bone marrow infiltration or splenic sequestration associated with coagulopathy (prolonged aPTT) and cholestasis. The patient was put on mechanical ventilation and given full respiratory and hemodynamic support with antibiotic cover. He developed massive ascites requiring frequent paracentesis but progressively deteriorated and died before starting the specific treatment.

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