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Difficulties in Diagnosis of Hemophagocytic Lymphohistocytosis: Overdiagnosis or Underdiagnosis; A Case Report

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Introduction

Hemophagocytic lymphohistocytosis (HLH) is a potentially life threatening condition occurring as a familial disease (FHLH) or secondary to marked immunological activation during viral, bacterial and parasitic infections, malignancies, rheumatologic conditions or immune deficiencies with cytotoxic T and/or NK-cell dysfunction [1, 2]. Although FHLH is an autosomal recessive disease that affects immune regulation, sporadic cases with no obvious family inheritance occur[1]. All organ systems might be affected in HLH. Eventually multiple organ dysfunction syndrome (MODS) develops and death occurs as a result of progressive or persistence MODS[3]. Clinical presentation of HLH might be confused with sepsis, metabolic disorders and immune deficiency syndromes. Early recognition and treatment may contribute to the survival of patient. Therefore, having useful diagnostic criteria is crucial and the pediatrician should know the clinical presentations of HLH [3, 4, 5].

Case Report

A 52-days-old girl was admitted to our hospital with fever and bicytopenia. She was born at 38-weeks gestational age following an elective caesarean section and was admitted to NICU 7 days after birth with diagnosis of pneumonia. She was admitted again to a local hospital with a history of high fever and poor feeding that had lasted for seven days where she was treated for suspected sepsis with ampicillin- ceftriaxon- gentamicin combination. She had not received transfusion in that ward and after one-week admission in that hospital, she was referred to our center. She had normal complete blood count (WBC: $5.5\times10^3/\mu L$, Hb: 11.7 g/dl, HCT 33.6%, Platelete: $364\times10^3/\ \mu L$, absolute neutrophil count: 2750/ µL), urine analysis, urine culture, blood culture and chest X-ray in the local hospital on admission. On admission to our center, she weighted 5400 g (birth weight: 3200g). Birth time vaccination had been performed (BCG, OPV and HBV). The infant was the third child of her relative parents .They had a 9-years-old healthy daughter and a positive family history of infantile death in their second child with a similar presentation after receiving DPT and OPV vaccines when she was 2-months-old. Positive findings in this second infant were fever, spelnomegaly and pancytopenia. We did not have more data about the disease status of the second child except for a bone marrow aspiration report signifying relative depletion of bone marrow cellularity with maturation arrest at myeloid series with no evidence of storage cells or malignant cells .She had expired within 10 days after onset of her disease without any significant diagnosis.

Our patient upon admission in our center looked ill, pale and irritable. She had high fever, mild respiratory distress with mild intercostal retraction

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.The respiratory rate at that time was 48/min and oxygen saturation was between 88- 98%. A small (1×1 cm) firm, nontender and mobile lymph node was palpated at her right axillary region. The scar of BCG vaccine was noted on the upper right arm. On physical examination, the abdominal distention of infant was prominent due to hepatomegaly and massive spelnomegaly .The liver span was 8 cm on right midclavicular line. Hepatospelnomegaly was confirmed by an expert sonologist. The pattern of CBC at the time of admission revealed bicytopenia with a total white count of 6.1×10^3 / µl, 14% PMN (absolute neutrophil count :714/ µl), Hb: 8.7 gr/dl and platelet count : 55×10^3 / µl .The other laboratory data was AST:108 IU/L , ALT:70 IU/L , CRP: +1, LDH: 950, BUN :10 mg/dl, creatinine:0.5 mg/dl, uric acid:6 mg/dl, glucose: 70 gr/dl, PTT: 47 s , PT:12.5 s, TG : 240 mg/dl and normal fibrinogen and ferritin levels. The first chest X-ray disclosed bilateral perihillar haziness. Before transfusion of packed cells and platelet concentrates, TORCH study (toxoplasma, rubella, CMV and HSV), metabolic assays such as chromatography of urine and blood amino acids , arterial blood gases, ammonia and pyruvate levels, reducing substances of the urine and virological studies to find EBV , HCV and HIV infections were performed. Bone marrow aspiration was performed which indicated 60% cellularity with maturation arrest at myeloid series without evidence of hemophagocytosis. Four days after admission, abdominal distention and respiratory distress worsened. The patient was treated with broad spectrum antibiotics such as meropenem and vancomycin according to her poor general condition, and also intravenous immunoglobin (IVIG) for her thrombocytopenia. Right pleural effusion and free abdominal fluid were detected on thorachoabdominal ultrasound. Because one of the most probable differential diagnoses was disseminated BCG, plural and ascitis fluids, CSF and bone marrow aspirate were examined for acid fast bacilli using Polymerase chain Reaction (PCR) method, direct smear and culture with negative results. Flowcytometry of bone marrow and peripheral blood sample indicated reversed CD4/CD8 ratio. In liver biopsy, the prominent feature was chronic active hepatitis. Lack of acid fast bacilli and hemophagocytosis in liver biopsy was supported by two pathologic-cytologic clinical laboratories. Also a second bone marrow aspiration did not detect hemophagocytosis. We repeated all laboratory evaluations ten days after admission. At this time the following values were observed: TG: 794 mg/dl (normal range <110 mg/dl), ferritin: 1135 µg /l (normal range: 25-200 µg /l) and fibrinogen was less than 2 g/dl (normal range: 2.5-4 g/dl). Therefore, the patient fulfilled five of the eight diagnostic criteria for HLH including fever, splenomegally, hypertriglyceridemia/hypofibrinogenemia, cytopenia and hyperfrritinemia (Table 1). Unfortunately, 14 days after admission, despite supportive therapy, the patient expired and her parents did not agree with an autopsy.

Discussion

HLH is a disease characterized with macrophage mediated destruction of hematopoietic elements[1, 6] and consists of primary and secondary HLH. The age of onset for FHLH is less than one year of age in 70% of cases but it can rarely be observed in the first two weeks of life[1, 7]. Clinical manifestations of our case (fever, splenomegally, pancytopenia) suggested these differential diagnoses: FHLH, metabolic disorders and immune deficiency syndromes. Considering the positive familial history of death in her sibling with similar presentation and familial relationship of parents, FHLH was the first suspected diagnosis[1, 8]. Some metabolic diseases like lysinuric protein intolerance [1, 9] have a similar clinical presentation with HLH. Therefore we checked our patient's metabolic profile including serum levels of lactate, ammonia, pyruvate and also chromatography of amino acids and sugars in blood and urine. All the results were normal therefore metabolic disorders were ruled out. Because the presence of palpable axillary lymph nodes in our patient after BCG injection could be a sign of immune deficiency syndrome, we performed bone marrow flow cytometry immunophenotype analysis. The results were not specific and did not support this diagnosis. Considering some reports about association between tuberculosis and secondary HLH [1, 3, 10], PCR and culture of CSF, liver biopsy, bone marrow aspiration and ascitis fluid were performed. No evidence of TB was found. The clinical findings in children with infection associated HLH are similar to those in FHLH [1].The most

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***Table 1**. Diagnostic criteria for HLH as outlined by Henter et al.* [6]

The diagnosis of HLH can be established if 1of either 2 below is fulfilled:

A) A molecular diagnosis consistent with HLH

B) Diagnostic criteria for HLH fulfilled five of eight criteria below:

1- Fever

2- Splenomegaly

3- Cytopenia (affecting >2 of 3lineages of peripheral blood): Hb <9 gr/dl (infants <4 weeks Hb<10 gr/dl) Plt < 100 $\times 10^9$ /l, noutrophils< 1×10^9 /l.

4- Hypertriglyceridemia and / or hypofibrinogenemia: fasting TG >265 mg/dl fibrinogen <1.5 gr/dl

5- Hemophagocytosis in bone marrow or spleen or lymph nodes without evidence of malignancy

6- Low or absent natural killer cell activity

7- Ferritin > 500 µg /l

8- Soluble CD25 (IL2 receptor) > 2400/ml

***Table2.** Five of the eight criteria for FHLH in our patient*

1-Fever

2-Hepatosplenomegaly

3- Bicytopenia with a total white count at 6.1×10^3 / µl , and 14% PMN (absolute neutrophil count :714), Hb: 8.7 gr/dl and platelet count:55×10^3/µl

4-Ferritin: 1135 µg /l (normal range: 25-200 µg /l)

5- TG: 794 mg/dl (normal range <110 mg/dl), fibrinogen was less than 2 g/dl (normal range: 2.5-4 g/dl).

common agents causing this syndrome are viruses, predominantly the herpes group viruses including EBV, HSV and CMV [1, 10, 11]. A search for these etiologic agents were performed in our patient .She was found to be negative for EBV, HIV, CMV and rubella virus.

A distinctive diagnosis of FHLH can be made if there are genetic defects involving the perforin gene on chromosome 9q21.3 locus (FHLH type 1), 10q 21-22 mutations (FHLH type 2)[1]. Perforin acts by perforatings the cytolytic target cell membrane and in turn initiates the apoptotic cell death pathway [1, 9]. The other genetic defects are inactivation of the MUNC 13-4 gene which is essential for cytolytic granule fusion at chromosome 17q 25 (FHLH type 3)[1, 6] and mutations in syntaxin 11 gene which is located on chromosome 6q24[12]. Hemophagocytosis might be found in the first bone marrow aspiration of a FHLH patient but the absence of it will not rule out this diagnosis. Previous reports of FHLH [11, 13] without hemophagocytosis have been published. As a result, if the bone marrow is not conclusive, material should be obtained from other organs (liver, spleen or lymph nodes) and serial aspirates over time may also be helpful[1].

In our case, the bone marrow aspiration was performed two times and liver biopsy one time revealing no site of hemophagocytosis. At the end after ruling out other diagnoses and considering the fact that our patient had five of the eight criteria for FHLH (fever, spelnomegaly, pancytopenia, hypertriglyceridemia, hyperferritinemia and hypofibrinogenemia), we decided that FHLH is the most probable diagnosis. It is important to consider the fact that none of these eight criteria are specific for FHLH diagnosis and might be found in sepsis, SIRS and MODS[3, 14, 15]. For example the etiology of hypertriglyceridemia in these states can be multifactorial such as insulin resistance [16, 17] and inhibition of lipoprotein lipase activity [18, 19]. High level of serum ferritin has also been associated with inflammatory states and is frequently seen in toxic patients due to the up regulation of hemoxygenase-1 (heat shock protein)[20, 21] that is a response to inflammatory process. Ferritin is also an antiapoptotic agent in ischemia-reperfusion injury [22]. Elevated soluble IL2 receptor (CD25) is also observed in sepsis, SIRS and can be a predictive marker in neonatal sespsis [23, 24]. Similar to HLH disease, NK-cell activity is also decreased in septic patients and in thermal injury[25].

The fact that our patient had five of the eight criteria for FHLH as outlined by Henter et al. , a positive familial history of death in her sibling with similar presentation, familial relationship of parents -plus ruling out other probable differential diagnosis guided us to believe that FHLH is the best diagnosis

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despite the absence of hemophagocytosis. In this decision we realized that this set of criteria in the absence of hemophagocytosis is very broadly designed and might be found in other conditions like MODS or BCGosis.

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