MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 5(4) pp. 197-201, April, 2017
Available online http://www.meritresearchjournals.org/mms/index.htm

Case Report

Hemophagocytic lymphohistiocytosis (HLH): Case Report

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Abstract

Hemophagocytic lymphohystiocytosis (HLH) represents a severe hyper-inflammatory condition with the cardinal symptoms prolonged fever, hepatosplenomegaly, and cytopenias. The most prominent histopatho-logical feature of HLH is an accumulation of activated T lymphocytes and macrophages predominantly in lymphoid tissues. Although it can occur in all age groups, neonatal-onset HLH is very rare. The present study reported a case of HLH presenting with anemia and hepatosplenomegally at age of two month.

Keywords: Hemophagocytic lymphohistiocytosis, neonatal-onset.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare life threatening disorder presenting with high fever, hepatosplenomegaly, pancytopenia, liver dysfunction, hypertriglyceridemia, and hemophagocytosis in the bone marrow, spleen, or lymph nodes. HLH comprises two different conditions: primary or genetic HLH, and secondary or acquired hemophagocytic syndrome (secondary HLH, sHLH). These two forms may be difficult to distinguish from one another (Henter, et al., 2007). Familial hemophagocytic lymphohistiocytosis (FHL) is a subgroup of genetic HLH inherited in an autosomal recessive manner. The incidence has been estimated to 1.2/1.000.000 children per year, i.e. 1:50.000 live-born. Most children develop the disease very early in life with around 70% less than 1 year of age at onset. FHL may also present at birth or even at prenatal investigations. Several genetic defects underlying FHL have been discovered recently and have elucidated the pathophysiology of the disease (Janka and zurStadt, 2005). Without treatment, FHL is invariably fatal, with a median survival of 2 months after diagnosis.

The present work presents a two-month-old male infant with very early neonatal presentation. The patient was referred to our hospital as a case of leukemia versus viral infection and accompanying anemia for ten days prior to diagnosis of HLH.

MATERIAL AND METHODS

Biochemical and Antioxidant Analysis

Blood samples were collected by cardiac puncture, allowed to clot and then centrifuged at 3,000 rpm for 15 minutes to separate serum. Serum kept at -20℃ until required. The activities of aspartate aminotransferase (AST), and alanine aminotransferase (ALT), by using commercial kinetic kits (Prolabo, France) and expressed as (U/L). For kidneys function determination; urea was determined according to the method of Patton and Crouch (1977), creatinine was determined following the method of Young et al. (1975), and uric acid was determined by the method of Schirmeister et al. (1964); and expressed as (mg/dl). IgA, IgG, and IgM are often measured together. That way, they can give doctors important information about immune system functioning, especially relating to infection or autoimmune disease.

Hematological Methods

Blood was collected by cardiac puncture. The collected samples of blood from control and experimental groups were processed for carrying different hematological

studies according to Dacie and Lewis (1984).

Evaluation of Total Erythrocytes Count (RBCs)

The RBCs were counted by means of Hemocytometer apparatus, using a diluting fluid of 0.9 % saline. The number of red cells in 5 secondary squares (80 tertiary squares) was recorded in Neubauer chamber, multiplied by a factor "N x 10,000" which determines the number of red blood corpuscles in 1 mm^3 of blood.

Determination of Hemoglobin Concentration (Hb)

The Sahli's method was presently applied by a Sahli Adam's hemoglobinometer. Appropriate dilutions with N/10 hydrochloric acid were conducted and readings were taken in gm/ml of blood.

Evaluation of Total Leukocytes Count

With the use of Neubauer chamber and Tarek's solution as a diluting fluid (Miller, 1960), the leukocytes count was performed in 16 median squares. The obtained number of white cells was multiplied by a factor "N x200" which determines the number of cells in 1mm^3 of blood.

Case Report

A two months old boy was referred to maternity and children hospital in Dammam from private hospital with generalized lymphadenopathy and pancytopenia for further investigation. He is products of normal uncomplicated delivery with birth weight around two kilograms and discharged with his mother in good condition. No history of ICU admission. Ten days prior to admission he had frequent vomiting and history of fever on and off. Parents seek medical advice in private hospital and found to have generalized lymphadenopathy and splenomegaly. Also he had microcytic anemia and thrombocytopenia which they were thinking he may have leukemia or viral infection for that they referred him to our hospital.

Parents are 1st degree cousin, mother is 21 years old; known case of iron deficiency anemia for which she was treated by injectable iron supplement. Also she had urinary tract infection in last trimester which was treated by antibiotics.

The patient was pale but not jaundice with no dysmorphism. He had generalized lymphadenopathy (occipital, axilliary and inguinal) ranging from 1 to 2 cm not tender not matted with normal skin overlying. His abdomen was distended with spleen 4 cm below costal margin and liver 7 cm below costal margin.

The laboratory findings were as follows: CBC: WBC 18.3, ANC 1290 (mild neutropenia), Hb 5.8, Plt 92000 hematocrits 16.6. Peripheral blood film showed microcytic hypochromic anemia, tiny RBC view fragmented RBC, mild neutropenia 1200, lymphocytosis 15000. Liver and renal function test was within normal range. Fibrinogen 141, serum ferritin 1060, cholesterol 113, AHDL 5, triglyceride 964.

TORCH screening: TOXO –ve, Rubella IgG +ve, HSV1 IgG +ve&IgM –ve, HSV2 IgG –ve&IgM –ve, CMV antibodies IgG +ve&IgM –ve, EBVIgG +ve&IgM –ve.

Immunoglobulin IgG 470, IgA 7.66, IgM 77, and IgE 13.3. Brain CT was normal. Abdominal ultrasound showed enlarged liver and spleen with lymph node noted. Bone marrow aspiration showed: peripheral bicytopenia, erythroid hyperplasia and increase hemophagocytic activity of bone marrow. So the diagnosis of Hemophagocytic lymphohystiocytosis (HLH) was established and patient referred to tertiary hospital urgently for management.

DISCUSSION

HLH encompasses a heterogeneous class of rare but potentially fatal disorders characterized by multisystem inflammation, which results from prolonged and intense activation of antigen- presenting cells (macrophages, histiocytes) and CD8+T-cells, and excessive proliferation and ectopic migration of T-cells (Filipovich, 2008). It comprises two different conditions: primary or genetic, and secondary or acquired form. Genetic HLH is inherited in an autosomal recessive or X-linked fashion and can be divided into two subgroups: familial hemophagocytic lymphohystiocytosis (FHL) in which the clinical syndrome of HLH is the only manifestation, and HLH associated with inherited immune deficiencies Chediak-Higashi syndrome, Griscelli syndrome, and X-linked lymphoproliferative syndrome which have distinctive clinical features besides the sporadic development of HLH (Janka, 2007; Sieni et al., 2014).

Acquired (secondary) forms of HLH may develop as a result due to strong immunological activation of the immune system, which may be caused by a severe infection and malignancy. Leading triggering agents in infection-associated hemophagocytic syndrome (IAHS) are viruses of the herpes group, especially EBV and CMV. Acquired HLH in association with malignant disease (malignancy-associated hemophagocytic syndrome, MAHS), especially lymphomas, can develop before or during treatment. Macrophage-activation syndrome (MAS) is a special form of HLH which occurs in children and adults with autoimmune diseases (Janka, 2007).

Despite attempts to differentiate primary from secondary HLH, the clinical presentation is highly overlapping (Filipovich, 2008). Prolonged fever (>7 days)

Table 1. Revised diagnostic guidelines for hemophagocytic lymphohystiocytosis

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled
(1) A molecular diagnosis consistent with HLH
(2) Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
(A) Initial diagnostic criteria (to be evaluated in all patients with HLH)
Fever
Splenomegaly
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):
Hemoglobin <90g/L (in infants <4weeks: hemoglobin <100g/L)
Platelets <100x10 /L
Neutrophils <1.0 x10 /L
Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides
Fasting triglycerides >3.0 mmol/L (i.e 265mg/dl)
Fibrinogen ≤1.5g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
(B) New diagnostic criteria
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin ≥500 mg/L
Soluble CD25 (i.e. soluble IL-2 receptor) 2.400 U/mL

and hepatosplenomegaly are cardinal findings. Neurological symptoms may dominate the initial clinical course, including irritability, seizures, hypo- and hypertonia, cranial nerve palsies, and altered consciousness. Lymphadenopathy, skin rash, jaundice, edema, and diarrhea are less frequent. In the early days to months of the disease, symptoms may improve spontaneously, followed by exacerbationsas reported by Filipovich (2008). Characteristic laboratory findings are cytopenias, especially anemia and thrombocytopenia, coagulopathy with hypofibrinogenemia, and hypertriglyceridemia. Liver dysfunction, hypoal-buminemia, elevated lactate dehidrogenase, and hyponatremia are often present (Henter, et al., 2007; Filipovich, 2008). Two highly diagnostic parameters are an increased plasma concentration of the alpha chain of the soluble interleukin-2 receptor (sCD25), and impaired NK cell activity. In patients with FHL, NK cell number is normal, but the activity is persistently decreased or absent. Patients with acquired HLH may have low NK cell number; NK cell function is decreased with active disease, but usually reverts to normal after treatment (Janka, 2007). A lumbar puncture is also recommended as part of a diagnostic workup, and more than half of patients will have a moderate pleocytosis and/or increased protein content, even in the absence of neurological symptoms. The caution with lumbar puncture must be taken with regard to a possibly increased intracranial pressure (Janka and ZurStadt, 2005). All patients should have a bone marrow aspiration. However, frank hemophagocytosis may not be observed early in the course of the disease, and serial marrow aspirates may be helpful. Genetic studies showed that familial form of HLH may result from mutations in different proteins involved in granule exocytosis and perforin-dependent induction of target cell apoptosis, mediated by NK-cells and cytotoxic T lymphocytes. Depending on the geographical and ethnic origin, 15 to 50% of patients with FHL (also referred to as FHL2) have mutations in perforin gene PRF1 at locus 10q24 that lead to impaired perforin production. Perforin is a soluble cytolytic protein; it is able, in the presence of calcium, to perforate into the membrane of a target cell, where it polymerizes to form a cell death-inducing pore. UNC13D mutations, at locus 17q25, account for 15 to 20% of FHL (also referred to as FHL3). Encoding protein Munc13-4 is essential for priming of secretory vesicles and the subsequent release of cytolytic enzymes. Recently, a third gene defect responsible for FHL4 has been identified in Turkish families on chromosome 6q24 with mutations in STX11. The encoded protein, t-SNARE sintaxin 11 (Machowicz et al., 2016), facilitates fusion in intracellular membrane trafficking events(Janka, 2007; Filipovich, 2008). (Table 1)

The revised diagnostic criteria for HLH, based on the recommendations of the Histiocyte Society, are summarized in Table 1. In the absence of a family history or specific molecular diagnosis, an assemblage of at least five of the eight diagnostic criteria are needed for a diagnosis of HLH and initiation of therapy.HLH is a challenging condition not only to diagnose but as well as to treat. The immediate aim of the treatment is to suppress life threatening hyperinflammation, caused by excessive levels of cytokines (Janka, 2007). Another aim is to kill pathogen-infected antigen-presenting cells, and thus to remove the stimulus for the ongoing activation of

T-cells. The need to treat coexisting infections as potential triggers of HLH is obvious, but usually not sufficient to control hyperinflammation (Machowicz et al., 2016).

The overall prognosis for patients with HLH has improved dramatically during the last decades as has the biological understanding of the disease. Current international HLH 2004 protocol is designed for all patients with newly diagnosed HLH, with or without evidence of familial or genetic disease, and regardless of suspected or documented infection1. The protocol represents systemic chemo-immunotherapy including dexamethasone, cyclosporine A, etoposide upfront, and, in selected patients, intrathecal therapy with methotrexate. Corticosteroids show cytotoxic effect and inhibit expression on cytokines. In pediatric protocols dexamethasone is preferred than prednisolone since it crosses the blood brain barrier better. Cyclosporine A prevents T-lymphocyte activation. Etoposide is an antineoplastic agent highly effective in monocytic and histiocytic disorders. Intrathecal methotrexate is used only in patients with persistently abnormal cerebrospinal fluid or progressive neurological symptoms (Janka and ZurStadt, 2005). The overall 3-year disease-free survival is 55% (Filipovich, 2008).

In genetic HLH the ultimate aim must be hematopoietic stem cell transplantation (HSCT) to replace congenitally defective immune system with normal functioning immune effector cells of healthy donors. Whereas FHL was uniformly fatal without HSCT, with this protocol the overall survival rate is 58 to 64% (Cesaro et al., 2008).

Although HLH can occur in all age groups, neonatal onset within 4 weeks after birth is rare, accounting for 4% of all HLH cases (Isaacs, 2006). Most patients have been published as case presentations or included in childhood HLH studies, and there are very few reported series (Gurgey et al., 2008; Suzuki et al., 2009). The frequency of primary and secondary HLH neonatal cases have not been well defined, and are sometimes indistinguishable from one another clinically and histologically (Isaacs, 2006). The diagnosis is frequently delayed, made on autopsy or missed completely. The course of neonatal HLH is quite devastating with high mortality13. Chemoimmunotherapy results in the control of the disease in some cases; however, remission is rarely sustained. The only reported survivors were those who received conventional therapy followed by HSCT (Isaacs, 2006; Suzuki et al., 2009). The patient presented with severe anemia, hepatosplenomegally and fever on and off since age of two months. During the second month of his life he developed typical findings for HLH, but episodes of fever were misinterpreted as systemic infection, although repeated microbiological examinations (bacterial cultures and serologic tests) were negative. All HLH neonatal reports emphasize the difficulties in establishing the diagnosis, as HLH may mimic a number of other diseases most frequent being congenital infection, sepsis, inherited metabolic disorders or hemochromatosis. Immunoglobulins down-regulate proinflammatory cytokines, block Fc receptors on macrophages, suppress inducer T and B-cells, and augment suppressor T-cells (Schwartz, 2009). They have been mainly used in adults with HLH (Emmenegger et al., 2005). Although molecular analysis did not reveal any known genetic defect, very early presentation, serious clinical course, the lack of infectious or immunological triggering, and a family history with consequent marriage, suggest that the presented case more likely suffered familial HLH. As specific genetic defects account for less than one half of FHL, we can only speculate that reported FHL case is caused by mutations in as yet unidentified genes. This patient is noteworthy for the presentation in the first months of life. Previous reports from the literature have shown that patients with FHL were usually born healthy but became ill in the first 2 to 6 months of life (Isaacs, 2006). In the present case HLH masqueraded as leukemia versus systemic infection in the beginning. We suggest that HLH should be considered in the differential diagnosis of multisystem organ involvement in newborns, especially when no infectious or metabolic cause can be found. Ferritin, fibrinogen and triglycerides measurements should be routinely determined in these patients. In the presence of cytopenias and hyperferritinemia, referral to the experienced hematologist is highly recommended. The absence of hemophagocytosis in bone marrow should not be a reason to rule out the diagnosis of HLH, as finding in up to two thirds of initial bone marrow aspirates may be nondiagnostic. If hemophagocytic activity is not proven in bone marrow, material may be obtained from other tissues, or serial marrow aspirates over time may be required to document hemophagocytosis.

CONCLUSION

Early establishment of the diagnosis of HLH has very important implications for timely commencement of the treatment, before overwhelming disease activity makes irreversible damage and a response to treatment less likely. Because neonatal HLH can be rapidly fatal without specific intervention, it is recommended to start a treatment when a high clinical suspicion exists and results of diagnostic studies are still pending (Filipovich, 2008). HSCT should be performed as early as possible, when an acceptable donor is available. Genetic counseling and family planning is of utmost importance. Subsequent pregnancies should be closely monitored and offspring referred for genetic testing.

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