Hemophagocytic Lymphohistocytosis-Familial Type

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Abstract *- HLH is not a single disease entity but rather a syndrome of clinical signs and laboratory abnormalities that result from the uncontrolled proliferation and activation of cells of the monocyte/macrophage lineage. HLH is broadly divided into 2 forms: familial (FHL) and secondary(sHLH). We present a case of 2 months 4 days old male infant, 2nd-degree consanguinity, who was clinically suspected of HLH. A diagnostic workup is suggested. Familial HL type 2 with genetic testing showing Perforin Expression on CD56 + NK Cells.*

Keywords *- HLH(Hemophagocytic lymphohistiocytosis), FHL -Familial HLH, sHLH- Secondary HLH.*

I. INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is one of type of histiocytosis with morphologically normal reactive macrophages with prominent erythrophagocytosis and CD8+ T cells. There is uncontrolled hemophagocytosis (Ingestion of RBCs by activated macrophages) and uncontrolled upregulation of inflammatory cytokines with some similarities with Macrophage Activation Syndrome[(1).] There are two major types of HLH with indistinguishable pathologic findings but are important to distinguish because of its implication in the treatment and prognostication of the condition. Primary HLH also known as familial HLH, was originally named as familial erythrophagocytic lymphohistiocytosis. Another form of HLH is known as an infection-associated hemophagocytic syndrome and is recognised as secondary HLH. Both are cahracterised by the infiltration of multiple organs by hyperactive lymphocytes and activated phagocytic macrophages[(2,3).]

As a result of inherent intrinsic defects in the patient with FHL, even a common viral infection can provoke uncontrolled hyperinflammatory immune response functions of multiple proteins that participate in lymphocyte cytotoxicity are disturbed because of mutations in genetically heterogeneous individuals. FHL is classified on the basis of different loci namely FHL-1 to FHL-5. Gene responsible for FHL-2(Perforin), FHL-3 (Mammalian homologue of Caenorhabditis elegans, Unc 13), FHL-4 (Syntaxin-11), FHL-5 (Syntaxin binding protein-2) have been identified whereas gene for FHL-1 is unknown. The prevalence of FHL is 1 In 50,000 Live Births. As it is X –linked l lymphoproliferative disorders males are more affected. [(4).]

2. CASE PRESENTATION

A 2-month 4day old male infant, born by 2nd-degree consanguinity brought with complaints of cough, cold, and fever for a week.

On admission child was febrile (103deg F), irritable, pallor, tachycardia (164/min), and tachypnoea (64/min) with a saturation of 98 percent with O2 by the hood. Respiratory distress in form of tachypnoea and subcostal retractions were present. Per Abdomen Liver was 6cm, firm, non-tender, with a liver span of 8 cm. Spleen was 7cm, soft to firm, non-tender. CVS -no murmur, CNS –no neuro deficit.Investigations were done, CBC s/o Hb 8 g/dl, platelets 96000 lakh/cumm, TLC of 2300.

3. INVESTIGATIONS

In view of the above differential diagnosis, further investigations were planned: which showed very high levels of Serum Ferritin 24980 ng/ml, CXR PA view was Normal, Vertebrae and Humerus showed black shadow suggestive of the presence of marrow, Coagulation was deranged in the form of prolonged PT/PTTK, Hb Electrophoresis showed normal AA2 pattern, KFT was Normal, LFT: SGOT:600 U/L, SGPT: 189UNITS/L.

Gastric aspirate for AFB and ZN Stain showed no AFB. ABG was normal and absence of glucose and reducing substances in the urine. Macroerythtophagocytosis were seen on bone marrow with no Gaucher cells.

4. AFTER LABORATORY WORKUP HLH WAS CONFIRMED.

Further workup was done to differentiate between primary versus secondary HLH.

1. Immunodeficiency test

Lymphocyte subset analysis: Normal
Nitro blue tetrazolium test(NBT) : Normal

2. HLH- genetic workup

HLH test-Perforin Expression on CD56 + NK Cells: Absent perforin expression.
Granule release assay (GRA): Was not defective.

5. DIFFERENTIAL DIAGNOSIS

With organomegaly and pancytopenia in an Infant, the following differential diagnosis was thought of- storage disorder with sepsis; osteopetrosis with sepsis; HLH (HLH suspicion was in accordance with HLH- 2004 Revised diagnostic guidelines, fulfilling 5/8 criteria) [(5);] Beta Thalassemia Major.

6. TREATMENT

Immune suppressive therapy is the main modality for the treatment of HLH, hence Methyl Prednisolone Pulse therapy was started and Antibiotics were started (Injection Piperacillin-Tazobactum with Amikacin) on admission were continued

7. OUTCOME AND FOLLOW-UP

As per the investigations, the diagnosis of Familial HLH type 2 was confirmed. The patient was referred to a higher center for Stem Cell Transplant. Currently, the patient is in regular follow-up at a higher center.

8. DISCUSSION -INCLUDE A VERY BRIEF REVIEW OF SIMILAR PUBLISHED CASES

As opposed to the name, Infection-associated hemophagocytic syndrome is not associated with an identifiable infectious cause. Whereas FHL is commonly followed by an identifiable infection [(6)]

FHL is mainly a disease of early childhood. 70% of cases occur in infancy. Such children are normal at birth and have normal growth till they acquire common childhood infections. [(7).] Sensitivity and specificity of serum ferritin level > 10,000 microg/L is 90% and 96% respectively for HLH [(8).] Mutations in the gene that encodes perforin (PRF1) cause FHL-2, wherein 257,258 Perforin is a component of T-lymphocyte and NK cell cytotoxic granules which is similar to the pore-forming complement component C9. Hence, it also facilitates lysis[(9).]

Mortality of FHL is very high if not treated promptly as it progresses rapidly in one to two months. According to the current Histiocyte Society HLH-1994 and HLH-2004 protocol, combination therapy with etoposide, corticosteroids, cyclosporine, and intrathecal methotrexate is used for treating Primary HLH. Pancytopenia and the presence of an infection are not contraindications to cytotoxic therapy, as we have to reach the point of initiating stem cell transplantation. To date, this is the only known potentially curative treatment for primary HLH and is effective in achieving a cure in >60% of patients. Chemotherapy is inadequate for a sustained cure of primary HLH, which is ultimately fatal without transplantation[(10).] Treatment is aimed at the destruction of activated CD8+ T lymphocytes and macrophages and taking care of triggers and suppression of hyperinflammatory status. Accurate diagnosis of HLH is essential as early treatment can reduce the high morbidity and mortality leading to early referral to higher centers for stem cell transplantation.

9. LEARNING POINT / TAKE HOME MESSAGES 3 BULLET POINTS

- HLH is a fatal disease. Hence though familial HLH is rare it should be considered a differential diagnosis in a male infant with pancytopenia and organomegaly.
- As genetic diagnosis is feasible in this era, a detailed molecular anaylasis should be done to categorize primary HLH.
- Genetic diagnosis can help families with precise genetic counseling and prenatal diagnosis for future pregnancy.

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