Original Research Paper

Volume-9 | Issue-3 | March-2019 | PRINT ISSN - 2249-555X

Paediatrics

A CASE REPORT OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SYNDROME (HLH)

Dr S Srilatha Assistant professor, Department of paediatrics, Government General Hospital, Kurnool-518001, Andhra Pradesh

Dr S Padmapriya* Junior resident, Department of paediatrics, Government General Hospital, Kurnool-518001, Andhra Pradesh *Corresponding Author

Dr R Murarji Junior resident, Department of paediatrics, Government General Hospital, Kurnool-518001, Andhra Pradesh

ABSTRACT Childhood histiocytoses constitute a diverse group of disorders, which although individually rare, are frequently seen in their clinical expression, of which HLH is uncommon, a life threatening hyper inflammatory syndrome. We report a case of Hemophagocytic Lymphohistiocytosis in a 5 year old boy.

KEYWORDS : Chromosomal abnormality, Bad obstetric history, genetic counseling.

INTRODUCTION

HLH is an uncommon hematologic disorders seen more often in children than in adults. It is a disease of severe hyper inflammation caused by uncontrolled proliferation of activated lymphocytes and macrophages characterised by proliferation of morphologically benign lymphocytes and macrophages that secrete high amounts of cytokines. It is a fatal syndrome with high grade fever, organomegaly and characteristic laboratory abnormalities like pancytopenia, coagulopathy, hyper inflammation, hyper triglyceridemia, hemophagocytosis [1-4].

It was first described in 1939 by Scott and Robinson and considered a malignant histiocytic reticulosis[5] initially. Farquhar and claireaux correctly described in 1952. [6]Risdall in 1979 first recognised HLH secondary to viral infection and coined the term Viral Associated Hemophagocytic Syndrome (VAHS). Most common infections which trigger HLH are EBV, CMV[7, 8], HSV, HHV, Kochs, salmonella, malaria, kala azar in India but virtually any infection can trigger HLH[9,10].

Case report

5 year old boy born for a nonconsanguinous couple, referred from outside presented with c/o fever for 10 days. Fever was high grade associated with chills, relieved by taking medication. It was not associated with any rash, joint pains. No h/o cold, cough, ear discharge, head ache, vomiting, loose stools, malena, burning micturition, abdominal pain, puffiness. No h/o malaria, dengue in the surrounding areas. No h/o TB contact.

At admission vitals were PR-106/min, RR-24/min, BP-100/60mm Hg, CVS-S1 S2 +, RS- BAE+, P/A- soft, liver 2 cms ↓ RCM and spleen 2 cms ↓ LCM soft to firm in consistency, non tender, CNS- conscious, no anemia, lymphadenopathy. Outside reports were platelet counts-30,000, PS for MP-negative, Widal test-1:80 dilution. Platelets were repeated on D2 of admission and counts were 28,000. On D4 of illness persistent high grade fever was present, child was sick looking, P/A-spleen was 4 cms with firm to hard consistency. CBP showed pancytopenia. At this time thought of complicated malaria and child was put on inj. Artesunate. On D6 of admission mother complained of persistence of fever, malena, epistaxis. Petechiae and purpura were present. CBP showed 9,000 platelet count. For PT, APTT, INR not done because of financial constraints. Child was given FFP and PRP, and fresh whole blood. On D7 of illness suspected HLH secondary to infection, serum ferritin and serum triglycerides were sent. And child was started on inj. Methyl prednisolone and IV immunoglobulins. Two days later fever spikes decreased and platelet counts were increasing. Bone marrow was done 7 days later as thrombocytopenia was present.

Date	Hb	WBC	Platelets
7/2	7.8	3700	30000
8/2	7.4	3700	28000
9/2	6.6	3300	27000
12/2	6.1	1500	9000
13/2	4.9	1300	13000
14/2	7.5	1200	9000
15/2	6.8	1200	7000
17/2	6.9	1800	17000
18/2	7.3	2100	29000
20/2	7.5	3000	35000
22/2	8	5000	56000

Other investigations:

Peripheral smear : severe degree of microcytic hypo chromic anemia with leucopenia and thrombocytopenia with retic count 0.01% s/o pancytopenia with bone marrow suppression.

Widal test negative, CUE- N, Sickling test was negative, and urine cultures were negative HBsAg, HIV, HCV negative, Dengue serology NS1Ag positive and IgM positive Serum ferritin- >2000ng/mL, Serum triglycerides- 226 mg/dL

Bone marrow aspiration

Bone marrow taken from posterior superior iliac spine under aseptic conditions.

Erythroid lineage: Hypo cellular , increased number of cells with normoblastic reaction.

Myeloid lineage : N
Lymphoid lineage: N, with increase in number of Histiocytes (5 were present) , showing hemophagocytosis.
Plasma cells : N
Impression : mild hypo cellular bone marrow with Hemophagocytosis and Lymhohistiocytosis.

DISCUSSION

HLH also known as hemophagocytic syndrome, characterized by fever, organomegaly, hemophagocytosis in bone marrow, liver, lymphnode.

Pathogenesis

Hallmark of HLH is defective NK cell and cytotoxic T cell activity. NK cells and cytotoxic T cells are recognized morphologically as large lymphocytes with azurophilic granules in wrights preparation. NK cells are components of innate immunity and cytotoxic T cells are components of acqiured immunity. MHC 1 molecules inhibit NK cells and cytotoxic cells.

Classification

Primary HLH:

Most common perforin gene mutations are present. Perforin perforates target cell membrane and induce apoptosis by activating apoptotic mechanisms[11]. Inactivity to kill target cells by NK cells and cytotoxic cells, there is excessive stimulation of immune system with increase in antigen presentation and increase in T cell proliferation with infiltration of various organs like CNS, liver, spleen, lymphnode. This results in hyper cytokine storm producing TNF alfa, INF gamma, IL-1,

GM-CSF.

Secondary HLH:
In most cases of secondary HLH cytotoxicity and cytotoxic lymphovyte degranulation are not impaired[12]. There is increased APC activation that disrupts the balance between APC activation and CTL mediated control.

Causes of secondary HLH:
Infections :
Viruses- EBV, CMV, HHV-6, HHV-8, HIV, adeno, parvo, hepatitis.
Bacteria- kochs, salmonella.
Parasites-malaria, kala azar

Malignancies:
Leukemia, lymphoma, GCT

Autoimmune diseases:
SLE, systemic sclerosis, sjogrens syndrome.

Clinical features
Presentation of HLH in initial period is nonspecific and confused with common infection, autoimmune disorders and malignancy. HLH typically presents with prolonged fever, unresponsive to antibiotics, hepatosplenomegaly, rash, lymphadenopathy, cytopenias, liver dysfunction, hypofribinogenemia, hypoalbunimeia, hypertryglyceridemia, hyponatremia.

In 1987, histocyte society defined a set of diagnostic criteria (table 1).

Table 1: diagnostic guidelines for HLH[13,14]
Diagnosis of HLH if either 1 or 2 below is fulfilled
A molecular diagnosis consistent with HLH
Diagnostic criteria for HLH fulfilled (five out of 8 criteria below)
Clinical criteria
Fever
Splenomegaly
Laboratory criteria
Cytopenias
Hypertryglceridemia, hypofibrinogenemia
Hemophagocytosis in bonemarrow/spleen/lymph nodes
New diagnostic criteria
Low or absent NK cell activity
Ferritin >500µg/L
Soluble CD25 >2400 U/mL.

The criteria subsequently was revised by Filipovich et al in 2009 (table 2). The HLH must be suspected in setting of rapidly evolving cytopenias, LFT dysfunction, organomegaly, coagulopathy. Therefore it is prudent to ask for serum ferritin and triglycerides. If ferritin >500 ng/mL a bone marrow is done to rule out.

Table 2: Filipovich HLH diagnostic criteria[15]
Molecular diagnosis of HLH or XLP OR
at least 3 of 4
fever
splenomegaly
hepatitis
cytopenias
and atleast 1 of 4
hemophagocytosis
hyperferritinemia
increased soluble IL2R alpha
supportive of HLH
hypertryglyceridemia
hypofibrinogenemia
hyponatremia

Work-up for patient of HLH[14]:
Laboratory evaluation of HLH is directed with following consideration:
Establish diagnosis of HLH
Cbp platelet
ESR
PS (look for peripheral blood HLH)
LFT
LDH
Creatinine
Serum electrolytes
Serum ferritin
Serum triglyceride
Coagulation profile (PT, APTT, plasma fibrinogen, D- dimer)
CSF for pleocytosis and elevated proteins.

Supportive evidence for HLH
Bone marrow aspiration, liver biopsy

Sophisticated lab investigations
Scd25 >2400 IU/L
NK cell activity (may be normal in 30 % of cases)
Serum beta 2 micoglobulin

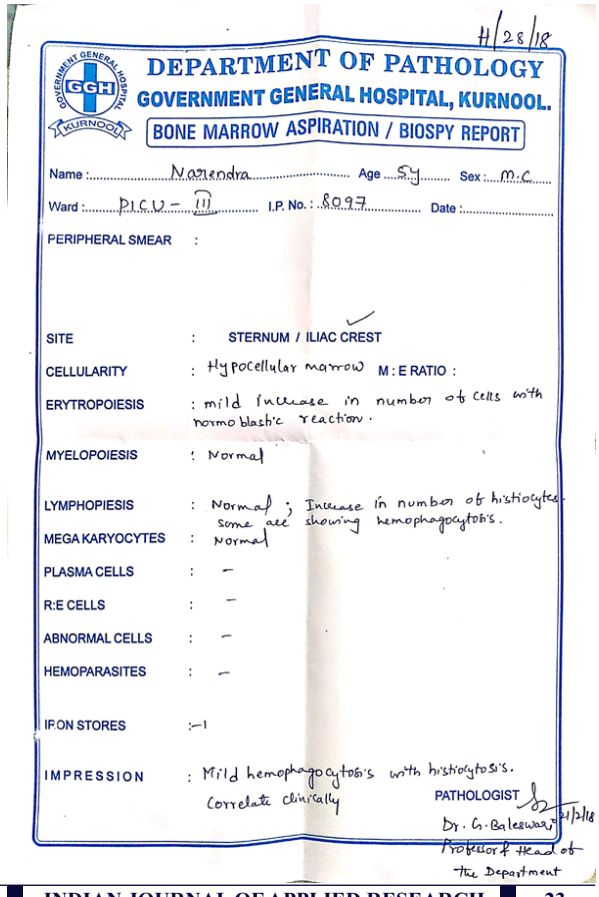
Etiological work-up
Anti EBV VCA IgM, PCR
Anti CMV Abs, antigen, PCR
Appropriate microbiological cultures
Hair mount studies for pigmentary dilution disorders

Work-up for familial HLH
Perforin by flow cytometry
Granule release assay
Gene sequencing to identify mutations.

Management[12]
Initial therapy
Dexamethasone, 10mg/m^2/day for 2 weeks followed by a decrease every 2 weeks to 5 mg/m^2, 2.5 mg/m^2, and 1.25 mg/m^2 for a total of 8 weeks. Patients with nonfamilial disease of HLH continuation therapy is suggested only if the disease is active after the initial therapy. If there is poor response to 4 weeks of HLH protocol, started on salvage treatment with ATG, fludarabine, alemtuzumzab, daclizumab, anti TNF alpha receptor blocking agents, etc.

Continuation therapy
It is given for 9-40 weeks if there is familial HLH with dexamethasone pulses every second week, 10 mg/m^2 for 3 days.

Poor prognostic factors: degree of CSF pleocytosis, severity of thrombocytopenia, hyperbilirubunemia, hyperferritinemia, HLH associated with EBV infection with high viral load, persistent fever are associated with poor outcome[16].


11/28/18

DEPARTMENT OF PATHOLOGY
GOVERNMENT GENERAL HOSPITAL, KURNOOL.
BONE MARROW ASPIRATION / BIOSPY REPORT

Name : Narendra Age : 5y Sex : M.C
Ward : PICU - III I.P. No. : 8097 Date :

PERIPHERAL SMEAR :

SITE : STERNUM / ILIAC CREST
CELLULARITY : Hypocellular marrow M : E RATIO :
ERYTROPOIESIS : mild increase in number of cells with normoblastic reaction.
MYELOPOIESIS : Normal
LYMPHOPIESIS : Normal ; Increase in number of histiocytes some are showing hemophagocytosis.
MEGA KARYOCYTES : Normal
PLASMA CELLS : –
R:E CELLS : –
ABNORMAL CELLS : –
HEMOPARASITES : –

IRON STORES :–1

IMPRESSION : Mild hemophagocytosis with histiocytosis. Correlate clinically

PATHOLOGIST
Dr. G. Baleswari 21/12/18
Professor & Head of the Department

REFERENCES

1. Janka GE. Hemophagocytic syndrome. Blood Rev. 2007;245-53.
2. Filipovich AH. Hemophagocytic lymphohistiocytosis (HLH) and related disorders. Curr Opin Allergy Clin Immunol.2006;6:410-5.
3. Osugi Y, Hara J, Tagawa S, Takai K, Hosoi G, Matsuda Y, Ohta H, Fujisaki H, Kobayashi M, Sakata N, et al. Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. Blood. 1997 Jun 1;89(11):4100–4103.
4. Pachlopnik Schmid J, Côte M, Ménager MM, Burgess A, Nehme N, Ménasché G, Fischer A, de Saint Basile G. Inherited defects in lymphocyte cytotoxic activity. Immunol Rev, 2010; 235:10-23
5. Scott R, Robb-Smith A. Histiocytic medullary reticulosis. Lancet 1939;2:194-8.
6. Farquhar, James W.; Claireaux, Albert E. (December 1952). "Familial Haemophagocytic Reticulosis". Archives of Disease in Childhood. 27 (136): 519–525.
7. Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour HH, Jr, Simmons RL, Brunning RD. Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct from malignant histiocytosis. Cancer. 1979 Sep;44(3):993–1002.
8. Risdall RJ, Brunning RD, Hernandez JI, Gordon DH. Bacteria-associated hemophagocytic syndrome. Cancer. 1984;54(12):2968–2972
9. Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection- and malignancy-associated hemophagocytic syndromes. Secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am. 1998 Apr;12(2):435–444
10. Kumakura S, Ishikura H, et al. Autoimmune-associated hemophagocytic syndrome. Mod Rheumatol.2004;14(3):205-15.31. Bryceson YT, Pende D, Maul-Pavicic A, et al. A prospective evaluation of degranulation assays in the rapid diagnosis of familial hemophagocytic syndromes. Blood. 2012;119(12):2754–2763
11. Tschopp J, Nabholz M. Perforin-mediated target cell lysis by cytolytic T lymphocytes. Annu Rev Immunol.1990;8:279-302.
12. Bryceson YT , Pende D, et al. A prospective evaluation of degranulation assaysin the rapid diagnosis of familial hemophagocytic syndromes. Blood.2012;119:2754-63.
13. Verbsky JW, Grossman WJ. Hemophagocytic lymphohistiocytosis: diagnosis, pathophysiology, treatment, and future perspectives. Ann Med. 2006;38(1):20–31
14. Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124–131.
15. Filipovich AH. Hemophagocytic lymphohistiocytosis and other hemophagocytic disorders. Hematology Ash Education Book.2009;1:127-31.
16. Trottestam H, Horne A, Arico M, et al. Risk factors for early death in children with hemophagocytic lymphohistiocytosis. Acta Paediatr.2011;101:313-8.