

Familial Hemophagocytic Syndrome in A Neonate- A Rare Case Report

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Abstract: ***Background:** Hemophagocytic lymphohistiocytosis (HLH) is a rare life threatening disease of the immune system characterised by proliferation of activated T lymphocytes and macrophages which are morphologically benign. The onset of HLH occurs under the age of 1 year in ~70% of cases & the estimated incidence is 1.2 cases per million children = 1 in 50,000 births. It has 2 types Primary/Familial HLH & Secondary HLH which is associated with viral/ bacterial infections or Malignancy like lymphoma. **Case report:** A 26 days old boy presented with fever, poor feeding, jaundice & Pancytopenia. On examination there is hepatosplenomegaly, lymphadenopathy, light coloured hair and a rash. The triglyceride level and serum ferritin were markedly increased & fibrinogen level was reduced. Bone marrow examination showed Hemophagocytosis & lymphohistiocytic proliferation. A diagnosis of HPS was made which was later confirmed by Molecular diagnostic techniques which showed Mutation in PRF1 gene. Various studies on HLH gave the conclusions regarding Clinico Pathological features which was very well correlated with this case. **Conclusion:** Familial HPS is a very rare entity. There is a considerable overlap of clinical & pathological findings of Familial HPS & Secondary HPS, Griscelli syndrome & Macrophage activation syndromes possessing a great diagnostic challenge. The very rare nature of the disease & its grave prognosis merits its Reporting.*

Keywords: Lymphohistiocytosis, Hepatosplenomegaly, Molecular tests, Griscelli syndrome, Hemophagocytosis

1. Introduction

Synonyms: Hemophagocytic Syndrome (HPS), Primary Hemophagocytic lymphohistiocytosis (HLH), familial haemophagocytic lymphohistiocytosis (FHL), familial erythrophagocytic lymphohistiocytosis¹

Hemophagocytic lymphohistiocytosis (HLH) is a rare life threatening disease of the immune system characterised by proliferation of activated T lymphocytes and macrophages which are morphologically benign. The onset of HLH occurs under the age of 1 year in ~70% of cases & the estimated incidence is 1.2 cases per million children = 1 in 50,000 births^{2,3}

The first case report of HLH was published in 1952. It has 2 types Primary/Familial HLH & Secondary HLH. Familial HLH is a heterogeneous autosomal recessive disorder prevalent with parental consanguinity. The five subtypes of FHL are each associated with a specific gene mutation:

- FHL1: HPLH1
 - FHL2: PRF1 (Perforin)
 - FHL3: UNC13D (Munc13-4)
 - FHL4: STX11 (Syntaxin 11)
 - FHL5: STXBP2 (Syntaxin binding protein 2)/UNC18-2⁴
- 50% are affected, 25% are disease free & 25% are carriers

2. Case Report

A 26 days old boy presented with fever, poor feeding, jaundice & Pancytopenia. On examination there is hepatosplenomegaly, lymphadenopathy, fair hair and a rash.

Clinical Provisional DD – Chediak-Higashi syndrome, Griscelli syndrome, Acute Leukemia

Past History- One Sibling died with similar complaints.

Laboratory investigations

WBC- 4,200/mm HGB- 6.6 g/dl MCV- 74flMCH- 23pg PLT- 45,000/mm

Manual diff:- Neutrophils – 00 Lymphocytes- 36% Monocytes- 11% Atypical lymphocytes- 53% Retic – 0.7% PBS – Agranulocytosis with thrombocytopenia & 53% Atypical Lymphocytes

RFT – NORMAL, LFT – NORMAL, VIRAL SEROLOGY- NEGATIVE

BLOOD CULTURE- NO GROWTH, ALBUMIN- 26 (38 – 54), CRP – 27 (0-10)

PROTEINS- 58 (60-80) LDH- 406 (110-295), FERRITIN* – 2037* (13-150)

TRIGLYCERIDES* - 5.18* (0.4-1.24), CHOLESTEROL – 3.5 (N)

Fibrinogen Level is Reduced

Bone Marrow Aspiration Report:- The B.M. aspirate shows good number of hypercellular B.M. fragments. Lymphohistiocytic proliferation is very prominent. Erythroid cells, lymphocytes & Platelets are Phagocytosed by histiocytes. Megakaryocytes are mildly reduced. Granulocyte precursors and Neutrophils are absent. BLASTs are less than 05%

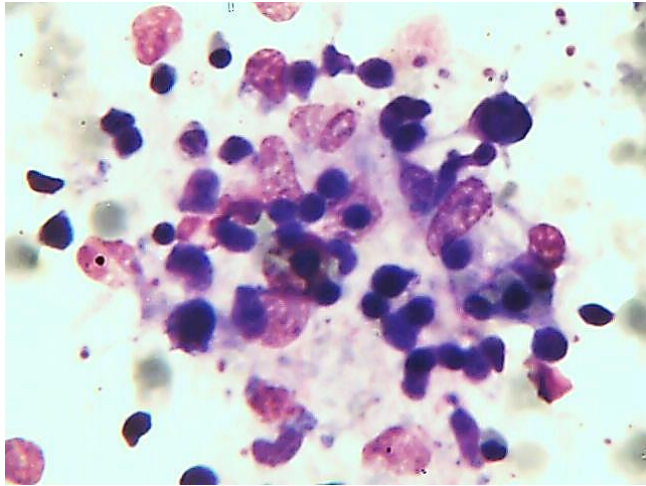


Figure 1: Giemsa ,HP: Hemophagocytosis (Macrophages Engulfing Erythroid Cells)

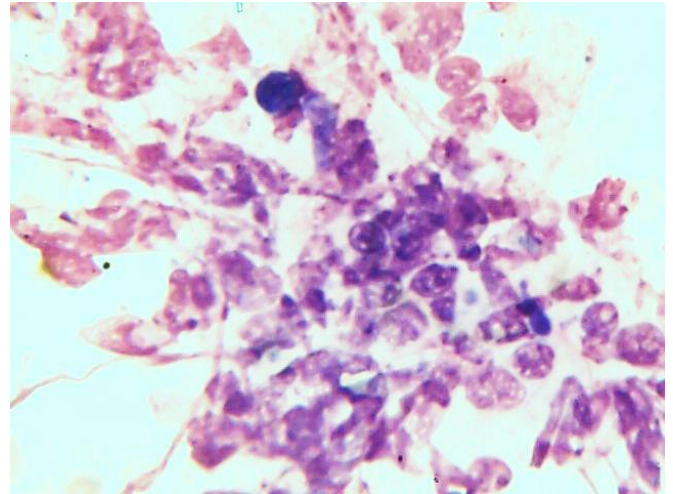


Figure 4: Giemsa ; HP: - Histiocytic Proliferation

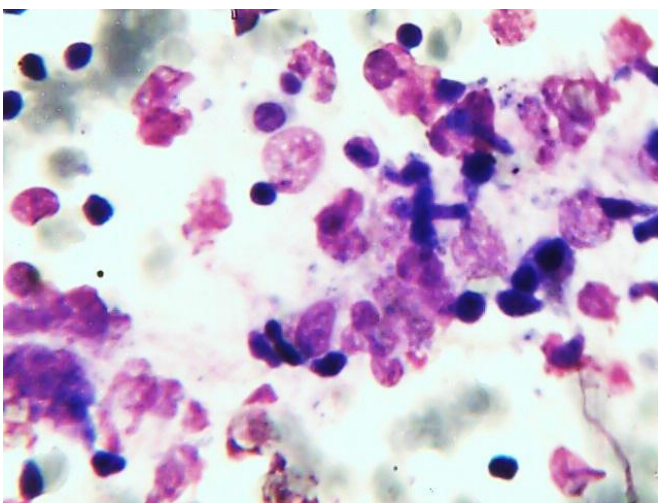


Figure 2: Giemsa ; HP : - Hemophagocytosis)

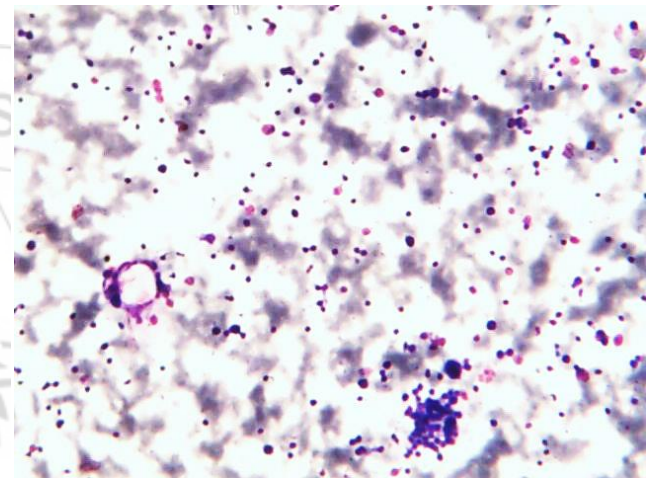


Figure 5: Giemsa ; LP :- Lympho-Histiocytic Proliferation

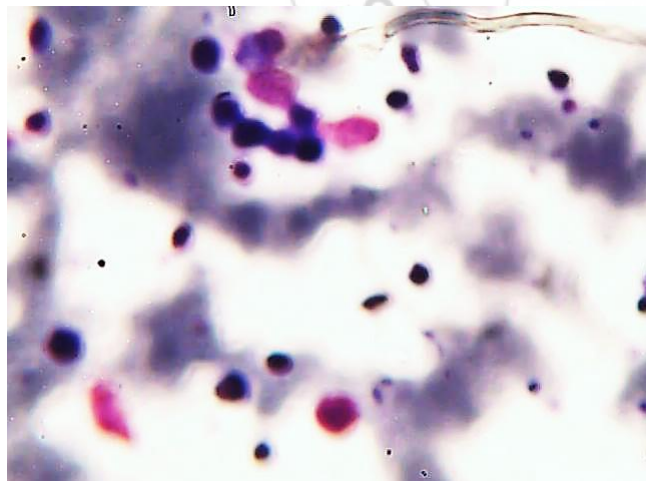


Figure 3: Giemsa , LP: - Macrophage Engulfing Many Erythroid Cells.

3. Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a rare life threatening disease of the immune system characterised by proliferation of activated T lymphocytes and macrophages which are morphologically benign. It has 2 types Primary/Familial HLH & Secondary HLH¹

The current (2008) diagnostic criteria for FAMILIAL HLH^{3,4,5}

1. A molecular diagnosis consistent with HLH. These include the identification of pathologic mutations of PRF1, UNC13D, or STX11.
OR
2. Fulfillment of five out of the eight criteria below:
 - a) Fever (>100.4 degrees F)
 - b) Splenomegaly
 - c) Cytopenias affecting at least two of three lineages in the peripheral blood:
 - Haemoglobin < 9 g/100 ml (in infants < 4 weeks: haemoglobin < 10 g/100 ml)
 - Platelets < 100 × 10⁹/L
 - Neutrophils < 1 × 10⁹/L

- d) Hypertriglyceridemia (fasting, greater than or equal to 265 mg/100 ml) and/or hypofibrinogenemia (≤ 150 mg/100 ml)
- e) Ferritin ≥ 500 ng/ml
- f) Haemophagocytosis in the bone marrow, spleen or lymph nodes
- g) Low or absent natural killer cell activity
- h) Soluble CD25 (soluble IL-2 receptor) >2400 U/ml.

In addition, in the case of familial HLH, no evidence of malignancy should be apparent.

A 26 days boy presented with hepatosplenomegaly, lymphadenopathy, Jaundice and light hairs. There was history of sibling death with similar complaints. All the typical clinical features of HPS were present in this case. There was no evidence of Malignancy or any Viral, bacterial & fungal infections ruling out Secondary HLH. The common age of HPS is between 5-8 months but in this case Neonate was affected making it a Rare case presentation⁶

Clinical signs and laboratory abnormalities associated with HPS⁵

Clinical sign% of patient affected	
Fever	60-100
Splenomegaly*	35-100
Hepatomegaly	39-97
Lymphadenopathy	17-52
Rash	3-65
Neurologic signs	7-47

Laboratory abnormality	
Anemia*	89-100
Thrombocytopenia*	82-100
Neutropenia*	58-87
Hypertriglyceridemia*	59-100
Hypofibrinogenemia*	19-85
Hyperbilirubinemia	74-19

The various studies on HLH gave the following conclusion which was very well correlated in this case report⁵. The B.M. aspirate shows good number of hypercellular B.M. fragments. LymphoHistiocytic proliferation is very prominent. Erythroid cells, lymphocytes & Platelets are Phagocytosed by histiocytes. No Giant granules noted ruling out CHS.

The Diagnosis was confirmed by Molecular testing which showed Mutation in PRF1 gene. So this case falls under FHS type⁶

Differential Diagnosis

Secondary HLH Macrophage-activation syndrome or other primary immuno deficiencies that present with hemophagocytic lymphohistiocytosis, such as X-linked lympho proliferative disease. Autoimmune lympho proliferative syndrome.⁷

The diagnosis of acquired or secondary HLH is usually made in association with infection by viruses, bacteria, fungi or parasites or in association with lymphoma, autoimmune disease, or metabolic disease.

A major differential of HLH is Griscellis syndrome (type 2) which have mutations in RAB27A. This is a rare (less than 100 reported cases) autosomal recessive disorder characterized by partial albinism, hepatosplenomegaly, pancytopenia, hepatitis, immunologic abnormalities, and lymphohistiocytosis. Most cases have been diagnosed between 4 months and 7 years of age.

4. Conclusion

Familial HPS is a very rare entity. There is a considerable overlap of clinical & pathological findings of Familial HPS & Secondary HPS, Griscelli syndrome & Macrophage activation syndromes possessing a great diagnostic challenge.

The very rare nature of the disease & its grave prognosis merits its Reporting.

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6. Conflict of interest: None declared

7. Ethical approval: Not required

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