Case report: Hemophagocytic lymphhistiocytosis

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Introduction

HLH stands for hemophagocytic lymphhistiocytosis. It is a life-threatening condition that can be defined as either primary or secondary HLH. Primary, or “familial,” HLH is when the condition is inherited. The term secondary HLH is used when your doctor thinks the condition may have occurred for a variety of other non-inherited reasons.

Patients with primary HLH have cells of the immune system called T and NK cells that don’t work properly. These cells become overactive, causing too much inflammation. Ordinarily, these cells should destroy infected, damaged cells of the body. In HLH, the immune system begins to damage the patient’s own tissues and organs, including the liver.

Background

Rare and potentially fatal disease of normal but overactive histocytes and The overwhelming activation of the T cells and macrophages lead to the clinical alterations Lymphocytes Primary type (FEL) : familial erythrophagocytic lymphhistiocytosis is Commonly in infancy Secondary type : acquired : systemic infection, immunodeficiency, underlying malignancy

Pathophysiology

Aggressive proliferation of activated macrophages and histocytes which phagocytose RBCS, WBC, PLATELETS

Highly stimulated but ineffective immune response with nonmalignant uncontrolled growth result in life - threatening cytokine storm

Underlying process still not understood

Theories : genetics : perforin deficiency, EBV
Decrease NK cell activity result in T cell activation which lead to production of large quantities of cytokines

Decrease NKC function

T cell activation

TNF INF GM-CSF

Macrophage activation

Epidemiology

Incidence is 1.2 /million/year [1/ of FEL 50000 is to perforin due to mutation) Race : similar statistical incidences for different races

Sex : equal distribution among males and females

Age : familial form is affects children from birth to age of 18 month

Mortality /morbidity

FEL : is uniformly fatal if not treated Median survival time is 2-6 month after the diagnosis Survive for 3 years is less than 10% probability 25% expected to survive 5 years with the treatment.

Study : 50% of deaths were due to invasive fungal infection

HLH presentation

family history of HLH

History of immune deficiency or autoimmune disorders

History of underlying malignancy

Recent viral infection

Fever ........> 38 c

Cholestatic jaundice ,coagulopathy signs

Hepatosplenomegaly

Lymphadenopathy

Skin rash : ranging from erythroderma to maculopapular and morbiliform eruption

CNS : irritability, convulsion, ataxia, hemiplegia

HLH : workup

Histological finding : histocytes infiltration

Skin biopsy : usually not diagnostic

Bone marrow aspirate : is undiagnostic initially in 2/3 of HLH pts

Liver biopsy : picture of chronic persistent hepatitis can support HLH

CSF : presence of mononuclear cells also supports the diagnosis

Classification

Primary HLH, also known as familial haemophagocytic lymphhistiocytosis (FHL) or familial erythrophagocytic lymphhistiocytosis, is a heterogeneous autosomal recessive

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disorder found to be more prevalent with parental consanguinity. Secondary haemophagocytic lymphohistiocytosis (acquired haemophagocytic lymphohistiocytosis) occurs after strong immunologic activation, such as that which can occur with systemic infection, immunodeficiency, or underlying malignancy. Both forms are characterized by the overwhelming activation of normal T lymphocytes and macrophages, invariably leading to clinical and haematologic alterations and death in the absence of treatment.

**Figure 1.** The bone marrow may show hemophagocytosis
Bone marrow biopsy shows histiocytosis

**Bone marrow**

**Case scenario**

Full term female, outcome of SVD
- Mother: PG with uneventful history with average normal lab investigations
- Risk: first degree consanguinity
- Uncomplicated delivery with good APGAR score and faire normal examination, average wt 3.5 kg, so baby discharged home after one day
- At age of 5 days baby admitted through ER with complain of fever and lethargy
  - Physically: maintained vitally in room air, temp 39.0, jaundiced, abdominal distension with splenomegaly (3-4 cm bcm), hepatomegaly (6 cm bcm), others were unremarkable
  - Blood gas: ph: 7.18 PCO2 40 base -9
  - Baby was admitted in nicu

**Differential diagnosis was put as**

- Sepsis
- Congenital infection
- Hemolytic anemia
- Metabolic disorders
- Immunodeficiency disorders
- Neonatal malignancy

**ON EXAMINATION**

Vital sign is stable no dysmorphic feature, baby is conscious alert, good air entry bilateral, 1st and 2nd heart sound is normal no murmur, abdomen soft hepatosplenomegaly, fever on an off (38.0), progressive increase in the liver and spleen with deep jaundice and skin rash (maculopapular)

- ICBC: Hb 15g/d WBC 15.000 Plateau 14.000, neutrophils 2.7.000
- Rectics: 2%
- DCT: -ve (BG is o +ve)
- Coagulation profile: normal
- Peripheral smear: normocytic normochromic anemia, with target cells, WBCs: left shift, toxic granulation.
- CRP: 3.9 investigation:
  - persistent thrombocytopenia (5 – 30.000)
  - neutropenia (0.00) with recovery
  - anemia (8 g/d)
- LFT: AST: 1500, ALT: 500, TB/DIRECT 400/250, GTT 246, PTT: 66 INR 9 PT 78
- CRP: 9.2 mg/dl
- Creatinine: 43 umol/l urea: 5.7 umol/l
- Na: 133 mmol/l
- Ca: 2 mmol/l
- K: 3.2 mmol/l
- Total bilirubin 98 umol/l direct 78umol/l
- Ammonia: 51 umol/l
- Lactate: 10 mmol/l
- Sepsis screening: -ve
- Torch screening: -ve
- HIV + hepatitis B: -ve
- TANDAM?
- Storage disorders screening?
- Flow cytometry?
- Ferritin level: 31340 ng/ml (10-120)
- Fibrinogen: 1.3 g/l (2-4)
- Serum ferritin > 10000 ng/ml is 100% sensitive for HLH
  - H score is > 90%
- Plan: referral to higher centre
  - Tissue biopsy
  - Further management
- CBC: Persistent pancytopenia
- Liver enzyme is high AST289, ALT 116. Total bilirubin 321, direct bilirubin 286, ggt 327, high ferritin 31000ng/ml
- Screening is negative for TORCH + Hepatitis B
- Tandem + Screening is negative for store disorders were pending
- Imaging: Echocardiogram septal hypertrophy
- Brain us: normal
- Abdominal us: small liver cyst
- CT abdomen done

**Course and prognosis**

Baby admitted in NICU follow up by hematologist ask for referral to higher center for biopsy and further management, baby received platelet transfusion and PRBC transfusion, Immunoglobulin, GCSF, and antibiotics

**Prognosis**

The prognosis is guarded with an overall mortality of 50%. Poor prognostic factors included HLH associated with malignancy, with half the patients dying by 1.4 months compared to 22.8 months for non-tumour associated HLH patients.[16]
Secondary HLH in some individuals may be self-limited because patients are able to fully recover after having received only supportive medical treatment (i.e., IV immunoglobulin only). However, long-term remission without the use of cytotoxic and immune-suppressive therapies is unlikely in the majority of adults with HLH and in those with involvement of the central nervous system (brain and/or spinal cord).[3]

References
8. Lymphohistiocytosis,+,Hemophagocytic at the US National Library of..