CASE REPORT

A Case Report of Hemophagocytic Lymphohistiocytosis (HLH)

Anjali Rajadhyaksha*, Archana Sonawale**, Ajay Agrawal***, Kiran Ahire****, Juhi Kawale*****

Abstract
Hemophagocytic lymphohistiocytosis (HLH), is an uncommon, life-threatening hyperinflammatory syndrome caused by severe hypercytokinemia with excessive activation of lymphocytes and macrophages due to a highly stimulated but ineffective immune process. We report a case of Hemophagocytic Lymphohistiocytosis in a 15 year old boy presenting with fever, lymphadenopathy and pancytopenia due to infection caused by Klebsiella Pneumoniae and Acinetobacter.

Introduction
HLH is a syndrome characterized by fever, pancytopenia, splenomegaly, and hemophagocytosis in bone marrow, liver, or lymph nodes. It can be classified as familial (primary) or acquired (secondary) HLH. Acquired HLH is associated with several viral, bacterial, fungal and parasitic infections as also autoimmune diseases and malignancies. It is associated with high mortality if not treated early. HLH needs to be differentiated from other conditions like Sepsis, SIRS, MODS and Macrophage activation syndrome which can mimic HLH, as the management strategies and outcome of each differ according to the etiology. A patient is said to have SIRS or systemic inflammatory response syndrome if he has two or more of the following: fever or hypothermia, tachypnoea, tachycardia and leucocytosis or leucopenia. SIRS that has a proven or suspected microbial etiology is defined as sepsis. MODS or multiorgan dysfunction syndrome is dysfunction of more than one organ requiring intervention to maintain homeostasis. The term macrophage activation syndrome (MAS) refers to a condition caused by excessive activation and expansion of T lymphocytes and macrophagic histiocytes that exhibit hemophagocytic activity.

Case Report
A 15 year old boy, born of non consanguineous marriage, 2nd child of his parents, right handed, resident of Ratnagiri, 10th class student, symptomatic since 4 months, presented with complaints of fever with chills on and off and bilateral inguinal and axillary lymphadenopathy. He had no significant past or family history. He was admitted in a private hospital where lymph node biopsy was suggestive of reactive lymphadenitis. Ecternal bone marrow aspiration was suggestive of myeloid hyperplasia (M/E=6:1) with 25% blasts. Hence patient was suspected to have acute leukemia. Investigations revealed a total WBC count ranging from 2530/cumm to 4900/cumm and platelet counts ranging from 92000/cumm to 1.38 lacs/cumm. (Table 1), Lepto IgM, Dengue IgM, HAV IgM, HEV IgM, HCV Antibody – negative, USG Abdomen- Normal, Urine R/M - 6-7 pus cells/hpf, Urine Culture/ sensitivity - E.coli >10^9 colonies/hpf, sensitive to ceftriaxone, total bilirubin- 2.68mg%, direct of 2mg%, SGOT 663U/L, SGPT 210U/L. He was referred to a local cancer hospital but bone marrow examination was
normal. Patient was treated with oral cefixime and vitamin supplements. In view of persistent fever and diagnostic uncertainty, patient was referred to our institute.

On admission patient was febrile (39°C) with a pulse of 110/min, BP-110/70, oral cavity showed mucositis and lip excoriation (Figure 3). Patient had pallor, icterus, bilateral axillary, inguinal, sub mental, sub mandibular nontender lymphadenopathy, peripheral cyanosis (Figure 1) and blanchable rash all over the body. Per abdominal examination revealed a palpable liver 2-3 cm, tender, no splenomegaly. Rest of the systemic examination was normal. Patient was started on Ceftrixoone and Artesunate injections. Investigations done at our institute are as shown in Table 2. Other investigations revealed, Left axillary lymph node biopsy -- Reactive Hyperplasia, USG Abdomen-, mild hepatomegaly, sub centimeter sized mesenteric lymph node, Urine Routine/ Microscopy -- albumin 1+, Granular cast+, No cells, CT chest and abdomen revealed mild ascites, right basal pleural thickening, basal pneumonitis in lower lobe of right lung, 0.5 cm lymph nodes in axilla, para tracheal, subcarinal regions and retro peritoneal region of renal hilum. 2D-ECHO -normal cardiac function without any vegetation or any valvular abnormality. HBsAg, HCV, HAV IgM, HEV IgM, Widal, HIV-- negative.

Six days after admission patient developed pancytopenia with a sudden drop in Hb from 9.8gm/dl to 2.9 gm/dl and drop in platelet count to 20,000/ cumm. Patient was also transfused with packed cells and platelets and antibiotics were continued. Complete hemogram and bone marrow aspiration was done. Complete Hemogram showed a Hb 6.9gm/dl, WBC count of 6830/cumm with anisopikilocytosis, hypochromasia, nucleated RBCs and occasional schistocytes.

**Bone Marrow Aspiration**

**Cellularity** - Erythroid – occasional megakaryocytes, **Lymphoid** – mature 30%, Plasma cells– mature 2% **Myeloid** --Promyelocytes – 01,Myelocytes – 03,Metamyelocytes – 12, PMN – 36, Basophils – 00, Eosinophils – 00,Monocytes – 15, Promonocytes – 00, Abnormal cells/blasts– 01%.

**Morphology** – increase in macrophages showing

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**Table 1 : Investigations done in private hospital before coming to our institute**

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**Table 2 : Investigations done in our institute**

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**Fig. 1 : Peripheral cyanosis**

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hemophagocytosis

Final Report - mildly hypo cellular bone marrow with hemophagocytosis and erythroblastopenia.

Bone marrow culture grew Klebsiella Pneumoniae sensitive to Piperacillin-tazobactam, Cefoperazone-sulbactam, Imipenem, colistin, meropenem and Acinetobacter species sensitive to colistin and tigecycline. AFB Smear and culture were negative. Blood culture grew Klebsiella Pneumoniae sensitive to Levofloxacin, Impenem, Meropenem, Piperacillin-Tazobactam

In view of hemophagocytosis with infection patient was started on injection Piperacillin tazobactam, inj. dexamethsone10 mg bd, cap.Cyclosporin 100 mg bd as per HLH protocol.

After 3 days the patient started improving. He was transfused 16 bags of platelets, 2 pints of FFP and 2 units of packed cells. Further work up revealed –

- Blood Perforin levels 81% of normal and NK cell activity- 11% (borderline low)
- S.ferritin = 1163 (NR--30 to 400), S.LDH = 1482.70
- S.Triglycerides 401.88, S.Methemoglobin 2.9% (n 0.0-2.0%)  
- Parvo virus IgM, Parvo virus IgG, EBV IgM, CMV IgM, CMV IgG,Lepto IgM, Lepto IgG,
- Brucella IgM, and Brucella IgG - negative
- ANA, anti dsDNA -- negative

After 1 week, dose of Cyclosporine was increased to 200 mg/day and 300mg/day alternate day. Patients counts started improving by day 8. Patient received 2 weeks of Injectable Piperacillin tazobactam and showed gradual improvement. On Day 15 patient deteriorated with fever, a drop in Hemoglobin to 5.7gm/dl, oliguria and raised serum creatinine of 2.1mg%. He was given one unit of packed cells. Injectable Amoxicillin- clavulinate was added. Inspite of the above patient succumbed on day 16, the probable cause being sepsis with acute renal failure in a case of HLH. Due to unwillingness of relatives an autopsy could not be performed.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) : Also known as haemophagocytic syndrome, it is characterized by fever, pancytopenia, splenomegaly, and hemophagocytosis in bone marrow, liver, or lymph nodes.  The syndrome, which has also been referred to as histiocytic medullary reticulosis, was first described by Scott and Robb-Smith in 1939.  It includes common features of haemophagocytosis, hyperferritinaemia, hypercytokinaemia, variable cytopenias, hypofibrinogenaemia, multi-organ failure and very often death.

Pathophysiology : In a healthy individual histiocytes, Natural Killer cells(NK) and cytotoxic T lymphocytes (CTL) are activated in response to any infective stimulus, subsequently resulting in killing of the infective antigen and then termination of the immune response. In HLH due to defect in the cytokotic activity of the NK and CTL, this immune response is excessive and uncontrolled, with ineffective clearance of antigens along with excessive accumulation of activated T-lymphocytes, activated macrophages and histiocytes with increasingly high levels of cytokines.

The present case was that of secondary HLH with features like fever, pancytopenias, hepatomegaly, hyperferritenemia and evidence of hemophagocytosis on bone marrow.

Classification

Primary (genetic) HLH

Most primary HLH episodes are triggered by an infection. Etiologies related to primary HLH are

1. FamilialHLH which has four subtypes FHLH-1,2,3 and 4 are all autosomal recessive disorders with various genetic mutations. Until recently it was believed that familial HLH generally arose during infancy and early childhood. But with availability of genetic testing it is apparent that the first episode can occur at any age.

2. Immune deficiency syndromes

   - Chediak-Higashi syndrome (CHS-1)
   - Griscelli syndrome 2 (GS-2)
   - X-linked lymphoproliferative syndrome (XLP)

Secondary (acquired) HLH

It occurs in all age groups. It can occur secondary to infections, autoimmune diseases, malignancies, and immune suppression/organ transplantation. However most patients with secondary HLH are not obviously immunosuppressed.

Infections : Among infections viruses are the predominant pathogens eg EBV, CMV, Measles, HHV-8, adenovirus, HIV. Other infections include brucella, gram negative bacteria, rickettsia, leptospira, tuberculosis, malaria, leishmania and fungal infections. In our patient secondary HLH was triggered by Klebsiella pneumoniae infection as evident on blood and bone marrow cultures.

Autoimmune diseases : Systemic lupus erythematosus, systemic sclerosis, dermatomyositis and Sjogren’s syndrome may be associated with secondary HLH.

Malignancies : HLH is seen in association with several malignancies. In a study from six different hospitals in Turkey, 27 patients were diagnosed to have malignancy associated HLH. Twenty patients
had acute leukemia while other malignancies seen included rhabdomyosarcoma, neuroblastoma, Hodgkins disease and non Hodgkins Lymphoma.

Immunosupression/Transplantation can also lead to secondary HLH.

Criteria for the diagnosis of HLH (Table 3), proposed by the Histiocyte Society, include clinical, laboratory, and histopathologic features. Fever and splenomegaly are the most common clinical signs, but hepatomegaly, lymphadenopathy, jaundice, and rash are also seen. The rash is commonly described as maculopapular, but nodular eruptions have also been described. Of central nervous system manifestations, encephalopathy, meningism, and seizures are the most common.

The most prominent laboratory abnormalities noted are cytopenias, which may be profound. Serum chemistry findings may suggest hemolysis, with hyperbilirubinemia and elevation of lactate dehydrogenase, hypertriglyceridemia and marked elevation of ferritin. Serum fibrinogen is typically low, and there may be disseminated intravascular coagulation. Elevated circulating fibrin degradation products and serum ferritin in patients with HLH appear to be associated with increased risk for death. The clinical diagnostic criteria evident in our patient included fever, hepatomegaly, pancytopenia, hypertriglyceridemia, hyperferritinemia, haemophagocytosis on bone marrow and reduced NK cell activity.

The overlap between HLH and sepsis syndromes has been known. Most of the patients of secondary HLH have features like fever, hypotension, distributive shock and multisystem organ failure which are also common in severe sepsis and septic shock. Some of the HLH 2004 diagnostic criteria like fever, anemia, thrombocytopenia, hyperfibrogenemia and hypertriglyceridemia are common features of sepsis as well. In such scenarios NK cell activity and soluble CD4 counts are two tests which will help us differentiate these conditions from HLH as their sensitivity in HLH is 100%.

Histopathologically (Figure 2), hemophagocytosis is seen in bone marrow, spleen, and lymph nodes and occasionally the central nervous system and skin. Activated macrophages may engulf erythrocytes, leukocytes, and platelets, their precursors, and cellular fragments.

For patients with reactive HLH associated with pathogens other than EBV, supportive care and treatment of the underlying infection is associated with recovery in 60%-70%. Epstein-Barr virus-associated HLH is associated with high mortality if not treated early. The poor prognosis of this syndrome suggests that patients should be treated initially with combination chemotherapy and immunotherapy, regardless of whether they are thought to have familial HLH. Chemotherapy with etoposide, Anti thymocyte globulin (ATG), dexamethasone, cyclosporine A is recommended, with the use of intrathecal methotrexate in patients with neurologic symptoms or persistent cerebrospinal fluid abnormalities.

According to HLH 2004 protocols 8 weeks of therapy is given for secondary non-genetic disease and for genetic disease therapy should be continued after week 8 until Stem cell transplantation.
HLH associated with infection may be difficult to distinguish from familial HLH triggered by an infection. The distinction is important; as allogeneic bone marrow transplantation is the therapy of choice in patients with familial HLH who attain remission. Sporadic HLH carries a better prognosis. HLH triggered by bacterial infection is associated with a high recovery rate. The condition may mimic a number of systemic infections. Appropriate broad spectrum antibiotics and supportive therapy should be given. Early recognition and treatment with chemotherapeutic agents or bone marrow transplant may reduce mortality.

We conclude that physicians must possess a high index of suspicion for diagnosing HLH amongst patients presenting with fever and cytopenia especially with underlying infection, malignancy or immunosuppressive states.

References