

Haemophagocytic Lymphohistiocytosis: A Review Article

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Abstract: ***Background:** Haemophagocytic lymphohistiocytosis (HLH) is a hyper inflammatory syndrome characterized by the aggressive non-malignant proliferation of activated macrophages and histiocytes, which phagocytose other cells, namely red blood cells, white blood cells and platelets leading to the clinical symptoms of fever, hepato-splenomegaly, bone marrow, skin, and central nervous system (CNS) infiltration. The presumed underlying pathogenesis is a highly stimulated but ineffective immune response to antigens, mediated mainly by activated T-cells and associated macrophage activation that eventually heightens to a life threatening cytokine storm. **Interpretation:** In this case series, we present 2 cases of HLH their different presentations, clinical course and outcome. **Conclusion:** HLH is not an uncommon entity and it has multifaceted clinical presentation with nonspecific signs and symptoms that are often found in other clinical conditions. Therefore, there is need to know the importance of its Incidence in Indian scenario, specific management guidelines and prognosis to prevent high mortality and adverse outcomes.*

Keywords: Fever of Unknown Origin, Haemophagocytic Lymphohistiocytosis, Hypertriglyceridemia, Hepatosplenomegaly, Pancytopenia, Serum Ferritin

1. Introduction

Hemophagocytic Lympho-Histiocytosis (HLH) is an aggressive and lethal syndrome of undue immune activation. Hemo-phagocytosis is the engulfment of hematopoietic cells by activated macrophages acting outside of usual immune system regulations. It usually affects infants from birth to 18 months of age, but it is also observed in children and adults of all ages.¹ HLH can occur as congenital or sporadic disorder and can be provoked by a variety of events that disturb immune homeostasis.

Hemophagocytic Lympho-Histiocytosis (HLH) includes Autosomal Recessive Familial HLH (FHL), Familial Erythrophagocytic Lymph-Histiocytosis, viral-associated hemophagocytic syndrome and autoimmune-associated macrophage activation syndrome (MAS).

The term primary HLH refers to an underlying genetic abnormality causing the disorder, whereas secondary HLH indicates that the disorder is secondary to underlying conditions such as infection, malignant autoimmune/rheumatologic or metabolic conditions. In sporadic cases and patients with genetic predisposition infection is a common triggering factor.

'FHL' indicates cases with a primary genetic cause while 'secondary HLH' refers to cases secondary to infection, malignancy or metabolic disorders, and 'MAS' refers to cases associated with autoimmune diseases. In this case series, we present 2 cases of HLH their different presentations, clinical course and outcome.

2. Review of Literature

Much has been learned about HLH in the 75 years since it was first discovered. One of the earliest descriptions of the disease was in 1939 when Scott and Robb-Smith described a disorder with erythrophagocytosis by proliferating histiocytes in the lymphoreticular system and called it as "histiocytic medullary reticulosis" or HMR². It was later classified among malignant histiocytosis. Later in 1952, the

familial form of HLH was more extensively described by Farquhar and Claireaux with the cases of two siblings who succumbed to HLH and later in 1958, another sibling from this same family presented in the same manner³.

An association between HLH and viral infection was first postulated by Risdall and he called it virus associated HLH which is clinically distinct from Malignant Histiocytosis⁴. In the years since, researchers have recognized the wide scope of this disease and the fact that infection often triggers both primary and secondary HLH.

Pathophysiology: Excessive cytokine production by macrophages, NK cells, and CTLs is thought to be a primary mediator of tissue damage⁵.

Immunologic abnormalities: The absence of normal immune down regulation by activated macrophages and lymphocytes causes hyperinflammatory and dysregulated immune state. In HLH, macrophages get activated and secrete excessive amounts of cytokines, ultimately causing severe tissue damage that can lead to organ failure. NK cells and/or CTLs fail to eliminate activated macrophages. This lack of normal feedback regulation results in excessive macrophage activation and highly elevated levels of interferon gamma and other cytokines.

Other lymphocyte abnormalities include altered numbers of CD4 and CD8 lymphocyte subsets⁶. Best survival was observed in patients with decreased CD4/CD8 ratios and increased CD8 numbers, whereas bad outcome in decreased CD3 counts.

Hemophagocytosis - Hemophagocytosis refers to the engulfment (literally "eating") of host blood cells by macrophages. Hemophagocytosis is characterized by the presence of red blood cells, platelets, or white blood cells (or fragments of these cells) within the cytoplasm of macrophages. In biopsies of immune tissues (lymph nodes, spleen, liver) or bone marrow, hemophagocytosis was observed. Though hemophagocytosis is a marker of excessive macrophage it is neither pathognomonic nor required for the diagnosis of HLH.

Volume 8 Issue 6, June 2019

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Cytokine storm-Extensive activation of macrophages, NK cells, and CTLs in patients with HLH causes excessive cytokine production by all of these cell types, and is thought to be responsible for multiorgan failure and the high mortality of this syndrome^{7,8}.

Triggers-Patients with familial HLH have higher chances of relapse. Infection or an alteration in immune homeostasis is a common instigating factor for an acute episode.

The two broad categories of triggers include those that cause immune activation and those that lead to immune deficiency.

Immune activation from an infection is a common trigger both in patients with a genetic predisposition and in sporadic cases with no underlying genetic cause identified. The most common infectious trigger is a viral infection, especially Epstein-Barr virus (EBV)⁵.

HLH may also be caused by excessive cytokine release in patients with chronic granulomatous disease (CGD).

Clinical Features

Initial presentation

Febrile illness associated with multiple organ involvement is a common presentation with HLH. Thus, initial signs and symptoms are similar to common infections, fever of unknown origin, hepatitis or encephalitis.

The HLH-2004 study, which included 369 patients, reported the following clinical findings⁹.

Fever – 95 %

Splenomegaly – 89 %

Hypertriglyceridemia or hypofibrinogenemia – 90 %

Hemophagocytosis – 82 %

Ferritin >500 mcg/L – 94 %

3. Evaluation and Diagnostic Testing

Initial evaluation

Most patients with HLH are acutely ill with multiorgan involvement, cytopenias¹⁰, liver function abnormalities, and neurologic symptoms. Before the possibility of HLH can be suspected patients may have had a prolonged hospitalization without a clear diagnosis. In such cases a rapid evaluation for organ involvement including testing for signs of bone marrow insufficiency, LFT abnormalities, neurologic involvement and immune activation should be considered with the aim of starting treatment as soon as possible once the diagnosis (or a high likelihood) of HLH is established. Extensive testing for underlying infecting organisms should be done, correlating epidemiologic data and the patient's medical history.

The physical examination should focus on identifying rashes, bleeding, lymphadenopathy, hepatosplenomegaly, and neurologic abnormalities. A thorough examination for signs of other organ involvement (e.g., cardiac, respiratory) is also necessary. Others, including serum ferritin, triglycerides, and screening immunologic studies, should be done immediately. Identifying signs of infection and specific organ injury is helpful in making the diagnosis of HLH, as well as for management of organ-specific complications.

Immunologic and cytokine studies are appropriate for those suspected of having HLH based on the results of the initial evaluation

HLH-2004 Guidelines For Diagnosis of HLH

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| HLH-2004 requires 1or 2 of the below to be fulfilled |
| 1.Molecular Diagnosis Consistent With HLH |
| 2.Diagnostic Criteria With 5 Or 8 Of the Following Symptoms: |
| Fever |
| Splenomegaly |
| Cytopenias Affecting >2 Lineages in Peripheral Blood |
| Haemoglobin <9 G/Dl (<10 G/Dl in Infants <4 Weeks Of Age) |
| Platelets <100000/ μ l |
| Neutrophilia <1000/ μ l |
| Hypertriglyceridemia :Fasting Triglycerides >265 Mg/Dl and/or Hypofibrinogenemia: <1.5 G/L |
| Hemophagocytosis in the Bone Marrow, Spleen, Lymph Nodes or Liver |
| Low or Absent NK Cell Activity |
| Ferritin >500 μ g/L |
| Increased Soluble CD25(IL-2r) Concentration:>2400 U/ml |

Several other characteristics are associated with HLH including cerebrospinal fluidpleocytosis, elevated cerebrospinal fluid protein, liver histology consistent with chronic persistent hepatitis, cerebro-meningeal symptoms, lymphadenopathy, skin rash, hypoproteinemia, hyponatremia, increased Very Low Density Lipoprotein or decreased High Density Lipoprotein.

Currently, a clinical diagnosis of HLH currently requires 5 of the 8 criteria originally based on the Treatment Protocol for Hemophagocytic Lymphohistiocytosis 2004 (HLH-2004) trial (Table 1) or a molecular diagnosis using the genetic tests of FHL. The primary difficulty in all cases of HLH is an early suspicion of disease before end-organ damage is inordinate. In the case of HLH in malignancy, the situation is complicated further because many of the signs and symptoms of HLH may result from HM, HLH or both. The symptoms such as fever, multiple cytopenias and hepatosplenomegaly may be missed on initial presentation. These symptoms, when considered together, are useful in identifying HLH, but some symptoms present later in disease course, whereas others may not develop at all in cases of malignancy-induced HLH. Prognosis in malignancy-induced HLH is poor overall compared with other forms of HLH. Life span of patients with HLH was estimated to be as low as 4%.The median survival without treatment is estimated as < 2 months¹¹.

4. Treatment

Before application of modern treatment regimens, survival with HLH was minimal¹². Untreated HLH is nearly uniformly fatal, therefore early diagnosis and prompt treatment are critical. Broadly, treatment of HLH involves immuno-suppressive and modulatory agents, biological response modifiers, treatment of the inciting illness if secondary, and subsequent stem-cell transplantation¹³.The treatment of HLH should be aimed at suppressing the immune system and treating the underlying disorder. It is pivotal to neutralize infected antigen-presenting cells to eliminate the stimulus for continuing immune activation. Management of HLH varies with different etiology.

The first international treatment protocol for HLH included an 8-week induction therapy with etoposide, high-dose dexamethasone, and intrathecal methotrexate for patients with central nervous system involvement followed by maintenance with cyclosporine; however, this regimen is used mainly in FHL¹⁴.

Treating the inciting infectious agent is important in infection-related HLH, treating the identified organism alone is not enough^{15, 16}. In a multivariate study of patients on treatment with different regimens like corticosteroids alone, intravenous immunoglobulins alone, CSA alone or a combination of treatments without etoposide with another group of patients receiving only Etoposide, significant survival rate was observed with early introduction of etoposide¹⁷.

Salvage therapy:

Irrespective of many advances in treatment regimens, up to 25% of children with HLH cannot undergo HSCT due to advancing disease. Discarding of cytokines and other inflammatory mediators via plasmapheresis has been described to support patients until other therapies have reached therapeutic effect.¹⁸⁻²⁰ Recombinant human thrombopoietin has been used as supportive therapy for thrombocytopenia in HLH.²¹ The use of monoclonal antibodies (MABs) like Alemtuzumab, Daclizumab and Infliximab has been described in many case reports. Alemtuzumab targets the CD-52 antigen, which is expressed on most lymphocytes, monocytes, macrophages, and dendritic cells.²²⁻²⁴ Infliximab targets TNF, and daclizumab targets CD-25. Both have been used with reported success.²⁵⁻²⁷ Additionally, etanercept, a TNF inhibitor, was used with success in a patient with acute lupus hemophagocytic syndrome.²⁸ Various case reports have elaborated on treatment of refractory cases with splenectomy²⁹ and even liver transplant for the damage caused by the unbridled macrophage activity.³⁰

5. Case Presentation

Case I

A 30-year-old married male presented with complaints of fever since 25 days and cough with expectoration since 15 days. Fever was high grade and intermittent with two to three spikes every day. The fever used to come to baseline with medication. After ten days, he started having whitish expectoration, 6 - 7 spoons per day which increased in supine position. He also complained of chills, headache, bodyache, nausea, vomiting, decreased appetite, and sleep disturbances. There was no other complaint. He had a history of pulmonary tuberculosis for which he took nine months' treatment in his childhood. He also gave history of jaundice seven years ago. General and systemic examinations were normal except for the presence of pallor and hepatosplenomegaly. At the time of admission, his hemoglobin was 9.9 gm/ dL, white blood cells 4, 100/cu.mm, platelets 1.20/cu.mm, all of which decreased with progression of the disease. Lymphocytosis was noted on peripheral smear with no abnormal cells (Table 1). Other remarkable findings on investigations were hepatosplenomegaly on ultrasonography abdomen, inflammatory changes in retina on fundus examination and

elevated serum levels of ferritin, lactate dehydrogenase, and triglycerides. The bone marrow examination revealed normal hematopoiesis. On admission, the patient was given empirical broad-spectrum antibiotics (third-generation cephalosporins and quinolones). As the fever did not respond, β -lactams with linezolid and antibiotics with anaerobic and atypical coverage were also given. (Blood culture was negative twice during the first 2 weeks of stay.) As no response was seen, he was also given empirical carbapenems, antimalarial, antitubercular, and antifungal therapy with multivitamins and other supportive treatments. However, he did not respond to any of the above treatments. As the fever still persisted, his general condition appeared to be worsening with persistence of high-grade fever, so we started intravenous methylprednisolone. The patient became afebrile the very next day of starting methylprednisolone, but fever relapsed as soon as it was stopped. Multiple blood transfusions, i.e., packed cell volume and platelet-rich concentrate, were also given as a part of supportive treatment. However, the fever persisted with pancytopenia. He then developed difficulty in breathing with a few infiltrates on chest X-ray. The patient was discharged against medical advice due to his personal problems. He was taken to another tertiary care hospital in his city where all investigations were repeated including bone marrow with no different yield in the results. His condition continued to deteriorate and he expired about a month after his discharge from our ward.

Case II:

A 64 year old lady without any comorbid conditions presented with fever since 3 months which was acute onset, low grade, continuous, associated with dry cough and was relieved by anti-pyretics. Later, she developed breathlessness which was insidious in onset not associated with chest pain, wheeze or pedal oedema. The patient had similar complaints in the past i.e, continuous fever associated with breathlessness and dry cough. She had multiple hospital admissions for similar complaints and on evaluation, complete blood picture revealed pancytopenia for which bone marrow biopsy was done and was inconclusive. She was managed conservatively with antibiotics and hematinics for a week and referred to higher center for further management.

On general examination, patient was pale and rest of the examination was within normal limits. On investigation, she had pancytopenia, chest x ray showed right basal consolidation and ultrasonography of abdomen and pelvis showed mild hepatosplenomegaly. Peripheral smear revealed presence of microcytosis, hypochromia, target cells and occasional promyelocytes and band cells. Further investigations showed elevated serum ferritin levels, hypertriglyceridemia and raised lactate dehydrogenase levels. Investigation for malaria and Dengue IgM were negative but Dengue IgG was positive. Bone marrow examination showed hypercellular marrow with maturation arrest in myeloid series. Cytogenetic analysis revealed normal karyotype. FISH panel showed no evidence of deletion of chromosomes 5, 7, 20. The patient was given intravenous antibiotics (Carbapenams and Glycopeptides), steroids, antifungals, hematinics and nebulization along with other symptomatic and supportive treatment. However, she

did not respond to any of the above treatments. She developed difficulty in breathing and then patient needed ventilatory support. However, it also did not make any difference in the patient's condition who deceased following cardio respiratory arrest after one hour.

6. Conclusion

Despite many studies and research, specific management guidelines and evidence based options are very few and much work remains to raise awareness regarding diagnosis and improve the effectiveness of treatment regimens.

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