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Hemophagocytic Lymphohistiocytosis - Revisited

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ABSTRACT

Hemophagocytic lymphohistiocytosis is a potentially life threatening condition characterized by aggressive proliferation of macrophages and T lymphocytes leading to haemophagocytosis of other blood cells and multi organ failure. It can be primary or genetic & secondary or reactive. Secondary form commonly occurs in adult population in the setting of infections, malignancies, autoimmune diseases & drugs. The immune response leads to hypersecretion of proinflammatory cytokines. Diagnosis is based on the criteria laid down by the Histiocytic Society in 2004. Raised serum ferritin level is an important laboratory hallmark for diagnosis. Corticosteroids, cyclosporine, etoposide can be used in the treatment. Macrophage activation syndrome if left untreated has been associated with rapidly fatal outcome hence high index of suspicion is needed among the physicians.

Introduction

Macrophage Activation Syndrome is more properly referred as "Hemophagocytic Lymphohistiocytosis" (HLH). It is a potentially fatal hyper inflammatory state. The characteristic signs & symptoms are due to overactive but ineffective immune response. The activated macrophages engulf erythrocytes, leukocytes, platelets and other blood precursor cells which is described as hemophagocytosis. HLH is classified as primary or genetic & secondary or reactive[1]. Secondary form commonly occurs in adult population in the setting of infections, malignancies, autoimmune diseases & drugs. In case of HLH secondary to infections the most common triggers are viruses, bacteria, parasites & fungi[2].

The spectrum of HLH in adults has not been well characterised & it is the presence of certain clinical features in a unique pattern that define HLH.

Although there are diagnostic guidelines for familial HLH, they are far from being satisfactory and gold standard is missing. For instance according to literature, morphological evidence of hemophagocytosis in bone marrow or other tissues is considered "gold standard" however histiocytic society guidelines say it is not a must for diagnosis and is taken as a supportive criteria only. All symptoms of HLH to a lesser extent may also be found in a normal immunological response. However it is the severity of clinical picture, laboratory findings along with rapid progression of symptoms which should alert the physician[3]. The limited awareness of this type of disorder & the absence of robust clinical guidelines are to blame for delayed diagnosis & dire consequences.

In such scenario waiting for all diagnostic criteria laid down by histiocytic society to be fulfilled & histological confirmation on bone marrow may be too late, resulting in negative impact on the outcome. Hence there is a need to suspect and catch the disease at an early stage even when 3-4 diagnostic criteria out of 8 are present.

Pathogenesis :

The sequence of events leading to reactive HLH remains incompletely understood. Mechanisms currently accepted are[2,4].

1) Inappropriate immune response leading to persistent macrophage & T cell activation.
2) Prolonged stimulation by the antigen leading to repeated cascade of cytokine production.

Common infectious diseases prevalent in our country like tuberculosis, malaria, typhoid, leptospira, scrub typhus have been commonly associated with it[5]. Studies have shown that Leptospiral outer membrane constituents activate macrophages through CD14 and the Toll-like receptor 2 (TLR2). The hallmark of this syndrome is severe impairment of cytotoxic activity of Natural killer (NK) cells and T lymphocytes which is mediated through release of cytolytic granules containing perforins[6].

Commonly associated malignancies include lymphomas & leukaemia especially Acute lymphoblastic leukaemia. Among the infectious causes Epstein Barr virus is most commonly found in association with HLH[7,8].

Clinical features

Clinical manifestations are due to hyper activation of macrophages & T cells and infiltration of these cells into various organs causing damage. Patients with HLH commonly have evidence of hepatitis which ranges from mild elevation in transaminases to fulminant hepatic failure. Coagulation abnormalities are often noted that lead to bleeding diathesis. Neurological manifestations like seizures, drowsiness, irritability, cranial nerve palsies may be predominantly present[9].

Neurological features although being common & distinct, are not part of current diagnostic criteria. Skin manifestations like maculopapular rash, petechiae, may be seen.

The revised diagnostic guidelines by histiocytic society 20041

Persistent fever
Hepatosplenomegaly
Cytopenias affecting ≥2 of 3 lineages in the peripheral blood • Haemoglobin <9gm/dl • Platelets <100000/cumm • Neutrophils <1000/cumm
Fasting triglycerides ≥3.0 mmol/L (i.e., ≥ 265mg/dl) & /or Fibrinogen ≤1.5 g/L
Serum ferritin ≥ 500µg/L (i.e., 500 ng/ml)
Hemophagocytosis in bone marrow or spleen or lymph nodes
Low or absent NK cell activity

Hyperferritinemia is an important laboratory hallmark of HLH that has received increased attention. Mechanism leading to hyperferritinemia in HLH is not entirely understood. Allen et al found that S.ferritin >10000 mcg/L 90% sensitive and 96% specific for the diagnosis of HLH[10]. Such high Ferritin levels have

been reported in the early acute phase of HLH and is considered to an indication for IVIG therapy. A bone marrow examination is recommended in all patients with hyperferritinemia.

Good correlation between ferritin levels & response to therapy has been observed. Recent studies show that low levels of glycosylated ferritin in the presence of high levels of total serum ferritin may be another helpful marker in the diagnosis[11].

SCD25 produced by activated T cells has turned out to be very useful in estimating disease ACTIVITY[7]. Schaer et al suggested that sCD163 is a specific marker for activation of macrophages and levels are elevated in HLH[12].

Bone Marrow Study :
It is an important procedure for the morphological diagnosis of HLH. Though a good criterion for diagnosis of HLH it is not an obligatory feature. Initial bone marrow study may be negative & repeat examination may be required. Failure to reveal hemophagocytosis does not exclude the diagnosis HLH[7,13].

Therapy :
The immediate aim in the treatment of any patient with HLH is to suppress the severe inflammation that is responsible for life threatening symptoms. Another aim is to remove the stimulus for the ineffective activation of T cells. There is no need to distinguish between primary or secondary HLH at the time of diagnosis as treatment for majority of forms of HLH remains on the similar lines[8]. Effective therapy can considerably reduce the mortality. All primary HLH patients need bone marrow transplant for definite cure.

Corticosteroids :
They are one of the cornerstone of HLH treatment. Hyper inflammation can be controlled with corticosteroids which inhibit expression of cytokines. Dexamathasone is extensively used in standard treatment protocols. Pulse therapy in the form of methylprednisolone 1gm is also employed.

IVIG :
It is used mainly for its anti-inflammatory potential. IVIG act by alteration of the activity of pro-inflammatory cytokines along with their synthesis and release[14]. Viral infection associated HLH patients seem to benefit the most. The main predictive factor for the response is early administration. IVIG is generally well tolerated however renal function has to be monitored. It may control both the virus replication and lymphohistiocytic dysregulation induced by infection.

Etoposide :
Standard treatment protocol includes etoposide along with dexamethasone. Etoposide induces apoptosis in lymphocytes as well as in macrophages. It may be life saving especially in patients with Epstein Barr virus associated HLH & inhibits protein synthesis in EBV infected cells[8].

Cyclosporine A[15]:
It prevents cytotoxic T lymphocyte activation. Cyclosporin A has also been shown to affect macrophage function of cytokine production. It has proven effective in treating severe or steroid resistant cases of HLH. Resolution of fever & other laboratory abnormalities occur in a short period of 2-3 days.

Newer modalities:
Several treatment modalities are now being tried with variable results. infliximab, rituximab, antithymocyte globulin, alemtuzumab are noteworthy[7,8]. ATG (Antithymocyte Globulin) – although ATG might be equivalent to etoposide in situation of refractory HLH, cost & potential side effects limit its use. Rituximab can help in EBV related HLH. Alemtuzumab (anti CD52 antibody) has demonstrated significant activity in suppression of T lymphocytes and shown promise in refractory HLH.

Salvage therapy
Many patients fail to respond to the standard treatment regimens hence high dose pulse corticosteroids in the form of methylprednisolone, alemtuzumab & ATG have proved successful in such patients. However treatment needs to be individualised in each case.

Summary
The correlation between all variables poses a tremendous diagnostic challenge.
We emphasize the importance of early suspicion of HLH because diagnostic difficulty lies in the lack of pathognomonic features or specific diagnostic tests for it. As physicians are commonly confronted with patients presenting with persistent fever, hepatosplenomegaly & pancytopenia it should be remembered that this may masquerade a more sinister & fatal syndrome.

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