Hemophagocytic Lymphohistiocytosis: An Uncommon Clinical Syndrome

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an acute life threatening clinical syndrome that is characterized by an uncontrolled activation and proliferation of the cells of monocyte/ macrophage lineage secondary to various inherited or acquired disorders of immune function[1,2]. This rare clinico-pathological syndrome is characterized by uncontrolled systemic hyperinflammation caused by hyper-cytokinemia driven by an ineffective immune system that has gone haywire[3].

Histologically, it is characterized by the presence of activated macrophages and histiocytes with hemophagocytosis in reticuloendothelial tissues including bone marrow, lymph nodes and spleen.[3] Hemophagocytosis is the pathological appearance of erythrocytes, leucocytes, platelets or their precursors phagocytosed by large histologically benign appearing activated macrophages. Macrophages, being important as one of the first line of body defense against infection are important in capturing, processing and later presenting an antigen to NK cells and T cells. Therefore these cells have an important role in both innate and acquired immunity by way of direct phagocytosis and by secretion of various cytokines and chemokines respectively. Hereditary or acquired abnormalities of this function of macrophages and the secondarily dysregulated chemical signals that propagate the immune response cause abnormal control and low or absent natural killer (NK) cell and CD8+ cytotoxic T lymphocyte (CTL) cytotoxicity which is one of the hallmarks of HLH.[4]

Hemophagocytic Lymphohistiocytosis (HLH) is a rare condition with an estimated incidence of around 1.2 per million individuals per year[5,6,7]. However it is almost certainly an underestimate[7]. Farquhar[2] presented the first cases of 4 sibling afflicted in early infancy by a syndrome of irritability, fever, hepatosplenomegaly and pancytopenia. All 4 siblings expired. Autopsy showed proliferation of histiocyte like cells in the reticuloendothelial system with prominent hemophago-cytosis and it was named as "Familial Hemophagocytic Reticulosis". Later similar clinical presentations were seen with a host of other conditions including infect-ions, malignancies and rheumatological diseases.

The Histiocyte Society in 1987, by consensus, adapted a single unifying appellation of "Hemophago-cytic Lymphohistiocytosis" for this syndrome and defined a set of clinical and laboratory criteria for diagnosis that have been updated twice, latest in 2004.[8,9]

The predominant clinical findings of hemophago-cytic lymphohistiocytosis (HLH) include persistent fever and splenomegaly[5]. Lymphadenopathy, skin rash, jaundice and edema are also seen. The laboratory findings include cytopenias, coagulopathy with hypofibrinogenemia, hypertriglyceridemia, elevated levels of ferritin and serum transaminases. Serum Ferritin >10,000 μg/L has been seen to have a particular specificity for the diagnosis.[10,11] Not uncommonly, the condition manifests as neurological symptoms including lethargy, irritability, seizures or focal deficits that is associated with CSF pleocytosis and elevated protein.[12] Histopathologically there is widespread accumulation of activated lymphocytes and mature macrophages with hemophagocytosis that is noticeable in the bone marrow, spleen, lymph nodes, liver and even the CSF. Liver histology is commonly akin to chronic persistent hepatitis[7]

Broadly, HLH can be classified according to the underlying etiology into either primary (genetic) or secondary (acquired) HLH.[13] The distinction is difficult since the clinical presentation is similar in both. The primary form is known as familial hemophagocytic lymphohistiocytosis (FHL) and it has an estimated incidence of around 1:50,000 live-born children.[6] It is a constellation of disorders inherited in an AR or X Linked recessive manner that have a common phenotypic manifestation of abnormality in the proteins involved in the cytolytic pathway of macrophages, NK cells and Cytotoxic T Lymphocytes. The genetic defects have been identified in all except a few (FHL1) (Table.1).[7,13]

Table 1: Genetic defects causing Familial Hemophagocytic Lymphohistiocytosis

Disease	Gene	Chromosome	Defect
FHL1	Unknown	9q22.1-23	-
FHL2	PRF1	10q22	Absent perforin in vesicle
FHL3	Unc13	17q25	Vesicle Priming
FHL4	STX11	6q24	Vesicle docking and fusion
FHL5	STXBP2	19P13	Vesicle docking and fusion
Griscelli Syndrome type 2	RAB27A	15q21	Vesicle fusion and release
Lysinuric protein intolerance	SLC7A7	14q11.2	Protein transport
Chediak Higashi Syndrome	LYST	1q42.1-42.2	Vesicle trafficking
Hermansky Pudlak type II	AP3B1	5q14.1	Vesicle trafficking
XLP1	SH2D1A (SAP)	Xq25	CD8+/ NK cell cytotoxicity
XLP2	BIRC4 (XIAP)	Xq25	Multiple signaling pathways

If left untreated, FHL is a universally fatal disease with a median survival of less than 2 months after diagnosis. The onset is typically during infancy or early childhood.[13] Family history is often negative since the disease is recessive and is usually made retrospectively.

Those patients who manifest HLH without an inherited genetic defect are classified as having secondary HLH. Though the data on its incidence is scarce, it is probably more frequent than primary HLH[3]. Secondary HLH (sHLH) may develop as a result of strong antigenic activation of the immune system, which may, for example, be caused by a severe infection. sHLH has also been described in immune-compromised hosts in association with infections like EBV (VAHS),[13,14] bacterial infections like tuberculosis[15] and even protozoal infections like malaria and leishmaniasis (IAHS)[16]. sHLH may also be occurring as a complication of some malignancies, rheumatological disorders or some metabolic diseases also[7].

There are no reliable criteria to distinguish primary and secondary HLH, clinically and histologically. The onset of FHL is most common in infancy, but has been reported also in adolescents and young adults. Secondary HLH is found in all ages. In infants, a primary cause of HLH is more likely than a secondary cause[9,17]. Neonatal HLH with an onset within four weeks after birth is rare and sometimes presents with unusual presentations[18]. The diagnosis is frequently delayed.[19]

Pathophysiology

The pathogenesis of HLH, despite all the gain in knowledge and ongoing research is still unclear and speculative. Primary HLH is thought to be caused by defective immunological signals that start the cascade at the outset. These results in persistent activation of macrophages and cytotoxic T cells that are secondarily ineffective in removing the antigenic stimulus that leads to ongoing stimulation of the immune effecter cells. Failure to clear the pathogen and to terminate the immune response both play important roles in perpetuating the cycle of persistent inflammation and hyper-cytokinemia. The pathogenesis of secondary (acquired) HLH is even more complex and unclear. Many patients with secondary forms of HLH have however been found to have polymorphisms in the set of genes causing familial HLH.[7]

The mechanism of the cytolytic activity of macrophages involves the lysosomes containing Granzyme B and perforin. By steps of activation, polarization, docking, priming and fusion in sequence, there is release of the lysosomal contents into the immunological synapse. Perforin causes formation of holes in the target cell membrane wherefrom the other lysosomal contents enter and lead to target cell killing.

Secondary HLH has been seen in association with infections (IAHS), most often with viruses like EBV but not uncommonly with bacteria like M tuberculosis, protozoa like leishmaniasis and malaria. It occurs with greater frequency in immunocompromised host but can occur in an immunocompetent individual also. IAHS has a presentation similar to FHL and it may be difficult to distinguish the two. Quite often, the first presentation of Familial HLH is in association with an infection and to make matters more complicated primary HLH may have a secondary infection due to immune dysregulation. So, merely the isolation of an organism from blood in a patient with HLH does not per se mean that

the patient has secondary HLH and therefore rule out FHLH.[20-23]

Malignancy associated HLH has been seen in pediatric age group in association with Leukemias (AML and ALL) and solid organ malignancies like Rhabdomyosarcoma, neuroblastoma, Hodgkin's and Non-Hodgkin's Lymphoma.[20,24] It might present as a complication of the chemotherapy or as de novo presentation of the masked cancer itself.[25] It has been proposed that the malignant clone potentiates the state of hyper-cytokinemia leading to HLH. An interesting observation is that some of these cancers have been linked to EBV infection.

Macrophage activation syndrome is a life threatening condition associated with systemic inflammation in certain immunological syndromes like Juvenile idiopathic arthritis and SLE. It has common clinical and laboratory features with HLH as has been classified as a form of secondary HLH. It is characterized by a "cytokine storm" that is secondary to over activation of lymphocytes and macrophages.[26]

Clinical Features

The cardinal clinical signs and symptoms are grossly nonspecific and include fever and splenomegaly (with or without hepatomegaly).

Persistent and high grade fever is universal and usually the first sign. Other clinical features that may be present include abdominal distention, edema, jaundice, ascites and bleeding. Encephalopathy and CNS dysfunction like seizures and focal deficits may be present and may be associated with CSF pleocytosis. Cytopenias especially thrombocytopenia, with suboptimal response to transfusions is characteristic; leucopenia and neutropenia are more variable. Elevated transaminases, hypertriglyceridemia, hyperferritinemia, hypofibrinogenemia and elevated levels of IL-2, IL-6, IL-8, IL-10, interferon, and TNF are seen. Although the levels of these cytokines are not measured routinely, the serum level of IL2 receptor (sCD25) have been seen to be particularly specific for this condition and has therefore been included in the diagnostic criteria. Bone marrow or other tissue like spleen, lymph nodes and even lungs and CSF may show evidence of hemophagocytosis.

Diagnostic Criteria (Table 2)

The diagnostic criteria were proposed on the basis of HLH 1994 trial and later revised in 2004 by the Histiocyte Society (Henter JI).[9,22,23]

Table 2. Diagnostic guidelines for HLH-2004 (Henter JI)

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled.
1. A molecular diagnosis consistent with HLH.
2. Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below).
A) Initial diagnostic criteria (to be evaluated in all patients with HLH).
Clinical criteria * Fever * Splenomegaly
Laboratory criteria * Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood: Hemoglobin (<90 g/L), Platelets (<100 x 109/L), Neutrophils (<1.0x 109/L). (In infants <4 weeks: Hemoglobin <100 g/L) * Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides ≥3.0 mmol/L (i e ≥265 mg/dL), fibrinogen ≤1.5 g/L).
Histopathologic criteria * Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy.
B) New diagnostic criteria. (2004)
* Low or absent NK-cell activity (according to local laboratory reference) * Ferritin ≥500 microgram/L * Soluble CD25 (i.e. soluble IL-2 receptor) ≥2400 U/ml

In HLH-94, diagnosis was based on five criteria (fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis) which were increased to eight in 2004 (low/absent NK-cell- activity, hyperferritinemia, and high-soluble interleukin-2- receptor levels).

Five out of eight criteria must be fulfilled for diagnosis unless there is a family history or the molecular diagnosis is consistent with HLH.

Management

Untreated HLH has a high mortality rate. The uncontrolled inflammation leads to persistent neutropenia and secondary immunodeficiency and death usually from bacterial or fungal infections as well as from cerebral dysfunction. Before the institution of chemotherapy with epipodophyllotoxin along with immunosuppression, the outcome was universally fatal. The first organized therapeutic protocol, HLH-94, used combined chemotherapy with etoposide, dexamethasone, cyclosporine upfront and in cases with CNS symptoms, intrathecal methotrexate and corticosteroids, that resulted in the estimated 3-year overall survival rate of 55% and 51% in sHLH and FHLH respectively. The probability of survival for patients with FHLH after hematopoietic cell transplantation (HCT) was 62%[8,9].

Reported mortalities in secondary HLH vary from 8%-22% in rheumatologic-HLH (macrophage activetion syndrome or MAS) to 18%-24% in EBV-HLH[21,22]. Spontaneous partial remissions are common[22]. Nonetheless delay in diagnosis and multiorgan involvement is associated with an inferior prognosis, and whether primary or secondary, therapy needs to be instituted promptly to prevent irreversible tissue damage.[7]

Management of HLH varies depending on the cause. HLH is treated primarily with the treatment of inciting causes in secondary HLH, along with immunosuppressants and immunomodulators, and in FHLH, subsequent stem cell transplantation. If undertreatted, patients with HLH were found to succumb to progressive multi-organ failure.[27]

In cases of familial HLH Hematopoietic stem cell transplantation alone offers the possibility of a permanent cure. In literature to date two protocols have been used in treating primary HLH: The HLH 94 protocol which was proposed in 1994 and subsequently revised in 2004 and an alternative regimen as described by Mahlaoui et al.[28]

HLH-2004 protocol[9] consists of a chemotherapy regime along with immunosuppressive therapy. Chemotherapy regimen includes etoposide and dexamethasone with intrathecal methotrexate (If CNS is involved). Immunotherapy is with cyclosporine. HLH 2004 includes three stages of treatment:

1. The initial therapy with intention to achieve resolution and reduce complications.
2. Continuation therapy to maintain resolution of disease followed by
3. Hematopoietic stem cell transplantation.

Combination of dexamethasone, etoposide and cyclosporine with or without intrathecal methotrexate is used at the outset. Supportive care with broad spectrum antibiotics, antifungals and antivirals play a crucial role in the management and should be continued. In primary HLH patients without HSCT the disease will progress inevitably. Once suitable donor is available all patients should proceed with HSCT. In case of secondary HLH treatment should be discontinued once disease is in resolution. However, close follow up of the patients is warranted once therapy is stopped as there is a chance of reactivation. If disease reactivation occurs or the disease progresses, continuation of chemotherapy or intensification should be done followed by HSCT. Among total 249 patients in HLH-94 protocol study, the overall survival rates was 54±6% at a median follow up of 6.2 years.[29]

An alternate regimen was proposed by Mahlaoui et al[28] that included combination of ATG, corticosteroids, cyclosporine and methotrexate. In a study that extended over 14 years, 38 patients of FHL were followed up. Patients underwent HSCT when a HLA identical donor was available. Patients in whom ATG was used as first line therapy, 82% had complete remission while as when used as second line only 50% achieved complete remission. Overall ATG achieved complete remission in 73% of patients.

In infection associated HLH, treating inciting infection along with standard HLH protocol is important in achieving best results. Inclusion of etoposide early in the HLH protocols appears to have improved outcomes in patients with EBV infection.[30] Rituximab, which can eliminate EBV containing B cells has also become a useful addition to the treatment.[31] However, Leishmania associated HLH is treated with liposomal amphotericin alone without HLH protocol chemotherapy[32-36]

MAS associated HLH usually responds to high dose corticosteroids alone.[37,38]

HSCT in HLH: HSCT is the only curative treatment for patients with primary HLH with survival ranging from 50% for haploidentical donor HCT to 70% for a matched family donor HCT using a myeloablative-conditioning protocol.[39] For FHLH better results have been obtained after myeloablative allo-HSCT using HLA-matched related or unrelated donors and also when CNS disease was absent or quiescent at the time of transplant.[40] Reduced intensity conditioning before allo HSCT has been shown to have improved the overall survival up to 92% in FHLH.[41] However the problems with primary graft failure and loss of chimerism requiring donor lymphocyte infusions have limited more widespread application.

Horne et al in a study of 86 children treated with HLH-94 chemotherapy protocol followed by HSCT showed identical long-term disease-free survival (70% at 3 years) with both matched unrelated donor as well as with matched sibling transplants.[42] This was better than the survival seen with family haploidentical donor transplants or mismatched unrelated donor transplants that showed much less favorable results (DFS 50%). The same study also showed mortality of 30% in patients who received cord blood transplant[42].

The disease status at the time of transplant portends the possibility of better overall outcome with patients going into transplantation in good remission showing a better survival in most, but not all, studies. Moreover patients with FHLH not achieving remission should still undergo HCT as they have a 50% chance of survival after transplant.[43] For patients not achieving remission, salvage therapies with high-dose pulse corticosteroids and/or alemtuzumab have proven to be a successful strategy.[44] Other salvage therapies include antithrombin III,[45] infliximab (anti-TNF antibody)[46,47] and daclizumab (anti-CD25 antibody).[48]

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