Open Access Case Report

Haemophagocytic Lymphohistiocytosis (HLH) a Life-Threatening Complication of Tuberculosis

Nadeem Ikram
Tahir Mukhtar Sayed
Fakhira Noreen
Jahanzaib Maqsood

Akhtar Saeed Medical College & Farooq Hospital, Rawalpindi

Address for Correspondence
Dr. Nadeem Ikram
Akhtar Saeed Medical College & Farooq Hospital, Rawalpindi
drnadeemikram@gmail.com

Abstract

Haemophagocytic Lymphohistiocytosis (HLH) is an uncommon, potentially fatal, syndrome, that may rarely complicate the clinical course of disseminated tuberculosis.[1] Here we discuss clinico-pathologic and diagnostic parameters of a patient who satisfied the HLH diagnostic criteria 2004, as well as is showing strong probability according to H-Score for HLH .[2,3]
Keywords: Haemophagocytic Lymphohistiocytosis

Case Report

A middle aged woman whose ailment started with backache eight months back. Then she became unable to walk. Low grade fever was noticed. She presented in Farooq Hospital in a bed ridden state with pallor and jaundice. She received two units of red cells concentrate. MRI revealed fracture of lumber region. In laboratory investigations there was pancytopenia, with hyperbilirubinemia and very high alkaline phosphatase. She had hyertriglyceredima with hyperferrtinemia. Her condition deteriorated further. She became unconscious and was shifted to Medical ICU. Because of her pancytopenia, her bone marrow examination was performed. On aspiration labelled as Haemophagocytic Lymphohistiocytosis (HLH), due to presence of histiocytes with intense phagocytic activity. The assessment of histiocytic haemophagocytosis, on bone marrow aspiration smears was done: Low/mild:1-5 haemophagocytic cells per entire slide; Moderate: 6-10 haemophagocytic cells per entire slide; Severe: > 10 haemophagocytic cells per entire slide.1 Bone marrow trephine biopsy revealed granulomas with Langhan type of giant cells. Findings were suggestive of Tuberculosis. Her condition deteriorated further. She failed to survive (Table I; Figures 1-5)

Discussion

Haemophagocytic Lymphohistiocytosis (HLH), previously labelled as Haemophagocytic Syndrome, is a life threatening immune dysregulatory syndrome, caused by severe hypercytokinemia, due to highly stimulated, but ineffective immune response. Clinical manifestations of HLH are due to Hyper-activation of Cytotoxic T-Lymphocytes and Macrophages. Now it is well established that not just Histiocytes, but lymphocytes also play an important role in the pathogenesis of HLH, so it is labelled as Haemophagocytic Lymphohistiocytosis, rather than Haemophagocytic Syndrome.[4-7]

The hallmark pathophysiologic mechanism of HLH is exacerbated, but deregulated Th 1 cell –mediated immune response against an intracellular pathogen, macrophages hyperactivity, widespread haemophagocytosis and hypercytokinemia leading to multiorgan dysfunction. These results due to impaired or suppressed function of cytotoxic T cells and NK cells to effectively clear the antigenic stimulus and thus to check the inflammatory response.[8]

Organomegalies is the result of activation and proliferation of macrophages in that organ. The cytokine milieu in HLH is characterized by increased levels of IFN-γ, TNF- α,GM-CSF and IL-18. That cytokine's storm is largely responsible for cytopenias, hypertriglyceridemia (cytokine mediated inhibition of lipoprotein lipase), hyperferritenemia, fever and other pathognomonic findings. Highly elevated ferritin levels are strongly associated with HLH and its successive levels may provide a prognostic markers.[9]

HLH is broadly divided in two groups, genetic or familial and secondary. (Table I) Familial or childhood presentation of HLH is well established. This is associated with different mutations many of which are now will delineated. The familial form of HLH is an autosomal

recessive disease. Several defects in genes with important immune functions have been reported in patients with familial HLH, including mutations in the genes for perforin (PRF1), Munc 13-14(UNC12D) and Syntaxin 11(STX11), Mutations in the perforin gene have been reported in several patients with familial HLH and result in defective lymphocytes cytotoxic activity. Secondary HLH is associated with malignancies, infections and autoimmune diseases. In infections viral, most importantly EB virus, bacteria and fungi are incriminated as causative factors.

Table I: HLH associated with Tuberculosis: Clinical and Diagnostic Findings.

Clinical Presentation	
❑ Backache = 9 months ❑ Fever (intermittent; low grade= 03 months ❑ Difficulty to walk=03 months ❑ Unable to walk=01 months ❑ Altered consciousness=15 days ❑ Yellowish discolouration of eyes= 10 days ❑ Transfusion = 2 pints of Red Cells Concentrates	
Physical Examination	
Temperature	100 ^{O}F
Pallor	Present
Jaundice	Present
Liver	Enlarged (2 cm below costal margin)
Spleen	Enlarged (4 cm below costal margin)
Central Nervous System	-Unable to walk due to lumbo-sacral fracture -Patient progressively deteriorated with drowsiness and ultimately became unconsciousness
Investigations	
M.R.I	Fracture Lumbar Spine
Blood Complete Picture	Haemoglobin=7.0gram/dl;TotalLeucocytesount=1100/cmm;Platelet Count=17000/cmm;Reticulocytes Count= 0.4%
ESR	95 mm at the end of one hour
Ferritin	2100 ng/ml (R.R=15-120)
Triglycerides	570 mg/ml(R.R=Upto 150)
Fibrinogen	140 mg/dl (R.R=200-400)
Liver Function Tests	Total Bilirubin= 4.7mg/dl (R.R:Upto 1.0);ALT(SGPT)=95 U/L (R.R:7-43);Alk – Phosphatase=1108 U/L(R.R:65-360);Albumin=2.8 g/dL (R.R:3.2.-5.5)
Bone Marrow Aspiration	Erythropoiesis=Depressed;Megakaryocytes =Decreased;Myelopoiesis=Dysplastic; Histiocytes=Increased with Haemophagocytosis Diagnosis: HaemophagocyticLymphohistiocytosis ;HLH (Secondary to infection)
Bone Marrow Trephine Biopsy	Architecure:Effaced;Erythropoiesis/Myelopoiesis/Megakaryopoiesis: Depressed;Fibrosis: Focal; Granulomas with epithelioid cells and Langhan Type of Giant Cells are seen Diagnosis:Granulomatous Disease (Tuberculosis)

Mycobacterium is a rare, but documented cause of HLH. [5,6 10,11]

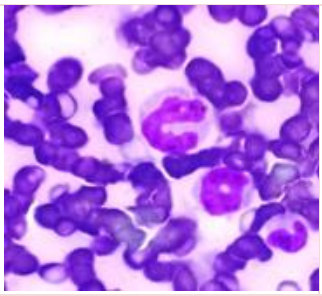

Figure 01. Tuberculosis associated HLH:Myeloid Dysplasia with doughnut shaped myeloid cell (Bone marrow aspiration)

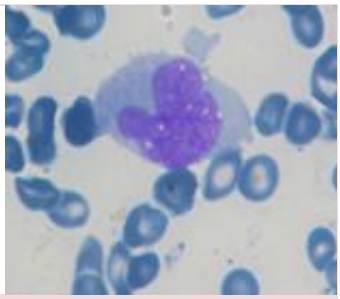

Figure 02. Tuberculosis associated HLH:Myeloid Dysplasia (Bone marrow aspiration)

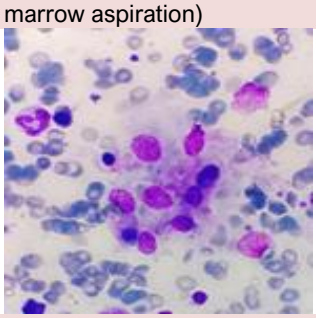

Figure 03. Tuberculosis associated HLH: Haemophagocytosis (bone marrow aspiration)

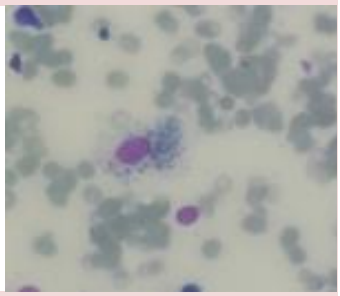

Figure 04. Tuberculosis associated HLH: Haemophagocytosis (bone marrow aspiration)

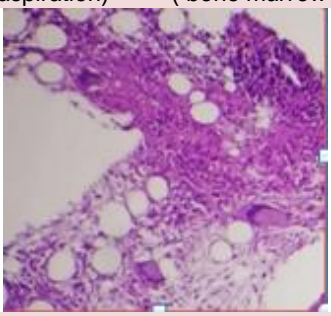

Figure 05. Tuberculosis associated HLH: Langhan type giant cell with peripheral arrangement of nuclei (bone marrow trephine)

What so ever is the triggering factor,at the outset it will initiate uncontrolled, but ineffective, immune activation and release of cytokines. In normal immune response cytotoxic T cells and natural killer cells act on target cells and kill the target cells through many mechanisms, for example release of Perforin. In HLH though immune system is hyper-regulated but is ineffective to kill target cells. There is excessive release of cytokines(Cytokines Storm). These cytokines lead to ectopic migration of lymphocytes to different organs, where they lead to multi-organ failure. Cytokines also lead to uncontrolled

activation of macrophages. These macrophages then phagocytose haemopoietic cells (Haemophagocytosis). Excess proinflammatory cytokines results in tissue infiltration by lymphocytes and macrophages leading to haemophagcoytosis and chacterisitic laboratory abnormalities inclusingcytopenias, coagulopathies, hyper-ferritienimia and hyper-trigylceridemia[10, 12]

Table II: Causes of HLH.

(I)Primary / Familial HLH (Mendalian inherited conditions lead to Familial HLH) (ii)Defects in the cytolytic functions of Cytotoxic T-cell and/or NK-Cells ;(ii)Defects in inflammasomes regulation (e.g., impaired Perforin expression and functions)		
(II)Secondary /Acquired HLH		
(A)Infection Related HLH	-Viral	(i)Herpesviridae(EpsteinBarr,Cytomeglo virus, Human Herpes Virus B, Herpes Simplex virus);(ii)-HIV;(iii)-Hepatitis B
	-Bacterial	(i)StaphAureus;(ii)Mycobacterium Tuberculosis;(iii)Mycoplasma
	-Fungal	(i)-Candida;(ii)Cryptococcus;(iii)Aspergillus
(B)Malignancy Related HLH	-Haematological Malignancies	(i)-Nk/T-cell Lymphomas;(ii)Acute Lymphoblastic Leukaemia;(iii) Hodgkin's Lymphoma;-(iv)Plasma Cell Leukaemia
	-Non-Haematological Malignancies	(i)Prostatic cancer;(ii)Lung cancer;(iii)Hepatocellular carcinoma
(C)Autoimmune Associated HLH	(i) Systemic Lupus Erythematosis ; (ii)Sajogran Syndrome;(iii) Spondyloarthropathies; (iii)Juvenile Idiopathic Arthritis (iv) Kawasaki disease	

For the diagnosis of HLH it is required to demonstrate a mutation or to have five out of eight criterias. (Table III). An Indian study demonstrated organomegaly , cytopenias, high ferritin and haemophagocytosis as persistent findings in majority of cases.[1] Early diagnosis of HLH is critical because of high early mortality, varying from 20% to 70% and the availability of effective therapy.[8,12]Different factors are associated with poor survival in patients of HLH with tuberculosis .Age more than 30 years, presence of co-morbidities, non-usage/ delayed usage of anti – tuberculous therapy (ATT), end- organ damage and persistently high levels of cytokines are important in determining the prognosis. End organ damage is due to cytokines mediated proliferation, ectopic migration and infiltration of cytotoxic lymphocytes and macrophages into various organs.[4,6] In the present case liver functions derangement and impaired consciousness depicts hepatic and neurological involvement, predicting poor prognosis. In our set up an important factor is the late diagnosis which ultimately leads to failure in getting proper treatment. Present case is an example of late diagnosis. Most likely her disease started as Pott's Disease Spine, but remained undiagnosed and eventually it entered into a dangerous stage of HLH, where she failed to survive .

Table III: HLH –Diagnostic Criteria.

Molecular identification of an HLH-associated gene mutation (i.e,PRF -1, UNC -13D, STX-11,STX-Bp2,Rab- 27A,SD-2DIA,BIRC-4);Children require documentation of homozygosity or compound hetrerozygosity of HLH-associated gene mutations. By comparison, hetrozygosity may be sufficient for adults if they have clinical findings associated with HLH
OR
Requires to fulfil 05 out of 08
1.Fever 2.Splenomegaly 3. Cytopenias in two or more lines: -Haemoglobin< 9.0 gram/dl - Platelets < 100 X 10^9/l - Neutrophils < 1 X 10^9 /l 4. Hypertriglyceredimia and/or Hypofibinogenemia - Fasting triglycerides ≥ 265 mg/dl OR - Fibrinogen <150mg/dl 5..Ferritin≥500 ng/ml 6. Soluble CD 25 ≥2400 U/ml 7.Haemophoagocytosis in bone marrow ,CSF or lymph node 8. Low or absent NK cells activity
Supportive evidence includes neurological symptoms with CSF pleocytosis and/or elevated protein,elevated transaminases and bilirubin, LDH > 1000 U/L, hypoalbunemia and hyponatremia

In Tuberculosis associated HLH it is hypothesized that Macrophages, T Lymphocytes, Cytokines and Mycobacterium tuberculosis all interact that ultimately leads to a vicious cycle. Tuberculosis disrupts immune homoestasis as well as leads to high levels of different cytokines. Both this immune dysregulation and excessive release of cytokines, inturn promotes haemophagocytic activity. Once phagocytosed the Mycobacterium tuberculosis can further act as an obligate intrcellular pathogen. This further increases the activity of Cytotoxic T Lymphocytes and to further increase hpercytokinemia. Mycobacterium can induce migration of macrophages to regional lymph nodes. In lymph nodes,these macrophages can lead to Cytotoxic T cells expansion and increased Cytokines release. [1,6]

Principles of management in HLH encompasses immnomodulation and tackling the triggering factor (Table IV). In the elimination of triggering factors effective anti-infectious therapy is pivotal. Red cell concentrates, platelets concentrates and Fresh Frozen Plasma, are required to be administered as per requirements. Dexamethasone is preferred over prednisolone due to its ability to cross blood –brain barrier. Intrathecal therapy using methotrexate with or without corticosteroids is mentioned in patients with CNS disease.[10-12] Etoposide containing regimens are generally recommended for children with HLH. In adults use of Etoposide is favoured in selected cases of HLH with refractory or severe disease with threatening multiorgan-failure HLH-2004 protocol confirms that a majority of patients may be rescued by Etoposide/Dexamethasone/Cyclosporine combination.

Table IV: Principles of Management in HLH.

Objective	Treatment Modality
1.Suppression of Hyper-inflammation (Immunosuppressives and immunomodulators)	-Corticosteroids -Intravenous immunoglobulins -Cyclosporins -Anti-cytokine agents
2.Elimination of activated immune cells and infected cells (Ctytotoxic T Lymphocytes and Histiocytes)	-Corticosteroids -T-cell antibodies (Antithymocyteglobulins ,Aletuzumab) -Retuximab)
3.Elimination of trigger	Anti-infectious therapy
4.Supprotive therapy (For cytopenias,coagulopathy,etc)	-Red Cell Concentrates Fresh Frozen Plasma -Anti Fungal agents -Antibiotics
5.Etoposide/Dexamethasone/Cycolosporine (HLH -2004 Protocol)	
6.Haematopoietic Stem Cell Transplantation	
7.Gamifant (Emapalumab-lzsg) for primary HLH	

Etoposide treats HLH by selectively eliminating pathologic activated T lymphocytes and may have utility as a novel immune modulator in a borad array of immunopathologic factors in HLH.[13] Allogenic hematopoietic stem cell transplantation and anti- FIN γ , Emapalumab (Gamifant) is approved for the treatment of primary HLH, in patients with refractory, recurrent or progressive disease or intolerance to conventional therapy. [14,15]

HLH by itself is a disease difficult to be managed. Init's association with Tuberculosis the situation further becomes difficult. First line anti-tuberculous drugs, such as Rifampicin, have an enzyme- inducing activity, which can lower the efficacy of drugs, such as Cyclosporin and Etoposide used in HLH 2004 protocol. HLH per se leads to significant derangement of liver functions, making the administration of Anti Tuberculous Therapy (ATT) as well as Etoposide difficult. HLH may even be exacerbated after initiation of ATT, which may be challenging .[16] In patients with severe disease , sepsis and with multiorgan failure it may be difficult to use cytotoxic agents ,such as Etoposide. In such situations, immunosuppression with corticosteroids and/or cyclosporins can be helpful. Targeted therapy for underlying disease is crucial in determining the outcome. It is required to individualize the treatment as per patient's clinico-laboratory status .[17,18]

Conclusion

HLH should be considered in patients of tuberculosis who present with organomegalies, cytopenias and end organ damage.

Tuberculosis in association with HLH, in the absence of prompt and effective therapy may lead to significant morbidity and mortality.

Prompt treatment of tuberculosis, in association with HLH, can reduce the mortality significantly

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