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Original Research Article

Hemophagocytic lymphohistiocytosis secondary to infections: a tertiary care experience

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ABSTRACT

Background: Hemophagocytic lymphohistiocytosis is an uncommon complication of various conditions. It is characterized by immune dysregulation and massive cytokine release causing multiorgan dysfunction. It is classified as primary and secondary to various etiologies like infections, malignancies and autoimmune disease. As it has high mortality, clinician awareness is important for early diagnosis and improved outcome. Aim of the study was to study the etiologies, clinical manifestations, complications and laboratory features in patients diagnosed with infection associated hemophagocytic syndrome (IAHS).
Methods: We have done retrospective analysis of all cases diagnosed to have Infection Associated Hemophagocytic Syndrome (IAHS) between March 2012 to November 2015 in a 1000 bedded tertiary care hospital in south India.
Results: Total five cases detected. Most of the cases are related to tropical infections (80%). All of them presented with fever, cytopenias and organomegaly. Ferritin and Triglycerides were elevated in all patients. Bone marrow hemophagocytosis was observed in 80% of cases. Diagnostic protocol of HLH 2004 was followed. Only 20% survival observed.
Conclusions: IAHS is a rare fulminant complication associated with diagnostic and therapeutic challenges because of overlapping clinical features with sepsis. Increased physician awareness, early diagnosis and therapeutic interventions may improve survival.

Keywords: Hemophagocytic lymphohistiocytosis, Infections, Tertiary care

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is an under recognized fatal condition occurring in many clinical situations. It is an uncontrolled hyper inflammatory state characterized by cytokine storm, multiorgan dysfunction leading to poor outcomes. However increasing awareness, new research, evolving knowledge about pathophysiological processes has led to considerable improvement in outcomes. HLH can be familial or acquired due to infections, malignancy, autoimmune diseases or metabolic conditions. Key players are cells like macrophages lymphocytes including cytotoxic T cells, Natural Killer (NK) cells and various mediators like Interleukins 1 and 6 (IL), Tumour Necrosis Factor (TNF) α and Interferon Gamma (IFNG).

India is a vast country with wide variations in geographical and atmospheric conditions. Infections are very common causes of mortality and morbidity in India

and this trend is reflected in HLH prevalence also.[1] Very small information is available regarding HLH from our country. High index of suspicion is required for early diagnosis. Although hemophagocytosis in bone marrow is a remarkable feature, it may not be seen in all cases. Clinical, biochemical and histological criteria have been proposed for diagnosis as a syndromic approach.[2] Outcomes depend upon underlying condition, early detection and treatment. Here we want to share our experience with infection associated hemophagocytic syndrome (IAHS).

METHODS

This is a retrospective analysis of clinical information of patients presented to our hospital between March 2012 and November 2015. All fulfilled the revised criteria of HLH -2004. Henter.[2]

Diagnostic criteria

One of the following criteria should be fulfilled:

- Molecular diagnosis consistent with HLH.
- At least 5 out of 8 criteria should be fulfilled:

a) Fever
b) Splenomegaly
c) Cytopeni as (at least 2 cell lines i.e. Hb less than 10gm/dL, Neutrophils less than 1 x 109 /L, Platelets less than 100x 109 /L).
d) Hypertriglyceridemia and/or Hypofibrinogenemia (Fasting triglycerides more than 265 mg/dL, Fibrinogen levels ≤ 1.5gm/d L)
e) Ferritin levels ≥ 500 µg/d L.
f) Hemophagocytosis in bone marrow or lymph nodes or spleen.
g) Low or absent NK cell activity.
h) Soluble CD 25 (soluble IL 2 receptors) ≥2400 U/m L.

RESULTS

Total 5 cases were segregated with IAHS diagnosis. The mean age at diagnosis was 34 years (range 28 to 50 years). All were males. Mean duration of fever was 30 days. Fever, hepatomegaly and/or splenomegaly were seen in all patients. All of them had at least a bi- or trilineage cytopenia, elevated liver enzymes, hyperferritinemia and hypertriglyceridemia. Four out of five patients had hypofibrinogenemia and hemophagocytosis in bone marrow.

Table 1: Clinical, laboratory, treatment and outcomes of all patients.

Serial No	Case 1	Case 2	Case3	Case4	Case5
Age	28	28	50	35	29
Etiology	Enteric fever	Sepsis	Scrub typhus	HIV	Miliary tuberculosis
Symptoms duration (days)	30	60	10	30	21
Fever	Yes	Yes	Yes	Yes	Yes
organomegaly	spleen	Spleen, liver	Spleen, liver	Spleen, liver	Spleen
HB gm /dl	8.4	6	8.4	6	11
TLC /cumm	600	2800	3400	2300	1800
Platelets /cumm	40000	100000	50000	1.9 l	50000
Total bilirubin mg/dl	0.7	4.6	7.9	1.4	2
Transaminases U/L(SGOT)	120	152	3176	289	86
Triglycerides mg/dl	518	888	243	362	264
Ferritin µg/L	1039	1650	1130	2036	2000
Fibrinogen gm/L	140	152	55	NA	190
S.LDH U/L	NA	843	11304	1068	2217
BM hemophagocytosis	Absent	Present	present	Present	Present
Treatment	Antibiotics	Antibiotics +steroids	Antibiotics	Antiretroviral Therapy	ATT +Steroid
Outcome	Survived	Death	Death	Death	Death

The etiological agents were scrub typhus, miliary tuberculosis, enteric fever, HIV infection and sepsis of unknown origin. Diagnostic methods used were weil felix for scrub typhus, miliary tuberculosis was diagnosed based on radiological and tissue diagnosis, enteric fever was diagnosed based on high titers in Widal test. All of them received treatment for underlying primary infection like doxycycline for srub typhus, antituberculous drugs for miliary tuberculosis, ceftriaxone for enteric fever, antiretroviral drugs for HIV infection and broad spectrum antibiotics in sepsis along with supportive care. Four out of five patients have developed multi organ dysfunction

and required mechanical ventilation. Two patients received steroids for HLH. Four patients expired due to multi-organ dysfunction and one with enteric fever survived. Entire data is displayed in Table1.

DISCUSSION

Hemophagocytic Lymphohistiocytosis is a rare underdiagnosed entity associated with varied spectrum of diseases ranging from familial and secondary to infections, malignancy and rheumatological illnesses. It is characterized by excessive and persistent antigenic stimulation due to defect in NK cells and cytotoxic T cells leading to immune dysregulation causing excessive release of many inflammatory mediators damaging several organ systems. Common infectious triggers include viruses like Epstein Barr Virus (EBV), Herpes, Dengue, HIV and many bacterial infections like tuberculosis, Rickettsiae, Salmonella and parasites like malaria and leishmania especially in North India.[3-14]

HLH secondary to infections has been classified as a separate entity under International classification of diseases by World Health Organization by ICD code 76.2. Very few studies have mentioned about incidence and prevalence of HLH. Reported incidence from Sweden was 1/50,000 live births and 7.5/10,000 live births from Turkey.[15,16] Although many case reports are available from India, no studies have mentioned incidence and prevalence to the best of our knowledge. Recent knowledge has contributed to pathogenesis of familial form rather than secondary form.

Only very few patients with infections develop HLH. This indicates that some unidentified genetic defect from host might predispose to this complication. The pathogenesis of secondary HLH is not clear but pathogenesis of EBV associated HLH is well established. It is believed that EBV latent membrane protein (LMP1) interferes with the T cell adoptor protein, signaling lymphocyte activation molecule associated protein (SAP) which in turn results in excessive T-cell activation and the cytokine secretion.[17] Defect in the function of cytotoxic T and NK cells causes persistent macrophage activation as these cells are involved in clearance of antigenic stimuli and termination of inflammatory response, excessive release of cytokines like IL1, 2, 6, INFG, TNF alpha causing various clinical manifestations of HLH.[18]

Fever is caused by IL 1, hepatopathy and coagulopathy are caused by TNF alpha. Hypertriglyceridemia is secondary to lipoprotein lipase inhibition by TNF alpha. IFNG causes macrophage activation in bone marrow leading to hemophagocytosis and engulfment of heme mediated by CD 163 leading to cytopenia and hyperferritinemia respectively.[19] Diagnosis of HLH is complicated by overlap of clinical features with sepsis. In adults presentation of HLH is less typical.[20] In a study done by Goel et al it was shown that bone marrow hemophagocytosis has a sensitivity of 83% and specificity of 60%.[21] Various combinations of high grade fever sometimes a second spike of fever after a brief period of recovery which coincides with fresh cytopenias, unresponsiveness to broad-spectrum antibiotics, new onset organomegaly or sudden increase in size of visceral organs in the setting of an infectious disease are some of the diagnostic clues for this disease.[22] Also in the resource poor settings, a single value of ferritin more than 10,000 in the absence of iron overload conditions like hemochromatosis and thalassemia syndromes can act as a surrogate marker for HLH with a sensitivity of 90% and specificity of 96%.[23]

High ferritin level is considered as both diagnostic and prognostic marker and high fibrinogen at the time of diagnosis is associated with prolonged survival.[24] Triglycerides have been evaluated as a diagnostic and prognostic marker for HLH with good sensitivity.[25] In present study diagnosis of HLH was done based on HLH 2004 criteria. We have not performed genetic and molecular analysis, NK cell activity and soluble IL2 receptor levels because of nonavailability. All our patients fulfilled 5 out of 8 criteria. Male preponderance was seen in this study may be due to increased exposure to infectious agents because of high outdoor activity.

In a systematic review of HLH in Indian subcontinent, Srinivasa et al have shown that age was not a predictor of etiology, usage of cyclosporine A, Etoposide was very low, major correlate with mortality was time of diagnosis and offending pathogen.[1] Infection was the most common etiological agent in secondary HLH.

In present study endemic infections have dominated. Diagnosis of scrub typhus was made based on high titres of Weil Felix (OXK 1:640 dilution) ,enteric fever by high titres of Widal test (O 1:640 and H 1:320) and miliary tuberculosis was diagnosed based on typical radiological features and demonstration of acid fast bacilli (AFB) on lung biopsy.

In a study done by Sankhyan in children of scrub typhus, hepato-splenomegaly was a prominent feature and 3 out of 15 patients developed HLH.[26] No clinical or lab features could reliably distinguish between groups of patients with and without HLH. HIV has been reported as an etiological agent of HLH in not only late stages of infection but also in acute infection.[27,28]

In a systematic review of HLH secondary to tuberculosis done by Padhi S, age more than 30years, associated comorbidities, marked hemophagocytosis in bone marrow and delayed administration of ant tubercular therapy were associated with poor prognosis.[10] Usage of steroids and immunomodulators did not alter the outcomes. High mortality was observed in this review.

Enteric fever is an uncommon cause of HLH. Few case reports are available in the literature.[13] Sepsis mimics

closely HLH. Progressive pancytopenia could be a differentiating feature of HLH from sepsis.[29,30] Several reasons have been proposed for increased mortality in HLH like delay in confirming etiologic agent, hesitancy to start immunosuppression in view of background infection, fear of drug related complications in view of background organ dysfunction.[1] Present study has shown male preponderance similar to other studies.[31]

Age, clinical features, lab abnormalities like ferritin level and cytopenia were in concordance with other studies.[32,33] Lactate dehydrogenase (LDH) is one finding not included in diagnostic criteria but elevated in all our patients similar to studies done by Fei Li et al and Riviere.[31,33] Low glycosylated Ferritin was found to be useful in assisting the diagnosis in patients with ferritin values between 500 and 10,000 µg/L.[34,35]

Bone Marrow (BM) score is based upon number of hemophagocytic cells per high power field, and classified as mild (1-2), moderate (3-5), severe (6-8), very severe (>8).[36] Bone marrow finding may be a late manifestation with false negativity if done early. It may be needed to repeat bone marrow examination to increase yield. H Score consisting of clinical, biochemical and cytological parameters has been proposed to assess individual risk of developing HLH.[37]

Mortality rates were significantly better in infection associated HLH.[31,38,33] An optimistic view is that we can expect good results from infection associated HLH as infection burden is high in India. The high mortality (80%) in present study could be due to delayed presentation and multiorgan dysfunction. Though we considered immunosuppression, in view of underlying infections we could not start in 3 patients.

Poor prognostic markers are age more than 50 years, fever of more than 3 days duration and DIC (38), immunosuppression, high ferritin, triglycerides, increased transaminases, C-Reactive Protein (CRP), LDH, low haemoglobin, leukopenia, thrombocytopenia and low sodium levels.[31] Though our patient cohort were young all of them had most of the above mentioned markers which could be the reason for high mortality.

CONCLUSION

To conclude, HLH is an unfamiliar, fatal condition associated with diverse etiologies. Recent awareness has increased recognition of this entity by clinicians. In our study by the time we made HLH diagnosis and considered immunosuppressive therapy patients developed multiorgan dysfunction, deteriorated rapidly and succumbed to illness. A high index of suspicion especially in patients with unresolving/recurrence of fever, persistent or worsening cytopenia along with elevated ferritin helps in early diagnosis. There is an urgent need for a surrogate marker for early diagnosis, management and better outcomes.

There are no definitive guidelines specifically for management of infection associated HLH (IAHS) which will resolve clinician's dilemma for early initiation of immunosuppression.

Present study is a small cohort and single centered study and there is a need for studies with large numbers.

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