Original Article

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Spectrum of Hemophagocytic Lymphohistiocytosis: Experience from a Tertiary Care Centre

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Abstract

Background: Hemophagocytic Lymphohistiocytosis (HLH) is a hyperinflammatory syndrome resulting from hypercytokinemia due to highly stimulated but ineffective immune response. Early recognition remains a challenge because its presenting features overlap with many other infective and inflammatory conditions. Prompt identification hence requires a high index of suspicion and detailed analysis of clinical and laboratory findings to arrive at a conclusive diagnosis. At the same time identifying the underlying cause is important as it guides treatment decisions thus reducing morbidity and mortality associated with this disease.

Materials and Methods: Consecutive patients meeting the diagnostic criteria for HLH, based on the HLH 2004 protocol of the Histiocyte Society, over a period of one year were included in the study. For these patients clinical features, laboratory parameters and etiological factors were studied.

Results: In the course of over one year 16 patients were diagnosed with HLH . Common presenting symptom was fever in all patients. The etiology in our study was mainly secondary to infections namely Dengue-2, Leptospirosis-1, Visceral Leishmaniasis-1, EBV infection=1, Tuberculosis-3 and other causes like Hodgkin lymphoma (NLPHL)-1, SLE-2 and 1 patient with Primary HLH. In 4 cases the etiology was unclear. All patients fulfilled the HLH 2004 criteria.

Conclusion: Clinicians should keep a high degree of suspicion in any patient presenting with fever, rapidly developing cytopenias and organomegaly. Also an attempt to identify specific etiology should be made in every patient as early diagnosis and specific treatment helps to reduce the high mortality associated with this disease.

***Keywords**: Benign histiocytes, hypercytokinemia, hyperinflammatory syndrome*

Introduction

Hemophagocytic Lymphohistiocytosis is a distinct clinical entity characterized by fever, pancytopenia, splenomegaly, and hemophagocytosis in bone marrow, liver or lymph nodes and is associated with considerable mortality and morbidity [1]. It is a disease of mononuclear phagocyte system with proliferation and activation of benign histiocytes [2]. It can be further classified into: 1) Primary/Genetic / Familial (Farquhar Disease) and 2) Secondary/ Sporadic /Reactive or Acquired HLH [3] which can be triggered by underlying infections, malignancies (particularly leukemia and lymphoma), immunodeficiency disorders and autoimmune disorders (the "macrophage activation syndrome" or MAS [3].

Macrophage activation syndrome (MAS) is usually associated with rheumatologic diseases like systemic-onset juvenile idiopathic arthritis (SOJIA), adult-onset Still disease, and systemic lupus erythematosus [4,5].

The basic defect in both genetic and acquired cases lies in the NK/T cell cytotoxic pathway. This leads to inability of NK/T cells to kill activated macrophages, which in turn leads to uncontrolled proliferation of activated macrophages [6] . Due to this immune dysregulation it leads to cytokine storm, unregulated macrophage and natural killer and T cell (NK/T cell) activity leading to progressive cytopenias and death if untreated [7]. Relapses are common and ultimate treatment is bone marrow

transplantation in primary or familial HLH due to tendency of recurrence and associated high mortality [8] . Genetic cases can be further divided into familial and those associated with immunodeficiency syndromes [9] .

Since the 1st description of perforin gene mutation by Stepp et al in 1999 significant insight has been gained into genetic mutations that give rise to primary HLH phenotype [2]. Familial HLH is due to mutations in various proteins involved in packaging, transport and release of cytolytic granules, namely Perforin 1, UNC13D, STX11 and STXB2. The common immunodeficiency syndromes associated with HLH are Chediak Higashi syndrome, Griscelli syndrome, Hermansky Pudlak syndrome and X linked lymphoproliferative syndrome [10].

Familial HLH is usually restricted to young children with an incidence of 1.2/1,000,000 children per year [11,12] . However actual incidence and prognosis of secondary HLH is not well known [8]. Secondary HLH, especially in tropics, can be associated with host of infections like leishmaniasis, malaria, dengue, tuberculosis and rickettsia. HLH as a disease entity thus presents major diagnostic and therapeutic challenges and hence often goes under-recognised due to which specific therapy is not considered early in the disease course contributing to higher mortality.

Aims and Objectives: The study was undertaken to describe clinical and laboratory features of patients diagnosed with Hemophagocytic Lymphohistiocytosis and to study their etiology and prognosis.

Material and methods

We conducted a prospective cohort study. Consecutive patients meeting the diagnostic criteria for HLH, based on the HLH 2004 protocol of the Histiocyte Society, over a period of one year were included in the study [13] .Age, sex, family history, parental consanguinity and relevant clinical features like fever, organomegaly, lymphadenopathy were noted. Following laboratory investigations were noted prior to instituting specific treatment : Complete blood counts including platelet counts, Serum ferritin , Serum triglycerides, Plasma Fibrinogen, Serum LDH, SGOT/AST, SGPT/ALT. Bone marrow examination was done for each patient.

Ethics: The Ethics Committee approval was obtained for the study and was in accordance with the Ethics Committee guidelines. In view of the pure observational nature of study, a waiver for consent was granted.

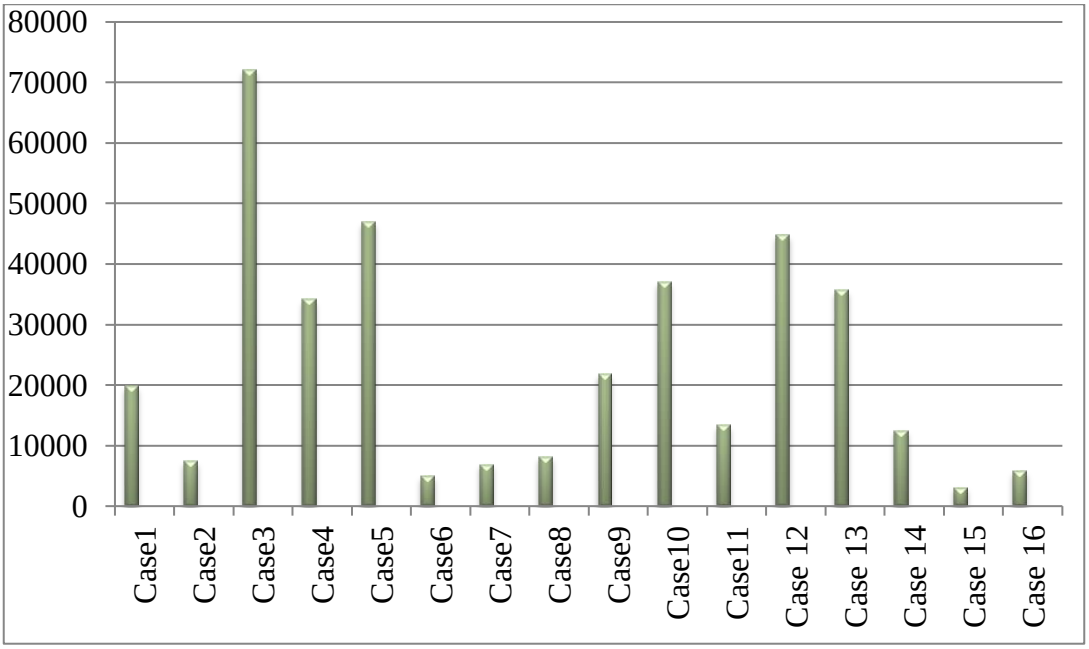
Statistical method: The continuous variables used in the data were represented as mean (standard deviation, SD) or median (interquartile range, IQR) while the categorical data was represented as percentages.

Result

In the course of over a year we diagnosed 16 patients with HLH. All these patients fulfilled at least five criteria required to establish HLH as per the HLH diagnostic criteria, 2004 [13] . Out of these 16 patients, seven were males and nine were female patients (M: F ratio= 1:1.28). The age distribution was variable, with mean age being 31.5 years { median 23 (range 2 months to 67 years) }. 8/16 patients were of pediatric age group out of which only one was an infant aged 2 months. 4/16 patients succumbed to their disease, mortality rate being 25% (Table 1.1, 1.2). Most common presenting symptom was fever which was present in all sixteen patients at the time of diagnosis (Table 1.1, 1.2).

Fever was of variable duration ranging from 7 days to maximum of 2 months. 3/16 patients in addition had bleeding manifestations in the form of petechiae, epistaxsis and hematuria. None of the patients had any neurological manifestations. 4/16 patients were born of third degree consanguineous marriage and only one patient had a positive family history of previous sibling death. Splenomegaly was present in all 16 patients, hepatomegaly in 9/16, and lymphadenoapthy in 6/16 (Table 1.1, 1.2). Bicytopenia was present in 56.25% (9/16) patients while 7/16 patients (43.75%) had pancytopenia (Table 2). Variable derangement of liver enzymes was observed in all patients (Table 3). Hypofibrogenemia (levels <150 mg/L) was present in 8 /16 patients. (Table 3), while hypertriglyceridemia was noted in 15/16 patients . Hyperferritinemia (>500 ng/ml) was present in all 16 patients with 10/16 cases having values >10,000 ng/ml (Graph 1) and the mean S. ferritin level being 23,397 ng/ml.

The etiology in our case series was mainly secondary to infections as depicted in Table 4. There was one infant aged 2 months for whom a diagnosis of primary HLH was suspected and which was confirmed by detection of perforin gene mutation. In four



Graph 1: Peak S. ferritin values in each patient before instituting treatment (S. Ferritin: males=30-400 ng/ml, females= 13-150ng/ml)

Table 1.1: Clinical features (Case1-8)

Patient	**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**
Age	14 y	55 y	17 y	2 m	29 y	56 y	62 y	41 y
Sex	F	M	M	F	F	F	F	F
Family history	Absent	Absent	Absent	Present	Absent	Absent	Absent	Absent
Consanguinity	Present	Absent	Absent	Present	Absent	Absent	Absent	Present
Fever	20 days	10 days	7 days	14 days	1 month	13 days	22 days	1 month
Spleen	8 cm	4 cm	2 cm	3 cm	1 cm	2 cm	2 cm	2.5 cm
Liver	2 cm	1 cm	1 cm	3 cm	-------	------	1cm	1 cm
Lymphadenopathy	Absent	Absent	Absent	Absent	Cervical + Axillary +	Absent	Absent	Coeliac +
Skin rash	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
CNS/other symptoms	Absent	Absent	Petechiae epistaxis	Absent	Absent	Absent	petechiae	Hematuria
Outcome	Survived	Survived	Survived	Expired	Survived	Expired	Survived	Survived
Etiology	Visceral Leishmaniasis	Leptospirosis	Dengue	Primary HLH	Tuberculosis	Unspecified	Dengue	SLE
Bone marrow Examination	Hemophagocytosis: (HP) absent in first bone marrow HP +ve in repeat aspiration done 1 m later with LD bodies+	Hemophagocytosis +	HP+	HP+	HP+	HP+	HP+	HP+
Treatment	Amphotericin	Dexamtheasone 2 weeks and antibiotics	Dexamethasone for 2 weeks, supportive care.	HLH-94 protocol	ATT	Dexamethasone 2 weeks	Dexamethasone 2 weeks	Methylprednisolone 2-3 weeks

Table 1.2 Clinical features (Case 9-16)

Patient	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14	Case 15	Case 16
Age	67 y	14 y	37 y	10 y	10 y	15 y	10 y	67 y
Sex	M	F	M	M	M	F	F	M
Family History	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
Consanguinity	Absent	Present	Absent	Absent	Absent	Absent	Absent	Absent
Fever	15 days	23 days	10 days	24 days	2 months	13 days	8 days	12 days
Spleen	3 cm	1 cm	1 cm	2 cm	1 cm	1.5 cm	6 cm	2 cm
Liver	-----	-----	1 cm	1 cm	----	----	3 cm	----
Lymphadenopathy	Cervical Axillary+	Absent	HRCT- Hilar LN+	Absent	Cervical LN+	Cervical LN+	Absent	Absent
Skin rash	Absent	Absent	Absent	Absent	Present	Present	Absent	Absent
CNS/other symptoms	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
Outcome	Expired	Survived	Expired	Survived	Survived	Survived	Survived	Survived
Etiology	Nodular Lymphocyte Predominant Hodgkins Lymphoma	Unspecified	Disseminated Tuberculosis	EBV	Tuberculosis	SLE	Unspecified	Unspecified
Bone marrow examination	Hemophgocytosis +	HP+	HP+	HP+	HP+	HP+	HP+	HP+
Treatment	Patient expired before chemotherapy	Short course of steroids	ATT	HLH-94 + rituximab	ATT	Methylprednisolone 2-3 weeks	Short course of steroids	Short course of steroids

Table 2: CBC Parameters

	Hb (gm%)	TLC (x10*9/L)	Platelet count (x10*9/L)
Case 1	7.8	2.7	25
Case 2	8.4	7.5	88
Case3	6.4	2.4	17
Case 4	6.4	5.2	70
Case 5	7.1	7.2	82
Case 6	8.8	4.5	72
Case 7	7.5	6.9	74
Case 8	8.4	12	56
Case 9	7.3	5.8	63
Case 10	5.9	13.5	45
Case 11	8.7	2	59
Case 12	6.9	2.1	77
Case 13	8.5	2.9	96
Case 14	8.4	2.3	102
Case 15	8.8	4.8	24
Case 16	9.2	2.75	65

cases the etiology was unclear (Table 4). Additional investigations performed in individual cases to find out the etiology are summarized in Table 5 . 2 patients were diagnosed with dengue fever based on NS1 and Anti IgM positivity had mucocutaneous bleeding in form of petechiae and epistaxsis. 2 patients who were known cases of SLE and in whom ANA and Anti-ds-DNA were positive, one of them presented with complaints of fever, cytopenia along with hematuria. 3 patients were diagnosed with tuberculosis, out of which one was diagnosed as having disseminated tuberculosis and who succumbed to the cervical and

Table 3: Biochemical Parameters

	Plasma fibrinogen (180-350 mg/L)	S.LDH (81-234 mU/ml)	SGOT (AST) (15-37mU/ml)	SGPT (ALT) (30-65mU/ml)	S. Triglycerides (30-200mg%)
Case 1	145.3	1174	114	92	145.3
Case 2	183	644	65	80	724
Case3	96.3	468	198	219	246
Case 4	94	658	102	96	713
Case 5	159	1243	234	110	540
Case 6	210	491	97	64	279
Case 7	176.6	640	122	67	398
Case 8	200	1542	324	165	453
Case 9	160.9	1152	257	130	379
Case 10	107.1	614	96	50	291
Case 11	83.1	507	95	75	420
Case 12	314	913	542	242	508
Case 13	99	3360	309	207	311
Case 14	103	3582	306	168	373
Case 15	108	410	128	99	477
Case 16	216	650	196	106	502

axillary lymphadenopathy was diagnosed to have Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) based on the histopathological and IHC features. Foci of hemophagocytosis were found in every case. (Figure 1, 2, 3). In one of the case, hemophagocytosis and amastigote forms of Leishmaniasis (LD bodies) were found only on repeat bone marrow examination done one month later (Figure 4).

Table 4: Etiological distribution

Diagnosis	Number
Dengue	2
Leptospirosis	1
Epstein Barr virus	1
Tuberculosis	3
Visceral Leishmaniasis	1
Nodular Lymphocyte predominant Hodgkins Lymphoma (NLPHL)	1
Primary HLH	1
SLE (Systemic Lupus Erythematosus)	2
Unspecified etiology	4
TOTAL	**16**

Treatment and outcome: Two patients diagnosed with dengue fever were managed with supportive care along with steroids for 2 weeks. Both the patients survived and there was gradual improvement of the counts with full recovery at 1 month. One patient aged 10 years diagnosed with EBV infection was treated with HLH 94 protocol along with rituximab. The patient is alive at follow up of 2 months with full recovery. 3 /16 patients diagnosed with tuberculosis were started on ATT, however one patient succumbed due to underlying disease. A two month old infant diagnosed as primary HLH was put on HLH-94 protocol , however she succumbed due to septic shock. 2 patients with SLE were treated with Methylprednisolone for 3 weeks. Both patients are alive. One patient who was diagnosed as NLPHL, he succumbed to his disease before institution of chemotherapy. One patient with Lesihmaniasis was given Amphotericin after which she showed full recovery. One case diagnosed with

Table 4: Etiological workup in each case

Case Number	Diagnosis	Investigations
Case 2	Leptospirosis	Leptospira IgM + Antibodies
Case 3	Dengue	NS1 + and Dengue IgM + Antibodies
Case 4	Primary HLH	Perforin gene mutation (PRF1) +
		CD 56 NK cell activity: decreased
Case 5	Tuberculosis	Cervical Lymph node biopsy – Granulomatous lymphadenitis
Case 7	Dengue	Dengue NS1+
Case 9	NLPHL	Axillary lymph node biopsy - Histological features and IHC s/o NLPHL
Case 11	Tuberculosis	Radiological investigations suggestive of disseminated tuberculosis, ESR =84
Case 12	EBV infection	EBV IgG +ve (Nuclear Antigen) + (Viral capsid Ag)+
Case 13	Tuberculosis	USG (neck) Large matted, highly vascular nodes, s/o TB, Mantoux +ve.
Case 8 & 14	SLE	ANS +, dsDNA +

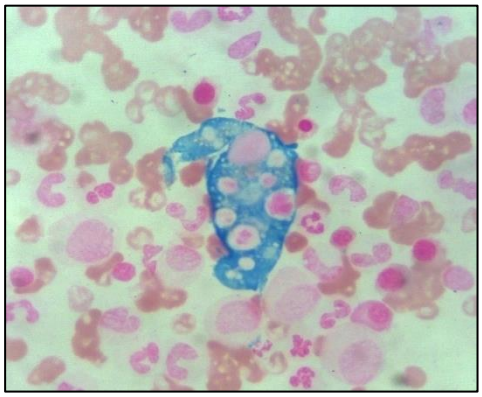


Figure 1: Bone marrow aspirate- macrophage with engulfed erythroids and neutrophils. (X100, oil immersion, Perls stain).

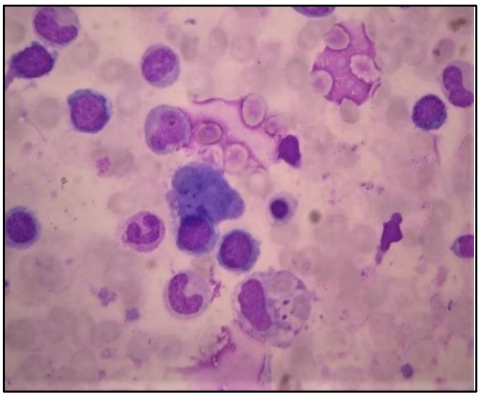


Figure 2: Bone marrow aspirate showing macrophage with

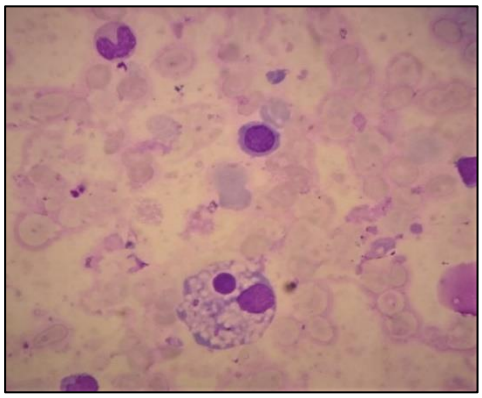


Figure 3: Bone marrow aspirate showing macrophage with engulfed Nrbc (x100, oil immersion , Leishman stain

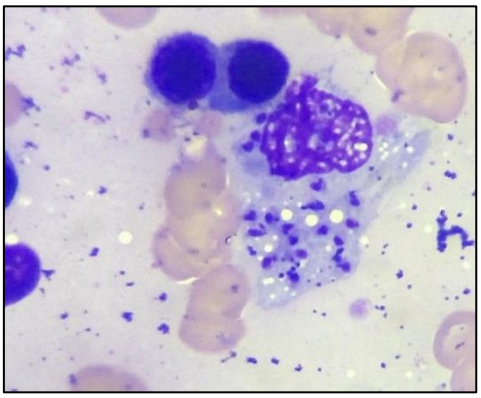


Figure 4: Bone marrow aspirate showing amastigote forms of LD bodies present intracellularly (X100 , oil immersion, Leishman stain).

Leptospirosis was treated with short course of steroids and antibiotics. In 4/16 patients in whom the etiology could not be confirmed but in whom clinical and laboratory parameters were pointing towards HLH were treated with short course of steroids out of which one patient succumbed. All these patients were monitored with hemogram, renal functions, liver function every alternate day. Median duration of follow up was 18 months (range 6-24 months). 12 /16 patients are healthy and alive after median follow of 18 months without any relapse.

Discussion

The purpose of this prospective study was to describe the clinical features, laboratory approach and treatment of HLH in our setting. Although HLH is not a rare entity in India, but it is often under reported especially in adolescents and adult population. From the present study we concluded that HLH has a very wide age spectrum and can present in age group ranging from infancy (2 months) to elderly with mean age being 31.5 years and (median of 23 years). This is similar to the study conducted by Ray U et al [1] where they studied 12 patients diagnosed as Infection associated HLH (IA-HLH). In their study mean age at diagnosis was 28.4 years {median 23 (range 4-67)}. In another study by Verma et al where they reported 8 cases of HLH had mean age of 27 years (range 13-57 years) [8] , while Kumar et al [9] in their study had patients ranging in age from 3 months to 65 years with mean age of 14 years. The male to female ratio in the present series was almost equal, ie 1:1.28 while in a study done by Reddy et al [14] they found a male preponderance (M:F 4:1) whereas Joshi et al [15] found a female preponderance (M:F 1:4).

The most frequent presenting symptom was fever with cytopenia and splenomegaly which is similar to the finding reported by Ray S et al and Verma et al [1,8] . Joshi et al [15] in their case series also concluded that HLH should be suspected in any patient experiencing unresolving fever with cytopenia and splenomegaly. Similarly Ramachandran et al [16] also found fever and hepatosplenomegaly as the most common presenting complaint in their case series of 33 pediatric patients. In the present study there were 3 /16 patients who had mucocutaneous bleeding (18.75%) which is similar to study done by Verma et al in whom bleeding manifestations were seen in 12.5% [8].

We could determine the underlying etiology in 12/16 patients amongst which an infectious cause was found in 8/16 patients (50%). Ramachandran et al [16] similarly found an infectious cause in 42% of the pediatric patients and Joshi et al [15] in 30% of the patients. Unlike other forms of HLH, infection associated HLH carries a relatively better prognosis provided the inciting infection is diagnosed early and treated promptly [1] . Out of the infectious causes, the most common ones in our study were secondary to tuberculosis and viral causes like dengue and EBV. This result was also similar to finding of study conducted by George MR et al [17] where they concluded that infection are major triggers of HLH and around 50% of secondary HLH are triggered by infections, the majority being viral infections (29%). In our study we had 2 patients of dengue related HLH. In literature a total of 74 dengue associated pediatric and adult HLH cases have been described in the published literature since 1966, with a cumulative case-fatality rate (CFR) of 9.5% [18] .Our study had three patients of tuberculosis related HLH. There has been increasing number of reports of TB HLH in the recent years [1] . Padhi et al [19] reviewed a total of 55 articles describing nearly 70 cases of TB-HLH published in the world literature till March 2014. Since then around 16 more cases have been reported in the literature including a series of 8 cases by ZhangYun et al [20] . In our present study we had one child diagnosed with EBV infection, The incidence of EBV-HLH is relatively high in Asian countries, indicating the underlying genetic background in the pathogenesis of EBV-HLH. In Japan EBV associated HLH is seen in around 40% of all secondary HLH patients [21] . Thus in our case series, the most common cause of secondary HLH was attributable to infection, for which specific antimicrobial treatment was administered. Infection associated HLH (IAHLH) remains undiagnosed due to lack of awareness amongst clinicians about this entity. Various tropical infections such as dengue, typhoid, kala azar, leishmania, tuberculosis, leptospirosis, malaria (both Plasmodium vivax and Plasmodium Plasmodium falciparum), scrub typhus, HIV/AIDS are important triggers of HLH [3] .

In the present study bicytopenia was present in 56.25% (9/16) patients while 7/16 patients (43.75%) had pancytopenia (Table 2) while Verma et al [8] in their study reported pancytopenia in 6 out of 8 (75%) patients, one patient with bicytopenia. Kumar et al [9] in their study of 12 patients of HLH found bicytopenia in 8 and pancytopenia in only 1 patient.

Variable derangement of liver enzymes was observed in all patients (Table 3). In study done by Verma et al [8] all but one had elevation of hepatic enzymes ranging from 2 to 10 times upper limit of normal. One Recent study also describes the commonness of hepatic dysfunction in HLH patients [22] . Recently proposed HLH diagnostic criteria (2009) by Filipovich AH et al., also includes hepatitis as one of the important criteria's in diagnosis of HLH [12] .

The mean ferritin level in our study was 23,397 ng/ml, which is similar to the mean ferritin level of 30,893.545 ng/ml in a study conducted by Ray U et al [1] however it is higher as compared to study done by Verma et al [8] where they reported median serum ferritin was 13,500 mcg/L. In their study all patients had serum ferritin > 500 mcg/L and one patient with underlying diagnosis of juvenile rheumatoid arthritis had extreme elevation of serum ferritin (90,000 mcg/L). Ferritin is thus a valuable and easily available marker and levels >10,000 mcg/L were found to be highly sensitive and specific for diagnosis of HLH [23] .

In our study 15/16 (93.75%) of patients had hypertriglyceridemia. (Table 3) while Verma et al [8] reported hypertriglyceridemia (>265mg/dl) in 75% of our patients. Elevated triglyceride levels have been reported in upto 64%-70% of pediatric patients with HLH [11].

Our study had 8/16 patients with hypifibrogenemia, while Kumar et al reported hypofibrogenemia in 2/3rd of their patients [9]. In the present study all patients demonstrated foci of hemophagocytosis in the bone marrow, while Verma et al [8] demonstrated bone marrow hemophagocytosis was present in 75% of their patients.

Treatment and Outcome: From the treatment point of view the management approach depends on the underlying etiology, hence search for underlying etiology has to be done is every.. For infection associated HLH, the treatment of the underlying infection and supportive care is sufficient in 60-70% of cases [1] . The 2004 HLH treatment protocol by the Histiocyte Society recommends use of 8 weeks of induction therapy of cyclosporine, etoposide and corticosteroids. Permanent cure is possible only with stem cell transplantation for primary HLH . The prognosis of genetic HLH is dismal [24] . The prognosis of acquired HLH is variable depending on the underlying cause, with malignancy associated cases having the worst outcome [25] . Verma et al [8] in their study used Cyclosporin and dexamethasone without etoposide in most of their patients. Overall survival in that study was 62.5% at a median follow-up of 18 months. Three patients died (37.5%) and all deaths occurred in the first few week. In a retrospective series of 162 patients with HLH, 94 patients survived (58%). Of the patient who did not survive , half died within 1 month of diagnosis especially those with hematological malignancies [26] .

Diagnostic challenges: The knowledge about the profile of HLH in the Indian subcontinent is limited despite the disease being life threatening, and is available in the form of few case series [9,27]. The main challenge in recognizing HLH is due to its wide spectrum of manifestations and lack of specificity in the clinical findings. The clinical presentation often mimics other disorders like severe sepsis, MODS , meningitis, hepatic failure and malignancies which can come into close differentials. Hence there has to be a very high index of suspicion for HLH for any patient presenting with fever, cytopenias , high LDH and a high S.ferritin value .A single value of ferritin more than 10,000 ng/ml 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%. [11] . In our study the mean ferritin level was found to be as high as 23,397 ng/ml. For familial HLH the only confirmatory test is genetic testing for mutations, the most common being mutations in the perforin gene However, this is available in only limited laboratories. Recently, flow cytometry for perforin expression has been introduced for screening of HLH. It can prove to be useful as it is economical and readily available [28] . Sometimes all the criteria for HLH are not met but a high index of suspicion is required for the diagnosis of such cases in the initial stages [9]. Although hemophagocytosis is the hallmark of the disease, it is seldom found at presentation in case of secondary HLH and may not be evident until late in the course of disease progression. Bone marrow examination performed in the initial stage of disease may be normal or demonstrate very non-specific changes, and thus its absence does not negate the diagnosis of HLH [29.30]. The incidence of bone marrow involvement varies between 25% and 100% [29,31]. This implies that the diagnosis of HLH requires a comprehensive clinical, biochemical and hematological approach. In such cases the clinician may consider a repeat bone marrow as seen in one of our cases diagnosed with Visceral Leishmaniasis. The initial marrow did not show hemophagocyosis. However a repeat marrow done one month later demonstrated hemophagocytosis along with LD bodies. Moreover presence or absence of

hemophagocytosis in bone marrow is not a confirmatory evidence of HLH, as it is just a supportive one , which has to be interpreted in the light of clinic findings hence the criteria of "bone marrow hemophagocytosis" is becoming increasingly less important nowadays as it has a poor specificity in the diagnosis of HLH, and this may not even be evident during initial marrow evaluation [3] . The aim should be at finding out the underlying etiology and to differentiate genetic HLH from secondary HLH as the latter is treatable by finding the underlying cause.

Limitations: This study includes limited number of newly diagnosed patients with HLH over a period of only one year and includes mainly adolescent and adult patients. Majority of them being diagnosed as secondary HLH. Our study had only one infant with primary HLH. Hence studies including large number of patients including pediatric patients are thus required for better understanding of best management strategy in HLH and their long term follow up.

Conclusion

Hemophagocytic lymphohistiocytosis is a life threatening clinicopathological condition caused by excessive immune activation which is now been increasingly recognised in clinical practise. The mortality of HLH is very high without HLH directed therapy. Early recognition and initiation of therapy is therefore of utmost importance. In addition a thorough etiological workup of each case suspected of being HLH is essential , as it holds important prognostic and therapeutic implications. Especially in India where tropical infections are very common and where prompt recognition will help to institute specific treatment and reduce morbidity and mortality associated with the disease. Also an attempt should be made to differentiate primary HLH from secondary HLH in every patient. From a pathologist's perspective, it is highly essential to be aware of HLH as a differential diagnosis in the evaluation of prolonged fever, pancytopenia, and splenomegaly. From a clinical perspective, not all patients will fulfil the diagnostic criteria but since the outcome can be fatal, treatment should be initiated early in the disease course if strong clinical suspicion is present.

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