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Research Article

REACTIVE HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS - AN INSTITUTIONAL STUDY

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ABSTRACT

Hemophagocyticlymphohistiocytosis(HLH) is an uncommon and likely underdiagnosed disease ,potentially life threatening, hyperinflammatory syndrome involving a final common pathway of hypercytokinemia resulting in end organ damage. Although an early diagnosis is crucial to decrease the mortality, the definitive diagnosis is often challenging in spite of the well known diagnostic criteria put forth by HLH society because of the lack of specificity of currently accepted diagnostic criteria. We describe 13 patients with secondary HLH who satisfied HLH-2009 diagnostic criteria. Definitive evidence of hemophagocytosis on initial bone marrow aspiration was present in all the cases. The underlying etiologies were EBV,bacteria (known c/o infective endocarditis), autoimmune disorder, malaria, SLE with HIV and associated disseminated Histoplasmosis, JIA and Lymphoma. Cause could not be ascertained in four patients. Out of thirteen patients four patients died with multiorgan failure and disseminated intravascular coagulation (DIC). Due to lack of specificity of diagnostic criteria, diagnosing and differentiating HLH from its closest mimickers like sepsis/septic shock may be quite challenging in critically ill patients. Therefore increasing awareness among physicians is essential for early diagnosis and effective therapy to reduce the mortality.

INTRODUCTION

Hemophagocyticlymphohistiocytosis(HLH) is an uncommon, potentially lifethreatening hyperinflammatory syndrome caused by severe hypercytokinemia due to a highly stimulated but ineffective immune process[1]. It is not a single disease but a clinical syndrome that can be associated with variety of underlying conditions leading to such hyperinflammatory state along with excessive activation of lymphocytes and ,macrophages[2]. The main mechanism lies in the defect in the cytotoxicity of the natural killer (NK) cells and cytotoxic T lymphocytes which results in over activation of benign macrophages resulting in engulfment of blood precursors (hemophagocytosis) in several organs. Such dysfunctional immune system is activated by several factors which in turn trigger a cytokine storm leading to multiorganfailure[3,4]. HLH has been traditionally divided into two forms; a primary form, which typically manifests in children with documented genetic abnormalities of the cytotoxic function of NK/T cell and a secondary form that tends to occur at older ages in the setting of an associated condition such as infection and malignancy without an identifiable genetic abnormality[5]. In the absence of verified gene mutations or a positive family history, the diagnosis of HLH is based upon the presence of atleast five out of eight HLH-2004 criteria which include 1) fever ($\geq 38^{o}C$) persisting for 1 week, 2) splenomegaly, 3) unexplained progressive peripheral blood cytopenias involving at least 2 cell lines (hemoglobin, < 90 g/L; platelet count, < 100 x 10^9 /L; absolute neutrophil count, < $1x10^9$ /L), 4) fasting hypertriglyceridemia ($\geq$ 265 mg/dl) and/or hypofibrinogenemia (fibrinogen $\leq$ 150 mg/L), 5) hyperferritinemia ($\geq$ 500 µg/L), 6) evidence of histiocytic hemophagocytosis in the examination of bone marrow, spleen, liver, or lymph nodes, 7) low or absent natural killer (NK) cell activity, and 8) high levels of soluble CD25 ($\geq$ 2400 U/ml)[6]. With additional experience, these criteria have been further modified in the proposed HLH-2009 criteria [7]. The HLH -2004 criteria are considered to be the gold standard in primary/ familial HLH[3,4]. The proposed HLH-2009 criteria are a modification of the previous one. As per this updated criteria, in the absence of molecular diagnosis, the diagnosis of HLH required at least 3 of 4 features (fever, spleenomegaly, bicytopenia, hepatitis) and minimum one of 4 parameters (hemophagocytosis, increased ferritin, absent/decreased NK cell activity, increased soluble IL2Rα). Other results supportive of HLH diagnosis include

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hypertriglyceredemia, hypofibrinogenemia, and hyponatremia[7].

The exact incidence of HLH is not known though the studies have reported that it may range from 0.8% to 4% among all critically ill patients presenting with cytopenias[8]. The clinical signs and symptoms of HLH, sepsis, septic shock, systemic inflammatory response syndrome (SIRS), multiorgan dysfunction syndrome (MODS) may overlap in some patients, especially in intensive care unit (ICU), making the distinction quite challenging. The condition still poses diagnostic challenges to treating physicians due mainly to lack of awareness as well as poor reproducibility of the diagnostic criteria in severely ill patients. Bone marrow examination is the most useful diagnostic test, but may yield false negative result on initial evaluation for which serial marrow examination may be necessary [1,8,9].

In this manuscript, we describe the clinicopathological, haematological, biochemical, and therapeutic outcome data of 13 patients with various aetiologies.

MATERIAL AND METHODS

The present study is a prospective observational study, carried out in the Department of Pathology at Sri Ram Chandra Bhanja Medical College, Cuttack, Odisha, over a period of 24 months extending from September 2015 to September 2017.

All the cases presented with fever, cytopenias and hepatosplenomegaly were included in this study. A total of 160 cases were evaluated.

Routine Hematological studies like Hb,DC, TLC,TPCalong with PT, APTT, fibrinogen levels, D-dimer was done. After taking written consent bone marrow aspiration was done in all the cases. All these cases were further evaluated for the study of HLH.. Biochemical tests like ferritin, liver function test, serum triglyceride, LDH,was done. Other tests like viral serology to ascertain the aetiology were performed. We followed the diagnostic criteria of 2009 for confirmation of HLH.

RESULTS

A total number of 160 cases were evaluated of which 13 cases satisfied the diagnostic criteria of 2009 HLH which constitute the study group. Within the study group there were 11 adults and 2 paediatrics cases and male to female ratio was 2.25:1 (9males& 4 females). Maximum patients (4 out of 13) presented with a presumptive clinical diagnosis of pyrexia of unknown origin (PUO), followed by leukemia, autoimmune disorder and severe anemia. Fever and hepatosplenomegaly was the constant clinical manifestation in all the cases. However, 3 patients had lymphadenopathy and 4 patients had joint pains in addition to fever and organomegaly [Table 1].

Haematological investigations showed bicytopenia being the most common finding seen in all the cases followed by pancytopenia seen in 4 cases. Hypertriglyceridemia (sr TG >265mg/dl) and hypofibrinogenemia (<150mg/L) was present in 4 cases. Out of 13 cases 5 cases manifested hyperferritenimia (>500mg/dl), LDH was raised in 2 cases & D- dimer was positive in 3 cases.

Table 1 Clinical Menifestations

cases	age	sex	Clinical diagnosis	fever	spleenomegaly	hepatomegaly	lymphadenopathy	Joint pain
1	35	M	Acute leukemia	+	+++	+	+	+
2	7	M	?Leukemia	+	+	-	-	-
3	35	F	AIHA	+	+	-	-	+
4	15	F	Severe anemia	+	+	-	-	-
5	70	M	Severe anemia	+	-	+	-	-
6	65	M	?MDS	+	-	+	-	-
7	59	M	PUO	+	-	+	-	-
8	16	M	PUO	+	+	+	-	-
9	42	F	PUO	++	-	+	+	-
10	55	M	PUO	+	-	+	-	-
11	43	F	SLE	+	+	-	-	+
12	10	M	JIA	+	+	-	-	+++
13	60	M	Lymphoma	+	+	-	+	-

Table 2 Haematologicaland Biochemical parameters

cases	cytopenia			Hemophagocytosis in BM	TG (>265mg/dl)	Fibrinogen(<150mg/L)	Ferritin(>500)	LDH (IU/L)	D- Dimer	Viral serology	Liver transaminases
	Hb (gm%)	TPC	ANC (<1000/l)								SGOT/SGPT (IU/L)
1	7.0	1	1000	+(marked)	760	111	810	-	-	EBV+	-
2	8.6	2.8	999	+	increased	146	640	-	-	-	70/60
3	10.6	1.0	630	+	-	-	640	1245	-	-	-
4	2.7	1	836	++	-	-	-	-	-	-	-
5	4.5	2.4	1000	+	-	-	-	-	-	-	-
6	8.0	1.5	900	+	-	-	-	-	-	-	-
7	11.0	2.4	950	+	-	-	-	-	-	-	-
8	6.5	1.5	990	+++	536	81.2	7499		+	-	96/829
9	7.5	17000	900	+++(marked	460	82.2	24,560	840	+	HIV+	128/82
10	8.5	1.3	-	+	-	-	-	-	-	-	-
11	8.9	1.5	900	+	-	-	-	-	-	-	-
12	7.5	1.5	830	+	-	100	-	-	+	-	-
13	8.5	1.0	-	+	-	-	-	-	-	-	-

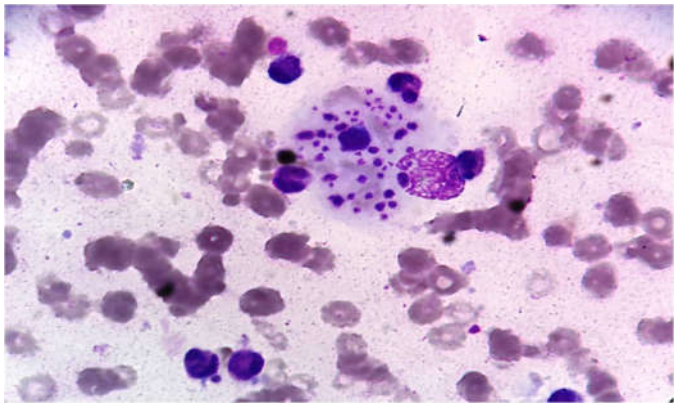

Figure 1 a

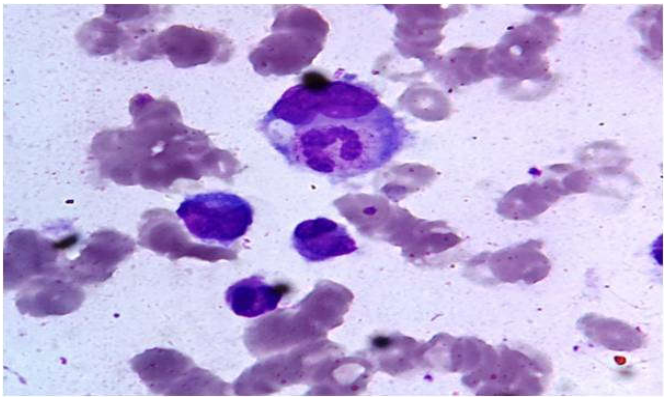

Figure1 b

Fig 1 Reticulum cells showing hemophagocytosis in BM (Leishman stain 1000x)

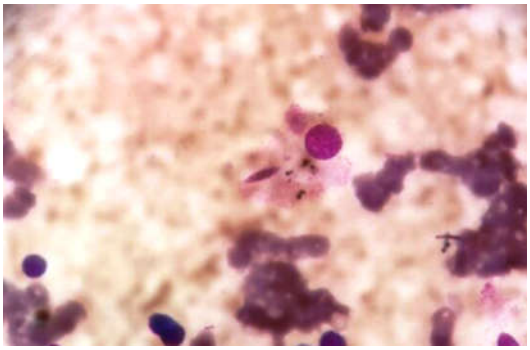

Figure 2 a

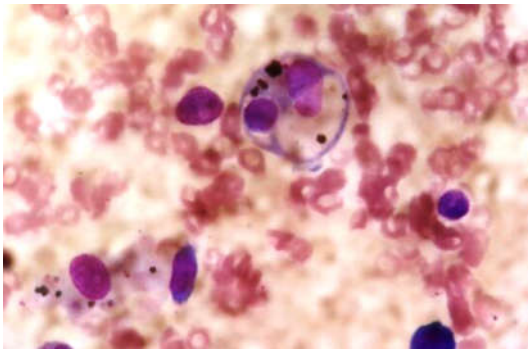

Figure 2 b

Fig 2 Reticulum cell showing Pf. Gametocyte and pigments in BM(Leishman stain 1000x)

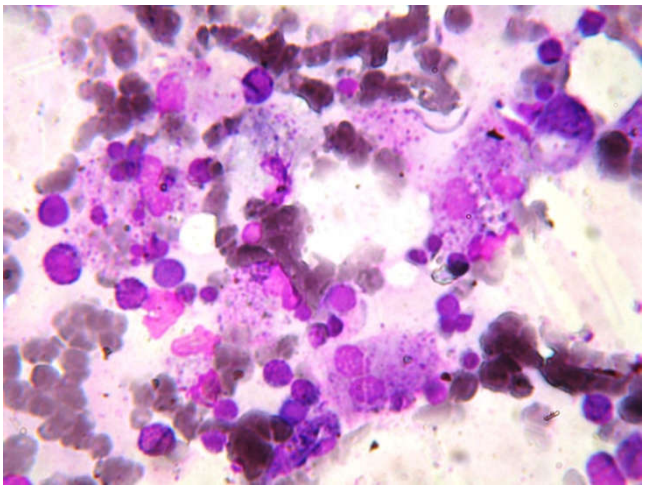

Figure 3 a

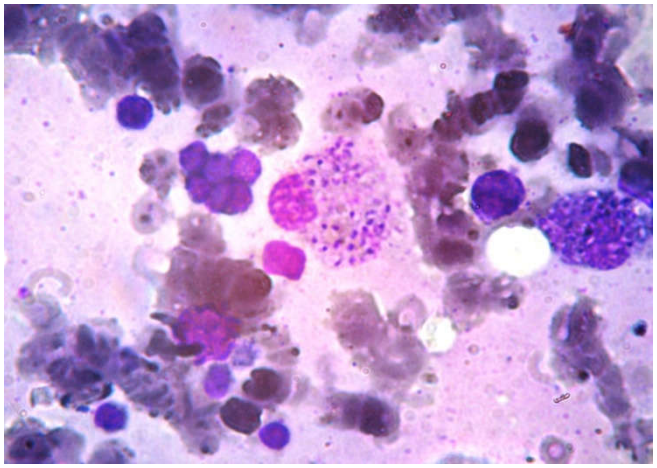

Figure 3 b

Fig 3 BM aspirate smear showing intracellular yeast form of Histoplasma Capsulatum. (Leishman stain 1000x)

Hemophagocytosis was present in all the cases on bone marrow aspiration cytology, and was marked in 3 cases. Intracellular Pf. gametocyte was elicited in one case.[Table 2]. Viral serology of 2 cases could be possible due to financial constraints which showed EBV positivity and another was HIV positive.

DISCUSSION

This single centre based prospective study emphasised on the secondary causes of HLH along with the clinicopathological characteristics and biochemical parameters. The incidence of HLH in the present study was 8.13% which is slightly higher than the incidence found in the literature i.e 0.8% to 4% [8] probably due as to the tertiary centre of the study. Our study cohort represent the eastern India as being a tertiary centre with maximum facilities, it is a referral centre for patients from West Bengal, Chattisgarh, Jharkhand, Bihar, Andhra Pradesh & Assam.

Adult cases were more than the paediatric group and male were more than the females. In the present study aetiologies of nine cases could be ascertained whereas aetiology of four cases could not be found as the patients coud not afford the higher investigation as and Whenever necessary. However, these four cases satisfied the 2009-HLH diagnostic criteria.

There were four cases of autoimmune aetiology viz. two cases of SLE, one case was a case of autoimmune haemolytic anemia with ANA positivity and systemic onset juvenile idiopathic arthritis (soJIA).. Out of these, 3 cases developed Macrophage activation syndrome. Macrophage activation syndrome (MAS) is characterised by pancytopenia, liver insufficiency, coagulopathy, and neurologic symptoms and is thought to be caused by the activation and uncontrolled proliferation of T lymphocytes and well- differentiated macrophages, leading to widespread hemophagocytosis and cytokine overproduction [10]. It is associated with rhematolic arthritis, SLE, soJIA & adult onset Stills disease. In the study by SomnathPadhi *et al*. [1] there was one case of autoimmune disorder and another was a case of soJIA [1]. In a multinational multicentre study Parodi A *et al* [11] has reported 38 cases of MAS in juvenile SLE. They opined that unexplained fever, cytopenia in accompany with hyperferritenimia in a patient of juvenile SLE should raise the suspicion of MAS.

In the present study viral serology was positive in two cases one was EBV virus & another HIV. Secondary HLH is often associated with infectious episode most notably Ebstein-Barr virus(EBV) or Cytomegalovirus(CMV) [12]. Clonal proliferation and hyper activation of EBV infeted T cell resulting in excess production of cytokines. In the study by Somnath Padhi *et al*.[1] there was one case of CMV.

Bacterial aetiology was identified in one of the cases which was a known case of infective endocarditis. In the study by Somnath Padhi *et al*.[1] there was one case of Mycobacterium tuberculosis. Cases with tuberculosis associciated with HLH have been reported by several authors [12, 13]. Other bacterial causes like Brucella melitensis [14] and leptospira [15] have also been identified.

There was one case of malaria caused by Plasmodium Falciparum identified in the present study. Study by Somnath Padhi *et al*.[1] found one case of Plasmodium vivax malaria. Other parasites associated with HLH like Leishmaniadonovani, Leishmaniainfantum, toxoplasma, babesia, strongyloidosis were identified [16,17].

One of our case was disseminated histoplasmosis associated with SLE and seropositive for HIV who developed MAS. Patient developed immunosuppression due to treatment by steroid for SLE and acquired HIV infection leading to AIDS (CD4 count =11/cumm) and later acquired opportunistic infection disseminated Histoplasmosis. In this case HIV and Histoplasmosis directly trigger MAS. Other fungal infection associated with HLH are Candida, Cryptococcus, Pneumocystis spp. Aspergillus spp. & Fusarium spp.[18,19,20].

Apart from autoimmune and infectious causes there was also one neoplastic cause i.e. Lymphoma which was identified in the present study. Various hematolymphoid neoplasms like Hodgkins and Non Hodgkins lymphoma have been reported in the literature.

All the cases were differentiated from other mimickers like septic shock/SIRS/MODS (mildly raised serum ferritin levels) and SOJIA flare (neutrophilic leucocytosis, increased fibrinogen). However, further study for NK cell activity, soluble CD25 and mutation analysis could not be done in the present study due to unavailability of these tests.

Definite triggering cause couldn't be ascertained in 4 cases in the present study. However, four cases succumbed to death during the course of treatment and rest of the cases could not be followed traced for follow up. MAS with soJIA has a reported mortality of 8% to 22% [21]. Overall reported mortality for acquired HLH exceeds 50%[22].

CONCLUSION

Reactive HLH is associated with infectious, autoimmune and neoplastic diseases. The main mechanism of pathogenesis lies in an unopposed macrophage activation and proliferation leading to cytokine overproduction which ends up with high mortality. An unexplained persistent fever, cytopenias, organomegaly, with hyperferritenimia, unexplained raised serum transaminases and deranged coagulation profile should raise high degree of suspiscion to rule out HLH. Early diagnosis and timely intervention is warranted to reduce mortality.

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