Original Article

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Pathology Section

Haemophagocytic Lymphohistiocytosis: New Insights into Diagnosis

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ABSTRACT

Introduction: Haemophagocytic lymphohistiocytosis (HLH) or haemophagocytic syndrome is a very fatal and an underdiagnosed disease which involves a pathway of hypercytokinemia, that results in Multiorgan Dysfunction Syndrome (MODS) and poor survival. Although an early diagnosis is important to decrease mortality, the definitive diagnosis is an enigma due to the absence of confirmatory gold standard tests. Since the range of laboratory assays involved in the diagnosis of HLH is wide, practicing pathologists should be familiar with the disease so, that they can appropriately flag results and convey them to the clinicians.

Aim: To diagnose Haemophagocytic lymphohistiocytosis and find its advantage over the criteria used in 2004.

Materials and Methods: The cross-sectional study was accomplished in the Pathology Department of Sriram Chandra Bhanja Medical College and Hospital Cuttack, Odisha, India over a period of 5 years and 4 months in which 26 cases were evaluated. A complete clinical history, haematological, biochemical work-up and H-scoring by Fardet L et al., in 2014 was done to dwell into the depths of aetiology of HLH. Univariate statistical analysis was done to understand the basic statistics of the data in term of frequency and percentage.

Results: Total of 26 patients were diagnosed and the age ranges from 47 days to 65 years; two were infants. The average age of the patients was 28 years. The H-score was more accurate than the previous (2004) criteria to diagnose HLH. The diagnostic sensitivity improved by 7.7% by using H-score. The underlying aetiology was found to be infective, autoimmune and malignancies in our cases.

Conclusion: H-score, a new scoring system proposed helps to diagnose HLH in a robust and efficient way for early diagnosis and treatment.

Keywords: Ferritin, Fever, H-Score, Pancytopenia, Splenomegaly

INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is a life-threatening haematologic disease of uninhibited activation of immune cells causing extensive inflammation and tissue damage resulting in multiorgan dysfunction and failure. It is thought to be caused by the upregulation of activated macrophages and lymphocytes, possibly by failure of natural killer cells and/or cytotoxic T-cells to kill these activated macrophages [1,2]. The syndrome was first described in 1939 by Scott Robin and Smith as poorly controlled histiocyte proliferation and named as 'Histiocytic medullary reticulocytosis.' HLH can be primary (familial) or secondary (acquired). HLH is sporadic about 75% of time and remaining cases are familial. Primary HLH is due to gene mutations or associated with immunodeficiency syndrome like Chediak Higashi syndrome, Griscelli syndrome. Secondary HLH patients have a clear trigger for development of HLH. They are either due to underlying infections or malignancies like lymphomas, medications that suppress the immune system, autoimmune diseases and/or metabolic diseases [3,4] but genetic mutation is absent unlike primary HLH. There can also be an overlap between these two designations as any factor that triggers secondary HLH can precipitate the condition in those with a known genetic mutation. Familial Haemophagocytic Lymphohistiocytosis (FHLH) is relatively rare.The incidence of familial HLH in children in India has been reported as 1.2 per million [5] but that of infection associated HLH is still uncertain.

Untreated HLH has a very high mortality rate. Immediate treatment is critical, but the greatest barrier to a successful outcome is often a delay in diagnosis as HLH is a rare syndrome. Variable clinical presentation, and lack of specificity of the clinical and laboratory findings add to the delay. Immunochemotherapy followed by allogenic bone marrow transplantation results in long-term survival in these patients [6]. As this form of treatment is currently available to limited population in India [7], early diagnosis of HLH is important so that appropriate treatment can be rendered. The aim of the present study is to diagnose HLH using H-score proposed by Fardet L et al., [8] and find its advantage over the previous HLH 2004 guidelines.

MATERIALS AND METHODS:

The present cross-sectional study was carried out in the Pathology Department of Sriram Chandra Bhanja Medical College and Hospital, Cuttack, Odisha, India between June 2015 and October 2020 extending over a period of 5 years and 4 months. Ethical clearance was obtained from the Institutional Ethics Committee (No.742).

Inclusion and Exclusion criteria: A total of 93 cases with high index of clinical suspicion of HLH were evaluated, out of which 26 cases were confirmed to be HLH. These 26 cases were included in the final analysis. Patients admitted in Intensive Care Unit (ICU) were excluded from the study.

Procedure

A total of 26 cases were evaluated. On presentation, a complete history was taken including past history, relevant drug history and physical examination was done for recording the positive findings. Routine complete blood count was done followed by peripheral smear examination. All necessary investigations like serum triglyceride level, fibrinogen level, liver function tests, ferritin level, viral serology and further case specific investigations were carried out for a diagnostic workup. Patients provided written informed consent prior to the bone marrow aspiration. Care was taken to carry out the procedure under sterile conditions. The bone marrow aspirate smears were stained with Leishman stain after drying. Special stains like Myeloperoxidase and Perl's iron were done wherever necessary to reach a diagnosis. Bone marrow biopsy was done wherever indicated and cores were collected in formalin vial, imprints of the core was taken. Cases were

diagnosed by two experienced pathologists of the Department of Pathology, SCB Medical College, Cuttack who were blinded to avoid observation bias. The diagnostic criteria proposed by Fardet L et al., (2014) was followed to score the findings and to stamp the case as HLH. Nine parameters were taken to calculate H-score [Table/Fig-1]. Cut-off value to diagnose HLH was 169. Univariate statistical analysis was done. Due to unavailability of genetic molecular tests or flow cytometry for perforin protein on routine basis, these tests were not done.

Parameters	Variable categories	Score
1. Known immunosupression	No	0
	Yes	18
2. Temperature (°C)	<38.4	0
	38.4-39.4	33
	>39.4	49
3. Organomegaly	No	0
	Hepatomegaly or Splenomegaly	23
	Hepatomegaly and Splenomegaly	38
4. Cytopenias	1 lineage	0
	2 lineages	24
	3 lineages	34
5. Ferritin (ng/mL)	<2000	0
	2000-6000	35
	>6000	50
6. Triglyceride (mmol/L)	<1.5	0
	1.5-4	44
	>4	64
7. Fibrinogen (g/L)	>2.5	0
	≤2.5	30
8. SGOT(U/L)	<30	0
	≥30	19
9. Haemophagocytosis features on bone marrow aspirate	No	0
	Yes	35

[Table/Fig-1]: Parameters for H-Score.
SGOT: Serum glutamic oxaloacetic transaminase

STATISTICAL ANALYSIS

Post the data collection, pre-processing was done on the dataset and tabulated. Univariate analysis was done on the dataset to understand the basic statistics of the data in term of frequency and percentage.

RESULTS

Total 26 patients were diagnosed as HLH over a period of 5 years and 4 months. The age of patients ranged from 47 days to 65 years; two were infants. The average age of the patients was 28 years. Parental consanguinity was present in four of the patients: two had affected siblings and one had a history of sibling death due to pyrexia of unknown origin. Male to female ratio was 9:4. The most common presenting symptom was fever in 92.3% cases followed by splenomegaly in 38.5% cases.The other clinical findings according to their decreasing order of frequency were hepatomegaly, joint pain, lymphadenopathy, abdominal pain, rash, pedal oedema and seizures. Both splenomegaly and hepatomegaly were seen in three cases [Table/Fig-2].

Case no.	Age (in years)	Sex	Fever	Splenomegaly	Hepatomegaly	Lymphadenopathy	Joint Pain	Rash	Abdominal Pain
1	21	F	+*	-**	-	-	-	-	-
2	35	M	+	+	+	+	+	-	-
3	26	M	+	-	-	-	+	-	-
4	7	M	+	+	-	-	-	-	-
5	27	F	+	-	-	-	-	-	-
6	35	F	+	+	-	-	+	-	-
7	16	M	-	-	-	+	-	-	-
8	15	F	+	+	-	-	+	-	-
9	9	M	+	-	-	-	+	+	-
10	70	M	+	-	+	-	-	-	-
11	65	M	+	-	+	-	-	-	-
12	7	M	+	+	+	-	+	-	-
13	59	M	+	-	+	-	-	-	-
14	4	M	+	-	-	-	-	-	+
15	16	M	+	+	+	-	-	-	-
16	47 Days	M	-	-	-	-	-	-	-
17	42	F	+	-	+	+	-	-	-
18	55	M	+	+	-	-	-	-	-
19	43	F	+	-	+	-	+	-	-
20	20	F	+	-	-	-	+	-	-
21	1	M	+	-	-	-	-	-	-
22	10	M	+	+	-	-	+	-	-
23	60	M	+	+	-	+	-	-	-
24	23	M	+	-	-	-	+	-	-
25	18	M	+	+	-	+	-	-	+
26	45	F	+	-	-	-	-	-	-

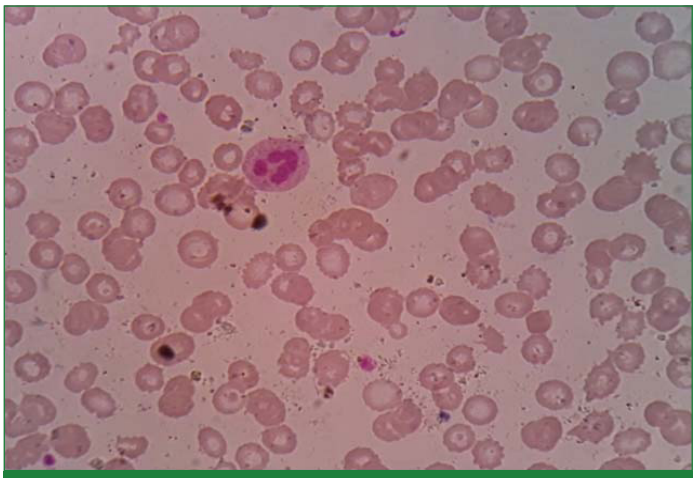
[Table/Fig-2]: Clinical presentation.
* + : Present; **- : Absent

Total 23 patients (88.5%) had elevated levels of Serum Glutamic Oxaloacetic Transaminase (SGOT) (≥30). Serum ferritin >2000 ng/mL was seen in 50% cases; hypertriglyceridemia (>132.7 mg/dl) was seen in 80.8% and 73.1% patients had fibrinogen level ≤250 mg/dL [Table/Fig-3]. Pancytopenia was noted in 23.07% cases [Table/Fig-4], bicytopenia in 46.1% cases and unicytopenia in 11.53% cases (2 case of Microcytichypochromic anemia are also to be included, total 3 case). Total 73.1% of the patients had haemoglobin <9.2 gm/dL; 73.1% patients had total leucocyte count <5000/cubic mm and 38.5% had total platelet count <110,000/cubic mm [Table/Fig-5]. Peripheral smear revealed neutrophilic leucocytosis in 15.4% patients, monocytosis in 3.8% and thrombocytosis in 3.8% of patients. Myeloid leukemoid reaction was seen in a single case and sickle cells were seen in a 15-year-old female. A 10-year-old child who presented with fever and splenomegaly showed the presence of gametocytes of *Plasmodium falciparum* in peripheral

Case no.	Serum ferritin (ng/mL)	Serum Triglyceride (mg/dL)	Serum Fibrinogen (mg/dL)	SGOT (U / L)	Aetiology
1	2341	452	99	34	Systemic sclerosis
2	810	760	111	29	Epstein Barr Virus Positive
3	3222	412	67	38	Systemic lupus erythematosus
4	640	720	146	70	Still's disease
5	765	443	170	65	-***
6	620	226	276	110	SLE
7	>2000	333	289.9	74	Sickle Cell Anaemia, FNA of lymphnode- Rosai Dorfmann Disease, Parvo Virus Antibody Positive
8	588	320	154	54	-
9	996	228	122	42	Still's disease
10	702	129	220	45	-
11	3200	122	260	70	-
12	4500	116	136	46	ASO Positive, Beta Thalassemia

13	765	372	272	68	-
14	11224	124	87.5	89	EBV, HSV-1 positive,IgM positive
15	7499	536	81.2	96	-
16	6543	432	67	59	-
17	24560	460	82.2	128	HIV positive
18	657	356	287	67	-
19	780	245	267	90	-
20	>2000	389	78	57	-
21	6240	112	98	20	*Gametocytes of Plasmodium falciparum*
22	899	234	100	25	Still's disease
23	768	302	95	54	-
24	72000	275	278	83	Mixed connective tissue disease with interstitial lung disease
25	37700	144	99	62	Evans syndrome associated, Lymph node biopsy-Hodgkin lymphoma
26	987	189	87	44	EBV positive

[Table/Fig-3]: Biochemical Investigations.
***-: Lost to follow up; EBV: Epstein-barr virus; FNA: Fine needle aspiration; ASO: Antistreptolysin O; HSV-1: Herpes simplex virus; IGM: Immunoglobulin M

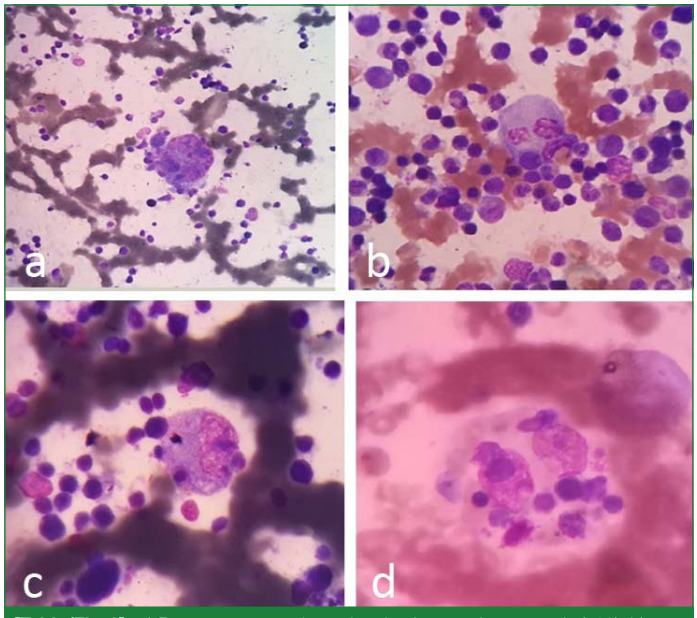


[Table/Fig-4]: Peripheral smear showing pancytopenia (x40).

Case no.	Hb (gm/dL)	TLC (/cmm)	Platelets (in lakhs / cumm)	No. of cytopenia	Peripheral Smear	Bone marrow haemophagocytosis
1	10.8	43000	6.9	1	Neutrophilic Leucocytosis	+
2	7	1600	1	3	Pancytopenia	+
3	10.8	13650	6	1	Neutrophilic Leucocytosis & Thrombocytosis	+
4	8.6	1700	2.8	2	Bicytopenia	+
5	10.2	12300	2	1	Neutrophilic Leucocytosis	+
6	10.6	1260	1	2	Bicytopenia	+
7	5.9	4600	1	2	Bicytopenia and Neutrophilia	+
8	2.7	1300	1	3	Pancytopenia	+
9	11.3	16400	3.6	0	Neutrophilic Leucocytosis and reactive lymphocytes	+
10	4.5	1600	2.4	2	Bicytopenia	+
11	8	1500	1.5	2	Bicytopenia	+
12	8	7400	2.8	1	Microcytic hypochromic anaemia	+
13	11	1580	2.4	1	Monocytopenia	+
14	5.1	2600	0.3	3	Pancytopenia	+
15	6.5	1650	1.5	2	Bicytopenia	-
16	3.6	14200	2.6	1	Microcytic Hypochromic Anaemia	+
17	7.5	1500	0.17	3	Pancytopenia	Increased reticulum cells
18	8.5	1420	1.3	2	Bicytopenia	+
19	8.9	1555	1.5	2	Bicytopenia	+
20	6.4	17000	3.3	1	Microcytic Hypochromic Anaemia and Myeloid Leukemoid Reaction	+
21	7.1	2500	0.3	2	Pancytopenia	+
22	7.5	1276	1.5	2	Bicytopenia	+
23	8.5	1330	1	2	Bicytopenia	+
24	6.3	180	1	3	Pancytopenia with monocytosis	+
25	5.2	4200	16000	2	Bicytopenia	+
26	9.2	2200	2.2	1	Bicytopenia	+

[Table/Fig-5]: Hematological Investigations.

smear following which immunochromatographic test was done and found positive. Schistocytes were seen in 11.5% cases and bone marrow haemophagocytosis was seen in 92.3% cases [Table/Fig-6a-d]. One case had increased number of reticulum cells but haemophagocytosis was not evident within the reticulum cell.

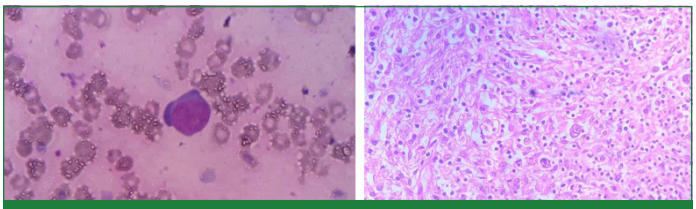


[Table/Fig-6]: a) Bone marrow aspirate showing haemophagocytosis (x10); b) Bone marrow aspirate showing reticulum cell with haemophagocytosis (x40); c) Bone marrow aspirate showing haemophagocytosis (x40); d) Bone marrow aspirate showing haemophagocytosis in a hypocellular smear (x100)

Patients were extensively investigated to find out the underlying cause of HLH. Bone marrow samples were sent for culture to rule out fungal and tubercular aetiology. Cartridge-based Nucleic Acid Amplification Test (CBNAAT) on Fine Needle Aspirates (FNA) and blood samples were done to exclude tuberculosis. Tests like blood culture, NS-1 antigen and IgM antibodies for dengue, Widal, malaria parasite by smear and antigen test, Weil-Felix, Brucella serology, Leptospira serology, HIV/Enzyme-Linked Immunosorbent Assay (ELISA), Hepatitis B surface Antigen (HBsAg), Hepatitis C Virus (HCV) antibody, antinuclear antibody tests were done in all patients. Viral serology was sent wherever anticipated.

Underlying aetiology was detected after extensive investigations in 15 cases. Three cases were EBV positive, one was HSV positive

and one was positive for Parvovirus [Table/Fig-7]. A single patient was HIV positive. FNA of cervical lymph node of a patient with lymphadenopathy showed granulomatous lymphadenitis following which a biopsy of the same node was processed which showed features of Hodgkin's lymphoma [Table/Fig-8]. He had developed HLH over a setting of Evans syndrome. Direct Coombs test was positive. A sickle cell anaemia patient was found to have Non Hodgkin's lymphoma on lymph node biopsy. He was positive for Parvovirus also. High performance liquid chromatography of a 7-year-old child showed a beta thalassemia picture and he was antistreptolysin O positive. Apart from malignancies and infective causes, seven cases had autoimmune aetiology; two cases of SLE and three cases of Still's disease, one of mixed connective tissue disease with interstitial lung disease and one of systemic sclerosis. The diagnostic accuracy of H-score was 100%. Using 2004 criteria, 92.3% cases were diagnosed as HLH while H-score showed a sensitivity of 100% proving to be a better diagnostic method. The two cases which were undiagnosed by 2004 criteria and diagnosed as HLH by H-score responded well to steroids.



[Table/Fig-7]: Bone marrow aspirate showing cytoplasmic dog ear protrusions in early normoblast (x40). **[Table/Fig-8]:** Cervical lymph node biopsy showing features of Hodgkin's lymphoma (H&E stain,x10). (Images from left to right)

DISCUSSION

Haemophagocytic lymphohistiocytosis (HLH) is a syndrome which poses major diagnostic and therapeutic challenges. The clinical features of secondary HLH mimic sepsis with multiorgan dysfunction syndrome, scrub typhus and severe malaria, visceral leishmaniasis, disseminated tuberculosis, leptospirosis, autoimmune disease in adults, haematological malignancy like leukaemia and lymphoma [9]. HLH is under reported in India especially in adolescents and adult population. The relative unawareness of this condition results in a high threshold of suspicion for the same. The biggest barrier in the workup of HLH patients is the unavailability of diagnostic facilities. In such a scenario, the diagnosis of HLH is a team work needing communication between pathologists and clinicians so as to carry out all necessary investigations to arrive at a diagnosis as early as possible. HLH should always be kept in mind as a differential diagnosis in any patients presenting with pancytopenia and febrile illness and H-scoring is to be done. H-score proposed by Fardet L et al., incorporates relatively simpler laboratory parameters to arrive at a diagnosis of HLH.

The serum ferritin level of all the patients was greater than 500 mcg/L. Two patients diagnosed with HIV, Non hodgkin's lymphoma had serum ferritin levels of 24560 ng/mL and 37700 ng/mL respectively. One patient had extreme elevation of serum ferritin (72,000 ng/mL) at presentation which led to suspicion for HLH. Ferritin levels >10,000 mcg/L were found to be highly sensitive and specific for diagnosis of HLH [10]. In a 2015 study conducted by Otrock ZK et and Eby CS 73 patients, greater than 85% of the patients displayed fever, cytopenias and elevated ferritin levels [11]. Serum ferritin rise is due to inhibitory cytokines IL-1β elevation. Hypertriglyceridemia was present in 81% of our patients. 64%-70% of paediatric patients with HLH reported elevated triglyceride levels [12].

Hypertriglyceridemia is due to lipoprotein lipase inhibition by Tumor Necrosis factor-α (TNF-α). Bone marrow evidence of haemophagocytosis was present in 92% cases. One patient had no evidence of haemophagocytosis but showed only increase in number of reticulum cells. Presence of bone marrow haemophagocytosis can be seen in various infections without full clinical syndrome. Hence it is not a diagnostic marker. In HLH, the incidence of haemophagocytosis on bone marrow examination ranges from 25-100% [13].

The most common trigger for HLH is viral infection, most commonly EBV [14]. Viruses associated with our cases were EBV, HSV, HIV and Parvovirus. Viruses are believed to have triggered HLH. Haematological malignancies can be a secondary cause of HLH. In this study, two patients had Hodgkin's and Non hodgkin's lymphoma. A multicentre study by Parodi A et al., demonstrated autoimmune aetiology like we reported in seven cases [15].

Without treatment, FHL has a median survival of about two months [16,17]. Survival in our patients was 52% at a median follow-up of 5 years. The survival was prolonged by the combined use of steroids and epipodophyllotoxins. Recently, effective cure has been achieved by immunotherapy with cyclosporin and antithymocyte globulin [18]. A major therapeutic breakthrough was achieved with allogenic Bone Marrow Transplantation (BMT) [19]. Chemotherapy followed by BMT is the current recommendation for treatment purpose [20]. The prognosis is better in sporadic HLH. Infection associated haemophagocytic syndrome caused by bacterial infection has a high recovery rate. However, the outcome of EBV associated HLH is poor [21].

Limitation(s)

The underlying aetiology could not be revealed in all cases as patients were lost to follow-up.

CONCLUSION(S)

Haemophagocytic lymphohistiocytosis (HLH) is an underdiagnosed and rare disease. Because of the high mortality rate, a timely diagnosis is very crucial. Infections and malignancies are the major precipitating factors in HLH. So in a patient with fever and cytopenias, HLH should be suspected as a culprit and H-scoring should be done since early diagnosis and treatment can save patients life. H-scoring needs laboratory tests which are comparatively affordable and available than the tests used in HLH criteria 2004. So it is critical to create a multicenter database where the information about HLH cases can be maintained and tracked. Even if a diagnostic dilemma is created due to the initial clinical findings mimicking other disorders, a comprehensive investigation and a close follow-up could address this problem.

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