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Pathology

Etiology of Haemophagocytic Lymphohistiocytosis (HLH) in a Tertiary Care Centre

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Abstract **Original Research Article**

Introduction: Haemophagocytic lymphohistiocytosis (HLH) is an aggressive and life threatening syndrome of highly stimulated but ineffective immune process. It can be triggered by a variety of events that disrupt immune homeostasis. Infection is a common trigger both in those with a genetic predisposition and in sporadic cases. Acquired HLH, with or without genetic disorders, may be due to infectious like bacterial, fungal, parasitic and viral or non-infectious etiologies such as malignancies, autoimmune disorders, and drugs. Although an early diagnosis is crucial to decrease mortality, it is often challenging due to lack of specificity of the clinical and laboratory findings and less availability of genetic tests in developing country. ***Materials and Method:*** In this prospective study, total 370 patients referred to our department for bone marrow aspiration from other departments of Calcutta National Medical College and Hospital from July'17 to July'19 and out of these 370 patients, 150 patients who are suspected for hemophagocytosis, evaluated for etiology. ***Result:*** Among 150 patients clinically suspicious of haemophagocytic lymphohistiocytosis 30 patients had haemophagocytic lymphohistiocytosis. 18 patients (60%) are male and 12 patients (40%) are female. The patients' age ranged from 1 year to 85 years. Among them 8 cases (26.68%) associated with infective etiology, 3 cases (10.0%) with megaloblastic anemia, 4 cases (13.33%) with acute leukemia, 5 cases (16.67%) with myelodysplastic syndrome, 3 cases (10.0%) associated with plasma cell dyscrasia, 4 cases (13.33%) have normoblastic erythroid hyperplasia and 3cases (10.0%) are of unknown etiology. ***Conclusion:*** Haemophagocytic lymphohistiocytosis has a wide spectrum of causes which can be diagnosed by detailed history, peripheral smear examination supported by bone marrow examination, biochemical tests, specific antibody detection and other relevant investigations. It's an expected situation for haemophagocytic lymphohistiocytosis reasons that the high rate of infections are one of the major causes in tertiary care centre.

Keywords: Clinical features, Haemophagocytic lymphohistiocytosis, bone marrow aspiration, biochemical tests.

INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is an often fatal syndrome of exaggerated but ineffective inflammatory responses, characterized by excessive macrophage and T-cell activation as well as impairment of the ability of natural killer (NK) and cytotoxic T cells to kill target cells [1-4]. HLH is a group of disorders that include familial and acquired forms of the syndrome and macrophage activation syndrome that is associated with certain autoimmune diseases [1-3, 5]. The acquired form of HLH is associated with infections, especially with Epstein-Barr virus, and malignancies, particularly peripheral T/NK-cell or anaplastic large cell lymphomas, and certain medications used for conditions such as systemic lupus erythrematosus [1-3, 5, 6].

Histiocyte Society HLH-2004 diagnostic criteria [7, 8]
The diagnosis HLH requires that either 1 or 2 below are fulfilled:

- A molecular diagnosis consistent with HLH: Pathological mutations of PRF1, UNC13D, STXBP1, RAB27A, STX11, SH2D1A, or XLAP
- Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below)

A) Initial Diagnostic Criteria

- Fever 38.5^0C or more for more than 7 days.

- Splenomegaly
- Cytopenias (affecting at least 2 of 3 cell lineages in the peripheral blood):
  - Hemoglobin <90g/L (in infants < 4 weeks: hemoglobin < 100g/L)
  - Platelets < 100 X 10^9/L
  - Neutrophils < 1.0 X 10^9/L
- Hypertriglyceridemia and/ or hypofibrinogenemia:
  - Fasting triglycerides more than or equals to 3.0mmol/L (i.e. more than or equals to 265 mg/dL)
  - Fibrinogen less than or equals to 1.5 g/L
- Haemophagocytosis in bone marrow or spleen or lymph nodes or liver

B) New Diagnostic Criteria

- Low or absent NK-cell activity
- Ferritin more than or equals to 500 mg/L
- Soluble CD25 (i.e. soluble IL-2 receptor) more than or equals to 2400 U/ml (new data show normal variation by age. Level should be compared with age-related norms).

Bone marrow examinations are often performed to check for evidence of hemophagocytosis when there is suspicion for HLH. Several diagnostic criteria for HLH, such as fever, cytopenias, and splenomegaly, are not very specific findings. Conventional wisdom suggests that finding evidence of hemophagocytosis can increase clinicians' confidence in making a diagnosis of HLH. Furthermore, genetic mutation analyses, NK-cell activity and sCD25 levels are usually send out tests done at specialized laboratories, which may not be as helpful in acute settings when prompt treatment decisions are crucial. In HLH, as a result of exaggerated immune activation, macrophages nonselectively phagocytize hematopoietic elements, presumably leading to the microscopic finding of hemophagocytosis. However, histologic evidence of hemophagocytosis is not specific to HLH and can be seen in other conditions as well, such as after blood transfusion, chemotherapy administration, and major operations, but the expected amount of hemophagocytic cells (HPCs) seen in these conditions has not been well defined [9-12]. At the same time, although it has been suggested that a positive finding in marrow for HPCs requires careful examination of at least three smears, each revealing at least two HPCs [11], there is so far no accepted interpretative threshold for positive findings or standardized reporting guidelines when such findings are present.

The exact pathophysiology of HLH varies depending on the cause and trigger [13]. Based mainly on the pathophysiology of primary HLH, defective granule-mediated cytotoxicity of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells is considered the main abnormality that causes HLH. Since CTLs and NK cells cannot insert perforin channels into the membranes of antigen presenting cells (e.g. Macrophages and histiocytes) and deliver granzymes. So, osmolysis and apoptosis of the antigen presenting cells do not occur. With persistent antigenic stimulation of CTLs and NK cells by the antigen presenting cells, an abundant release of cytokines ensues. The cytokine storm creates a systemic inflammation that can cause tissue destruction, progressive organ failure and death. Activated macrophages may engulf blood cells and create hemophagocytosis [14], one of the features of HLH.

A small case-control study found bone marrow quantitation of hemophagocytosis to be higher in patients with HLH, and hemophagocytosis had a sensitivity of 83% and a specificity of only 60% in diagnosing HLH [9]. Only bone marrow aspirates, but not biopsy specimens, were evaluated.

In this prospective study, among 370 bone marrow aspirates, 150 cases are suspected to have HLH, in which 30 cases have bone marrow haemophagocytosis. We are searching for the etiology from bone marrow examination and reviewing the bed tickets.

AIMS AND OBJECTIVES

1. To study the incidence of bone marrow haemophagocytosis.
2. To study the different causes of haemophagocytic lymphohistiocytosis.

MATERIALS AND METHODS

Study design- Prospective study.

Study duration- from July'17 to July 2019.

Place of study- Department of Pathology at Calcutta National Medical College and Hospital.

Period of study – 2 years.

Study population- Those patients who fulfilled physical and biochemical criteria of HLH (i.e. fever ≥38.5^0C for more than 7 days, splenomegaly, bi- or pancytopenia, Hypertriglyceridemia and/or hypofibrinogenemia, ferritin≥500µg/L), included in this study.

Bed head ticket- Patients clinical presentations, symptoms, laboratory results, impressions and assessments of the treating clinicians, and disease courses were all taken into consideration, and data for each diagnostic criterion in the HLH-2004 guidelines and specific antibody tests were recorded.

RESULTS

Patients' Characteristics

Table 1 & 2 summarize the patients' characteristics, including age and sex. Of the 30 patients, 18 are male (60.0%) and 12 are female (40.0%). The median age of diagnosing haemophagocytic lymphohistiocytosis was 39.0years, with an age range of 1 to 85 years.

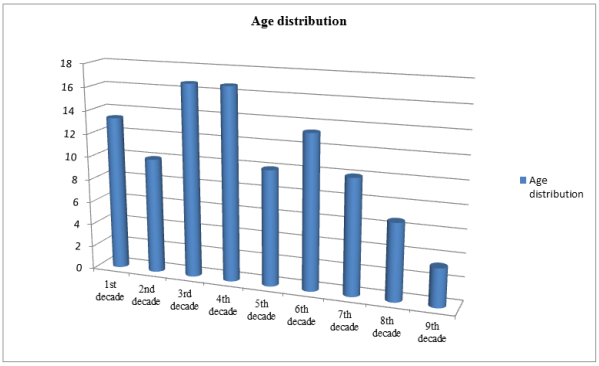


Table-1: Age distribution (n=30)

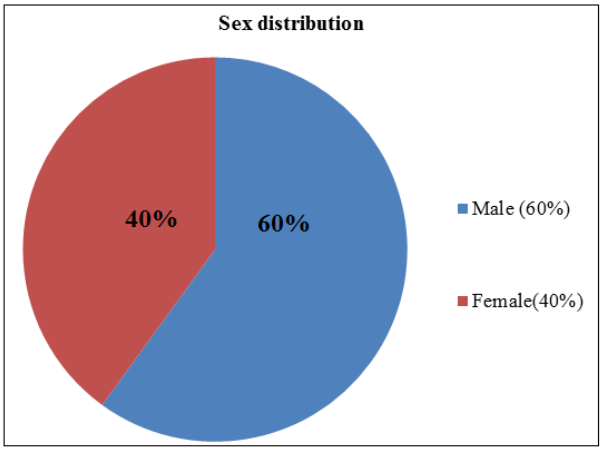


Table-2: Sex distribution (n=30)

Peripheral Blood Smears Findings

Table-3 summarizes the peripheral blood smears findings. Of the 30 cases, 18 cases (60.0%) showed pancytopenia and 12 cases (40.0%) showed bicytopenia.

Table-3: Cases showing cytopenia in peripheral blood smear (n=30)

Pancytopenia	No. of cases	% of total cases
Present	18	**60**
Absent	12	40

Bone Marrow Cellularity

At times initial stage of disease, no marrow involvement may be seen but may be seen in later in the course of disease. Varied cellular pattern of high, low or normal cells can be noted in HLH. Table-4 summarizes the bone marrow cellularity. Of the 30 cases, 26 (86.67%) showed hyper cellular marrow; whereas only 4 (13.33%) showed hypo cellular marrow.

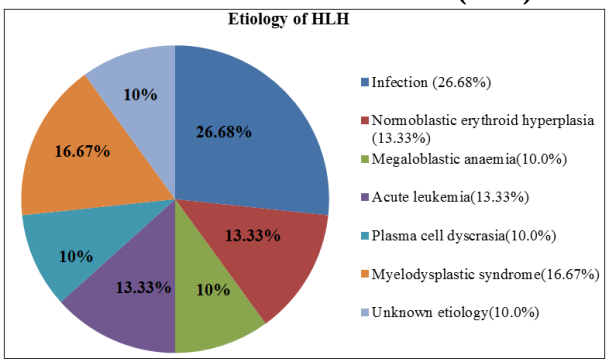
Table-4: Cases showing bone marrow cellularity (n=30)

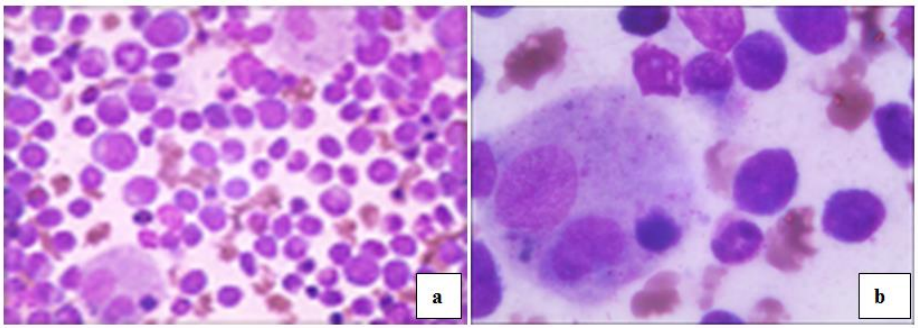
Cellularity	No. of cases	% of total cases
Hyper cellular	26	86.67
Hypo cellular	4	13.33

Causes of Haemophagocytic Lymphohistiocytosis (HLH)

Table-5 summarizes the different causes of HLH. Of these 30 cases, 8 (26.68%) associated with infection (Kala-azar, Enteric fever, AIDS, Histoplasmosis, Malaria), 4 cases (13.33%) having normoblastic erythroid hyperplasia, 3 cases (10.0%) with megaloblastic anemia, 4 cases (13.33%) are of acute leukemia, 5 cases (16.67%) of myelodysplastic syndrome and 3 cases (10.0%) associated with plasma cell dyscrasia. But, 3 (10.0%) out of 30 cases are of unknown etiology.

Table-5: Different causes of HLH (n=30)



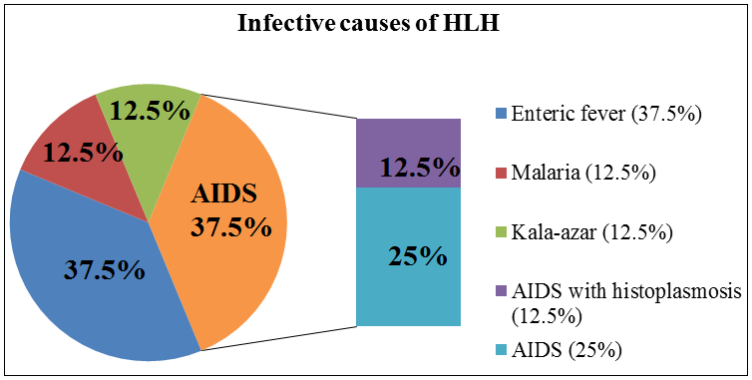


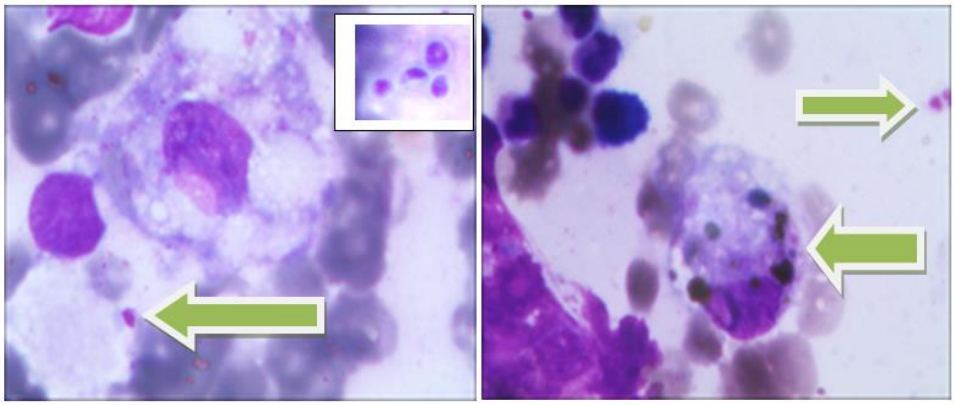
Photomicrograph 1: Bone marrow smear, Leishman stain – Acute promyelocytic leukemia with haemophagocytes under high power (a) and oil immersion (b)

Infective causes of Haemophagocytic lymphohistiocytosis (HLH)

Table-6 summarizes different infective causes of HLH. Out of 8 cases of infective etiology, 3 cases (37.5%) are of enteric fever, 1 patient (12.5%) has malaria, 1 patient (12.5%) has kala-azar, 3 cases (37.5%) have AIDS. From these 3 cases of AIDS, 1 (12.5%) case is associated with histoplasmosis.

Table-6: Different infective causes of HLH (n=8)



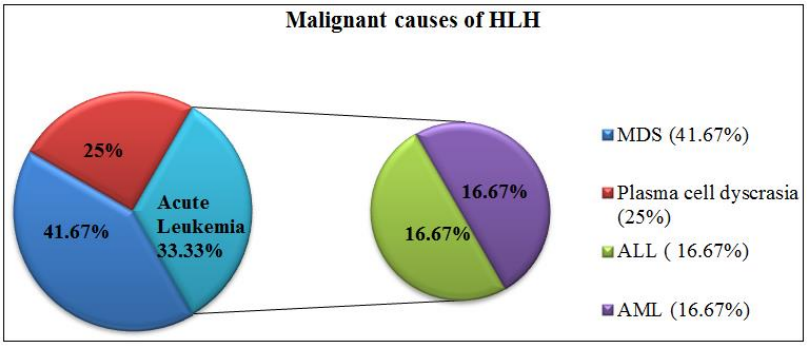


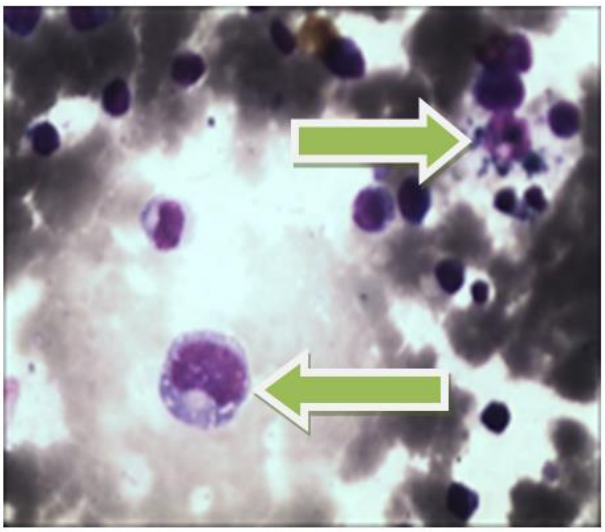
Photomicrograph 2: Bone marrow smear, Leishman stain – Histoplasma with haemophagocytosis under oil immersion

Malignant causes of Haemophagocytic lymphohistiocytosis

Table-7 summerizes different malignant causes of HLH. Out of the total 12 cases of haematological malignancy associated HLH, 5 cases (41.67%) are of MDS, 3 cases (25.0%) are of plasma cell dyscrasia and 4 cases (33.33%) are of acute leukemia. From these, 2 (16.67%) patients are suffering from acute myeloid leukemia and 2 (16.67%) patients have acute lympoblastic leukemia.

Table-7: Different malignant causes of HLH (n=12)





Photomicrograph 3: Bone marrow smear, Leishman stain – Burkitt's lymphoma with haemophagocytosis under high power

DISCUSSION

HLH is a syndromic disorder that can lead to life-threatening symptoms in a short interval. In a study by Janka GE *et al*., has showed that the disease is seen in all ages and has no predilection for race or sex [2]. Kaito *et al.*, described poor prognostic factor of adult HLH, including age over 30 years, presence of DIC, hyperferritinemia, increased beta 2-microglobulin, jaundice and worsening of anemia and thrombocytopenia [15]. Imashuku S *et al.*, has showed that HLH appears to affect all ages, although the hereditary and sporadic cases are reported more often in children [16]. The incidence of HLH in Sweden has been estimated to 1.2 children per 1 million children per year, or 1 in 50,000 live births with equal sex distribution [17]. In 2019, Joon Young Hur *et al.*, have showed that out of 44 patients 27 were male and 17 were female and 19 -85 years, all age groups were involved, median age 51.5 years [18]. In this study, 4 out of 30 (13.33%) patients were under 10 years, 7 out of 30 patients (23.33%) were in 5^{th} and 6^{th} decade. The median age of diagnosing haemophagocytic lymphohistiocytosis was 39.0 years. Of these 30 patients, 18 are male (60.0%) and 12 are female (40.0%).

In 2011, Troltestam H *et al.*, have showed that cytopenias, especially anemia and thrombocytopenia, are seen in greater than 80% of patients on presentation [19-21]. In 2016, Gevorg Tamamyan et al have showed that 48% patients have thrombocytopenia, 39% have anaemia and 30% have neutropenia.[22] Platelet counts range from 3000 to 2,92,000 (median 69,000)/ microL, and hemoglobin levels of 3.0 to 13.6 (median 7.2) g/dl are typical [19]. In this study, 18 patients (60.0%) with pancytopenia and 12 patients (40.0%) have bicytopenia.

In our study, 8 out of 30 cases (26.68%) associated with infection whereas 3 cases (10.0%) are of unknown etiology and 3 cases (10.0%) with megaloblastic anemia, 4 cases (13.33%) with acute leukemia, 5 (16.67%) with myelodysplastic syndrome and 3 (10.0%) associated with plasma cell dyscrasia. 8 cases of infective etiologies are- Kala-azar, enteric fever, AIDS, malaria, histoplasmosis. Dhote R *et al.*, have showed that a number of conditions are associated with secondary HLH. By prevalence, these include viral infections (29%), other infections (20%), malignancies (up to 27%), rheumatologic disorders (7%), and immune deficiency syndromes (6%) [23]. As has been described by the others, the most common underlying malignancies were AML and MDS (21%) [24]. Pancytopenia in typhoid fever may result from either bone marrow suppression or infection associated hemophagocytic syndrome (IAHS) [25, 26]. Typhoid fever is rarely associated with HLH [27]. Viruses are most frequently associated with secondary HLH, particularly Epstein- Barr Virus (EBV) [28], but tuberculosis, malaria, leishmaniasis and typhoid fever are important tropical infections that act as a trigger for IAHS [29]. Waseem Iqbal *et al.*, have showed that megaloblastic anemia is the most common cause (24.4%) in non malignant hematological conditions with HLH [30] which is also similar to this study. In 2016, Mahtat EM *et al.*, have showed that the most common causes of secondary HLH in adults are infections (49%), neoplasms (27%), rheumatoid arthritis (7%), and immune deficiencies (6%) [31]. In this study, 13.33% cases associated with acute leukemia and 16.67% also associated with myelodysplastic syndrome. Whereas, in 2014 Parikh SA *et al.*, also showed that the most common underlying malignancies were AML and MDS (21%) [24]. In 2018, Amitabh Singh et al have found 2 cases of ALL, 2 cases of AML and 1 case of Hodgkin lymphoma out of 5 pediatric malignancy associated HLH [32]. In 2015, Chandra H et al have showed that 18.7% patients have normoblastic erythroid hyperplasia [33]. In this study, 13.33% patients have normoblastic erythroid hyperplasia in their bone marrow findings.

Different studies described that perforin mutations are causative in the majority of familial haemophagocytic lymphohistiocytosis (FHL) cases, accounting for up to 58% and are considered a defining feature of FHL-2 [3, 19, 34]. Genes involved in cytotoxic granule exocytosis have been demonstrated to bear mutations in FHL-3, FHL-4, FHL-5. FHL-3 cases, which account for 10%-32% of genetic HLH feature UNC13D mutations [2].

CONCLUSION

HLH is a diverse condition with many causes and is likely under recognized, which contributes to its high morbidity and mortality. Though clinical findings, biochemical markers and tissue diagnostic markers fulfill diagnostic criteria, genetic analysis is warranted in all relevant cases as it has specific therapeutic and prognostic implication. Facilities for genetic study in

diagnosis of haemophagocytosis lymphohistiocytosis are still less available and costly in our country. Infections are common triggers in both genetic and acquired HLH. Fair number of HLH occurs due to infection and it may be manageable. This study is too small to conclude, further study is required for better comment.

REFERENCES

1. Arceci RJ. When T cells and macrophages do not talk: the hemophagocytic syndromes. Current opinion in hematology. 2008 Jul 1;15(4):359-67.
2. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Annual review of medicine. 2012 Feb 18;63:233-46.
3. Gupta S, Weitzman S. Primary and secondary hemophagocytic lymphohistiocytosis: clinical features, pathogenesis and therapy. Expert review of clinical immunology. 2010 Jan 1;6(1):137-54.
4. McCall CM, Mudali S, Arceci RJ, Small D, Fuller S, Gocke CD, Vuica-Ross M, Burns KH, Borowitz MJ, Duffield AS. Flow cytometric findings in hemophagocytic lymphohistiocytosis. American journal of clinical pathology. 2012 May 1;137(5):786-94.
5. Bryceson YT, Pende D, Maul-Pavicic A, Gilmour KC, Ufheil H, Vraetz T, Chiang SC, Marcenaro S, Meazza R, Bondzio I, Walshe D. A prospective evaluation of degranulation assays in the rapid diagnosis of familial hemophagocytic syndromes. Blood. 2012 Mar 22;119(12):2754-63.
6. Larroche C. hemophagocytic lymphohistiocytosis in adults: diagnosis and treatment, Joint Bone Spine. 2012; 79:356-361.
7. Weitzman S. Approach to hemophagocytic syndromes. ASH Education Program Book. 2011 Dec 10;2011(1):178-83.
8. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. The Lancet. 2014 Apr 26;383(9927):1503-1516.
9. Goel S, Polski JM, Imran H. Sensitivity and specificity of bone marrow hemophagocytosis in hemophagocytic lymphohistiocytosis. Annals of Clinical & Laboratory Science. 2012 Dec 21;42(1):21-5.
10. Risdall RJ, McKenna RW, Nesbit ME, Krivit W, Balfour Jr HH, Simmons RL, Brunning RD. Virus-associated hemophagocytic syndrome A benign histiocytic proliferation distinct from malignant histiocytosis. Cancer. 1979 Sep;44(3):993-1002.
11. Favara BE. Hemophagocytic syndrome. Semin Diagn Pathol, 1992; 9:63-74.
12. Suster S, Hilsenbeck S, Rywlin AM. Reactive histiocytic hyperplasia with hemophagocytosis in hematopoietic organs: a reevaluation of the benign hemophagocytic proliferations. Hum Pathol. 1988;19: 705-712.
13. Ammann S, Lehmberg K, zur Stadt U, Janka G, Rensing-Ehl A, Klemann C, Heeg M, Bode S, Fuchs I, Ehl S, HLH study of the GPOH. Primary and secondary hemophagocytic lymphohistiocytosis have different patterns of T-cell activation, differentiation and repertoire. European journal of immunology. 2017 Feb;47(2):364-73.
14. Rosado FG, Kim AS. Hemophagocytic LymphohistiocytosisAn Update on Diagnosis and Pathogenesis. American Journal of Clinical Pathology. 2013 Jun 1;139(6):713-27.
15. Kaito K, Kobayashi M, Katayam T, Otsubo H, Ogasawara Y, Sekita T, Saeki A, Sakamato M, Nishiwaki K, Masuoka H, Shimad T, Yoshida M, Hosoya T. Prognostic factors of hemophagocytic syndrome in adults: analysis of 34 cases. European Journal Haematol. 1997; 59: 247-253.
16. Imashuku S. Advances in the management of hemophagocytic lymphohistiocytosis. International Journal Hematol. 2000;72:1-11.
17. Henter JI, Elinder G, Soder O, Ost A. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand. 1991; 80:428-35.
18. Hur JY, Lee KK, Jang JH, Kim K, Jung CW, Kim WS, Kim SJ. Clinical Relevance of Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis (HLH) and Survival Outcome of Adult HLH Patients: A Single-Center Prospective Cohort Study. Blood. 2018,132:3718
19. Niece JA, Rogers ZR, Ahmad N, Langevin AM, McClain KL. Hemophagocytic lymphohistiocytosis in Texas: observations on ethnicity and race. Pediatric blood & cancer. 2010 Mar;54(3):424-428.
20. Trottestam H, Horne A, Aricò M, Egeler RM, Filipovich AH, Gadner H, Imashuku S, Ladisch S, Webb D, Janka G, Henter JI. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood, The Journal of the American Society of Hematology. 2011 Oct 27;118(17):4577-84.
21. Palazzi DL, McClain KL, Kaplan SL. Hemophagocytic syndrome in children: an important diagnostic consideration in fever of unknown origin. Clin Infect Dis, 2003; 36:306.
22. Tamamyan GN, Kantarjian HM, Ning J, Jain P, Sasaki K, McClain KL, Allen CE, Pierce SA, Cortes JE, Ravandi F, Konopleva MY. Malignancy-associated hemophagocytic lymphohistiocytosis in adults: Relation to hemophagocytosis, characteristics, and outcomes. Cancer. 2016 Sep 15;122(18):2857-66.
23. Dhote R, Simon J, Papo T, Detournay B, Sailler L, Andre MH, Dupond JL, Larroche C, Piette AM, Mechenstock D, Ziza JM. Reactive hemophagocytic syndrome in adult systemic disease: report of twenty-six cases and literature

review. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2003 Oct 15;49(5):633-9.

24. Parikh SA, Kapoor P, Letendre L, Kumar S, Wolanskyj AP. Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. InMayo Clinic Proceedings 2014 Apr 1, 89(4), 484-492. Elsevier.
25. Pathak R, Sharma A, Khanal A. Enteric fever with severe pancytopenia in a four year girl. Journal of the Nepal Medical Association. 2010 Oct 1;50(180):313-315.
26. Udden MM, Bañez E, Sears DA. Bone marrow histiocytic hyperplasia and hemophagocytosis in Taiwanese adults. J Microbial Immunol Infect, 1986;44: 191-197
27. Khalaf D, Toema B, Al-sadadi S, Al-jehani F, Sammak M. Salmonella typhi associated hemophagocytic lymphohistiocytosis in a previously healthy 23 years old woman. 2011.
28. Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. The Lancet infectious diseases. 2007 Dec 1;7(12):814-22.
29. Singh z, Rakheja D et al: Infection- associated haemophagocytosis: the tropical spectrum. Clin Lab Haematol. 2005; 27:312-315.
30. Iqbal W, Alsalloom AA, Shehzad K, Mughal F, Rasheed Z. Hemophagocytic histiocytosis: A Clinicopathological correlation. International journal of health sciences. 2017 Jan;11(1):1-7.
31. Mahtat EM, Zine M, Allaoui M, Kerbout M, Messaoudi N, Doghmi K, Mikdame M. Hemophagocytic lymphohistiocytosis complicating a T-cell rich B-cell lymphoma. BMC hematology. 2016 Dec 1;16(1):28.
32. Amitabh S. Malignancy associated hemophagocytic lymphohistiocytosis in children. Journal of Cancer Research and Therapeutics. 2018;14(3):559-562
33. Chandra H, Chandra S. Case of hemophagocytic lymphohistiocytosis with leishmaniasis. Tropical parasitology. 2015 Jul 1;5(2):135-136.
34. Mancebo E, Allende LM, Guzmán M, Paz-Artal E, Gil J, Urrea-Moreno R, Fernández-Cruz E, Gayà A, Calvo J, Arbos A, Duran MA. Familial hemophagocytic lymphohistiocytosis in an adult patient homozygous for A91V in the perforin gene, with tuberculosis infection. haematologica. 2006 Jan 1;91(9):1257-60.