ABSTRACT

INTRODUCTION

Haemophagocytic syndrome (HPS) also known as the Haemophagocytic lymphohistocytosis (HLH) is an aggressive and potentially fatal syndrome that results from inappropriate prolonged activation of lymphocytes and macrophages. The first reported case of HLH was described in 1952 by Farquhar and Claireaux who called the disease as “Familial Hemophagocytic Reticulosis”. It is traditionally divided into Primary\ Familial and Acquired\ Secondary. The Familial HLH is due to gene mutations most commonly involving the perforin gene while secondary HLH can occur in a wide variety of conditions including infections, autoimmune disorders to malignancies. The pathological hallmark of the syndrome is aggressive proliferation of macrophages/histiocytes in the reticuloendothelial system that are seen phagocytosing the haematopoietic elements.

The incidence is more common in the paediatric population, the highest between birth to 18 months of age. The estimated incidence of HLH is 1.2 cases per million individuals per year. However this is most likely an under estimate because most of the cases results in death before they are diagnosed, some remain undiagnosed while some are not reported.

The pathogenetic hallmark for HLH is defective NK cell function. NK cell is a cell of innate immunity which plays an important role in removing stress induced and virus infected cells. In HLH there is a defective NK cell function which can be familial or acquired. Defective NK cell leads to persistent activation of macrophages
and T helper cell which results in hypercytokinemia. This hypercytokinemia leads to the various manifestations of HLH.

Patients with HPS are commonly very ill at the time of presentation. They usually present with high persistent fever, anaemia, splenomegaly and CNS manifestations. The HLH society-2004 has laid down guidelines for the diagnostic criteria for HLH. Minimal diagnostic parameters are fever, cytopenia, splenomegaly, abnormal liver function tests, elevated serum triglycerides and serum ferritin, low serum fibrinogen and haemophagocytosis in bone marrow aspiration. The HLH society in 1994 has laid down therapeutic guidelines for the treatment of HLH. An improved revised therapeutic criteria came in 2004. This 2004 guideline mainly involves three treatment regimens - initial, continuation and reactivation therapy. However though disease control can be established with these treatment regimens, a complete cure can be established mainly by haematopoitic stem cell transplantation. After the advent of improved conditioning and graft versus host disease regimen the success of HSCT in patients with HLH has dramatically improved.

AIM & OBJECTIVES:

The Department of Pathology, PSGIMS & R receives bone marrows of patients with a spectrum of various neoplastic and non-neoplastic disorders. In this study we propose.

1. To evaluate the clinicopathological profile of haemophagocytosis diagnosed in the bone marrow in the Department of Pathology during the study period.
2. To correlate the clinical, biochemical and other haematological parameters of these patients with the findings in the bone marrow.

3. To highlight the haemophagocytic activity in bone marrow trephines using CD 68, an immunohistochemical marker for macrophages.

4. To elucidate the aetiopathogenesis of this diverse disorder.

MATERIALS & METHODS

About thirty two bone marrow aspirates and biopsies received in the clinical pathology laboratory, Department of Pathology, PSGIMS & R were analysed in the following manner:
RESULTS

- The mean age of presentation of HLH is 30.7 years
- Prolonged and persistent fever is the most common presentation of patients with HLH
- Mild to moderate anaemia, severe leucopenia and mild to moderate thrombocytopenia are common
- Ferritin levels of > 2000ng/ml are more diagnostic of HLH than any other parameter. In our study almost 100% of cases with ferritin levels of > 2000ng/ml were specific for HLH.
- CD 68 can be used to highlight haemophagocytosis in trephine biopsy. However in our study it did not help to increase the sensitivity of detection.
- The incidence of primary HLH is only 3% which can be an underestimate due to our limited facilities for molecular diagnosis.
- The most common cause for secondary HLH is infections followed by malignancies.
- Tuberculosis is the most common bacterial infection while Dengue is the most common viral infection associated HLH
- Lymphoma is the most common malignancy associated HLH.
- We had rare cases of Kikuchi Fujimoto disease & Diffuse large B cell lymphoma presenting as HLH.
- Prognosis of malignancy associated HLH was bad.
CONCLUSION

HLH is a diverse disorder which can present with varied clinical manifestations. There are many factors which contribute to the aetiopathogenesis of HLH. Because of the complex pathway of pathogenesis and different clinical presentations many of the HLH cases go under recognised. This remains the main cause for increased morbidity and mortality in persons with HLH.

In our study we have made conclusions regarding the clinical manifestations and aetiologies of HLH which will aid in the early diagnosis. Hereby we recommend that all patients with the clinical suspicion of HLH have to be carefully evaluated for the possible aetiology. A thorough and careful screening of bone marrow of these patients suspected to have HLH is essential for early diagnosis and prompt treatment. In spite of emergence of many treatment regimens for HLH, haematopietic stem cell transplantation remains the final option for treatment of patients with HLH. Hence more studies are required to raise awareness of this syndrome and improve the effectiveness of the existing treatment regimen.

KEY WORDS:

Haemophagocytic lymphohistiocytosis(HLH), Haemophagocytic syndrome, NK cell, Macrophages, Cheidiak Higashi Syndrome(CHS), Tuberculosis , CD 68 & Haematopoietic stem cell transplantation (HSCT).