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DIFFERENTIAL DIAGNOSIS OF HISTIOCYTIC DISORDER ON THE BASIS OF BONE MARROW EXAMINATION

Pathology

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ABSTRACT

Introduction :- The histiocytosis are rare disorders characterized by the accumulation of cells thought to be derived from dendritic cells (DCs) or macrophages. Their clinical behavior ranges from mild to disseminated and, sometimes, life-threatening forms. Histiocytosis are a group of uncommon disorders characterized by proliferation of cells of the mononuclear phagocyte system and the dendritic system. Each of the histiocytosis of childhood is characterized by localized or generalized, reactive or neoplastic proliferation of cells .

Aim: Aim of this study was to do differential diagnosis of Histiocytic disorder on the basis of morphological changes in bone marrow.

Method and material - Prospective study, carried out in Department of Pathology from January 2014 to March 2019. A total of 20 cases were studied. Bone marrow examination done in department of pathology and relevant clinical details of the patients diagnosed as Histiocytic discords were collected.

Hemograms were done in all cases. Special stains (PAS) were done whenever required.

Result :-The age of these cases ranged from 3 months to 12 years. There were 09 males and 11 females. Pathological diagnosis was made on bone marrow aspiration. Four cases of Langerhans cell histiocytosis (LCH), 11 cases of Hemophagocytic syndrome, 01 case of Hemophagocytic lymphohistiocytic disorder (HLH) and 04 cases of Granulomatous disorder were diagnosed on the basis of bone marrow morphology and relevant clinical history and investigations.

Conclusion :- we concluded that on the basis of bone marrow morphology and clinical features differential diagnosis of Histiocytic disorder is possible

KEYWORDS

Histiocytic disorder, Langerhans cell histiocytosis (LCH), Hemophagocytic syndrome, Hemophagocytic lymphohistiocytic disorder (HLH), Lysosomal storage disease

INTRODUCTION –

Histiocytes are derived from committed stem cells (colony forming unit- monocytes, CFU-M) in the bone marrow by passing through maturation stages of monoblast, promonocyte and monocyte.

Histiocytic disorders are a group of diseases derived from macrophages and dendritic cells. They result in a wide range of clinical conditions that are restricted primarily to children but can affect adults as well. The World Health Organization's contemporary classification arranges histiocytic disorders into three groups according to the type of histiocyte involved: dendritic cell disorders, macrophage-related disorders, and malignant histiocytic disorders (1). Langerhans cell histiocytosis (LCH) is the most common dendritic cell disorder. Less common diseases in this group include Erdheim-Chester disease (ECD) and juvenile xanthogranuloma (JXG). Macrophage-related disorders include sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease [RDD]) hemophagocytic syndrome and hemophagocytic lymphohistiocytosis (HLH). Malignant histiocytic disorders include certain leukemias and malignant tumors and will not be discussed here. We include the cases of Langerhans cell histiocytosis (LCH), hemophagocytic syndrome and hemophagocytic lymphohistiocytosis (HLH). Each of these diseases is unique, with varying symptoms, diagnostic tests, and treatments. This review describes the clinical manifestations and pathophysiology of each disease, with a focus on differential bone marrow findings.

Aim:

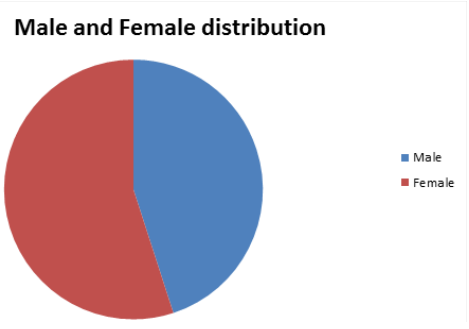
Aim of this study was to do differential diagnosis of Histiocytic disorder on the basis of morphological changes in bone marrow.

Method and material -

Prospective study, carried out in Department of Pathology from January 2014 to March 2019. A total of 20 cases were studied. Bone marrow examination done in department of pathology and relevant clinical details of the patients diagnosed as Histiocytic discords were collected.

Hemograms were done in all cases. Special stains (PAS) were done whenever required.

RESULT :- The age of these cases ranged from 3 months to 12 years. There were 09 males and 11 females (Graph 1). Of these 20 patients, all 20 patients were anemic, 13 showed leucopenia, 16 had thrombocytopenia while 12 had pancytopenia.



Graph 1 : Male and female distribution

According to morphological and clinical findings cases were divided in following categories of disorders (Table 1).

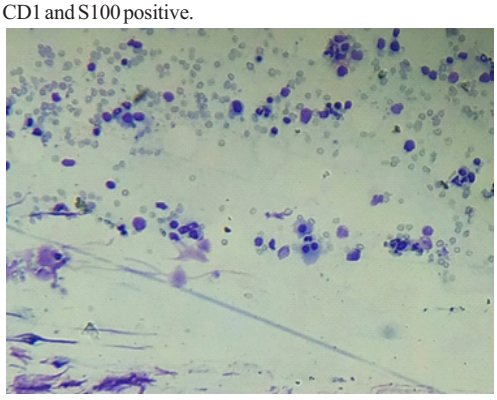
Table 1: shows distribution of cases

Disorder	Number of cases
Langerhans cell histiocytosis	04
Hemophagocytic syndrome	04
Hemophagocytic lymphohistiocytosis (HLH)	01
Granulomatous disorder	04

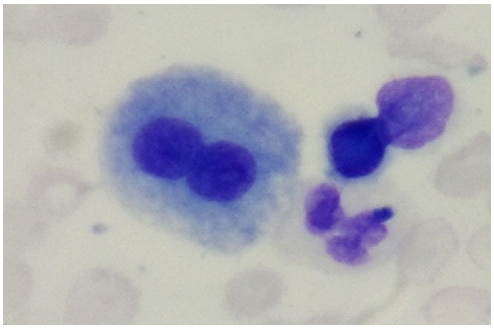
The morphological features of these 20 cases were as follows:

Langerhans cell histiocytosis: The abnormal cells in LCH are actually derived from myeloid dendritic cells that exhibit the same antigens (CD1a, S100, and CD207) and exhibit the same unique intracytoplasmic organelles as in Langerhans cells. These intracytoplasmic organelles, known as Birbeck granules, appear racquet-shaped at electron microscopy and help differentiate LCH from other histiocytic disorders and xanthogranulomatous diseases (2,3). The proliferation and accumulation of LCH cells in various organs results in the clinical disease (4). It typically is diagnosed in the first 2 years of life and is characterized by disseminated involvement of the reticuloendothelial system, anemia, and thrombocytopenia (5). The clinical manifestation of LCH depends on its severity and the number of organs involved and ranges from self-limited to fatal disease (in cases where disease has disseminated to multiple systems) (6). Langerhans cell Histiocytic (LCH cells) proliferation was observed in 04 cases. In bone marrow

smears showed diffuse infiltration of large mononuclear cells with abundant eosinophilic to foamy cytoplasm with large vesicular folded nucleus. There were binucleate forms as well. These histiocytes, were seen admixed with inflammatory cells particularly eosinophils with polymorphs, lymphocytes and plasma cells. Eosinophilic infiltrate was marked in 02 cases diagnosed as eosinophilic granuloma and sparse in 02 case of Letterer-Siwe disease. (Figure 1,2,3) These latter patients showed preponderant proliferation of histiocytes. In cases of eosinophilic granuloma patient had lytic bone lesions. In cases of letterer siwe disease patients presented with hepatomegaly and lymphadenopathy and characteristic skin rash. Flow cytometry report collected from patient show CD1 and S100 positive.

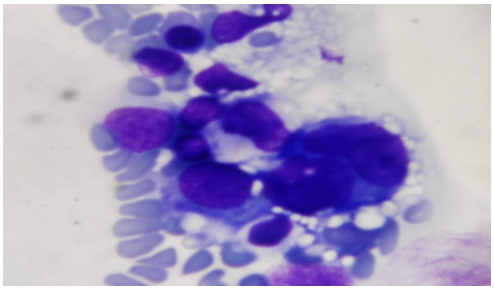


(1 A)

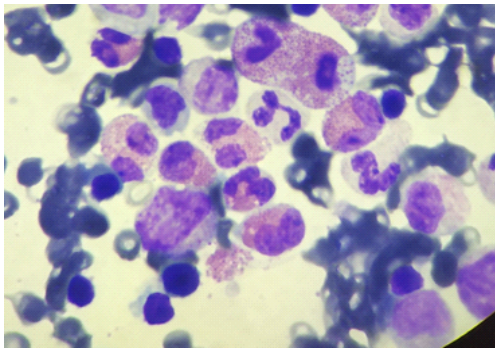


(1 B)

Figure 1 : (A and B) Binucleated form of large histiocytes



(2A)



(2B)

Figure: 2 Bone marrow aspiration show large mononuclear cell with abundant cytoplasm and folded nuclei (A) and eosinophilia (B).

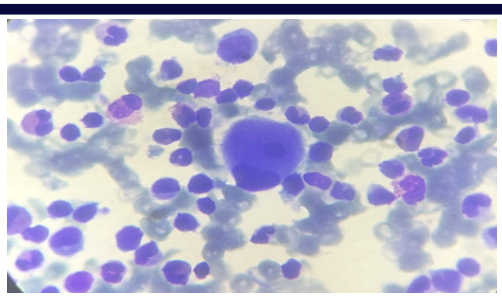
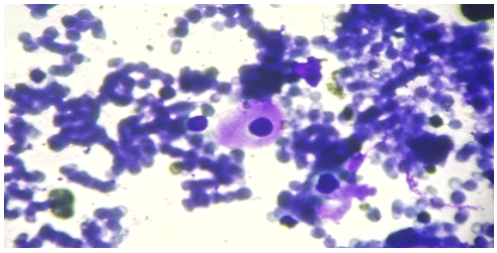


Figure 3: bone marrow aspiration smear with a single histiocytes showing hemophagocytosis with eosinophilia (100 x).

Hemophagocytic histiocytosis: These 11 cases showed marked increase in histiocytes with significant phagocytosis of platelets, erythroid and myeloid cells *(Fig. 4)*. Hemopoiesis was diminished to a variable degree and decreased myelopoiesis, decreased megakaryopoiesis and erythropoiesis.

These cases showed infection associated hemophagocytosis. Bone marrow revealed reduced cellularity with reactive histiocytosis and hemophagocytosis. No Lymphocytosis in these cases.



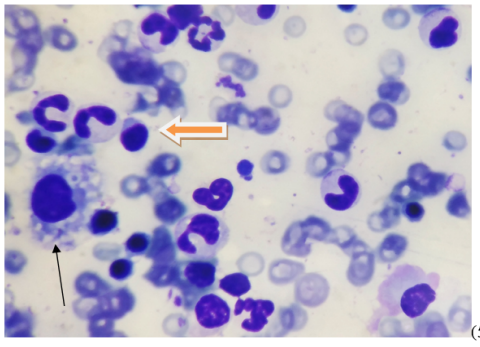
(4)

Figure 4 : bone marrow aspiration show large histiocytes with abundant foamy cytoplasm

Hemophagocytic Lymphohistiocytosis

HLH is an additional macrophage-related disorder characterized by an excess of lymphocytes and activated macrophages, typically with hemophagocytosis, in the bone marrow, spleen, liver, and lymph nodes (**7**). Currently, diagnosis of HLH requires five of the following eight criteria: fever, splenomegaly, cytopenia of at least two cell lineages, hypertriglyceridemia and/or hyperfibrinogenemia, tissue hemophagocytosis, low and/or absent natural killer cell activity, hyperferritinemia, and high-soluble interleukin-2 receptor levels (7). Because the presenting symptoms are nonspecific, initial diagnosis is often delayed; rarely, a diagnosis of HLH is not considered until postmortem examination. Recently, serum ferritin levels greater than 10,000 µg/L have been shown to be 90% sensitive and 96% specific for the diagnosis of HLH (8).

One case was diagnosed as primary Hemophagocytic lymphohistiocytosis on the basis of above criteria, patient was presented with fever, Splenomegaly, Pancytopenia, hypertriglyceridemia , hyperferritinemia and bone marrow revealed histiocytosis with hemophagocytosis and Lymphocytosis (figure-5). Histiocytes are mature and bland appearing with no cytological atypia.



(5)

Figure 5 : bone marrow aspiration with a large histiocytes with abundant foamy cytoplasm (4A) showing hemophagocytosis (black arrow) Lymphocyte (orange arrow) .

Granulomatous disorder – granulomatous disorder was observed in 04 cases. Bone marrow aspiration showed well formed granuloma comprising of epithelioid histiocytes surrounded by lymphocytes, and plasma cells.(Figure 6)

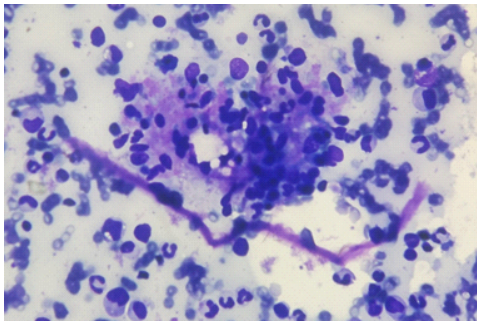


Figure 6; Bone marrow aspiration show granuloma formation

DISCUSSION

In our study, *Hemophagocytic histiocytosis* was the commonest cause of histiocytosis in bone marrow, in contrast to the other study which showed, a series of 120 cases of histiocytosis in children documented 54 cases of Langerhans cell histiocytosis, 9 of *Hemophagocytic histiocytosis* and 47 of malignant histiocytosis (9). LCH is more common than HLH in our study . We found 2 cases of LCH and one case of HLH out of 20 cases included in our study. Other disorders like granulomatous disease we take separately because of typical granuloma formation in these cases. Cases of malignant hisytiocytosis were not included in our study.

CONCLUSION :

We concluded that on the basis of bone marrow morphology and clinical features differential diagnosis of Histiocytic disorder is possible. In all cases of histiocytosis, it is suggested that clinical features, bone mar row findings must be correlated to subtype the class of histiocytosis for adequate diagnosis.

Footnotes
Source of Support: Nil
Conflict of Interest: None declared.

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