Section: Pathology

Original Research Article

HISTIOCYTIC LESIONS OF BONE MARROW WITH EMPHASIS ON HISTIOCYTIC SARCOMA - AN INSTITUTIONAL STUDY

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ABSTRACT

Background: Histiocytic lesions of the bone marrow include both reactive and neoplastic proliferations. While reactive histiocytosis is relatively common and associated with infections, inflammatory conditions, and increased cellular turnover, neoplastic histiocytic disorders such as histiocytic sarcoma are rare and aggressive.

Materials and Methods: This study was conducted in the Institute of Pathology, Rajiv Gandhi Government General Hospital, Chennai, over a period of one year (January 2025–December 2025). A total of 1800 bone marrow biopsies were evaluated. Histopathological examination and immunohistochemistry were performed when required.

Results: Among the cases studied, histiocytic lesions included 5 cases of granulomatous inflammation, 3 cases of hemophagocytic lymphohistiocytosis (HLH), 1 case of macrophage activation syndrome (MAS), and 1 rare case of histiocytic sarcoma involving the bone marrow. Granulomatous lesions were commonly associated with fever and cytopenias. HLH cases presented with cytopenias and elevated ferritin levels with hemophagocytosis on bone marrow examination. The diagnosis of histiocytic sarcoma was established by histomorphology and immunohistochemistry demonstrating positivity for histiocytic markers.

Conclusion: Reactive histiocytic lesions are more frequently encountered in bone marrow biopsies, whereas neoplastic histiocytic disorders such as histiocytic sarcoma are extremely rare. Accurate diagnosis requires careful histomorphological evaluation and appropriate immunohistochemical analysis.

Keywords: HLH, MAS, LCH Histiocytic sarcoma , WHO

INTRODUCTION

Macrophages are members of the mononuclear phagocyte system.

A histiocyte is a morphological term referring to tissue-resident macrophages.

Macrophages are large ovoid cells mainly involved in the clearance of apoptotic cells, debris, and pathogens

The bone marrow is a preferential site for both reactive and neoplastic histiocytic proliferations. The differential diagnosis of reactive histiocytic hyperplasia includes systemic infections, vaccinations, storage diseases, post-myeloablative therapy, and conditions associated with increased cell turnover leading to histiocytic proliferation, as well as hemophagocytic lymphohistiocytosis and extranodal Rosai–Dorfmann disease. The differential diagnosis of neoplastic histiocytoses includes histiocytic sarcoma (HS), Langerhans cell histiocytosis (LCH), Erdheim–Chester disease (ECD), and disseminated juvenile xanthogranuloma (JXG).

In this article, we discuss cases of reactive and neoplastic histiocytic lesions involving the bone marrow. In our institute, approximately 1,800 bone marrow biopsies are reported annually. The majority of these cases comprise hematological malignancies,

particularly leukemia, including newly diagnosed cases and those undergoing evaluation for treatment response, suspected relapse or recurrence, and post–bone marrow transplantation.

In addition to leukemia, bone marrow biopsies are performed for the diagnosis of metastatic carcinoma deposits, evaluation of cytopenias such as suspected aplastic anemia of unknown origin, anemia, treatment-resistant cases, suspected immune thrombocytopenic purpura, lymphomatous infiltration, infections, and histiocytic disorders such as hemophagocytic lymphohistiocytosis (HLH).

Revised classification of histiocytosis is based on histology, phenotype, molecular alterations, and clinical and imaging characteristics. It consists of 5 groups of diseases: (1) Langerhans-related, (2) cutaneous and mucocutaneous, and (3) malignant histiocytoses (4) Rosai-Dorfman disease and (5) hemophagocytic lymphohistiocytosis and (6)macrophage activation syndrome
Current World Health Organization (WHO) classification of histiocytic and dendritic neoplasms, which is primarily based on morphological and phenotypical criteria recognizes (1) histiocytic sarcomas, (2) tumors derived from Langerhans cells (LC), (3) indeterminate dendritic cell tumors, (4) interdigitating and (5) follicular dendritic cell sarcomas, (6) fibroblastic reticular cell tumors, (7) disseminated juvenile xanthogranulomas (JXG), and (8) ECD.

MATERIALS AND METHODS

This study was conducted in Institute of Pathology, Rajiv Gandhi Government Hospital, Chennai for a period of one year from Jan 2025 to Dec 2025. All the cases received in Clinical Pathology for one year taken into study. Only inadequate samples are rejected. A total of 1,800 bone marrow samples were received, of which 1,250 were cases of leukemia; 397 were cases of pancytopenia, aplastic anemia, myelodysplastic syndromes (MDS), or multiple myeloma; 87 were myeloproliferative neoplasms; 45 were evaluated for thrombocytopenia; and 21 were suspected cases of hemophagocytic lymphohistiocytosis (HLH). All the samples were processed as per standard protocol and examined .Immunohistochemical markers were added whenever needed . Among the 21 cases with suspected hemophagocytic lymphohistiocytosis (HLH), 5 were confirmed as HLH, 5 showed granulomatous lesions of the bone marrow, 1 was diagnosed as macrophage activation syndrome, and 1 as histiocytic sarcoma. The remaining cases were reported as hypoplastic marrow or marrow showing trilineage hematopoiesis.

Aims and Objectives

1. To analyse the occurrence of histiocytic lesions in bone marrow, their clinical features, criteria for diagnosis and histomorphological features
2. To analyse the clinical features, histomorphological and immuno histochemical features of histiocytic sarcoma.

RESULTS

In our study there were many cases showing reactive histiocytosis, but we consider only those cases which is the primary etiology of the clinical presentation. We include Granulomatous lesions, HLH, Macrophage activation syndrome and a rare case of Histiocytic sarcoma.
In our study we had 5 cases of granulomatous inflammation, 3 cases of HLH, 1 case of macrophage activation syndrome and 1 case of histiocytic sarcoma.

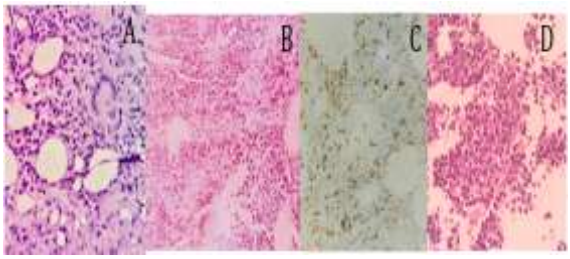
DISCUSSION

The phagocytic system consists of monocytes/macrophages and dendritic cells mononuclear phagocytes arise from the myeloid haematopoietic lineage and located among the erythropoietin islands as nursing histiocytes and constitute about 10% of bone marrow microenvironment. These macrophages are affected by reactive, inflammatory and neoplastic histiocytic disorders. Non-neoplastic proliferations of histiocytes are associated with increased cell turnover, as seen in myeloproliferative neoplasms and thalassemia (manifesting as sea-blue histiocytes), as well as in systemic infections, Bacillus Calmette–Guérin (BCG) vaccination, and plasma cell disorders. Other important non-neoplastic conditions include granulomatous inflammation secondary to tuberculosis, fungal infections, and sarcoidosis. In contrast, histiocytoses—neoplasms derived from histiocytes—are rare disorders characterized by the accumulation of histiocytes and dendritic cells in various tissues and organs.

As per WHO Classification of haematolymphoid malignancies 5th edition histiocytic disorders are classified into - Langerhan cell and other dendritic cells neoplasms constituting Langerhan cell histiocytosis, Langerhan cell sarcoma and other dendritic cells neoplasms constituting indeterminate Dendritic cell tumor and Interdigitating dendritic cell sarcoma

In this article we discuss about various histiocytic lesions emphasising on rare disorders like macrophage activation syndrome and histiocytic sarcoma.

The most common histiocytic disorder other than reactive proliferations is granulomatous disorders. The clinical presentation was mostly pancytopenia and some were refractory anaemias. Two out of five cases had previous history of tuberculosis and its treated. Trephine biopsy shows well formed granulomas composed of epithelioid histiocytes and occasional multinucleated giant cells.[2]



A. High power view showing a granuloma B) Low power showing sheets of macrophages in macrophage activation syndrome C) CD 163 positivity in macrophage activation syndrome D) High power showing emperipolesis in HLH.

A **Granuloma** is a compact aggregate of macrophages mainly Epithelioid macrophages (large amount of pale pink cytoplasm with ovoid or round nuclei with a dispersed chromatin), Giant cells (Langhans type, Foreign body type). Other cells like Lymphocytes, Plasma cells, Neutrophils, Eosinophils, Fibroblasts may be found within granuloma

ETIOLOGY includes

1. INFECTION: Bacterial/ Viral/ parasitic
2. SARCOIDOSIS
3. AUTOIMMUNE DISORDERS: RA, SLE
4. MALIGNANT DISEASE: Hodgkin Lymphoma, Non Hodgkin Lymphoma, MM, ALL, MDS, Polycythemia Vera, Metastasis
5. HYPERSENSITIVITY: Phenytoin, Chlorpropamide, Ibuprofen, Indomethacin, Allopurinol, Carbamazepine, SAS
6. ASSOCIATED WITH EOSINOPHILIC INTERSTITIAL NEPHRITIS
7. REACTION TO FOREIGN OR EXTRANEOUS SUBSTANCES: Anthracosis and Silicosis, Talc, Keratin driven into bone marrow

Among the 5 cases of granulomatous lesions, the age at presentation ranged from 16 to 60 years. Clinical symptoms included evening rise of temperature and fatigability. Two patients had a past history of tuberculosis. One case, a male patient, presented with fever of 40 days' duration, associated with evening rise of temperature.

Peripheral smear reports shows normocytic normochromic anaemia in 2 cases , leucocytosis in one case and pancytopenia in two cases.

Bone marrow biopsy shows trilineage haematopoiesis with adequate megakaryocytes with multiple epithelioid granulomas in 4 cases and one case shows hypoplastic marrow with ill formed epithelioid granulomas . All the cases were reported as granulomatous inflammation and suggested CBNAAT to rule out tuberculous etiology.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) is a rare, potentially fatal disorder characterized by a dysregulated activation of cytotoxic T lymphocytes, natural killer (NK) cells, and macrophages resulting in hypercytokinemia and immune-mediated injury of multiple organ systems.[3]

Primary HLH or Familial HLH - due to genetic mutations inherited in a homozygous or compound heterozygous manner, which fully eliminates function of Cytotoxic T lymphocytes and NK cells. It occur during the 1st year of life in 70 to 80% of individuals. All mutations associated with F-HLH either involve Perforin or defective granular exocytosis by T and NK cells.

Impairment of function of CTL and NK cells→ Inability to clear the antigenic stimulus→ Release of pro-inflammatory cytokines (IFN-gamma, TNF-alpha,IL-1beta,IL-2,IL-6,IL-12,IL-16 and IL-18)→ Chronic activation and abnormal behaviour of macrophages.

Hemophagocytosis by upregulation of pro phagocytic molecules like calreticulin on mature blood cells and downregulation of CD47 on hematopoietic stem cells.

Secondary HLH or Acquired HLH occurs due to external factors like infection, malignancy, rheumatological disease, post allogenic hematopoietic stem cell transplantation, drug hypersensitivity, etc. The most common infectious agent associated with secondary HLH is EBV.

HLH—2004 Diagnostic Criteria

Molecular diagnosis consistent with HLH

Or 5 of the 8 criteria listed below

1. Fever ≥38.5°C
2. Splenomegaly
3. Cytopenia (affecting at least two of the three lineages in the peripheral blood) Hemoglobin <9 g/dL (in infants <4 weeks: <10 g/dL), Platelets <100 × 10^3/μL, Neutrophils <1,000/μL
4. Hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (≤150 mg/dL)
5. Hemophagocytosis in bone marrow or spleen or lymph nodes or liver
6. Low or absent NK cell activity
7. Hyperferritinemia (≥500 ng/mL)
8. Elevated soluble CD25 (sIL-2 receptor α) (≥2,400 U/mL).

In our study, we identified 3 cases of hemophagocytic lymphohistiocytosis (HLH) in patients aged 17 to 40 years. Clinically, all patients presented with cytopenias, mild to moderate splenomegaly, and elevated ferritin levels. Peripheral smear examination revealed normocytic normochromic anemia with leukopenia and thrombocytopenia in all cases. Bone marrow aspiration (BMA) showed trilineage hematopoiesis with erythroid hyperplasia and adequate megakaryocytes. However, bone marrow

trephine biopsy demonstrated features consistent with Hemophagocytic Lymphohistiocytosis**.** Another case, a 32-year-old male, presented with complaints of tiredness. Notably, all cases showed evidence of hemophagocytosis on bone marrow biopsy despite relatively preserved trilineage hematopoiesis on aspiration, highlighting the importance of bone marrow biopsy in suspected hemophagocytic lymphohistiocytosis.

MACROPHAGE ACTIVATION SYNDROME, a severe hyperinflammatory complication of systemic juvenile idiopathic arthritis characterized by uncontrolled activation of T lymphocytes and macrophages, resulting in cytokine overproduction and hemophagocytosis.[4]**.** A 14-year-old female with clinically suspected Systemic Juvenile Idiopathic Arthritis presented with fever and cough for three weeks. Peripheral smear showed normocytic normochromic anemia with neutrophilic leukocytosis. Bone marrow aspiration revealed trilineage hematopoiesis with adequate megakaryocytes, while biopsy demonstrated a hypercellular marrow with occasional CD68-positive histiocytes. In the appropriate clinical context, these findings raise the possibility of MAS. MAS typically presents with persistent fever, cytopenias, liver dysfunction, coagulopathy, and hyperferritinemia[5,6]. Although hemophagocytosis in bone marrow is considered a characteristic feature, its absence does not exclude the diagnosis, particularly in early or evolving disease. Therefore, diagnosis relies on a combination of clinical findings and laboratory parameters such as elevated ferritin, thrombocytopenia, elevated transaminases, and hypofibrinogenemia.[1] Early recognition is critical because MAS can rapidly progress to multi-organ failure if untreated.

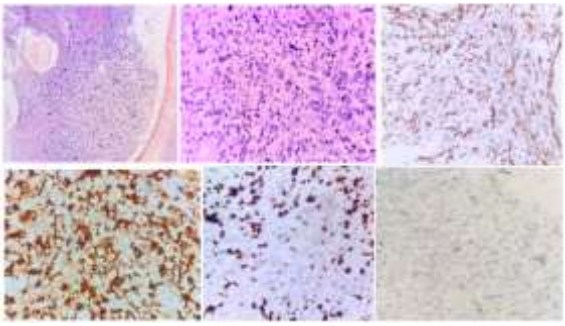


Fig 2 : A) low power view showing cellular marrow with sheets of atypical cells.B)high power view of neoplastic cells of HS C)CD 68 positivity in neoplastic cells D)CD163 positivity in neoplastic cells E) KI 67 -80%F)CD1a - negative

The diagnosis of macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis requires presence of **at least two or more of the following laboratory criteria or two or more of the following clinical criteria**:

Laboratory criteria

Decreased platelet count (<262 × 10^9/L)

Elevated aspartate aminotransferase levels (>59 U/L)

Decreased white blood cell (WBC) count (<4 × 10^9/L)

Hypofibrinogenemia (≤2.5 g/L)

Clinical criteria

CNS dysfunction (eg, irritability, disorientation, lethargy, headache, seizures, coma)

Hemorrhages (eg, purpura, easy bruising, mucosal bleeding)

Hepatomegaly (≥3 cm below the costal margin)

Histopathologic criterion

Evidence of macrophage hemophagocytosis is found in the bone marrow aspirate sample. The demonstration of hemophagocytosis in bone marrow samples may be required in doubtful cases.[7]

HISTIOCYTIC SARCOMA is an extremely rare non-Langerhan's histiocytic malignancy, constituting less than 1% of all hemato-lymphoid neoplasms. Documented in a wide range of age group, a subset of cases are associated with primary mediastinal germ cell Tumors

Most of the patients present with lymphadenopathy or manifestations of extranodal disease such as intestinal obstruction, skin lesions and splenomegaly.

Primary involvement of HS in bone marrow is very rare.

The diagnosis is often challenging due to its rarity and the possibility of overlapping morphological and immunophenotypical features. The clinical presentation depends on the organ of involvement, often shows an aggressive clinical course and systemic symptoms, such as fever, weight loss, adenopathy, hepatosplenomegaly and pancytopenia.

Histopathology of the bone marrow trephine biopsy will show diffuse sheets of tumor cells that are large, oval to round sometimes spindled, with abundant cytoplasm. The cytoplasm may often show vacuoles the nuclei are oval, round showing indentations, grooves with vesicular chromatin and distinct nucleoli.may show haemophagocytosis.

On immunohistochemistry, HS shows expression of positive expression of the macrophage associated antigen CD68, CD 163; negative expression of the T-cell associated and Langerhans cell antigen CD1a, S-100 protein, and the dendritic cell-associated antigens CD21 and CD35. Differential diagnosis includes lymphoma with large cells like ALCL, Langerhan cell sarcoma, follicular dendritic cell sarcoma, melanoma, carcinoma and undifferentiated pleomorphic sarcoma.[9,10,11]

As per the WHO Essential Criteria, HS is considered as a Tumor composed of non-cohesive large cells with abundant cytoplasm that is eosinophilic , with variable pleomorphic neoplastic cells with rein form, grooved or irregularly folded nuclei and distinct nucleoli that shows positive immunisation in for two or more histiocytic markers and negative for CD1a, Langerin(CD207), CD21 and CD35.[8]

HS is usually aggressive showing high mortality rate, hence its diagnosis is crucial .

In our study, a 19-year-old female was clinically suspected to have aplastic anemia. Peripheral smear examination revealed dimorphic anemia with leukopenia and thrombocytopenia. Bone marrow aspiration was grossly diluted. Bone marrow trephine biopsy showed sheets and singly scattered atypical cells that were spindle to bizarre in shape, with scant cytoplasm and pleomorphic hyperchromatic nuclei. Although the morphology did not resemble routine leukemia, an immunohistochemistry (IHC) panel was performed, including leukemia/lymphoma markers such as CD34, CD117, TdT, CD3, and CD20. Pan-cytokeratin (PanCK) was included to rule out metastatic carcinoma, CD30 to evaluate for germ cell tumors, S100 to exclude melanoma, CD163 to assess histiocytic lineage, and Ki-67 to determine the proliferation index. Subsequently, flow cytometry and PET-CT were performed. Flow cytometry was inconclusive due to a dry tap on bone marrow aspiration. PET-CT demonstrated increased uptake in the axial skeleton, and ultrasonography of the abdomen revealed mild hepatosplenomegaly. Immunohistochemistry showed positivity only for CD163, with a high Ki-67 proliferation index of approximately 80%. A second panel of markers, including CD1a, Langerin, and CD21, was performed to further classify histiocytic neoplasms. All these markers were negative, thereby excluding Langerhans cell histiocytosis, Langerhans cell sarcoma, and interdigitating dendritic cell sarcoma. Based on these findings and in accordance with WHO criteria, a diagnosis of histiocytic sarcoma was made. Given the aggressive nature of the disease, the patient unfortunately succumbed to the illness.

CONCLUSION

Although reactive histiocytic proliferations are common, identifying the neoplastic potential of histiocytes, as in histiocytic sarcoma, remains challenging. A comprehensive panel of immunohistochemical (IHC) markers is required to exclude more common leukemic and other neoplastic etiologies and to establish a definitive diagnosis. As histiocytic sarcoma is an aggressive neoplasm with very high mortality rate diagnosing this rare entity is essential.

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