



Case Series

Navigating the enigma of bone marrow granulomas: A case series exploration

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ABSTRACT

Introduction: Granulomatous diseases of marrow can result from a varied group of disorders ranging from infectious diseases to hematological malignancies. Finding granuloma in bone marrow biopsy is a rare finding. Detection of granulomatous disease is possible on Bone marrow biopsy and sometimes it changes the treatment modality.

Aims and Objectives: To study incidence and etiologies of granulomatous diseases of marrow.

Materials and Methods: This was a retrospective study conducted in Department of Pathology, M.K.C.G. Medical College and Hospital, Berhampur. Bone marrow biopsy performed in the period of 1st January 2021 to 31st December 2022 were reviewed along with medical records of these patients.

Results: We reviewed 185 cases of Bone marrow biopsy confirming presence of granuloma in ten patients. The age of the patients varied from 5 years to 55 years. Out of the 10 cases seven (70%) had history of fever, two (20%) with history of pain in abdomen and loss of appetite and (10%) one with weakness. Eight (80%) out of the ten cases had organomegaly. CBC and peripheral smear evaluation of all the cases were done and the finding was pancytopenia in six (60%) cases followed by bicytopenia in four (40%). Seven out of the 10 cases were diagnosed as case of Tuberculosis, one as Hodgkin's Lymphoma one as Sarcoidosis in Bone marrow trephine biopsy. Despite of thorough investigations no definite etiology was detected in one case.

Conclusion: Bone marrow trephine biopsy is very helpful in finding out Granuloma which is though a non-specific finding may narrow down the diagnosis to various possible differentials.

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1. Introduction

Examination of Bone marrow is considered a significant diagnostic modality for various hematological and non-hematological disorders. This may help in confirmation of a clinical diagnosis and may provide diagnosis of a clinically unsuspected disease thereby changing the treatment protocol.¹ Incidence of bone marrow granuloma ranges 0.3-3% as reported in various literatures.² Thus Granulomatous disorders are infrequently detected in bone marrow and they

are very nonspecific. However, presence of granuloma in bone marrow denotes certain diseases like Mycobacterium Tuberculosis, Fungal infections, Sarcoidosis, Mycoplasma, Hodgkin's lymphoma, Non Hodgkin's lymphoma and occasionally drug reactions.³ Granulomatous lesions are detected in bone marrow trephine biopsy, clot preparations and occasionally even in bone marrow aspiration samples.⁴

Most of the studies on granulomatous lesions in bone marrow are conducted in foreign countries but there is paucity of data regarding granulomatous lesions in bone marrow in India. The present study aims at determining

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incidence and etiologies of granulomatous lesions in bone marrow.

2. Case Series

This was a retrospective study conducted in Department of Pathology, M.K.C.G. Medical College and hospital, Berhampur in the period of 1st January 2021 to 31st December 2022. All cases that showed granulomatous lesions in bone marrow biopsy were included in the study. Records of all the cases were obtained from Medical Record Department and reviewed. The Bone marrow trephine biopsy and aspiration along with the peripheral blood smears were reviewed by two pathologists to confirm the presence of granuloma.

Bone marrow biopsies were performed under all available aseptic conditions by insertion of Jamshidi needle. Undecalcified bone marrow biopsy samples were put into AZF solution (containing Glacial acetic acid, Zinc chloride, concentrated formaldehyde and distilled water) and allowed to fix overnight. Next day the solution was decanted and the biopsy specimens were washed in distilled water for 30mins and then kept in decalcifying solution (containing 5% formaldehyde and 10% formic acid) for 6 hours. The biopsy specimens were then sent to Histopathology section for further processing. The samples were processed in Automated tissue processor manufactured by Leica and embedded in paraffin wax and cut in thickness of $2\mu\text{m}$ using a rotary microtome. The sections were stained with Hematoxyline and Eosin (H&E). Fibrosis was assessed using Reticulin stain and Masson's Trichrome stain. Immunohistochemical stains were performed as per requirement.

Epithelioid granuloma was defined as focal collection of macrophages and epithelioid cells with or without multinucleated giant cells, with or without accompanying cells such as lymphocytes.

Information regarding other serological tests and various radiological investigations were obtained from the medical records.

We reviewed 185 cases of Bone marrow biopsy confirming presence of granuloma in bone marrow biopsy of 10 patients representing incidence of granuloma in bone marrow biopsy of 2.89% and annual incidence of 5 cases per year. Age group of the patients varied from 5 years to 55 years. Out of the 10 patients 3 (30%) were females and 7 (70%) were males.

Most common clinical presentation was fever in 7 cases (70%) followed by pain in abdomen and loss of appetite 2 cases (20%) and weakness in 1 case (10%). Hepatosplenomegaly was present in 8 patients (80%).

Most common hematological alteration was found to be Normocytic normochromic anemia (70%) followed by Macrocytic anemia (20%) and Microcytic hypochromic anemia (10%). Reticulocyte count was low in all

cases. Leukopenia was found in 60% of cases and thrombocytopenia in 70%. Pancytopenia was found in 6 (60%) cases and Bi-cytopenia in 4 (40%) cases.

Out of the ten cases seven had well defined epithelioid granuloma with caseous necrosis in H&E stain. (Figures 1 and 2) Reticulin and Masson trichrome stain demonstrated bone marrow fibrosis. (Figures 3 and 4) One of these seven cases showed AFB positive bacilli in biopsy. Three of the seven cases were detected as tuberculosis in culture of bone marrow aspirate. Rest three cases were culture negative but empirically treated with ATT and patients responded to treatment and clinico-hematological improvement was noticed. These patients were followed up for a period of 1 year and they were doing well. Thus provisional diagnosis of Tuberculosis was established in these 7 cases.

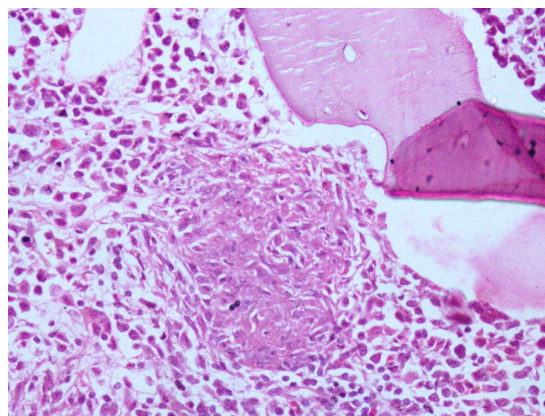


Figure 1: Photo micrograph of bone marrow biopsy showing caseating granuloma in tuberculosis composed of epithelioid cells, lymphocytes. (H&E 200X)

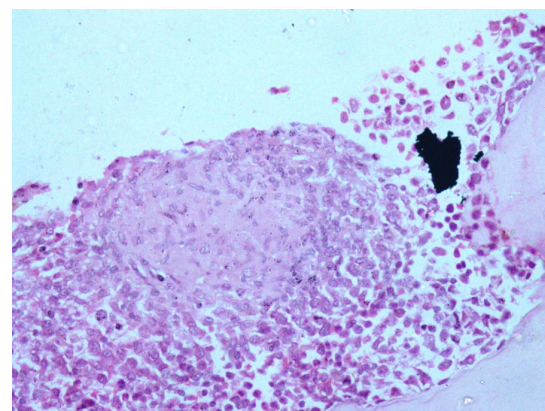


Figure 2: Photo micrograph of bone marrow biopsy showing epithelioid cell granuloma in tuberculosis (H &E 200X)

One of the cases having fever and splenomegaly but no lymphadenopathy showed presence of epithelioid granuloma with presence of Reed Sternberg cells admixed with small lymphocytes and macrophages in H&E stain.(Figure 5) IHC

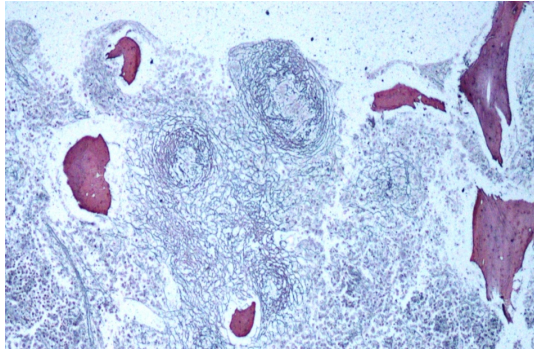


Figure 3: Photo micrograph of bone marrow granuloma in tuberculosis showing fibrosis (Reticulin 100X)

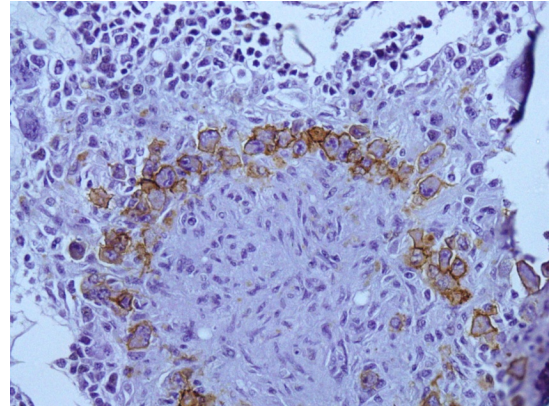


Figure 6: Photo microphagh showing CD 15 positive ReedSternberg cells (IHC -CD-15 400X)

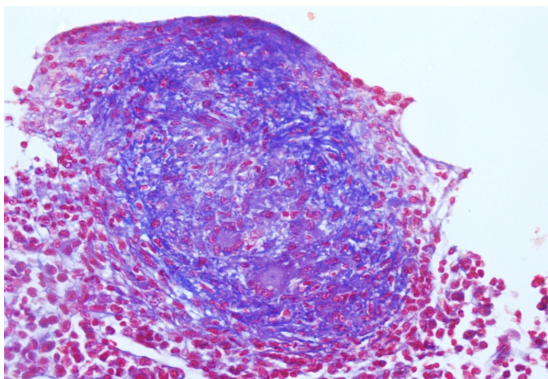


Figure 4: Photo micrograph of bone marrow granuloma in tuberculosis (Masson's Trichrome 200X)

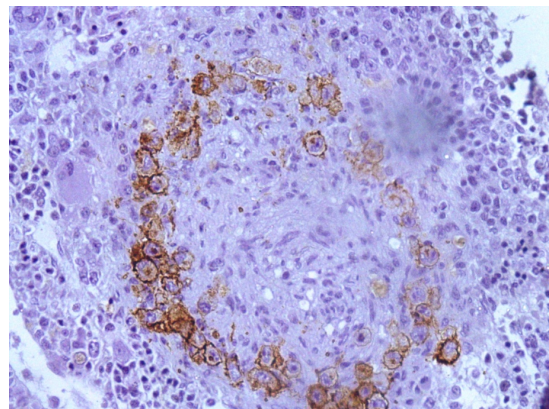


Figure 7: Photo micrograph showing CD-30 positive Reed Sternberg cells (CD-30 IHC 400X)

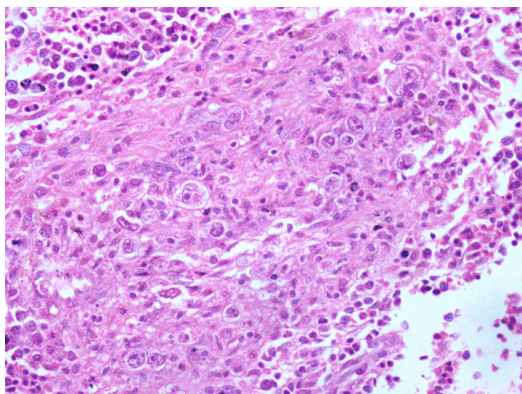


Figure 5: Photo micrograph of bone marrow biopsy inHogdkin's lymphoma showing epithelioid granuloma (H&E 200X)

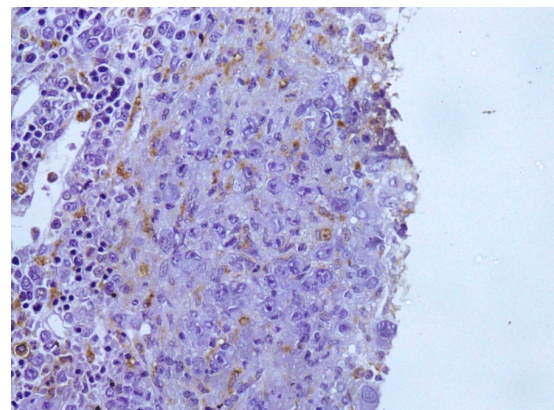


Figure 8: Photo micrograph showing CD68 positiveepithelioid cells and macrophages in Hodgkin's lymphoma (CD-68 IHC 200X)

stains further highlighted the Reed Sternberg cells (CD 15, CD30 positive) (Figures 6 and 7) surrounded by CD3 positive T cells. The epitheloid cells and histiocytes were positive for CD 68. (Figure 8) CT scan of abdomen and pelvis and CT thorax showed no mesenteric or mediastinal lymphadenopathy. Splenic biopsy was performed but found to be negative for lymphoma. Thus it is confirmed to be a case of primary mixed cellularity Hodgkin's lymphoma of bone marrow.

One of the cases showed presence of epitheloid granuloma without necrosis. Bone marrow culture was negative for mycobacterium tuberculosis. Chest X-Ray showed diffuse nodular infiltration. Serum calcium and ACE level was elevated. Patient had mediastinal lymphadenopathy. CT guided biopsy of mediastinal lymph node was suggestive of sarcoidosis. Patient was diagnosed and treated in line of Sarcoidosis.

In another case no definitive etiology could be established despite of thorough investigations.

3. Discussion

Granulomatous diseases can involve multiple systems including lungs, lymph nodes, liver and spleen¹ However granuloma in bone marrow is an infrequent but nonspecific finding that can denote many systemic diseases. Granuloma formation is a non-specific response by reticuloendothelial system to a persistent antigenic stimulus.^{5,6} Majority of cases of bone marrow granuloma are attributed to infectious sources.

Incidence of bone marrow granuloma in our study was 2.89% which coincides with the reported incidence.² Most of the cases in the present study presented with non-specific symptoms like fever, pain in abdomen, weakness, loss of appetite. Other studies also found similar presenting features in patients diagnosed with granulomatous lesion in bone marrow.^{3,7} After thorough history and laboratory investigations a specific diagnosis can be made in most cases. In this study we could establish a specific etiology in 9 out of 10 cases. Similar findings were detected by other studies.^{3,8} Most of the granulomatous lesions in the present case were due to tuberculosis. Other studies have also found infectious diseases like tuberculosis as the most common cause of granulomatous lesions in bone marrow.^{3,9}

One of the cases was reported as primary Hodgkin's lymphoma of bone marrow. Atypical presentation of Hodgkin's lymphoma with bone marrow granuloma formation has been reported.¹⁰ These granulomas may present before the onset of primary malignancy and may delay the diagnosis.¹¹ In lymphomas bone marrow granuloma could be due to invasion of the bone marrow or due to non-specific immunologic change due to malignancy.¹²

4. Conclusion

Although nonspecific finding, granuloma in bone marrow is helpful to narrow down the differential diagnosis to a group of related disease. Etiology of bone marrow granuloma varies according to the geographic region with tuberculosis still remaining the most common cause despite of various control programmes for tuberculosis. But atypical presentation of Hodgkin lymphoma in bone marrow may get missed if all cases of granulomas of bone marrow are not properly investigated.

5. Source of Funding

None.

6. Conflict of Interest


None.

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