

# Bone marrow granulomas: A retrospective study of 47 cases (A single center experience)

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**Abstract:** Background: Granulomas in bone marrow are an infrequent finding; however several diseases may be associated with granuloma formation and an etiologic diagnosis is essential. Bone marrow examination plays an important role in the diagnosis of various disorders associated with bone marrow granulomas and is useful in the investigation of pyrexia of unknown origin (PUO) as it leads to an etiological diagnosis in many of the cases. Aim: This study was undertaken to ascertain the frequency and etiological background of bone marrow granulomas. Material and methods: In the present study, forty seven cases with bone marrow granulomas were included. Clinical details, peripheral blood and marrow morphological findings were analyzed. Results: Pyrexia of unknown origin was the commonest presentation and anemia was noted in all cases. Twenty five cases had associated clinical conditions, including 7 with past history of tuberculosis and 8 with retroviral disease. Of the 47 cases, 7 showed granulomas in bone marrow aspiration, while bone marrow biopsy was diagnostic in all cases. Caseous necrosis was seen in 11(23.4%) cases. Acid fast bacilli were demonstrated in one bone marrow aspirate. Culture studies grew *Brucella* organisms in one case. Tuberculosis was the commonest in the present study as compared to other studies probably due to the endemicity of tuberculosis in this region. Conclusion: If the granuloma is associated with caseous necrosis and Langhan giant cells and correlated with clinical features, a possibility of the tuberculous etiology may be suggested to allow empirical treatment to be initiated before microbiological confirmation.

**Keywords:** Bone Marrow Aspiration, Granuloma, PUO, Trephine Biopsy, Tuberculosis

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## 1. Introduction

Bone marrow examination plays an important role in the diagnosis of haematological and non-haematological malignancies as well as various other diseases<sup>1</sup>. It is one of the commonly done procedures in the investigation of pyrexia of unknown origin (PUO)<sup>2</sup>. Granulomas are found in 0.5 to 2.2% of trephine biopsies<sup>3-6</sup>. Diseases that are associated with bone marrow granulomas include a variety of infections, connective tissue disorders, lymphoma and metastatic carcinoma<sup>4</sup>.

The first published article on bone marrow granulomas was by Pease in 1956. It stated that in approximately 25% of cases with bone marrow granulomas, etiology could not be detected<sup>7</sup>. By correlating the morphological features of the granulomas with the clinical features, special stains, culture studies and newer ancillary techniques, a definite etiological diagnosis can be made in most cases. The present study was

conducted to compare the role of bone marrow aspiration (BMA) cytology and bone marrow biopsy (BMB) and to formulate an effective and rapid method for diagnosing bone marrow granulomas. We also tried to study the spectrum of disorders presenting with bone marrow granulomas.

## 2. Material and Methods

All cases with bone marrow granulomas diagnosed between January 2007 to July 2010 were included in this study. The case records of these patients along with clinical details, biochemical and culture studies were analyzed. Complete blood counts were recorded and peripheral blood smear was reviewed. BMA and BMB were done in the same sitting under local anesthesia. Two of the representative smears were stained with Giemsa stain and the biopsy was paraffin embedded and sections stained with Haematoxylin and Eosin. The morphological features of the marrow that were studied

included marrow cellularity, location & morphology of the granulomas, fibrosis, caseous necrosis and inflammatory cells like plasma cells, histiocytes. All cases were stained with special stains like Ziehl-Neelsen stain for demonstration of acid fast bacilli and Methenamine Silver stain for fungi. The morphological features of granulomas were correlated with microbiology culture studies, wherever available.

### 3. Results

Of the three thousand three hundred and forty one bone marrow trephine biopsies performed at our institute over the study period, 47 cases (1.4%) showed presence of epithelioid granulomas in the bone marrow. The age of the patients ranged from 16 to 58 years, with a median age of 35 years. The male: female ratio was 1.5:1. In 47 of these cases, 26 had associated clinical conditions with some form of immunosuppression (7 with past history of tuberculosis and 8 were HIV positive, 5 were diabetes mellitus, 3 had history of renal transplantation and one patient of AML, Hodgkin lymphoma and Ewing's sarcoma respectively each). Pyrexia of unknown origin was the commonest presentation seen in 47 (100%) cases. Nineteen (40.5%) cases had generalized weakness. Anaemia was present in all cases. Pancytopenia and bicytopenia was observed in 10 cases & in 14 cases respectively. Blood and bone marrow culture reports for tuberculosis, typhoid and Brucella were available in 7 cases. None of the culture reports showed any significant findings except one case, which showed Brucella growth on bone marrow culture. Serological studies were done to rule out the possibility of connective tissue disorders.

#### 3.1. Bone Marrow Aspiration Findings

**Table 1.** Bone marrow aspirations(BMA) findings

BMA findings	No of patients (n=47)
Granulomas	7(14.9%)
Cellularity	
Increased	21(44.6%)
Decreased	9(19.1%)
Aparticulate	3(6.38%)
Normal	14(29.78%)
Erythropoiesis	
Megaloblastoid	3(6.4%)
Normoblastic	44(93.6%)
Lymphoplasmacytic prominence	29(61.7%)
Histiocyte prominence	9(19.1%)

Bone marrow aspiration smears were hypercellular in 21 (44.6%), normocellular in 14 (29.78%), hypocellular in 9 (19.4%) cases and in three (6.38%) cases it was aparticulate. The aspiration cytology smears revealed epithelioid cell granulomas in 7 (14.8%) cases. Erythropoiesis was normoblastic in 44(93.6%) and megaloblastoid in 3(6.38%) cases. Myeloid series and megakaryocytes were unremarkable. There was prominence of lymphocytes and plasma cells in 62 % cases and histiocytic aggregates in 19% cases. Acid fast bacilli were demonstrated in one case (Fig-1. E). Stains for fungi were negative. The details of the bone marrow aspiration

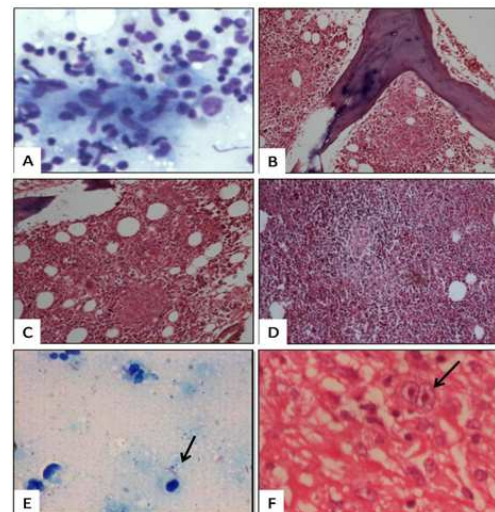
findings are given in Table 1.

**Table 2.** Bone marrow biopsy(BMB) findings

BMB findings	No of patients (n=47)
Well formed granulomas with giant cells	26(55.3%)
Ill defined granulomas	21(44.6%)
Caseous necrosis	11(23.4%)
Location of granulomas	
Para-trabecular	15(32%)
Interstitial	32(68%)
Reed Sternberg cells	1(2.1%)
Ziehl- Neelsen stain	1 (2.1%)
Silver methanamine	0%
Reticulin - Increased condensation in & around granulomas	10(21.2%)

#### 3.2. Bone Marrow Biopsy Findings

The histopathology of the trephine sections revealed 47 cases of granulomatous inflammation with granulomas ranging from one to three in number per section. They were mainly interstitial (68%) in location with 32% being paratrabeular (Fig-1. B). Well-formed granulomas, composed of epithelioid cells surrounded by Langhan's giant cells and lymphocytes were seen in 26 (55.3%) and ill-formed epithelioid granulomas in 21 (44.6%). Caseous necrosis was noted in 11 (23.4%) cases. There was increased reticulin condensation especially in and around the granulomas in 10 cases (21.2%). Stains for Acid fast bacilli and fungi were negative in all the cases. The details of the bone marrow biopsy findings are given in Table 2. In 8 HIV positive cases, ill-defined granulomas were seen in 5 cases and the remaining cases showed well formed granulomas.



**Figure 1.** A) BMA – epithelioid cell aggregation (granuloma). B) BMB. Granuloma located at paratrabeular region. C) BMB - Granuloma located at interstitial region. D) BMB - Granuloma with lymphocytic cuffing. E) BMA - Ziehl- Neelsen stain: highlighting the Acid fast bacilli. F) Reed Steinberg cell.

Seven of the cases were empirically started on anti-tuberculous treatment. Few cases had underlying immunosuppressive states like post-renal transplant status,

AML and HL on treatment, Ewing's sarcoma and Diabetes mellitus which presented as pyrexia of unknown origin. In all these cases, granulomas were identified in the bone marrow. There was one case that showed few large binucleated cells with prominent nucleoli (?Reed- Sternberg cells); apart from granulomas. This was later diagnosed as Hodgkin lymphoma and proved with immunohistochemistry on lymph node biopsy.

## 4. Discussion

Granulomatous inflammation is a distinctive pattern of chronic inflammation that is encountered as a response to a persistent antigenic stimulus and characterised by aggregates of epithelioid cells, giant cells and surrounded by mononuclear cells with or without caseous necrosis.

Granulomas have been identified in a wide range of illnesses<sup>7</sup>. Morphology of granulomas in the bone marrow is similar to those seen in other organs. Granulomas in bone marrow are an uncommon finding, were detected in 1.4% of trephine biopsies in the study period, which is comparatively higher than the other studies<sup>3-6</sup>, but lower than one Indian study - 2.46% described by Basu *et al*<sup>8</sup>.

Pyrexia of unknown origin (PUO) was the commonest presentation in the present study. Patients with PUO origin were more likely to have marrow granulomas than patients biopsied for other reasons<sup>5,9</sup>. BMB and BMA are important diagnostic tools in arriving at an etiological diagnosis of patient with long-duration febrile illness, and should be routinely performed in such cases to allow treatment to be initiated before microbiological confirmation and antibiotic susceptibility<sup>10</sup> reports are available.

Haematological parameters were altered in all the cases. Anemia was the commonest finding in all patients. Pancytopenia was seen in 10 (21.3%) and bicytopenia in 14 (29.7%) cases. Pancytopenia, anemia, leukopenia and thrombocytopenia have been reported in patients with granulomatous bone marrow disease<sup>4</sup>.

Granulomas in marrow aspiration cytology smears are difficult to identify probably because of the fibrosis in and around the granulomas. In the present study, granulomas were detected in 7/47 (14.8%) of marrow aspirates (Fig-1. A), which is comparatively higher than that detected by Basu *et al*<sup>8</sup> (1/14 cases, 7.14%) and Chandra *et al*<sup>11</sup> (0/6 cases, 0%). All these 7 cases were subsequently confirmed on marrow biopsy sections and 100% positive correlation was found between bone marrow aspiration and biopsy. BMB is a better tool than BMA to demonstrate granulomas as the morphology is better preserved and more amount of tissue is available for study. The detection rates are higher if serial sections of trephine biopsies are studied when the original sections do not show granulomas in suspected cases<sup>12</sup>.

Seven of the cases who were already on anti-tuberculosis treatment had undergone bone marrow aspiration and biopsy due to persistent fever not responding to therapy. Acid fast bacilli were detected in one case by Ziehl-Neelsen stain. These were considered as disseminated tuberculosis owing to

clinical details and characteristic morphology. Tuberculosis is one of the most frequent causes of bone marrow granuloma constituting 6% to 48% of the cases<sup>13</sup>.

There were 8 HIV positive cases presenting with PUO which had granulomas in the bone marrow. Of the 8 cases, 5 cases had pulmonary tuberculosis. Acid fast bacilli and fungi could not be identified in both BMA and BMB. Culture studies were also not helpful in these cases. As expected, there were more number of cases with ill-defined granulomas (5 cases, 62.5%) than well-defined granulomas (3 cases, 37.5%). Bone marrow abnormalities are seen in 90% of HIV infected cases during the course of the disease in form of increased cellularity, dyspoiesis and granulomatous inflammation<sup>14</sup>. Exact mechanism of HIV induced marrow changes are not known, however there are possibly due to either direct effect of HIV or opportunistic infections or by anti-retroviral drugs<sup>15</sup>.

Malignant neoplasms have been reported as the cause of bone marrow granulomas in 20% to 25%<sup>3-5, 13</sup>. Acute myeloid leukemia (AML) is an aggressive hematolymphoid neoplasm with characteristic bone marrow findings. Some studies have led to a hypothesis for granulomas in bone marrow that there is a strong induction of anti-leukemic immune response to tumor-associated antigens and a high incidence of circulating immune complexes in AML patients<sup>16, 17</sup>. In this study, there was a case of treated AML, with a granuloma in bone marrow. Regarding the association between AML and granulomas - it is not sure whether the relationship is causal or coincidental. There was one case with few large binucleated cells and prominent nucleoli in addition to the granuloma in bone marrow (Fig-1.F). This was later proved as Hodgkin lymphoma on lymph node biopsy. The presence of a granulomatous lesion along with a hematolymphoid neoplasm has been associated with a good prognosis; particularly in patients with Hodgkin lymphoma<sup>18, 19</sup>.

There were three post-renal transplant patients presenting with PUO, showing post-renal transplant patients. These transplant patients are immunosuppressed and are prone to develop various types of opportunistic infections including TB, and a majority of these infections are a result of reactivation of dormant disease. The prevalence of TB among renal transplant recipients varies widely in different parts of the world and ranges from less than 1% in Western countries and nearly 15% in India<sup>20-24</sup>. A single follow up case of Ewing's sarcoma and five cases of diabetes mellitus, presenting with PUO, showed granulomas in bone marrow. This can be explained by immunosuppressed state of the patients.

Bone marrow cultures (BMCs) and blood cultures (BCs) are frequently obtain in the evaluation of PUO and important investigations in patients with PUO. Bone marrow can be collected at same time of BMA procedure for culture studies and is especially helpful in disseminated bacterial, fungal and tuberculous infection. BMCs are particularly useful for patients who are immunocompromised. BMCs can be positive when blood culture (BC) is negative<sup>25</sup>. The viable organism counts in the bone marrow are considerably less affected by antibiotic treatment than blood counts<sup>26</sup>. In this study, BMC

studies could not pick up any organisms barring one patient, where *Brucella* organisms were grown.

There are no distinguishing features in the morphology of bone marrow granuloma to permit a definitive diagnosis of the underlying conditions<sup>4, 7</sup>. Though the granulomas associated with caseous necrosis and Langhan type giant cells would be seen more frequently in tuberculosis, the diagnosis cannot be made solely on pathologic criteria. Rather, it will have to be

correlated with clinical, laboratory, and radiological data. In this study, the underlying illness, associated with bone marrow granulomas was identified in 36%, which is much less than other studies<sup>3,4,,8</sup> (table-3). In the present study, infectious etiology is the commonest cause for bone marrow granulomas, similar to other studies<sup>7,8</sup>. The higher incidence of tuberculosis in the present study is due to the endemicity of tuberculosis in our country.

**Table 3.** Comparison of the present study with various other studies

Feature	Bodem et al <sup>4</sup>	Basu et al <sup>8</sup>	Vilalta-Castel E et al <sup>3</sup>	Our study
No. of cases studied	58	14	40	47
Granulomas in BMA	-	1(7.14%)	-	7(14.9%)
Underling etiology Identified	87%	78%	82.5%	36%
Commonest etiology	Infections (Rocky Mountain spotted fever)	Infections (Tuberculosis)	Infections (Tuberculosis, Brucellosis)	Infections (Tuberculosis)

## 5. Conclusion

Bone marrow granulomas are uncommon. When detected, it is essential to look for the underlying etiology. There are no morphological features which allow reliable differentiation between the causes of granulomas, hence clinical features; morphology, culture and serology are to be combined to arrive at an etiologic diagnosis. If the granuloma is associated with caseous necrosis and Langhan giant cells and correlated with clinical features, a possibility of the tuberculous etiology may be suggested to allow empirical treatment to be initiated before microbiological confirmation. Bone marrow examination is a useful tool to diagnose possible etiology in patients with PUO. BMB is always superior to the BMA to diagnose granulomas.

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