Original Article

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Clinicopathologic Study of Granulomatous Lesions in the Bone Marrow

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Abstract

Introduction: Granulomatous lesion in the bone marrowis not a common finding and can be attributed to a variety of conditions ranging from infections to malignancies to drugs. Though tuberculosis is the most common etiology, bone marrow granulomas can be associated with a number of infections and other non infective conditions. The incidence of bone marrow granulomas has been increasing over the years due to the increasing surge of HIV infection. *Aims:* This study basically aims to study the prevalence of bone marrow granulomas, to identify the various causes and to study the pattern of granulomas in different conditions. *Materials & Methods:* This is a retrospective analysis of 100 cases of bone marrow granulomas conducted in the Clinical Laboratory of Kasturba hospital for a period of four and a half years from January 2009 to May 2013.The clinical details were collected from medical records and bone marrow biopsy slides were retrieved and studied. *Results:* Out of the 100 cases, 66% cases were diagnosed as tuberculosis. 17% cases were due to other infections like Typhoid fever (5%), Brucellosis (4%), Scrub typhus (2%), Hansen's disease (1%), Cryptococcosis (2%) and HIV infection itself without any other opportunistic infections (3%). Malignancies accounted for 9% cases, Sarcoidosis (1%) and in 7% cases a definitive diagnosis was not reached. Among the 66 cases of tuberculosis, 40 (60%) cases were immunodeficient due to HIV infection. HIV positive cases predominantly showed single (52%), ill defined granulomas (73%), with caseation necrosis (52%), while HIV negative cases predominantly showed single (54%), small (50%), well defined or ill defined granulomas with plump epithelioid cells (58%) and Langhans giant cells (42%). *Conclusion:* There can be varied etiology for bone marrow granulomas with tuberculosis being the most common cause.The morphology and pattern of granulomas can aid in the diagnosis of the condition hence study of bone marrow for granulomas should be considered as an important diagnostic tool in such conditions.

Keywords: Bone Marrow; Granuloma; Tuberculosis; HIV; Drugs; Morphology.

Introduction

Granulomatous inflammation is a distinctive pattern of chronic inflammation that develops as a cellular attempt to contain an offending agent that is persistent or difficult to eradicate thus inducing a cell mediated immune response [1].

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Although granuloma is an infrequent finding in a bone marrow biopsy, recognition of the granulomatous lesion is important because of the limited number of possible conditions associated with it and the significance of the diagnoses associated with the lesion [1]. Most of the associated diseases present with nonspecific symptoms and the finding of a granuloma can be a very important clue to a specific diagnosis and should be thoroughly investigated.Thus the histologic finding of bone marrow granuloma, although nonspecific, narrows the differential diagnosis to a well-known spectrum of diseases.

Aims

In our study we analysedthe bone marrows with granulomatous lesions and correlated with the clinical aspects and other laboratory investigations

to evaluate the prevalence of granulomatous lesions in bone marrow, associated morphology and the common etiology in our region.

Materials & Methods

This is a retrospective analysis of 100 cases of bone marrow granulomas, conducted in the Clinical Laboratory, Department of Pathology, Kasturba Medical College, Manipal, for a period of four and a half years, from 1 January 2009 to 31 May 2013. The study was approved by the Manipal institutional ethics committee.The relevant clinical details and laboratory data of patients were collected from thecase files of the patients. Bone marrow biopsy slides were retrieved and reviewed. The distinguishing features of granulomas were recorded using the proforma. Statistical analysis of the data was done using SPSS16.

Results

A total of 5693 bone marrow biopsies were received out of which, 100 cases showed granulomas on microscopic examination. This yielded a rate of 1.75 cases of granulomas per 100 biopsies or 22.64 cases of bone marrow granulomas per year.There were 68 males and 32 females with a male to female ratio of 2.1:1.

The patients belonged to a broad age group, ranging from 5 - 88 years, with a median age of 45 years, 50% of cases being in the 40 - 60 yrsage group.

The most common presenting symptoms were fever (81%), weight loss (31%), cough and dyspnoea (23%), fatigue and weakness (17%), anorexia (16%). Other complaints like abdominal pain, nausea and vomiting, diarrhoea, headache, myalgia, chills and rigor were present in < 10% of cases. Symptoms were present for more than 6 weeks in 39% cases, between 2 to 6 weeks in 30% and for less than 2 weeks in 30% of patients.

The most common physical finding on admission was pallor in 53% cases followed by hepatomegaly in 48% cases, lymphadenopathy in 36% cases and splenomegaly in 35% cases. Cervical lymph nodes were most commonly involved (21%).

The most consistent lab finding was decreased hemoglobin which was seen in 83% cases, of which 55% had moderate anaemia (Hb< 11 - 8 gm/dL).46 cases were positive for HIV. 14 out of 66 cases (21%) of tuberculosis showed X-ray findings suggestive of TB.

Out of the 100 cases, 66% cases were diagnosed as tuberculosis. 17% cases were due to other infections like Typhoid fever (5%), Brucellosis (4%), Scrub typhus (2%), Hansen's disease (1%), Cryptococcosis (2%) and HIV infection itself without any other opportunistic infections (3%). Malignancies accounted for 9% cases, Sarcoidosis (1%) and in 7% cases a definitive diagnosis was not reached. Among the 66 cases of tuberculosis, 40 (60%) cases were immunodeficient due to HIV infection.

Table 1: Different etiologies for bone marrow granulomas

Diagnosis	Number of Cases (%) (n=100)
Disseminated tuberculosis in hiv positive cases	40
Disseminated tuberculosis in hiv negative cases	26
Other infections	17
Malignancy	9
Sarcoidosis	1
Unknown	7

When the morphology of granulomas in 66 cases of tuberculosis were analysed the following features were seen. 35 (53%) cases showed a single granuloma in the bone marrow biopsy. A well circumscribed granuloma was seen in 25 (38%)cases, while 41 cases (62%) showed ill defined granulomas. Small granulomas were seen in 29 (44%) cases, 17 (26%) showed medium sized granulomas while 20 (30%) cases showed large granulomas. Caseous necrosis was seen in 29 (44%) cases. Plump epithelioid cells were seen in 25 (38%) cases, multinucleated Langhans giant cells in19 (29%) cases and lymphocyte cuffing in 21 (32%) cases. None of the granulomas showed significant increase in eosinophils.

Table 2: Comparison of morphology of tuberculous granuloma in hiv positive and hiv negative cases

Histopathologic findings	No. of Cases of Tuberculosis (n=66) HIV (n=40)	Non HIV (n=26)
Number of granuloma		
Single	21	14
2 - 4	17	9
Multiple (>4)	2	3
Well defined	11	14
Ill defined	29	12
Size of granuloma		
Small	16	13
Medium	9	8
Large	15	5
Plump epithelioid cells	10	15
Langhans giant cells	8	11
Caseation necrosis	21	8
Lymphocyte cuffing	12	9

The number of granulomas in HIV positive and negative cases were not statistically significant (P value= 0.513). Both HIV positive and negative cases of tuberculosis showed predominantly small granulomas (40% & 50% respectively), however large granulomas were seen more frequently in HIV positive cases (38%) as compared to HIV negative cases (19%). 54% cases of HIV negative tuberculosis showed well defined granulomas, where as 73% cases of HIV positive tuberculosis cases showed ill defined granulomas. Thus HIV positive cases were more associated with ill defined granulomas and this was statistically significant (p value = 0.031).

Plump epithelioid cells and multinucleated Langhans giant cells were more common in HIV negative cases (58% & 42%) as compared to HIV positive cases (25% & 20%). Caseous necrosis was seen more commonly in HIV positive cases (52%) as compared to HIV negative cases (31%). Lymphocyte cuffing was seen in both cases (30% & 35%). But on statistical analysis of these parameters, there was no significant difference.

Hence it was seen that HIV positive cases predominantly showed single (52%), ill defined granulomas (73%), with caseation necrosis (52%), while HIV negative cases predominantly showed single (54%), small (50%), well defined or ill defined granulomas with plump epithelioid cells (58%) and Langhans giant cells (42%).

Four of our cases with disseminated tuberculosis, had a coexistent granuloma associated entity. Two cases showed positive Weil Felix test thus suggestive of scrub typhus infection, one was a case of collagen vascular disease and other showed toxoplasma IgG and IgM positivity.

Table 3: Different infectious etiologies of bone marrow granulomaS

Infections	Number of Cases (n=83)
Tuberculosis	66
Typhoid	5
Brucellosis	4
Hansen's disease	1
Scrub typhus	2
Cryptococcosis	2
HIV	3

Besides tuberculosis, other infectious etiologies associated with bone marrow granulomas in our study were typhoid fever (5%), brucellosis (4%), scrub typhus (2%), Hansen's disease (1%), cryptococcosis (2%) and HIV infection itself without any other opportunistic infection (3%).

In typhoid the granulomas were smallill defined with absence of caseous necrosis, multinucleated giant cells and lymphocyte cuffing.All brucellosis cases showed one to two, ill defined granulomas without caseous necrosis, multinucleated giant cells or lymphocyte cuffing. Three cases showed small granulomas while one case showed medium sized granulomas. Plump epithelioid cells were seen in two cases. One case of Hansen's disease on multi drug therapy showed multiple small ill defined granulomas with numerous foamy macrophage. There was no caseous necrosis, multinucleated giant cells or lymphocyte cuffing. Two cases of scrub typhus showed characteristic ring granulomas,with multiple small well-formed granulomas around fat spaces, with no caseous necrosis. Two cases of culture confirmed cryptococcosis showed bone marrow granulomas, both patients were HIV positive. One case showed single, medium sized, ill-defined granuloma, while the other case showed single, small, well-formed granuloma, in both there was no caseation necrosis, multinucleated giant cells or lymphocyte cuffing. Both cases showed cryptococcal spores in the granuloma, which were positive for mucicarmine stain.In two patients infected with HIV without any other demonstrated concurrent opportunistic infections, bone marrow granulomas were identified. Both cases had bicytopenia and bone marrow showed single medium to large, ill-defined granulomas without caseous necrosis.

Nine percent (9%) of cases of bone marrow granulomas were due to malignancies, 8% due to hematologic neoplasms like Non Hodgkin lymphoma (3%), Hodgkin lymphoma (2%), Myeloma (2%), Acute myeloid leukemia(1%) and 1% due to non-hematologic malignancy.

The three cases of NHL were one case each of Follicular lymphoma, T cell/Histiocyte rich B cell lymphoma andDiffuse large B cell lymphoma. A case of T cell/Histiocyte rich B cell lymphoma showed small, ill defined granulomas with infiltration by occasional large atypical mononuclear cells while the other twocases showed small well defined granulomas without any infiltration by malignant cells. Caseation necrosis and multinucleated giant cells were absent in all three cases.

Two cases of Hodgkin lymphoma- mixed cellularity showed large, ill-defined granulomas. One case showed infiltration by mononuclear Hodgkin cells within the granuloma, while the other case had no evidence of infiltration by lymphoma. There was no caseation necrosis,

multinucleated giant cells or lymphocyte cuffing in both the cases. Bone marrow biopsy of a case of AML showed a well formed, medium sized granuloma surrounded by sheets of blasts.

Bone marrow biopsy of a case of non-secretory myeloma with cardiac amyloidosis, showed thickened blood vessels showing pink eosinophilic material in the vessel wall, which was Congo red positive along with collection of histiocytes forming an ill-defined granuloma. Another case of multiple myeloma also showed two small well defined granulomas with plump epithelioid cells and foreign body giant cells. A small, well formed granuloma was seen in a case of carcinoma pancreas on chemotherapy with Erlotinib induced leukemoid reaction. Patient had metastasis to the lung and liver but bone marrow did not show any metastasis.

A case of sarcoidosis showed bone marrow granulomas; four, ill defined, large non caseating granulomas with Langhans and foreign body giant cells, with no lymphocyte cuffing.

In seven of our cases showing bone marrow granulomas, confirmatory laboratory evidence for diagnosis was lacking. Five cases were treated as tuberculosis considering granuloma in bone marrow biopsy and showed improvement. One case presented with fever and pancytopenia and improved with symptomatic management and a diagnosis of post viral fever pancytopenia was reached. Another case had fever, petechiae and severe thrombocytopenia and was diagnosed as immune thrombocytopenic purpura.

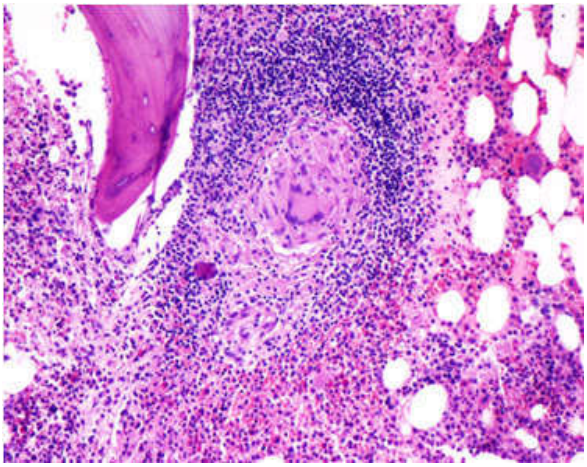

Fig. 1: Well formed granuloma with lymphocyte cuffing and Langhans giant cells in an immunocompetent patient with disseminated tuberculosis.
[Hematoxylin & Eosin; X100]

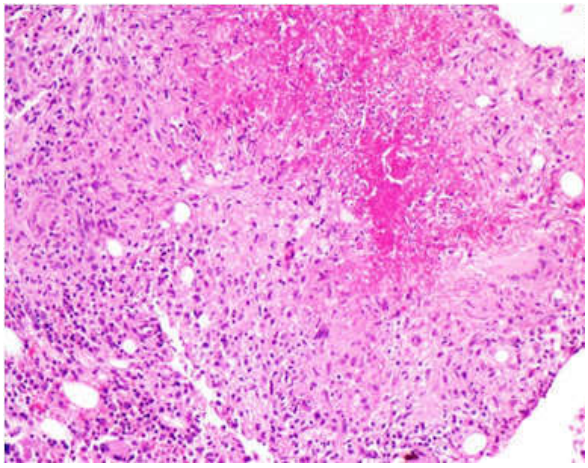

Fig. 2: Ill formed granuloma with extensive caseation necrosis in a HIV positive patient with tuberculosis. [Hematoxylin & Eosin; X 200]

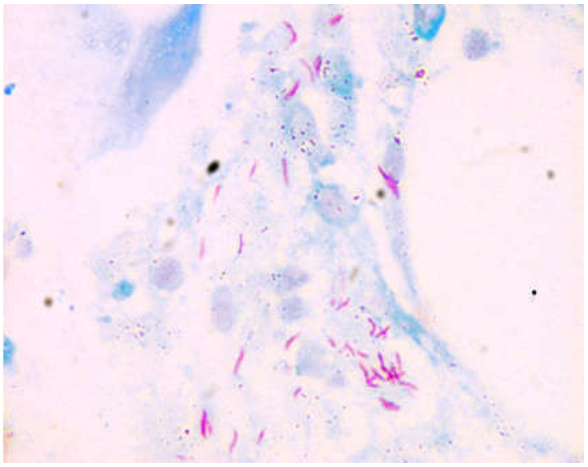

Fig. 3: AFB positive tuberculous bacilli. [ZN stain; X 400]

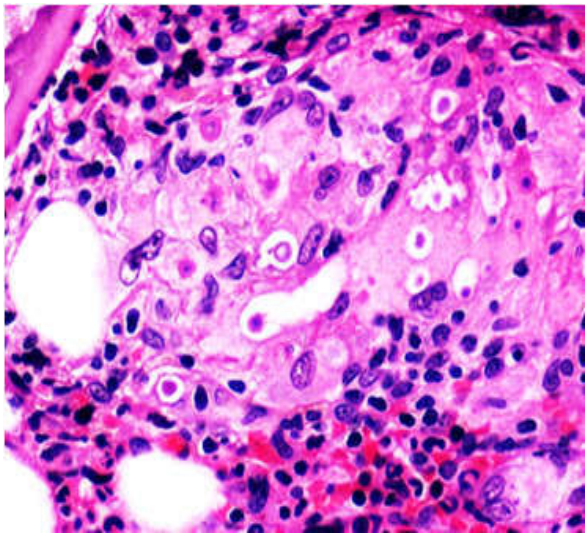

Fig. 4: Granuloma with spores of Cryptococcus in a HIV positive patient. [Hematoxylin & Eosin; X 400]

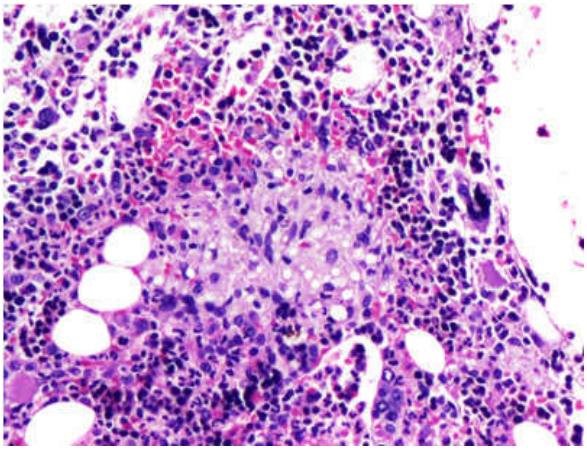

Fig. 5: Ill definedsmall granuloma with foamy macrophages in a case of leprosy.[Hematoxylin & Eosin; X 200]

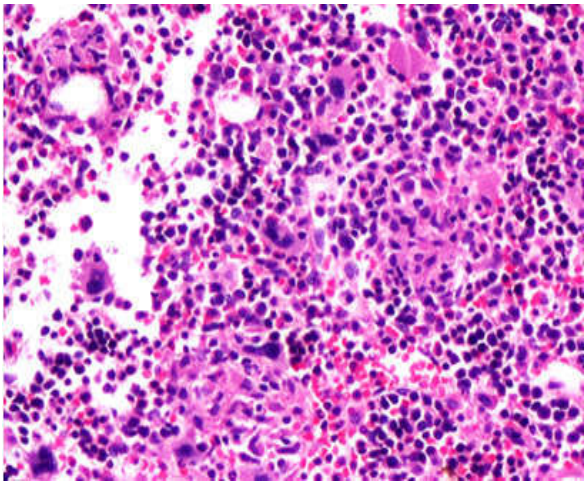

Fig. 6: Multiple small ill defined granulomas in a case of Typhoid [Hematoxylin & Eosin; X 200]

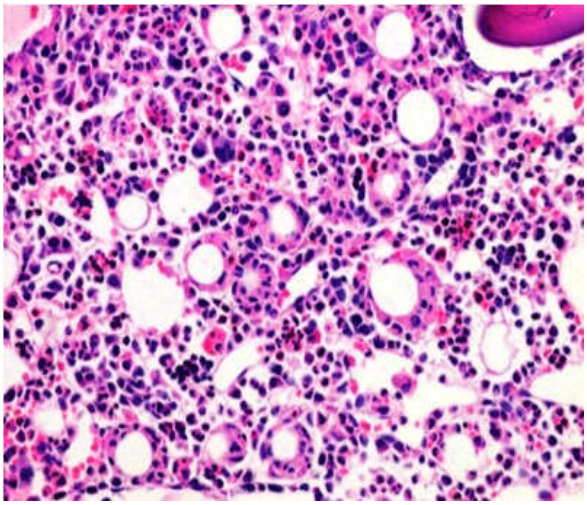

Fig. 7: Fibrin ring granuloma composed of central lipid vacuole, fibrinoid outer ring, epithelioid histiocytes and lymphocytes in Scrub Typhus. [Hematoxylin & Eosin; X 200]

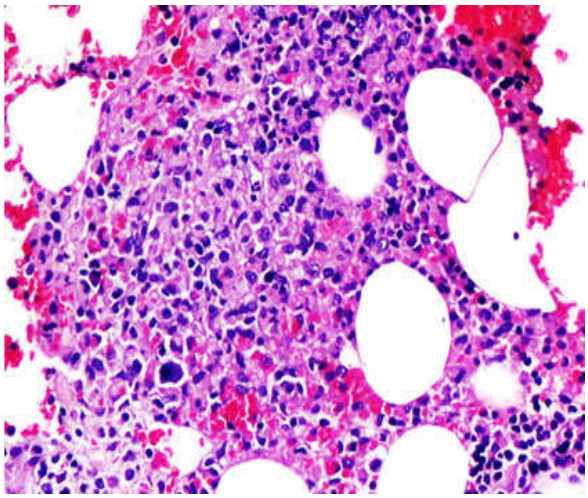

Fig. 8: Non Hodgkin Lymphoma. Granuloma with occasional large atypical mononuclear cell. [Hematoxylin & Eosin; X 200]

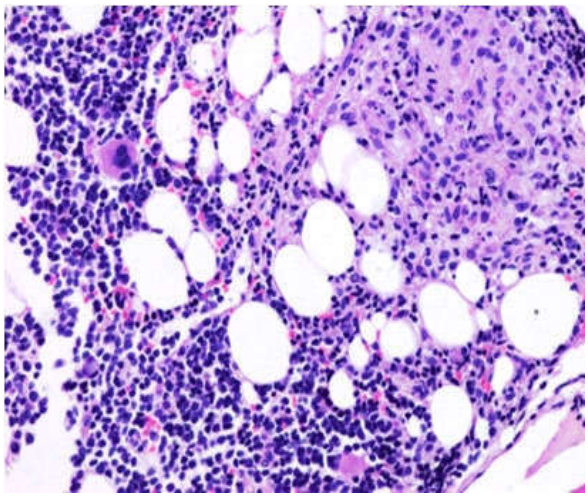

Fig. 9: AML with granuloma. [Hematoxylin & Eosin; X 200]

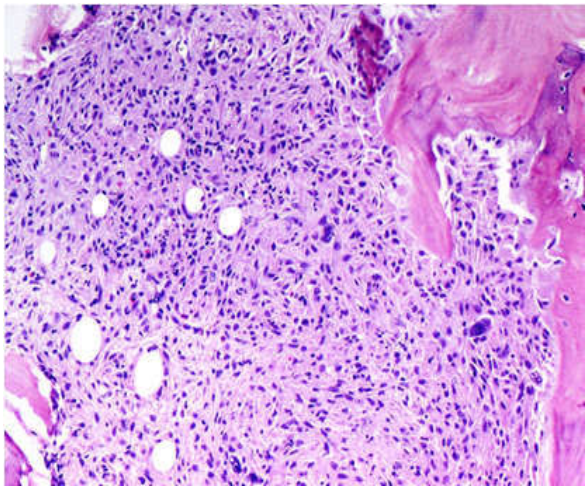

Fig. 10: Hodgkin lymphoma- Classical (Mixed cellularity). Mononuclear Hodgkin cells surrounded by epithelioid histiocytes and lymphocytes. [Hematoxylin & Eosin; X 200]

Discussion

The present study reported an incidence of 1.75 granulomas per 100 biopsies, which was higher than the incidence reported in western studies [2,3]. A study by Basu etal done in JIPMER, Pondicherry reported an incidence of 2.46 granulomas per 100 biopsies [4]. Thus it shows that the incidence of bone marrow granulomas is higher in Indian studies. Predominant age group affected in most of the studies is 30-60 yrs [2,3,5]. The present study showed male predominance, which was in concordance with the study by L. Brackers de Hugo etal and Bodem etal, except for the study by Vilalta-Castel etal which showed almost equal male to female ratio [2,3,5]. Fever,weight loss and fatigue are the common presenting symptoms [2,5]. Most of the patients in the present study presented with a chronic history with duration of symptoms existing for > 6weeks, as was seen in the study by Bodemetal. The common clinical findings were pallor; lymphadenopathy and organomegaly.

Among laboratory investigations, anemia was a consistent finding in the present study (83%) as well as in the study by L. Brackers de Hugo etal (71%) and Vilalta-Castel et al. (60%) [3,5]. Another important feature noted in our study was elevated ESR (61% cases). Other significant laboratory parameters in our study were thrombocytopenia (45%), leukopenia (34%) and pancytopenia (19%). These findings were in concordance with the study by L. Brackers de Hugo etal who reported thrombocytopenia, leukopenia and pancytopenia in 35%, 31% and 21% respectively. The present study reported 46% HIV positive cases, which is much higher when compared to study by L. Brackers de Hugo et al. (10.5%) [5].

Most studies have shown infections as the leading cause of bone marrow granulomas. But Indian studies have shown a higher proportion of bone marrow granulomas associated with infections when compared to the western studies. The increased incidence of infectious etiology in the present study can be attributed to the increased prevalence of tuberculosis in India. Next common cause in the present study was malignancy (9%) as well as in the studies by Bodem et al. (21%) and Vilalta-Castel et al. (22.5%), but the proportion of cases of granulomas associated with malignancy were less in our study as compared to the other studies [2,3].

L. Brackers de Hugo et al. reported sarcoidosis (21%) as the second leading etiology of bone marrow granulomas [5]. But the present study reported only a single case of bone marrow granuloma associated with sarcoidosis.

Though Tuberculosis is the most common infection associated with bone marrow granuloma in most studies, western studies have reported relatively lower number of cases as compared to Indian studies [3,4,5]. This shows the higher prevalence of tuberculosis in India.

Evaluation of morphology of granuloma in the cases of tuberculosis (66/100) showed that majority were ill defined with presence of caseation necrosis. Only 38% of cases showed well defined granulomas. Langhans giant cells and lymphocyte cuffing were seen in 30% cases. Peace etal reported 19 cases of bone marrow granulomas associated with

Table 4: Comparison of incidence of bone marrow granulomas

	Incidence in the Series	Annual Rate
Present study	1.75 per 100 biopsies	22.64 cases per year
Vilalta-Castel et al[6]	0.50 per 100 biopsies	3.80 cases per year
Bodem et al[4]	0.52 per 100 biopsies	4 cases per year
Basu et al[10]	2.46 per 100 biopsies	4.7 cases per year

Table 5: Comparison of diagnosis

Diagnosis	Number of Cases (%)				
	L. Brackers de Hugo et al[5] (n=48)	Bodem et al[2] (n=58)	Vilalta-Castel et al[3] (n=40)*	Basu et al[4] (n=14)	Present study (n=100)
Infection	16(33%)	22(38%)	20(50%)	10(71.4%)	83(83%)
Malignancy	9(19%)	12(21%)	9(22.5%)	1(7%)	9(9%)
Sarcoidosis	10(21%)	4(7%)	2(5%)	-	1(1%)
Autoimmune	-	5(9%)	1(2.5%)	-	-
Drugs	3(6%)	7(12%)	-	-	-
Unknown	10(21%)	8(13%)	7(17.5%)	3(21.4%)	7(7%)

tuberculosis and described well defined granulomas (84%) with caseation necrosis and Langhans giant cells (>60%) in majority of cases [6]. Thus, Peace et al. reported a higher proportion of cases with well defined granulomas and Langhans giant cells as compared to the present study. This may be because 61% of the tuberculosis cases in the present series were HIV positive and bone marrow granulomas in AIDS are usually described as small, subtle, loosely cohesive and difficult to detect [7].

When the morphology of tuberculous granulomas were compared between the HIV positive and negative patients, it was seen that HIV positive cases commonly showed ill defined granulomas (73%) with caseous necrosis (52%) whereas HIV negative cases showed predominantly well defined granulomas (54%) and other features like plump epithelioid cells, multinucleated giant cells and lymphocyte cuffing. HIV negative cases predominantly showed small sized granulomas whereas HIV positive cases had more or less equal number of small and large granulomas. In a study by Nichols etal on morphologic evaluation of tuberculous granuloma in HIV patients, large (59%) and tightly cohesive (52%) granulomas were described [8]. In a study of 49 patients with HIV by Castella et al., 8 (16%) cases showed granulomas, which were small andpoorly formed in most [9]. This shows that there is variation in the morphology of granulomas in HIV patients in different studies.

Typhoid accounted for 5% cases of bone marrow granulomas in the present study, which was similar to the study by Vilalta-Castel et al. (10%). In the present study all 4 cases showed small ill defined granulomas with absence ofcaseous necrosis, multinucleated giant cells and lymphocyte cuffing. In a study by B M Shin etal, bone marrow of 16 culture proven typhoid cases were analysed and 8 cases showed granulomas, 4 were well defined and 4 were ill defined without caseation necrosis or Langhans giant cells [10].

The present study reported 4% cases of brucellosis associated with bone marrow granulomas while Vilalta-Castel et al. reported 12.5% cases and Bodem et al reported 2% cases.The granulomas in brucellosis are usually small, ill defined without caseous necrosis, multinucleated giant cells or lymphocyte cuffing [6].

The present study reported 2% cases of cryptococcosis, which was in concordance with the study by Bodem et al. (2%). But L. Brackers de Hugo et al and Vilalta-Castel etal did not report any case of cryptococcosis in their study [2,3,5]. This may be because 46% cases in the present study were HIV patients as compared to 10.5% cases in the series by L.Brackers de Hugo et al. The present study described non caseating granulomas in both the cases; the cryptococcal spores were mucicarmine positive and bone marrow culture grew the organism. Bodem et al also reported noncaseating granulomas but special stains and bone marrow culture were negative for cryptococcus [2].

Scrub typhus accounted for 2% cases in the present study, but L. Brackers de Hugo etal, Vilalta-Castel etal and Bodem etal did not report any cases in their study. In the present study both cases of scrub typhus showed characteristic ring granulomas. Doughnut-ring granulomas described as a central empty space surrounded by eosinophilic fibrinoid material and rimmed by polymorphonuclear leucocytes and epithelioid cells, once thought to be charactertistic of Q fever, can also be seen in patients with leishmaniasis, toxoplasmosis, scrub typhus, viral infections like Ebstein Barr virus (EBV), Cytomegalovirus (CMV), Hepatitis A virus, in malignancies like Hodgkin lymphoma, peripheral T

Table 6: Comparison of infections associated with bone marrow granulomas

Infections	Number of Cases			
	L. Brackers de Hugo et al[5] (n=48)	Vilalta-Castel et al[3] (n=40)	Bodem et al[2] (n=58)	Present study (n=100)
Tuberculosis	10(21%)	8(20%)	4(7%)	66(66%)
Histoplasmosis	-	-	11(19%)	-
Typhoid	-	4(10%)	-	5(5%)
Brucellosis	-	5(12.5%)	1(2%)	4(4%)
Hansen's disease	-	-	-	1(1%)
Scrub typhus	-	-	-	2(2%)
Cryptococcosis	-	-	1(2%)	2(2%)
Hiv	1(2%)	-	-	3(3%)
Total no. of cases of infections	16*	20*	22*	83

*Not all the infectious causes are given in the table, so the columns do not add up to the total in the series

cell lymphoma, therapeutic agents like allopurinol hepatitis. In a review of 24 cases with bone marrow fibrin ring granuloma by Chung HJ et al., chronic or acute EBV infection accounted for majority of cases; 41.4% of patients (10/24). Remaining cases wereleukemia or lymphoma patients after chemotherapy (33.3%), hepatic failure and fever of unknown origin (20.8%) [11].

Hansen's disease accounted for 1% cases of bone marrow granulomas in the present study, butthere are not many reports of Hansens associated bone marrow granulomas in the literature. Bone marrow involvement in lepromatous leprosy is characterised histologically by granuloma formation, with accumulation of Virchow cells which are foamy histiocytes containing lepra bacilli. In lepromatous leprosy, the bacilli are found throughout the body diffusely involving the reticuloendothelial system in addition to the skin and nerves. Suster etal studied the bone marrow in three cases of biopsy proven lepromatous leprosy and demonstrated by Fite staining numerous bacilli lying free in the interstitium, in the absence of Virchow cells or focal collection of macrophages, and concluded that bone marrow may act as a reservoir for viable organisms in the absence of host response in lepromatous leprosy. It has been proposed that persistence of viable organisms in the bone marrow may be a factor in the high rate of relapse and/or recrudescence of leprosy following premature cessation of specific therapy [12,13]. 3% of cases in the present study had HIV infection without any other demonstrated concurrent opportunistic infection or lymphoproliferative process. L. Brackers de Hugo et al. also reported bone marrow granulomas in one HIV patient (2%) without any other granuloma associated causes [5]. Nichols etal examined 342 bone marrows from patients with HIV infection and granulomas were detected in 102 biopsies out of which 82 (80%) were associated with opportunistic infections. However 22 (20%) of 102 HIV patients had no subsequently or previously diagnosed opportunistic infection to potentially account for their bone marrow granulomas [8]. Thus, Human immunodeficiency virus in itself can cause bone marrow granulomas.

In the study by Bodem etal the most common infectious cause of bone marrow granuloma was histoplasmosis (19%), but in the present study no case of histoplasmosis was reported. Also Bodem etal reported infectious mononucleosis (2%), cytomegalovirus (2%), rocky mountain spotted fever (2%), tularemia (2%), Saccharomyces (2%) in his study, but none of these cases were reported in the present study [4]. Vilalta-Castel et al. reported Kala azar (5%), Viral hepatitis (2.5%) and L. Brackers de Hugo et al. reported M. genavense (4%), B. henselae (4%) and EBV (2%) infection associated with marrow granulomas in their series but none of these cases were reported in the present study [3,5].

The present study reported malignant etiology in 9% cases which was lower when compared to study by L. Brackers de Hugo et al. (19%) and Bodem et al. (21%) [2,5]. The commonest malignancy associated with bone marrow granuloma was lymphoma. Non Hodgkin lymphoma accounted for 3% cases in the present study but only one case showed abnormal cells. Bodem et al. reported 4 (7%) cases, which showed non caseating granulomas without malignant cells in the bone marrow [2]. Yu and Rywlin described 9 cases of bone marrow granulomas in patients with non Hodgkin lymphoma and malignant lymphoma cells were seen in 3 cases.

In the present study granulomas were seen in two cases of Hodgkin lymphoma and both showed large, ill defined granulomas. One case showed infiltration by mononuclear Hodgkin cells within the granuloma, while the other case had no evidence of infiltration by lymphoma. Peace et al. reported 15 (10%) cases of malignant lymphomas associated with bone marrow granulomas which included 2 cases of Hodgkin disease showing Reed Sternberg cells in the bone marrow lesion. Bodem et al. reported 4 (7%) cases of Hodgkinlymphoma with bone marrow granulomas and Reed Sternberg cells were absent in the marrow in all cases [2,6]. Hence, presence of granuloma does always indicate bone marrow infiltration in Hodgkin lymphoma. O'Carroll et al. analysed the bone marrow biopsies of 107 patients of Hodgkin disease, of which 6 (5%) showed granulomas, none had evidence of marrow infiltration by Hodgkin disease [14]. Bone marrow granuloma in patients with lymphoma is considered as a nonspecific immunologic response to cancer and is rarely due to the invasion of the bone marrow. The finding of a Reed-Sternberg cell within the granuloma is rare. Presence of granulomas has been associated with a good prognosis in patients with Hodgkin disease [15,16].

Present study reported 3 cases of other hematologic malignancies associated with bone marrow granulomas which included one case each of AML, Myeloma and non secretory Myeloma. Other studies have also shown association of bone marrow granulomas with other hematologic malignancies. L. Brackers de Hugo et al. reported 3 (6%) cases, one case each of hairy cell leukemia,

multiple myeloma and Waldenstroms disease. Bodem et al. reported 2 (3%) cases, one case of Mycosis fungoides and other of acute lymphoblastic leukemia [2,5].

In the present study 1 case of non hematologic malignancy ie, carcinoma pancreas was associated with bone marrow granuloma. Other studies have also reported non hematological malignancies associated with bone marrow granulomas. L. Brackers de Hugo et al. reported 3 (6%) cases of non hematologic malignancy associated with bone marrow granulomas which includes ovarian carcinoma, bladder cancer and hepatic sarcoma. Bodemetal reported two (3%) cases of non hematologic malignancies, one case each of large cell lung carcinoma and breast cancer [2].

Sarcoidosis has been reported as a common cause for bone marrow granulomas in the series by L. Brackers de Hugo et al. (21%), Bodem et al. (7%), Vilalta-Castel et al. (5%) and Peace et al. (6%) however, our study reported only one case [2,3,5,6]. This case showed four, ill defined, large non caseating granulomas with Langhans and foreign body giant cells, with no lymphocyte cuffing. Peace et al. described well formed lesions in two third cases, with Langhans giant cells in one third cases, without any caseous necrosis. Bodem et al. described well formed non caseating granulomas in all cases [2,6].

Yanardag H et al. analysed bone marrow samples of 50 patients with sarcoidosis and 10 patients revealed non caseating granulomas. Sarcoidosis patients with bone marrow involvement showed higher incidences of extrapulmonary involvement, leucopenia-lymphopenia and anaemia than those without bone marrow involvement, so they concluded that bone marrow involvement should be considered in sarcoidosis patients with anaemia, leucopenia-lymphopenia, and also extrapulmonary involvement [17].

In the present study in 93% cases an associated etiology for the granuloma was identified, while in 7% cases no definitive diagnosis was reached. Bodem etal found associated etiology in 87% cases, L. Brackers de Hugo et al. in 79% cases, Vilalta-Castel et al. in 82.5% cases [2,3,5].

In the present study out of the seven cases without confirmatory laboratory evidence for diagnosis, five cases were treated as tuberculosis considering granuloma in bone marrow biopsy and they improved with treatment. One case presented with fever and pancytopenia and improved with symptomatic management and a diagnosis of post viral fever pancytopenia was reached. Another case had fever, petechiae and severe thrombocytopenia and was diagnosed as immune thrombocytopenic purpura. Peace etal studied granulomatous bone marrow lesions in 150 patients and diagnosis of 20 patients was indeterminate. 3 of these cases were diagnosed as immune thrombocytopenic purpura [6]. Vilalta-Castel et al. also reported a case of bone marrow granuloma in a patient with sarcoidosis who also had idiopathic thrombocytopenic purpura [3]. Thus immune thrombocytopenic purpura can be considered as a rare cause of bone marrow granulomas.

L. Brackers de Hugo et al. reported 10 cases (21%) of bone marrow granulomas without any definitive diagnosis or who were diagnosed with a disease that was not associated with granuloma formation. On follow up one patient died from an unrelated disease. Out of the remaining 9 for four of them, their symptoms disappeared without treatment. So they concluded that bone marrow granulomas of undetermined origin has a good prognosis and is not associated with the development of underlying disease, such as tuberculosis or lymphoma [5].

Bodem etal reported 8 (13%) cases in whom definitive diagnosis for marrow granuloma was unknown. Five among them had presumptive evidence for tuberculosis and responded to anti tuberculous treatment. One was a case of silicosis and systemic granulomatous reaction has been described with silicosis, while the other two cases were unexplained [2].

Drugs were not found to be an etiologic factor of granulomatous bone marrow lesions in the present study, which was in concordance with the study by Peace et al. and Vilalta-Castel et al. [3,5]. L. Brackers de Hugo etal reported 3 (6%) cases of therapy induced granulomas associated with intravesical Bacillus Calmette Guerin installation for bladder cancer [8]. Bodem et al. described 7 (12%) cases associated with drugs including procainamide (1case), ibuprofen (2 cases), phenylbutazone (1 case) and indomethacin (1 case). The granulomas were non caseating and of variable sizes [2].

Conclusion

Although granuloma is not a very common finding in bone marrow, when present it is of utmost clinical significance and can aid in the diagnosis of the condition. Morphology of the granuloma also helps in differentiating different etiologies. The incidence is higher in India due to the higher prevalence of

tuberculosis which is further accentuated by the prevalence of HIV positive cases. Though in more than 90% of cases a definite etiology can be established, some cases may still remain a diagnostic dilemma and the treatment may purely depend upon clinical correlation.

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