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Original Article

Clinico-haematological spectrum of patients with extrapulmonary tuberculosis undergoing bone marrow examination- A 12 year study

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ABSTRACT

Introduction: Extrapulmonary tuberculosis although common, can present with variable clinical presentation intricating the diagnosis. The prognosis is usually poor in such cases. Symptoms can be non-specific like pyrexia of unknown origin(PUO), bodyaches, loss of weight/loss of appetite, bleeding diathesis, lymphadenopathy, hepatosplenomegaly and rarely haematological abnormalities like anemia, leucocytosis/leucopenia, pancytopenia, leukemoid reaction in peripheral blood smears alongwith various other bone marrow findings. In such cases, sometimes only bone marrow examination helps in reaching the accurate diagnosis, which is confirmed by reviewing the patients with extrapulmonary tuberculosis in our case series. ***Materials and Methods:*** We hereby report the case series of 45 patients who underwent bone marrow examination(BME) from the year2004 to 2015 in tertiary care hospital and were diagnosed with granulomatous reaction consistent with tuberculosis on bone marrow examination. Spectrum of non-specific clinical presentations and haematological abnormalities were reviewed. ***Result:*** Confirmatory diagnosis i.e. granulomatous reaction in bone marrow consistent with tuberculosis was made in all the cases. Bone marrow aspirate of all the cases were also sent for isolation of *Mycobacterium* by culture in Lowenstein-jensen medium. ***Conclusion:*** This study highlights the significance of non-specific but numerous important clinical pointers as well as haematological parameters in extra-pulmonary tuberculosis particularly involving bone marrow.

Keywords: Bone marrow, Granulomatous, Extrapulmonary, Tuberculosis, Clinical manifestations, Haematological findings

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INTRODUCTION

Tuberculosis (TB) remains the commonest amongst the all contagious diseases, especially in developing countries. This when associated with pulmonary lesions is easily diagnosed. However if tuberculosis presents with extra-pulmonary involvement with varied range of non-specific symptoms or with abnormal haematological findings only, number of differential diagnosis are likely unless confirmed by bone marrow examination. Bone marrow tuberculosis involves two-third of all the disseminated tuberculosis cases.[1] In contrast to the good prognosis of pulmonary TB, literature review of various similar reported cases of bone marrow tuberculosis (BM TB) has revealed high mortality in range of 50-100%.[2-4] High mortality may be attributed to the delay in reaching the exact diagnosis with non-specific clinical presentation in such cases. The extra-pulmonary tuberculosis accounts for 20-50% of all tuberculosis cases.[5] As of 2012, India and China accounted for about 40% of world's TB cases. BM TB has been reportedly associated with fatal outcome. Hence the prompt and accurate diagnosis is highly challenging.

Clinical features can be so variable and non-specific that they can perplex even the most experienced clinicians. Clinical symptoms that are to be considered include PUO, weakness, dizziness, headache, bodyaches, lymphadenopathy, hepatosplenomagaly etc. The criteria for considering a patient to be having PUO is an elevation in body temperature of 101°F or more, for a period of two weeks or more if the diagnosis cannot be made during one week of investigations. The radiological findings may not be evident till the late manifestations of the disease.[6] Haematological abnormalities associated with it include anemia, leucocytosis, leucopenia, pancytopenia, leukemoid reaction.[7,8] Other ancillary techniques like microbiological investigations i.e. culture methods take weeks to isolate the organism. Hence the bone marrow examination can be very beneficial for early diagnosis of bone marrow tuberculosis.[9,10]

We reviewed cases of 45 patients presenting with wide range of clinical features or abnormal haematological findings who were diagnosed with granulomatous reaction consistent with tuberculosis on the bone marrow examination over the past 12 years from 2004 to 2015. The purpose of this study is to draw attention to the importance of correlating uncommon clinical features of commonly encountered condition and variable haematological findings.

MATERIALS AND METHODS

A retrospective study was done on 45 patients who were subjected to bone marrow examination on clinical suspicion and on abnormal haematological findings. Study was done over the past 12 years, from the year 2004 to 2015 in Government Medical College and Hospital, Sector-32, Chandigarh. Complete haemogram (read by automated 3-parts differential haematology cell counter) and Leishmann stained peripheral smears made from EDTA sample were reviewed. Bone marrow aspirate smears stained with May Grünwald Geimsa (MGG) and bone marrow biopsies with Hematoxylin and eosin (H&E) stain were also reviewed alongwith the special stains like Zeihl Neelson stain. In addition, the microbiological investigation i.e. culture reports of bone marrow aspirate were also reviewed.

The reference range for anemia was less than 11g/dl, thrombocytopenia less than 150 $X10^9$/L, thrombocytosis more than 450 $X10^9$/L, leucocytosis more than 11.0 $X10^9$/L and leucopenia less than 4.0 $X10^9$/L. Granulomatous lesion was defined as collection of epithelioid cell macrophages surrounded by lymphocytes and rarely plasma cells, eosinophils, fibroblasts with Langhan's giant cells with or without caseating necrosis.[3,7,11] Inclusion criteria was to include the patients who underwent bone marrow examination on the basis of clinical suspicion and/or abnormal haematological findings. One case of granulomatous reaction in bone marrow was excluded which on special stain- mucicarmine showed the presence of Cryptococcus.

OBSERVATIONS AND RESULTS

Retrospective study was done on 45 patients who underwent bone marrow examination after clinical suspicion and/or abnormal haematological findings for definite diagnosis. The age group was between 9 to 84 years with mean of 35.77. Maximum patients i.e. 14 (31.11%) were of age group between 21-30 years. Out of these 31 (68.88%) were male and 14 (31.11%) females with M:F of 2.2:1. Both males and females were more in the age group between 21-30 years i.e. 10 (22.22%) and 4 (8.88%) respectively (Table I). Clinical presentations studied were PUO in 42 (93.33%) patients and rest were headache, weakness/bodyaches, loss of weight or appetite, respiratory illness, bleeding tendencies- bleeding gums, epistaxis, malena, hematemesis, hematuria and fever associated with rigors and chills. The duration of illness varied from 1-80 weeks (Table II&III).

The majority of patients i.e. 33 (73.33%) had duration of illness between 0-10 weeks. On examination, pallor was in 14 (31.11%) patients, palpable spleen in 18 (40%), rest included palpable liver, palpable lymphadenopathy, icterus, pleural effusion (Table II). No patient on chest radiograph showed any evidence related to miliary tuberculosis like infiltrates/Koch's focus/military mottling except 4 presenting with mild pleural effusion. Hilar lymphadenopathy on radiological examination was in 3 (6.67%). Risk factors included chronic smoker in 3 (6.66%) patients, asthma in 3 (6.66%) and other associated features were hypertension in 1 (2.22%) and diabetes mellitus in 1 (2.22%). There was history of blood transfusions in 6 (13.33%) patients.

Haematological examination showed anemia in 19 (42.22%) patients, bicytopenia 14 (31.11%), pancytopenia 10 (22.22%). Leucocytosis, thrombocytopenia/thrombocytosis and shift to left also seen. On peripheral smear, dual deficiency anemia was most common form of anemia i.e. in 26 (57.77%) patients than those of microcytic hypochromic anemia and normocytic normochromic smear. Bone marrow aspirate cellularity was normocellular in most of the cases i.e. in 21 (46.66%) patients. Iron stores were between 4-5+ in 13 (28.88%) patients. Silver stain for reticulin fibres was graded and most showed grade 0 i.e. in 22 (48.88%) patients (Table IV&V). Bone marrow biopsy revealed granulomatous lesions in all the 45 patients (100%) (Figure 1-3). Special stain i.e. Zeihl Neelson stain was subjected in all, however the acid fast bacilli was not seen.

On the basis of clinical grounds alongwith unexplained abnormal haematological findings, patients were provisionally diagnosed as cases of PUO in 42 (93.33%) and rest as of Leishmaniasis and miliary tuberculosis. These all patients underwent bone marrow examination and confirmatory diagnosis i.e. granulomatous reaction in bone marrow consistent with tuberculosis was made. Bone marrow aspirate of all the cases were also sent for isolation of *Mycobacterium* by culture in Lowenstein-jensen medium, however the culture results for all of these were non-contributory.

DISCUSSION

A number of non-specific but important clinical presentations and number of haematological alterations have been described in the patients with extrapulmonary or miliary/disseminated tuberculosis. There is no systematic pattern of diagnostic approach in any of the previous literatures. Many diagnostic tests including invasive procedures have been used to confirm the diagnosis. High mortality rate with tuberculosis involving bone marrow has been studied in previous literature in contrast to the good prognosis of pulmonary tuberculosis. Several factors may contribute to the variable outcome such as severity of the disease or other underlying pathologies leading to immunocompromised state, immunosuppressive therapies and delay in initiation of appropriate treatment.[4]Bone marrow tuberculosis has fatal outcome if detected late or if it remains untreated. So it is important to keep a differential of extrapulmonary/miliary tuberculosis in patients with unexplained clinical symptoms like PUO, headache/ bodyaches, weakness, loss of weight/appetite, bleeding tendencies, pallor, icterus, lymphadenopathy, hepatosplenomegaly etc. Abnormal haematological findings associated are like anemia, bi/pancytopenia, leucocytosis, leucopenia, leukemoid reaction especially in the developing countries.[3,7,8] Risk factors are equally important to take care of, as these may contribute to the immunocompromised state and hence adding up to the increased morbidity and mortality of the patients with bone marrow tuberculosis.

In our study, patients diagnosed with granulomatous bone marrow consistent with tuberculosis presented most commonly with PUO i.e. in 93.33% as compared to 40% patients presented with PUO in the study done by Koley KC et al in 1991.[1] So when patient presents with PUO, one of the differentials considered should include tuberculosis which could be extrapulmonary, especially in a country like India, where the incidence of tuberculosis is quite high. The early diagnosis becomes more difficult since we usually do not find any evidence of characteristic military pattern on chest radiograph in these cases. Pancytopenia was seen in 22.22% patients compared to previous studies i.e. 8% and may rarely result in bleeding diathesis. Pancytopenia can be due to disseminated/extrapulmonary TB alongwith hypersplenism, histiocytic hyperplasia, hemophagocytosis, maturational arrest or infiltration of bone marrow by caseating or non-caseating epithelioid cell granulomas which cause reversible/irreversible bone marrow fibrosis. [12]

Leucocytosis is usually seen in patients with tuberculosis and in our study, it was present in 8.88% patients comparable to 6-16% in study done by Chakrabarti AK et al in 1995. There may be shift to left with increased precursor forms in the peripheral blood.[7,8] On bone marrow trephine biopsy and its histopathological examination, changes may vary from normal marrow to marrow hypoplasia, granuloma formation and bone marrow

necrosis. Normal to hypercellular marrow is more frequent in these patients as seen in the present study.[13] Reactive increase in bone marrow cellularity leading to leukocytosis as well as raised monocyte to lymphocyte ratio may be seen. Bone marrow suppression with maturation arrest may occur, which could be due to multiple factors. This was the least common change in the cellularity which could have occurred only in late stage of diagnosis when factors like fibrosis would have ensued. Although the incidence of finding the epithelioid cell granulomas on bone marrow biopsy ranges from 0.38% to 2.2%.[14] Presence of caseation necrosis alongwith epithelioid cell granulomas and Langhan's type of giant cells in bone marrow biopsy associated with hematological and clinical features should prompt the diagnosis of extra-pulmonary tuberculosis. Studies show that bone marrow aspirate for culture of *Mycobacterium* is usually non-contributory. This may be due the reasons such as: centrifugation and concentration of the marrow which may lead to increased sensitivity as compared to that with the direct smears. Also, the combination of direct smears alongwith the additional microscopic techniques may have added benefit and increased rate of positivity in culture results.[15] Hence the empirical anti-tubercular treatment should be initiated without waiting for microbiological culture confirmation. Moreover in the developing countries like India where tuberculosis is considered most common cause of granulomatous inflammation, anti-tubercular treatment considered at the earliest.

CONCLUSION

In literature till date, there is no systematic pattern of diagnostic approach and several diagnostic tests including invasive procedures have been used to confirm the diagnosis. Patients with prolonged fever and cytopenias should be promptly investigated. Radiological findings may be non-contributory in case of extra-pulmonary involvement by tuberculosis. The microbiological investigations i.e. culture usually takes weeks to diagnose tuberculosis. On the basis of non-concluding and non-specific clinical symptoms, specifically extra-pulmonary or with abnormal haematological findings, the bone marrow examination can be very helpful for reaching final diagnosis at the earliest. Fatal outcomes occur frequently if bone marrow tuberculosis remains undetected and untreated for long time due to its associated complications. Now since the prognosis is poor in such cases of bone marrow tuberculosis, a high index of suspicion should always be kept in my mind. In the absence of more sophisticated techniques like polymerase chain reaction, the examination of bone marrow assumes importance as demonstrated by the cases studied.

CONFLICTS OF INTEREST

Nil

Table I. Age-wise and gender-wise distribution of patients (n=45)

Age Group	Number (%)	Males (%)	Females (%)
0-10	02 (4.44%)	01 (2.22%)	01 (2.22%)
11-20	06 (13.33%)	04 (8.88%)	02 (4.44%)
21-30	14 (31.11%)	10 (22.22%)	04 (8.88%)
31-40	06 (13.33%)	05 (11.11%)	01 (2.22%)
41-50	07 (15.55%)	04 (8.88%)	03 (6.66%)
51-60	08 (17.77%)	05 (11.11%)	03 (6.66%)
61-70	01 (2.22%)	01 (2.22%)	-
71-80	-	-	-
81-90	01 (2.22%)	01 (2.22%)	-

Table II: Distribution of patients on the basis of various clinical presentations (n=45)

Clinical Presentation	Number (%)
Pyrexia Of Unknown OriginFever associated with chills and rigors	42 (93.33%)
Respiratory involvement	05 (11.11%)
Headache/ bodyache	11 (24.44%)
Weakness	15 (33.33%)
Loss of weight/appetite	13 (28.88%)
Bleeding tendencies	12 (26.66%)
Pallor	08 (17.77%)
Icterus	14 (31.11%)
Lymphadenopathy	01 (2.22%)
Hepatomegaly	03 (6.66%)
Splenomegaly	13 (28.88%)
Pleural effusion	18 (40.00%)
	04 (8.89%)

Table III: Distribution of patients on the basis of duration of illness (n=45)

Duration of illness (Weeks)	Number (%)
0-10	33 (73.33%)
11-20	06 (13.33%)
21-30	03 (6.66%)
31-40	01 (2.22%)
41-50	01 (2.22%)
51-60	-
61-70	-
71-80	01 (2.22%)

Table IV: Distribution of patients on the basis of various abnormal haematological findings- Peripheral blood count (n=45)

Laboratory investigations	Number (%)
COMPLETE BLOOD COUNT	
Anemia	19 (42.22%)
Thrombocytopenia	04 (8.88%)
Thrombocytosis	01 (2.22%)
Leucocytosis	04 (8.88%)
Pancytopenia	10 (22.22%)
Bicytopenia	14 (31.11%)
Shift to left	14 (31.11%)
Absolute lymphocytosis	05 (11.11%)
Absolute monocytosis	2 (4.44%)
PERIPHERAL SMEAR	
Microcytic hypochromic anemia	10 (22.22%)
Dual deficiency anemia	26 (57.77%)
Normocytic normochromic	09 (20.00%)

Table V: Distribution of patients on the basis of various abnormal haematological findings- Bone marrow examination (n=45)

Laboratory investigations	Number (%)
BONE MARROW ASPIRATE	
Hypercellular	17 (37.77%)
Hypocellular	07 (15.55%)
Normocellular	21 (46.66%)
IRON STORES	
0-1+ (Decreased)	14 (31.11%)
2-3+ (Normal)	18 (40.00%)
3-4+ (Increased)	13 (28.88%)
SILVER STAIN FOR RETICULIN	
0	22 (48.88%)
1+	09 (20.00%)
2+	10 (22.22%)
3+	04 (8.88%)

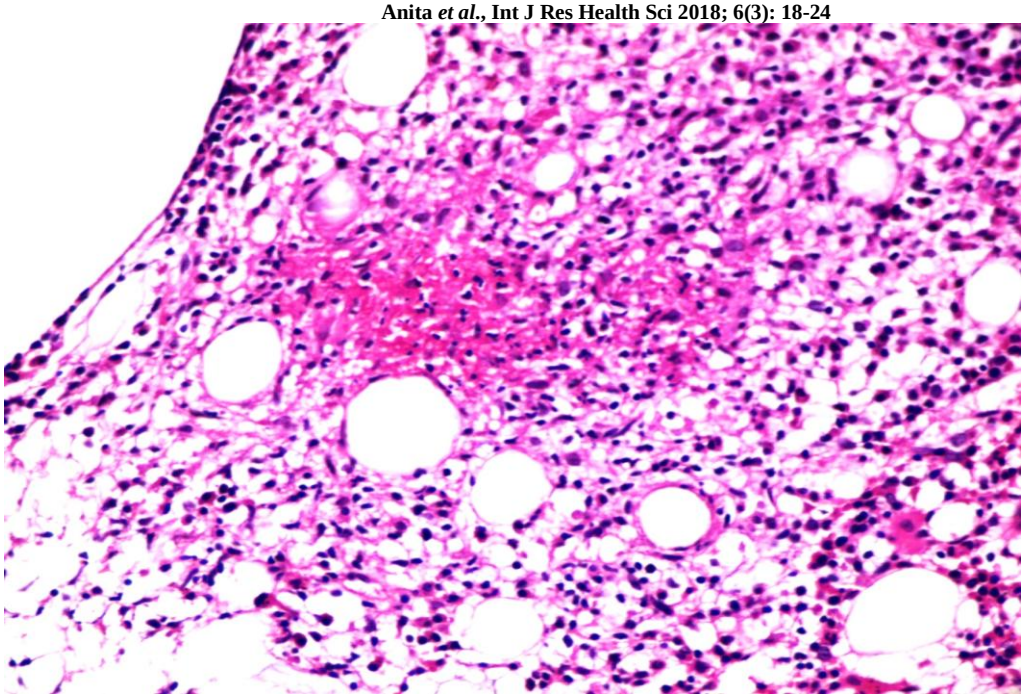

Figure1. Caseating epithelioid cell granuloma in bone marrow biopsy (400X, H&E stain)

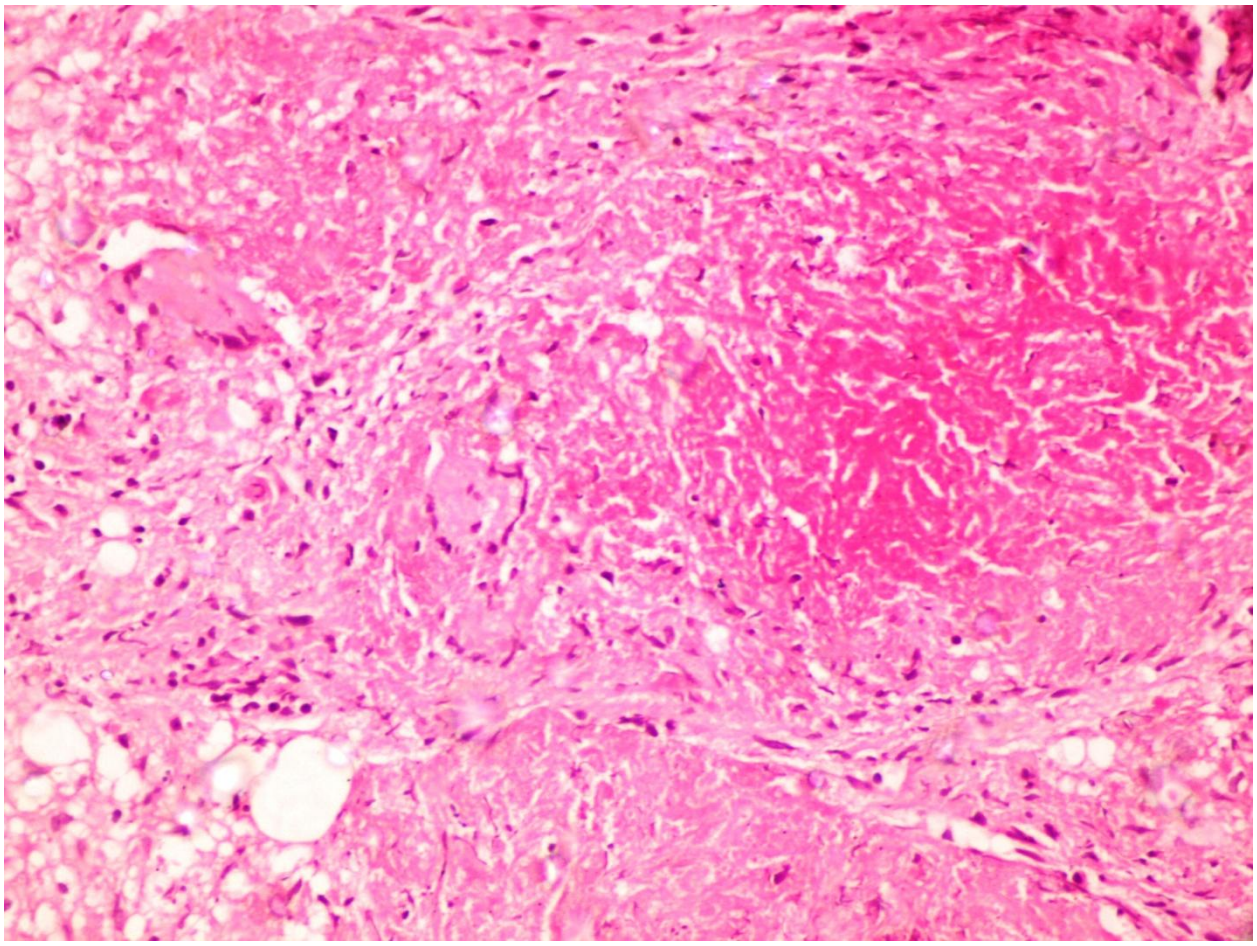

Figure2: Caseoous necrosis in bone marrow biopsy (400X,H&E stain)

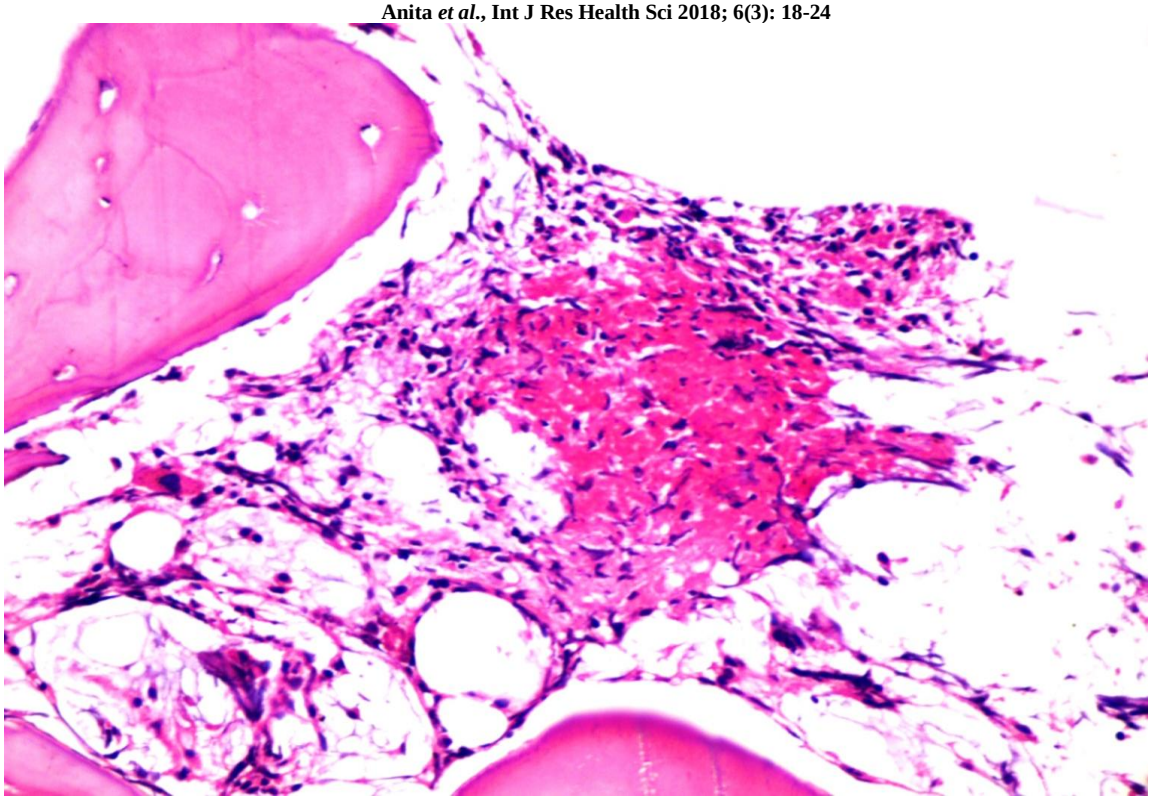

Figure3. Epithelioid cell granuloma in bone marrow biopsy (100X, H&E stain)

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