Section: Pathology

Original Research Article

UNRAVELLING THE MYSTERIES OF BONE MARROW GRANULOMA: A COMPREHENSIVE CASE SERIES STUDY

Sushmitha N[1], Channa Basavaraj B[2], Deepa P[2], Sree Lakshmi Kuruba[3], Ramya B S[3], Siddiq M Ahmed[4]

[1]*Senior Resident, Department of Pathology, Bangalore Medical College and Research Institute, Bangalore, India*
[2]*Senior Resident, Department of General Medicine, Bangalore Medical College and Research Institute, Bangalore, India*
[3]*Professor, Department of Pathology, Bangalore Medical College and Research Institute, Bangalore, India*
[4]*Professor and Head, Department of Pathology, Bangalore Medical College and Research Institute, Bangalore, India*

Received *: 04/03/2026*
Received in revised form *: 18/03/2026*
Accepted *: 21/04/2026*

Corresponding Author:
Dr. Channabasavaraj B
Senior Resident, Department of General Medicine, Bangalore Medical College and Research Institute, Bangalore, India
Email: uzumakicbr@gmail.com

DOI: 10.70034/ijmedph.2026.3.326

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (3); 2042-2045

ABSTRACT

Background: Granuloma identified in a trephine biopsy of bone marrow is a rare and incidental finding, with a reported incidence of 0.3-2.2% among all bone marrow findings. A wide range of infectious and non-infectious conditions - including tuberculosis and other bacterial, viral and fungal infections, as well as autoimmune disease, sarcoidosis, drug reactions and haematological malignancies - have been implicated in its formation. The objective is to evaluate the various causes of granuloma in bone marrow, along with their diagnosis and follow-up.

Materials and Methods: This was a prospective study conducted over five months in the Department of Pathology, Bangalore Medical College and Research Institute. All cases showing well-formed granulomas or histiocytic aggregates on bone marrow trephine biopsy sections (haematoxylin and eosin) were included.

Results: Of 120 bone marrow studies, 15 showed granuloma (8 well-formed epithelioid granulomas, 7 histiocytic aggregates). One case, later diagnosed as Hodgkin lymphoma, showed granuloma with Reed-Sternberg cells, confirmed by PAX-5 and CD30 positivity; only one case was acid-fast bacilli-positive on Ziehl-Neelsen staining. Just one of fifteen cases had a prior tuberculosis history, with ten cases started on anti-tubercular therapy (six improved, four showed minimal response); four patients died before follow-up. The Hodgkin lymphoma patient improved markedly after six cycles of ABVD chemotherapy.

Conclusion: Bone marrow granuloma is a rare finding with varied aetiology. A complete diagnostic work-up is essential to establish the underlying cause and guide appropriate treatment, thereby helping to reduce associated mortality.

Keywords: Bone marrow granuloma; trephine biopsy; tuberculosis; Hodgkin lymphoma; Granulomatous marrow.

INTRODUCTION

Granuloma in a trephine biopsy of bone marrow is a rare and incidental finding, with an incidence ranging from 0.3% to 2.2% of all bone marrow findings.[1] A wide variety of diseases have been implicated in the formation of granuloma in bone marrow, including infections such as tuberculosis and other bacterial, viral and fungal aetiologies. Non-infectious causes, including autoimmune diseases, sarcoidosis, drug reactions, haematological malignancies and others, have also been implicated. Rocky Mountain spotted fever, cytomegalovirus infection, ibuprofen, acute lymphocytic leukemia, and various collagen vascular diseases can also be added to the list of causes of marrow granuloma.[2]

Bone marrow examination remains an important investigation tool when a diagnosis cannot be reached on peripheral blood assessment alone, particularly in patients presenting with unexplained fever, pancytopenias, severe anemia, thrombocytopenia or systemic illness.[3] While bone marrow aspiration allows rapid assessment of cellular morphology, granulomas are frequently missed or under-represented on aspirate smears. Trephine biopsy, which samples an intact core of marrow architecture,

is considerably more sensitive for their detection and often reveals granulomas that aspirates alone would fail to identify. For this reason, trephine biopsy is very essential in adjunct to aspiration whenever granulomatous marrow disease is suspected.[4] A Good bone marrow biopsy is more than 2 cms core with good 8-10 bony trabeculae.

The finding of a granuloma on trephine biopsy is only a starting point, since histomorphology alone frequently cannot distinguish between its many possible causes. In India and other regions with a high background prevalence of tuberculosis, mycobacterial infection remains the single most frequent explanation,[5] and is associated with considerable morbidity and mortality of 25% to 50%,[6] particularly when marrow involvement signifies disseminated disease. However, the differential remains broad, spanning other granulomatous infections, sarcoidosis, drug-induced reactions, autoimmune disorders and, less commonly, an underlying haematological malignancy such as Hodgkin lymphoma. Because the downstream management of these conditions differs substantially, an accurate aetiological work-up combining special stains, microbiological testing, immunohistochemistry and clinical correlation is essential once a granuloma is identified.

Objectives: To evaluate the various causes of granuloma in bone marrow, their diagnosis and follow-up.

MATERIALS AND METHODS

This is a Prospective study of 5 months duration from August 2024 to December 2024, done in Department of Pathology and Medicine, after approval by ethics committee, at a tertiary care teaching hospital. Once a request is received in Department of pathology for various indications like cytopenias, severe anemia, thrombocytopenias, pyrexia of unknown origin and so on, complete history of the patient is collected. After obtaining informed consent, under sterile aseptic precautions and local anaesthesia, Bone marrow aspiration and trephine biopsy is done. Posterior superior iliac crest is the most commonly preferred site in adults. Multiple aspirate smears are made and stained with giemsa stain. Few unstained slides are preserved for additional stains if required. Biopsy core is fixed in 10% formalin, decalcified and processed like a histopathology slide. 3-4 mm thickness sections are cut and H and E staining is done.

Any granulomatous conditions identified on bone marrow were subjected to further Ziehl-Neelsen staining and Periodic Acid Schiff special staining.

Followup of the cases was done for a period of 1 year.

RESULTS

Among 120 cases of bone marrow study performed in the Department of Pathology, over a period of five months, 15 cases (12.5%) of trephine biopsy sections showed granuloma. Of these, 8 cases (53.3%) had well-formed epithelioid granuloma and 7 cases had aggregates of epithelioid-type histiocytes. Most of the cases aspiration was hypocellular. 5 cases Aspirate yielded dry tap.

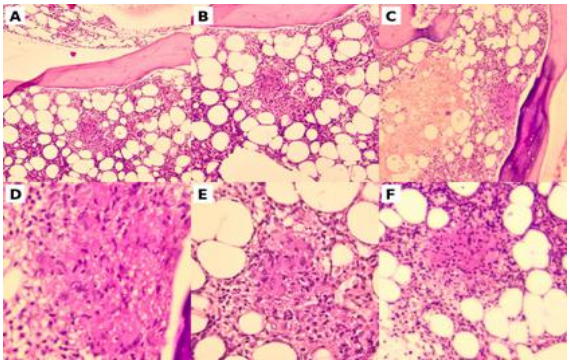

Figure 1: (A-F). Haematoxylin and eosin-stained sections of bone marrow trephine biopsy showing granuloma in the intertrabecular space, along with other haematopoietic elements and adipose tissue (original magnification 100×).

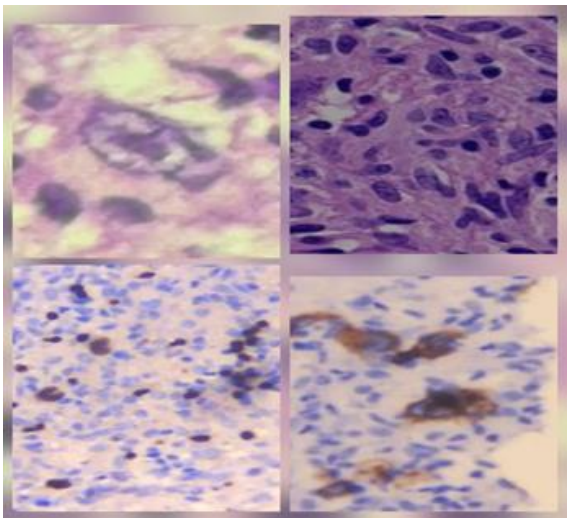

Figure 2: A case of Hodgkin lymphoma showing a Reed-Sternberg cell , epithelioid cell , PAX-5 positivity (lower left) and CD30 positivity (lower right).

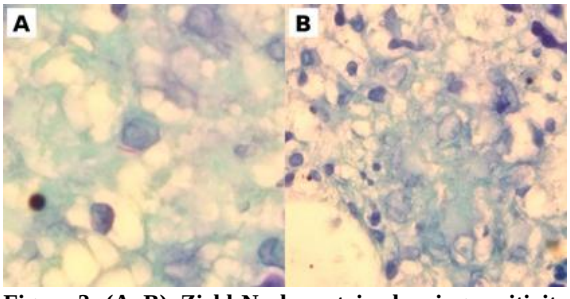

Figure 3: (A, B). Ziehl-Neelsen stain showing positivity for acid-fast bacilli.

One case of Hodgkin lymphoma, showed the presence of granuloma along with classic Reed-Sternberg cells, with plasma cells and eosinophils in the background. Further work-up with

immunohistochemistry showed PAX-5 and CD30 showed positivity.

Ziehl-Neelsen (Z-N) staining was performed in all cases; one case(7.1%) showed positivity for acid-fast bacilli, while the rest were negative for acid-fast bacilli. PAS staining was negative for fungal elements in most of the cases(0).

Only 1 of the 14 non-lymphoma cases (7.1%) had a previous history of disseminated tuberculosis; the rest were incidental findings on bone marrow trephine biopsy, without any clinical suspicion of tuberculosis. Two cases (14.2%) also had lymph node involvement, with fine-needle aspiration cytology (FNAC) showing granulomatous lymphadenitis. Sputum CBNAAT was negative in all the cases.

Four patients (28.5%) died within one week to one month of testing and were consequently lost to follow-up. The remaining 10 cases(71.4%) were started on anti-tubercular therapy (ATT): 6 patients improved symptomatically and completed 6 months of ATT, while 4 cases remained on ATT with little reduction in clinical symptoms and no definitive cause could be established.

The case diagnosed as Hodgkin lymphoma was a 35-year-old male who presented with pyrexia of unknown origin. Following bone marrow diagnosis of Hodgkin lymphoma, he completed six cycles of chemotherapy under the ABVD regimen and showed marked symptomatic improvement.

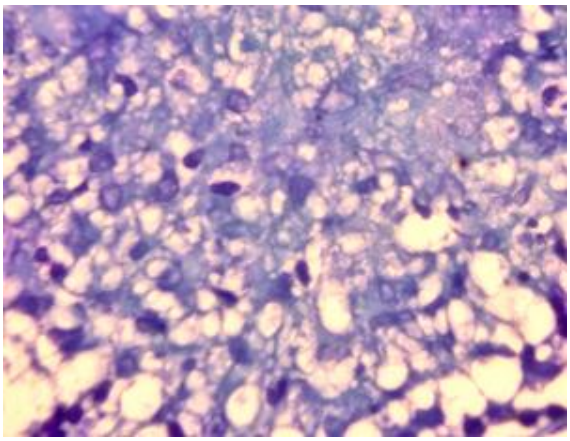

Figure 4: Periodic acid-Schiff (PAS) stain, negative for fungal elements.

DISCUSSION

Granuloma is defined as an aggregate of histiocytes, epithelioid cells and other inflammatory cells, with or without giant cells. Bone marrow granulomas are very rare and are mostly incidental findings. In our study 12.5% was the incidence of granulomas in the bone marrow, which is little higher than the study done by Hugo et al,[7] which showed 0.59% incidence rate.

Granulomas may be missed on aspiration smears because of dilution and loss of tissue architecture. Trephine biopsy preserves marrow architecture and allows accurate assessment of granuloma distribution, morphology and associated pathological findings. The present study further emphasizes the value of trephine biopsy as an important component of bone marrow evaluation. Hence aspiration should always be done adjunct to the trephine biopsy, and neither alone. Also significant number of cases the bone marrow procedure yielded dry tap, in which case imprint smears and trephine biopsy are essential for the diagnosis.

In our country, the most common cause, owing to its high prevalence, is tuberculosis. Bone marrow involvement due to tuberculosis is seen in advanced stages of the disease and indicates a high rate of mortality.8 Granulomas may show central caseous necrosis. However, caseation may not always be present in bone marrow biopsies, particularly in early lesions or in immunocompromised patients. Hence, Ziehl–Neelsen staining and molecular diagnostic techniques may be useful in establishing the diagnosis. But AFB positivity in Ziehl–Neelsen staining in bone marrow is very rare(1 case in our study). And in a resource limited setting, molecular techniques are less frequently done. In our study, despite no molecular tests done, 10 cases were started on ATT and more than 50% of the cases on ATT showed clinical improvement, which signifies the fact of high prevalence of Tuberculosis in India.

Other studies have similarly shown tuberculosis to be the most common cause, followed by other aetiologies. Other causes include viral and fungal infections, sarcoidosis, haematological malignancies, autoimmune diseases and drugs. Despite extensive investigations, no definitive cause can be identified and such cases are categorized as idiopathic granulomas. The varied etiological spectrum emphasizes the importance of a systematic diagnostic approach whenever granulomas are identified in bone marrow specimens. PAS stain should always be done to exclude fungal etiology.

One our case of Hodgkin lymphoma, he was a 35 year old male patient presented with pyrexia of unknown origin, and significant loss of weight, with cytopenias. Bone marrow biopsy showed the presence of granuloma along with classic Reed-Sternberg cells, with plasma cells and eosinophils in the background. Further work-up with immunohistochemistry showed PAX-5 and CD30 showed positivity. After Bone marrow study, PET-CT showed few mm of enlarged peripancreatic lymph nodes. Patient has completed 6 cycles of Chemotherapy and is responding well to the treatment. Bone marrow helped primarily in the diagnosis and remained conclusive in this case.

Follow-up data demonstrated the clinical significance of bone marrow granulomas. Four patients died within one month of diagnosis, reflecting the severity of the underlying systemic illness and supporting previous reports that marrow granulomas may be associated with poor clinical outcomes, particularly in disseminated infectious diseases.

Bone marrow granulomas represent a diagnostic challenge because they are associated with a wide spectrum of infectious and non-infectious disorders. Although the presence of granulomas may provide an important clue to the underlying disease process, the morphology of the granuloma alone is often insufficient to establish a definitive diagnosis. Therefore, interpretation should always be made in conjunction with clinical findings, laboratory investigations, microbiological studies, radiological findings, and ancillary tests.

CONCLUSION

Bone marrow granuloma is a very rare finding, with varied aetiologies present. Despite this rarity, we identified a good number of cases at our tertiary care centre. This study was therefore undertaken to determine the various causes of marrow granuloma. A complete diagnostic work-up is necessary to establish the cause and guide appropriate treatment, thereby helping to reduce mortality.

Limitations: The major limitation of the present study is the relatively small sample size Additionally, complete microbiological and molecular confirmation was not available in all cases, which may have influenced etiological categorization. Larger studies and multicentric studies incorporating ancillary investigations such as culture and molecular diagnostics would provide a better understanding of the clinicopathological spectrum of bone marrow granulomas.

REFERENCES

1. Wang Y, Tang X-Y, Yuan J, Wu S-Q, Chen G, Zhang M-M, et al. Bone marrow granulomas in a high tuberculosis prevalence setting: a clinicopathological study of 110 cases. Medicine. 2018;97(4):e9726.
2. Bodem CR, Hamory BH, Taylor HM, Kleopfer L. Granulomatous bone marrow disease. A review of the literature and clinicopathologic analysis of 58 cases. Medicine (Baltimore). 1983 Nov;62(6):372-83
3. Rindy LJ, Chambers AR. Bone marrow aspiration and biopsy. StatPearls Publishing, Treasure Island; 2025.
4. Jawed MA, Paswan MK, Mahto SK, Patra S, Ashok C, Ansari MA, et al. An extensive analysis and comparison of bone marrow aspiration and bone marrow trephine biopsy at a tertiary care hospital in Jharkhand for various hematological and non-hematological illnesses. Cureus. 2024;16(6):e62661.
5. Chauhan A, Parmar M, Dash GC, Solanki H, Chauhan S, Sharma J, Sahoo KC, Mahapatra P, Rao R, Kumar R, Rade K, Pati S. The prevalence of tuberculosis infection in India: A systematic review and meta-analysis. Indian J Med Res. 2023 Feb-Mar;157(2&3):135-151.
6. Sathees V, Hynniewta Y, Lynrah KG, Dey B, Chakrabarty A, Lynser D, Chakraborty D. Tuberculosis of the bone marrow with secondary hemophagocytic lympho-histiocytosis presenting as obstructive jaundice: A clinician's challenge for the ages. Indian J Tuberc. 2024 Jul;71(3):370-373.
7. Brackers de Hugo L, Ffrench M, Broussolle C, Sève P. Granulomatous lesions in bone marrow: clinicopathologic findings and significance in a study of 48 cases. Eur J Intern Med. 2013;24(5):468–73.
8. Maccio U, Gianolio A, Rets AV. Granulomas in bone marrow biopsies: clinicopathological significance and new perspectives. Pathobiology. 2024;77(1):8-15.