# BONE MARROW BIOPSY IN EVALUATION OF HAEMATOLOGICAL DISORDERS

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**ABSTRACT**

**BACKGROUND**

Bone Marrow Trephine Biopsy (BMTB) and aspiration is critical for diagnosis, prognostic evaluation and monitoring therapeutic response. BMTB is of greater value in assessing cellularity, degree of fibrosis, marrow architecture and especially when aspiration is dry tap. At the same time, it provides sample for immunohistochemistry.

**MATERIALSAND METHODS**

It is a single centre observational study conducted from July 2014 to July 2016 in Department of Pathology, S.C.B. Medical College, Cuttack, which included both cell block and touch imprint along with trephine biopsy. Cases selected where lymphoma studied for pattern and extent of infiltration. Aspiration with dry tap and selected cases of myeloproliferative disorders, myelodysplastic syndrome, leukaemia (both acute and chronic), anaemia, multiple myeloma were studied. Jamshidi needle was used for biopsy. Samples obtained were formalin preserved, kept in decalcification solution (Hammersmith protocol) and H and E slides prepared. Special stain-like reticulin and Masson's trichrome were used for grading of fibrosis. Immunohistochemistry was done on selected cases of lymphoma.

**RESULTS**

Out of total 100 cases studied, 60 were of haematopoietic and lymphoid neoplasms, 12 anaemia, 20 secondary metastasis, 8 miscellaneous (1 haemophagocytic lymphohistiocytic disease, 1 storage disease, 1 granulomatous and 5 ITP).

**CONCLUSION**

The study was conducted to establish the advantage of bone marrow biopsy in inadequate and failed aspiration, but both are complementary to each other and together provide a comprehensive evaluation of the bone marrow. Bone marrow fibrosis are well accessed and increased detection of tumour cells in suspected secondary metastasis. Special stains, IHC, cytogenetic study can be done over biopsy block.

**KEYWORDS**

BMTB, Haematological Disorders, Reticulin, IHC.

**HOW TO CITE THIS ARTICLE:** Sahoo SR, Mohanty P, Bhuyan P, et al. Bone marrow biopsy in evaluation of haematological disorders. J. Evid. Based Med. Healthc. 2017; 4(28), 1623-1629. DOI: 10.18410/jebmh/2017/317

## BACKGROUND

Bone marrow examination plays an important role in both haematological and non-haematological disorders. Marrow aspiration and biopsy can be done simultaneously in one setting without need of additional needle puncture.

Recent advances in the treatment of haematological malignancies have been paralleled by renewed interest on the part of pathologist and haematologist in methods of obtaining and preparing bone marrow for diagnostic studies.

*Financial or Other, Competing Interest: None.*
*Submission 16-03-2017, Peer Review 23-03-2017,*
*Acceptance 31-03-2017, Published 04-04-2017.*
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Bone marrow trephine biopsy is critical for diagnosis in unexplained anaemias, staging in both HL and NHL, prognosis in chronic leukaemia's and monitoring therapeutic responses by taking serial biopsies. It is of greater value in assessing marrow cellularity, architecture, degree of fibrosis and morphology especially in dry taps. It is very helpful where there is suspicion of disorders like disseminated granuloma, malignant lymphoma, amyloidosis, myeloproliferative disorders, myelofibrosis, secondary metastasis and metabolic bone diseases. Additionally, multiple or serial biopsies maybe useful in assessing total marrow space involved in aplasia, myelofibrosis, metastatic carcinoma and malignant lymphoma.

There is virtually no contraindication to bone marrow trephine biopsy. It can be performed in patients with severe thrombocytopenia and in other haemorrhagic disorders without any significant haemorrhage. No patients have complained of persistent pain or disability.

A properly obtained and processed trephine biopsy specimen will have its full effective value only when assessed in conjunction with the clinical findings, peripheral blood smear and marrow aspiration smear findings of patients with haematological disorders.

Though combined evaluation of marrow aspirate and biopsy specimens considerably enhances the diagnostic ability of haematopathologist, but trephine biopsy provides an extensive information and adequate material for any further ancillary studies like immunohistochemical and reticulin stains. The present study will document this observation.

**AIMS AND OBJECTIVES**

- To establish the diagnosis in dry tap and bloody tap.
- To have a comprehensive analysis of marrow cellularity, architecture, degree of fibrosis and infiltration in a spectrum of haematological diseases.

To clinically correlate these data with special reference to marrow biopsy and to compare prospectively using special stain and immunohistochemistry for the final diagnosis.

**MATERIALS AND METHODS**

This study was carried out in the Department of Pathology, S.C.B. Medical College and Hospital, Cuttack, Odisha, during the period from July 2014 to July 2016.

Present study include patients of 0-80year's age group of both sexes diagnosed haematologically as cytopenias (anaemia, leukaemia and thrombocytopenia) either singly or in combination. Suspected leukaemia, lymphoma and multiple myeloma, pyrexia of unknown origin were also included in the study to establish the cause. A total number of 100 cases were studied.

A detailed clinical history, general examination and different systemic examination were carried out with special attention to hepatosplenomegaly, lymphadenopathy, bleeding manifestations (skin and mucous membrane).

Patients were subjected to undergo haematological investigations, which included estimation of complete blood count, haemoglobin percent and total leucocyte count, differential count of leucocyte, comment on peripheral smear and total platelet count. Bone marrow aspiration were done in all cases along with biopsy, touch imprint and cell blocks (where biopsy couldn't be done) to confirm the diagnosis.

**Inclusion and Exclusion Criteria**

Leishman's stain was used to stain aspiration and touch imprint smears. Biopsy and cell blocks were subjected to Haematoxylin and Eosin stain. Special staining like myeloperoxidase was done in leukaemia cases. Reticulin silver impregnation, Masson's trichrome stain were done wherever necessary. Immunohistochemistry (CD3, CD138, NSE, Kappa, Lambda and CK20) were done in selected cases.

The posterior superior iliac spine was the safe and referred site for both bone marrow aspiration and biopsy.

Bone marrow biopsy was done first by Jamshidi bone marrow biopsy needle followed by aspiration using Salah's needle through the same skin puncture, but piercing the periosteum little away from the biopsy point. Any extra material was allowed to clot for cellblock preparation.

Hammersmith protocol was followed for fixation and decalcification of the biopsy tissue. For fixation, AZF solution was used, which comprises of zinc chloride 12.5g,concentrated formaldehyde150mL,glacial acetic acid 7.5mL,distilled water1000mL and the tissue was kept for 20-24hrs.in that solution. Then, the tissue was washed in distilled water for 30mins.and then it was kept in decalcification solution, i.e. Gooding and Stewart's fluid (10%formic acid, 5% formaldehyde) for 6hrs.After that, the core was subjected to usual histological tissue processing and paraffin embedded block formation. Three sections of nearly 4-5µm thick were cut. Out of three sections, one for H and E stain, second for reticulin silver stain and the third for immunohistochemistry if needed.

**RESULTS**

In the present study, bone marrow biopsy was conducted more on neoplastic lesions, i.e.80% and nonneoplastic comprises only about 20% (Table1).In the spectrum of haematological disorders, 60 cases were of haematopoietic and lymphoid neoplasms,12 anaemia,20 secondary metastasis, 8 miscellaneous (1 haemophagocytic lymphohistiocytic disease,1 storage disease,1 granulomatous and 5 ITP).

In the hematolymphoid category, maximum cases were of non-Hodgkin's lymphoma (50%), followed by primary myelofibrosis (12.5%) and rest were in nearly equal frequency (Table2).

The overall M:F ratio is nearly equal to 2.8:1.0.

The maximum number of cases over, which biopsy was conducted had pancytopenia in peripheral smear (Table3) and among them maximum cases of metastatic tumour and hypo plastic anaemia presented as pancytopenia.

BMTB has better diagnostic implications in cases of hypocellular marrow, focal lesions and dry tap associated with fibrosis (Table4).

Maximum number of cases, which metastasise to bone marrow were within age group of 0-5years with highest infiltration from PNET/Ewing's sarcoma and in the elderly age group adenocarcinomatous deposits in bone marrow were common (Table5).

Cases with fibrosis in the present study showed that longstanding chronic cases led to marrow fibrosis along with diseases of primary myelofibrosis (Table6).

Different cases showed different stages of fibrosis and the degree of fibrosis was assessed by doing reticulin silver and Masson's trichrome stain.

The grading was done according to "European Clinicopathological Criterias", ECP.

| Sl. No. | Type of Disease | Number of Cases | Percentage | Total |
|---|---|---|---|---|
| **Neoplastic** | | | | |
| 1. | Hematolymphoid malignancies | 40 | 40% | 80 |
| 2. | Multiple myeloma | 20 | 20% | |
| 3. | Metastasis | 20 | 20% | |
| **Non-Neoplastic** | | | | |
| 4. | Anaemia | | | |
| | Hypo/aplastic | 9 | 9% | 20 |
| | Megaloblastic | 2 | 2% | |
| | IDA | 1 | 1% | |
| 5. | Miscellaneous | | | |
| | ITP | 5 | 5% | |
| | Granulomatous disorder | 1 | 1% | |
| | Storage disorder | 1 | 1% | |
| | Haemophagocyticlymphohistiocytosis | 1 | 1% | |
| | **Total Number of Cases** | **100** | **100** | |

***Table 1. Spectrum of Haematological Disorders***

| Sl. No. | Entities | Number of Cases | Percentage |
|---|---|---|---|
| 1. | ALL | 02 | 5% |
| 2. | AML | 02 | 5% |
| 3. | CLL | 04 | 10% |
| 4. | CML | 01 | 2.5% |
| 5. | PCV | 02 | 5% |
| 6. | PMF | 05 | 12.5% |
| 7. | RCUD | 02 | 5% |
| 8. | RCMD | 02 | 5% |
| 9. | NHL | 20 | 50% |

***Table 2. Disorders in the Hematolymphoid Group***

| Sl. No. | PSC | Number of Cases | Percentage |
|---|---|---|---|
| 1. | Pancytopenia | 30 | 30% |
| 2. | Bicytopenia | 09 | 9% |
| 3. | Thrombocytopenia | 05 | 5% |
| 4. | Microcytic hypochromic anaemia | 10 | 10% |
| 5. | Dimorphic anaemia | 02 | 2% |
| 6. | Normocytic normochromic anaemia | 10 | 10% |
| 7. | Polycythaemia with thrombocytosis | 02 | 2% |
| 8. | Neutrophilicleucocytosis | 09 | 9% |
| 9. | Acute leukaemia | 03 | 3% |
| 10. | Atypical lymphoid cells | 15 | 15% |
| 11. | Absolute lymphocytosis | 04 | 4% |
| 12. | CML | 01 | 1% |
| | **Total** | **100** | **100%** |

***Table 3. Peripheral Blood Findings***

| Sl. No. | Disease | Total Number of Cases | BMA Diagnosis | BMTB Diagnosis |
|---|---|---|---|---|
| 1. | ALL | 02 | 02 | 02 |
| 2. | AML | 02 | 02 | 02 |
| 3. | CLL | 04 | 04 | 04 |
| 4. | CML | 01 | 01 | 01 |
| 5. | PCV | 02 | 02 | 02 |
| 6. | PMF | 05 | 00 | 05 |
| 7. | RCUD | 02 | 02 | 02 |
| 8. | RCMD | 02 | 02 | 02 |
| 9. | NHL | 20 | 18 | 20 |
| 10. | Multiple myeloma | 20 | 17 | 20 |
| 11. | Metastasis | 20 | 16 | 20 |
| 12. | Hypo/aplastic anaemia | 09 | 07 | 09 |
| 13. | Megaloblastic anaemia | 02 | 02 | 02 |
| 14. | IDA | 01 | 01 | 01 |
| 15. | ITP | 05 | 05 | 05 |
| 16. | Granulomatous disease | 01 | 00 | 01 |

| | | | | |
|---|---|---|---|---|
| 17. | HLH | 01 | 01 | 01 |
| 18. | Storage disease | 01 | 01 | 01 |
| | **Total** | **100** | **83** | **100** |

***Table 4. Bone Marrow Biopsy Vs. Aspirate Smear Diagnosis***

| Sl. No. | Type of Disease | Age Group (in Yrs.) | Number of Cases | Percentage |
|---|---|---|---|---|
| 1. | Retinoblastoma | 0-5 | 01 | 5% |
| 2. | PNET/Ewing's sarcoma | 0-5 | 07 | 35% |
| 3. | Medulloblastoma | 0-5 | 01 | 5% |
| 4. | Neuroblastoma | 0-5 | 03 | 15% |
| 5. | Rhabdomyosarcoma | 0-5 | 02 | 10% |
| 6. | Pleomorphic sarcoma | >50 | 01 | 5% |
| 7. | Adenocarcinoma | >50 | 05 | 25% |
| | **Total** | | **20** | |

***Table 5. Frequency of Metastatic Deposits in Different Age Group***

| Sl. No. | Type of Disease | Total Number of Cases | Number of Cases with Fibrosis | Percentage |
|---|---|---|---|---|
| 1. | CLL | 04 | 02 | 50 |
| 2. | CML | 01 | 01 | 100 |
| 3. | NHL | 20 | 02 | 10 |
| 4. | PMF | 05 | 05 | 100 |
| 5. | Metastasis | 20 | 02 | 10 |
| 6. | Multiple myeloma | 20 | 01 | 05 |

***Table 6. Haematological Disorders Showing Fibrosis***

**DISCUSSION**

Bone marrow trephine biopsy is an indispensable adjunct to the study of diseases of blood and at times the only way by, which a correct diagnosis can be made.

In particular, it is suitable in hypoplasia, focal infiltration like metastasis and granulomatous disorders.

Excluding some negligible disadvantages, this procedure has advantage of providing large chunk of tissue leading to extensive study of the marrow.

In the present study, "bone marrow biopsy in evaluation of haematological disorders", bone marrow biopsy was conducted in 100 patients having haematological disorders in the age range of 0 to 80 years. Similarly, Naznin et al (2003)[1] studied 61 cases in the age range of 9 months to 93 years. Saeed et al (2006)[2] studied 789 patients in the age range from 9 to 75 years. Muhammad Usman Anjum et al (2014)[3] did bone marrow study on 168 cases in the age range of 0 to 50 years. Shilpa et al (2015)[4]conducted bone marrow study on 120 cases in the age range of 3 to 70 years.

Out of 100 patients, there were 74(74%) males and 26(26%) females with M:F ratio being 2.8:1.Similar sex incidence was observed by Saeed et al(2006),[2] i.e. they had 69.83% males and 30.16% females and D'Costa et al(2007)[5] had 62.5% and 37.5% females in their study. Shilpa et al(2015)[4] in their study on 120 cases had M:F ratio of 2.4:1.

Pancytopenia was the most frequent (30%) indication of bone marrow biopsy in our study followed by lymphoma (15%), i.e. presence of atypical lymphoid cells in peripheral smear and unexplained anaemia(10%), (Table3). Similarly, Nanda et al (2002)[6] advised bone marrow biopsy in cases of hypoplasias, myelofibrosis, metastasis and lymphomatous infiltration as the bone marrow aspiration gave incomplete informations for making diagnosis. D Costa et al (2007)[5] found that acute leukaemic blood picture were the most frequent indication for bone marrow biopsy. Shilpa et al (2015)[4] found anaemia (44.2%) to be the most common indication followed by pancytopenia (25%). S Tripathy et al (2013)[7] in their study found that the commonest indication was anaemia (40.3%) followed by pyrexia of unknown origin (36.2%), and among cases with pancytopenia, allhypoplastic anaemia and primary myelofibrosis showed marrow suppression of all the lineages and subsequently pancytopenia in peripheral smear as in the study of Shilpa et al (2015).[4] The most common finding in a patient with pancytopenia was megaloblastic anaemia (29.4%) and hypocellular marrow (23.5%).

The classification of spectrum of haematological disorders into broad categories revealed that neoplastic group constitute majority of cases (80%) and nonneoplastic group only 20% (Table1) and (Table2).In the neoplastic category, maximum cases were of non-Hodgkin's lymphoma(20%), metastatic tumours(20%) and multiple myeloma(20%), followed by myeloproliferative neoplasms (12%) and acute(4%) and chronic leukaemias(4%) and in the non-neoplastic group aplastic anaemia (9%) and ITP(5%) cases were in maximum number. Similarly, Sitalaxmi et al (2005)[8] found that more cases were in the non-neoplastic category and granulomatous inflammation was seen in 34 out of 60 cases. D Costa et al(2007)[5] found that the majority of cases(61.66%) were anaemia followed by infection(11.66%).Shilpa et al(2015)[4] found megaloblastic anaemia (13.3%) was commonest followed by ITP(9.1%) and hypocellular marrow(8.3%).

In our study, bone marrow biopsy was done first using Jamshidi bone marrow biopsy needle from the posterior superior iliac spine followed by aspiration using Salah's BM

aspiration needle, a little away from the biopsy site. By following this sequence, suction effect artefact was minimised. Naznin et al (2003)[1] also did biopsy first than aspiration to avoid aspiration artefact. Burkhadt et al (1982),[9] Paulman et al (1989),[10]Sabharwal et al(1990)[11] in their study found that biopsy done by Jamshidi needle gave excellent morphology. Bone marrow aspiration was done prior to core biopsy using an aspirate needle for aspiration, then using a separate bone marrow core biopsy needle for obtaining the solid core (two-needle technique) as suggested by (Islam in 2006).[12]

We found that by following "Hammersmith protocol", i.e. fixation in acetic acid-zinc-formalin fixative solution and decalcifying in Gooding and Stewart's solution (10%formic acid and 5% formaldehyde) and embedding in paraffin provided good morphology. In their study, Hyun (1986)[13] and Burkhadt et al (1982)[9] suggested that plastic embedding is the preferred method for cellular identification. But, Marcus et al (2005),[14] Schmid et al(1992)[15] and Bain(2001)[16] found that the formalin fixed paraffin wax embedded biopsy specimen had given excellent results. Naresh et al (2006)[17] proposed that the "Hammersmith protocol" is the optimal method of processing bone marrow trephine biopsy and it provides excellent morphology.

Sections containing atleast five intertrabecular spaces or containing obvious tumour were found to be adequate. Average length of biopsy tissue was 1.4cm.Biopsy on elderly patients with likely osteoporotic bone and lytic bone of multiple myeloma failed to provide adequate length of tissue. In those cases, blood clot obtained was subjected to cell block preparation. Reid et al (1996)[18] found that whatever length of core is considered optimal determining the amount of well-preserved marrow is considered optimal. Schmid et al (1992)[15] and Bain (2001)[16] found that an adequate specimen contained at least five to six intertrabecular spaces (any such statement as to "adequate" length is arbitrary, because the larger the amount of tissue that is biopsied, the greater is the likelihood of focal lesions being detected).[19]

Out of 100 cases, 83 cases were diagnosed by bone marrow aspiration and the findings in biopsy correlated well with the aspiration features, and in the rest 17 cases, bone marrow biopsy was helpful in reaching at the diagnosis. Among those cases where biopsy provided extra information were of non-Hodgkin's lymphoma, multiple myeloma, metastasis, primary myelofibrosis, hypoplasticanaemia and granulomatous disorder (Table 4).

In non-Hodgkin's lymphoma, out of 20 cases, 18cases showed infiltration both in bone marrow aspiration and biopsy, but the rest two cases revealed focal infiltration, which was missed in the aspirate. B-cell lymphomas (60%) had a higher incidence than T-cell lymphomas (40%) and predominant pattern of involvement was diffuse type. (BM involvement by malignant lymphoma indicates stage IV disease and generous bilateral BM bip sy had been recommended, trephine biopsy being preferred to marrow aspiration for detecting marrow infiltration. Bone marrow biopsy is an integral part of staging workup for non-Hodgkin's lymphoma. Critical examination of BM biopsies can increase the diagnostic accuracy, thereby contributing to the prognosis and appropriate treatment modalities.) Suneet K et al (July 2009).[20]

The Bone Marrow Biopsy (BMB) was diagnostic for myeloma in three cases, which were missed in aspiration as the aspirates were hypocellular; two had early myeloma and one had extensive marrow fibrosis. Similar case of aspiration failure in multiple myeloma were observed by Singhal N et al (2004).[21]

Similarly, metastasis in four cases were diagnosed by biopsy, which were missed in aspiration as the infiltration was only focal. Moreover, in two cases IHC like CK20 was done to confirm the primary site to be intestinal adenocarcinoma.

Two out of nine cases of hypoplastic anaemia could not be diagnosed by aspiration because of extreme hypocellularity and bloody tap, but confirmed by bone marrow biopsy.

Bone marrow biopsy was extremely helpful in a case of pyrexia of unknown origin where well-formed granuloma was demonstrated while aspirate was not informative as the lesion was focal.

In all five cases of primary myelofibrosis, aspiration was dry tap. Exact assessment of cellularity and degree of fibrosis was well established by biopsy.

Myelofibrosis (MF) may develop in all types of myeloproliferative disorders and its identification is of clinical relevance. The MF grade and extent were evaluated semi-quantitatively in archival slides stained by reticulin silver impregnation. The analysis was based on the" European clinicopathological criteria 2004 "(ECP) defining.

a. Normal bone marrow fibrosis (MF0).
b. Slight reticulin fibrosis (MF1).
c. Advanced reticulin and initial collagen fibrosis (MF2).
d. Advanced collagen fibrosis (MF3).

In this present study, total 13 cases showed marrow fibrosis.

Out of those, all cases of primary myelofibrosis (100%), CML (100%), CLL (50%) followed by NHL (10%), metastasis (10%) and multiple myeloma (5%) showed marrow fibrosis (Table6).

In five cases of primary myelofibrosis-

- One case showed MF0.
- Two cases showed MF1.
- One case showed MF2.
- One case showed MF3 grade.

One case of CML showed MF3 grade (increased collagen fibres showed blue colour positivity in Masson'strichrome stain).

In two cases of CLL- one case showed MF2 and the other showed MF3 grade.

Both cases of NHL showed MF2 grade.

In two cases of metastasis-one showed MF0 and the other showed MF2 grade.

Single case of multiple myeloma showed extensive fibrosis of grade MF3.

So, "BM of patients with myelofibrosis in initial phase shows either MF0 or focal slight increase of reticulinfibers (MF1). In addition, the long course of the disease and/or applied therapy may lead to more developed MF and more advanced MF stages (diffuse MF1 or MF2)".[22]

The BMA and BMB findings showed 100% correlation in all the four cases of CLL, but information about the pattern of infiltration, which was diffuse type suggested worst prognosis. Also, the degree of fibrosis in two cases could be assessed and the grade ascertained.

## CONCLUSION

For the present study "Bone Marrow Biopsy in Evaluation of Haematological Disorders", patients having haematological disorders were selected. Bone marrow biopsy along with aspiration was conducted in 100 such patients in the Department of Pathology, S.C.B. Medical College and Cuttack in the age range of 0-80 years. There were 74 males and 26 females, the male-to-female ratio being 2.8:1.0.

Both bone marrow aspiration and biopsy was done from the posterior superior iliac spine using Salah's aspiration needle and Jamshidi bone marrow biopsy needle, respectively. Sections containing at least 4-5 intertrabecular spaces or containing obvious tumours were found to be adequate. Pancytopenia (30%) was found to be the most frequent indication for bone marrow biopsy. The diagnosis in 83 cases (83%) was given from bone marrow aspiration where the findings correlated well with biopsy findings and in rest 17 cases (17%). It was only the bone marrow biopsy that helped us to provide a definitive diagnosis.

Bone marrow biopsies were found to be diagnostic in dry tap cases of primary myelofibrosis and in focal lesions like granulomatous disease, multiple myeloma (15%) and metastasis (20%). Biopsy provided additional information about fibrosis in chronic myeloproliferative cases and degree of fibrosis and grading was confirmed by reticulin silver and Masson's trichrome stain. Pattern of infiltration suggesting the prognosis was well established in chronic leukaemias. Ancillary studies like IHC was done to classify the type of lymphoma, primary site for metastatic deposit and for clonality of multiple myeloma.

After evaluation of the procedure and comparing its results with previous studies it can be concluded that trephine biopsy of bone marrow should be included as a regular practice in every haematological laboratory for complete evaluation of patients with haematological disorders. Moreover, bone marrow biopsy was more advantageous than aspiration in the accurate assessment of cellularity, but cell morphology was better appreciated in bone marrow aspiration. Thus, biopsy and aspiration both are complementary to each other.

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