

Bone marrow metastases - A 7 years study from a single tertiary centre in eastern India

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SUMMARY Introduction: Haematogenous spread of tumours to bone marrow is a common phenomenon and implies advanced stage of disease with poor prognosis. In most instances, the site of primary malignancies is known and is demonstrated in the bone marrow, when the procedure is carried out as a part of the staging process. However in some cases, detection is incidental and bone marrow involvement may be the first clue to these unsuspected non hematopoietic malignancies.

Objective: In this study, we aim to analyse the clinico-pathological spectrum of non-hematopoietic neoplasms detected in bone marrow biopsies carried out in our setting.

Methods: This is a descriptive cross-sectional study, where the Laboratory Information System (LIS) was used to screen all the bone marrow trephine biopsies done over the last 7 years, from January 2014 to December 2020. Out of total 4370 bone marrow trephine biopsies performed, 53 cases of bone marrow metastases by nonhematopoietic malignancies were detected. All the stained slides and the tissue blocks of metastases were retrieved for observation and their laboratory parameters were retrieved from the Laboratory Information System (LIS).

Results: Out of these 53 cases, primary was known in 16 (30.2%) cases prior to performing marrow biopsies. 15 (28.3%) cases presented with severe backache and/or presence of lytic lesions on radiological examination and underwent marrow examination with a clinical suspicion of multiple myeloma versus metastases. 16 (30.2%) cases were incidentally detected while evaluating for causes of cytopenias and leucoerythroblastic blood picture. Adenocarcinoma prostate was the most common tumour with first presentation as bone marrow metastases followed by adenocarcinomatous deposits from gastrointestinal tract.

Conclusion: Bone marrow metastases by non-hematopoietic neoplasms can be the first presenting feature in many cases as seen in our study. So, performing a trephine biopsy routinely along with aspiration for any unexplained cytopenias is of paramount importance in clinching the primary diagnosis.

Key words: Bone marrow, metastases, cytopenias and leucoerythroblastic, non-hematopoietic neoplasms, eastern India

INTRODUCTION

Haematogenous spread of tumours to bone marrow is a common phenomenon and implies advanced stage of disease with poor prognosis [1]. Bone marrow infiltration by non-haematological malignancies is usually suspected when there are few alarming signs like severe bone pain with pathological fractures, hypercalcemia, abnormal radiological findings like hotspots on Positron Emission Tomography/Computed Tomography (PET/CT) scan and deranged haematological parameters like presence of leucoerythroblastic blood picture [2]. However, radiological procedures like bone scans and Magnetic Resonance Imaging (MRI) are expensive and available at limited number of centres. On the other hand, bone marrow aspiration and trephine biopsy is simple and cost effective procedure for detecting bone marrow metastasis of solid tumours. In most instances, the site of primary malignancies is known and is demonstrated in the bone marrow, when the procedure is carried out as a part of the staging process [3]. In some cases, detection is incidental and bone marrow involvement may be the first clue to these unsuspected non-haematopoietic malignancies [3,4].

Here, in this study we have analysed the morphological spectrum of metastases detected in bone marrow biopsies carried out in our setting and its clinicopathological characteristics.

MATERIAL AND METHOD

This is a descriptive cross-sectional study, where the Laboratory Information System (LIS) was used to screen all the bone marrow trephine biopsies done over the last 7 years, from January 2014 to December 2020. Out of total 4370 bone marrow trephine biopsies performed, 53 cases of bone marrow metastases by nonhematopoietic malignancies were detected. All the stained slides and the tissue blocks of metastases were retrieved for observation. Their clinical, biochemical and radiological parameters were retrieved from the LIS and the Test Request Forms (TRF). We also collected the relevant histopathology reports of the tissue biopsies from primary sites, whenever available.

Cases included belonged to both adult as well as paediatric age group. All the bone marrow aspirate and biopsies were

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performed using disposable Jamshidi needles (adult and paediatric) from posterior superior iliac spine (both in adults and paediatric age group), using standard protocols of asepsis and local anaesthesia. Bone marrow aspiration, imprint smears and peripheral smears were stained by Leishman-Giemsa stains. Trehpene biopsies were fixed and decalcified using Hammersmith protocol, processed and then stained with Haematoxylin and Eosin. Special stains like Reticulin, Periodic Acid Schiff (PAS) were done routinely in all cases, Mucicarmine (MC) and Alcian blue-PAS were done wherever necessary. Morphological features predictive of the nature and origin of the tumour, and associated stromal response were studied. Immunohistochemistry (IHC) was used wherever required using a panel of markers based on morphology and clinical history. Relevant basic statistics were used, as and when required.

RESULTS

A total of 4370 trephene biopsies were done during the period from June 2013 to May 2020, out of which 53 (1.2%) cases showed metastatic deposits in bone marrow. Indications for bone marrow among these 53 cases were divided broadly into three categories as described by P Mishra, et al. [5]. Category 1(a) were positive bone marrows done as a part of staging in case of known solid tumours. Included in category 1(b) were cases of known malignancies, now presenting with increasing cytopenias. In category 2, the cases presented with backpain and with lytic/sclerotic lesions of bone, where multiple myeloma or metastatic deposits needed to be ruled out. In category 3, cases included had either a clinical suspicion of primary hematological malignancies or were worked up for cytopenias and leucoerythroblastic blood picture. Category 3(a) comprised of cases with a primary clinical diagnosis of NHL as they presented with multiple lymphadenopathies and 3(b) were the cases evaluated for abnormalities in the hemogram, namely cytopenias and leucoerythroblastic blood picture.

Out of these 53 cases, primary was known in 16 (30.2%) cases prior to performing marrow biopsies. Total of seven out of 16

cases were done as a part of staging marrow for solid tumours (category 1a) and rest 9 cases were of known malignancies presenting with increasing cytopenias during the course of treatment (category 1b, Table 1).

Total of 15(28.3%) cases presented with severe backache and/or presence of lytic lesions on radiological examination and underwent marrow examination with a clinical suspicion of multiple myeloma *versus* metastases [6]. Six (11.3%) cases were evaluated for suspicion of lymphoma as they presented with multiple lymphadenopathies. Rest 16 (30.2%) cases were incidentally detected while evaluating for causes of cytopenias and leucoerythroblastic blood picture (category 3b, Table 1). Bicytopenia was the most common presentation in this group followed by leucoerythroblastic blood picture. None of these cases had any signs or symptoms related to the primary malignancy detected in the bone marrow [7,8].

Age distribution ranged from one year to 81 years with a total of six (11.3%) paediatric cases (age<14 years) and all but one of them were done as a part of staging for known solid tumours. One paediatric case (4 years old) was clinically suspected as ALL, as he presented with multiple lymphadenopathies and anaemia, but marrow examination revealed presence of metastatic Neuroblastoma (Figure 1) [9].

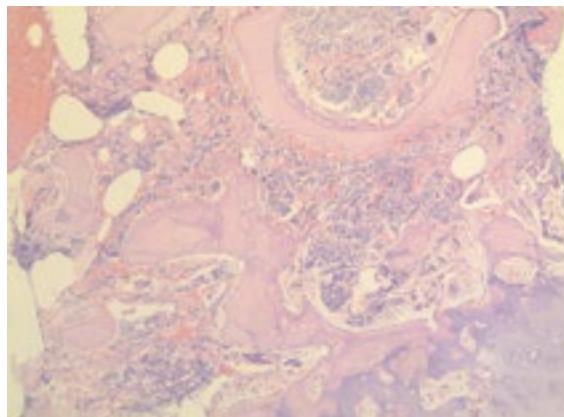


Fig. 1. Metastatic Neuroblastoma, x400, H&E

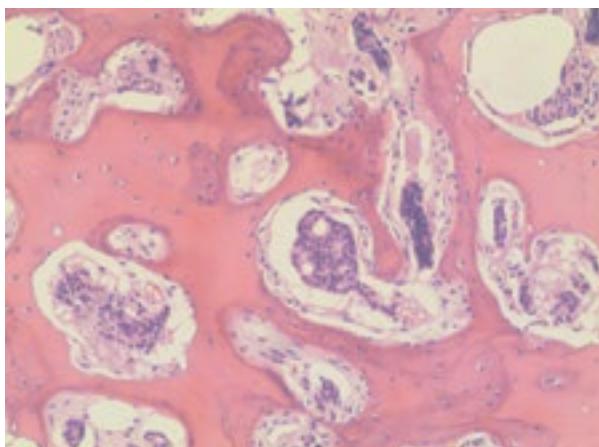
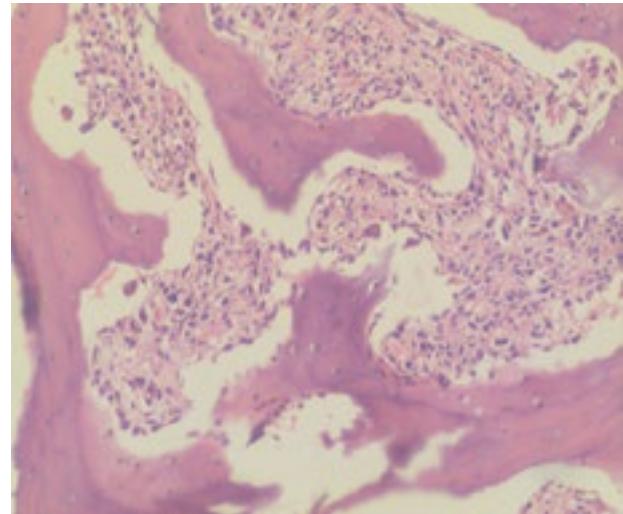
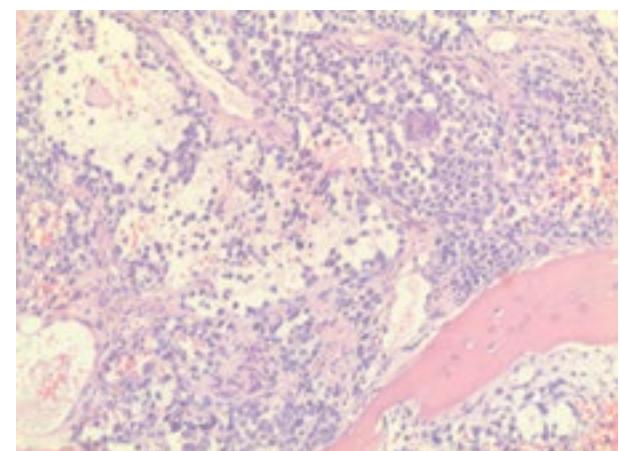
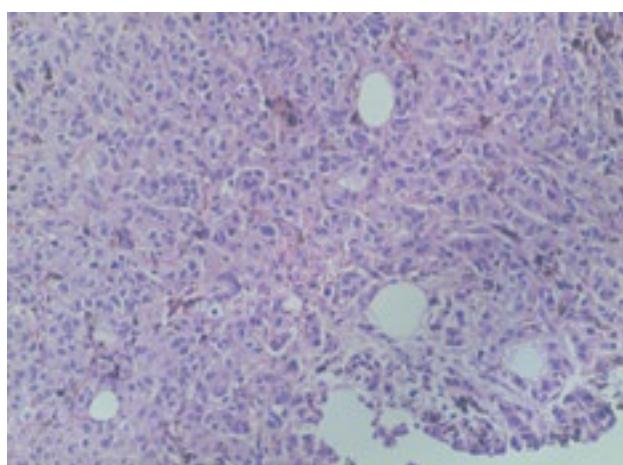
Tab. 1. Indications of Bone Marrow examination in cases showing metastatic deposits (n=53 cases)	Category 1(a)- Staging marrow in solid tumors Neuroblastoma-3 Ewings/PNET-2 Embryonal Rhabdomyosarcoma-2	7
	Category 1(b)- Known malignancies with increasing cytopenias Ca lungs- 2 Ca Breast- 2 Ca Stomach-2 Ca ovary -1 Ca prostate- 1	9
	Alveolar Rhabdomyosarcoma-1	
	Category 2- Severe Backpain with Multiple lytic lesion in bone	15
	Category 3(a)-Lymphadenopathy under evaluation	6
	Category 3(b)-Cytopenias and leucoerythroblastic blood picture under evaluation- Pancytopenia-2 Bicytopenia-6 Thrombocytopenia-1 Anemia -2 Leucoerythroblastic blood picture -5	16

Tab. 2. Age distribution of cases showing metastatic deposits (n=53)

Age in years	Total numbers
<14	6
15-30	5
31- 45	5
46-60	22
Above 60	15

On further, radiological evaluation the patient had an intraabdominal mass lesion. 47 (88.7%) out of total 53 cases were adults, which also included young adults below 40 years of age (8 cases). Male to female ratio was 2.1:1. Leucoerythroblastic blood picture was present in 17 cases altogether, including 5 cases where it was the primary indication of bone marrow examination. Hematological parameters were normal in 9 out of 53 cases of metastases in bone marrow (Table 2).

Bone marrow aspirate was difficult in 22 cases where marrow fragments were absent on the smears (Table 2). The length of Trephine biopsies showing metastatic deposits, ranged from 1 cm to 3.5 cm with an average range of 2.0 cm. Metastatic deposits were missed in 9 (16.9%) marrow aspirates, but detected in the corresponding biopsies. One case was misdiagnosed as plasma cell dyscrasias on aspirate smears and later reviewed to poorly differentiate metastatic adenocarcinomatous deposits in the corresponding biopsy. Morphological assessment revealed adenocarcinomatous deposits in 30 cases, small round cell tumour in 10 cases, poorly differentiated/undifferentiated tumour in 08 cases, neuroendocrine differentiation in 4 cases and spindle cell morphology in one case. Out of 37 cases belonging to category 2 and 3, adenocarcinoma prostate (Figure 2) was the most common tumour with bone marrow metastases followed by adenocarcinomatous deposits from gastrointestinal tract including carcinoma stomach (Figure 3), colon and hepatobiliary system (Table 3). One case of known nasal alveolar rhabdomyosarcoma with increasing cytopenias while on treatment, showed extensive replacement of the bone marrow by metastatic deposits (Figure 4). Two cases of occult invasive ductal carcinoma of breast were detected first in the bone marrow, and the trephine biopsy tissue was used for assessment of Estrogen Receptor (ER), Progesterone Receptor (PR) and Her2Neu by immunohistochemistry (Figures 5 to 8). In 10 cases, all of which showed adenocarcinomatous deposits in morphology, no primary site of malignancy could be ascertained.

**Fig.2.** Metastatic adenocarcinoma Prostate with extensive osteosclerosis,**Fig.3.** Metastatic adenocarcinoma stomach, signet ring cells x400, H&E**Fig.4.** metastatic Alveolar Rhabdomyosarcoma, tumour cells seen in sheets and clusters separated by thin fibrovascular septa, occasional tumour giant cells seen, x 400, H&E**Fig. 5.** Metastatic invasive ductal carcinoma Breast, x400, H&E

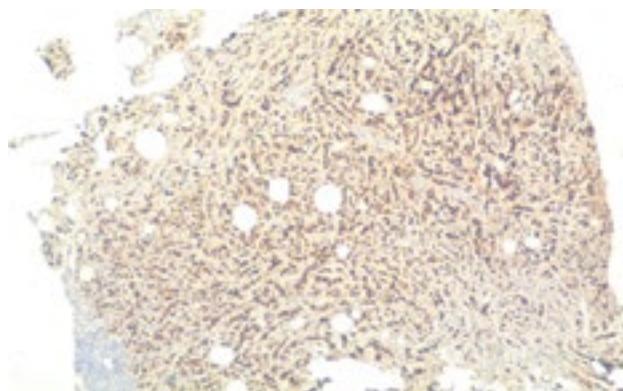


Fig.6. Diffuse strong nuclear positive Allred score 8, immunohistochemistry for ER (Estrogen Receptor)

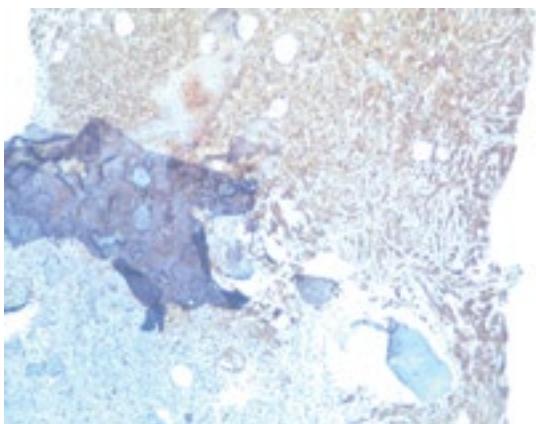


Fig.7. Diffuse strong membranous positive, score 3+, Immunohistochemistry for Her2Neu

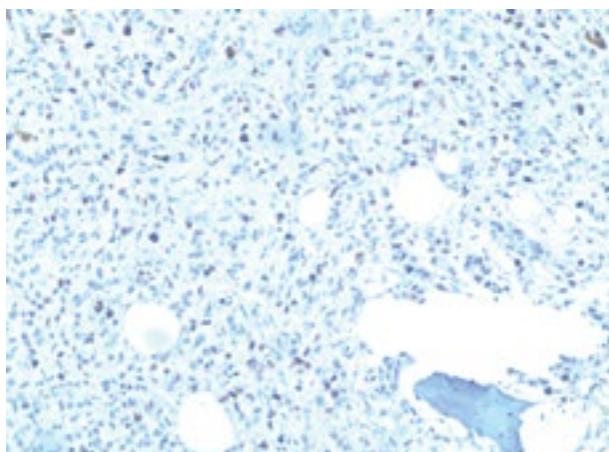


Fig.8. Multifocal nuclear positivity Allred score 6, Immunohistochemistry for PR (Progesterone Receptor)

Tumour burden and stromal changes were analysed in the trephine biopsies. Necrosis was present in 14 cases, and ranged from focal areas of necrosis comprising of less than 10% of marrow spaces to as extensive as 90% of the entire trephine biopsy. Fibrosis grade 2/4 and above was noted in 31 cases out of which osteosclerosis was present in 20 cases. Residual hematopoietic elements were reduced in majority of the cases (n=31), while some showed reactive eosinophilia (n=08), plasmacytosis and megakaryocytic clustering.

DISCUSSION

Bone marrow is an important site of involvement in patients with disseminated solid tumours, but it is uncommon as a presenting sign of the disease [10]. With the advent of whole body PET/CT scans, staging of tumours has become relatively easier and precise, and use of bone marrow procedure routinely has been questioned. However its availability, especially in developing countries remains a logistic issue. In this scenario, utility of bone marrow trephine biopsy for assessing the spread and staging of solid tumours cannot be underscored. Sometimes, detection of marrow metastases gives the first clue to presence of a neoplastic condition elsewhere [11]. In such scenario, it becomes utmost important to ascertain the morphological type and tissue of origin, because a specific and directed therapy may exist and can be beneficial even in the face of metastatic disease [4]. Also, bone marrow aspiration and biopsy is more widely used for detection of bone marrow metastasis as the tissue can be further utilized for immunohistochemistry.

Marrow involvement due to diffuse hematogenous spread of the tumour results in cytopenias, predisposing to bleeding and infection. Cytopenias also further complicates anti-neoplastic treatment, as almost all chemotherapeutic agents lead to reduced blood cell counts [5]. All these factors add up to yield a worse prognosis for the patient who has BM metastasis. We encountered cytopenias in all but 9 (16.9%) cases. So, metastases can still be kept as a differential diagnosis with relevant clinical findings, even with normal hemogram. Out of 53 cases leucoerythroblastic blood picture was seen in 17 cases (32%), though it is said to be the commonest presentation of metastases to the bone marrow. Contreras, et al. and P. Mishra, et al. found leucoerythroblastic reaction in 22% and 26% of their cases [7, 9].

Most of the cases with bone marrow metastases posed difficulty during aspiration and smears were aperturate. Extensive

Tab. 3. Primary malignancies detected in cases belonging to Category 2 and 3 of table1

Serial Number	Cancer Types	Category
1	Carcinoma Prostate	12
2	Adenocarcinoma (GIT, hepatobiliary)	6
3	Adenocarcinoma breast	2
4	Metastatic Neuroendocrine Tumors (NET)	2
5	Carcinoma parathyroid	1
6	Carcinoma thyroid	1
7	Renal cell carcinoma	1
8	Adenocarcinoma unknown primary	10
9	Neuroblastoma	2

marrow fibrosis and hypercellularity have been proposed as mechanisms to account for the inability to withdraw marrow by aspiration [12].

All the 37 cases belonging to category 2 and 3 (Table 1) had no known malignancies at the time of performing bone marrow study. Under category 2 (15 cases), were the cases which showed multiple lytic lesions on radiological investigations and had a clinical suspicion of metastases versus myeloma. Altogether 22 cases (category 3a and 3b) were evaluated with a primary suspicion of a hematopoietic neoplasm leading to cytopenias and lymphadenopathies. Out of these cases, adenocarcinoma prostate was the most common tumor presenting first with bone marrow metastases followed by adenocarcinomatous deposits of gastrointestinal tract origin (Table 3). Ozkalemkas, et al. in their study described adenocarcinoma gastrointestinal tract (42%) as the most common cause of bone marrow metastases [8]. Mohanty, et al. in their study population, revealed neuroblastoma (100%) in pediatric population and prostatic adenocarcinoma (48%) in adult population as the most common malignancy metastasising to bone marrow respectively ^{13}P . Mishra, et al. in their study, described neuroblastoma and Ewing's sarcoma (40% each) as the most common tumour metastases to bone marrow in children and adenocarcinoma of GI tract (30.7%) as the commonest cause of marrow metastases in adults [9].

Mohanty, et al. described a number of features like presence of osseous metaplasia, necro inflammatory reaction, desmoplasia and granulomas which could be associated with bone marrow metastasis and their presence should raise a suspicion of metastases elsewhere, if not detected in the same slide [13]. In our study, out of 53 cases, osseous changes like new bone formation and Fibrosis grade 2/4 and above was noted in 20 cases and osteosclerosis was present in 21 cases. Residual hematopoietic elements were reduced in majority of the cases (n=29). Reactive eosinophilia (n=08), plasmacytosis and megakaryocytic clustering (n=16) were noted in the rest of the cases.

CONCLUSION

Bone marrow metastases by non-hematopoietic neoplasms can be the first presenting feature in many cases as seen in our study. So, performing a trephine biopsy routinely along with aspiration for any unexplained cytopenias is of paramount importance in clinching the primary diagnosis. However, identifying marrow metastases and predicting the possible primary sometimes poses a diagnostic challenge to the pathologist and needs extensive use of ancillary studies like immunohistochemistry and relevant radiological workup [14]. However, it may be a limiting factor especially, in resource poor settings. Therefore careful scrutiny of morphology to enable a judicious use of markers can help in solving these diagnostic dilemmas.

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