Nigerian Medical Journal
NIGERIA MEDICAL ASSOCIATION
Print ISSN 0300-1652, E-ISSN 2229-774X

Original Research

Undesirable occupants of bone marrow creating a menace: A 4.5-year audit from a tertiary care centre in Eastern India.

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Abstract

Background: Bone marrow (BM) in addition to being the origin of primary hematological malignancies is also commonly involved in metastatic solid tumors. Bone marrow examination includes aspiration and biopsy, and it is a well-known procedure not only to diagnose hematological malignancies but also for staging and prognosis of various solid tumors. The presence of metastasis in the bone marrow is of grave prognostic significance and it is imperative to rule out marrow involvement in any malignancy where curative treatment is considered. The study's objectives were to evaluate the clinical, hematological, and biochemical characteristics of patients with BM metastases of solid tumors diagnosed by bone marrow (BM) aspiration and trephine biopsy and to find out the accuracy rate of diagnosing metastatic infiltration between bone marrow aspiration, trephine imprints, and trephine biopsy procedures.
Methodology: It was a 4.5-year retrospective hospital-based observational study where relevant clinical, biochemical, and hematological parameters including bone marrow aspirate and biopsy were analyzed and compiled from hospital medical records.
Results: The total number of BMA and trephine biopsies that came during the duration of 4.5 years were 3850 and 2980 respectively. Out of the 3850-bone marrow aspiration and 2980 trephine biopsies received in the dept of Hematology, 305 cases were referred to look for metastatic bone marrow infiltration. Out of these 305 cases, 69 cases showed the presence of metastatic deposits (12.6%). 45 patients (65.2%) were males, and 24 patients (34.7%) were females with M:F ratio of 1.8:1. Most common age group was 51-60 years (31.8%). The most common complaints were fever, body aches, weight loss, and weakness. Clinical examination revealed pallor in 38 out of 69 cases (55%) and organomegaly in 14 cases (20.2%). Microcytic hypochromic anemia (26%) was the most common finding on peripheral blood smear examination followed by pancytopenia (18.8%). The biochemical findings most commonly observed were raised LDH (60.8%), serum PSA (36.3%), and alkaline phosphatase (21.7%)
Conclusion: Trephine biopsy is a sensitive method for detecting marrow metastasis and should be done in all cases being investigated for this purpose. BMA alone may miss marrow metastases in almost half of cases. Trephine imprint cytology is more sensitive than BMA and can provide rapid diagnoses while waiting for trephine biopsy results.

Keywords: *Bone Marrow Aspiration, Bone Marrow Trephine Biopsy, Metastasis, Solid Tumors, Bone Marrow Imprint Smear.*

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How to cite: Jamal I, Smita S, Raman RB, Choudhary V, Atreya K, Choudhary MK, Rajan A. Undesirable occupants of bone marrow creating a menace: A 4.5-year audit from a tertiary care centre in Eastern India. Niger Med J 2024;65(6):1101-1111. https://doi.org/10.60787/nmj.v65i6.574.

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Introduction:

The bone marrow, in addition to being the primary site of origin for hematological malignancies is also commonly involved in metastatic solid tumors. Bone marrow examination includes aspiration and biopsy, and they are well-known procedures to diagnose hematological malignancies.[1] Besides diagnosis, the bone marrow examination is a commonly employed tool for staging and prognosis of various solid tumors. In a few cases, the demonstration of tumor cells in marrow might be the first available evidence of malignant solid tumors. The malignancies of the prostate, breast, lungs, kidney, thyroid, and gastrointestinal tract in adults and small blue round cell tumors like neuroblastoma and rhabdomyosarcoma in children are the primary tumors that frequently involve the bone marrow. The presence of metastasis in the bone marrow is of grave prognostic significance and it is imperative to rule out marrow involvement in any malignancy where curative treatment is considered. [2] Bone marrow aspiration is a cost-effective method of reporting metastasis in a very short span of time.[2] Here, we present a hospital-based observational study spanning over a period of 4.5 years where bone marrow metastasis by solid organ malignancies was analyzed.

The objectives of this study were to evaluate the clinical, hematological, and biochemical characteristics of patients with BM metastasis of solid tumors diagnosed by bone marrow (BM) aspiration and trephine biopsy and to find out the accuracy rate of diagnosing metastatic infiltration between bone marrow aspiration, trephine imprints, and trephine biopsy procedures.

Methodology:

Study design: A retrospective 4.5-year **(**June 2019 to December 2023) observational study conducted at a tertiary care centre in Bihar, India.

Place of study: The study was carried out in Hematology section of the Department of Pathology of a tertiary care institute in North Eastern India.

Study Population: All patients coming to the Hematology section with presence of metastatic deposits in bone marrow aspiration or trephine imprints and or bone marrow biopsy.

Inclusion criteria: All patients presenting with relevant clinical features and bone marrow findings suggestive of the presence of metastatic infiltration by any solid malignancy in bone marrow. Patients who gave consent for the study and all cases where detailed clinical, biochemical, and hematological records were available.

Exclusion criteria: Patients whose bone marrow examination showed the absence of metastatic deposits in bone marrow; patients on prior chemotherapy or radiotherapy; cases without documented clinical and hematological records and cases showing bone marrow infiltration by hemato-lymphoid malignancies.

Sample collection and parameters estimation:

This study was conducted retrospectively by looking at archival records and bone marrow aspiration and biopsy slides over a period of 4.5 years. Bone marrows were sent for either refractory anemia or pancytopenia or for staging of the tumor. The age, sex, chief complaints, physical examination, lymph node status, relevant biochemical findings, and peripheral blood smear findings were retrieved and tabulated.

The radiological findings (X-ray, ultrasonography, or Computed Tomography (CT) findings) wherever available were also noted. Biochemical investigations mostly included serum calcium, lactic acid dehydrogenase (LDH), alkaline phosphatase (ALP), and serum tumor markers like PSA level, CA19-9, CEA, and CA-125 and they were also correlated as and when applicable. The peripheral blood smear,

BMA, trephine imprint smears, and trephine biopsy smears (minimum 2 slides each) were reviewed. BMA and imprint smears were stained with Leishman stain. The trephine biopsy sections were stained with routine hematoxylin and eosin (H&E). Special stains like reticulin, PAS, PAS-D and immunohistochemistry were done as per the requirement. The changes in adjacent bony trabeculae and stromal matrix were also evaluated along with the morphology of tumor cells.

All procedures in the present study were approved by the Institutional ethical committee/review board of our institute. (2034/IEC/IGIMS/2023).

Results: The total number of BMA cases was 3850 while trephine biopsies and touch imprints were 2980 that came during the duration of 4.5 years. Out of the 3850-bone marrow aspiration and 2980 touch imprints and trephine biopsies received in the dept of Hematology, 305 cases were referred to look for metastatic bone marrow infiltration. Out of these 305 cases, 69 cases showed the presence of metastatic deposits (12.6%). The male-to-female ratio was 1.8:1 with 65.2% of patients being males and the rest 34.2% being females.

The most common age group was 51-60 years (31.8%) 14 cases were in the pediatric age group (20.2%) with an age range of 1.2 years to 11 years. Among the pediatric age group, boys had a higher incidence 59.4% as compared to girls. 3 cases (4.3%) were in the adolescent age group. (Table 1)

Table1: showing the distribution of metastatic solid tumors among various age groups.

Age range (in years)	**No. of cases**	**% by age group**
0-10	12	17
11-20	05	7.2
21-30	01	1.4
31-40	05	7.2
41-50	08	11.5
51-60	22	31.8
61-70	13	18.8
>70	03	4.3

The most common complaints were fever, body aches, weight loss, and weakness. Clinical examination revealed pallor in 38 out of 69 cases (55%) and organomegaly in 14 cases (20.2%). Radiological findings were available in 18 cases at the time of bone marrow examination.

Microcytic hypochromic anemia (26%) was the most common finding on peripheral blood smear examination followed by pancytopenia (18.8%). (Fig. 1).

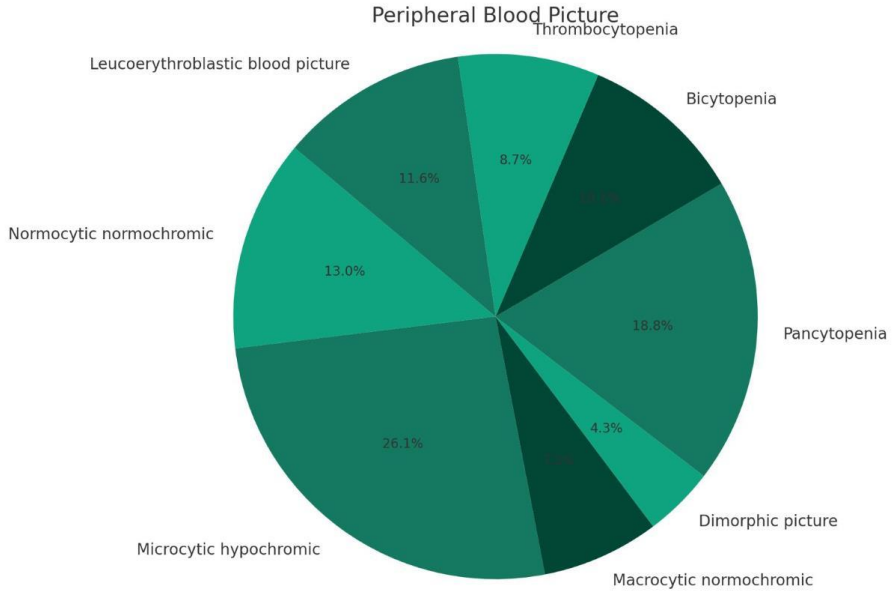

Fig 1: pie-chart showing hematological features observed in various metastatic solid tumors.

The biochemical findings most observed were raised LDH (60.8%), serum PSA (36.3%), and alkaline phosphatase (21.7%). (Fig.2)

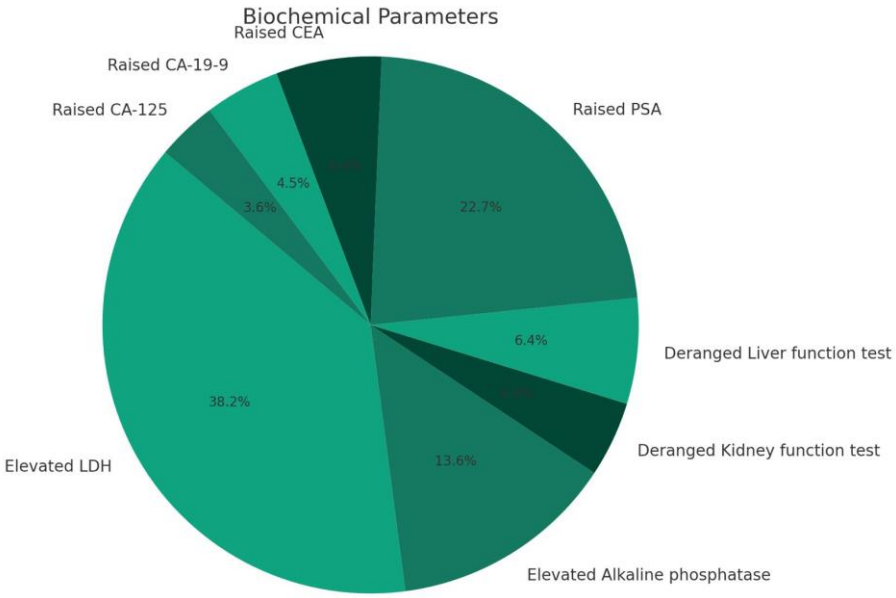

Fig 2: pie-chart showing biochemical parameters in various metastatic solid tumors infiltrating bone marrow.

Bone marrow examination:

Bone marrow aspirate smears were cellular in 82% of the cases and hemodiluted in the remaining. Trephine imprint smears were prepared in all BM biopsy cases with 20% being paucicellular and the rest variably cellular. The morphology of tumor cells on imprints varied depending on the morphology of primary malignancy. In 55 hemodilute smears, trephine imprints were made in 32 cases where the majority (73%) showed the presence of either singly scattered or loose clusters of malignant cells. All bone marrow biopsies met the required criteria for adequacy as per the International Council for Standardization in Hematology (CSH)guidelines. The length of trephine biopsies ranged from 0.8 cm to 5 cm with an average length of 2.5 cm. Of these, 45.4% showed diffuse replacement of the marrow by tumor cells with focal involvement in the remaining 54.6%. Trephine biopsy was found to be the most sensitive technique, and it demonstrated marrow metastasis in all 69 cases with a sensitivity of 100%followed by bone marrow imprint (BMI) with a sensitivity of 91.3% (63/69). BMA was less sensitive with a detection rate of 73.9 51/69). In 6 cases there was discordance between BMI smears and bone marrow biopsy. Immunohistochemistry was done only in 8 cases due to financial constraints of the patients. 2 cases of metastatic prostatic carcinoma showed marked fibrosis on trephine biopsy.

Among the pediatric tumors, the most common solid tumor to metastasize to bone marrow was Retinoblastoma accounting for 11.6% of all the cases closely followed by 8.6% cases of Neuroblastoma.

Among adolescents,3 cases were of metastatic Ewing's tumor and one case of small cell sarcoma of the urinary bladder.

Metastatic carcinoma prostate was the most common malignancy diagnosed in adult males(39.1%) followed by gastrointestinal malignancy (10.1%).In females, metastasis from breast carcinoma was most commonly observed accounting for 7.2% of all cases. (Fig. 3, fig 4)

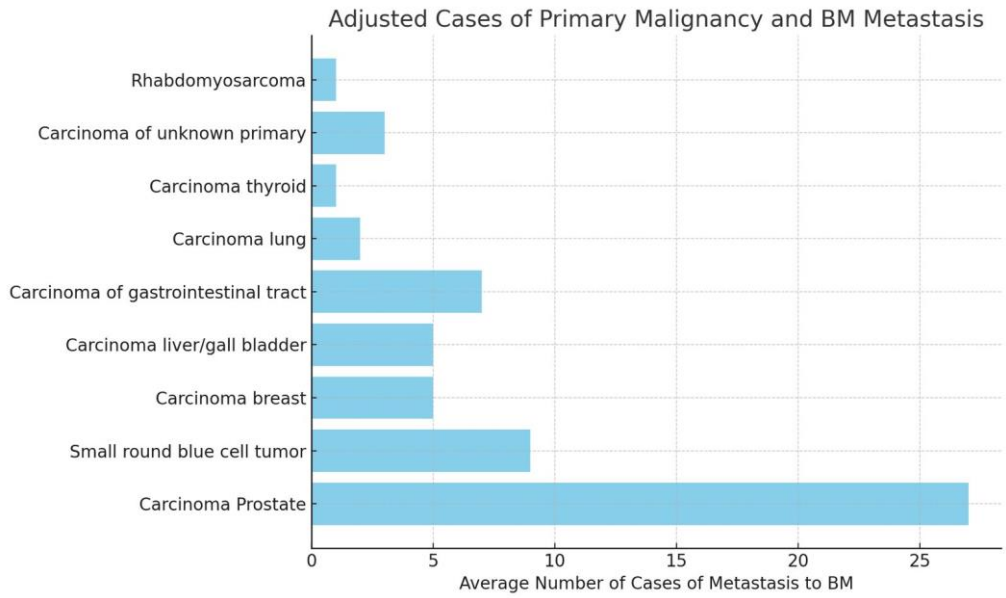

Fig 3: bar diagram showing the frequency of various primary solid malignancies metastasizing to bone marrow

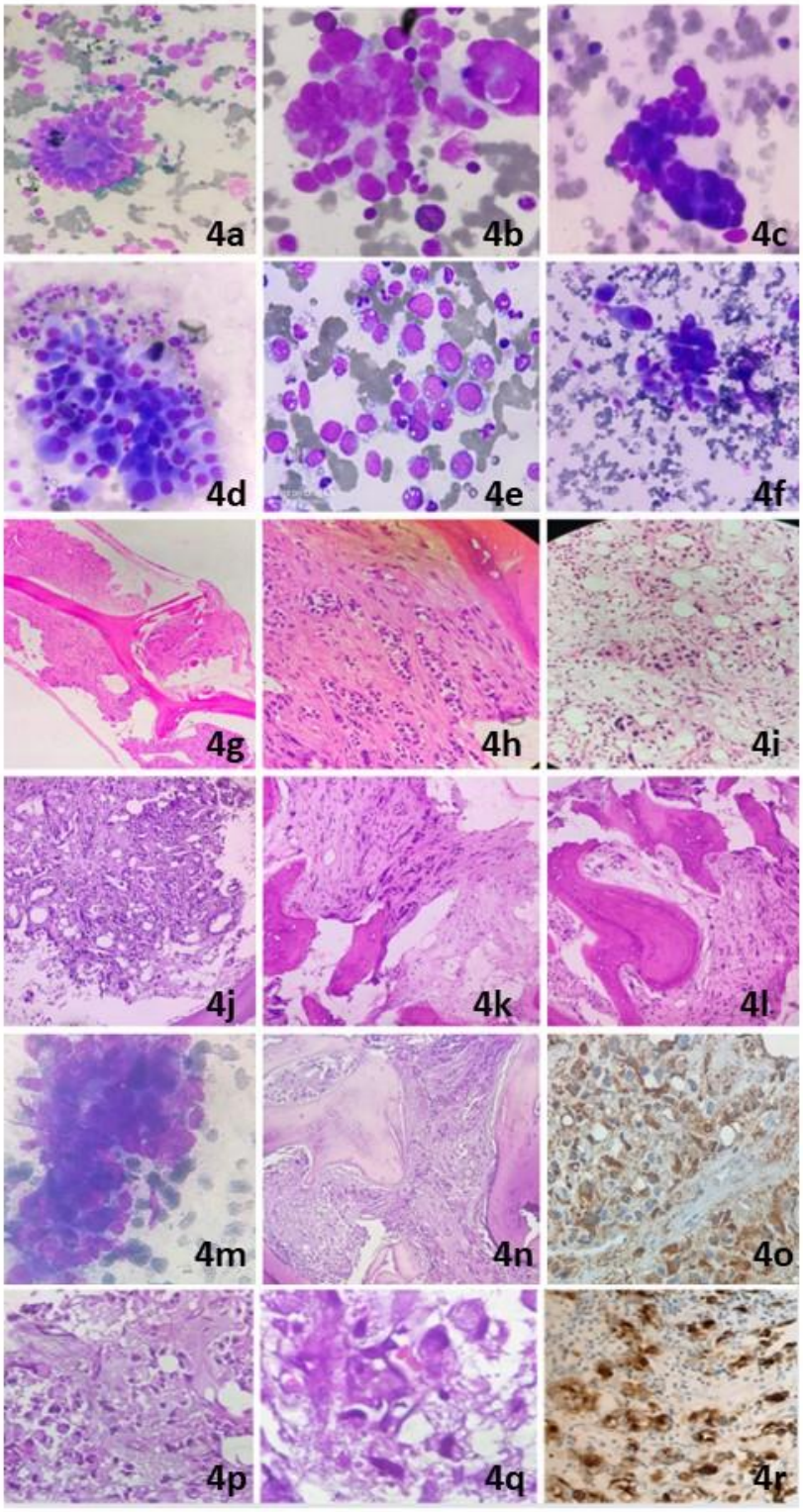

Fig 4a-Microphotograph of bone marrow aspiration showing metastatic deposit of neuroblastoma (Leishman stain; x 40X)

Fig 4b -Microphotograph of bone marrow aspiration showing presence of metastatic deposit of invasive breast carcinoma (Leishman stain; x 100X)

Fig 4c- Microphotograph of bone marrow aspiration showing presence of metastatic deposit of adenocarcinoma colon (Leishman stain; x 40X)

Fig 4d- Microphotograph of bone marrow aspiration showing presence of metastatic deposit of adenocarcinoma lung (Leishman stain; x 40X)

Fig 4e- Microphotograph of bone marrow aspiration showing metastatic deposit of round cell sarcoma of the urinary bladder of a 20-year-old boy presenting with urinary obstruction (Leishman stain; x 100X)

Fig 4f- Microphotograph of bone marrow aspiration showing metastatic deposit of rhabdomyosarcoma of left shoulder Inset shows fibromyxoid matrix. (Leishman stain; x 40X).

Fig 4g- Microphotograph of bone marrow trephine biopsy showing metastatic infiltration by invasive breast carcinoma. (H &E stain; x10X)

Fig 4h- Microphotograph of bone marrow trephine biopsy showing metastatic infiltration by adenoacarcinoma lung. (H &E stain; x10X)

Fig 4i- Microphotograph of bone marrow trephine biopsy showing metastatic infiltration by Neuroblastoma. (H &E stain; x10X)

Fig 4j- Microphotograph of bone marrow trephine biopsy showing metastatic infiltration by adenocarcinoma colon. (H &E stain; x40X)

Fig 4k- Microphotograph of bone marrow trephine biopsy showing metastatic infiltration by invasive breast carcinoma with associated fibrosis. (H &E stain; x10X)

Fig 4l: Microphotograph of bone marrow trephine biopsy showing metastatic infiltration by prostate adenocarcinoma with osteosclerotic changes in bony trabeculae. (H &E stain; x40X)

Fig 4m: Microphotograph of bone marrow biopsy trephine imprint smear showing the presence of malignant epithelial cells in clusters having high N/C ratio, scanty cytoplasm, and hyperchromatic nuclei. (Leishman stain; x40X)

Fig 4n: Microphotograph of bone marrow biopsy showing the presence of diffuse infiltration of single cells with fibrosis and sclerotic bony trabeculae (H & E; x 100X)

Fig 4o: Microphotograph of bone marrow biopsy showing infiltration by signet cells having abundant eosinophilic cytoplasm and eccentrically located hyperchromatic nuclei (H & E; x40X)

Fig 4p: Microphotograph of bone marrow biopsy showing signet cells in higher magnification (H&E; x100X)

Fig 4q: IHC microphotograph of metastatic prostatic carcinoma showing anti-PSAP positivity (DAB; x 40X)

Fig 4r: IHC microphotograph of metastatic prostatic carcinoma showing EMA positivity (DAB; x40X)

Discussion:

Primary solid tumors do not usually cause early death of the patient if treated properly and timely. But, once the tumor cells reach and get established in various organs, the mortality of the patient increases markedly. [3,4] The different tumors have their distinct pattern of dissemination. This is due to the anatomical and mechanical structure in the human body which results in the organ preference of tumor metastasis. The communication between the detached tumor cells and the distant microenvironment is crucial for the progression of metastatic deposits.[5,6] Bone marrow (BM) involvement by metastasis is the most common malignancy of bone, far more than primary bone malignancies.[7] The bone has been placed overall as the third most common site of malignancy after the lungs and liver and is the most common site of metastasis from primary breast and prostate carcinomas.[5] In accordance with the study done by Mehdi et al[8], and Mohanty et al[9], we also found that prostate carcinoma was the most common solid tumor metastasizing to the bone marrow in adult males (39.1%) followed by gastrointestinal

malignancy (10.1%).[8,9] However Mehdi et al. reported in the same study that metastasis of breast carcinoma in females was not that common in their part as compared to India.[8] In our study bone marrow involvement by metastasis from breast carcinoma was most common among females (7.2%). In the pediatric cases, the most common solid tumor metastasizing to marrow was retinoblastoma (11.6%) followed by neuroblastoma (8.6%) which is in accordance with the study done by Kumar et al [10]; where all paediatric cases that were positive for metastasis had infiltration by small round cell tumor only [10] the most common tumor metastasizing was neuroblastoma in that study. There was one case in which it was challenging to identify the morphology of tumor cells that were singly scattered and resembled blasts but on IHC they turned out to be metastatic rhabdomyosarcoma.

Among adolescents, 3 cases were of metastatic Ewing's tumor and one case of small cell sarcoma of the urinary bladder was found in our study. Many studies have been done in the past in emphasizing the significance of BMA, BMI, and bone marrow biopsy in diagnosing bone marrow involvement in various hematological and non-hematological disorders. [11-13] The present study observed that the diagnostic accuracy of bone marrow biopsy was highest (100%) followed by BMI (91.3%). This contrasts with other studies where BMI cytology was found to be of limited value except in cases of dry tap.[14] However, the studies done by Chandra et al [15]. and Donald et al [16], were in support of our findings where on comparative evaluation of BMA, BMI, and bone marrow biopsy, bone marrow biopsy topped the rank in terms of diagnostic accuracy closely followed by BMI.[15,16] Although another study[17] have shown that trephine biopsy was 2.6 times positive compared to BMA for the detection of metastasis they also showed the significance of meticulously prepared BMI smears where the diagnostic accuracy rate increased.[17] In our study, only 6 cases showed discordant results between BMI and trephine biopsy and it was due mostly due to haemorrhagic trephine biopsy obtained that was rolled on the slides to get BMI smears. Some authors also suggested that the detection of metastatic cells on BMI in suspected cases can be increased by performing bilateral bone marrow examination which can detect focal marrow involvement. [15,16] Although bone marrow biopsy is the best way to study the topographical arrangement of tumor cells this could also be done to some extent through meticulously prepared BMI smears as well. [17] This can be done not only by gentle touch of the biopsy core on the slides to prevent crushed artefacts but also by preparation of touch smears by gently rolling the core. Another precaution to be taken is to prevent getting hameorrhagic biopsies which dilute BMI, and the touch smears show plenty of red blood cells in the background obscuring the true picture.[18] The study of BMI smears also avoids unnecessary delay caused by decalcification and processing of trephine biopsy sections. The bone marrow contains various cells comprising of hematopoietic origin and cells involved in bone formation and remodeling. BM metastasis upgrades any solid tumor, hence early detection is the mainstay for treatment. [8,9] Recently radiological studies have established PET/CT and PET/MRI as sensitive modalities for diagnosing bone involvement. However, confirmation of the suspected cases requires bone marrow and histopathological examination including immunohistochemistry (IHC) wherever needed. [10-12] Moreover, in view of the huge cost of these modalities, particularly in developing countries, bone marrow examination is a preferred investigation as it is a simple, rapid, economical and, yet effective procedure for diagnosis of the disease. [13,14]

In addition, it is also useful as an important tool for prognostication and to detect an unknown primary in case of a patient presenting with pathological fracture with no detectable primary lesion [using techniques like IHC and FISH, etc].[15-17] Primary solid tumors are the source of metastatic deposits and hence relapse of the disease process. Therefore, the detection of these cells is significant regarding staging, prognosis, and therapeutic decision. The presence of detached tumor cells in BM has been correlated with a poor prognosis.[18] The recent published papers on BM metastasis have encouraged more research in order to establish the exact mechanism of cross talk between malignancy and BM microenvironment. Although BMA gives reliable information in the majority of the cases regarding presence of metastasis,

trephine biopsy along with IHC is pertinent in establishing the definitive diagnosis of BM metastasis particularly in difficult cases.[19-24]

In our study, 69 cases showed metastatic bone marrow infiltration by solid tumors after reviewing altogether 3850 bone marrow aspiration and biopsy cases. In concordance with previous Indian and international studies, we also found out that carcinoma prostate was the most common solid tumor to metastasize to bone marrow in adult males.[23] Metastasis from gastrointestinal and breast carcinoma were other common tumors observed.[22]

Tumor cell identification on morphology is a challenging task and needs ancillary tests like immunohistochemistry for confirmation.

Initially, the metastases were broadly classified into carcinomas and non-epithelial malignancies/sarcomas. Adenocarcinomas were the most common metastatic adenocarcinoma followed by poorly differentiated carcinomas. The prostate, gastrointestinal tract, and breast were the most frequent primary sites of metastatic carcinomas with known primary. In 12/69 cases there was no known primary site found at the time of bone marrow aspiration.

Metastatic non -epithelial tumors/sarcomas mostly affect children and young adolescents. The most common tumor was neuroblastoma followed by Ewing's sarcoma and retinoblastoma. Involvement by metastatic epithelial and non-epithelial tumors is depicted in Fig 4(a -r).

Figure 5 shows one rare case of metastatic signet cell carcinoma of the prostate involving the bone marrow where immunohistochemistry confirmed the prostate as the primary site.

In a few cases of metastatic adenocarcinomas, marked desmoplastic stromal response and fibrosis adjacent to the tumor cells were also noted. Adjacent bony trabeculae also revealed marked thickening with osteodysplastic changes in the form of hooks and spikes of bony trabeculae.

Trephine biopsy sections are advantageous over bone marrow aspiration (BMA) because they provide clearer morphology and patterns of marrow involvement. These sections can also be used for special stains and immunohistochemistry (IHC) to help identify the primary tumor in cases where it is unknown.[11] However, a downside of trephine biopsy is that it takes longer to report results due to the need for decalcification and processing.

BMA and trephine imprint cytology offer a quicker turnaround time compared to trephine biopsy. Early diagnosis through BMA and trephine imprint cytology can aid in planning further tests and treatment while waiting for trephine biopsy results. A study found that trephine imprints were more sensitive than BMA in detecting marrow metastases, indicating that preparing imprints is now standard practice in the institute.[24]

It is recommended to perform both aspiration and biopsy as they complement each other. This approach can be helpful when the tumor causes significant stromal fibrosis, leading to a dry tap. Some cases missed on trephine biopsy and imprint cytology were diagnosed on BMA due to the tumor's patchy distribution.[15]

Although bone marrow metastases are generally easy to identify, determining the exact primary site of origin may not always be possible. Additional tests like special stains and IHC may be needed. Stromal changes, such as fibrosis, were observed in about 10% of the cases, which is consistent with other studies in India[7-12]. Carcinomatous osteodysplasia was found in a significant number of cases, although less

frequently than in a study by Burkhardt et al.[18] These changes in the marrow can affect the material obtained from BMA, influencing its ability to detect marrow metastases.

Conclusion:

The study concludes that all three preparations of aspirate cytology, touch imprint cytology, and trephine biopsy complement each other for evaluating any bone marrow. Trephine biopsy is the most sensitive method for detecting marrow metastasis and should be done in all cases being investigated for detecting metastasis to the marrow. BMA alone may miss marrow metastases in a good number of cases. Trephine imprint cytology is more sensitive than BMA and can provide rapid diagnoses while waiting for trephine biopsy results. The significance of BMI cannot be overemphasized especially in conditions where there is a dry tap on BMA and when rapid diagnosis is needed.

Strengths and limitations of the study:

Clinical, hematological, and biochemical properties were analyzed with bone marrow aspiration, imprint cytology and trephine biopsy sections, highlighting the importance of correlation of these parameters in establishing a definitive diagnosis. Bone marrow imprint smears were also studied simultaneously, and it was observed that they could be of significant importance when bone marrow aspirate smears are hemodiluted and failed to show the presence of any metastatic deposit. However, immunohistochemistry was not done in all bone marrow metastatic cases due to financial and resource constraints which was one significant limitation of this study.

Implications: Considering the importance of BMI smears in the detection of bone marrow metastasis, a protocol should be made especially in low socio-economic countries like ours with limited resources in which BMI smears should be made in all cases where bone marrow examination is done and should be routinely evaluated. Since turnaround time for trephine biopsies is a bit longer, the efficacy of immunocytochemistry can be studied on BMI smears, and this could serve as a good topic to explore in future research studies.

Funding: Authors received no funding for the writing.

Conflict of interest: none

Acknowledgment: We would like to thank the study participants (patients) for their willingness to take part in the study and our laboratory technicians for their invaluable support.

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