https://doi.org/10.48047/AFJBS.6.Si4.2024.6402-6408

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Bone Marrow Infiltration by Solid Tumors: Clinical and Hematological Correlations in a Cross -Sectional Study

Dr. Meenakshi Mohapatro[1]*, Dr. Saswati Das[2], Dr. Kalyani Gouda[3], Dr. Phalgunee Priyadarshini[1], Dr. Yugosmita Patra[1], Dr. Pallavi Mishra[1], Prof. Lity Mohanty[4]

[1]Assistant Professor, Department of Pathology, SCB Medical College and Hospital, Behera Colony, Mangalabag, Cuttack, Odisha 753001, India
[2]Junior Resident, Department of Pathology, SCB Medical College and Hospital,Behera Colony, Mangalabag, Cuttack, Odisha 753001, India
[3]Professor, Department of Pathology, SCB Medical College and Hospital,Behera Colony, Mangalabag, Cuttack, Odisha 753001, India
[4]Professor and HOD, Department of Pathology, SCB Medical College and Hospital,Behera Colony, Mangalabag, Cuttack, Odisha 753001, India
Corresponding author-**Dr. Meenakshi Mohapatro***

Article History

Volume 6, Issue Si4, Sep 2024

Received: 15 July 2024

Accepted: 25 Aug 2024

Published: 05 Sep 2024

doi:10.48047/AFJBS.6.Si4.2024.6402-6408

Abstract: ***Introduction*:** The involvement of bone marrow by solid tumors signifies an advanced stage of disease and portends a grim prognosis. It is atypical for bone marrow metastases to be the initial manifestation of a solid tumor, particularly when the primary site of the neoplasm remains elusive despite clinical examination, laboratory testing, and imaging techniques. In such instances, a bone marrow examination can be pivotal for diagnosing the primary malignancy. ***Aims and Objectives*:** The study aimed to evaluate the pattern of bone marrow infiltration by various solid tumors and their correlation with clinical and hematological findings. ***Material and Methods*:** This retrospective cross-sectional study was conducted in the Pathology Department of SCB Medical College and Hospital over six months. Among 78 bone marrow aspirations and biopsies performed, 11 cases of bone marrow metastases from non-hematopoietic malignancies were encompassed in this study. ***Results*:** Of the 11 patients included, 8 were male and 3 were female, with ages ranging from 20 to 60 years. The predominant clinical manifestations were generalized debility, weight loss, body aches, and anorexia. The most frequent hematological finding was the coexistence of anemia and thrombocytopenia. The prevailing histological subtype was adenocarcinoma. After comprehensive evaluation, the primary focus was identified in eight patients, while the other three cases were categorized as tumors of unknown origin. ***Conclusion*:** Bone marrow is an important yet uncommon site for metastasis of solid tumors. Therefore, routinely performing a trephine biopsy along with aspiration for any inexplicable hematological abnormalities is crucial for establishing the primary diagnosis.

Keywords: Bone marrow, Metastases, Biopsy, Solid tumors.

INTRODUCTION

The discernment of bone marrow metastasis assumes paramount significance as it elucidates treatment methodologies. While the bone marrow typically serves as the primary site of origin for hematological malignancies, it is also commonly infiltrated by metastatic solid tumors. In adults, the routinely involved tumors are carcinoma of the prostate, breast, lungs, kidney and gastric, though any tumor that give rise to blood borne metastases may involve the marrow. Notable metastatic solid tumors encountered in children include neuroblastoma, rhabdomyosarcoma, medulloblastoma, and retinoblastoma [1-3]. Despite extensive investigations, the primary site often remains occult in the majority of cases [4]. Although bone marrow involvement is typically surmised via imaging, bone marrow aspiration and biopsy examination remain the most efficient modalities for confirming marrow involvement. This study delves into the pathological findings in patients with marrow metastasis from solid tumors.

Materials and Methods

This descriptive cross-sectional study entailed a retrospective analysis of bone marrow aspiration smears and biopsies received at the Department of Pathology of a tertiary care institute over a 6-month period. The hematological malignancies involving bone marrow were excluded. Clinical characteristics, including age, sex, presenting symptoms, and clinical examination findings, were meticulously documented. Biochemical investigations such as serum calcium, lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) were available for some cases. All procedures were conducted with due informed consent from the patient's attendant. Two milliliters of blood samples were collected in EDTA vials and analyzed using an autoanalyzer to ascertain hematological parameters. The bone marrow aspirates and biopsies were collected from posterior superior iliac spine using Jamshidi needle. Six to ten smears were meticulously prepared using the push and squash technique. The peripheral smear, BMA and trephine biopsy imprint smears were stained with Leishman stain. The trephine biopsy section were stained with routine H & E section and reticulin stain. Immunohistochemistry were performed in eleven cases to confirm the primary. IHC panel was selected depending upon the clinical history and morphology.

RESULTS

Out of 78 bone marrow examinations conducted at our institute, 23 were undertaken for suspected metastatic bone marrow infiltration by solid malignancies. Out of these, 11 patients revealed metastasis by nonhematologic malignancies, accounting for 14.1% of samples.

The age range of the affected individuals spanned from 20 to 60 years, with the majority being males in the adult age group .Predominant clinical findings at presentation encompassed generalized weakness, weight loss, back pain, and loss of appetite. The most prevalent laboratory findings included peripheral cytopenias and a leukoerythroblastic blood picture. Among cytopenias, anemia emerged as the most common abnormality, followed by thrombocytopenia and leukopenia. Peripheral smear revealed a leukoerythroblastic blood picture in 5 patients (45.4%). Microcytic hypochromic anemia was seen in 3 patients (27.3%). A single case showed neutrophilic leukocytosis and the remaining two showed normal smear (Table 1). Hemoglobin level in these patients ranged from 5.2 to 14 g/dl, total WBC count from 3200 to 22,000 cells/cumm and platelet 1.4-4.5 lakhs/cumm. In seven cases, there was evidence of tumor cells in both aspirates and touch imprints. Additionally, in other four cases, there was no evidence of tumor cells in aspirates as well as touch imprints, though the bone marrow biopsy sections showed presence of tumor deposits.Aspirates were hypocellular in eight cases and normocellular in three cases. Megakaryocytes were not seen in four cases. Of the 11 cases, where both bone marrow aspirate and biopsies were done, 7 cases showed malignant cells in both. Adenocarcinoma emerged as the most common histological subtype. IHC was done on all bone marrow biopsy section and was diagnostic in 9 cases. Among the eleven cases, four patients presented with lung carcinoma, three patients presented with gastric carcinoma while two patients were diagnosed with breast carcinoma subsequent to the identification of bone marrow metastasis and immunohistochemistry. The remaining two cases were classified as tumors of unknown origin despite exhaustive investigations. Fibrosis emerged as the most common stromal change observed in this study.

Table 1: Peripheral smear, bone marrow aspirate and bone marrow biopsy findings

Case No.	P/S Findings	BM Aspirate Smear Findings			Bone Marrow Biopsy Findings
		Cellularity	Megakaryocytes	Malignant Cells	Morphology
01	Leukoerythroblasticbloodpicture	Hypocellular	Seen	Malignantcells singly placed as well as in clusters forming acini.	Malignant cells in glandular forms,cordsand tubules in a desmoplasticstroma.
02	Normal smear	Cellular	Seen	Reactive marrow	Single and clusters of

					malignant cells seen.
03	Microcytic hypochromic anaemia	Hypocellular	Seen	Occasional atypical cells seen.	Moderately pleomorphic malignant cells in clusters and singly.
04	Leukoerythroblastic blood picture	Hypocellular	Seen	Reactive marrow	Nests of malignant cells witheosinophilic cytoplasm with high N:Cratioandhyperchromatic nucleus.
05	Microcytic hypochromic anemia	Cellular	Seen	Few clusters of hyperchromatic cells with scant cytoplasm.	Malignant cells with high N:Cratio,molding and marked crushing artifacts.
06	Leukoerythroblastic blood picture	Hypocellular	Not seen	Clusters of bizzare cells with moderate cytoplasm and hyperchromatic nucleus	Sheets of malignant cells with plasmacytoid morphology and eosinophilic cytoplasm.
07	Normal smear	Hypocellular	Not seen	Reactive marrow	Clusters of malignant cells with scant cytoplasm and nuclear molding.
08	Leukoerythroblastic picture with circulating atypical cells .	Hypocellular	Not seen	High N:C ratio cells in clusters and singly seen.	Diffusely arranged cells with eosinophilic cytoplasm and prominent nucleoli.
09	Microcytic hypochromicanaemia	Hypocellular	Seen	Large pleomorphic cells present in clusters and singly with moderate eosinophilic cytoplasm having prominent nucleoli.	Diffusely arranged cells with high N/C ratio ,nuclear molding in a desmoplasticstroma.
10	Neutrophilic leukocytosis	Cellular	Seen	Reactive marrow	Malignant cells singly placed as well as in clusters forming acini
11	Leukoerythroblastic picture	Hypocellular	Not seen	Clusters of malignant cells with moderate eosinophilic vacuolated cytoplasm,clumped chromatin and multiple conspicuousnucleoli.	Glands and cords of cells with high N:C ratio in a desmoplasticstroma.

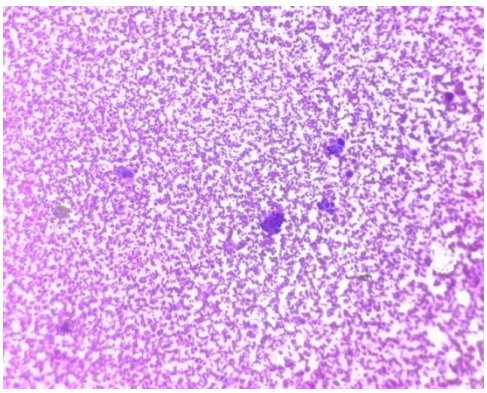


Figure 1a :Aspirate [illegible] 40x ,Leishman)

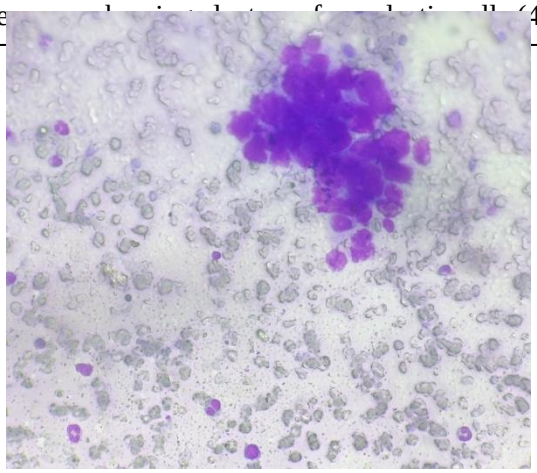


Figure 1a :Aspirate smear showing clusters of neoplastic cells (40x ,Leishman)

Figure 1b: Aspirate smear showing foci of cluster of neoplastic cells(400x, Leishman)

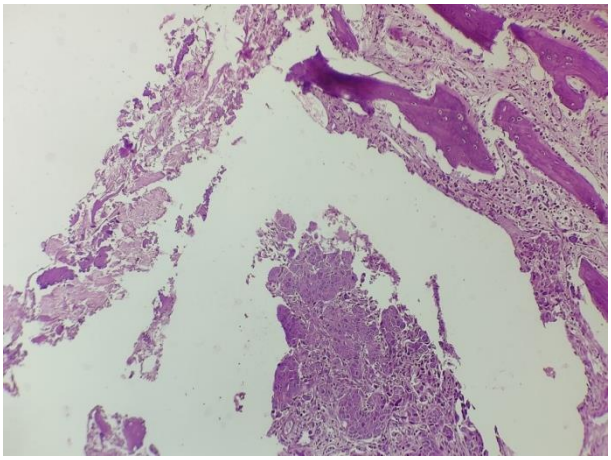
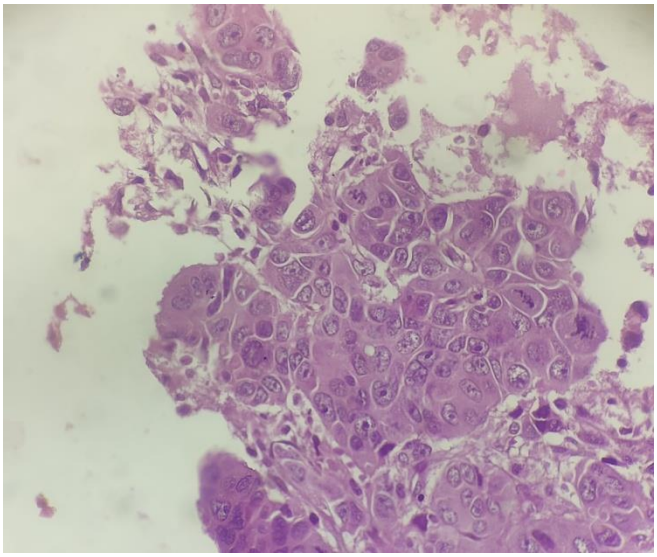


Figure 2a: Trephine biopsy showing clusters of malignant cells (100x,H&E)



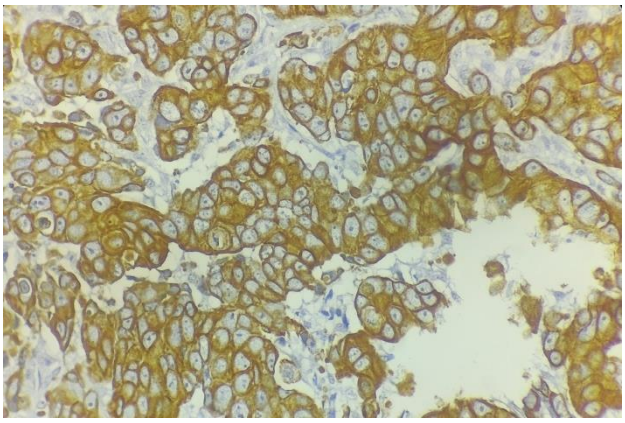


Figure 2b: Bone marrow is involved by clusters of malignant cells with hyperchromatic nuclei, prominent nucleoli

Figure 3: Tumor cells showing strong membranous positivity for CK7 (400X)

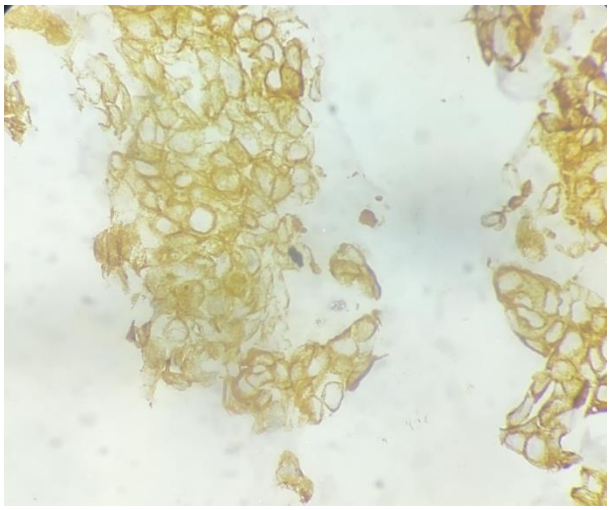


Figure 4 : Tumor cells showing strong membranous positivity for CK20 (400X)

DISCUSSION

While bone marrow metastases are commonly observed in patients with disseminated solid tumors, they are infrequently encountered as a presenting sign [5]. There are instances wherein bone metastasis by malignant tumors may evade detection by bone scans or advanced radiography techniques, which are also very expensive and only accessible at advanced medical centers. Consequently, bone marrow examination, a relatively simple and cost-effective procedure, retains its pivotal role in the diagnosis and prognostication of cancer patients [6-8]. The metastatic process is a multiphase cascade which includes local invasion, migration from primarytumor, intravasation into blood capillaries, survival in circulation, extravasation, colonization and proliferation in distant organs [9, 10]. The factors contributing to marrow metastasis are poorly defined. Nevertheless, this process can be interpreted by unique marrow environment that is rich in adhesion molecules, cytokines, chemokines and growth factors [9-11]. Cytokines such as IL-16, IL-11, and TNF-α appear to play a contributory role in metastasis, particularly within the bone and bone marrow milieu.

Identical to other studies, the common hematological abnormalities observed in this study were anemia,

leucoerythroblastic blood picture and thrombocytopenia [12, 13]. The infiltration of extramedullary tumor cells into the bone marrow disrupts the normal hematopoietic system, precipitating the proliferation of cancerous cells [14. These observations resonate with the work of Ozkalemkas*et al*., who documented the prevalence of anemia and thrombocytopenia across all cases they examined. Hence, it is prudent to conduct a thorough examination of the bone marrow for foreign cells when encountering unexplained hematological anomalies.

One of the merits of bone marrow aspiration (BMA) and trephine imprint cytology over bone marrow biopsy lies in their minimal turnaround time, facilitating prompt planning of further management while awaiting trephine sections. Reporting of trephine biopsy is comparatively delayed due to requirement of decalcification and processing. Our study revealed trephine imprints had greater sensitivity than BMA in detecting marrow metastasis, aligning with the findings of Gupta *et al*., who highlighted the diagnostic utility of BMA in 76% of cases and imprints in 97% of cases with non-hematological disorders. Thus, the inclusion of imprints as a mandatory practice in all institutes is advocated. It is always suggested to do both aspiration and biopsy and these are considered complementary to each other [15]. This approach proves particularly valuable in instances where the tumor induces marked stromal fibrosis, leading to a dry tap during aspiration. Moreover, the morphology and recognition pattern of marrow involvement are better elucidated through trephine biopsy sections. Stromal changes in form of fibrosis was seen which is compatible with other Indian studies [16, 17]. As per previous literature, the evidence of disseminated tumor cells in bone marrow is corelated with the presence of minimal residual disease, clinical relapse or development of metastasis and may help in follow up after treatment. In this study, abnormal cell population was seen in BMA in seven patients while the trephine biopsy showed the presence of tumor cells in all eleven cases. While positive results of bone marrow biopsy for tumor cells are frequently reported, aspirates often yield negative results. Current research endeavors are focused on unraveling the intricate biology of marrow metastases, with a particular emphasis on the role of marrow stromal cells in promoting the survival of tumor cells.

CONCLUSION

To conclude, metastasis to bone marrow in patients with solid cancers represents a dire and incurable condition. There is no single clinical feature that can be isolated to be predictive of bone marrow involvement in cancer patients. Trephine biopsy corroborated by immunohistochemistry continues to be a gold standard in establishing the diagnosis in marrow metastasis.

REFERENCES

1. Wong, K. F., Chan, J. K. C., & Ma, S. K. (1993). Solid tumour with initial presentation in the bone marrow—a clinicopathologic study of 25 adult cases. *Hematological oncology*, *11*(1), 35-42.doi: 10.1002/hon.2900110105.
2. Mohanty, S. K., & Dash, S. (2003). Bone marrow metastasis in solid tumors. *Indian journal of pathology & microbiology*, *46*(4), 613-616.
3. Sharma, S., &Murari, M. (2003). Bone marrow involvement by metastatic solid tumors. *Indian journal of pathology & microbiology*, *46*(3), 382-384.
4. Ozkalemkas, F., Ali, R., Ozkocaman, V., Ozcelik, T., Ozan, U., Ozturk, H., ...&Tunali, A. (2005). The bone marrow aspirate and biopsy in the diagnosis of unsuspected nonhematologic malignancy: a clinical study of 19 cases. *BMC cancer*, *5*, 1-9.
5. Kołda, A., Helbig, G., Kopińska, A., Wichary, R., Pająk, J., &Kyrcz-Krzemień, S. (2017). Metastasis of solid tumors into bone marrow–Single center experience. *ActaHaematologicaPolonica*, *48*(2), 130-134.
6. Kiliçkap, S., Erman, M., Dinçer, M., Aksoy, S., Harputluoglu, H., &Yalçin, S. (2007). Bone marrow metastasis of solid tumors: Clinicopathological evaluation of 73 cases. *Turkish Journal of Cancer*, *37*(3), 85-88.
7. Moriwaki, S., Mandai, K., Okabe, K., Yamauchi, M., Yamamoto, A., & Kamei, T. (2003). Pathological analysis for the bone marrow metastasis by aspiration and core needle biopsy. *Jpn J Cancer Clin*, *49*(3), 203–209.
8. Tasleem, R. A., Chowdhary, N. D., Kadri, S. M., &Chowdhary, Q. A. (2003). Metastasis of solid tumours in bone marrow: a study from Kashmir, India. *Journal of clinical pathology*, *56*(10), 803-804.
9. Rahim, F., Hajizamani, S., Mortaz, E., Ahmadzadeh, A., Shahjahani, M., Shahrabi, S., & Saki, N. (2014). Molecular regulation of bone marrow metastasis in prostate and breast cancer. *Bone marrow research*, *2014*(1), 405920.
10. Erez, N., &Coussens, L. M. (2011). Leukocytes as paracrine regulators of metastasis and determinants of organ-specific colonization. *International journal of cancer*, *128*(11), 2536-2544.
11. Schneider, J. G., Amend, S. R., &Weilbaecher, K. N. (2011). Integrins and bone metastasis: integrating tumor cell and stromal cell interactions. *Bone*, *48*(1), 54-65.
12. Filanovsky, K., Feldberg, E., Miller, E. B., &Shvidel, L. (2017). Predictive value of clinical and laboratory parameters for overt bone marrow metastasis in patients with solid malignancy. *Journal of Cancer Therapy*, *8*(08), 773-784.
13. Cotta, C. V., Konoplev, S., Medeiros, L. J., &Bueso-Ramos, C. E. (2006). Metastatic tumors in bone marrow: histopathology and advances in the biology of the tumor cells and bone marrow environment. *Annals of Diagnostic Pathology*, *10*(3), 169-192.

14. Hofbauer, L. C., Bozec, A., Rauner, M., Jakob, F., Perner, S., &Pantel, K. (2021). Novel approaches to target the microenvironment of bone metastasis. *Nature reviews Clinical oncology*, *18*(8), 488-505.
15. Atac, B., Lawrence, C., & Goldberg, S. N. (1991). Metastatic tumor: the complementary role of the marrow aspirate and biopsy. *The American journal of the medical sciences*, *302*(4), 211-213.
16. Chauhan, K., Jain, M., Grover, S., Shukla, P., Rusia, U., & Grover, R. (2016). Bone marrow metastasis in nonhematologic malignancies: Data from a cancer hospital. *Clinical Cancer Investigation Journal*, *5*(2-2016), 103-109.
17. Sreelakshmi, I., Sunethri, P., Bheeshma, B., Geetha, V., Bai, P. J., Kumar, O. S., ...& Reddy, K. R. (2012). Interesting lesions of bone marrow with special reference to metastasis. *Journal Of Evolution of Medical and Dental Sciences-Jemds*, *1*(3), 160-165.