E-ISSN:2456-1487
P-ISSN:2456-9887
RNI:MPENG/2017/70771
Research Article
Bone Marrow

Tropical Journal of Pathology and Microbiology
2015 Volume 1 Number 1 JUL-DEC

Publisher
MEDRESEARCH
www.medresearch.in

Bone Marrow Metastasis- Morphology, Molecular features and Diagnosis: A Study from a regional cancer Centre in India

Namrata NR[1*]

DOI:10.17511/jopm.2015.i1.08

[1*] Namrata N Rajakumar , Associate Professor, Pathology, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India.

Objective: bone marrow biopsies are frequently done for histologically documented malignancies for staging and also in suspected malignancies Bone marrow involvement by solid tumours implicates advanced disease and a bad prognosis..It is important to rule out bone marrow involvement before planning for any definitive, curative treatment hence diligent and exhaustive search for metastatic cells in Bone marrow which aids in accurate staging treatment and prognosis was done.

Materials and Methods: This was a retrospective observational study of bone marrow involvement by solid tumours and their haematological manifestation

Results: Evaluation of Bone marrow evaluation during the past 7 years, in solid malignancies, revealed Out of 772, 342 were pediatric cases and 430 were adult cases. Bone marrow was involved in 82 patients, In adults, bone marrow involvement was diagnosed in 40 cases. Neuroblastoma was the most common malignancy, which involved the bone marrow in pediatric cases. In adults common was neuroendocrine carcinoma metastasis to bone marrow followed by carcinoma breast in women and carcinoma prostate in men.

Conclusion: A diligent and exhaustive search for metastatic cells in Bonemarrow helps in accurate staging treatment and prognosis, morphological examination is still the gold standard for suspected marrow involvement, Use of immunohistochemistry markers on bone marrow biopsies results in a higher detection rate, also aids in picking very few neoplastic cells, thereby helps in detecting early metastasis. Immunohistochemistry may be useful in recognizing some tumors in the marrow and confirming primary tumor origin.

Keywords: Bone Marrow,.Metastasis. IHC, solid malignancies

Corresponding Author

Namrata N Rajakumar , Associate Professor, Pathology, Kidwai Memorial Institute of Oncology, Bangalore, Karnataka, India.
Email: nrnamrata@yahoo.com

How to Cite this Article

Namrata NR, Bone Marrow Metastasis- Morphology, Molecular features and Diagnosis: A Study from a regional cancer Centre in India. Trop J Pathol Microbiol. 2015;1(1):36-41.
Available From
https://pathology.medresearch.in/index.php/jopm/article/view/668

To Browse

Manuscript Received	Review Round 1	Review Round 2	Review Round 3	Accepted
2015-09-04	2015-09-11	2015-09-17	2015-09-23	2015-09-30

Conflict of Interest	Funding	Ethical Approval	Plagiarism X-checker	Note
None	Nil	Yes	13.36	

Introduction

Bone marrow biopsies are frequently done for histologically documented malignancies for staging and also in suspected malignancies Bone marrow involvement by solid tumor implicates advanced disease and bad prognosis [1]. The tumours most frequently detected in bone marrow biopsies in adults are carcinoma of the breast, lung, prostate stomach colon, kidney and thyroid gland.[2],[3]. Among adult solid tumours, involving bone marrow, breast carcinoma is common in women and prostatic carcinoma in men [3],[4]. The Metastases of solid tumours in the bone marrow are rarely reported, and laboratory findings and clinical presentations are not characteristic [4].

Marrow involvement by Sarcomas is relatively low and tumour cells are invariably seen in groups or clusters. They are generally sharply demarcated, and look alien to the marrow environment [3], [5]. Sometimes marrow involvement is focal and the yield of marrow biopsies is increased by the amount of tissue obtained. [4]

The final step in cancer progression is metastasis and most cancer patients die from metastasis and not from primary disease. [5],[6],[7]. In this study, we attempted to study the haematological picture and clinical picture morphological /IHC in patients with metastasis. This is the study of solid tumors, and metastasis to bone marrow, The period of study was 7 years (2006-2013), from a regional cancer center in India.

Materials and Methods

We at Kidwai Cancer Center retrospectively analysed, medical records of patients with bone marrow metastasis suspected to have non-haematological malignancies and were referred to the Department of Pathology between January 2006 to January 2013, patients records included history, general physical examination, laboratory and radiological data blood and BMA /Biopsy as well as IHC staining. Also, haematological malignancies, lymphoma, and SRCT were excluded in this study. Haemogram details were reviewed. Bone marrow was obtained from the posterior iliac crest by Jamshidi needle. Bone marrow smears and peripheral smears and stained by Romanowsky stains, Bone marrow biopsies were stained with hematoxylin and eosin.

Immunohistochemistry was done to confirm primary tumor site detection in a few cases. The patient's name, age, gender, diagnosis, and clinical, and radiological findings were noted.

Results

Bone marrow examinations, of solid malignancies patients were evaluated. Out of 772 total cases, 342 were pediatric cases and 430 were adult cases. (Table 1)

Table 1: Distribution of bone marrow involvement among all patients

	number of cases	Number of positive cases
Pediatric cases	342	42
Adult cases	430	40
Total	772	82

Bone marrow was involved in 82 patients.. bone marrow involvement was present in 40 cases, in Adults. The bone marrow was considered to be 'involved by tumour' if tumour cells were detected in bone marrow aspirate, biopsy, or both. Female to male ratio was 1;1.5

Table 2: Distribution of bone marrow involvement among Adult patients

Neuroendocrine carcinoma	9
Breast cancer	8
Prostatic carcinoma	7
Colon cancer	6
Gastric cancer	3
Unknown primary and other	7
total	40

Anaemia was commonly seen in 28 cases. Leucopenia/neutropenia and thrombocytopenia were seen in 5 cases. Pancytopenia was found in 5 patients 13 patients showed Leuco -erythroblastic anaemia. Bone marrow was normocellular in majority of cases and hypocellular in 2 cases.. in a few cases final diagnosis of solid tumor metastasis was established using IHC markers CK, LCA EMA, PSA, CD99, vimentin, synaptophysin, desmin, etc Among adult solid tumors, involving bone marrow, breast being common in women On H&E 20x Bone marrow Aspiration and Biopsy showed characteristic Metastatic carcinoma breast, atypical cells in clusters with hyperchromatic nucleus and scant cytoplasm. Many cancers especially carcinoma breast and carcinoma prostate are associated with marked desmoplastic reaction, reason for dry tap in a few cases.

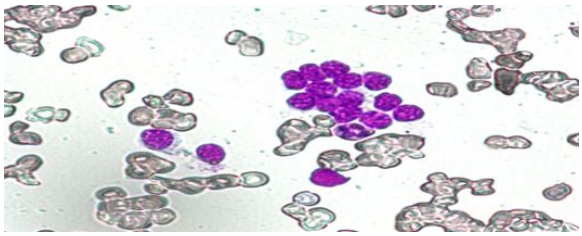

Figure 1: On H&E 20x Bone Marrow smears showing Metastatic carcinoma breast

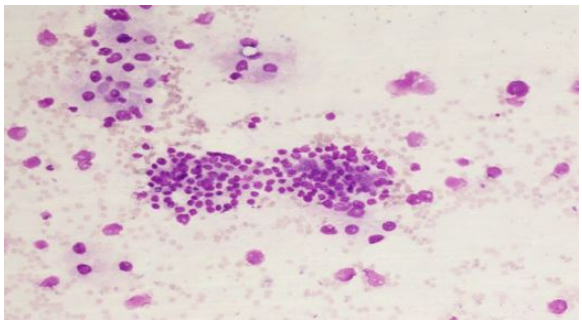

Figure 2: On H&E 20x Bone Marrow smears showing metastatic prostatic carcinoma

We didn't have any dry tap, carcinoma breast metastatic to marrow had fibrosis. , was a very difficult differential diagnosis of myelofibrosis. There could be difficulty in a few cases which resemble hematopoietic origin because of the giant cells, resembling megakaryocytes.

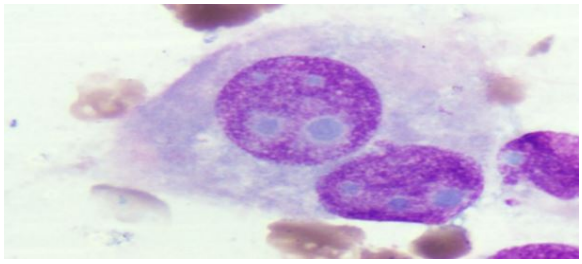

Figure 3: Metastatic Carcinoma prostate cells in High power

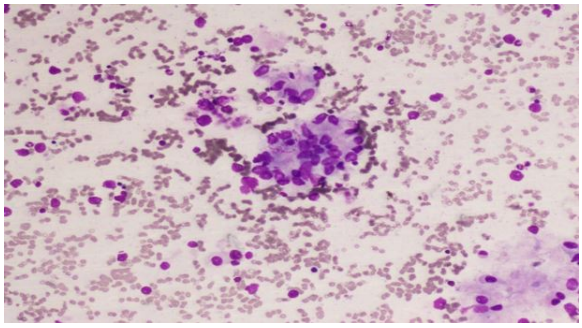

Figure 4: Metastatic Carcinoma prostate cells in low-power, glandular pattern

Discussion

The bone marrow biopsies are frequently done for histologically documented malignancies for staging and also in suspected malignancies Bone marrow involvement by solid tumor implicates advanced disease and bad prognosis [1],[2],[3]. Among adult solid tumors, involving bone marrow, the breast is common in women and prostatic carcinoma in men. Gastric cancer, metastasis was seen in younger patients. Cancer metastasis is the major cause of death in over 90%of patients with solid tumors [3], [4], [5].

Detection increases with bilateral and multiple biopsies [6],[7],[8]. Metastatic marrow morphological diagnosis.IHC is not necessary [8], [9]. The metastatic process is a multi-step cascade including local invasion and migration from the primary tumour, the mechanisms of micrometastasis to the distal tissues are highly regulated and involve numerous intrinsic and extrinsic factors as well as signalling pathways. The factors promoting marrow metastasis are poorly defined. However, this process can be explained by the unique marrow environment that is rich in adhesion molecules, cytokines, chemokines, and growth factors. Cytokines such as IL-6, IL11, and TNF-Seem to contribute to metastasis specifically to the bone and bone marrow [10], [11], [12], [13], [14].

Kopp et al reported that the presence of erythroblasts in the blood smear is highly suggestive of bonemarrow infiltration in breast cancer [13] Sometimes marrow involvement is focal and the yield of marrow biopsies is increased by the amount of tissue obtained. [8] The tumors most frequently detected in bone marrow biopsies in adults are carcinoma of the breast, lung, prostate stomach colon, kidney and thyroid gland. [2], [3]. Even in the current study commonest was carcinoma breast and carcinoma prostate. Metastatic tumour cells in bone marrow, are invariably seen in groups or clusters. They are generally sharply demarcated, and look alien to the marrow environment [2,3,4] This is a characteristic feature as hematopoietic origin cancers do not show cohesive clusters., however with extensive involvement individual cells also can be found. Sometimes entire marrow can be replaced. Tumor cells in marrow can be analysed on bone marrow smears, crush particle smears, trephine imprints or bone marrow biopsy. [3],[4].

In the current study, marrow was said to be involved in any one of these had showed metastatic cells. The clinical and prognostic significance of leucoerythroblastic anemia in patients with metastatic prostatic cancer and general patients with disseminated solid tumors is not understood clearly. Leucoerythroblastic anemia has greater transfusion requirements .breast carcinoma involving marrow, the majority were infiltrating duct carcinoma, and bone marrow metastasis in gastric cancers are generally seen in younger patients and poorly differentiated tumours. The prognosis is worsened with poor histology and pancytopenia. Among adult solid tumors, involving bone marrow, the breast is common in women and prostatic carcinoma in men. Many cancers especially carcinoma breast and carcinoma prostate are associated with marked desmoplastic reaction, the reason for dry tap in a few cases. Also is a very difficult differential diagnosis from myelofibrosis. Some cases marked osteosclerosis.[3],[14]

Immunohistochemistry may be useful in recognizing some tumors in the marrow .routine IHC is not necessary for detecting marrow involvement. However, IHC may be required when individual tumour cells are scattered in the marrow, especially in invasive lobular carcinoma. [14],[15]. In the current study, all the cases of carcinoma breast were infiltrating duct carcinoma. It's always better to compare the H&E if the foci of metastasis are very small with the IHC reaction.[14] Many studies have confirmed that Molecular markers increase the detection rate of metastasis [16] our study lacked the molecular techniques. Immunological quantification of the metastatic cells in bone marrow also is being done. The coexistence of solid tumors and bone marrow metastasis is associated with a deteriorating clinical course and poor prognosis.[3], [4]. The approach to unknown primary lesions should be the same as metastatic lesion analysis in other sites. [8],[14],[15],[16], due to financial constraints our study couldn't use extensive IHC panels, however, the possibility of neuroendocrine, carcinoma, breast carcinomas, and cancer prostate was suggested in the limited IHC panel.

Immunohistochemistry was done and it showed Synaptophysin and chromogranin expression. In Neuroendocrine carcinomas, breast carcinoma involving marrow showed CK and ER positivity, and prostatic carcinomas showed positivity for CK and positivity for PSA in a case.

A deeper understanding of metastasis is essential for discovery of more effective therapies[17]

Conclusion

A diligent and exhaustive search for metastatic cells in Bonemarrow helps in accurate staging treatment and prognosis, morphological examination is still the gold standard for suspected marrow involvement. The tumors most frequently detected in bone marrow biopsies in adults are carcinoma of the breast and, prostate similar to other studies. Immunohistochemistry may be useful in recognizing some tumors in the marrow. IHC is required when individual tumour cells are scattered in the marrow. It's always better to compare the H&E if the foci of metastasis are very small with the IHC reaction. The present study lacked molecular techniques and immunological quantification of metastatic cells in bone marrow which can identify the high-risk disease at diagnosis and during treatment, future studies could concentrate on detecting metastasis early and also on preventing bone marrow metastasis.

Abbreviations: IHC ;Immuno histochemistry, cytokeratin; CK, PSA; prostatic specific antigen

Permission from Institutional Research Board (IRB)**:** Yes

Funding: Nil

Conflicts of interest: none

References

1. Ceci G, Franciosi V, Passalacqua R, Di Blasio B, Boni C, Lottici R, De Lisi V, Nizzoli R, Guazzi A, Cocconi G. The value of bone marrow biopsy in breast cancer at the time of first relapse. A prospective study. Cancer. *1988 Mar 1;61(5):1041-5. doi: 10.1002/1097-0142(19880301)61:5<1041::aid-cncr2820610531>3.0.co;2-f. PMID: 3338048 [Crossref][PubMed][Google Scholar]*

2. Ozkalemkas F, Ali R, Ozkocaman V, Ozcelik T, Ozan U, Ozturk H, Kurt E, Evrensel T, Yerci O, Tunali A. The bone marrow aspirate and biopsy in the diagnosis of unsuspected nonhematologic malignancy: a clinical study of 19 cases. BMC Cancer. 2005 Nov 1;5:144. *doi: 10.1186/1471-2407-5-144. PMID: 16262899; PMCID: PMC1310632 [Crossref][PubMed][Google Scholar]*

3. Anner RM, Drewinko B. Frequency and significance of bone marrow involvement by metastatic solid tumors. Cancer. 1977 Mar;39(3):1337-44. *doi: 10.1002/1097-0142(197703)39:3<1337::aid-cncr2820390349>3.0.co;2-x. PMID: 912663 [Crossref][PubMed][Google Scholar]*

4. Ballestrero A, Coviello DA, Garuti A, Nencioni A, Famà A, Rocco I, Bertorelli R, Ferrando F, Gonella R, Patrone F. Reverse-transcriptase polymerase chain reaction of the maspin gene in the detection of bone marrow breast carcinoma cell contamination. Cancer. 2001 Oct 15;92(8):2030-5. *doi: 10.1002/1097-0142(20011015)92:8<2030::aid-cncr1541>3.0.co;2-g. PMID: 11596016 [Crossref] [PubMed][Google Scholar]*

5. Ballestrero A, Coviello DA, Garuti A, Nencioni A, Famà A, Rocco I, Bertorelli R, Ferrando F, Gonella R, Patrone F. Reverse-transcriptase polymerase chain reaction of the maspin gene in the detection of bone marrow breast carcinoma cell contamination. Cancer. 2001 Oct 15;92(8):2030-5. *doi: 10.1002/1097-0142(20011015)92:8<2030::aid-cncr1541>3.0.co;2-g. PMID: 11596016 [Crossref] [PubMed][Google Scholar]*

6. Kopp HG, Krauss K, Fehm T, Staebler A, Zahm J, Vogel W, Kanz L, Mayer F. Symptomatic bone marrow involvement in breast cancer--clinical presentation, treatment, and prognosis: a single institution review of 22 cases. Anticancer Res. 2011 Nov;31(11):4025-30. *PMID: 22110237 [Crossref] [PubMed][Google Scholar]*

7. Wang J, Weiss LM, Chang KL, Slovak ML, Gaal K, Forman SJ, Arber DA. Diagnostic utility of bilateral bone marrow examination: significance of morphologic and ancillary technique study in malignancy. Cancer. 2002 Mar 1;94(5):1522-31. *doi: 10.1002/cncr.10364. PMID: 11920510 [Crossref][PubMed][Google Scholar]*

8. Ridell B, Landys K. Incidence and histopathology of metastases of mammary carcinoma in biopsies from the posterior iliac crest. Cancer. 1979 Nov;44(5):1782-8. *doi: 10.1002/1097-0142(197911)44:5<1782::aid-cncr2820440536>3.0.co;2-b. PMID: 498049 [Crossref][PubMed][Google Scholar]*

9. Rosai and ackermans surgical pathology. 10 th edn. vol 2; chapter 23;1927 -2012. . *[Crossref] [PubMed][Google Scholar]*

10. Mahdi EJ, Mahdi AJ. Leucoerythroblastosis and thrombocytopenia as clues to metastatic malignancy. BMJ Case Rep. 2014 Jan 31;2014:bcr2013202612. *doi: 10.1136/bcr-2013-202612. PMID: 24488663; PMCID: PMC3912367 [Crossref][PubMed][Google Scholar]*

11. Erez N, Coussens LM. Leukocytes as paracrine regulators of metastasis and determinants of organ-specific colonization. Int J Cancer. 2011 Jun 1;128(11):2536-44. *doi: 10.1002/ijc.26032. Epub 2011 Mar 25. PMID: 21387299; PMCID: PMC3084629 [Crossref][PubMed][Google Scholar]*

12. Schneider JG, Amend SR, Weilbaecher KN. Integrins and bone metastasis: integrating tumor cell and stromal cell interactions. Bone. 2011 Jan;48(1):54-65. *doi: 10.1016/j.bone.2010.09.016. Epub 2010 Sep 17. PMID: 20850578; PMCID: PMC3010439 [Crossref][PubMed][Google Scholar]*

13. Koh BI, Kang Y. The pro-metastatic role of bone marrow-derived cells: a focus on MSCs and regulatory T cells. EMBO Rep. 2012 May;13(5):412-22. *doi: 10.1038/embor.2012.41. PMID: 22473297; PMCID: PMC3343352 [Crossref][PubMed][Google Scholar]*

14. Kopp HG, Krauss K, Fehm T, Staebler A, Zahm J, Vogel W, Kanz L, Mayer F. Symptomatic bone marrow involvement in breast cancer--clinical presentation, treatment, and prognosis: a single institution review of 22 cases. Anticancer Res. 2011 Nov;31(11):4025-30. *PMID: 22110237 [Crossref] [PubMed][Google Scholar]*

15. Krishnan C, George TI, Arber DA. Bone marrow metastases: a survey of nonhematologic metastases with immunohistochemical study of metastatic carcinomas. Appl Immunohistochem Mol Morphol. 2007 Mar;15(1):1-7. *doi: 10.1097/01.pai.0000213134.09160.14. PMID: 17536301 [Crossref][PubMed][Google Scholar]*

16. Cote RJ, Rosen PP, Hakes TB, Sedira M, Bazinet M, Kinne DW, Old LJ, Osborne MP. Monoclonal antibodies detect occult breast carcinoma metastases in the bone marrow of patients with early stage disease. Am J Surg Pathol. 1988 May;12(5):333-40. *doi: 10.1097/00000478-198805000-00001. PMID: 3364618 [Crossref] [PubMed][Google Scholar]*

17. Rahim F, Hajizamani S, Mortaz E, Ahmadzadeh A, Shahjahani M, Shahrabi S, Saki N. Molecular regulation of bone marrow metastasis in prostate and breast cancer. Bone Marrow Res. 2014;2014:405920. *doi: 10.1155/2014/405920. Epub 2014 Jul 23. PMID: 25147739; PMCID: PMC4134798 [Crossref][PubMed][Google Scholar]*

18. Seeger RC, Reynolds CP, Gallego R, Stram DO, Gerbing RB, Matthay KK. Quantitative tumor cell content of bone marrow and blood as a predictor of outcome in stage IV neuroblastoma: a Children's Cancer Group Study. J Clin Oncol. 2000 Dec 15;18(24):4067-76. *doi: 10.1200/JCO.2000.18.24.4067. PMID: 11118468 [Crossref][PubMed][Google Scholar]*