

Bone Marrow Involvement in Non-Hematological Malignancy: A Clinico-pathological Study From a Tertiary Hospital

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ABSTRACT

Background: Bone marrow is an important site for metastasis in cases of non hematological malignancies and is routinely performed to stage the disease or to rule out metastasis in suspected cases..

Purpose: Purpose of the study is to evaluate bone marrow in cases of solid tumors and also to enumerate the types of tumors metastasizing to marrow at our institute.

Methods: This was a retrospective study and clinical and laboratory data were retrieved from case files and laboratory records. All the case where bone marrow aspirate was performed to rule out metastasis or for staging were included along with those cases where patient presented to us with hematological abnormalities and diagnosed to have a metastasis in marrow.

Results: Out of total 758 cases of total bone marrow performed, 89 were performed in proven cases of non hematological malignancies of which 31 showed tumor deposits. While in two cases metastatic deposits were first seen in marrow aspirate. Most common tumor metastasizing to marrow at our institute was adenocarcinoma of lung followed by breast and small cell carcinoma of lung. In pediatric age group most common tumor was Ewing's sarcoma followed by rhabdomyosarcoma. Most common peripheral smear abnormality seen was thrombocytopenia followed by anemia and leukoerythroblastic blood picture.

Conclusion: Bone marrow aspiration is an easy, rapid and sensitive technique to determine metastasis of solid tumors in bone marrow and can be performed in hematological abnormalities to rule out any metastasis in otherwise unsuspected cases.

Keywords: Bone Marrow Metastasis, Non Hematological Malignancies, Bone Marrow Aspiration, Hematological Findings.

Introduction

Bone marrow (BM) is one of the common and important sites to be involved by solid tumors. Presence of metastasis in bone marrow can alter the clinical course of disease by changing the stage and also hampering the clinical condition of the patient by suppressing the valuable blood components. BM examination is done in cases of non hematological malignancies in order to stage the disease or to know the involvement. Detection of the metastasis in bone marrow is very important as it may affect the clinical course, treatment, and overall prognosis of the disease.^[1]

Any tumor that metastasizes via blood may deposit in BM. BM involvement may be suspected in cases of solid tumors presenting with bone pains, pathological fractures, radiological findings and unexplained hematological abnormalities etc. However, BM involvement may also be asymptomatic.

Most common solid tumors which metastasize to marrow in adults are carcinoma of the prostate, breast and lung. And in pediatric age group neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma and retinoblastoma are the major tumors metastasizing to BM^[2-4].

Bone marrow may be involved focally in cases of non hematopoietic malignancies. According to many studies BM biopsy was found to be more sensitive than aspirate to identify metastasis.^[2] Thus, BM aspirate must be performed along with trephine biopsies in order to satisfactorily exclude marrow metastasis.^[2,5]

This study was performed at a tertiary care cancer hospital in central India and aims at analyzing the BM involvement in cases of non hematological malignancies and their presentation in hematological abnormalities.

Material & Method

This was a retrospective study performed over a period of 3 year duration (2013 to 2016). Data of the patients retrieved from laboratory and clinical records. The cases which were included in the study either had a known primary with suspected metastasis or cases where BM was performed for staging in asymptomatic cases. This study also includes cases where BM was performed for unexplained hematological abnormalities and metastasis was detected on BM examination. Hematological malignancies like lymphoma and Hodgkin's disease were not included in this study. Bone marrow aspiration was studied along with

biopsy wherever available to find the presence of tumor in them and then positive and negative metastasis were made.

Iliac crest was used to aspirate bone marrow and slides were stained by Leishman stain. The bone marrow biopsies were obtained by Jamshidi needle (8Gx10cm) and were fixed in 10% formalin solution. These biopsies were then transferred to Gooding and Stewart fluid in order to decalcify the bony bit. After decalcification, these were routinely processed and paraffin blocks were prepared. Approximately 3-4 micrometer sections were taken and stained with hematoxylin-eosin.

Results

During this study period of 3 year, bone marrow examination was performed in 758 patients for various reasons and of these 91 cases were of solid tumors. Out of this, 89 cases had known non-hematopoietic malignancies and bone marrow aspiration was performed to stage the disease. Two cases presented with unexplained thrombocytopenia with leukoerythroblastic picture and found to have metastatic deposits of carcinoma on bone marrow examination. Of these 91 cases BM aspirate was performed on a total of 20 pediatric cases (<18 years) and 71 adults. BM biopsy can be procured in 15 pediatric cases and 60 adult cases. A slight female preponderance was noted with an M: F ratio of 1:1.2. (Table 1).

Out of total 91 cases of solid tumors bone marrow showed fragments in 71.4% cases (65 cases). Remaining 26 cases were hemodiluted without any bone marrow elements of which 18 showed metastatic tumor cells and were considered adequate while 8 cases were considered as inadequate. Out of 65 cases where the fragments are seen, there were 30 cases which showed normocellular fragments, 15 were hypercellular and 20 cases were hypocellular. Biopsy was present in 60 cases of these 65 cases and correlated well in relation to cellularity.

In adults 27 cases out of 71 cases (38.02%) showed metastatic tumor deposits in bone marrow while 6 pediatric cases out of 20 were positive for metastasis (30%). Both bone marrow aspirate and biopsy were positive in 25 cases (75.8%) while 6 cases (18.2%) showed tumor deposits only on aspirate. Isolated BM biopsy was positive only in two cases (6%). Diffuse involvement of bone marrow was seen only in 5 cases and rest all showed focal tumor deposits.

Pediatric Cases: - Patients age ranged from 6 month to 12 years in 6 cases. The male to female ratio was 1:1. Maximum number of cases were of Ewing's sarcoma (9%) followed by rhabdomyosarcoma (6.1%) and Neuroblastoma (3%). Only two pediatric cases show

clinical features suspicious of metastasis and both cases were of Ewing's sarcoma (ES) (Table 2).

Most common presentation was weakness and pallor with peripheral smears showing anemia (1 case) and pancytopenia (1 case). One case of ES with pancytopenia also showed nucleated red blood cells in peripheral smear. Peripheral smear from the case of neuroblastoma does not show any abnormality and bone marrow was performed for routine staging purpose.

Adult Cases: Patients age ranged from 25 years to 75 years. The male to female ratio was 1:1.3. Maximum number of cases was of carcinoma of lung, including both small and non small cell type (27.3%) (Fig. 1), followed by carcinoma of breast (21.2%), Ovary (9.1%), and prostate (9.1%). One case each of carcinoma of stomach, gall bladder and esophagus (small cell carcinoma) were also seen metastasizing to marrow (3% each) (Fig. 1 & 2).

There were 2 cases where primary could not be found and the case was labeled as malignancy of unknown origin. Out of these two cases, one case showed bilateral adrenal metastasis and a primary from lung was suspected. In other case metastatic adenocarcinoma was identified but site of origin could not be fixed. (Table 3).

Out of total 33 cases, 31 patients already had a known primary and presented with symptoms related to primary malignancies. Only two cases were primarily diagnosed as metastasis on bone marrow examination and presented with complaints related to BM suppression. On further workup, one case showed primary in breast and in other case ovary was found to be primary site of malignancy. In both these cases, peripheral smear findings showed leukoerythroblastic picture. The most common symptoms related to bone marrow suppression were weakness and easy fatigability due to anemia. Three cases presented with fever possibly due to infections secondary to leucopenia (Table 4).

The most common peripheral smear findings for which bone marrow evaluation was performed were isolated thrombocytopenia (36.4%) followed by isolated anemia (30.3%) and pancytopenia (30.3%). A total of 10 cases (30.3%) showed leukoerythroblastic picture on peripheral smear with presence of nucleated RBC's and immature forms of neutrophils. (Table 5).

Discussion

Bone marrow is one of the important sites of metastasis of solid tumors and is diagnosed using aspiration or biopsy. These two techniques complement each other and should be performed simultaneously. BM involvement is rare

Table 1: Patient distribution by age:-

	Number of Cases	Positive	Negative
Pediatric group	20	6	14
Adult group	71	27	44
Total number	91	33	58

Table 2: Paediatric cases with peripheral smear findings:

Sr. No.	Age (yrs)/sex	Primary Diagnosis	Primary Site	Indication for BME	Peripheral smear
1	10/F	Ewing's	Tibia	Staging	Normal
2	10/M	Ewing's	Femur	R/O mets	Anemia
3	3/F	Ewing's	Shoulder	R/O mets	PCP
4	0.5/ M	Neuroblastoma	adrenal	Staging	Normal
5	3/F	RMS	Mediastinal	Staging	Normal
6	12/M	RMS	Orbit	Staging	Normal

Table 3: Adult cases with abnormal hematological findings in peripheral smear:

Sr. No.	Age (yrs)/sex	Primary Diagnosis	Primary Site	Indication for BME	Peripheral smear
1	60/M	Squamous cell carcinoma	Lung	Staging	Thrombocytopenia
2	45/M	Squamous cell carcinoma	Lung	To rule out metastasis	Anemia and Thrombocytopenia
3	60/M	Squamous cell carcinoma	Lung	Staging	Pancytopenia
4	57/M	Squamous cell carcinoma	Lung	To rule out metastasis	Anemia and Thrombocytopenia
5	50/F	Adenocarcinoma	Lung	To rule out metastasis	Thrombocytopenia
6	61/M	Adenocarcinoma	Lung	To rule out metastasis	Thrombocytopenia
7	54/M	Adenocarcinoma	Lung	To rule out metastasis	Pancytopenia
8	52/M	Adenocarcinoma	Lung	To rule out metastasis	Thrombocytopenia
9	57/M	Adenocarcinoma	Lung	To rule out metastasis	Pancytopenia
10	51/F	Adenocarcinoma	Breast	To rule out metastasis	Anemia
11	55/F	Adenocarcinoma	Breast	To rule out metastasis	Pancytopenia
12	50/F	Adenocarcinoma	Breast	To rule out metastasis	Anemia and Thrombocytopenia
13	53/F	Adenocarcinoma	Breast	To rule out metastasis	Pancytopenia
14	43/F	Adenocarcinoma	Breast	To rule out metastasis	Pancytopenia
15	50/F	Adenocarcinoma	Breast	To rule out metastasis	Leukoerythroblastic picture
16	51/F	Adenocarcinoma	Breast	Leukoerythroblastic picture	Thrombocytopenia with Leukoerythroblastic picture
17	70/M	Adenocarcinoma	Prostate	To rule out metastasis	Anemia and Thrombocytopenia
18	70/M	Adenocarcinoma	Prostate	To rule out metastasis	Anemia
19	65/M	Adenocarcinoma	Prostate	To rule out metastasis	Thrombocytopenia
20	55/F	Adenocarcinoma	Ovary	To rule out metastasis	Anemia and Thrombocytopenia
21	60/F	Adenocarcinoma	Ovary	To rule out metastasis	Pancytopenia
22	63/F	Adenocarcinoma	Ovary	Leukoerythroblastic picture	Thrombocytopenia with Leukoerythroblastic picture

Sr. No.	Age (yrs)/sex	Primary Diagnosis	Primary Site	Indication for BME	Peripheral smear
23	63/F	Squamous cell carcinoma	Esophagus	To rule out metastasis	Anemia
24	25/F	Adenocarcinoma	Stomach	To rule out metastasis	Pancytopenia
25	75/F	Adenocarcinoma	Gallbladder	To rule out metastasis	Anemia and Thrombocytopenia
26	60/F	Adenocarcinoma	Malignancy of unknown origin	To rule out metastasis	Anemia
27	55/M	Adenocarcinoma	Malignancy of unknown origin	To rule out metastasis	Pancytopenia

Table 4: Distribution of clinical profile of patients:

Type of malignancy	Positive cases	Male	Female	Symptoms related to bone marrow suppression
PEDIATRIC CASES				
Ewing's sarcoma	3	1	2	2
Rhabdomyosarcoma	2	1	1	0
Neuroblastoma	1	1	0	0
Total pediatric cases	6	3	3	2
ADULT CASES				
Lung- Non small cell carcinoma	5	4	1	5
Lung- small cell carcinoma	4	4	0	4
Breast	7	0	7	5
Prostate	3	3	0	3
Ovary	3	0	3	2
Esophagus	1	0	1	1
Stomach	1	0	1	1
Gall bladder	1	0	1	1
Malignancy of unknown origin	2	1	1	2
Total adult cases	27	12	15	24
Total of all cases	33	15	18	26

Table 5: Distribution of hematological profiles of patient:

Type of malignancy	Total cases	Pancyto- penia	Anemia	Thrombo- cytopenia	Leukoerythroblastic reaction
PEDIATRIC CASES					
Ewing's sarcoma	3	1	1	0	1
Rhabdomyosarcoma	2	0	0	0	0
Neuroblastoma	1	0	0	0	0
Total pediatric cases	6	1	1	0	1
ADULT CASES					
Lung- Non small cell carcinoma	5	2	1	3	2
Lung- small cell carcinoma	4	1	2	3	0
Breast	7	3	2	1	3
Prostate	3	0	2	2	1
Ovary	3	1	1	1	1

Type of malignancy	Total cases	Panicyto- penia	Anemia	Thrombo- cytopenia	Leukoerythroblastic reaction
Esophagus	1	0	1	0	0
Stomach	1	1	0	0	1
Gall bladder	1	0	0	1	0
Malignancy of unknown origin	2	1	0	1	1
Total adult cases	27	9	9	12	9
Total of all cases	33	10	10	12	10

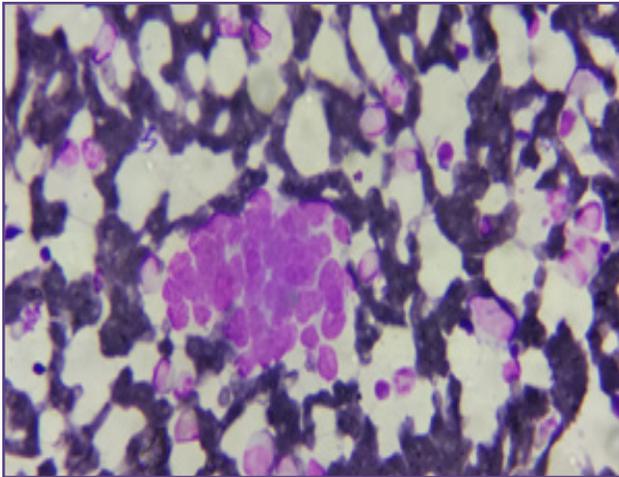


Fig. 1: Small cell carcinoma metastasis from oesophagus in bone marrow (MGG stain low power).

however results in various complications attributable to cytopenias such as bleeding, recurrent infections and symptoms related to anemia.^[4] Bone marrow aspiration and biopsy is the most sensitive, easiest cheapest and least time consuming procedure for the diagnosis of clinically suspected bone -marrow involvement.^[4,7,12]

Chemotherapeutic agents also lead to various degrees of cytopenias thus adding to the worse outcome of disease. Magnetic resonance imaging can give a clue for BM metastasis but confirmation is to be done by aspiration or biopsy.^[6]

Bone marrow examination is easy and cost effective procedure with rapid diagnosis and if positive, is confirmatory.

All tumors that can gain access to blood can metastasize to marrow; however cancers of prostate, breast, and lungs are the most common tumors showing marrow involvement.

There are many studies in western and Indian literature demonstrating bone marrow metastasis in non hematological malignancies^[8-12]^[7]

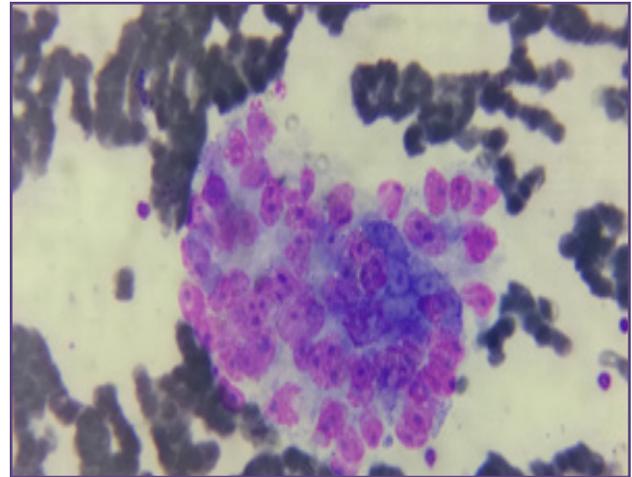


Fig. 2: Matastasis of adenocarcinoma from lung (MGG stain, high power).

According to literature, all malignancies can metastasize to bone marrow, but the common ones are malignancies of prostate, breast, lungs. In many instances, however, primary site of origin of primary cannot be ascertained. In our study, we found that the most common cancer to metastasize to marrow in females was breast and lung cancer in males which is not different from many other studies coated in literature which shows same results.^[7] But other studies shows prostate as the most common primary.^[2] In this study, prostate cancer stood 3rd after lung adenocarcinoma, breast and lung small cell carcinoma, possibly because of more lung cancer patients catering to our hospital and is in concordance to study done by few.¹²

In childrens, Ewing's sarcoma/PNET was the most common tumor to metastasize which is similar to the few studies in the literature.^[9] We also found 2 cases of rhabdomyosarcoma and one case of neuroblastoma in children. One case of primary small cell carcinoma of esophagus showed tumor cells in aspirate, which itself is a rare diagnosis. We found aspirate to be more sensitive than biopsy in picking up of malignant cells with only 2 false negative cases (one of lung and other of breast)

while bone marrow biopsy was falsely negative in 6 cases. The probable reason was inadequate length of the biopsy because in cases where the infiltration is focal, small foci of metastases can be easily missed. So, bone marrow biopsy should be performed along with aspiration in order to reduce the false negative cases and appropriate staging of the case.

Present study reveals many hematological abnormalities. Most common was isolated thrombocytopenia followed by pancytopenia and anemia. Leukoerythroblastic picture was seen in 30.3 % of cases and in our study also it was an important indicator of metastasis which is in concordance with other studies in literature^[1,11,13] There were no specific hematologic lineage changes in bone marrow aspirate smears which can suggest the possible metastasis other than the leukoerythroblastic picture in peripheral smears. Bone marrow should be performed in any known case of solid tumors with unexplained cytopenias or presence of leukoerythroblastic blood picture. However, few studies showed anaemia as a most common hematological abnormality during metastasis in bone marrow.^[14,15]

Newer techniques are used to demonstrate marrow involvement in early stage disease for this immunohistochemistry, flow cytometry and PCR techniques are used. These techniques indicate a greater frequency of tumor infiltration than has been evident, from standard histological methods.^[14,16,17,18]

Bone marrow aspiration and trephine biopsy are relatively sensitive technique for detecting bone marrow infiltration by metastatic tumors should be used in combination for increasing its efficacy^[19]

Conclusion

Bone marrow aspiration is an effective and cheap method for evaluating solid tumors metastatic to bone marrow. More over a clue to the primary site can also be suggested if the primary is unknown and metastatic lesions are detected in the bone marrow. Thrombocytopenia, anemia & leukoerythroblastic picture can be correlated with marrow metastatic in suspected cases. Hence it is concluded that aspiration of bone marrow provides an easy and quick way of detection of marrow involvement, however, biopsy with immunohistochemical and / or molecular techniques may be needed in case of microscopical tumor metastasis.

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Financial or other Competing Interests: None.