

Metastasis of solid tumors into bone marrow: An experience from a tertiary care centre.Nusrat Bashir¹, Tazeen Jeelani¹, Bilal Musharaf², Ruby Reshi³, Nausrat Ali², Ambreen Beigh²¹Lecturer department of pathology Government medical college Srinagar Jammu and Kashmir India 190010²Resident department of pathology Government medical college Srinagar Jammu and Kashmir India 190010³Professor and Head department of pathology Government medical college Srinagar Jammu and Kashmir India 190010**Correspondence Author:** Tazeen Jeelani, Lecturer, Department of Pathology Government Medical College Srinagar Jammu and Kashmir India 190010.**Type of Publication:** Original Research Paper**Conflicts of Interest:** Nil

Abstract: Bone marrow is one of the common sites to be involved by metastatic tumors. Bone marrow secondaries have been noticed in all types of tumors, the most common being carcinoma prostate, breast and lung in adults and small round cell tumors in paediatric age group. We present a clinicopathological profile of patients with metastatic deposits involving bone marrow over a period of two years.

Material and Methods: A total of 625 bone marrow aspirations were performed with biopsy done in 500 cases during the period of 2 years from Jan 2015 to Dec 2017. The patients' clinical findings, hematological and pathological features were reviewed. 11 cases had secondaries involving marrow. Biopsy was available in all the 11 cases.

Results: out of 625 cases of bone marrow reported 11 cases had metastatic deposits. 7 cases were picked on aspirate and 4 cases were missed on aspirate because of fibrosis and inadequate sample. These three cases were diagnosed on biopsy.

Conclusion: Bone marrow examination is a useful and cheap method for evaluating tumors metastatic to bone marrow. Additionally a clue to the primary site is suggested in cases with unknown primary. IHC on biopsy sections can help us to locate the primary site.

Key words: Bone marrow, Secondary, Dry tap, IHC.**Introduction**

Bone marrow is the site of primary myeloid and lymphoid hematological malignancies, however it is the organ with solid tumor metastasis in about 1-2% of the cases [1]. The route of spread being hematogenous. In adults the commonest tumors that metastasize to bone marrow are prostate, breast and lung cancers, however any tumor that has capacity of blood borne metastases may infiltrate the marrow [2, 3]. In children round cell tumors like neuroblastoma, retinoblastoma, rhabdomyosarcoma and Ewing's sarcoma account for major chunk of metastases to marrow [4]. Patients usually present with signs and symptoms related to cytopenias, including fatigue, orthostatic hypotension, dizziness, infections and bleeding [5]. These signs and symptoms remain uncharacteristic and may mimic common myeloid or lymphoid malignancies leading to misdiagnosis [6]. It has been found that bone marrow has unique environment rich in factors that facilitate the growth of circulating tumor cells and leading to cancer progression. However, the mechanisms of this process have not been completely defined [7]. Bone marrow aspiration and biopsy has importance in staging and prognosis of solid tumors [8]. The bilateral bone marrow biopsy is supposed to be more

accurate procedure for reporting of metastasis of solid tumors, however metastasis can be frequently reported on examination of aspirates only [9]. Bone marrow aspiration is quick, easy and cost effective method of reporting solid tumor metastasis and the tumors with marrow metastasis are regarded to have poor prognosis [10].

Material and Methods

Data was collected from the records section of the department of pathology Government medical college Srinagar Jammu and Kashmir India. It was a retrospective study extending from January 2015 to December 2017. Total of 625 bone marrow aspirations were done on patients referred from clinical side for anemias, cytopenias or suspected metastatic lesions during these two years. Biopsy was available in 500 cases only. Bone marrow aspiration was done by using Salahs 16 guage aspiration needle and for biopsy 14 guage Jamshidi needle was used. Bone marrow aspiration and biopsy were done from posterior superior iliac spine (PSIS), and the site was anesthetized by using 2% xylocaine injection locally. The patients' clinical findings, hematological and pathological features were reviewed. 11 cases had secondaries involving marrow. Biopsy was available in all the 11 cases. In cases of dry tap reticulin stains were available which revealed dense fibrosis of marrow biopsies due to infiltration by solid tumor.

Inclusion/exclusion criteria

Cases where both bone marrow aspiration and biopsy was available were included in the study.

Results

A total of 625 bone marrow aspirations were carried out in a span of two years and bone marrow biopsy was available in 500 cases. 11 cases showed evidence of bone marrow (BM) involvement by a solid tumor. In all the 11 cases bone marrow biopsy was available. Out of these 11 cases 7 were male and 4 were female patients. Mean age of presentation was 64 ± 11 years. Primary site of tumor was

known in 9 patients and unknown in 2 patients. 6 cases were diagnosed on aspiration smears and further confirmed on biopsy and immunohistochemistry (IHC) while as 5 cases needed bone marrow biopsy for diagnosis, as aspiration in these cases was inadequate either because of dilution or dry tap.

Histopathological profile showed that Lung adenocarcinoma (4 cases) (fig-1) was the most common malignancy associated with BM metastasis followed by infiltrating ductal carcinoma breast (3 cases) (Fig-2,3) in post mastectomy patients and prostatic adenocarcinoma (2 cases). One case each of malignant melanoma (fig- 4,5 & 6) and round cell tumor were also identified (Table-2).

The hematological profile of the cases with bone marrow involvement by secondaries showed that anemia was the commonest clinical presentation (6 cases) followed by pancytopenia (3 cases), bicytopenia and thrombocytopenia (1 case) each (Table-1).

In 2 cases where primary site of the tumor was not known, further evaluation and IHC of bone marrow biopsy was done to so that primary site could be ascertained.

Discussion

Metastasis is considered as one of the major causes of death in about 90% of patients with solid tumors [11], which makes detection of bone marrow metastasis important for clinical staging and prognosis and thus, has an impact on therapeutic decision. The factors that lead to bone marrow metastasis are poorly defined. The metastatic process is multi-step cascade including local invasion and migration from primary tumor, intravasation into blood capillaries, survival in circulation, extravasation, colonization and proliferation in distant organs [12, 13]. However, the process can be explained by the unique microenvironment of the marrow that is rich in cytokines, adhesion molecules, chemokines and growth factors [14,11]. It has been stated that only 0.01% of disseminating tumor cells (DTCs) that enter the

circulation will survive and proliferate at distant organs [15]. BM is one of the important site of metastasis of solid tumors, though not very frequent. Involvement of the BM is not only a sign of diffuse metastasis of the tumor but it also results in cytopenias that increase the risk of mortality. Cytopenias also decrease the delivery of effectiveness of anti-neoplastic drugs that are used in treatment [1]. Advanced diagnostic procedures like MRI and bone scan are more sensitive methods to assess the extent of bone marrow metastasis but these procedures are available at advanced medical centres and are expensive, While as bone marrow examination is a simple, quick and cost effective method and remains the best option to identify marrow metastasis of solid tumors and also to monitor the prognosis. Advanced stages of marrow infiltration may result in anemia and thrombocytopenia [10]. Patients with BM involvement could have normal blood counts, some disturbances in one or more series could result in cytopenias. Though severe anemia can be life threatening, the complications of neutropenia and thrombocytopenia result in more morbidity and mortality. Pancytopenic patients are known to have a higher complication risk than others [8]. In our study we also found anaemia, the commonest finding on haematological examination. The finding of anemia was similar to the study conducted by Sar R et al [16]. Many studies across the world have shown that metastasis from prostate cancer, breast and lung are the most frequently encountered ones in adults [10]. One more study carried out by Mohanty et al showed that prostate cancer (47.8%) was the most common tumor among adults, followed by breast cancer (28.2%) [14]. Previous studies from India and other parts of the world also show that carcinoma prostate (36%) is the solid tumor which most commonly metastasize to bone marrow, followed by gastric carcinoma and melanoma (25%) [17]. A study carried out by shivani dua et al showed that Lung cancer was the most

commonly encountered tumor [8]. Our study was in accordance with their study. Infiltration of marrow by metastatic tumor can be focal or diffuse. Reticulin and collagen fibrosis are common and are most marked in cases with greater degrees of marrow infiltration. Marked fibrosis is commonly seen in carcinomas of the breast, stomach, prostate and lung [18,19,20]. We detected fibrosis in 5 out of 11 cases with bone marrow involvement. Bone marrow aspiration and trephine biopsy are sensitive techniques for detection of bone marrow infiltration by metastatic tumors. The advantage of the trephine biopsy with respect to aspiration is that it preserves the histology of the tumor cells. Thus, glandular structures and rosettes can be identified in the trephine biopsy sections [21,22].

Clinically, the most frequent feature with which a patient with bone marrow involvement presents is bone pain and pathological fractures [23]. Ozkalemkas et al stated in their study that constitutional symptoms and pain were the most prominent presenting symptoms of the patient [24]. The demonstration of marrow involvement in early stage disease by application of newer technique is of interest. Immunohistochemistry, clonal growth, flowcytometry & polymerase chain reaction (PCR) techniques will indicate a greater frequency of tumor infiltration than has been evident from standard histological methods [25].

Classically, trephine biopsy is decisive when there is an inability to obtain the sample of marrow by aspiration. Positive results on trephine biopsy for tumor cells can thus frequently be observed while the aspirates may remain negative at times. The presence of bone marrow metastasis with associated solid tumor represents deteriorating clinical course and poor prognosis. [26].

Conclusion

In clinical practice patients presenting with unexplained haematological abnormalities like anemia and

thrombocytopenia, should raise the suspicion of bone marrow metastases. The examination of bone marrow smear and biopsy is a good modality for staging, monitoring prognosis and treatment in cases of malignant solid tumors. Trepine biopsy along with IHC remains gold standard in establishing the definitive diagnosis in marrow metastasis and can provide a clue regarding the primary site in unknown primary cases. BM involvement by solid tumors carries a poor prognosis.

Addition to existing knowledge: This study is first of its kind from our state, and supplements the world literature by adding to the already proven facts. Our study also shows that patients having unexplained anemia and thrombocytopenias, should raise the suspicion of bone marrow metastases.

Authors Contribution

Nusrat bashir : Reporting and reviewing of all bone marrow aspirations.

Tazeen jeelani : Writing and preparing of whole manuscript.

Bilal musharaf : Collection of data.

Nausrat Ali : Clicking and collecting relevant photomicrographs.

Ambreen beigh : Review of literature.

Ruby reshi : Overall supervision and editing of manuscript.

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Table-1: Hematological profile of the patients with bone marrow metastasis

Blood picture	No. of cases (n)
Anemia	6
Pancytopenia	3
Bicytopenia (anemia+neutropenia)	1
Thrombocytopenia	1
Total	11

Table-2: Histopathological diagnosis of the patients with bone marrow involvement.

Primary diagnosis	No. of patients (n)
Adenocarcinoma lung	4
Infiltrating ductal carcinoma breast	3
Adenocarcinoma prostate	2
Choroid Malignant melanoma	1
Round cell tumor	1
Total	11

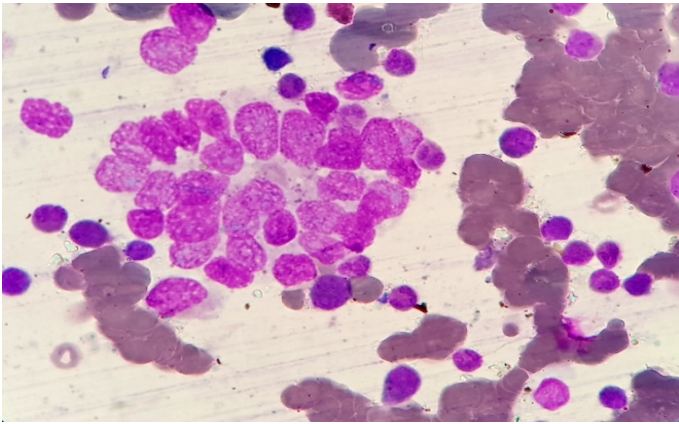


Fig-1: Aspiration smear showing metastatic deposits of adenocarcinoma lung.

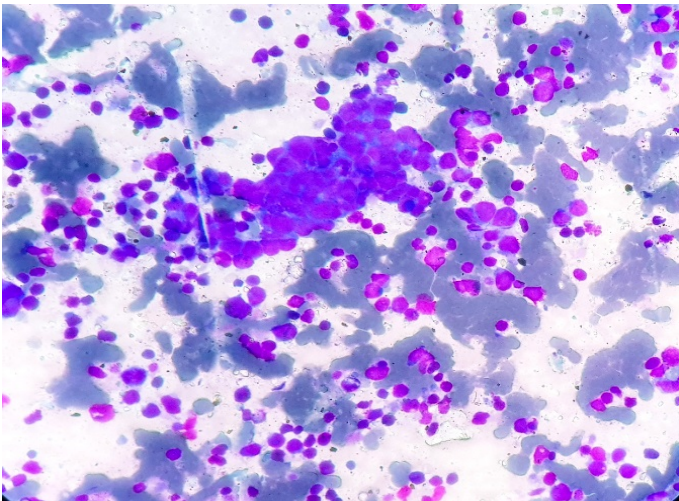


Fig-2: Aspiration smears revealing metastatic deposits from infiltrating ductal carcinoma breast.

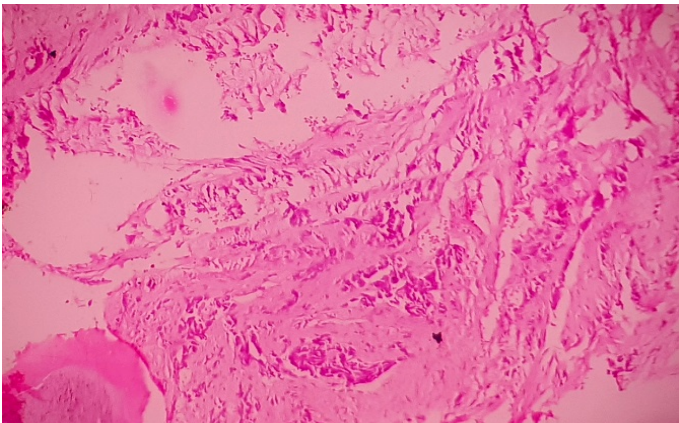


Fig-3: histopathology of bone marrow biopsy showing metastatic infiltrating ductal carcinoma.

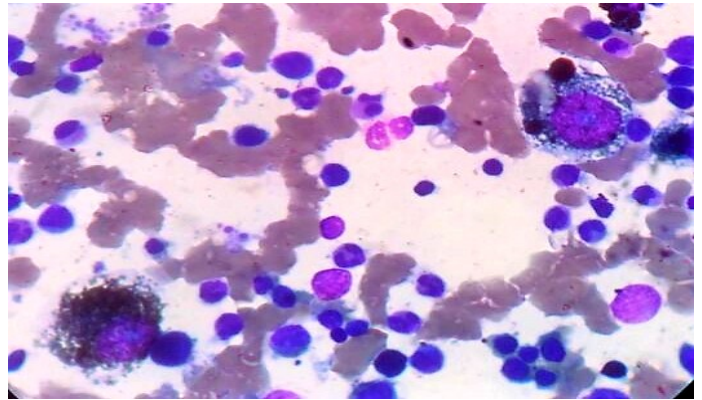


Fig-4: Aspiration smears showing metastatic deposits of malignant melanoma.

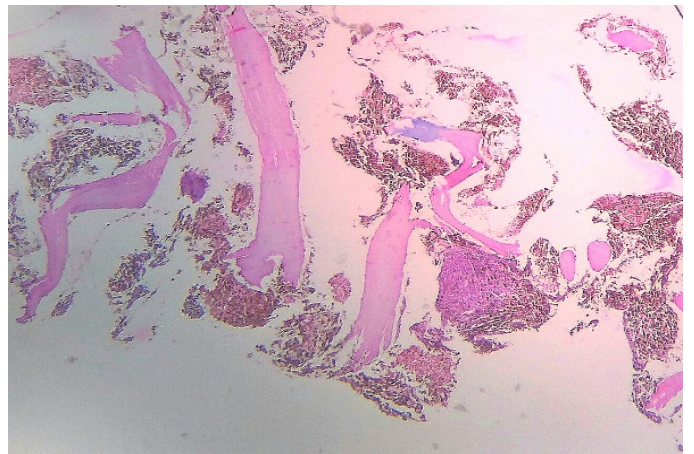


Fig-5: Histopathology showing bone marrow biopsy with extensive pigment in case of malignant melanoma.

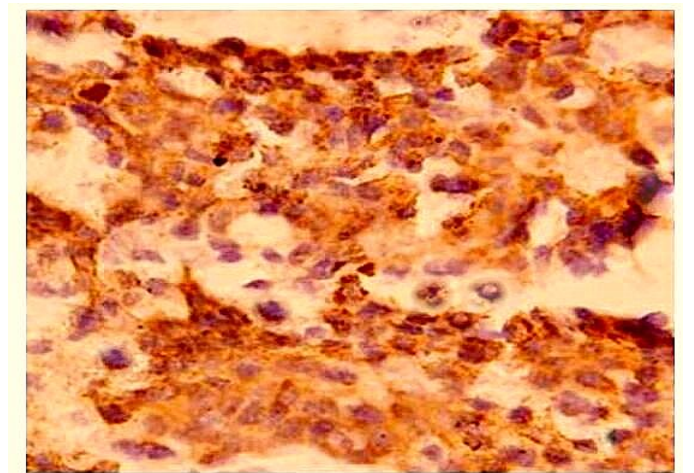


Fig-5: IHC showing positivity of tumor cells for HMB-45 in melanoma.