

# Non-Hematologic Malignancies Metastasing to the Bone Marrow: A Record-Based Descriptive Study From A Tertiary Center

Pelin AYTAN<sup>1</sup>, Nazım Emrah KOCER<sup>2</sup>, Mahmut YERAL<sup>1</sup>, Cigdem GEREKLIOGLU<sup>3</sup>,  
Mutlu KASAR<sup>1</sup>, Nur Hilal BUYUKKURT<sup>1</sup>, Suheyl ASMA<sup>3</sup>, Hakan OZDOGU<sup>1</sup>, Can BOGA<sup>1</sup>

<sup>1</sup> Adana Baskent University, Faculty of Medicine, Department of Hematology, Adult Bone Marrow Transplantation Unit

<sup>2</sup> Adana Baskent University, Faculty of Medicine, Department of Pathology

<sup>3</sup> Adana Baskent University, Faculty of Medicine, Department of Family Medicine, Adana, TURKEY

## ABSTRACT

The aim of this study is to assess the cases of nonhematologic malignancies that had bone marrow (BM) metastasis with respect to hematologic abnormalities, radiologic findings and pathologic findings. All of the patients with BM investigation were retrospectively evaluated. The patients with BM metastasis by a non-hematologic malignancy were assessed. Data regarding patient characteristics including peripheral blood evaluation findings, imaging findings, BM evaluation results and survival were obtained from patient files and computer based electronic database. 30 cases were detected among 1831 BM aspirations and biopsies. The most common malignancies were breast (36.7%), prostate (13.3%), gastric(13.3%) and lung (13.3%) adenocarcinomas. 90.9% and 75% of the cases had positive radiologic findings with PET/CT and CT respectively. 43.3% of the patients died during the study period and the median time from BM assessment to death was 2 months. Anemia, thrombocytopenia and leukopenia were present in 90%, 73.3% and 20% respectively. Lactate dehydrogenase and alkaline phosphatase were elevated in 90% and 80% respectively. In 76.2% a leukoerythroblastic blood picture was present. All the cases were diagnosed with biopsy and aspiration detected infiltration in 40% and in 4 metastatic patients (13.3%) the aspiration was false negative. In 46.7% the aspiration resulted with dry tap. Grade 3 fibrosis was present in 76.7%. BM assessment is a minimally invasive technique and provides very beneficial clinical data, however, because the survival is very short after BM assessment and the PET/CT has a considerable sensitivity it is not necessary to confirm BM metastasis in patients whose tumor stage is already known.

**Keywords:** Non-hematologic malignancy, Bone marrow, Biopsy, Aspiration

## ÖZET

### Kemik İliğine Metastaz Yapan Non-Hematolojik Malignansiler: Üçüncü Basamak Bir Merkezden Kayıt Tabanlı Tanımlayıcı Çalışma

Bu çalışmanın amacı, kemik iliğine metastaz yapmış olan nonhematolojik malignansilerin hematolojik anormallikler, radyolojik ve patolojik bulgular açısından değerlendirilmesidir. Ocak 2014 ile Ağustos 2018 arasında kemik iliği aspirasyonu ve biyopsisi yapılan tüm hastalar retrospektif olarak incelendi. Nonhematolojik bir malignansi tarafından kemik iliği metastazı olan hastalar değerlendirildi. 18 yaşından küçük hastalar, hematolojik malignansisi olan hastalar, supresif etki altında kemoterapi tedavisi alan hastalar çalışma dışı bırakıldı. Perifer kan değerlendirme, görüntüleme ve kemik iliği değerlendirme sonuçları ve sağkalım verilerini de içeren hasta özellikleri hasta dosyalarından, ve elektronik bilgisayar veri tabanından elde edildi. 1831 tane kemik iliği biyopsi ve aspirasyon içinden 30 vaka tespit edildi. En sık görülen malignansiler meme (%36.7), prostat (%13.3), mide (%13.3) ve akciğer (%13.3) adenokanserleri idi. PET/CT ve CT ile vakaların sırasıyla %90.9 ve %75'inde radyolojik bulgular tespit edildi. Hastaların %43.3'ü çalışma süresinde öldüler ve kemik iliğinden ölüme kadar geçen ortalama süre 2 ay idi.

**ORCID:** Pelin Aytan: 0000-0002-4213-1565  
Cigdem Gereklıoglu: 0000-0002-0886-9750  
Suheyl Asma: 0000-0001-5335-7976

Nazım E. Kocer: 0000-0003-3636-8109  
Mutlu Kasar: 0000-0003-3856-7005  
Hakan Ozdogu: 0000-0002-8902-1283

Mahmut Yeral: 0000-0002-9580-628X  
Nurhilal Buyukkurt: 0000-0002-0895-4787  
Can Boga: 0000-0002-9680-1958

Anemi, trombositopeni ve lökopeni sırasıyla vakaların %90, %73.3 ve %20'sinde mevcut idi. Hipoalbuminemi vakaların %40'ında vardı. Tüm vakalarda tanı biyopsi ile konulurken, aspirasyon hastaların %40'ında infiltrasyonu tespit etti ve 4 metastatik hastada (%13.3) aspirasyon yalnızca negatif idi. Hastaların %46.7'sinde aspirasyon sonucu dry tap olarak geldi. Evre 3 fibrozis %76.7 oranında tespit edildi. Kemik iliği değerlendirmesi minimal invaziv bir tekniktir ve çok faydalı klinik veri sağlar fakat sağkalımın kemik iliği değerlendirmesinden sonra çok kısa olması ve PET/CT'nin belirgin özgünlüğe sahip olması nedeniyle tümör evresi bilinen hastalarda kemik iliği metastazının konfirmasyonuna gerek yoktur.

**Anahtar Kelimeler:** Nonhematolojik malignansi, Kemik iliği, Biyopsi, Aspirasyon

## INTRODUCTION

Metastasis to bone marrow is a rare but important finding in non-hematologic tumors as it is related to advanced stage and poor prognosis. Carcinoma of the prostate, breast and lung are most common non-hematologic tumors that have tendency to metastasize to the bone marrow<sup>1</sup>; however, any malignancy that metastasize via blood may involve bone marrow.

Assessment of bone marrow consists of aspiration which allows assessment of cellular morphology and biopsy which provides samples for optimal evaluation of cellularity, fibrosis and infiltrative diseases and is shown to be more sensitive than aspirate to identify metastasis.<sup>2</sup> It is considered as a staging procedure in very few tumors including Ewing's sarcoma, neuroblastoma and rhabdomyosarcoma.<sup>3</sup> Otherwise it is only undertaken when abnormal peripheral hematologic findings or bone pains or pathologic bone fractures are present or when there is radiologic findings suggestive of bone marrow metastasis. However, finding metastatic tumor cells in the bone marrow may influence the stage of the cancer, response to therapy and overall survival as it suppresses the hematopoiesis and worsens the clinical condition and therefore early diagnosis is essential.

The aim of this study was to investigate the cases of nonhematologic malignancies that had bone marrow metastasis with respect to hematologic abnormalities, radiologic findings and pathologic findings of bone marrow.

## PATIENTS AND METHODS

All the bone marrow aspirations and biopsies that were performed in the hematology department of Baskent Adana University were retrospectively

evaluated over a period of about 4.5 years from January 2014 to August 2018. A total of 1831 bone marrow aspirations and biopsies were performed during this period according to standard techniques. All of the patients with bone marrow metastasis by a non-hematologic malignancy were evaluated. The cases 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. All the patients younger than 18 years of age, with hematologic malignancies, under chemotherapeutic therapy with suppressive effect were excluded. The study was approved by the institution's ethical committee (KA19/149).

Data regarding patient characteristics including peripheral blood evaluation findings, imaging findings, bone marrow evaluation results and survival were obtained from patient files and computer based electronic database.

Iliac crest was used to aspirate bone marrow. The aspiration smears and touch imprints are stained with May Grunwald Giemsa and Perl's Prussian Blue. The bone marrow biopsies were obtained by Matek needle (11Gx10 cm) and were fixed in 10% formalin solution. These biopsies were then decalcified from 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. Reticulin and other special stains were used when required. Immunohistochemical staining was performed according to clinical situation and characteristics of the metastasis.

**Table 1.** Characteristics of the patients

No.	Age/Sex	BM	Primary Site	Peripheral	LEB Smear	PET/BT	Brain Mts	Fibrosis	Grade
1.	45/M	AC	Unknown	A/T	+	+	-	+	3
2.	52/F	ASC	Cervix	A/T	+	+	+	+	3
3.	47/F	AC	Breast	A/T	+	+	-	Dry Tap	3
4.	58/M	AC	Prostate	A/T	NA	+	+	+	2
5.	59/F	AC	Breast	A/T	-	+	+	Dry Tap	3
6.	58/F	AC	Thyroid	Pancytopenia	NA	+	-	Dry Tap	3
7.	63/M	AC	Prostate	A	NA	+	+	Dry Tap	3
8.	46/F	AC	Breast	A/T	-	+	-	-	3
9.	43/M	AC	Stomach	A/T	+	+	-	+	3
10.	39/F	AC	Breast	Pancytopenia	+	+	-	Dry Tap	3
11.	43/F	AC	Breast	A/T	+	+	+	-	2
12.	49/M	AC	Lung	A/T	-	-	+	+	3
<b>Non small cell</b>									
13.	37/F	AC	Breast	Pancytopenia	NA	+	+	Dry Tap	3
14.	66/M	AC	Prostate	Pancytopenia	NA	-	-	+	3
15.	33/F	AC	Stomach	T	+	+	-	+	3
16.	57/F	A/C	Breast	A/T	+	+	-	+	3
17.	41/F	AC	Breast	Pancytopenia	+	+	+	Dry Tap	3
18.	41/M	AC	Stomach	A	NA	+	-	Dry Tap	3
19.	49/M	SCC	Esophagus	A	NA	-	-	Dry Tap	3
20.	66/F	AC	Lung	Normal	NA	+	-	Dry Tap	3
<b>Non small cell</b>									
21.	79/F	C	Neuroendocrine	A/T	+	-	-	-	2
22.	36/F	AC	Breast	A	NA	+	+	+	3
23.	69/M	AC	Lung	Normal	-	+	+	-	1
24.	62/F	AC	Unknown	A	+	+	+	Dry Tap	3
25.	59/M	AC	Lung	Pancytopenia	-	+	-	+	1
<b>Small cell</b>									
26.	58/M	AC	Surrenal	A/T	+	+	+	Dry Tap	3
27.	57/M	AC	Stomach	A/T	+	+	-	Dry Tap	1
28.	59/M	AC	Prostate	A/T	+	+	-	+	3
29.	66/F	AC	Breast	A/T	+	+	-	Dry Tap	3
30.	77/F	AC	Breast	A	+	+	-	+	2

M= Male, F= Female, AC= Adenocarcinoma, ASC= Adenosquamous carcinoma, SCC= Squamous Cell Carcinoma, C= Carcinoid, A= Anemia, T= Thrombocytopenia, LEB= Leukoerythroblastic blood picture

### Statistical Analysis

Statistical analysis was accomplished with statistical program for social sciences (SPSS 20, demo, Illinois, USA). Normality of the data was tested with Kolmogorov-Smirnov Test. Normally distributed data were compared with t test and Man-Whitney-U test was used for comparison of non-normally

distributed data. Chi square test was used for comparison of non-parametric data. A value of  $\leq 0.05$  was considered to be significant.

### RESULTS

Bone marrow aspiration and biopsies were performed to 1831 patients during January 2014 -

**Table 2.** Hematologic parameters of the patients

	Mean $\pm$ SD	Median (IQR)
Hemoglobin (g/dL)	9.3 $\pm$ 1.8	9.1 (2.68)
White Blood Cell (x10 <sup>3</sup> /microL)	8831.7 $\pm$ 6120.1	7125.0 (5957.5)
Lymphocyte	23.6 $\pm$ 11.9	22.0 (15.1)
Neutrophil	63.7 $\pm$ 16.3	64.9 (22.0)
Basophil	0.93 $\pm$ 0.81	0.70 (0.86)
Platelet	117366 $\pm$ 168452	59500 (142500)
Mean Corpuscular Volume	85.3 $\pm$ 5.6	86.3 (5.6)
Red Cell Distribution Width	17.8 $\pm$ 2.3	18.0 (3.8)
Lactic Dehydrogenase (IU/L)	645.7 $\pm$ 356.7	637.0 (424.0)
Alkaline Phosphatase (IU/L)	348.8 $\pm$ 411.1	191 (291.25)
Total protein (g/dL)	6.3 $\pm$ 0.8	6.3 (1.41)
Albumin (g/dL)	3.3 $\pm$ 0.6	3.5 (0.8)

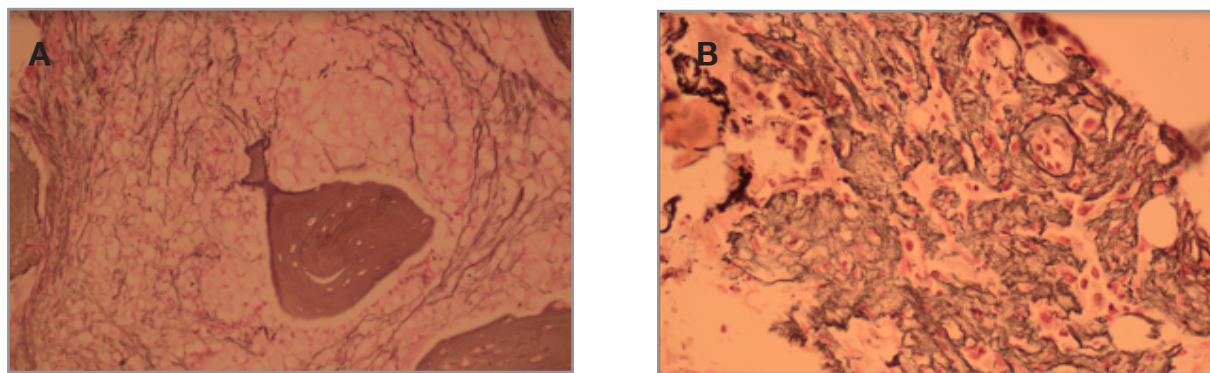
SD= Standard deviation, IQR= Interquartile range

August 2018. 35 patients have been found to have bone marrow metastasis in this population. Two patients who were 15 and 16 years old with rhabdomyosarcoma and one patient who was 16 years old with Ewing's sarcoma were excluded as they were under 18 years old. Two other patients with prostate and metastatic tumor with unknown primary carcinoma were also excluded because their follow-up data were missing. The data of the remaining 30 patients were depicted in Table 1.

Female to male ratio was 17/13 in the studied population (56.7% vs 43.3%). The mean age at the time of diagnosis was 53.8 $\pm$ 12.0 years. The most common malignancy that had metastasis to the bone marrow was breast carcinoma (n= 11, 36.7%). It is followed by prostate (n:4, 13.3%), gastric (n= 4, 13.3%) and lung (n= 4, 13.3%) adenocarcinomas. Most of the malignancies were metastatic epithelial adenocarcinomas and there was one adenosquamous carcinoma of the cervix and one squamous cell carcinoma of the esophagus. In two cases the primary site could not be determined. In 22 patients PET/CT was performed and except two cases (in one of them imaging was 1 year before the bone marrow assessment) bone marrow involvement could be detected in all of the patients (90.9%). In the remaining 8 cases BT was performed and in 6 cases (75%) bone metastasis

was detected. In 2 cases where bone metastasis could not be detected with BT, the images were taken 1 year before the bone marrow assessment. Brain metastasis was present in 12 patients (40%). Presence of brain metastasis was significantly associated with death. 75% of the patients with brain metastasis and 22.2% of the patients without brain metastasis died (p=0.006). 43.3% of the patients died during the study period and the median time from bone marrow assessment to death was 2 months (range= 1 - 36 months).

The hematologic results of the patients at the time of bone marrow assessment were shown in table 2. Anemia, thrombocytopenia and leukopenia were present in 90% (n= 27), 73.3% (n= 22) and 20% (n:6) of the patients respectively. Concomitant anemia and thrombocytopenia was the most common (50%) presenting hematologic feature followed by pancytopenia (20%). RDW was increased in 24 patients (80%). Lactate dehydrogenase was elevated in 90% (n:27) and alkaline phosphatase was elevated in 80% (n:24) of the patients. Total protein was found to be decreased only in 2 patients (6.7%); however hypoalbuminemia was present in 40% (Table 2). Peripheral smear results of 21 patients were available and in 16 of these (76.2%) a leukoerythroblastic blood picture was present (Table 1).



**Figure 1A and B.** Bone marrow fibrosis (Reticulin staining, x400, **A.** Grade 2 myelofibrosis; **B.** Grade 3 myelofibrosis)

All the cases were diagnosed with bone marrow biopsy (n= 30, 100%). Bone marrow aspiration detected infiltration in 12 patients (40%) and in 4 metastatic patients the metastasis could not be detected with aspiration (13.3%). In 14 patients (46.7%) the aspiration resulted with dry tap. Of these 14 dry tap aspiration cases 6 were from bone marrow of breast carcinoma patients (42.9%) (Table 1). In 76.7% of the bone marrow biopsies (23/30), there were grade 3 fibrosis (Table 1, Figure 1A, B). There was a positive correlation between grade of fibrosis and obtaining dry tap with the aspiration ( $\rho=0.433$ ,  $p=0.017$ ).

## DISCUSSION

Bone marrow is a common site for solid tumor metastasis as it has a rich blood supply and contains various growth factors and therefore any tumor capable of hematologic dissemination can metastasize to the bone marrow. It has been reported that bone marrow metastasis is found in 2 to 26% of cases with cancer<sup>4</sup> and the most common tumors are carcinomas arising from breast, prostate, lung and gastrointestinal tract with various reported incidences.<sup>3,5-8</sup> In this large series of bone marrow evaluation the most common nonhematologic malignancies with bone marrow metastasis were found to be carcinomas of breast, prostate, gastric and lung which is in accordance with the literature. The overall incidence was found to be 1.64% in adults. In 36.7% of these the primary site was breast carcinoma, followed by prostate, lung and gastric carcinomas all having an incidence of 13.3%.

In clinical practice trephine biopsy and aspiration are the two main procedures for the definitive diagnosis of bone marrow infiltration. These two techniques are considered to be complementary because detection of tumor cells in a biopsy and not in aspirate or vice versa can be seen.<sup>9-11</sup> However in many reports biopsy is considered to be more sensitive<sup>9,12</sup> and the gold standard technique when performed with aspiration simultaneously.<sup>2</sup> It is suggested that in cases in which infiltration cannot be detected with biopsy but positive in aspirates, an adequate bone depth could not be achieved during biopsy.<sup>3</sup> In the present study all of the 30 patients had tumor cells in the biopsy specimens, however, the sensitivity of aspiration was 40% and the false negativity was 13.3%. Syed et al reported that with aspirate they could detect only 35% of the tumors that were diagnosed on bone marrow biopsy<sup>13</sup> and Toi et al reported 50% correlation between aspiration and biopsy sections in cases of metastasis from solid tumors.<sup>14</sup> Tyagi et al also reported a 100% sensitivity with biopsy and a false negative rate of 14.3% with aspiration.<sup>15</sup> Similarly Mishra et al reported a 100% sensitivity for the biopsy.<sup>5</sup> Although in the present study all the cases could be detected with biopsy, there are studies in which tumor cells could be detected with aspiration but not with biopsy<sup>16</sup> and therefore aspiration and biopsy must be performed concomitantly as these two techniques complement each other.

Dry tap was seen in 46.7% of the aspirates. It refers to inability to obtain bone marrow on attempted marrow aspirations and is suggested to be due to reactive myelofibrosis which is diagnosed with re-



ticulin staining of trephine biopsy and represents greater degrees of marrow infiltration.<sup>17,18</sup> Marked myelofibrosis has been reported to be most common in carcinomas of the breast, stomach and lung.<sup>19-21</sup> In the present study similarly 42.9% of the dry tap cases were from aspirates of breast carcinoma cases, followed by cases with gastric carcinoma (14.3%). In 92.9% of the dry tap cases, the fibrosis was very significant. Myelofibrosis with collagen and reticulin was present in all cases, but in 76.7% fibrosis was grade 3 representing an advanced stage. Kaur et al reported myelofibrosis in 6 of the 9 cases (66.7%) however they did not grade the extent of fibrosis. Mishra et al reported grade 3 fibrosis in 22.2% of the patients; however, when osteomyosclerotic and necrotic bone marrow biopsies are encountered fibrosis rate increases to 77.8% which is similar to our findings.<sup>5</sup>

Infiltration of bone marrow by malignant cells is associated with normocytic normochromic anemia and thrombocytopenia and there may be myelo-suppression induced leukopenia. In our study anemia was present in 90% of the patients. Thrombocytopenia and leukopenia were detected in 73.3% and 20% of the patients respectively. Anemia and thrombocytopenia were concomitant in 50% and cytopenia was present in 20% of the patients. Ozkalemkas et al in their study reported anemia and thrombocytopenia in all the patients, whereas Kaur et al and Sar et al detected anemia in 77.7% and 66.6% respectively.<sup>2,22,23</sup> Various other studies reveal an incidence of anemia in neoplastic diseases from 55-90%.<sup>24-26</sup> Again the reported rates of thrombocytopenia and leukopenia differ among studied patients, ranging from 33.3% to 100% and 30.3% to 50% respectively.<sup>1,2,22,23</sup> In 6.7% of the studied patients all the hematologic parameters were within normal ranges which is not an uncommon finding. In these two patients red cell distribution width was found to be increased. RDW was found to be increased in 80% (n= 24) of the patients. Similarly in another study from Turkey, Ozkalemkas et al reported an increased RDW in all of the patients with non-hematologic tumors that had bone marrow metastasis.<sup>22</sup> They proposed a tetrad consisting of anemia, thrombocytopenia, elevated RDW and hypoproteinemia in patients with disseminated tumors that were diagnosed via bone

marrow examination.<sup>22</sup> In the present study albumin level was low in 40% of the patients and the other parameters are found to be increased in most of the patients suggesting that this tetrad may be a useful marker for such patients.

A leukoerythroblastic reaction refers to an increase in the peripheral blood of immature red blood cells (normoblasts, immature granulocytes, metamyelocytes, bands), and is suggested to be associated with metastatic cancer, hematopoietic malignancy, hemolytic anemia, Gaucher's disease, polytrauma and BM infiltration by various processes like infection. Peripheral smear was available in 21 patients. Leukoerythroblastic blood picture was present in 76.2% (n= 16) of these patients. Leukoerythroblastic blood picture is thought to be resulted from the early release of some cytokines even before the marrow is completely invaded and is associated with the degree of the bone marrow fibrosis rather than the extent of malignant cell invasion.<sup>19</sup> In the present study advanced fibrosis was present in 76.6% of the patients.

Alkaline phosphatase was elevated in 80% and lactate dehydrogenase was found to be elevated in 90% of the patients. Similarly Ozkalemkas et al reported an increased level of LDH in 95% of the cases and Wong et al reported an increased ALP in 95% of the cases.<sup>22,27</sup> These findings together with the leukoerythroblastic blood picture indicate an infiltrative process in the marrow.

PET/CT has gained wide acceptance for evaluation of the primary site or the metastasis in malignancies. In the present study 22 patients had been evaluated with PET/CT and in 20 of the patients (90.9%) FGD entrapment was detected in the bones. And in one PET/CT negative, but infiltration positive patient the imaging was done 1 year before the bone marrow assessment and it may be suggested that rather than missing out the present metastasis, there was no metastasis at the time of the imaging. CT had also a significant sensitivity to detect bone marrow involvement in the studied patients (75%). Again in one of the CT negative patients the imaging was 1 year before the bone marrow assessment. From this point imaging modalities, especially PET/CT, have very high sensitivities for detection of bone marrow metastasis.

At the time of diagnosis of bone marrow metastasis, brain metastasis was also present in 40% of the patients showing the progressive stage of the malignancy. Concomitant presence of brain and bone marrow involvements were associated with poor prognosis. During the study period 43.3% of the patients died after the bone marrow aspiration and biopsy in a median time of 2 months. Survival was similar in the study by Ozkalemkas et al<sup>22</sup> in which it was only a few weeks or months except few patients. The survival of many patients is very short and therefore the therapeutic significance of detection of bone marrow metastasis may be questioned. One may question if it is necessary to confirm bone marrow metastasis in patients whose tumor stage is already known as PET/CT imaging has such a high sensitivity (much more than aspiration) in detection of these metastasis. We believe that the only indication of bone marrow assessment in such patients may be the tumors with unknown primary site.

In conclusion bone marrow may be invaded by various non-hematologic tumors; breast, prostate, gastric and lung adenocarcinomas are being the most common ones. Bone marrow involvement is associated with advanced stage and poor prognosis. Biopsy and aspiration are the two main complementary procedures for the definitive diagnosis. There are many laboratory and peripheral blood findings. Bone marrow assessment is a minimally invasive technique and provides very beneficial clinical data, however, because the survival is very short after BM assessment and the PET/CT has a considerable sensitivity it is not necessary to confirm BM metastasis in patients whose tumor stage is already known.

## REFERENCES

1. Meenai AF, Ojha S, Ali MA, et al. Bone marrow involvement in non-hematological malignancy: a clinicopathological study from a tertiary hospital. *APALM* 5: 440-446, 2018.
2. Kaur G, Basu S, Kaur P, Sood T. Metastatic bone marrow tumors: Study of nine cases and review of the literature. *J Blood Disord Transfus* 2: 110, 2011.
3. Chauhan K, Jain M, Grover S, et al. Bone marrow metastasis in nonhematologic malignancies: Data from a cancer hospital. *Clin Cancer Invest J* 5: 103-109, 2016.
4. Casciato, DA. Metastatic cancer, in: *Cancer Treatment*, Haskell, C. H. (Ed.) Boston, W.B. Saunders, 1995, p: 1128.
5. Mishra P, Das S, Kar R, et al. Non-hematopoietic malignancies metastasising to the bone marrow: A 5 year record based descriptive study from a tertiary care centre in South India. *Indian J Cancer* 51: 30-34, 2014.
6. Kucukzeybek BB, Calli AO, Kucukzeybek Y, et al. The prognostic significance of bone marrow metastases: Evaluation of 58 cases. *Indian J Pathol Microbiol* 57: 3969, 2014.
7. Brahmbhatt B, Parikh B, Shah M. Bone marrow involvement by metastatic solid tumors. *Gujarat Medical Journal* 69: 54-57, 2014.
8. Mohanty SK, Dash S. Bone marrow metastasis in solid tumors. *Indian J Pathol Microbiol* 46: 613-616, 2003.
9. Singh G, Krause JR, Breitfeld V. Bone marrow examination for metastatic tumor aspirate and biopsy. *Cancer* 40: 2317-2321, 1977.
10. Savage RA, Hoffman GC, Shaker K. Diagnostic problems involved in detection of metastatic neoplasms by bone marrow aspirate compared with needle biopsy. *Am J Clin Pathol* 70: 623-627, 1978.
11. Moid F, DePalma L. Comparison of relative value of bone marrow aspirates and bone marrow trephine biopsies in the diagnosis of solid tumor metastasis and Hodgkin's lymphoma. Institutional experience and literature review. *Arch Pathol Lab Med* 129: 497-501, 2005.
12. Ingle JN, Tormey DC, Tan HK. The bone marrow examination in breast cancer; diagnostic considerations and clinical usefulness. *Cancer* 41: 670-674, 1978.
13. Syed NN, Moiz B, Adil SN, Khurshid M. Diagnostic importance of bone marrow examination in non-hematological disorders. *J Pak Med Assoc* 57: 123-125, 2007.
14. Toi PC, Varghese RG, Rai R. Comparative evaluation of simultaneous bone marrow aspiration and bone marrow biopsy: an institutional experience. *Indian J Hematol Blood Transfus* 26: 41-44, 2010.
15. Tyagi R, Singh A, Garg B, Sood N. Beware of bone marrow: Identical detection and primary diagnosis of solid tumours in bone marrow aspiration and biopsies; a study of 22 cases. *Iran J Pathol* 13: 78-84, 2017.
16. Sharma S, Murari M. Bone marrow involvement by metastatic solid tumors. *Indian J Pathol Microbiol* 46: 382-384, 2003.
17. Humpries JE. Dry tap bone marrow aspiration: Clinical significance. *Am J Hematol* 35: 247-250, 1990.
18. Hyun BH. Bone marrow examination: Adventures in diagnostic hematology. *Yonsei Med J* 27: 100-105, 1986.
19. Rubins JR. The role of myelofibrosis in malignant myelocleosis. *Cancer* 51: 308-311, 1983.
20. Kiely JM, Silverstein MN. Metastatic carcinoma simulating agnogenic myeloid metaplasia. *Cancer* 24: 1041-1044, 1969.

21. Spector JL, Levine PH. Carcinomatous bone marrow invasion simulating acute myelofibrosis. *Am J Med Sci* 266: 145-148, 1973.
22. Ozkalemkas F, Ali R, Ozkocaman V, et al. The bone marrow aspirate and biopsy in the diagnosis of unsuspected non-hematologic malignancy: a clinical study of 19 cases. *BMC Cancer* 5: 144, 2005.
23. Sari R, Aydogdu I, Ozen S, et al. Metastatic bone marrow tumours: a report of six cases and review of the literature. *Haematologia* 31: 215-223, 2001.
24. Contreras E, Ellis LD, Lee RE. Value of the bone marrow biopsy in the diagnosis of metastatic carcinoma. *Cancer* 29: 778-783, 1972.
25. Hyman GA, Harvey JE. The pathogenesis of anemia in patients with carcinoma. *Am J Med* 19: 350-356, 1955.
26. Samuels AJ, Bierman HR. Anemia in patients with neoplastic disease. *Calif Med* 84: 180, 1956.
27. Wong KF, Chan JK, Ma SK. Solid tumour with initial presentation in the bone marrow--a clinicopathologic study of 25 adult cases. *Hematol Oncol* 11: 35-42, 1993.

**Correspondence:**

Dr. Pelin AYTAN

Adana Baskent Universitesi

Dr. Turgut Noyan Uygulama ve Arastirma Hastanesi

Hematoloji Bolumu, Eriskin Kemik Iligi Nakli Unitesi

Dadaloglu Mah. 2591 Sok. No: 4/A

01250 Yüregir ADANA / TURKEY

Tel: (+90-532) 780 35 72

e-mail: drpelinaytan@gmail.com