Karya J Health Sci. 2023; 4(3): 187-191
ARAŞTIRMA MAKALESİ/RESEARCH ARTICLE doi: 10.52831/kjhs.1271864 e-ISSN:2717-9540

KARYA JOURNAL OF HEALTH SCIENCE

journal homepage: www.dergipark.org.tr/kjhs

THE IMPORTANCE OF CLINICAL AND LABORATORY PARAMETERS OF BONE MARROW METASTASIS IN PATIENTS WITH SOLID MALIGNANCY-SINGLE CENTER EXPERIENCE

KEMİK İLİĞİ METASTAZI OLAN SOLİD MALİGNİTELİ HASTALARDA KLİNİK VE LABORATUVAR PARAMETRELERİNİN ÖNEMİ-TEK MERKEZ DENEYİMİ

Sevil Sadri*[1], Jamshid Hamdard[2], Hüseyin Saffet Bekoz[3], Aslı Çakır[4], Ömer Fatih Ölmez[2], Ahmet Bilici[2]

[1]Department of Hematology, Bursa City Hospital, Bursa, Türkiye
[2]Department of Internal Medicine, Oncology, Faculty of Medicine, İstanbul Medipol University, İstanbul, Türkiye
[3]Department of internnal Medicine, Hematology, Faculty of Medicine, İstanbul Medipol University, İstanbul, Türkiye
[4]Department of pathology Faculty of Medicine, İstanbul Medipol University, İstanbul, Türkiye

ABSTRACT

Objective: Bone marrow biopsy is an efficient and reliable diagnostic procedure for the identification of bone marrow involvement. In recent years, bone marrow examination has become more helpful in documenting the metastatic involvement of malignancies.

Method: Patients with solid tumors and anomalies in hematological parameters had their peripheral blood morphology examined at our facility. Each instance included information on the patient's peripheral blood counts, peripheral blood morphology, and prior therapies. The purpose of this study was to analyze bone marrow biopsy and aspiration for unexplained hematological abnormalities in solid cancer patients and to look into the pathological findings, clinical and hematological laboratory features, and outcomes of such patients in our facility. Additionally, we provided information on the treatment and prognosis of these patients.

Results: When compared to the group that had bone marrow biopsy involvement, the lower RDW-Cv value in the former group was shown to be statistically significant (p=0.005; p<0.01). It was determined that the difference between the fibrosis values of the groups with and without bone marrow biopsy involvement was statistically significant (p=0.016; p<0.05). It was determined to be statistically significant (p=0.002; p<0.01) that the LDH value of the group without bone marrow biopsy involvement was lower than that of the group with BM biopsy involvement. Anemia (p=0.028; p<0.05), bone metastases (p=0.001; p<0.01), bone marrow biopsy involvement in PET-CT (p=0.001; p<0.01), and peripheral smear results (p=0.001; p<0.01) all showed a statistically significant correlation.

Conclusion: In conclusion, bone marrow metastasis should be considered when inexplicable hematological abnormalities, particularly unexplained anemia, and elevated RDW and LDH parameters are found in clinical practice. A bone marrow biopsy is advised for a conclusive diagnosis.

Key Words: Solid Malignancy, Bone Marrow Biopsy, Metastasis

ÖZ

Amaç: Solid tümörlerde kemik iliği biyopsisi, kemik iliği tutulumunun tanısında etkili ve kesin bir tanı yöntemidir. Son yıllarda, kemik iliği incelemesi tümörlerin metastatik tutulumunu belgelemede giderek daha kullanışlı hale gelmiştir.

Yöntem: Merkezimizde solid malignitesi olan ve hematolojik parametrelerinde anormallikleri olan hastaların periferik kan morfolojisi değerlendirildi. Hasta özellikleri; periferik kan sayımları, periferik kan morfolojisi, önceki tedavilerini dahil edecek şekilde kaydedildi. Bu çalışmanın amacı; solid kanserli hastalarda açıklanamayan hematolojik anormallikler için kemik iliği biyopsisi ve aspirasyonunu incelemek, bu tür hastaların patolojik bulgularını, klinik ve hematolojik laboratuvar özelliklerini ve sonuçlarını kurumumuzda araştırmaktı. Ayrıca bu hastaların yönetimi ve sağkalımı ile ilgili detaylar bildirildi.

Bulgular: Kemik iliği biyopsi tutulumu olmayan grupta daha düşük RDW-Cv değeri, kemik iliği biyopsi tutulumu olan gruba göre istatistiksel olarak anlamlı bulundu (p=0,005; p<0.01). Kemik iliği biyopsisi tutulumu olmayan grubun fibrozis değerinin kemik iliği biyopsisi tutulumu olan gruba göre daha düşük olması istatistiksel olarak anlamlı bulundu (p=0.016; p<0.05). Kemik iliği biyopsi tutulumu olmayan grubun LDH değerinin kemik iliği biyopsi tutulumu olan gruba göre daha düşük olması istatistiksel olarak anlamlı bulundu (p=0,002; p<0.01). Kemik iliği biyopsi tutulumu ile periferik yayma bulguları (p=0.001; p<0.01), PET-BT'de kemik iliği tutulumu (p=0.001; p<0.01), anemi (p=0.028; p<0.05) ve kemik metastazı (p=0.001; p<0.01) arasında istatistiksel olarak anlamlı ilişki bulundu.

Sonuç: Bu çalışmanın sonucunda klinik pratikte açıklanamayan hematolojik anormallikler, özellikle açıklanamayan anemi ve yüksek RDW ve LDH parametreleri saptandığında kemik iliği metastazı şüphesi düşünülmeli ve kesin tanı için kemik iliği biyopsisi önerilmektedir.

Anahtar Kelimeler: Solid Tümör, Kemik İliği Biyopsi, Metastaz

Makale Bilgisi/Article Info

Yükleme tarihi/Submitted: 27.03.2023, **Revizyon isteği/Revision requested:** 31.07.2023, **Son düzenleme tarihi/Last revision received:** 06.08.2023, **Kabul/Accepted:** 15.08.2023
***Sorumlu yazar/Corresponding author:** Bursa City Hospital, Department of Hematology, Bursa, Türkiye
[1*]Email: sevilsadri@hotmail.com, [2]Email: jamshidhamdard@hotmail.com, [3]Email: drhsynbkz@gmail.com, [4]Email: acakir@medipol.edu.tr,
[5]Email: omerfatih.olmez@medipol.com.tr, [6]Email: ahmetknower@yahoo.com

INTRODUCTION

Bone marrow metastases are found in 0.2%-12% of patients with solid tumors. It is most common in adults with breast, prostate, stomach, and small cell lung malignancies as well as in pediatric patients with neuroblastoma or Ewing sarcoma [1,2]. Bone marrow metastasis is a relatively uncommon occurrence, although it typically has a quickly progressing clinical course and a short survival time, which can influence the therapeutic strategy [3]. For the initial diagnosis of bone marrow metastasis in cancer, radiologic examinations using positron emission tomography (PET-CT), magnetic resonance imaging (MR), and computed tomography are the most often utilized non-invasive techniques [4]. Additionally, although bone marrow involvement can be suspected based on radiological imaging, a bone marrow biopsy is advised for a conclusive diagnosis. A bone marrow biopsy is specifically carried out to look at hematological parameter anomalies. The relatively invasive nature of this process makes it more prudent to use it when other approaches raise red flags. Anemia, thrombocytopenia, leukocytosis, elevated serum lactate dehydrogenase (LDH), and leukoerythroblastic picture are just a few of the laboratory characteristics related to bone marrow metastasis that have been highlighted in the literature, but their diagnostic significance has not yet been fully established [5].

For the accurate and conclusive diagnosis of bone marrow involvement, a bone marrow biopsy is used [6]. Examining the bone marrow has shown to be more and more helpful recently in identifying cancers that have spread to other organs. It has been proven to be more sensitive than biopsy specimen aspirate for evaluation of bone marrow, cellular morphology, cellularity, and fibrosis [7].

The current study's objectives are to assess the results of bone marrow aspiration and biopsy for unexplained hematological abnormalities in solid cancer patients, as well as to look into the pathological findings, clinical features, and hematological laboratory results of such patients at our institution. We also provided information on the treatment and survival of these patients.

METHOD

In the retrospective study, bone marrow biopsy and/or aspirations which were followed up in the oncology department with the diagnosis of solid malignancy, performed by a hematologist at İstanbul Medipol University were evaluated retrospectively. A sample was obtained from unilateral posterior iliac crest using a Jamshidi needle and employing standard technique. Based on its clinical details and morphological features, the sample was routinely stained with hematoxylin and eosin, immunohistochemical staining was performed, and reticulin and other special stains were used as needed. Bone marrow aspirates and biopsies were carried out concurrently between January 2014 and 2023 using the methods previously described. It was observed that there were more tumor cells in the bone marrow smears than there were in the bone marrow biopsies. The incidence of fibrosis, new bone formation, and necrosis were assessed in the biopsy specimens. White blood cell and platelet abnormalities, leukoerythroblastosis, anemia, and radiographic signs of bone metastases were all examined in the instances. When circulating normoblasts and a predominance of immature forms in the granulocytic series were found in the peripheral blood smear, leukoerythroblastosis was thought to be present. Leukopenia and thrombocytopenia were deemed to be indicated by values below 4,000 cells/mm^3 and 120,000 platelets/mm^3, respectively. Following a few successive processes, the pathologist successfully reached a conclusive diagnosis of the patient's metastases from an unidentified initial disease: With the use of morphological observations and, if necessary, immunohistochemical stains, we first attempted to identify the cell line of differentiation, such as carcinoma, lymphoma, melanoma, sarcoma, or germ cell. Each patient's features, such as presenting symptoms, time from start of symptoms, physical exam results, peripheral blood counts, peripheral blood morphology, diagnostic assessment, care, and survival, were noted. The following information was gathered: patient demographics, primary tumor, Eastern Cooperative Oncology Group performance status (ECOG PS), sites of involvement at the time bone marrow metastases were found, use of systemic antitumor therapy, time since diagnosis of bone marrow metastases, most common abnormality indicating a bone marrow aspiration should be performed, and survival times.

At our facility, bone marrow biopsies were carried out to assess and record the anomalies in hematological parameters. Each case included information on the patient's peripheral blood counts, peripheral blood morphology, prior therapies, and survival.

Ethical Approval

The study was approved by the research Ethics Committee of İstanbul Medipol University. Decision code:10840098-772.02-E.49752 (Date: 24.09.2020)

Statistical Analysis

At the beginning of the study, a power analysis was not performed. Responses was started with 78 cases. At the end of the study, it was determined that the parameters examined in the power analysis were medium effect size (d=0.65) in the groups, and the power of study was above 80% according to the post hoc power analysis. NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, descriptive statistical methods were used (Mean, Standard Deviation, Median, Frequency, Rate, Minimum, Maximum) along with Mann-Whitney-U test for two-group comparison with non-normal data distribution. Chi-square analysis was used to identify the relationship among qualitative data. Significance was evaluated at levels of $p<0.01$ and $p<0.05$. Pre-study strength analysis was not done for the weaknesses of the study, but 80% power analysis made over the values in the values in the groups after the study parameters.

RESULTS

In the present study, a total of 78 patients underwent bone marrow biopsy (Table 1).

Table 1. Distribution by diagnosis

Diagnosis	n	%
Prostate	10	12.8
Gastric Carcinoma	7	9
Breast Cancer	19	24.4
Lung	13	16.7
Pancreas	2	2.6
Colorectal	5	6.4
Bladder	2	2.6
Testicle	2	2.6
Ovary	3	3.8
Salivary gland	1	1.3
Uterus	4	5.1
HCC	2	2.6
GBM	3	3.8
Skin SCC	1	1.3
Head-Neck	1	1.3
Kidney	1	1.3
Thymus	1	1.3
Neuroblastoma	1	1.3

The mean diagnosis age was found to be 53.92±13.8. Leukocyte value varied between 0.73 and 20.12 10^3 /µL and the mean value was found to be 6.67 x 10^3 /µL±4.63. The hemoglobin value ranged between 6.5 to 14.7 g/dL with a mean value of 9.4±1.9. The platelet value ranged between 8 and 752x10^3 µL with a mean value of 96.78±120.69. The LDH value ranged from 141 to 3573 U/L with a median value of 300 (Table 2).

Table 2. Measurement averages

Variables	Mean±SD	Min-Max (Median)
Diagnosis Age	53.92±13.8	21-92 (55)
WBC	6.67±4.63	0.73-20.12 (5.33)
Neutrophil	4.8±3.77	0.25-18.6 (3.64)
HGB	9.4±1.9	6.5-14.7 (9.05)
PLT	96.78±120.69	8-752 (54)
MPV	10.35±1.1	7.6-13.3 (10.35)
RDWCv	17.15±3.04	11.7-25.8 (16.75)
BM Involvement Percentage	33.18±40.07	0-100 (7.5)
Ret. Fibrosis	0.69±0.84	0-3 (1)
LDH	601.91±748.7	141-3573 (300)
Calcium	8.8±0.91	6.21-10.41 (8.9)
BM Involvement Follow-Up Time (Months)	4.41±3.76	0.5-15 (4)

In the patient group with bone marrow involvement (n:39), the percentage of bone marrow involvement was 5-100 (median 70).

Evaluation of the PET-CT results of the patients revealed that 74.4% (n=58) had bone marrow involvement in PET, while 25.6% (n=20) had not. When evaluating the metastases, 66.1% (n=39) had bone metastasis, 62.7% (n=37) lymph node, 42.4% (n=25) liver, 33.9% (n=20) lung, 15.3% (n=9) brain, 13.6% (n=8) adrenal and 11.9% (n=7) peritoneal had bone metastases (Table 3).

Table 3. Distribution by metastasis type

Metastasis Type	N	%
Bone	39	66.1
LAP	37	62.7
Lung	20	33.9
Liver	25	42.4
Brain	9	15.3
Peritoneum	7	11.9
Surrenal	8	13.6

Peripheral smear evaluation performed by a hematologist prior to bone marrow biopsy revealed 51.3% (n=40) to be normal, while 48.7% (n=38) had a leukoerythroblastic picture.

79.5% (n=62) of the patients did not have pancytopenia, while only 20.5% (n=16) were pancytopenic. When examining the bone marrow biopsy results, 50% (n=39) had biopsy involvement, while 50% (n=39) did not. In line with these results, 56.9% (n=41) of the patients continued with the current treatment, while there was a change of treatment in 43.1% (n=31). Considering the final status of the patients, 66.2% (n=51) were exitus, while only 33.8% (n=26) were alive.

The parameters of age at diagnosis, diagnosis of disease, gender, leukocyte, neutrophil, hemoglobin, thrombocyte and MPV calcium values, and follow-up period did not have a statistically significant difference according to bone marrow biopsy involvement (p>0.05). The lower RDW-Cv value in the group without bone marrow biopsy involvement was found to be statistically significant compared to the group with bone marrow biopsy involvement (p=0.005; p<0.01). The fact that the fibrosis value of the group without bone marrow biopsy involvement was lower than the group with bone marrow biopsy involvement was found to be statistically significant (p=0.016; p<0.05). The fact that the LDH value of the group without bone marrow biopsy involvement was lower than the group with BM biopsy involvement was found to be statistically significant (p=0.002; p<0.01) (Table 4).

Table 4. Comparison of measurements according to BM biopsy involvement

Variables	n		Mean±SD	Min-Max (M)	p
Diagnosis Age	No	39	52.79±15.59	21-92 (55)	0.596
	Yes	39	55.05±11.84	29-85 (55)	
WBC	No	39	6.44±5.33	0.73-20.12 (4.06)	0.146
	Yes	39	6.9±3.88	2.09-16.46 (6)	
Neutrophil	No	39	4.77±4.56	0.25-18.6 (2.87)	0.129
	Yes	39	4.83±2.82	1.33-10.92 (3.96)	
HGB	No	39	9.76±2.05	6.5-14.2 (9.2)	0.098
	Yes	39	9.04±1.7	6.7-14.7 (8.8)	
PLT	No	39	118.23±154.29	8-752 (58)	0.294
	Yes	39	75.33±69.05	16-340 (50)	
MPV	No	39	10.51±1.05	8.6-12.4 (10.6)	0.140
	Yes	39	10.18±1.13	7.6-13.3 (10.1)	
RDW-Cv	No	39	16.24±2.81	11.7-25.8 (15.6)	**0.005****
	Yes	39	18.05±3.02	11.9-23.9 (17.8)	
Reticulin Fibrosis	No	39	0.44±0.55	0-2 (0)	**0.016***
	Yes	39	1±1.02	0-3 (1)	
LDH	No	39	311.96±239.41	141-1209 (227)	**0.002****
	Yes	39	1062.41±1022.81	162-3573 (768)	
Calcium	No	39	8.76±0.94	6.21-10.32 (8.95)	0.980
	Yes	39	8.84±0.88	7.72-10.41 (8.8)	
Follow-Up Time (Months)	No	39	4.2±3.83	1-10 (3)	0.875
	Yes	39	4.44±3.81	0.5-15 (4)	

*Mann Whitney U Test; *p<0.05; **p<0.01; M: Median.*

A statistically significant relationship was found between bone marrow biopsy involvement and peripheral smear findings (p=0.001; p<0.01), bone marrow involvement in PET-CT (p=0.001; p<0.01), anemia (p=0.028; p<0.05) and bone metastasis (p=0.001; p<0.01) (Table 5).

There was no statistically significant relationship between bone marrow biopsy involvement and thrombocytopenia and whether the patient reached the final status (p>0.05) (Table 4).

Table 5. The relationship between BM biopsy involvement and findings

Variables		BM Biopsy Involvement		p
		No	Yes	
Peripheral Smear Findings	N	29 (74.4%)	11 (28.2%)	**0.001****
	L	10 (25.6%)	28 (71.8%)	
Treatment	TO	34 (94.4%)	7 (19.4%)	**0.001****
	CT	2 (5.6%)	29 (80.6%)	
PetBM Involvement	No	37(94.9%)	21 (53.8%)	**0.001****
	Yes	2 (5.1%)	18 (46.2%)	
Anemia	No	7 (17.9%)	1 (2.6%)	**0.028***
	Yes	32 (82.1%)	38 (97.4%)	
Neutropenia	No	24 (61.5%)	33 (84.6%)	**0.020***
	Yes	15 (38.5%)	6 (15.4%)	
Pancytopenia	No	27 (69.2%)	35 (89.7%)	**0.024***
	Yes	12 (30.8%)	4 (10.3%)	
Bone Metastasis	No	30 (76.9%)	9 (23.1%)	**0.001****
	Yes	9 (23.1%)	30 (76.9%)	

*N: Normal; L: Leukoerythroblastic; TO: Treatment Ongoing; CT: Change in Treatment; Chi-Square Test; **p<0.01.*

DISCUSSION

The authors of the current investigation examined the clinical laboratory characteristics of this patient population as well as the efficacy and prognostic importance of osteoporosis in patients with metastatic cancer. Bone marrow is a significant metastatic site for solid tumors, even if this is not particularly common. This increases the risk of cytopenia, which in turn raises the risk of bleeding and infection [8]. Though theoretically any solid tumor could spread to the bone marrow, the most frequent cancers that do so in humans are lung, prostate, and breast cancers. Parallel to our study the most common cancer types that metastasize were determined to be breast Ca (24.49%), lung Ca (16.7%), and prostate Ca (12.8%) in the current study [9-12].

Bone marrow metastasis is an indicator of poor prognosis. An easy and quick way to detect it is bone marrow aspiration and biopsy. In cases with suspected bone marrow metastasis, biopsy is recommended for diagnosis [13].

Leukoerythroblastic picture, cytopenia and high RDW value have been accepted as indicators for bone marrow metastasis [14,15]. In the present study, high RDW value (p=0.005) and leukoerythroblastic picture in peripheral smear (p=0.0001) were significant indicators of bone marrow involvement.

Although Aksoy et al. [16] stated that low MPV value was also significant for bone marrow involvement, MPV value was not found to be statistically significant in the present study (p>0.05).

In the previous studies, high LDH and alkaline phosphatase (ALP) values and hypoproteinemia levels are considered important markers for bone marrow metastasis [9,14,15]. In the present study, ALP and protein levels could not be measured; LDH values, however, were found to be statistically significantly higher in patients with bone marrow involvement (p=0.002; p<0.01).

Many publications state that there is a significant decrease in survival rates in patients with bone marrow involvement [17,18]. Although, in the present study, the authors did not find it to be statistically significant, a large percentage (73.7%) of those with bone marrow involvement died in a short span of time (p=0.172).

Numerous studies show that leukoerythroblastic picture and fibrosis are associated with bone marrow involvement [19-21]. Parallelly, in the present study, statistically significant reticulin fibrosis is more common in patients with bone marrow involvement (p=0.016).

In their study, Kopp et al. stated that all patients with bone marrow metastases also had bone metastases [22]. Similar to this, a research performed at an Indian cancer center documented 90 bone marrow procedures carried out in cases of probable bone marrow involvement in nonhematologic malignancies. The majority of malignancies that metastasis are malignant tiny round cell tumors (Ewing's sarcoma and rhabdomyosarcoma), followed by carcinoma of the breast and prostate in 16 out of 90 individuals. Only one case of clear cell RCC metastasized to the bone marrow [12]. The present study also revealed a significantly close relationship between bone marrow metastases and bone metastases. A statistically significant correlation was found between BM biopsy involvement and bone metastasis (p=0.001; p<0.01).

The invasion of highly vascularized bone marrow and the hematogenous dissemination of circulating tumor cells are both symptoms of bone marrow metastases (BMM). They appeared as the supression of hematopoietic function, including anemia, thrombocytopenia, and aberrant coagulation [23]. Anemia was the most common reason for a bone marrow test in our study. The majority of cases for which a bone marrow examination is indicated include anemia (34.4%), according to Katiyar et al [24]. Compared to studies by authors from the Indian subcontinent, such Katiyar, who found that megaloblastic anemia was the most prevalent diagnosis, accounting for 28.1% of cases [25].

Additionally, with recent improvements in technical methods, bone scanning with PET/CT has become more crucial in the diagnosis of bone marrow metastases. In the Zhou et al. investigation, a PET/CT scan of the bone marrow samples taken from 5 patients who had bone marrow involvement validated the diagnosis of metastasis [26]. In the current study, 25.6% (n=20) of the participants exhibited PET involvement, and BM biopsy participation and PET BM involvement were found to be significantly correlated (p=0.001; p<0.01). Bone marrow biopsy is still advised for patients who may change their treatment modality, despite the fact that it is not currently regularly advised. Hematological abnormalities in solid tumors may have several sources. In order to raise suspicion, identify, and expedite the diagnosis process of bone marrow involvement, specific parameters should be given importance.

Limitations

The present study had limitations because it was retrospective, covered a variety of illness groups, and only looked at a small number of individuals. A prospective study would be helpful in this area. However, more research is need to verify this conclusion in the present era.

CONCLUSION

As a result of the current study, it is advised to suspect bone marrow metastasis whenever unexplained hematological abnormalities in particular, unexplained anemia, high RDW, and LDH parameters are found in clinical practice. A bone marrow biopsy is also advised for a definitive diagnosis.

Ethical Approval: *2020/703 Non-interventional Clinical Research Ethics Committee of İstanbul Medipol University*

Conflict of Interest: *The authors have no conflicts of interest to declare.*

Funding: *None.*

Acknowledgements: *None.*

Author Contribution: Concept: *SS,JH,HSB,ÖFÖ,AB;* ***Design:*** *SS,JH,HSB;* ***Data collecting:*** *AÇ;AB;ÖFÖ;* ***Statistical analysis:*** *AÇ,SS,JH;* ***Literature review:*** *SS,AÇ,AB,ÖFÖ;* ***Writing:*** *SS,AÇ,AB,ÖFÖ;* ***Critical review:*** *SS,JH,HSB,AÇ,ÖFÖ,AB.*

REFERENCES

1. 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;15(1):1-7.
2. Barekman CL, Fair KP, Cotelingam JD. Comparative utility of diagnostic bone-marrow components: a 10-year study. Am J Hematol. 1997;56(1):37-41.
3. Banys M, Solomayer EF, Becker S, et al. Disseminated tumor cells in bone marrow may affect prognosis of patients with gynecologic malignancies. Int J Gynecol Cancer. 2009;19(5):948-952.
4. Fischer BM, Mortensen J, Langer SW, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. Ann Oncol. 2007;18:338-345.
5. Chernow B, Wallner SF. Variables predictive of bone marrow metastasis. Cancer. 1978;42(5):2373-2378.
6. Papac RJ. Bone marrow metastases. A review. Cancer. 1994;74(9):2403-2413.
7. 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. 2011;2(3):110.
8. Kilickap S, Erman M, Dincer M, Aksoy S, Hakan H, Yalcin Y. Bone marrow metastasis of solid tumors: clinicopathological evaluation of 73 cases. Turk J Cancer. 2007;37(3):85-88.
9. Wong KF, Chan JK, Ma SK. Solid tumour with initial presentation in the bone marrow--a clinicopathologic study of 25 adult cases. Hematol Oncol. 1993;11(1):35-42.
10. Mohanty SK, Dash S. Bone marrow metastasis in solid tumors. Indian J Pathol Microbiol. 2003;46(4):613-616.
11. Sharma S, Murari M. Bone marrow involvement by metastatic solid tumors. Indian J Pathol Microbiol. 2003;46(3):382-384.
12. Chauhan K, Jain M, Grover S, Shukla P, Rusia U, Grover RK. Bone marrow metastasis in nonhematologic malignancies: Data from a cancer hospital. Clin Cancer Investig J. 2016;5:103-109.
13. Ingle JN, Tormey DC, Bull JM, Simon RM. Bone marrow involvement in breast cancer: Effect on response and tolerance to combination chemotherapy. Cancer. 1977;39(1):104-111.
14. Ozkalemkas F, Ali R, Ozkocaman V, et al. The bone marrow aspirate and biopsy in the diagnosis of unsuspected nonhematologic malignancy: a clinical study of 19 cases. BMC Cancer. 2005;5:144.
15. Yun HK, Shin MG, Bo D, et al. Laboratory evaluation of bone marrow metastasis: single institute study. Korean J Lab Med. 2007;27(2):96-101.
16. Aksoy S, Kilickap S, Hayran M, et al. Platelet size has diagnostic predictive value for bone marrow metastasis in patients with solid tumors. Int J Lab Hematol. 2008;30(3):214-219.
17. Demir L, Akyol M, Bener S, et al. Prognostic evaluation of breast cancer patients with evident bone marrow metastasis. Breast J. 2014;20(3):279-287.
18. Chou WC, Yeh KY, Peng MT, et al. Development and validation of a prognostic score to predict survival in adult patients with solid tumors and bone marrow metastases. Medicine (Baltimore). 2015;94(23):e966.
19. Navone R, Colombano MT. Histopathological trephine biopsy findings in cases of 'dry tap' bone marrow aspirations. Appl Pathol. 1984;2(5):264-271.
20. D'Angelo G, Hotz AM. Myelophthisis in breast cancer. Am J Hematol. 2011;86(1):70-71.
21. Makoni SN, Laber DA. Clinical spectrum of myelophthisis in cancer patients. Am J Hematol. 2004;76(1):92-93.
22. Kopp HG, Krauss K, Fehm T, et al. Symptomatic bone marrow involvement in breast cancer-clinical presentation, treatment, and prognosis: a single institution review of 22 cases. Anticancer Res. 2011;31(11):4025-4030.
23. Khan S, Awan SA, Jahangir S, Kamran S, Ahmad IN. Bone Marrow Metastasis in Clear Cell Renal Cell Carcinoma: A Case Study. Cureus. 2019;11(3):e4181.
24. AljadayehM, SaidatS, KamalN, Obeidat M. Comparative evaluation between bone marrow aspirate and biopsy morphological findings, Experience at King Hussein Medical Center. J Royal Med Serv. 2015;22(2):18-22.
25. Katiyar G, Arya A, Kumar P. Bone marrow aspiration; role and significance in haematological disorders. Indian J Appl Res. 2017;7(10):3-5.
26. Zhou MH, Wnag ZH, Zhou HW et al. Clinical outcome of 30 patients with bone marrow metastases. Journal of cancer Research and Therapeutics. 2018;9(14):512-515.