ISSN: 0975-1556

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(1);475-482

Original Research Article

Non haematogenous Metastatic Deposits to the Bone Marrow: A Case Series During a 5 year Period from a Tertiary Teaching Hospital in Manipur, North-East India

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Received: 02-11-2021 / Revised: 30-11-2021 / Accepted: 19-12-2021
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Conflict of interest: Nil

Abstract

The bone marrow is commonly involved in both primary and secondary malignancies. Detection of bone marrow metastasis has significant clinical implications with impact on therapeutic decisions and is associated with poor prognosis. In some cases, it may be detected incidentally providing a means to proper diagnosis & subsequent confirmation. Here, we present a case series of bone marrow metastasis by solid non-haematogenous malignancies over a period of 5 years. We emphasise the importance of bone marrow examination in providing an easy, cheap and quick yet effective way of detecting metastatic involvement in patients with malignancies that have a tendency to involve the bone marrow.

Keywords: Bone marrow, metastasis, immunohistochemistry, non-haematological solid tumors, bone marrow aspiration, bone marrow trephine biopsy.

Introduction

The bone marrow is commonly involved in both primary haematological and metastatic non-haematological malignancies [1-3] and is one of the commonest sites of metastasis. Any tumor that metastasizes via the haematogenous route may also get

deposited in the bone marrow, though the event may be rare [1,2]; this results in a worsened prognosis as it upgrades the clinical staging of the primary malignant tumor which results in a reduced overall survival, poor response to treatment and many other manifestations from impaired haematopoiesis [4-10].

Bone marrow metastasis by solid non-haematological malignant tumors may be suspected on the basis of bone pains, pathological fractures, radiologic features of lysis or sclerosis, unexplained "hot spots" on isotopic bone scans, hypocalcaemia or elevated serum alkaline phosphatase levels and unexplained cytopenias or a leucoerythroblastic picture on routine peripheral blood smear examination. However, some cases may also be asymptomatic [7,8].More advanced diagnostic procedures like bone scan, positron emission tomography (PET)/computed tomography (CT) and PET/magnetic resonance imaging (MRI) are more sensitive in assessing the bone marrow involvement [4,10], but these procedures have limited availability and are very expensive [1].Confirmation of the suspected metastasis cases, however, still requires bone marrow examination (BME) including immunohistochemistry (IHC) wherever needed [4]. In view of the huge cost of these procedures, especially in developing countries, BME is still the most preferred investigation as it is simple, fast, economical, safe yet effective in the diagnosis of metastasis as well as to monitor the prognosis [1,4]. The haematological findings especially the degree of cytopenias can be correlated with the extent of bone marrow metastasis for a good overview about patient survival [1].

Apart from knowing the stage and prognosis of solid tumors, BME can also detect metastatic marrow deposits from unknown asymptomatic primary lesions [1,4,6]. Some authors have reported that some malignant non-haematogenous solid tumors may present initially with metastasis in the marrow [1,6].

BME, whether bone marrow aspiration (BMA) or bone marrow biopsy (BMB), are well known procedures used for the diagnosis, prognosis and management of haematological diseases and malignancies and usually involves two separate preparations: a cytologic (aspiration) and a histologic (trephine biopsy) preparation. Aspiration helps to visualize individual cell morphology, while trephine biopsy helps to evaluate marrow cellularity, fibrosis or infiltration in marrow [1] and has been proven to be more sensitive in identifying metastatic lesions in many studies [1-3,11,12]. BMB is also preferred when the BMA fails to yield bone marrow material (dry tap) on attempted aspirations, which may be due to hypercellularity or marrow fibrosis [1].

Thus these two procedures, aspiration and biopsy should therefore be regarded as complementary in order to rule out or diagnose bone marrow metastasis, to stage and monitor the prognosis, as well as to further classify the type of metastatic tumor cells which is important in the work up of cases of unknown primary malignancies[1,2,6,7].

Thus, bone marrow examination is an easy, sensitive, rapid and cost-effective method of reporting metastasis in a very short span of time [1].

Aims and objectives: Here, we report a series of six cases, three of whom presented initially with bone marrow metastasis as the first presentation and the other three were known case of primary with marrow metastasis. We further emphasise the role of BME as a short-cut in establishing a diagnosis for disseminated tumors with non-hematologic malignancies.

Bone marrow examinations were carried out on 423 patients at the Hematology division of the Department of Pathology, Jawaharlal Nehru Institute of Medical

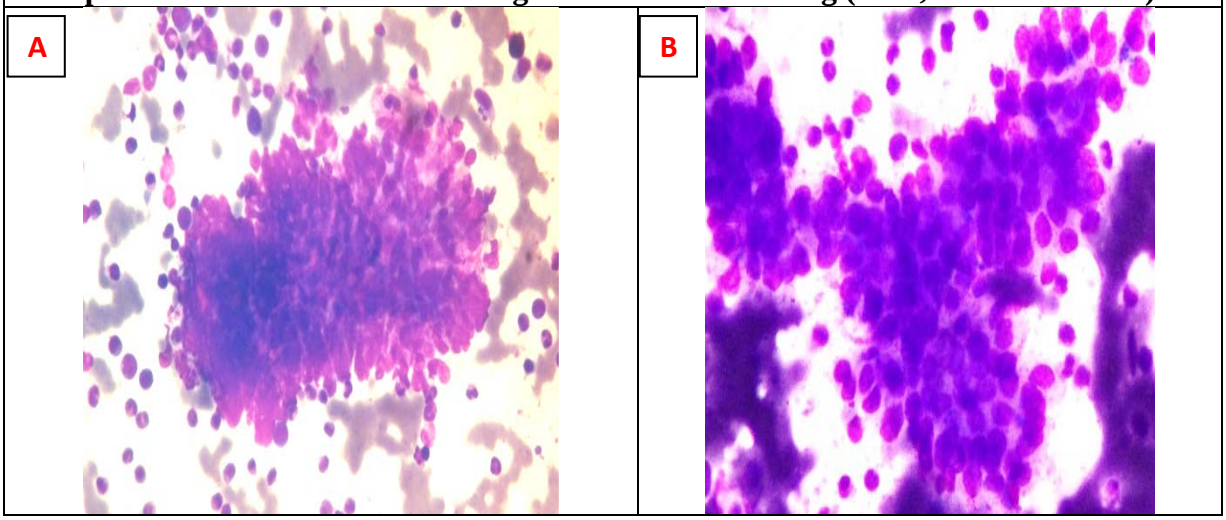
Sciences, Manipur, India over a period of 5 years (2017-2021). All case sheets, bone marrow registers and bone marrow slides during the study period were retrieved and reviewed. Ethical clearance was obtained from the institutional ethical committee.

Primary haematological malignancies like lymphoma (non-Hodgkin and Hodgkin), multiple myeloma, leukaemia and histiocytic malignancies were excluded from this study. Patient characteristics, including the age, sex, presenting symptoms and diagnostic evaluation were recorded for each case.

Clinical presentations.

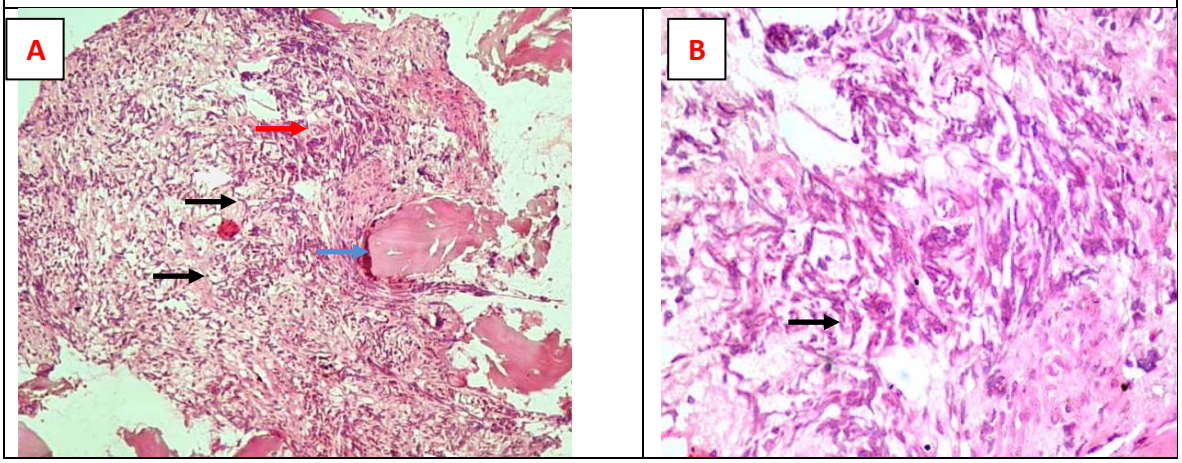
Case 1: A 64-year-old man was referred to our hospital from another centre. He was a known case of nasopharyngeal carcinoma (NPC) and presented with complaints of generalized weakness and loss of appetite. On general examination, there was pallor. BMA done was aparticulate and showed a few tight clusters of malignant cells with moderate nuclear: cytoplasmic(N:C) ratio, round nuclei with dispersed chromatin and moderate to scanty amount of cytoplasm. Features of overcrowding and nuclear moulding were also noted (Figure1). Megakaryopoiesis was increased and erythropoiesis showed normoblastic maturation.

Figure 1A-B: BMA smear from a patient with NPC showing clusters of metastatic epithelial cells with overcrowding and nuclear moulding (400x, Leishman stain)



Case 2: A 2 year 10-month-old girl was referred to our Hospital. She was a known case of neuroblastoma and presented with complaints of weakness. Both BMA and bilateral BMB were performed. BMA was aparticulate, poorly cellular and haemodiluted; megakaryocytes were not seen. BMB showed mostly washed-out spaces and a few well preserved intertrabecular spaces with extensive myelofibrosis; occasional areas showed clusters of small round cells (Figure 2). Reticulin stain showed Grade 2+ fibrosis (on a scale of 0 to 3+). Impression was given as suspicious of infiltration. IHC for chromogranin A, CD56 and synaptophysin markers were positive on the metastatic foci.

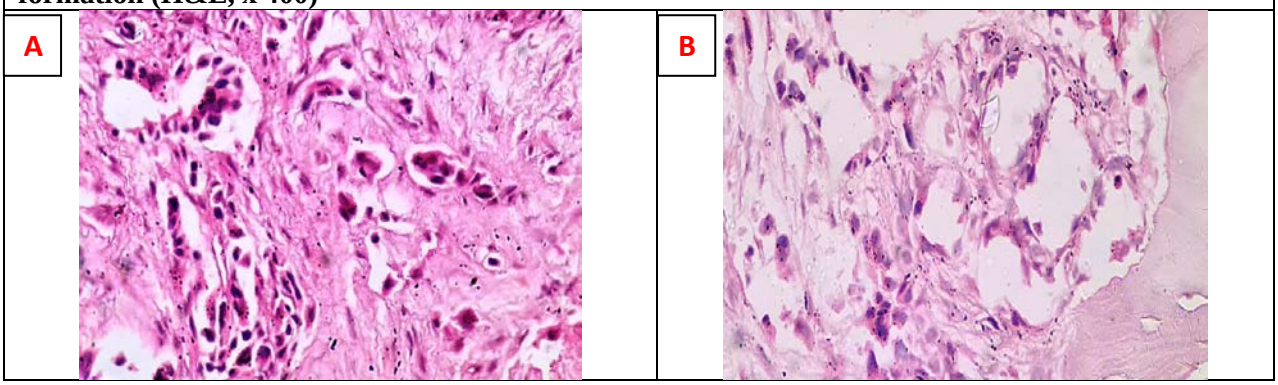
Figure 2 A-B: A-BMB showing a metastatic focus (red arrow) in a background of myelofibrosis (blue arrow) and dilated sinuses (black arrow) (H&E,x100). B-Nests of small round tumor cells with salt and pepper chromatin and round to ovoid nuclei (H&E, x400).



Case 3: A 3 year 6-month-old boy was referred to our Hospital. He was a known case of neuroblastoma and presented with complaints of weakness and loss of appetite. Bilateral BMB was performed which showed interstitial infiltration by small round cells with pseudorosette formation at places in a background of fibrosis and oedema; all three hematopoietic lineage elements were reduced. Impression was given as evident of infiltration. IHC for chromogranin A and CD56 stained positive.

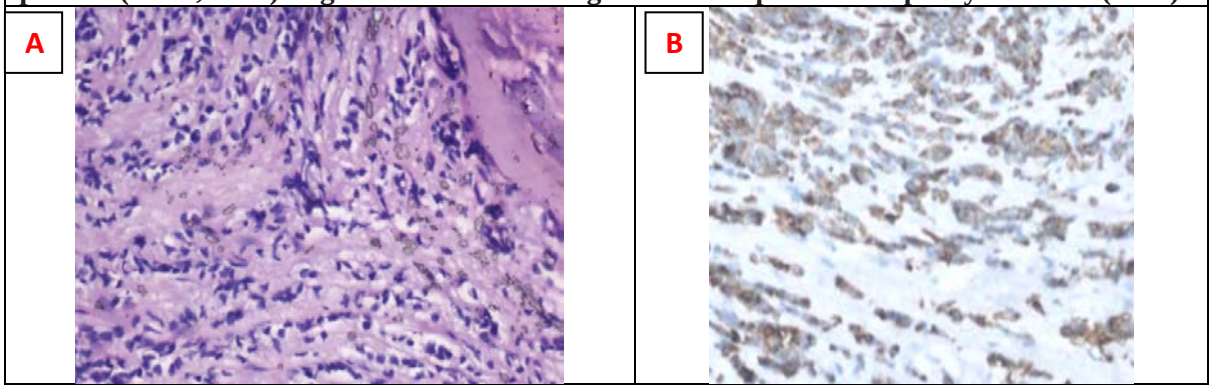
Case 4: A 70-year-old man was admitted to our Hospital (Orthopaedics Ward) with complaints of left inguinal swelling. On local examination, there was tenderness. There was no pallor/jaundice/purpura. X-ray pelvis revealed an osteolytic lesion over the right superior pubic ramus. Ultrasound abdomen showed no organomegaly. Laboratory findings revealed haemoglobin level of 12.5g/dl (N:13-15g/dl), packed cell volume of 37.7% (N:37-54%), total leucocyte count 8x103/cumm (N:4-10x103/cumm), platelets 440x103/cumm (N:150-500x103/cumm), ESR 20mm/hr, peripheral blood smear showed normocytic normochromic blood picture. Liver and kidney function tests were normal. The patient was advised for BME (both aspiration and bilateral trephine biopsy) under suspicion of multiple myeloma. BMA was particulate and cellular and showed normal megakaryopoiesis with normoblastic erythropoiesis. Bilateral BMB cores measured 1.5cm and 1.3 cm with normocellular to mildly hypercellular marrow spaces; all three haematopoietic elements were normal; focal areas of fibrosis were noted with malignant tumor cells in vague glandular pattern and in singles (Figure 3). Impression was given as suggestive of metastatic carcinoma. IHC was done which showed tumor cells positive for pancytokeratin. Further follow up revealed primary in the lungs (adenocarcinoma).

Figure 3A-B: A-BMB showing clusters of tumor cells in glandular formation with desmoplastic reaction in the surrounding stroma (H&E, x 100). B-Metastatic adenocarcinoma cells in glandular formation (H&E, x 400)



Case 5: A 60-year-old man was admitted to our Hospital (Medicine ward) with complaints of easy fatigability for 3 months. On general examination, the patient had pallor. Laboratory findings showed a haemoglobin level of 8.5g/dl (N:13-15g/dl), total leucocyte count of 5.6x103/cumm(N:4-10x103/cumm), platelet count of 388x103/cumm(N:150-500x103/cumm), red cell distribution width was 15.6% (N:11-16%). The patient was investigated for moderate anaemia. BM examination was advised. During the procedure, BMA was attempted thrice but the posterior iliac crest was extremely hard that 2 aspiration needles got bent and yielded a dry tap. Bilateral BMB was performed which showed a hypocellular marrow with extensive fibrosis; **t**here were malignant cells with scanty cytoplasm and vesicular nuclei with inconspicuous nucleoli arranged in trabecular and acinar pattern; trilineage haematopoietic elements were reduced (Figure 4). Impression was given as positive for metastasis. The patient was retrospectively re-evaluated for a possible primary and it was revealed that he had a prolonged history of prostate enlargement and was asymptomatic at the time of admission. IHC was done on the trephine biopsy sample and the tumor cells stained positive for pancytokeratin (Figure 4B) and negative for PSA, CD3, CD45 and CD4. Serum PSA level was found to be markedly increased (669.5ng/ml) with reduction in the ratio of serum free PSA: serum total PSA. So the final diagnosis was carcinoma prostate with metastasis to the bone marrow.

Figure 4A: HPE of BMB showing metastatic prostatic tumor cells in single files and acinar pattern (H&E, x100). Figure 4B: IHC showing tumor cells positive for pancytokeratin (x400)



Case 6: A 60-year-old man presented to our Hospital Casualty with back pain and burning micturition. Ultrasound abdomen done showed common bile duct dilatation. He developed pneumonia and was under ventilatory support for a few days after which his clinical condition improved. Computed tomography of thorax was done which showed multiple punched out lytic lesions in the bone. Complete blood count revealed a haemoglobin of 8.7gm/dl (N:13-15gm/dl), total leucocyte counts 6.7x103/cumm(N:4-10x103/cumm), platelet count 188x103/cumm(N:150-500x103/cumm), RBC count 3x106/cumm (N:3.8-6x106/cumm), RDW 13.5% (N:11-16%), peripheral blood smear showed normocytic normochromic blood picture. The patient was advised BM examination with a clinical suspicion of multiple myeloma. The BMA was aparticulate and hemodiluted and showed normoblastic erythropoiesis with normal megakaryocytes; however, there were clusters and dispersed malignant tumor cells having moderate N:C ratio, inconspicuous nucleoli and indistinct cellular margins; nuclear moulding was noted; background showed necrotic debris. BMB core measuring 1cm showed discrete clusters of malignant cells in the interstitium with focal areas of fibrosis; histiocytes appeared increased (Figure 5A, B). Impression was given as metastasis in the bone marrow (possibly from hepatocellular origin). The patient was lost to follow-up.

Figure 5A, B : HPE of BMB showing a metastatic cluster in the marrow A low power view (x100). B showing clusters of tumor cell (x400)

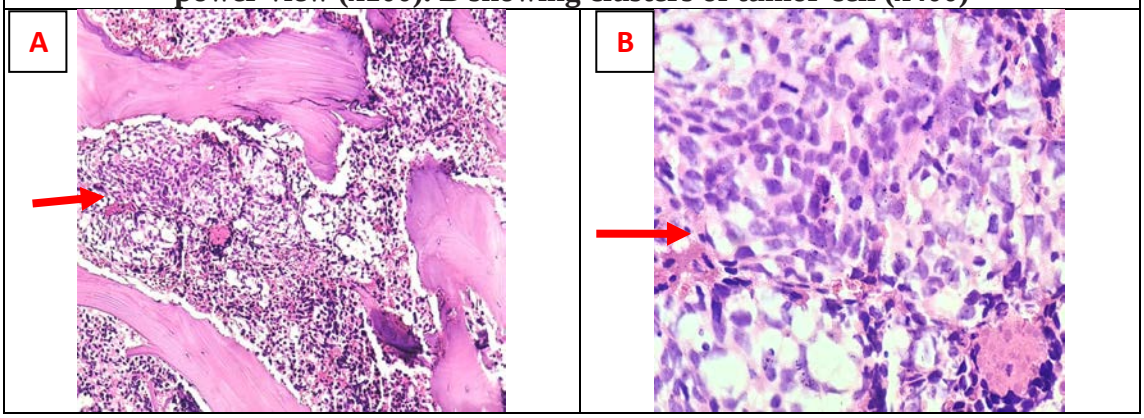


Table1: Frequency of cases with metastasis to bone marrow	
Primary malignant tumor	Frequency
Neuroblastoma	2
Prostate	1
Lung	1
Nasopharynx	1
Unknown (Probably Liver)	1

Table 2: Degree of marrow fibrosis of each case as per BM biopsy		
Sl no	Primary lesion	Degree of fibrosis
1	Neuroblastoma	Grade 2 fibrosis
2	Neuroblastoma	Background of fibrosis
3	Lung	Focal fibrosis
4	Prostate	Extensive fibrosis
5	(?) Liver	Focal fibrosis

Discussion:

Incidence: In our case series, 6/423 cases showed metastatic BM infiltration from solid non-haematogenous malignancies, showing an incidence of 1.42%, which was slightly higher than studies by Kumar et al[4] where the overall incidence was 0.74%. Incidental diagnosis of metastasis in the marrow was seen in 3/423 (0.71%), almost comparable to studies Ozkalemkas et al[2], where incidental diagnosis of metastasis was seen in 0.35% of the cases.

Detecting these metastatic cells in the marrow is not very difficult as they appear very different from the normal haematopoietic tissue; however, their morphology may not reveal the exact primary tissue of origin. In these cases, the morphology of these tumor cells should be correlated with the clinical presentation, histopathological findings aided by ancillary studies like IHC, and relevant biochemical and radiological profile to clinch the ultimate diagnosis [1,4,6]. In our case series, the 3 cases with unknown primary presented with bone pains and refractory anaemia. Further clinical work-up and investigations like IHC for pancytokeratin, PSA, etc clinched the diagnosis of lung carcinoma in one case and prostate carcinoma in the other. The third case was lost to follow up.

Metastasis from carcinoma prostate was equally as common as that from lungs, liver or NPC in contrast to other studies by Kumar et al [4], where prostate was the most common primary.

There is no specific finding that may indicate bone marrow infiltration [2]. The blood counts could be normal [1,2] and peripheral smear findings may not differ much from those without marrow involvement[2]. In some cases, normal haemopoiesis may be affected leading to cytopenias [1,4].Advanced stages of bone marrow infiltration may result in thrombocytopenia with bleeding tendencies. In our case series, unexplained anaemia was the most common haematological finding, similar to few other studies[1-4,6,11,12]. Normocytic normochromic anaemia was the most common peripheral blood smear finding in our series, similar to studies by Kumar et al[4]and Kaur et al [11], in contrast to other studies[2,10]where leucoerythroblastic blood picture was the main finding in cases with metastatic marrow.

Marrow infiltration by metastatic tumor may be focal or diffuse. Marked fibrosis has been reported to be most common in carcinomas of the prostate. We also detected marked fibrosis in the case of prostate carcinoma with bone marrow metastasis (Table 2), similar to studies by Kaur et al [11].

In our case series, neuroblastoma was the most common malignancy with metastasis to the marrow among paediatric cases, similar to other studies by Kumar et al [4] and Rudresha et al [6}.

The age of all the patients ranged from 2 to 76 years, with a mean and median age group of 45 and 62 years respectively, almost similar to other studies [2,4,5] , with majority 4(66.67%) being adults, comparable to studies by Kumar et al [4].

Conclusion:

Bone marrow examination (simultaneous bilateral trephine biopsy with bone marrow aspiration) is effective, quick and cheap and helps in evaluating solid non-haematogenous tumors metastatic to bone marrow. A clue to the primary site can also be suggested if unknown with the help of IHC and clinical history with radiological findings. This case series is being presented for its rarity.

References:

1. Mehdi SR, Bhatt ML. Metastasis of solid tumors in bone marrow: a study from northern India. Indian J Hematol Blood Transfus. 2011 Jun;27(2):93-5.

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.
3. Saigal A, Murgai P, Sharma SK, Gulati A and Kaushik R. 2019. "Bone marrow examination for metastatic tumor–a case series", International Journal of Current Research, 11, (04), 2922-2924.
4. Kumar V, Sardana R, Kishore M, Marwah S, Nigam AS, Bhardwaj M. (2019). Bone Marrow Cytomorphology and Clinico-Hematological Profile of Metastatic Solid Tumors: A 5-Year Audit from A Tertiary Care Centre in Northern India. 6. A-129. 10.21276/APALM.2290.
5. Zhou MH, Wang ZH, Zhou HW, Liu M, Gu YJ, Sun JZ. Clinical outcome of 30 patients with bone marrow metastases. J Can Res Ther 2018;14:S512-5.
6. Rudresha AH, Patidar R, Lakshmaiah KC, Babu KG, Lokanatha D, Jacob LA, Babu MCS, Namrata NR, Kadabur NL, Rajeev LK, Anand A, AsatiV. Pattern of bone marrow involvement by solid tumors: Experience from a tertiary care center from South India. Indian J Med Paediatr Oncol2019;40:S99-101.
7. JalalyMeenai F, Ojha S, Ali M, JainR,Sawke N. (2018). Bone Marrow Involvement in Non-Hematological Malignancy: A Clinico-pathological Study From a Tertiary Hospital. Annals of Pathology and Laboratory Medicine. 5. A440-446. 10.21276/APALM.1723.
8. YeşilÇınkır H, Bozdağ Z. Prostate Cancer and Bone Marrow Involvement. İstanbul Med J 2020; 21(3): 196-9.
9. Betsch DM, Gray S, Zed SE. A case of metastatic prostate cancer and immune thrombocytopenia. Curr Oncol. 2017 Oct;24(5):e434-e436
10. Assi R, Mukherji D, Haydar A, Saroufim M, Temraz S, Shamseddine A. Metastatic colorectal cancer presenting with bone marrow metastasis: a case series and review of literature. J Gastrointest Oncol. 2016 Apr;7(2):284-97.
11. Kaur G, Basu S, Kaur P, Sood T (2011) Metastatic Bone Marrow Tumors: Study of Nine Cases and Review of the Literature. J Blood DisordTransfus 2:110.
12. Mohammad NH, Hussein F, Ahmad I. The Role of Bone Marrow Aspiration and Bone Marrow Biopsy in Diagnosis of Bone Marrow Metastases. IJBC 2017; 9(3): 80-83.