Original Article

Bone marrow metastasis in nonhematologic malignancies: Data from a cancer hospital

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ABSTRACT

Background: Bone marrow metastasis by a nonhematologic malignancy signifies advanced stage of disease and confers a poor prognosis. The aim of this study was to analyze clinical presentation, hematological profile, biochemical profile, radiological presentation, and patterns of bone marrow involvement in patients with metastatic nonhematologic malignancies retrospectively. **Materials and Methods:** Ninety bone marrow procedures were done in cases of nonhematologic malignancies for suspected involvement or as a part of staging procedure. **Results:** Sixteen out of 90 patients showed metastasis by nonhematologic malignancies. The most common malignancy to metastasize was malignant small round cell tumor (Ewing's sarcoma and rhabdomyosarcoma) followed by carcinoma breast and prostate. The most common clinical presentation was backache, fever anorexia, and abdominal pain. The biochemical findings included raised serum calcium and lactate dehydrogenase. 62.5% had anemia and 37.5% had thrombocytopenia. Leukocytosis was seen in 37.5% of patients. Leukoerythroblastic picture was seen in 43.75% cases. Of the eleven cases where both bone marrow aspirate and biopsies were done, 10 cases showed malignant cells in both. Immunohistochemistry was conclusive in four cases. The combined procedure of aspiration and biopsy gives a higher yield and are essential in patients with suspected bone marrow metastasis in nonhematologic malignancies.

Key words: Bone marrow metastasis, immunohistochemistry, nonhematologic malignancies

INTRODUCTION

The bone marrow metastasis by nonhematologic malignancies is a rare event. After lymphoma, in adults the tumors most often seen to metastasize are carcinomas of the prostate, breast, and lung. In children neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma, and retinoblastoma account for the majority of metastases.[1,2] Bone marrow aspiration and trephine biopsy are often included as part of the staging procedures in few solid tumors such as small blue round cell tumors (Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma). In other cases, it is done in patients with abnormal peripheral blood findings (presence of atypical cells/blasts, unexplained cytopenias) or with radiological investigations suggesting bone marrow involvement. Both the bone marrow aspiration and biopsy are essential in such cases as some tumors are associated with a marked fibrotic stromal response thereby suppressing normal hematopoiesis that results in a dry tap. In such cases, bone marrow biopsy proves to be a useful tool in diagnosis. Bone marrow aspirates are helpful when bone marrow biopsies obtained are inadequate or fragmented. The adequacy of bone marrow biopsies is most often defined by trephine biopsy length. The 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues[3] recommends that the bone marrow trephine core biopsies have a minimum length of 1.5 cm. Dayton *et al*.[4] have also recommended that the bone marrow biopsy should be of adequate length

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and quality to allow for an accurate diagnosis and endorsed the WHO-recommended biopsy length of at least 1.5 cm.

Metastatic tumors in bone marrow may influence the tumor stage, response to treatment, and predicts the survival of patient; hence, it is important to diagnose such cases at the earliest.

The objective of this study was to analyze the clinical presentation, hematological profile, biochemical profile, radiological presentation, and patterns of bone marrow involvement in patients with metastatic nonhematologic malignancies retrospectively.

MATERIALS AND METHODS

A total of 2034 bone marrow aspirations and biopsies were performed during a period of 40 months from January 2011 to May 2014, out of which 90 were done to rule out metastasis in cases of nonhematologic malignancies. Patients diagnosed as non-Hodgkin's lymphomas and Hodgkin's lymphomas were not included in this study. The basis of performing bone marrow procedure was one or more cytopenias unrelated to chemotherapy, or radiological findings suggesting the involvement of the bone marrow, or as a part of staging procedure. The patient's clinical, hematological, radiological, and bone marrow findings were reviewed retrospectively. Clinical characteristics of the patients included age, sex, presenting symptoms, and clinical examination findings. Hematological data viz., hemoglobin (Hb) levels, total leukocyte counts (TLCs), platelet counts (PLTs), and peripheral blood smear findings were noted. Anemia was defined as Hb value <13 g/dl in males and <12 g/dl in females. Leukopenia and thrombocytopenia were defined when TLC and PLT were $<4.00 \times 10^3/\mu l$ and $<150 \times 10^3/\mu l$ respectively. Radiological data included X-ray, computed tomography/magnetic resonance imaging (MRI) and positron emission tomography (PET) findings if any was done. Biochemical investigations such as serum calcium, lactic acid dehydrogenase (LDH), alkaline phosphatase (ALP), and serum tumor markers were available for some cases. Bone marrow aspirations and trephine biopsies were performed on posterior superior iliac crest using Jamshidi needle. Bone marrow aspirate smears were adequately prepared and stained with Giemsa stain. The bone marrow biopsy adequacy criterion was taken as at least 1.5 cm length and was decalcified and hematoxylin and eosin stained sections were evaluated. The aspirates and biopsies were examined by hematopathologists to study the cellularity, megakaryocytes, pattern and arrangement of tumor cells, and fibrosis. Reticulin stain was done in all positive cases. Immunohistochemistry (IHC) was done in four cases.

RESULTS

Of 2034 bone marrows done at our institute between January 2011 and May 2014, 90 were performed for suspected metastatic bone marrow infiltration by solid malignancies. Out of these, 16 (17.7%) patients showed metastasis by nonhematologic malignancies. Both bone marrow aspirate and biopsies were available for 11 patients. Only bone marrow biopsy slides were received for review for two patients and only bone marrow aspirate slides were available for three patients as the bone marrow biopsies were very small or crushed.

The age range was 12–67 years (mean age - 36 years). Majority of the patients were males, (11/16), (68.7%) and belonged to adult age group, (15/16). Only one patient belonged to the pediatric age group.

The most common complaints were backache, fever anorexia and abdominal pain [Table 1]. Physical examination and radiological findings included pallor, organomegaly, tenderness over spine, and multiple skeletal lesions. Radiological suspicion of bone and bone marrow involvement was noted in 7 out of the 16 positive cases. The biochemical findings included raised serum calcium and raised serum LDH levels in six and seven cases, respectively [Table 1].

Malignant small round cell tumor was found to be the most frequent malignancy to show bone marrow metastasis which constituted of Ewing's sarcoma/primitive neuroectodermal tumor (PNET) and rhabdomyosarcoma showing metastases in two cases each. Remaining others were metastatic deposits from breast carcinoma (three cases), prostatic adenocarcinoma (two cases), squamous cell carcinoma of oral cavity (two cases) and small cell carcinoma of the lung (two cases). One case showed metastasis of clear cell variant of renal cell carcinoma on biopsy which was received for review. In two patients, the primary site could not be found however bone marrow aspiration/biopsy showed presence of a metastatic tumor [Table 1].

At the time of diagnosis, anemia was present in 10 patients (62.5%), leukopenia was seen in none and thrombocytopenia was seen in six patients (37.5%). The blood counts were normal in six patients (37.5%). Leukocytosis was observed in four patients (25%) [Table 2].

Peripheral smear revealed a leukoerythroblastic picture in seven patients (43.75%). Normal smear was seen in six patients (37.5%). A single case showed neutrophilic leukocytosis and the remaining two showed microcytic hypochromic anemia only. Circulating malignant cells were seen in one case of breast carcinoma [Table 3].

Table 1: Clinico-hematological and biochemical profile of positive patients

Case number	Age (years)	Sex	Clinical presentation	Physical examination and radiological findings	Biochemical findings	Primary diagnosis
1	65	Female	Backpain, anorexia - 3 months	Pallor, no organomegaly	CA 15.3, CA 19.9, CA 72.4 and CEA raised Serum calcium - 8 mg/dl SPE and IFE-negative	Unknown
2	18	Male	Watering and swelling in left orbit - 3 months	Ecchymosis left orbit with redness and watery discharge CT scan-enhancing lesion in left maxillary sinus, left ethmoid sinus and left nasal cavity	Serum calcium - 9.8 mg/dl	RMS
3	50	Female	Backache, fever, anorexia - 6 months	Generalized tenderness over spine. MRI spine - diffuse lesion in dorsolumbar vertebra	LDH - 1218 U/L, B.J. proteins and SPE-negative beta 2 micro globulin-normal, Serum calcium - 7.9 mg/dl	Unknown
4	12	Male	Post excision of tumor in chest wall, admitted for chemotherapy and radiotherapy	PET CT - residual disease in operated primary site. Increased uptake in proximal femur	Serum calcium - 8.8 mg/dl	Ewing's sarcoma/PNET
5	52	Female	Breast lump and abdominal pain - 1 year	Mammogram - lesion in right breast PET CT - sclerotic lesions in skull, vertebrae, ribs, scapula, sternum, pelvic bones		Carcinoma breast
6	63	Male	Abdominal pain and difficulty in micturition	Prostatomegaly with metastasis in liver, ribs, vertebra, sternum	PSA - 1918 U/L	Carcinoma prostate
7	60	Female	Lower backache - 4 months	MRI lumbosacral spine-multiple areas of marrow replacement and pathological fracture of L1 vertebra	Serum calcium - 8.8 mg/dl	Small cell carcinoma of lung
8	30	Male	Multiple lumps over body, fever - 15 days	PET - diffuse nodular lesions in mesentery and liver	LDH - 573 U/L	Ewing's sarcoma/PNET
9	67	Male	Cough, dyspnea - 4 months, abdominal pain - 20 days	PET - soft tissue density in right lower lobe of lung and hilar region	CA 19.9-1.92 U/L, CA72-4-1.18 U/L, CEA - 23.21 U/L, tPSA - 0.049 U/L	Small cell carcinoma lung
10	50	Female	Lump in bilateral breasts - 2 years	Palpable lump in bilateral breasts with axillary lymph nodes		Bilateral carcinoma breast
11	52	Male	Abdominal pain - 6 months	USG abdomen-prostatomegaly. X-ray chest-osteoblastic lesions in ribs, clavicle	PSA - 1201 U/L	Carcinoma prostate
12	48	Male	Abdominal pain - 3 months	USG abdomen- exophytic mass in lower pole of kidney	Serum calcium - 25 mg/dl	Renal cell carcinoma kidney
13	50	Male	Lump over right chest wall - 14-15 months, breathlessness for 2 months, backache and pain radiating to both lower limbs - 20 days	FNAC from the breast lump from the breast lump and axillary lymph nodes suggestive of ductal carcinoma. Skeletal survey - multiple lytic lesions involving skull and pelvic bones and vertebrae	Serum calcium - 8.4 mg/dl CA 15.3 - 130 U/ml	Carcinoma breast
14	35	Male	Lower backache - 4 months	Skeletal survey - multiple osteoblastic lesions in pelvic bones, vertebral bodies, humerus, scapula, clavicle and skull		Invasive basaloid squamous cell carcinoma of supraglottis
15	38	Male	A known case of carcinoma oral cavity postoperative and post chemo radiation 6 months back Backache, unable to sit or walk - 7 days	PET scan-hyper metabolic lesion in right temporal fossa, multiple skeletal lesions at multiple skeletal sites	LDH - 358 U/L Serum calcium - 18.3 mg/dl	Squamous cell carcinoma oral cavity
16	26	Male	Known case of RMS of perineum on chemotherapy and radiotherapy	MRI brain ill-defined soft tissue density in occipital bone and jugular foramen	LDH - 2749 U/L Serum ALP - 143 U/L Serum uric acid - 7.8 mg/dl	RMS of perineum

CEA: Carcinoembryonic antigen, SPE: Serum protein electrophoresis, IFE: Immunofixation electrophoresis, LDH: Lactate dehydrogenase, PSA: Prostate-specific antigen, tPSA: Total prostate-specific antigen, ALP: Alkaline phosphatase, PNET: Primitive neuroectodermal tumor, PET: Positron emission tomography, CT: Computed tomography, MRI: Magnetic resonance imaging, RMS: Rhabdomyosarcoma, USG: Ultrasonography, FNAC: Fine needle aspiration cytology

The bone marrow aspirate smears were hypocellular in nine cases and cellular in five cases. Megakaryocytes were not seen in six cases. Of the eleven cases where both bone marrow aspirate and biopsies were done,

10 cases showed malignant cells in both [Figures 1 and 2]. One case of small cell carcinoma of lung showed tumor cells in aspirate smears only as the biopsy was not adequate for evaluation. Reticulin stain performed on bone marrow biopsy sections showed fibrosis in seven cases [Table 3].

IHC was done on bone marrow biopsy section in four cases and was diagnostic [Table 4 and Figure 3].

Table 2: Hematological profile of positive patients

Blood counts	*n* (%)
Normal	6 (37.5)
Anemia	10 (62.5)
Leukopenia	0 (0)
Thrombocytopenia	6 (37.5)
Pancytopenia	0 (0)
Leukocytosis	4 (25)
Bicytopenia	5 (31.25)

DISCUSSION

Bone marrow metastasis in cases of nonhematologic malignancies is a rare phenomenon. Infiltration of the bone marrow may be suspected on the basis of: (i) Bone pain; (ii) pathological fractures, lytic lesions or sclerotic lesions demonstrated radiologically; (iii) unexplained

Table 3: Peripheral smear, bone marrow aspirate and bone marrow biopsy findings

Case number	Peripheral smear findings	Bone marrow aspirate smear findings			Bone marrow biopsy findings	
		Cellularity	Megakaryocytes	Malignant cells	Morphology	Fibrosis
1	Normal smear	Hypocellular	Not seen	Clusters of malignant cells with plasmacytoid morphology, binucleate and multinucleate cells seen, few rosettes also seen	Single and clusters of malignant cells seen	Not present
2	Normal smear	Cellular	Seen	High N:C ratio cells in clusters and singly, bizarre forms. MPO and NSE-negative	Sheets of malignant cells with plasmacytoid morphology and eosinophilic cytoplasm	Not present
3	Microcytic, hypochromic anemia	Hypo cellular	Seen	Clusters and acini of cells with eosinophilic cytoplasm and nucleoli	Not done	
4	Normal smear	Cellular	Seen	Clusters and single cells with high N:C ratio	Not done	
5	Leukoerythroblastic picture	Hypocellular	Not seen	Cohesive clusters, acini of high N:C ratio cells	Cords and tubules of cells in a desmoplastic stroma	Present
6	Leukoerythroblastic picture	Hypocellular	Not seen	Loose clusters and acini of cells with prominent nucleoli	Diffusely arranged cells with vacuolated/eosinophilic cytoplasm and prominent nucleoli	Present
7	Microcytic, hypochromic anemia	Cellular	Seen	Clusters of cells with scant cytoplasm, nuclear molding	Diffusely arranged cells with high N:C ratio, nuclear molding and apoptotic background	Present
8	Normal smear	Cellular	Seen	Clusters of high N:C ratio cells in acini/rosettes	Malignant cells with high N/C ratio, molding and marked crushing artifacts, few rosettes	Absent
9	Normal smear	Cellular	Seen	Clusters of cells with scant cytoplasm and nuclear molding	No malignant cells seen. Cellular reactive marrow	Absent
10	Leukoerythroblastic picture	Hypocellular	Not seen	Cohesive clusters of cells, acini of hyper chromatic cells	Malignant cells in cords and tubules	Present
11	Leukoerythroblastic picture	Not available			Glands and cords of cells with fibrosis and osteoblastic reaction	Present
12	Normal smear	Not available			Nests of cells with abundant clear cytoplasm, hyper chromatic nuclei	Absent
13	Leukoerythroblastic picture with circulating atypical/ malignant cells	Hypocellular	Not seen	Malignant cells singly placed as well as in clusters forming acini	Malignant cells in cords and tubules in a desmoplastic stroma	Present
14	Leukoerythroblastic picture	Hypocellular	Seen	Few clusters of hyper chromatic cells with scant cytoplasm. MPO and NSE-negative	Not done	
15	Neutrophilic leukocytosis	Hypocellular	Seen	Clusters of bizarre cells with moderate cytoplasm, hyper chromatic nuclei	Nests of malignant cells with hyper chromatic nuclei and eosinophilic cytoplasm	Absent
16	Leukoerythroblastic picture	Hypocellular	Not seen	Singly placed as well as clusters of malignant cells with moderate amount of basophilic vacuolated cytoplasm, clumped chromatin and multiple conspicuous nucleoli	Nests of malignant cells separated by dense fibrous septae. No normal hematopoietic cells seen	Present

MPO: Myeloperoxidase, NSE: Nonspecific esterase

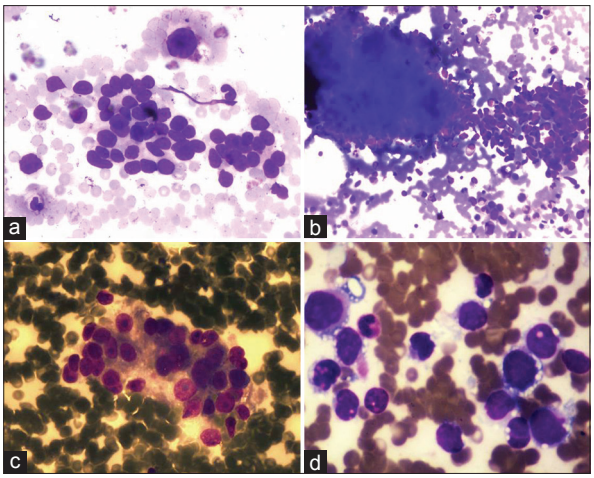

Figure 1: Giemsa stained bone marrow aspirates. (a) Duct carcinoma breast (×40); (b) small cell carcinoma lung (×20); (c) adenocarcinoma prostate (×40); (d) squamous cell carcinoma (×40)

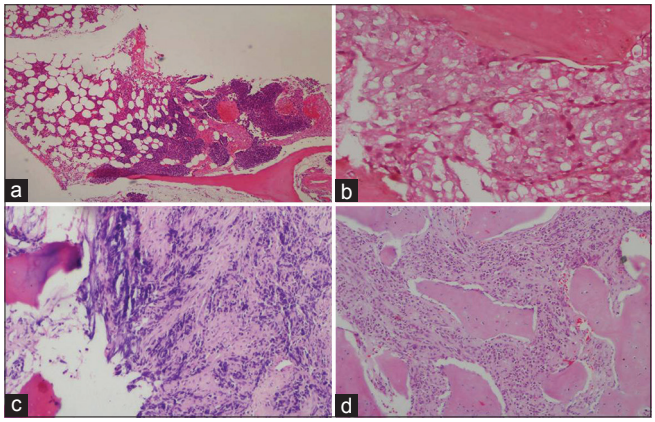

Figure 2: H and E stained bone marrow biopsy. (a) Small cell carcinoma lung (×20); (b) renal cell carcinoma (×40); (c) Ewing's sarcoma (×20); (d) duct carcinoma breast (×20)

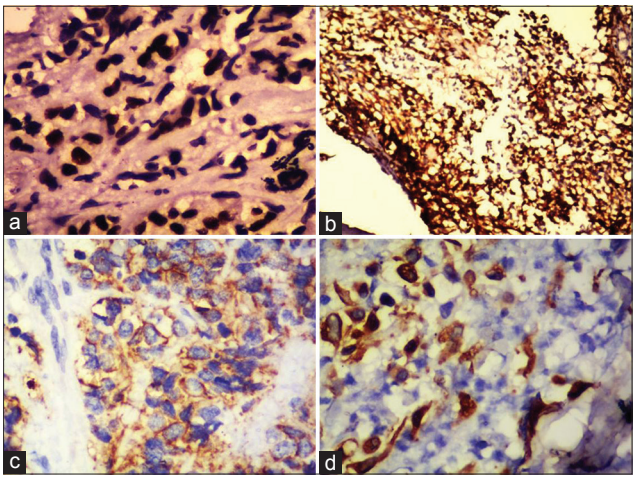

Figure 3: Immunohistochemistry on bone marrow biopsy. (a) Estrogen receptor positive duct carcinoma breast; (b) desmin positive rhabdomyosarcoma; (c) CD99+ Ewing's sarcoma; (d) CK+ squamous cell carcinoma

"hot spots" on isotopic bone scans; (iv) hypercalcemia or elevated serum ALP levels; and (v) unexplained cytopenias

Table 4: Immunohistochemistry markers on bone marrow biopsy sections

Case number	Diagnosis	IHC markers	Result
4	Ewing's sarcoma	CD99, CD34	CD99 positive
5	Carcinoma breast	ER, PR	ER PR positive
15	Squamous cell carcinoma buccal mucosa	CK, CD34, CD117	CK positive
16	Rhabdomyosarcoma	Desmin, CD34, CD117	Desmin positive

IHC: Immunohistochemistry, ER: Estrogen receptor, PR: Progesterone receptor

or a leukoerythroblastic picture on routine blood and peripheral smear examination.[1] MRI and PET scan can give some clues on the involvement of bone marrow. However, bone marrow examination is confirmatory. While cytologic preparation of bone marrow obtained by aspiration allows excellent visualization of cell morphology, the bone marrow biopsy allows optimal evaluation of cellularity, fibrosis, or infiltrative disease.[6] Immunohistochemical examination and molecular techniques prove to be useful in some of the cases. However, 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.[1,5]

Out of 2034 bone marrows done at our institute between January 2011 and May 2014, 90 were performed for suspected metastatic bone marrow infiltration by nonhematologic malignancies. Of these 16 (17.7%) patients showed metastasis by tumor cells. The percentage of involvement was lower in our study because most of the bone marrows were done as a part of staging procedure in small round blue cell tumors and were negative for any metastasis.

Clinically, the most frequent feature with which a patient with bone marrow involvement presents is bone pain and pathological fractures[1] which were seen in six patients (37.5%) in our study. Abdominal pain, generalized weakness, weight loss, and organomegaly were other common features seen in many patients. Ozkalemkas *et al.*[6] stated in their study that constitutional symptoms and pain were the most prominent presenting symptoms of the patient. However, clinical findings were highly variable according to the underlying disease. Sreelakshmi *et al.*[7] in their study found bone pain in 52%, generalized weakness and loss of weight in 100% and 84% of their cases. Similarly, Syed *et al.*[8] reported fever and weight loss in 12.6% and 27% of their cases, respectively.

The most common biochemical parameter to be found abnormal in our study was elevated LDH levels which were also observed by Papac[9] and Ozkalemkas *et al.*[6] Other findings were elevated calcium levels which are indicative of increased bone turnover/breakdown due to metastasis

or due to a renal failure associated with disseminated malignancy.

In the past, many studies have been done on bone marrow invasion by nonhematologic malignancies. Almost all malignancies can metastasize to bone marrow,[10] but the common ones are malignancies of prostate, breast, lungs. In many instances, however, primary tumors remain clinically undetected. In our study, breast cancer in females and prostate cancer in males were the most frequent tumors to metastasize to bone marrow followed by lung cancer which is in concordance with many studies.[2,7,8] In adolescents, Ewing's sarcoma/PNET was the most common tumor to metastasize which is similar to the study conducted by Anner and Drewinko.[11] We also found a case of renal cell carcinoma and two cases of squamous cell carcinoma of upper aerodigestive tract showing bone marrow metastases which is a rare finding. One case of small cell carcinoma of lung showed tumor cells in aspirate only, however, the biopsy did not reveal any metastatic foci. The probable reason could be an inadequate length of the biopsy because the probability of detection directly correlates with the size of the biopsy sections. If the pattern of infiltration is not diffuse, small foci of metastases can be easily missed if the biopsy is not long enough. In such cases, it is advisable to perform a contralateral biopsy if the clinical, radiological, and biochemical parameters are highly predictive of bone marrow marrow infiltration.

Myelophthisic anemia[12] is an anemia resulting from marrow infiltration, typically by tumor but also by any nonhematopoietic tissue. The anemia is usually normocytic normochromic. It can present with overt myelocytes and nucleated red cells in the blood (leukoerythroblastic reaction) or with only a few tear drop shaped red cells on a blood film.[13] Infiltration of the bone marrow by malignant cells and release of suppressive and destructive cytokines and fibroblastic growth factors results in a reduction of available bone marrow space causing pluripotent stem cells to migrate to the liver and spleen causing compensatory extramedullary hematopoiesis. The stromal support of these organs being suboptimal causes the premature release of hematopoietic elements into the circulation.[10] Sometimes extensive infiltration of the marrow may even lead to pancytopenia. Platelets can be increased, decreased or normal (megakaryocytic fragments are seen occasionally).[13]

In our study, anemia was detected in 62.5%, thrombocytopenia in 37.5% and leukopenia in none. The findings were quite similar to the study conducted by Kaur *et al*.[2] and Kilickap *et al*.[5] except for leukopenia which was seen in 33.3% and 23.3% of cases, respectively. Leukocytosis was seen in 25% of our cases.

Another interesting finding is microangiopathic hemolytic anemia (MAHA) which is a type of hemolytic anemia associated with red cell fragmentation caused by microangiopathy mechanically. MAHA has been described as an initial presentation of metastatic cancer of unknown origin.[14] Ozkalemkas *et al*.[6] suggested that MAHA, leukoerythroblastosis and unexplained cytopenias are strong indicators of the necessity of bone marrow examination and in a patient with disseminated cancer confers poor prognosis. However, in our study, no case showed features of MAHA.

Peripheral smear findings may suggest a possibility of metastasis to the bone marrow in form of leukoerythroblastic reaction. Leukoerythroblastic reaction refers to a condition accompanied by tear drop shaped cells, prematurely released nucleated red cells and immature myeloid. The presence of a leukoerythroblastic peripheral blood picture serves as a valuable clue to the presence of some underlying disease stressing hematopoiesis or as a signal to investigate further for the presence of malignancy.[15] In our study, 7 out of 16 patients (43.75%) had a leukoerythroblastic picture on peripheral smear. This usually correlates with the degree of bone marrow fibrosis and tumor cells "crowding out" of marrow elements due to their interaction with hematopoietic cytokines rather than with the extent of malignant infiltration. Various studies have reported the frequency of leukoerythroblastic changes ranging from 30% to 35%.[6,7,16,17] The automated hematology analyzers also give a clue to the presence of leukoerythroblastic reaction and, therefore, should be not be ignored while releasing complete blood count reports of patients with nonhematologic malignancies [Figure 4].

Bone marrow smears were hypocellular in nine cases and cellular in five cases. "Dry tap" is a term used to describe the failure to obtain bone marrow on attempted marrow aspirations or in cases where the material is obtained but

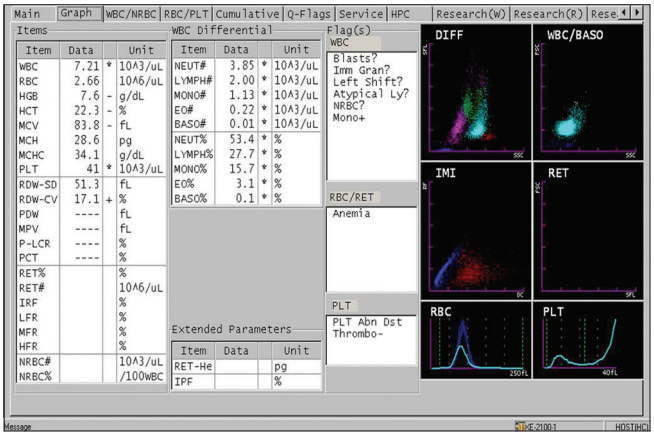

Figure 4: Automated hematology analyzer (XE 2100) suggesting leukoerythroblastic picture

no, or inadequate marrow cells are obtained on account of extensive fibrosis or hypercellularity.[6] Seven cases in our study were a dry tap. Fibrosis was detected in seven cases (44.4%) compared to 66% cases detected by Kaur *et al*.[2] Fibrosis is more in case of the greater degree of marrow infiltration. Marked fibrosis is the most common in carcinoma of breast, stomach, prostate, and lung.[7]

The combined procedures of aspiration and biopsy give a higher yield and are essential in patients with suspected carcinoma.[18,19] Therefore, it is important to examine both bone marrow aspirate and biopsy material together, as the two methods are often complementary.

Bone marrow aspiration/biopsy is useful tools for staging the patients with malignant disorders. It is recommended that the clinical findings, blood counts, hematology analyzer findings, and the peripheral smear should be carefully inspected in all cases of nonhematologic malignancies and bone marrow procedure should be advised on the part of hematopathologist if any abnormality is detected. Apart from this, in cases of metastasis of unknown origin, a workup including chest X-ray, serum LDH, serum ALP, serum prostate-specific antigen levels in men, and mammography in women should be performed as it may result in early diagnosis of metastasis and certain improvements in survival of patients with prostate cancer, lung carcinoma, and breast cancer which are the most common malignancies to show bone marrow metastasis. The aspirate and trephine biopsy specimens are complementary to each other. Hence, both should be performed for proper diagnosis and management of the disease. Most cases show a hypocellular marrow, therefore, a careful search should be made to detect malignant cells; however, a cellular bone marrow does not preclude the presence of metastasis. In such cases, biopsy proves to be a useful adjunct along with IHC.

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Conflicts of interest
There are no conflicts of interest.

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