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A STUDY OF THE INCIDENCE OF BONE MARROW NECROSIS IN PRIMARY & SECONDARY MALIGNANT BONE TUMORS

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Abstract

During one year period, 21 newly diagnosed patients with different malignant bone tumors were subjected to this study, 52.4% (11) of them were males & 47.6% (10) were females with a mean age of 50.2 years. Detailed history & physical examination were taken including the age, sex, the pathological type of the tumor, whether it is a primary or secondary & the site of the tumor, the existence of bone pain, fever, weight loss, pallor, pathological fractures, neurological deficit, any adjuvant treatment the patient had been put on, the existence of sickle cell disease, diabetes mellitus and any history of a previous surgery. All cases were subjected to the following tests: complete blood count (CBC) including the estimation of erythrocyte sedimentation rate (ESR) & reticulocyte count, estimation of lactate dehydrogenase(LDH) & alkaline phosphatase (ALP) enzymes & serum calcium. All cases were subjected to bone marrow examination including both aspirate & trephine biopsy (with its touch imprint). Smears & sections were examined thoroughly to assess marrow status with emphasis on the existence of bone marrow necrosis (BMN).

Results showed that 19.1 % of cases had bone marrow necrosis. Their mean age was 50.25 years, with equal sex distribution, half of them had primary tumors, and 75 % of them had their tumors situated in the spine. Clinically: all of them had weight loss, fever & bone pain while 75 % of them had pathological fractures. The mean values of the investigations done for them were: Hb 94 g/L, PCV 0.29, reticulocyte count 2.43 %, WBCs 14.75 x 10^9/L. Peripheral blood film for all showed leuco-erythroblastic picture. They showed an elevated mean serum LDH (307.50 IU/L) & ALP (116.06 IU/L) levels.

Cases that showed no evidence of BMN constituted 80.9 % of total. They had a mean age of 5.15 years. 52.9 % were males while 47.1 % were females. Just more than half of cases (52.9 %) had primary while 47.1 % had secondary type of tumors & 47.05 % of them were located in the spine. Clinically all of them had bone pain, 94.1 % had weight loss, 52.9 % pathological fractures, 29.4 % pallor & 23.5 % had fever. Their mean laboratory values were: Hb 108.1 g/L, PCV 0.33 %, reticulocyte count 1.36 %, WBCs 7.11 X 10^9/L, LDH 214.88 IU/L, ALP 83.48 IU/L.

Comparative study between cases with BMN & those without showed a significant relationship between the following parameters & the presence of BMN at a level ($p<0.05$): fever, leukocytosis, reticulocytosis, and high LDH levels. These results were comparable with some & contradicting with other studies.

The paucity of studies in this field created difficulties to relate the results of this study to others, especially in our Country. Further studies in the same field will probably clarify.

In conclusion, bone marrow necrosis, is not uncommon among primary & secondary malignant bone tumors. It is associated with severe clinical-pathological features that may reflect a poor outcome. Prolonged, follow up studies are in need to clarify this point.

Introduction

Malignant bone tumors have been traditionally divided into primary & secondary (metastatic). Primary bone tumors are sarcomas that are used to arise directly from a bony tissue & have the ability to spread throughout the rest of the body like the lungs with the ability to cause destruction of the bone or adjacent

tissues[1]. They are distinguished by certain features that are common for all, including: a predominant occurrence in the first 3 decades of life, a relatively specific radiographic presentation in such a way that the diagnosis can be sometimes confidently made based on the radiographic features alone and a common occurrence in the bones with the highest growth rate like the distal femur and proximal tibia[2]. Metastatic bone tumors are usually carcinomas (usually of breast, lung, prostate, kidney and thyroid)[1]. They are by far more common than primary bone tumors and are characterized by the predominant occurrence in two age groups: adults over 40 years of age and children in the first decade of life[2], by multifocality and by a predilection for the hemopoietic marrow sites in the axial skeleton (vertebrae, pelvis, ribs and cranium) and proximal long bones[2]. Metastases to long bones distal to the elbows and knees are unusual & metastases to the small bones of the hands and feet are even rarer[2]. The skeleton is the third most common site of spread of carcinomas that arise from organs after the lungs & the liver. Metastases to the lung and liver are often not detected until late in the course of disease because patients experience no symptoms. On the contrary, bone metastases are generally painful when they occur[3,4].

Bone tumors, primary or secondary, can present in any one or more of the followings; nonspecific pain pattern in character, time, and radiation, atypical soft-tissue or bony swellings, pathological fracture of long bones or clavicle and collapse of a vertebra[5,6], an unexplained paresis/ paralysis and sphincter problems. They can accidentally be discovered as osteolytic lesion(s) on an x-ray or as an unexpected abnormal blood test result: such as hypercalcemia, elevated alkaline or acid phosphatase, and lastly as headache resulting from skull metastases[5,6].

Bone tumors, after proper history taking, proper & thorough physical examination, can be diagnosed using many investigative tools including blood tests to exclude other conditions e.g. infection or metabolic bone disorders or a (brown tumor) in hyperparathyroidism, a complete blood count which may show; anemia, leukocytosis, increased ESR, abnormal cells etc., biochemical alterations like elevated serum alkaline phosphatase levels, raised serum acid phosphatase, serum protein electrophoresis & urine for Bence-Jonse proteins[7]. Besides, there are lots of imaging studies that can help to reach the diagnosis, including the simple, plain radiograph which is usually the first imaging technique for a suspected bone lesion since it is inexpensive and easily obtainable & is also the best for assessment of general radiological features of the tumor[3], computer tomography, (CT), which is a method of choice when plain film assessment is difficult owing to the nature of the lesion (eg. permeative pattern of destruction) or anatomic site (e.g. sacrum). In addition, CT is the best technique in assessment of matrix mineralization, cortical details, and detection of the cystic and fatty lesions[2]. MRI is another means & is a method of choice for local staging**.** It is superior to CT in the definition of medullary and extracortical spread and of the relationship of the tumor to critical neurovascular structures. However, it should be remembered that the MRI appearances of the majority of bone tumors are totally non-specific, and plain films or CT films are needed to be examined to define a neoplasm[2]. Bone scintigraphy is a highly sensitive but relatively non-specific technique. Its main role is in the detection of suspected metastases in the whole skeleton. It may also be helpful in the detection of osteoid osteomas in which a "double density sign" is present in about 50% of cases and is highly suggestive of this tumor[2]. Gallium scans are the most sensitive tests for locating non-pulmonary metastases but are no longer routinely used by most centers[8]. Ultrasonography is useful for distinguishing cystic from solid soft tissue lesions but otherwise offers lit-

tle information[8]. Angiography, which was previously used to determine the relationship of a neoplasm to the vessels, has been greatly supplanted by MRI. However, angiography still is useful to rule out non-neoplastic conditions, such as pseudo-aneurysms or arterio-venous malformations, and for preoperative embolization of highly vascular lesions, such as renal cell carcinoma and aneurysmal bone cysts[8].

Bone marrow necrosis (BMN)

Bone marrow necrosis is considered to be present when the marrow aspirate and /or biopsy show areas of poorly defined (smudge) cells with basophilic, indistinct nuclei surrounded by amorphous to granular acidophilic material. It was first reported by Wade and Stevenson in 1941[9] more than 50 years ago. It is characterized morphologically by destruction of haemopoietic tissue including the stroma with preservation of bone[10]. It's a rare entity[10,11]. Previous reports indicate that the incidence of bone marrow necrosis ranged from 0.5 % to approximately one-third of all bone marrow biopsies examined[12] with a relative frequency of 0.37%-6.5% [(13)]. It is most frequently associated with post-mortem changes[10,11,13]. However, in antemortem cases, BMN is commonly the end result of infiltration by a neoplastic process, chemotherapy or vaso-occlusion. It had been associated with hematologic malignancies like acute & chronic leukaemias, malignant lymphomas, multiple myeloma[9,10]. It can also be caused by solid tumors, in metastatic neoplasia[10], bacterial infection especially when hypovolaemia & septic shock are present, disseminated intravascular coagulation, following irradiation & antineoplastic therapy, in sickle cell disease and other non malignant states[10,14] like AIDS & some systemic diseases[12]. Rare cases have been reported in association with antiphospholipid syndrome, parvo virus B1 infection preceding the development of hematologic malignancies[10-15]. It has also been reported in typhoid fever & anorexia nervosa[15] & in some cases, no known etiology was identified[11,16].

The pathophysiology of BMN has been a subject of controversy and debate, and has included one or more of: the toxic effects of chemotherapy, microvascular infarction, decreased oxygen tension due to increased proliferative capacity of infiltrating malignant cells[13,17], effects of tumor necrosis factor (TNF), and thrombosis[13,17]. It presents clinically as; severe bone pain, fever, weight loss[10,11], fatigue, and jaundice[16].The most common laboratory findings besides those associated with the underlying disease are high alkaline phosphatase levels, hypercalcaemia, & elevation of LDH enzyme[11,16], uric acid, and alanine transferase levels[18]. Peripheral blood shows anaemia, leukopenia, thrombocytopenia, leukoerythroblastosis and schistocytosis & bone marrow aspirate & biopsy show amorphous material with isolated cells in different stage of necrobiosis & variable degrees of pancytopenia[10].

To diagnose BMN, marrow exam-ination is mandatory[19]. The histopath-ology of BMN is based on the demonstration of widespread necrosis of hematopoietic elements in BM trephine biopsies. It appears as eosinophilic material and should be differentiated from aspiration artifact, serous fat atrophy and amyloidal deposition. BM aspirates may show the presence of homogenous eosinophilic material in some cases, while the necrotic BM may resist aspiration in others, resulting in dry tap. This further emphasizes the role of trephine biopsies in diagnosis[11]. Microscopic examination of stained smears shows a variable number of cells, most of which are difficult or impossible to identify. They appear to be (smudged) and the nuclei may have ragged outline and thus assume satellite appearance[10]. Although the nucleus may stain deeply basophilic, morphological details are poor. The cytoplasmic margins are ill-defined, and cytoplasm may appear to be absent, often the

cells are surrounded by the masses of slightly acidophilic, granular material[10]. MRI comes to play an increasingly important role in the evaluation of BMN. Awareness of this entity and its MRI appearance and appreciation of its frequent association with underlying malignancy may assist in the early diagnosis of BMN and initiate an appropriate search for occult malignancy[18]. There is a suggestion that 99mTe bone scan be useful in the diagnosis of marrow necrosis[20].

The prognosis of BMN is generally considered very poor. However, this may be a reflection of the underlying life-threatening malignant disease. It appears that when milder degrees of BMN are present, the prognosis depends primarily on the underlying disorder, whereas severe BMN is associated with an unfavorable clinical outcome[11]. & death usually occurs within weeks or months [(18)]. The mortality rate is about 22 %[15].

Aims of the study

1. To define the incidence of BMN among cases with primary and secondary malignant bone tumors.
2. To clarify the clinical & pathological behavior of these tumors with BMN compared to these without in order to define whether BMN carries an indicator for the severity of those types of tumors.

Materials & methods

During a period of one year (from June 2007 to June 2008), twenty-one patients with various forms of newly diagnosed malignant bone tumors had been selected. All cases were taken from Orthopedic Wards, Basra General Hospital. All cases were questioned in a detailed history, including age, gender, site of suffering, duration of illness, type of biopsy taken(if any), pathological diagnosis of tumor, type of tumor (primary or secondary), symptoms (pain, fever), adjuvant treatment (chemotherapy, radiotherapy or combined), past medical & surgical history. All cases were subjected to thorough physical examination including measurement of body temperature, localized or generalized body tenderness, neurological deficit, the presence of deformity, pathological fracture, the site of a fracture. Hematologic lab tests were done, including complete blood count (CBC), including measurement of haemoglobin(Hb), packed cell volume (PCV), total & differential white cell counts, reticulocyte count, platelets count & the determination of ESR. Biochemical tests done included the estimation of lactate dehydrogenase (LDH), alkaline phosphatase(ALP) enzymes & serum calcium. Methodo-logy was done according to the standardized techniques adopted by the International Society for the Standardization of Haematology (ICSH)[21] & The standardized methods of biochemical methodologies were adopted.

Each case had been subjected to BM examination (including both aspirate & trephine biopsy) from the posterior superior iliac spines. Bone marrow aspirate was done by using Salah metal bone marrow aspirate needle under local anesthesia (2% xylocaine with adrenaline). Marrow material, after being aspirated & spread on glass slides, was stained with Lieshmann,s stain & examined thoroughly for cellularity, any infiltration by malignant cells & any evidence of bone marrow necrosis.

Bone marrow trephine biopsy had been done at the same time just after the aspiration by using the Jamshidi needle to obtain a core of 1.5 cm. long & 3mm. diameter including both cortices & medulla in between. BM touch slides were obtained by rolling the biopsy piece between 2 glass slides. Bone marrow touch smears were stained with Leishmann's stain & examined just like the aspiration, while the biopsy materials were put into Bowen's solution & sent for the Histopathology Lab in Basra General Hospital for sectioning & staining by the standardized hematoxylin & eosin stain(H&E). Smears were examined for the assessment of marrow cellularity as a panoramic view, any

evidence of marrow infiltration by a malignant process & for the existence of bone marrow necrosis[22].

Statistical analysis: was done using SPSS system, version 12. Descriptive statistics were obtained mainly.

Results

I. Results for all cases:

From all, (52.4%) (11) cases were males &10(47.6%)(10) were females (Table I). Cases were mainly distributed in the age groups (45-54) & (65-74) (Table II) with a mean age of 50.19 years (Table III).

Table I: Sex distribution of all cases

Sex	All cases	Without BMN	With BMN	P-Value
Male (No) Percentage	(11)52.4 %	(9)52.9 %	(2)50 %	0.669
Female (No) percentage	(10) 47.6 %	(8) 47.1 %	(2)50 %	0.669
(Total) Percentage	(21) 100 %	(17)100 %	(4)100 %	0.669

Table II: Age distribution intervals of all cases

Age in years	All cases		Without BMN		With BMN	
	No.	%	No.	%	No.	%
15-24	3	14.2%	3	17.64%	0	0
25-34	1	4.76%	1	5.88%	1	25%
35-44	1	4.76%	1	5.88%	1	25%
45-54	5	23.8%	5	29.4%	1	25%
55-64	1	4.76%	1	5.88%	0	0
65-74	5	23.8%	5	29.4%	1	25%
75-84	1	4.76%	1	5.88%	0	0
Total	21	100%	17	100%	4	100%

Table III: The mean age of all cases

Age in years	All cases	Without BMN	With BMN
Mean	50.19	50.18	50.25
Minimum	15	15.00	30.00
Maximum	83	82.00	73.00

Just more than half of cases (52.4%) had primary, while (47.6%) of them had secondary tumors from various primary sites (Table IV).

Table IV: Tumor origin in all cases

Tumor origin	All cases	Without BMN	With BMN
Primary (No.)Percentage	(11)52.4%	(9)52.9%	(2)50%
Secondary(No.) Percentage	(10) 47.6%	(8) 47.1%	(2) 50%
Total Number Percentage	(21) 100%	(17) 100%	(4)100%

For both types, tumors were most frequently located in spine (57.1%) (table V)

Table V: Site distribution of tumors in all cases.

Site of tumors	All cases		Without BMN		With BMN	
	No.	%	No.	%	No.	%
Spine	12	57.1	9	47.05	3	75
Tibia	2	9.52	2	9.52	0	0
Femur	3	14.2	3	14.2	0	0
Humerus	2	9.52	2	9.52	0	0
Forearm	1	4.7	1	4.7	0	0
Ilium	1	4.7	0	0	1	25
Total	21	100	17	100	4	100

Clinically, all patients had bone pain, 95.2% of them had weight loss, 33.3% were pale, 57.1% had pathological fractures, 47.6% had neurological deficits, 38.1% were feverish, 33.3% had vascular compression, 28.6% of them had history of previous surgery (either in the form of biopsy or surgery unrelated to their malignant disorders) & 14.3% were on adjuvant Treatment (radiotherapy, chemotherapy or both). All of cases had no history of steroid intake & had no sickle cell disease while 19.0% of them had diabetes mellitus (Table VI). All cases had positive findings in X-ray, CT or MRI or in more than one of them in the form of a fracture, soft tissue mass, destructive lesion in bone or wedging of vertebrae, etc).

Table VI: Clinical manifestations of all cases.

Parameter	All cases	Without BMN	With BMN	P-Value
Bone Pain	100%	100 %	100 %	0
Weight loss	95.2%	94.1 %	100 %	0.81
Pathological fracture	57.1%	52.9 %	75 %	0.669
Neurological deficit	47.6 %	47.1 %	50 %	0.66
Fever	38.1 %	23.5 %	100 %	0.012*
Pallor	33.3 %	29.4 %	50 %	0.407
Vascular compression	33.3 %	35.3 %	25 %	0.59
Previous surgery	28.6 %	29.4 %	25 %	0.86
DM	19.0 %	23.5 %	0 %	0.39
Adjuvant therapy	14.3 %	17.6 %	0 %	0.511
Steroid treatment	0 %	0 %	0 %	0
SCA	0 %	0 %	0 %	0

Hematologic evaluation of cases showed a hemoglobin concentration range between 82.0-127.0 gm/L with a mean of 105.48 gm/L, while PCV ranged between 0.24 - 0.38 & mean was 0.32 & erythrocyte sedimentation rate ranged between 30-125 mm/1st hr with a mean of 76 .The range of reticulocyte count was between 0.3-3.50% with a mean of 1.56. The range of total white blood cell count was from 3.70-19.90 x10^9/L with mean of 8.56. The range of neutrophils count was from 54.00-89.00 % with mean of 67.04 %. The range of lymphocytes count was from10-43% with mean of 28.86 %. The range of monocytes count was 1-4 % with mean of

1.90%. Thirteen of cases had normal peripheral blood film while 4 had peripheral blood film ranged from mild hypochromic to severe normochromic anaemia while 4 cases had leuco-erythroblastic picture (Table VII). Biochemical examination of cases showed that the range of LDH values was between 112-380IU/L with mean of 232.52 IU/L. The range of serum calcium was from 1.7-2.8 mg/dl with mean of 2.14.The range of serum alkaline phosphatase was between 29.10-204.00 IU/L with mean of 89.7905 IU/L (Table VII).

Table VII: Mean medium & range of laboratory data among all cases.

Parameter	Mean	median	Minimum	maximum
HB (gm\L)	105.48	105.00	82.00	127.00
PCV (L/L)	0.32	0.33	0.24	0.38
WBCS ($x10^9$\L)	8.56	7.80	3.70	19.90
Neutrophils (%)	67.05	63.00	54.00	89.00
Lymphocytes (%)	28.86	32.00	10.00	43.00
Monocytes (%)	1.90	2.00	1.00	4.00
Esinophils (%)	2.29	2.00	1.00	5.00
Platelets ($x10^9$\L)	190.76	182.00	160.00	292.00
ESR (mm/1^{st} hr)	76.10	80.00	30.00	125.00
Reticulocytes (%)	1.56	1.50	0.3	3.50
S. LDH (IU/L)	232.52	195.00	112.00	380.00
S. Calcium mg/dl	2.14	2.10	1.70	2.80
S. ALP IU/L	89.79	80.00	29.10	204.00

II. Cases without bone marrow necrosis (BMN)

Seventeen of all patients (80.9 %) had no bone marrow necrosis in their bone marrow aspirate or biopsy; most of them were located in 45-54 & 65-74 years interval of age with mean of age 50.18. Just more than half (52.9%) of them were males & (47.1%) were females (Tables I & II). Just more than half of cases (52.9%) had primary while 47.1% of them had secondary type of tumors (table4). Tumors were most frequently located in the spine (47.05%) (Table V).

All cases had generalized bone pain, (94.1%) weight loss, (52.9%) pathological fractures, (47.1%) neurological deficits, (35.3%) vascular compression, (29.4%) pallor, (29.4%) a history of previous surgery, 23. 5%) were diabetic & (17.6%) had adjuvant therapy. There was no history of SCA or chronic steroid intake (Table VI). Peripheral blood examination showed a haemoglobin concentration ranged between 89.00-127.00 gm/L with a mean of 108.1, while PCV ranged between 0.26-0.38 with a mean of 0.33 & erythrocyte sedimentation rate ranged between 35.00-125.00 mm/1^{st} hr with a mean of 74.06. The range of reticulocyte count was from 30-2.00% with a mean of 1.36 %. The range of total white blood cell count was from 3.70-10.90 $x10^9$\L with mean of 7.11.The range of neutrophils count was from 54.00-89.00% with a mean of 65.35 %.The range of lymphocytes count was from10.00-43.00 % with mean of 30.71%. The range of monocytes count was from 1-4 % with mean of 2 % (Table 8). Thirteen of cases had normal peripheral blood film while 4 had peripheral blood films ranged from mild hypochromic to severe normochromic anaemia. The range of LDH values was from 155.00-350.00 IU/L with a mean of 214.88. The range of serum calcium was from 1.70-2.70 mg/dl with mean of 2.12. The range of serum alkaline phosphatase was between 29.10-204.00 IU/L with mean of 83.48 (Table VIII).

Table VIII: Laboratory data of patients with no BMN

Parameter	Mean	median	Minimum	Maximum
Hb (gm\L)	108.1	109	89	127
PCV(L/L)	0.33	0.33	0.26	0.38
WBCs (x10^9\L)	7.11	7.30	3.70	10.90
Neutrophils (%)	65.35	62.00	54.00	89.00
Lymphocytes (%)	30.71	34.0000	10.00	43.00
Monocytes (%)	2.00	2.00	1.00	4.00
Eosinophils (%)	2.47	3.00	1.00	5.00
Platelets (x10^9\L)	188.71	189.00	160.00	219.00
ESR (mm/1st hr)	74.06	78.00	35.00	125.00
Reticulocytes (%)	1.36	1.50	0.30	2.00
S. LDH(IU\L)	214.88	192.00	155.00	350.00
S.Calcium(mg/dl)	2.12	2.10	1.70	2.70
S. ALP (IU\L)	83.48	70.00	29.10	204.00

III. CASES ASSOCIATED WITH BONE MARROW NECROSIS (BMN)

Four of all patients (19%) were found to have BMN in their BM aspirate & biopsy. Cases were equally distributed among age class intervals 25-34, 35-44, 45-54 & 65-74 years (table II) with a mean age of 50.25 years (table 3) & equal distribution in sex (Table I). Primary & secondary tumors had an equal frequency (Table IV). Most of the tumors (75 %) were in the spine (Table V). All patients had weight loss, bone pain, fever, three quarter of patients had pathological fractures & half of them were pale. All of them had no history of DM, adjuvant therapy, steroid treatment & sickle cell anemia (Table VI).

Peripheral Blood examination showed a hemoglobin concentration ranged between 82.00-108.00 gm/L with a mean of 94.0, while PCV ranged between 0.24-0.37 with a mean of 0.29 & erythrocyte sedimentation rate ranged between 30-122 mm/1st hr with a mean of 84.75. The range of reticulocyte count was from 0.5-3.5% with a mean of 2.5. The range of total white blood cell count was from 4.20-19.90 x10^9/L with mean of 14.75. The range of neutrophils count was from 61.00-79.00%with a mean of 74.25%. The range of lymphocytes count was from10.00-34.00 % with mean of 21 % (Table IX).The range of monocytes count was 1-2 %with mean of 1.5 % (Table IX). All cases had leuco-erythroblastic blood picture.

The range of LDH values was between 112.00-380.00 IU/L with mean of 307.50. The range of serum calcium was between 1.70-2.80 mg/dL with mean of 2.20. The range of serum alkaline phosphatase was from 80.00-155.00 IU/L with mean of 116.63 IU/L (Table IX).

Table IX: Laboratory data of cases associated with BMN

Parameter	mean	median	Minimum	Maximum
Hb (gm\L)	94.00	93.00	82.00	108.00
PCV (L/L)	0.29	0.28	0.24	0.37
WBCS ($x10^9$\L)	14.75	17.45	4.20	19.90
Neutrophils (%)	74.25	78.50	61.00	79.00
Lymphocytes (%)	21.00	20.00	10.00	34.00
Monocytes (%)	1.50	1.50	1.00	2.00
Esinophils (%)	1.50	1.00	1.00	3.00
Platelets ($x10^9$\L)	199.50	173.00	160.00	292.00
ESR (mm/1^{st} hr)	84.7500	93.500	30.00	122.00
Reticulocytes (%)	2.4250	2.8500	0.50	3.50
S. LDH (IU/L)	307.50	369.00	112.00	380.00
S.Calcium (mg/dl)	2.20	2.1500	1.70	2.80
S. ALP (IU\L)	116.63	115.75	80.00	155.00

IV. Comparative study between cases with & without BMN

The study showed that the clinical manifestations of both primary & secondary tumors were more severe when associated with BMN like weight loss, pallor, pathological fracture, neurological deficit. Yet, there was only a significant increase of incidence of fever (P-value <0.05) among them (Table VI). It also showed that patients had lower hemoglobin concentration (mean 94), & there was a significant relationship between presence of BMN & increase in number of WBCs, reticulocyte count & higher LDH enzyme values. (Table X).

Table X: Comparative study between cases with & without BMN.

	without BMN	**with BMN**		
Variable	**Mean**	**Mean**	**P. Value**	**Result**
Age	**50.18**	**50.25**	**0.1**	**NS**
Hb	**108.1765**	**94.0**	**0.06**	**NS**
PCV	**0.3318**	**0.29**	**0.10**	**NS**
WBCs	**7.12**	**14.75**	**0.00***	***S***
Neutrophils	**65.35**	**74.25**	**0.09**	**NS**
Lymphocytes	**30.71**	**21.00**	**0.05**	**NS**
Monocytes	**2.00**	**1.50**	**0.38**	**NS**
Esinophils	**2.47**	**1.50**	**0.16**	**NS**
Platelets	**188.71**	**199.50**	**0.05**	**NS**
ESR	**74.05**	**84.75**	**0.45**	**NS**
Reticulocytes	**1.36**	**2.43**	**0.01***	***S***
Serum LDH	**214.88**	**307.50**	**0.04***	***S***
Serum Ca	**2.12**	**2.20**	**0.70**	**NS**
Serum ALP	**83.48**	**116.63**	**0.16**	**NS**

(N=significant, NS=not significant)

So, in summary, the results showed that BMN is associated with the presence of fever, leuco-erythroblastic blood picture, leucocytosis, reticulocytosis & higher LDH enzyme activity. Malignant primary & secondary bone tumors were more aggressive & severe in features when associated with bone marrow necrosis.

Discussion

The study showed no significant relationship between age and sex & the existence of BMN in cases of malignant bone tumors, so, BMN may occur at any age & both sexes. The incidence of BMN in bone tumors in this study was 19% which seems higher than that found in the study done by Al-Gwaiz, L. 1997[11] who showed an overall incidence of BMN in metastatic carcinoma of (11.8%). The most prevalent manifestation was bone pain (100%). This agrees with that observed by Al-Gwaiz. L. 1997[11] & Bashawri, L, 2000[13] who reported that bone pain & fever were the most common manifestations among cases with BMN. The mean hemoglobin concentration in those with BMN was 94.0 gm/L which is comparable with Al-Gwaiz. L 1997[11] & Bashawri,L, 2000[13], & also agrees with that of Santana et al[23]. There was a significantly higher reticulocyte count in those with BMN than those without, which again comparable to the findings of Al-Gaiz & Bashawri[11,13]. In this study, there was a significant relationship between the presence of BMN & increase in total white blood cell count in patients with malignant bone tumors, this result does not agree with those of Al-Gwaiz. L 1997[11] & Bashawri, 2000[13], who both reported pancytopenia in their cases. All cases with BMN had leuco-erythroblastic pictures, & this agrees with studies done by Al-Gwaiz. L. 1997[11] & Bashawri, 2000[13]. & Dunn et al[24]. There was a significant relationship between the presence of BMN & increased LDH value. This agrees with studies was done by Al-Gwaiz. L 1997[11] & Bashawri, 2000,[13] & Kenneth etal.[14]. Serum calcium levels were nearly the som in both groups of cases with & without BMN. Although serum alkaline phosphatase level was higher among cases with BMN, yet, there was no significant relationship between it & the presence of BMN in patients with malignant bone tumors.

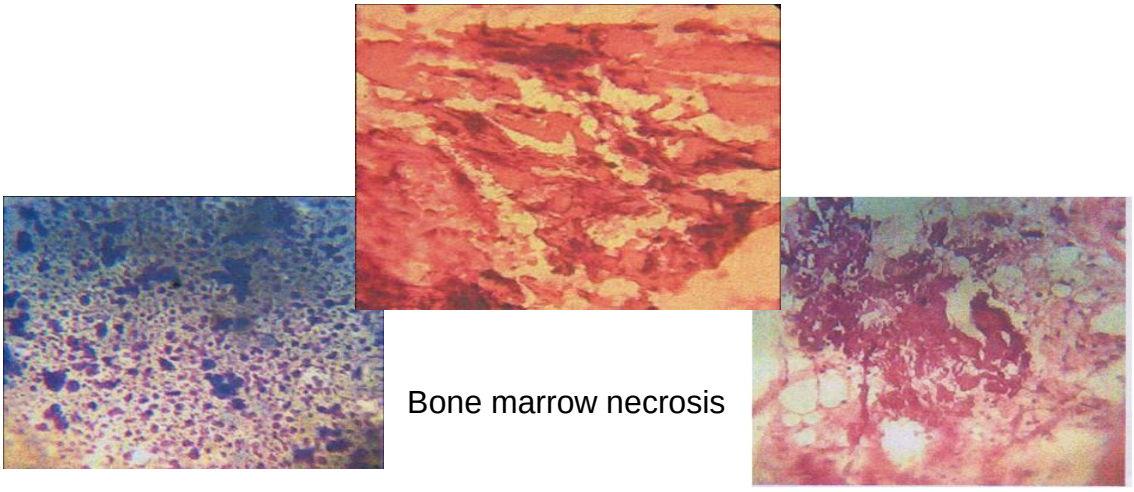
However, owing to the paucity of researches dealing with this aspect in primary & secondary malignant bone tumors, it was quite difficult to compare the results of this study with. Time & more researches will probably clarify more.

Conclusions

1. Bone marrow necrosis is not a rare entity in primary & secondary malignant bone tumors.
2. The presence of BMN is correlated with severe clinical-pathological features which may point to a poorer prognosis. However, it needs a longer period to follow up patients, which is beyond the period of this short duration study.

Recommendations

1. Bone marrow necrosis is to be kept in mind for the orthopaedic surgeon, hematologists & the pathologist when dealing with malignant bone tumors.
2. Prolonged time follow up studies are needed to clarify the outcome of cases of BMN in comparison with those without.



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