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Research Article

Comparison between Benign and Malignant Primary Bone Tumors-A Histopathological Study of 119 Cases

Farah F. Hasan[1]*, Haider L. Mohammed[2]
[1]*Department of Pathology, Collage of Medicine, Kerbela University, IRAQ.*
[2] *Department of Pathology, Alwasiti Teaching Hospital, IRAQ.*
**Correspondent author email: dr.farah.histopathology@gmail.com*

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Abstract

This is a prospective study done at Al wasity teaching hospital for reconstructive surgeries in Bagdad in a period from November 2015 to July 2017, using a Total of 119 samples of primary bone tumors which were diagnosed both histopathologically and radiologically. The main objective of this study was to make a comparison between benign and malignant bone tumors. Immunohistochemical staining was done to confirm the diagnosis of primary malignant bone tumors and the proliferative index of them were carefully evaluated. Out of 119 samples of primary bone tumors used in this study, 100 (84%) were benign and borderline (osteoclastoma) and 19 (16%) were malignant, the mean age for benign tumors was lower than the mean age for primary malignant one and both frequently present in the 2nd decade of life, male to female ratio for benign bone tumors was 3/2 and 8.5/1 for primary malignant one, femur was the most common location for benign bone tumors while tibia was the most common bone affected by primary malignant bone tumors. The study also showed that the most common benign bone tumors were osteochondromas (67%) and most common primary malignant bone tumors were osteosarcomas (52.63%), thus this study rise a conclusion that in general, primary bone tumors were mainly benign, occurred predominantly in the second decade of life with a male preponderance. All samples of osteosarcoma, ES/PNET showed a moderate proliferative index when evaluated by ki67 immunohistochemical marker, while a high proliferative index was found in fibrosarcoma and primary NHL of bone.

Keywords: primary bone tumors, osteosarcoma, osteochondroma, Ewing sarcoma.

الخلاصة

اقيمت هذه الدراسة للمقارنة بين الاورام العظمية الحميدة والاورام العظمية الاولية الخبيثة في مختبرالامراض النسيجية في مستشفى الواسطي التعليمي في بغداد حيث تم جمع 119 حالة من الورم العظمي الاولي للفترة من كانون الثاني 2015 الى تموز 2017 وتم اخذ المعلومات السريرية من سجل الحالات ولغرض تأكيد التشخيص لحالات الورم الاولي العظمي الخبيث والتي لايمكن تشخيصها الا باستعمال المعلمات الكيميائيه المناعية خضعت جميع بلوكات البارافين العائدة للاورام العظمية الاولية الخبيثة فيما عدا ساركومة العظم الى اعادة تقطيع و ثم الصبغ بالمعلمات السرطانية الضرورية لتشخيصها بصورة صحيحة فوجدت الدراسة ان نسبة الاورام العظمية الحميدة اعلى من نظيرتها الخبيثة وان متوسط عمر المصاب بالورم الحميد اقل من متوسط عمر المصاب بالورم العظمي الاولي الخبيث وكلاهما اكثر ظهورا في العقد الثاني من العمر وكانت نسبة الذكور الى الاناث المصابة بالورم العظمي الاولي الخبيث اعلى منها في الورم العظمي الحميد وكان عظم الفخذ من اكثر العظام المتاثرة بالورم الحميد وكان عظم الظنبوب من اكثر العظام المتاثرة بالورم العظمي الاولي الخبيث وشكل الورم العظمي الغضروفي اكثر انواع الورم الحميد 67 % بينماكانت الساركوما العظمية من اكثر انواع الاورام العضمية الاولية الخبيثة 52 %.

Introduction

Bone is the basic unit of the human skeletal system and making a framework for the body, protects the vital organs, supports mechanical movement, contain hematopoietic cells and play a significant role in iron homeostasis [1, 2]. Primary bone tumors are relatively less common among various human neoplasms but are diverse in their pathologic features [3]. The exact incidence of bone tumors is not well known because many benign lesions are not biopsied and recorded [3, 4]. In general when excluding myeloma and lymphoma bone tumors with a malignant biological behavior

constitute only 0.2% of all malignancies in adults and approximately 5% of childhood malignancies [4]. Close cooperation is needed between the histopathologist, radiologist, surgeon and oncologist in order to diagnose bone tumor properly and make a management decision [5, 6]. The nomenclature and classification of primary bone tumors is based mainly on the pathway of tumor cell differentiation which is usually identified by the connective tissue matrix made by tumor cells [7]. The histogenesis of many primary bone tumors however is not well confirmed and a number of bone tumors are classified by distinct morphological or clinicopathological features (e.g., osteoclastoma giant cell tumor of bone) or by molecular genetic abnormalities (e.g., Ewing's sarcoma) [7, 8]. Radiological information is mandatory for bone tumor diagnosis and it is highly recommended that wherever possible, the pathologists should have a radiological knowledge allowing them to personally see the radiological images of a bone tumour before establishing the final diagnosis. Otherwise, it should be recorded in the pathology report [9, 10, 11].

Materials and methods

This study is a prospective study carried out at Al-Wasity teaching hospital for plastic and orthopedic surgery in Bagdad (the period from November 2015 to July 2017) using a total of 119 cases of primary bone tumors which were diagnosed at histopathological and radiological aspects according to the recent WHO classification of bone tumors [10] . In orthopedic diseases OPD, patients clinically presented with bone mass were included in this study and X-ray of the affected bone had been taken while CT scan and MRI were done according to the need and advice of orthopedic surgeon. Biopsy was taken mainly by scrapping method, incision and excision. In laboratory department, any soft tissues present were fixed in 10 % formalin while for bone, 3 to 5 mm thick sections were made and fixed in 10% buffered formalin and then decalcification was done by placing the specimens in nitric acid for adequate time. After that all tissues were processed by the same routine basic method recommended for histopathological study, then all slides were examined under light microscope and different types of primary bone tumors were identified. Cases of secondary bone tumors were excluded. Clinical information include radiological features, age, sex and location of tumors were taken from the biopsy request forms. Some primary malignant bone tumors required diagnostic confirmation immunehisto-chemically [10]. Therefore, all of the paraffin embedded tissues which are diagnosed as primary malignant bone tumors were subjected to immunohistochemical staining using autostainer (X biogenex i6000) to confirm the diagnosis as shown in Tables 1 and 2.

Table 1: Immunohistochemical evaluation of certain primary malignant bone tumors.

Malignant bone tumor	Immunohistochemical primary antibody
Osteosarcoma	ki67, vimentin
Ewing sarcoma\Primitive neuroectodermal tumors ES\PNET	CD99, CD45, desmin, ki67
Chondrosarcoma	S100, ki67
Fibrosarcoma	Vimentin, ki67
Non Hodgkin lymphoma	CD45, CD3, CD20, CD99, desmin

Results of immunohistochemical study were interpreted based on the following scoring protocols:

CD99: − if absent; + between (0% - 10%) of tumor cells; 2+ if more than 10% and less than 50% of tumor area; and 3+, if 50% and\or more of tumor cells were positive [12].

Desmin: negative when no immunoreactivity was seen, focal/weak if less than 20% were positive and positive if strong positivity was seen in equal and more than 20% of tumor cells [13].

ki67: the scores were regarded as negative according to the percentage of nuclear reactivity (0% of nuclei stained), low (less than 10%), moderate (10%-40%), and high (more than 40%).Only nuclear staining (plus mitotic figures which are stained by Ki67) in hot spots, (areas in which Ki67 staining is particularly prevalent) should be incorporated into the Ki67 score [13].

Table 2: Immunohistochemical Staining Protocols.

Antibody	Clone	Dilution	Manufacturer	localization	Positive control
CD99	12E7	1:50-1:75	Dako	Cell memberane	normal tonsil
Ki67	MIB1	1:75-1:50	Dako	Nucleus	skin
Desmin	D33	1:50-1:100	Dako	Cytoplasm	Skeletal and smooth muscle
CD45	2B11 PD7\26	1:50-1:100	Dako	Cell memberane	Lymph node
CD3	CD3	1:200-1:400	Dako	Cell memberane	tonsil
CD20	L26	1:200-1:400	Dako	Cell memberane	tonsil
S100	S100	1:400	Dako	Nucleus	Skin
Vimentin	V9	1:50-1:100	Dako	Cytoplasm	Uterus

Vimentin: Tumors were considered to be positive when stained at least 10% of the neoplastic cells. A cut-off < 10% of positive tumor cells was used to identify negative cases [14].

S100: the score were (0 to 2), with a score of 0 indicate no staining, a score of 1 indicate focal nuclear staining, and a score of 2 indicate staining in the majority of tumor nuclei [15].

CD45: immunohistochemical stains were interpreted as positive if at least 10% of the neoplastic cells showed intense immune-reactivity. Specimens were considered focally positive if immunoreactivity was identified within the cells of interest but comprised less than 10% of the tumor [16].

CD3 and CD20: the positive results defined by the presence of at least 10% of antigen expressing cells [17].

Results and Discussion

This study enrolled 119 samples of primary bone tumors, 100 were benign and borderline tumors (osteoclastomas) and 19 were malignant as shown in Figure 1.

Regarding benign tumors, 60(60%) were male and 40(40%) were female with male \female ratio 3\2 .Their age range from 2.5 years to 50 years with a mean age of 16.66 ± 9.51 years, they were divided into six age groups each group reflects a decade of life from the 1st decade to the 6th decade, the results were respectively 25, 43, 21, 7, 3 and 1 as shown in Table 3. Topographically 76(76%) tumors involved the upper extremity, 22(22%) involved the lower extremity and only two (2%) involved the axial skeleton. The distribution of samples according to bone location indicate that the most common bone affected in benign bone tumor was femur represent 40% of samples followed by tibia represent 30% of samples. Histologically, benign bone tumors in decreasing order of frequency were shown in Table 4.

The study found that the most common benign bone tumor was osteochondroma which appeared microscopically as normal bony trabeculae covered by a cartilage resemble disorganized growth plate with ossification toward the base as shown in Figure 2, the mean age was 15.64± 4.61, with a slight male predominance, most frequently involve femoral bone.

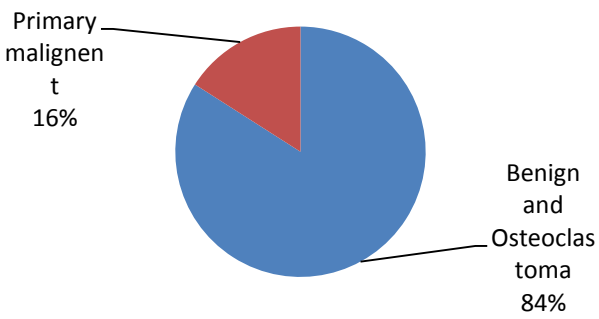

Figure 1: Distribution of Benign bone tumors and Osteoclastomas according to biological behavior.

Table3: Frequency of primary bone tumors according to histopathological aspect.

Age in years	Age in decade	Number of sample	Percentage (%)
0 to 9	1st	24	24
10 to 19	2nd	43	43
20 to 29	3rd	21	21
30 to 39	4th	7	7
40 to 49	5th	3	3
50 to 59	6th	2	2

Among 19 cases of primary malignant bone tumors, the study showed that 17 (89.47%) were male and only two(10.52%) were female with a male to female ratio 8.5/1, their age range from 8 to 83 years with a mean age of 21. 21± 17 years. According to the age interval from the 1st to the 6th decade, the results were respectively 1, 11.4, 2, 0, 0 and only one sample were 83 years old which was a male with primary NHL of bone in which the final diagnosis was made after a careful search done by the clinician to exclude the presence of any other primary foci (as shown in Figure 11).

Table 4: Frequency of different types of bone tumors according to the histological criteria of WHO classification [10].

Tumor	Number	Percentage (%)
Osteochondroma	67	67
Osteoid osteoma	1	10
Giant cell tumors (osteoclastomas)*	7	7
Osteofibtous dysplasia	7	7
Fibrous dysplasia	6	6
Chondromyxoid fibroma	1	1
Enchondroma	1	1
Chondroblastoma	1	1

* All cases of osteoclastomas were cytologically benign (grade I and II) which appeared microscopically as regular and uniform distribution of stromal cells and giant cells (as shown in Figure 4) with no clinical malignancy according to the microscopic grading of giant cell tumors [10].

Topographically, 13 (68.42%) located in the lower extremity, 4 (21%) located in the upper extremity and only 2 (10.52%) in axial skeleton. Tibia was the most common site in the percentage of 31.57%, followed by femur 21%.

Table 5: Frequency of cases with malignant tumor according to their age.

Age intervals in years	Age in decade	Number	Percentage (%)
0 to 9	1st	1	5.26%
10 to 19	2nd	11	57.89
20 to29	3rd	4	21
30 to 39	4th	2	10.52
40 to 49	5th	0	0
50 to 59	6th	0	0

The most common primary malignant bone tumor was osteosarcoma (which appeared histologically as malignant spindle cell tumors producing osteoid unconnected with cartilage). The mean age was 12.1 ±2.7 years, with a male to female ratio was 9\1, most commonly affect femoral bone of 10 sample of osteosarcomas, seven were conventional, one was chondro-blastic, one osteoblastic and one telangectatic (as shown in Figure 8)**.** All cases of osteosarcomas immunohistochemecally were evaluated using non-specific markers because of unavailability of markers of osteoblastic differentiation such as osteocalcin, osteonectin,

Table 6: Descending arrangement of cases frequency according to histological appearance.

Malignant bone tumors	**Number**	**Percentage (%)**
Osteosarcoma	10	52.63
Ewing sarcoma	6	31.57
Condrosarcoma	1	5.26
Fibrosarcoma	1	5.26
NonHodgkin lymphoma	1	5.26

SATB2 at our center and in all cases of osteosarcoma included in this study the diagnosis was straight forward due presence of abundant osteoid directly produced by tumor cells without an intervening areas of cartilage and confirmed radiologically. The 2nd most common primary malignant bone tumors was ES\PNET which appeared microscopically as a sheet of undifferentiated small round uniform cells with scant cytoplasm, indistinct cell membrane and minimal amounts of stroma (as shown in Figure 10), all cases affecting males, half of the cases involve tibia and the other half involve radius. The results of immune-histochemical staining of primary malignant bone tumors are shown in Table 7.

Accordingly, osteosarcoma ewing sarcoma and chondrosarcoma had a moderate proliferative

index and the strong proliferative index was observed in primary fibrosarcoma and non-Hodgkin lymphoma of bone.

Table 7: Immunohistochemical results in primary malignant bone tumors.

Malignant bone tumor	Positive antibodies	Negative antibodies
Case 1 osteosarcoma	Ki67 moderate 25%, vimentin	Not done
Case 2 osteosarcoma	Ki67 moderate 25%, vimentin	Not done
Case 3 osteosarcoma	Ki67 moderate 25%, vimentin	Not done
Case 4 osteosarcoma	Ki67 moderate 20%, vimentin	Not done
Case 5 osteosarcoma	Ki67 moderate 20%, vimentin	Not done
Case 6 osteosarcoma	Ki67 moderate 20%, vimentin	Not done
Case 7 osteosarcoma	Ki67 moderate 20%, vimentin	Not done
Case 8 osteosarcoma	Ki67 moderate 15%, vimentin	Not done
Case 9 osteosarcoma	Ki67 moderate 15%, vimentin	Not done
Case 10 osteosarcoma	Ki67 moderate 15%, vimentin	Not done
Case 1 Ewing sarcoma	CD99 strong, ki67 moderate 40%	CD45,desmin
Case 2 Ewing sarcoma	CD99 strong, ki67 moderate 25%	CD45,desmin
Case 3 Ewing sarcoma	CD99 strong, ki67 moderate 15%	CD45,desmin
Case 4 Ewing sarcoma	CD99 strong, ki67 moderate 20%	CD45,desmin
Case 5 Ewing sarcoma	CD99 strong, ki67moderate 25%	CD45,desmin
Case 6 Ewing sarcoma	CD99 strong, ki67moderate 30%	CD45,desmin
Chondrosarcoma (only one case)	Vimentin, S100 score2 ki67 moderate 30%	Not done
Fibrosarcoma(only one case)	Vimentin, ki97 strong 50%	Not done
Non Hodgkin lymphoma(only one case)	CD45,CD20,ki67 strong60%	CD3,CD45,desmin

Table 8: Comparison between benign and primary malignant bone tumors in 119 cases.

	Benign and osteoclastomas	Malignant
Number of cases during two years period	100	19
Mean age in years	16.66 ±9.5	21.21± 17
Most common decade of life affected	2nd decade 43 (43%)	2nd decade 11 (57.89%)
Male to female ratio	3\2	8.5\1
Involvement of axial skeleton	2 (2%)	2 (10.5%)
Most common location	Lower limb, femure 40 (40%)	Lower limb, tibia (31.57%)
Most common histology	Osteochondroma 67 (67%)	Osteosarcoma 10 (52.63%)
Second most common histology	Osteoid osteoma 10 (10%)	ES\PNET 6 (31.57%)

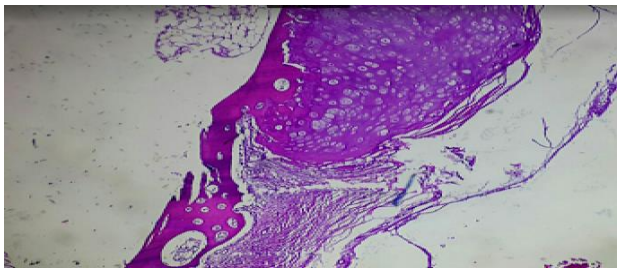

Figure 2: Histological section of osteochondroma in a femur of 10 years old male with H & E staining (X100).

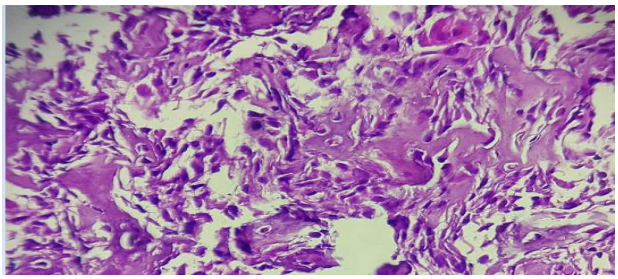

Figure 3: Histological section of osteoid osteoma in a tibia of 5 years old female with H & E staining (X100)

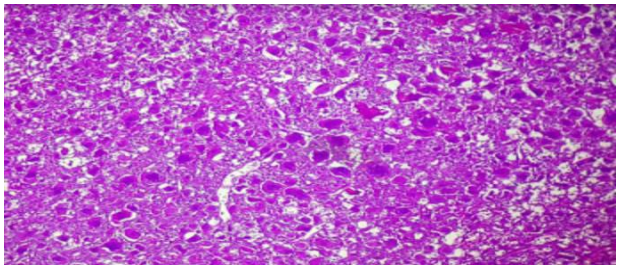

Figure 4: Histological section of osteclastoma in a femur of 28 years old female with H & E staining (X100).

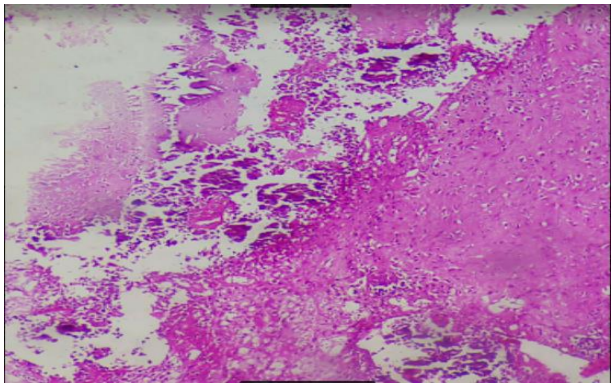

Figure 5: Histological section of chondroblastoma in a femur of 10 years old male with H & E staining (X100)

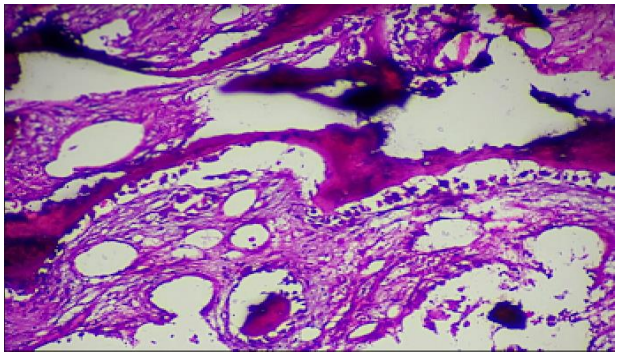

Figure 6: Histological section of osteofibrous dysplasia in a humeral bone of 8 years old female with H & E staining (X100)

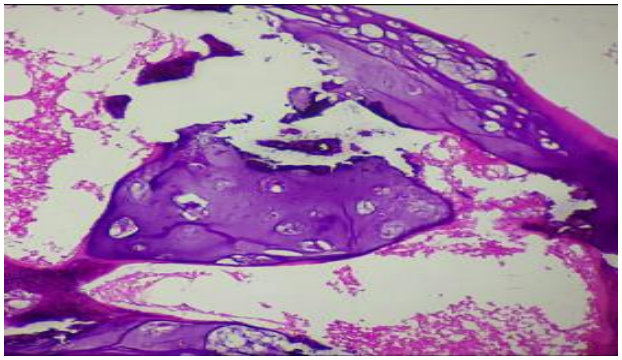

Figure 7: Histological section of enchondroma in a 42 years old male had a mass in middle phalenx with H & E staining (X100)

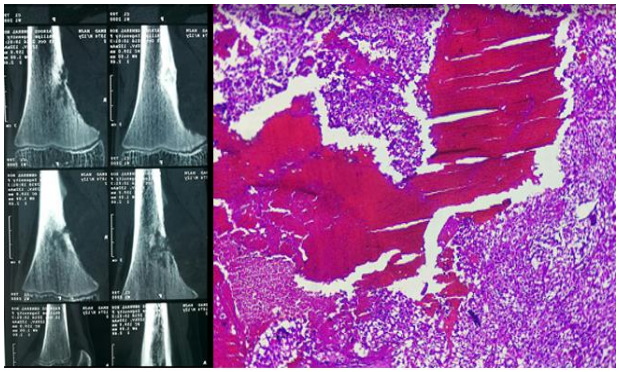

Figure 8: Telangectetic osteosarcoma involved lower end of femur in a 12 years old boy (A: ragiological image, B: histological section x100)

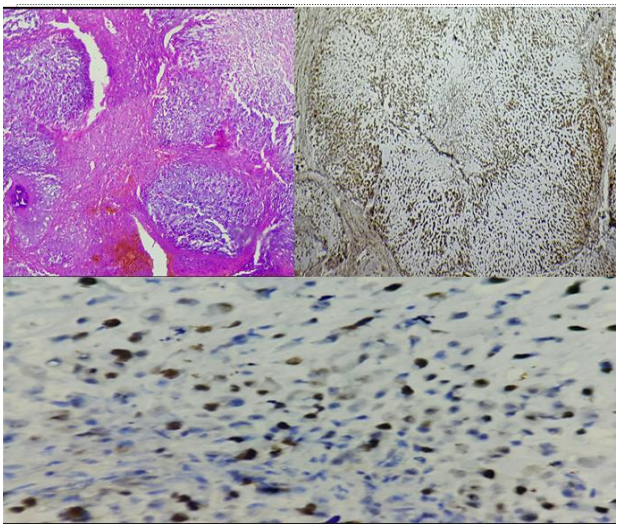

Figure 9: well differentiated chondrosarcoma in a 37 years old femaleA: histological picture x100, B: immunohistochemical stain with S100 showed score 2 positive nuclear stain x100,C: moderate nuclear staining for ki67 x400

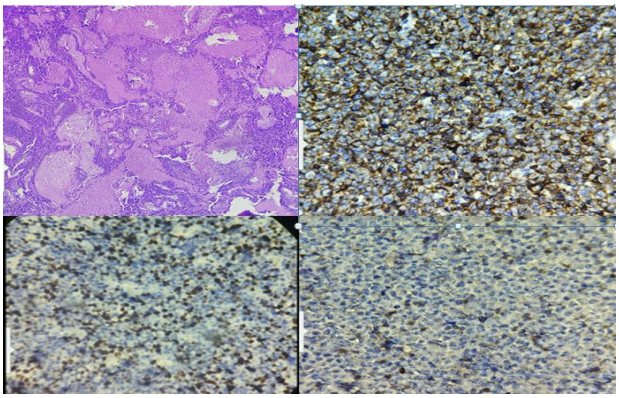

Figure 10: ES\PNET in a 17 years old male with a mass involving lower radius A: histological picture x100, B: strongly positive CD99 immunohistochemical stain x100, lower C: moderately positive ki67 immunohistochemical stain x100, D: negative CD45 immunohistochemical stain x100 .

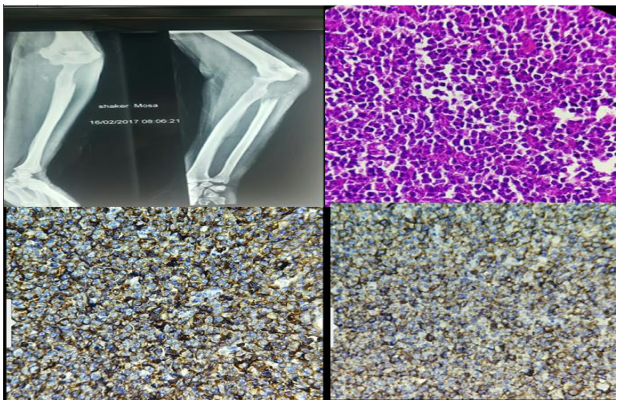

Figure 11: Primay NHL of bone in a 83 years old man with mass in proximal ulna. A: Radiological image, B: histological picture x100, C: positive CD45 immunohistochemical stain x100, D: positive CD20 immunohistochemical stain x100.

The Discussion

In the WHO classification, most bone neoplasms are classified as either benign or malignant. Although a sharp distinction between these two categories is feasible in most of them, some neoplasm exhibit borderline and intermediate characterstics as osteoclastoma (GCTs) [10], which have been described as the most challenging benign bone tumors because it shows a tendency for significant bone destruction, local recurrence and occasionally metastasis[18].

The present study showed that 84% of all sample were benign and only 16% were malignant which agree with one study done by Sunita *et al.* (2015) [19], but another study done by Karun *et al.* (2011) [20] showed that only (57.26%) of the bone tumors were benign, may be due to a non-random selection of samples used by the latter. The mean age range for benign bone tumors was lower than that of primary malignant tumors and the most common presentation for both was in the 2nd decade of life, our results agree with data obtained by sunita *et al.* (2015) and Karun *et al.* (2011) [19, 20]. In general bone tumor commonly affect male with a male to female ratio much higher in primary malignant bone tumors which agree with sunita *et al.* (2015) [19]. The most common location in benign bone tumors was femur, while in malignant bone tumors was tibia, the result disagree with sunita *et al.* (2015) [19] in which it showed femur was the most common location for both benign and malignant bone tumors followed by tibia. The most common benign bone tumor was osteochondroma with a male predo-minance and commonly affect femoral bone results agree with results of sunita *et al.* (2015) and karun *et al.* (2011) [19, 20], but the latter studies in contrast to this study showed that giant cell tumors were the second most common types. Although, osteochondroma in this study found to be the most common benign bone tumor, but in our center it presented with a much higher percentage (67%) than in many studies worldwide [19, 20, 21, 22, 23] in which the highest percentage reported among them was 34%.

This study also showed the most common primary malignant bone tumors was osteosarcoma commonly involved femoral bone and the second decade of life regarded as the most common age of occurrence, the results agree with one Iraqi study by Kareem *et al.* (2010) [21], but the latter study showed a slight male predominance in contrast to this study which showed a strong male predominance (90% of patients were males) may be merely due to variation in sample size or may indicate a recent rise in its incidence among Iraqi males. The second most common malignant bone tumor was ES\PNET, this results agree with an Iraqi study done by Kareem *et al.* (2010) [21] and two Indian studies done by sunita *et al.* (2015) and karun *et al.* (2011) [19, 20], but in contrast to the latter studies, surprisingly all cases in this study were males.

Conclusion

This study showed that in general primary bone tumors were mainly benign, occurred predominantly in the second decade of life with a male preponderance. The mean age for malignant bone tumors were more than for benign one although both frequently occurred in the 2nd decade of life, tibia was the most common location for malignant tumor while femur was the most common in benign one. Primary malignant bone tumors showed a strong male preponderance in contrast to a slight male preponderance occurred in benign tumors. Osteosarcoma and osteochondroma were the most common primary malignant and benign bone tumor respectively. All samples of osteosarcoma, ES/PNET showed a moderate proliferative index when evaluated by ki67 immunohistochemical marker, while a high proliferative index was found in fibrosarcoma and primary NHL of bone.

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